4. Vertebrate cardiovascular systems

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CHAPTER CONTENTS

THE CARDIOVASCULAR SYSTEM OF VERTEBRATES is arguably one of the more critical of all organ systems. By virtue of its role in transporting nutrients, metabolic waste products, respiratory gases, hormones, and heat, the cardiovascular system intervenes in a rate-limiting way between the acquisition of energy and its use in metabolic processes. Although it is important at every point in an animal's life cycle, the pivotal role of the cardiovascular system in vertebrates is perhaps best exemplified in the embryo, where it is the first organ system to function. Only when this system is established can the materials needed for organogenesis be transported to the metabolically active areas of the rapidly growing embryo. Serious cardiovascular defects in embryonic stages usually result in diminished tissue differentiation and growth and often portend embry-

onic or early fetal death. Simply put, the cardiovascular system of vertebrates is a "choke-point" for all other physiological processes.

This chapter presents an overview of cardiovascular form and function in vertebrates. Where possible, we describe general characteristics of the vertebrate circulation. Many readers already familiar with circulatory systems will recognize the gross oversimplification of talking about the "vertebrate circulation" or the "vertebrate heart" since there is great inter- and intraclass variation in vertebrate cardiovascular design. We begin this chapter by considering the evolutionary diversity of vertebrate circulations.

DIVERSITY OF VERTEBRATE CARDIOVASCULAR PATTERNS

Vertebrate Origins and Driving Forces behind Cardiovascular Evolution

The evolutionary history of vertebrates has been studied intensely ever since the theory of evolution was first proposed. Despite the application of modern techniques of molecular biology and powerful new forms of systematic analysis such as cladistics (biological systematics based on phylogenetic relationships), we remain uncertain about many important aspects of vertebrate phylogeny. Particularly poorly represented in the fossil record are the ancestors of the earliest vertebrates and how they interrelate phyletically. Figure 4.1 shows a simplified (and still debated) phyletic scheme relating the three subphyla within the phylum Chordata: the Urochordata (tunicates), the Cephalochordata (for example, the lancelet *Branchiostoma*), and the Vertebrata.

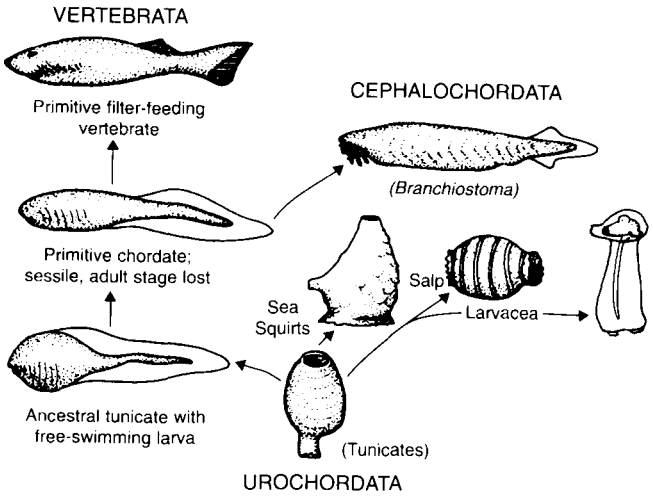

FIG. 4.1. Simplified phyletic scheme relating Urochordata, Cephalochordata, and Vertebrata (from ref. 511, after ref. 529).

It is generally assumed that some of the earliest vertebrates were comparatively large, actively swimming animals that acquired food by filter-feeding. A nonsessile life-style combined with a size too large for internal nutrient and gas transport to be served by diffusion alone required an efficient cardiovascular system that could rapidly distribute required nutrients and remove metabolic wastes from metabolically active tissue. (Many invertebrates place similar demands upon their cardiovascular systems [see Chapter 13 by McMahon, Smith, and Smith in this *Handbook*], and the early vertebrates were certainly not unique in requiring a highly efficient, high-capacity internal transport system.) Consequently, the early vertebrates are thought to have possessed a highly differentiated cardiovascular system consisting of a discrete heart or hearts, an arterial distribution system, a vascular bed comprised of capillaries or their functional equivalent (nonendothelial lined blood sinuses of very small diameter), and a venous collection system. Initially, evolutionary changes in the cardiovascular system may have come in response to nutrient uptake and transport rather than the transport of respiratory gases. Primitive chordates (tunicates, *Branchiostoma*) show early embryonic differentiation of the digestive organs and a highly developed intestinal circulation. Randall and Davie (511) interpret these observations as pointing to food distribution as the major selection pressure driving the evolution of the primitive vertebrate circulation. They suggest, for example, that the periodic reversals of blood flow in urochordates (276) are designed to disperse nutrient-garnering cells around the body. Indeed, promoting O_2 and CO_2 exchange with the environment initially may have been only a secondary function of the circulation. Given the potential effectiveness of the body's outer surface as an "all-purpose" respiratory organ (199, 200), highly specialized sites for gas exchange (for example, gills) may have been unnecessary in the earliest vertebrates, which presumably had not yet attained the much larger body size of their descendents.

As the ancestral vertebrates increased in size and began to adopt a more fusiform shape (47), the cardiac pump became consolidated into a central, multichambered heart, while the peripheral circulation assumed a more segmental arrangement in which smaller distribution vessels branched off at regular intervals from a larger distribution vessel running the length of the animal. This arrangement, with a central heart perfusing numerous vascular beds located in parallel, obvi-

ated any advantage of a cardiovascular system capable of alternating orthograde and retrograde pumping of blood. Randall and Davie (511) appropriately identify the shift toward a centralized cardiac pump and unidirectional blood flow as a major selection pressure in the evolution of one-way valves within the circulation.

The appearance of valves that maintained the movement of arterial blood from the heart to the tissues and the return of venous blood from the tissues toward the heart had far-reaching evolutionary consequences for cardiovascular physiology beyond the more efficient one-way flow. The arterial tree, isolated from the heart during diastole, could now serve as a pressure reservoir, while the venous drainage could serve a blood-storage role. Along with the centralization of blood-propulsion mechanisms into a single, highly differentiated pump, valves at the base of the major systemic arteries allowed the evolution of a highly muscularized heart developing higher blood pressures. Arterial pressures higher than those in the most simple ancestral circulation were certainly a necessary preadaptation for supporting increased convective blood flow associated with higher metabolic rate, longer and narrower exchange blood vessels (providing more effective material exchange), and an excretory system operating on ultrafiltration. Combined with the increasing metabolic rates of the primitive vertebrates, the circulation had to assume the additional important role of transporting O_2 and CO_2 between the environment and tissues. Higher arterial pressure permitted the evolution of a specialized aquatic gas-transfer site, with internal gills possessing large numbers of small-diameter blood channels that, though of intrinsically low resistance themselves, added to the overall resistance of the animal's vascular beds. Such gills would greatly enhance O_2 uptake and CO_2 elimination.

The development of a highly differentiated circulation perfused by a high-pressure, multichambered heart set the stage for the explosive growth of marine and freshwater fishes, which represents the single largest evolutionary radiation among vertebrates. During the Mesozoic era, air breathing as a supplemental source of oxygen evolved independently in many groups of fishes inhabiting warm fresh water. The selection pressures responsible for this could have ranged from decreasing oxygen availability in the aquatic medium (or seasonal decrease in the extent of the aquatic medium) to increased risk of predation to a search for additional sources of foraging or prey items (85, 241, 408, 509). CO_2 was probably not a selection pressure since most extant bimodal breathers use air breathing almost exclusively for O_2 uptake while continuing to rely upon aquatic CO_2 elimination across the skin or gills (199, 200). Some bimodal breathers used modifications of existing gas-exchange organs (gills, skin), while others evolved structures de novo to be used in aerial gas exchange.

Based on the morphology of extant phyletically ancient fishes, new dedicated sites for gas exchange were necessarily accompanied by increases in the complexity of the circulation. The development of distinct drainage vessels from the gas-exchange organs, conveying oxygen-rich blood directly back to the heart, was the key element in the evolution of anatomical and physiological mechanisms for maintaining separate bloodstreams in the heart. One of the earliest developments was the partitioning of the primitive single atrium into left and right atria by an interatrial septum, a condition found in extant Dipnoi (lungfishes), amphibians, reptiles, birds, and mammals. A spongy ventricle with trabeculate endocardium, already a feature of the ancient aquatic fishes, maintained separation of relatively oxygen-poor and oxygen-rich streams of blood during the filling and emptying of the ventricle. Partial septation of the ventricle probably developed from a mere elongation of trabecular ridges on the ventricle's inner surface, a process hinted at in extant amphibians such as *Siren* and *Necturus* (see later under *Cardiovascular Patterns in Vertebrates*). More complex patterns of partial ventricular septation arose in the hearts of squamate reptiles. The crocodilian pattern of complete ventricular division, while retaining the possibility of pulmonary bypass, represents in many respects the most flexible vertebrate cardiovascular system. The high body temperatures and metabolic rates in the early birds obviated the periods of apnea that occurred in their "crocodile-like" ancestors and consequently removed the selection pressure for maintaining the ability to achieve a pulmonary bypass. Consequently, as early birds evolved they were freed to develop completely separate pulmonary and systemic circuits, each with its own cardiac pump.

While this interrelated group of scenarios depicting the evolution of the cardiovascular system of vertebrates is somewhat speculative, we can state with certainty that vertebrate cardiovascular systems of extant animals should not be viewed as lying on some sort of a fictitious continuum from fishes to mammals. The heart of squamate reptiles, for example, is not a mammalian heart awaiting evolutionary mending of an intraventricular septal defect, as is sometimes portrayed. Instead, the cardiovascular system of each distinctive vertebrate group reflects the tortuous evolutionary path that led to the somewhat separate origins of fishes, amphibians, squamate reptiles, crocodilian reptiles, birds, and mammals. This diversity will now become

abundantly clear as we examine in detail the circulatory patterns of extant vertebrates.

Cardiovascular Patterns in Vertebrates

General Characteristics of the Chordate Circulation. Unlike the myriad of circulatory patterns and processes evident in invertebrates (see Chapter 13 by McMahon et al. in this *Handbook*), the cardiovascular systems of the chordates in general, and more specifically of the vertebrates, are more conservative with respect to functional design. While all biological "rules" have exceptions, the general characteristics of the circulation of animals from the phylum Chordata are as follows:

1. *A single, ventrally located myogenic heart.* Almost all chordates have a single, muscular heart that is myogenic in nature. The exceptions are *Branchiostoma,* which has no heart at all, and hagfishes, which have multiple hearts. Invertebrates do not necessarily have a "heart," and if they do, the single or multiple hearts can be either myogenic or neurogenic.
2. *Cephalically directed cardiac ejection of blood.* The artery or arteries emanate from the cephalic margin of the heart in vertebrates and, at least initially, convey blood cephalically before bending to serve the caudal regions of the animal. Invertebrate hearts can eject blood caudally, cephalically, and laterally.
3. *"Passive" arterial and venous valves.* The proximal regions of the central arterial circulation, as well as numerous sites in both the peripheral and central venous circulations, contain nonmuscularized, one-way valves. All valve closure and opening is dictated by the direction of blood flow through them. Because of the numerous outflow routes from certain invertebrate hearts and limited vasomotor activity, emerging evidence suggests that arterial valves are muscular and actively regulated.
4. *Muscular vessels capable of vasomotor activity.* Vascular smooth muscle in the walls of vertebrate arteries and veins empowers these vessels to constrict and dilate. Changes in degree of muscular contraction alter peripheral resistance, blood pressure pulsatility, and peripheral blood storage. Many invertebrate blood vessels lack the smooth muscle elements to regulate vascular tone.
5. *Closed vascular system.* The historical clear-cut distinction between "closed" and "open" circulatory systems is breaking down in light of the emerging view of many invertebrate circulatory systems, particularly of Crustacea (see ref. 427 and the chapter by McMahon et al. in this *Handbook*). Use of an anatomical vs. a functional definition of "open"and "closed" can lead to differing classifications. Certainly, the distinction between open and closed circulations is more easily based on an anatomical definition than a functional one. On the basis of an anatomical definition of a closed vascular system being lined by endothelial cells at all organizational levels (arteries, arterioles, capillaries, etc.), the circulation of nearly all vascular beds of almost all vertebrates is indeed closed. The functional definition of a closed circulation, in which circulating blood remains confined within a discrete set of conveying or exchange vessels, is less easily defended as an all-encompassing vertebrate characteristic because the primitive condition for vertebrates exemplified by the cyclostomes is one with open blood sinuses (see discussion of hagfish later in this section).

Having discussed the putative evolutionary events leading to the vertebrate circulation and some of their general characteristics, we turn now to examine specific cardiovascular patterns.

Urochordates and Cephalochordates

Urochordates. The urochordates (tunicates) consist of three classes, with the Ascidiaea, or sea squirts, being the most extensively studied with respect to their cardiovascular system. While the circulation of sea squirts is often assumed to be representative of urochordates generally (511), a tradition we will continue, additional work on the Thaliacea and Larvacea is clearly warranted.

Urochordates have a single heart that propels blood through a complex system of vessels, which has been variously classified as open (34, 656) or closed (511). All of the circulatory pathways lack an endothelial lining or even true walls, being merely sinus channels through the mesenchyme (34). Anatomically, then, the cardiovascular system of urochordates must be regarded as open. Nonetheless, blood is carried along discrete, well-defined channels to numerous separate vascular beds (Fig. 4.2).

The heart itself is a tubular structure located near the base of the digestive tract. In many species (for example, *Sydnium*) the heart is folded in a tight U-shape in the postabdominal region. This heart is peculiar in that it arises from a folding of the pericardium into the pericardial cavity and does not have chambers or a specialized lining, which makes this organ analogous rather than homologous with vertebrate hearts. This pericardial folding is invested with only a single layer of spindle-shaped striated muscle cells (see references listed in ref. 511 for details of heart structure). The anterior (dorsal) opening of the heart connects to the subendostylar channel, which conveys blood between the heart and the pharyngeal basket plexus of blood vessels. The posterior (ventral) opening to the

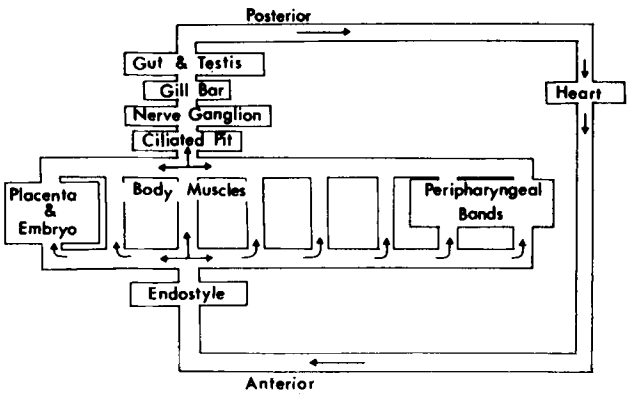

FIG. 4.2. Circulatory pattern of urochordates. Anatomical location of heart in ascidian urochordate *Clavelina*. Small *arrows* show direction of blood flow when heart is pumping from posterior to anterior (from ref. 511, after ref. 529).

heart connects to a large abdominal sinus. Both openings to the heart lack valves.

The heart is myogenic and, at least in *Ciona*, activated by independent pacemakers located at either end of the structure (9). The heart propels blood by peristalsis, with two or more waves occurring at any one time. Peristaltic waves pass along the heart at the rate of about 3–6 mm/s (9). The "noncardiac region" of the pericardium is quite stiff compared to the fold forming the heart, and contraction of one region of the heart aids filling of another. Assigning direction of blood flow through the tunicate heart is problematic inasmuch as one of the distinguishing features of tunicates is the frequent, spontaneous reversal of flow through the heart (567). Typically, the heart will beat at about 30–80 beats/min in a dorsal direction for 50–150 beats, then slow and stop or show only feeble beating for a few minutes (Fig. 4.3). The heart then begins to beat and propel blood in the opposite direction (as inferred from electrocardiographic [ECG] tracings—direct measurements of flow have not been made) before slowing, stopping, and then resuming the original direction of pumping. This flow pattern results from the alternating dominance of the independent pacemakers at either end of the heart. In the long term, this alternating direction of blood flow will ensure the distribution of nutrients and O_2 and the removal of wastes and CO_2 throughout the tissues. Experiments on decapod Crustacea have shown that, even though they possess an anatomically open cardiovascular system, a sophisticated redistribution of hemolymph can occur in response to a variety of external and internal stimuli. To our knowledge, the possibility of shunting or internally redistributing blood selectively to specific vascular beds in urochordates (or any primitive chordate) has not been investigated. It would certainly be advantageous for tunicates to be able to redistribute hemolymph during reversed heart beating rather than, for example, simply sending blood that had just acquired nutrients from the digestive tract back along that same vascular pathway.

Cephalochordates. The cephalochordates are represented by two genera—*Assymetron* and *Branchiostoma*, or the lancelet, formerly known as *Amphioxus*. The circulation of *Branchiostoma*, by far the more extensively studied of the two cephalochordates, has been well described anatomically, but physiological investigations are few indeed.

The most striking feature of the cephalochordate

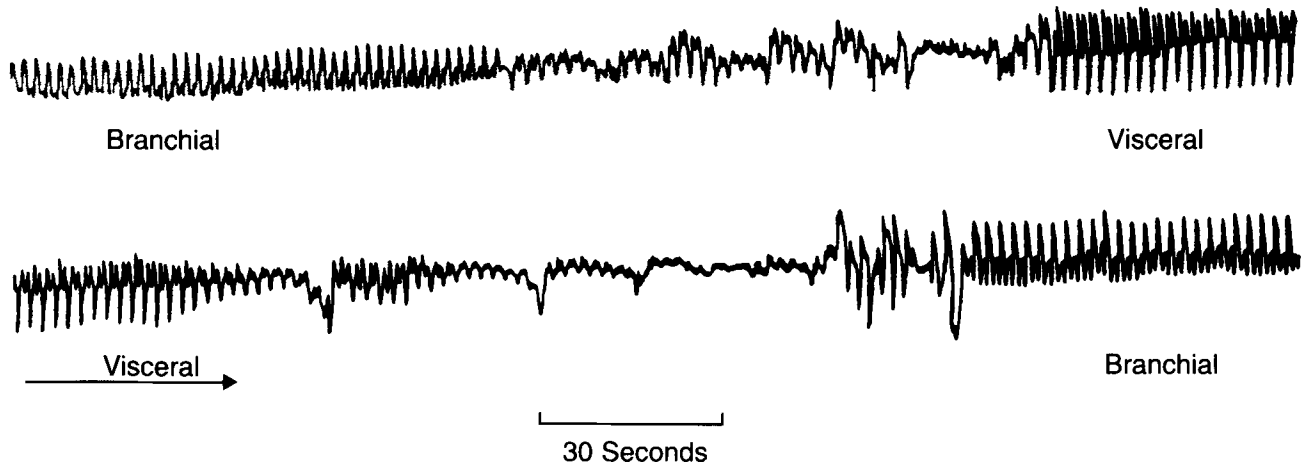

FIG. 4.3. Reversal of blood flow in tunicate circulation. This recording of in vivo electrical heart rate activity in *Ciona intestinalis* shows alternating periods in which blood is presumed to be pumped toward gills *(Branchial)* and toward viscera *(Visceral)* (from ref. 567).

circulation, and the feature that makes the cardiovascular system of animals in this subphylum an exception among the Chordata, is the absence of a heart. Instead, propulsion of blood through the vascular channels is achieved by contractile vessels located in various regions throughout the circulation (Fig. 4.4). Blood from the gut collects into a contractile intestinal vein that leads directly into the liver, making it part of a hepatic portal system. After passing through the liver, blood is carried through a contractile hepatic vein into a sinus venosus, which also receives blood from other systemic vascular beds, including the gonads, the tail musculature (a substantial proportion of the body), and the head region. Blood from the sinus venous flows into a contractile endostylar artery and then directly to either the gills or the renal sinus, two vascular beds that lie in parallel. At the base of each gill arch is a *bulbulus,* a contractile vessel segment that aids blood flow through the branchial vascular bed. Oxygen-rich blood from the branchial vessels collects into paired lateral aortae running along the dorsal surface of the body (Fig. 4.4). Only these paired dorsal vessels have an endothelial lining, and consequently *Branchiostoma* lacks true capillaries. The blood (which is thought to lack a respiratory pigment or, at least, any physiologically useful concentration of pigment) perfuses through tissue lacunae and, after nutrient, waste, and gas exchange, collects in the sinus venosus for recirculation.

Except for the prominent lack of a heart, the circulation of *Branchiostoma* conforms to the general vascular plan of chordates. Despite the obviously important evolutionary position of the cephalochordates in the evolution of the phylum Chordata, almost nothing is known about the mechanisms that regulate the cephalochordate circulatory and respiratory systems. Important unanswered issues include whether the contractile vessels are independently regulated, whether both intrinsic ("Starling-like") and extrinsic mechanisms exist (and their relative importance), and whether there are any reflexes that modulate blood flow.

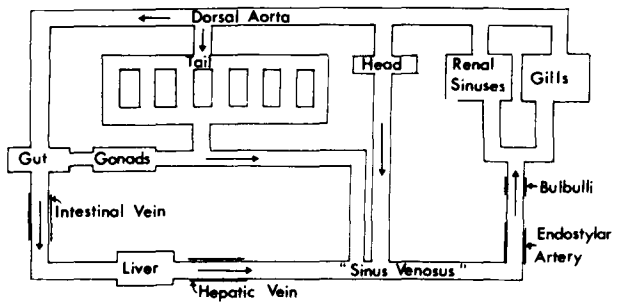

FIG. 4.4. Schematic representation of urochordate circulation. Contractile regions of vessels indicated by double-lined walls (from ref. 511).

The Agnatha: Hagfish and Lampreys. The systematics of the most primitive vertebrates—the myxines and lampreys—is still subject to dispute and confusion (47, 322, 543), in part due to the combination of both primitive and specialized features that they display. Most would agree that the combination of hagfish and lampreys in Cyclostomata is more convenient than accurate, so we discuss the cardiovascular system of each separately.

Hagfish. Several unusual features of the hagfish's circulation, and its obviously interesting, if confusing, taxonomic position, have long commanded scrutiny by cardiovascular physiologists (10, 139, 161, 180, 209, 210, 257, 301, 326, 330, 543, 669). Although the following account is based largely on the Atlantic hagfish *Myxine,* Davie et al. (139) have emphasized that differences in natural history, habitat, and morphology exist between *Myxine* and *Eptatretus,* the latter being much larger, more aerobic, and more active.

In many respects, the cardiovascular system of the hagfish follows the pattern of petromyzont, elasmobranch, and teleost fishes. A centrally located systemic heart (homologous with the heart of other fishes but by far the most primitive) propels blood to a branchial and a systemic vascular bed located in series and connected by the intervening dorsal aorta. This "systemic" heart, which is composed of true cardiac muscle, is devoid of autonomic innervation. Yet, heart rate (f_H) and cardiac output vary considerably in intact animals, suggesting that some mechanisms exist to regulate cardiac function. The systemic heart shows a Starling effect, responding to increased venous return with increased cardiac output. It is also rich in catecholamines, but early work using isolated muscle strips suggested that the systemic heart is minimally responsive or unresponsive to catecholamines (for example, epinephrine) or acetylcholine (ACh) (116, 326). However, studies by Axelsson et al. (20) using catecholamines infused into the caudal vein of intact *Myxine* indicated that epinephrine stimulates both f_H and stroke volume (SV) (and lowers peripheral resistance). A dose of 10 nmol/kg epinephrine increased cardiac output from 12 to 22 ml/min/kg. Epinephrine is contained within granulated subendothelial cells in the ventricle of *Myxine,* and it may exert a paracrine effect on myocytes when released. How catecholamine release may be engineered is unknown at this time.

Other unusual features of the systemic heart of *Myxine* include a relative insensitivity to extracellular Ca^{2+} (379, 499), since decreasing Ca^{2+} normally decreases contractility in vertebrate hearts, and a very high toler-

ance of extreme hypoxia conferred upon it by its relatively low energy demands (a low power output) being closely matched by its high anaerobic capability (20).

In addition to the systemic heart, hagfish have several accessory hearts located posteriorly (caudal heart), in the abdominal cavity (portal heart), and anteriorly (cardinal hearts). These accessory hearts are located on the venous side of the circulation and, aided by numerous one-way valves distributed throughout the veins, assist in the propulsion of blood back to the central heart. The portal heart similarly shows a Starling effect, but its normally very consistent rate of beating suggests rather little modulation by hormones; it is not innervated. The caudal heart is much more varied in its beating, and it permanently stops beating if the spinal cord is destroyed. This suggests the involvement of neural reflex regulation but not necessarily direct innervation of the heart.

The peripheral circulation of hagfishes resembles in many respects that of elasmobranchs and teleosts, particularly in the gills, gut, and much of the skeletal musculature, where venules and veins can be recognized. The caudal region and some of the head, however, contain large open sinuses devoid of an endothelial lining that appears more like those found in invertebrate circulations (85, 326). There are also large subdural blood sinuses located throughout the body. As much as 80% of oxygen uptake occurs through the skin in *Myxine* (582), but Satchell (543) summarizes evidence that suggests a limited respiratory role, if any, for the subdural sinuses. Knowledge of the pharmacology of the peripheral vasculature is incomplete, but what is known is that it is not far dissimilar from the vasculature of other fishes (543). Ultrastructural details of the hagfish circulation have been studied (161, 385).

Lampreys. Many comparative physiologists erroneously lump together as the "cyclostome condition" the anatomical and functional aspects of the circulation of the myxinoids and lampetroids. In fact, the lampetroids differ substantially from the myxinoids in many ways beyond the circulation.

Lampreys represent an intermediate position between that of hagfish and gnathostome fishes. The peripheral circulation of the lamprey generally resembles that of gnathostome fishes. The most obvious difference between hagfish and lampreys is the presence in lampreys of only a single ventral or "systemic" heart. This heart, unlike the systemic heart of hagfish, is innervated by a branch of the vagus nerve that tracks along the jugular vein. Paradoxically, vagal stimulation and the application of ACh increases, rather than decreases, f_H but reduces the strength of heart contraction (see ref. 455 for references). Catecholamines also stimulate the lamprey heart, but the effects are reduced compared to that of ACh. Although accessory hearts are lacking in lampreys, peripheral mechanisms in the form of a "massaging" action produced by rhythmic contraction of the branchial chambers no doubt assist in the return of venous blood to the heart.

Aquatic Gnathostome Fishes and the "Venous Heart." The gnathostome fishes not only were among the earliest vertebrates but also are the most diverse. If species number is an index, they are also the most successful. Along with this great diversity comes a myriad of cardiovascular patterns, particularly when comparing and contrasting phyletically ancient fishes (for example, *Latimeria, Lepisosteus, Amia, Acipenser,* and *Protopterus*) with the vast more recent radiation of teleost fishes. Comprehensive reviews have dealt with the great diversity of fish cardiovascular systems (95, 190, 543, 544), and the reader is directed to these works which reference earlier, more narrowly focused reviews on particular fish taxa or specific anatomical or physiological conditions. Our approach is to describe the general characteristics of the piscine cardiovascular system and to direct the reader to specific reviews for additional information. The diverse cardiovascular patterns that accompany air-breathing fish are discussed later in this section.

All gnathostome fish have a four-chambered, ventrally located "venous" heart consisting of a sinus venosus, atrium, ventricle, and bulbus arteriosus (sometimes called either the bulbus cordis or conus arteriosus in cartilaginous fishes). The ventricle is thickly walled and trabeculate and, depending on the species, has a rudimentary coronary system. The heart is enclosed by a pericardial sac, which in chondrichthyeans and chondrosteans is quite rigid. Blood ejected from the heart is directed anteriorly into a short ventral aorta. Depending upon the family, the ventral aorta gives rise to four (teleosts), five (acipensiforms), or six (most elasmobranchs) pairs of branchial arteries perfusing each gill arch pair. Oxygen-rich blood draining the gills enters into a dorsal aorta that carries blood caudally and internal carotid arteries that perfuse the cephalic regions. Blood from the dorsal aorta enters into separate gut and renal vascular beds, as well as the vasculature of the posterior body wall. A renal portal vein carries blood from the posterior body tissues to the kidneys, whereas a hepatic portal vein carries blood from the gut directly to the liver. Paired hepatic ducts return venous blood from the liver to the sinus venosus. Blood draining the head regions enters anterior cardinal veins, which convey it to the sinus venosus via the ducts of Cuvier.

A striking characteristic of the cardiovascular system of fishes is the presence of a secondary blood system,

a system of arteries, capillaries, and veins which runs roughly in parallel with the primary system (75, 543, 583, 584, 631). Arising from the efferent branchial arteries, dorsal aorta, and segmental arteries are short interarterial anastomotic vessels (Fig. 4.5). These vessels, which are usually very narrow and tightly coiled, coalesce to form a system of secondary arteries that perfuse the tissues of the gills, the intestinal lining, and the skin and scales (if present). Skeletal muscle, the central nervous system (CNS), and the liver and pancreas lack a secondary circulation. The capillaries of the secondary system occur almost exclusively in epithelial tissues exposed to water and the contents of the gut. Blood from the secondary system is collected into cutaneous veins and returned to the primary central venous circulation. Blood flow through the secondary venous circulation is assisted by a "caudal" heart or hearts consisting of venous sinuses that are rhythmically compressed by the tail musculature during swimming. The caudal heart is small and poorly developed in teleosts like eels but more extensively developed in some elasmobranchs (see ref. 543 for additional information).

The role of this secondary circulation in fishes (and even its existence) has been the source of some debate (583). Clues to its function may come from the fact that blood pressures and hematocrit in the secondary circulation are both low. However, its blood volume is around twice that of the primary circulation in rainbow trout. Studies by Ishimatsu et al. (320) on rainbow trout *(Oncorhynchus mykiss)* indicate that it contributes significantly to acid-base regulation during hypercapnic exposure.

Air-Breathing Fishes: Cardiovascular Implications of Multiple Respiratory Sites. Air breathing, as either a supplement to water breathing or as the main pathway for respiratory gas exchange, has independently evolved several times in fishes. There is, as a consequence, considerable diversity among fishes in the type of air-breathing organ, its importance relative to water breathing with gills, and its arterial supply and venous drainage. Several comprehensive reviews containing information on fish air-breathing organs and their vascularization have been published (84, 85, 134, 313, 327, 385, 408, 409, 509, 542), and the reader is directed to them for detailed information.

In his now classic review, Johansen (327) provided a generalized scheme showing the various cardiovascular patterns and pathways associated with the evolution of air-breathing organs in fishes (Fig. 4.6). Air-breathing fishes such as *Monopterus, Ophiocephalus, Electrophorus, Amphipnous, Periopthalamus,* and *Anabas* use a modified pharyngeal and or opercular mucosa as the air-breathing organ. The arterial supply to these aerial respiratory surfaces, which are relatively nonspecialized, is derived from the afferent branchial supply. Oxygen-rich blood draining the air-breathing organ is returned to the central venous circulation.

In air-breathing fishes like *Clarias* and *Saccobranchus,* which use buccal mucosa or dorsal elaborations of the gills extending into opercular cavities for air breathing, oxygen-rich blood draining the aerial gas-exchange site is returned primarily to the efferent branchial circulation for distribution along with efferent branchial blood into the dorsal aorta and on to the systemic tissues.

Several fishes use the gastrointestinal tract for air breathing (for example, *Misgurnus, Hoplosternum, Plecostomus,* and *Ancistrus*). Although regions of the stomach or intestine may be highly specialized for gas exchange, both the afferent and efferent circulations of these fishes are unremarkable, with afferent partially oxygen-rich blood derived from the systemic arterial circulation and oxygen-rich blood returned to the central venous circulation.

More complex cardiovascular patterns are found in phyletically ancient phystostome fishes such as *Polypterus* (the bichir), *Amia* (the bowfin), *Lepisosteus* (the gar pike), and *Hoplerythrinus* (the jeju). In these fishes, the efferent branchial circulation has become specialized such that blood draining the anterior arches preferentially enters the dorsal aorta and flows on to the systemic tissues, while blood draining the posterior arches is preferentially shunted into a ventilated air bladder. As in all previously mentioned fishes, however, oxygen-rich blood from the air bladder drains into the central veins.

An important feature of all of the above-described cardiovascular patterns is that oxygen-rich blood from the air-breathing organ is returned to the central veins, where it mixes with relatively oxygen-poor blood draining from the systemic tissues. The direct effect is an increase in venous blood oxygen content and partial pressure of oxygen (P_{O_2}). This may be advantageous in supplying oxygen to the heart, especially since these fishes routinely experience aquatic hypoxia. Obviously, oxygen added to the blood in the capillaries of the air-breathing organ likely reaches the systemic tissues after first transiting the branchial circulation. However, oxygen acquired in the air-breathing organs and transferred to central venous blood has the potential to be lost again to severely hypoxic water surrounding the gills if the venous P_{O_2} in the gill lamellae exceeds the water P_{O_2}. Not surprisingly, in contrast to exclusively water-breathing fishes that increase gill ventilation with hypoxia, many air-breathing fishes show a reduced rate of gill ventilation in severely hypoxic water, shifting

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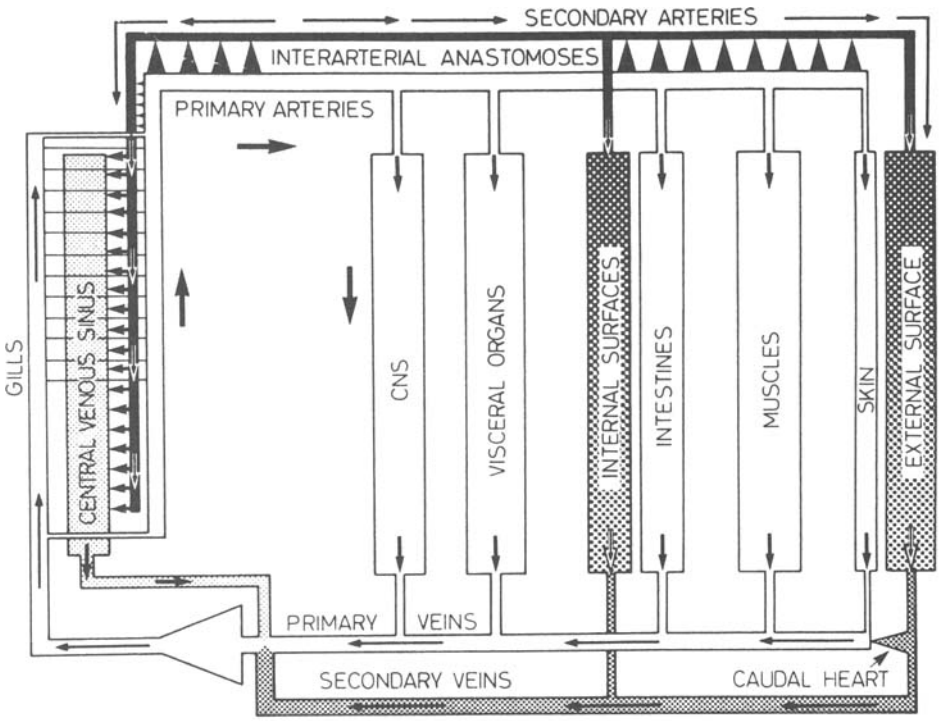

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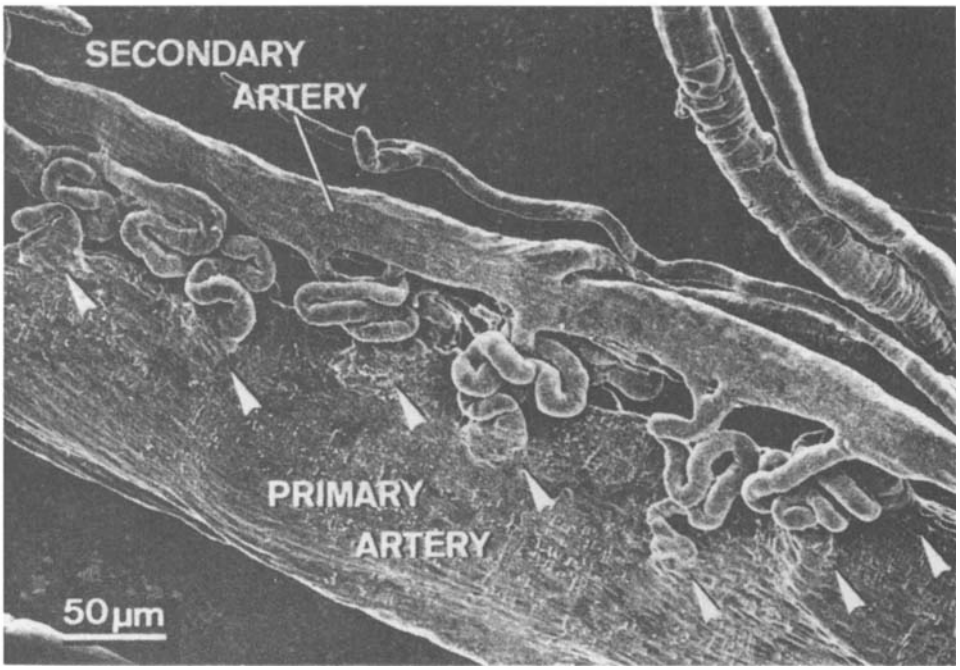

FIG. 4.5. Secondary circulation of fishes. *A:* Schematic representation of primary and secondary *(shaded)* circulation of a typical teleost fish. *B:* Scanning electron micrograph of a vascular corrosion cast of arteries from rainbow trout, *Oncorhynchus mykiss* (from ref. 631).

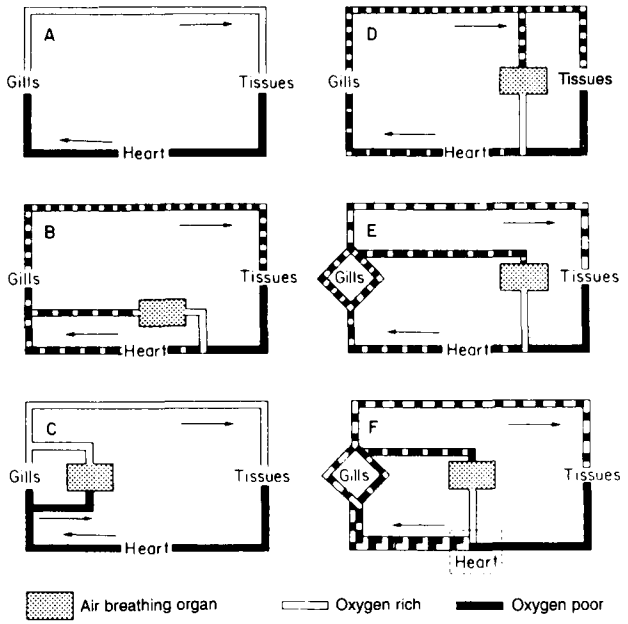

FIG. 4.6. Schematic of cardiovascular system in various air-breathing fishes. Relative amounts of black and white hatching within blood vessels indicate approximate degrees of oxygenation of blood. *A:* General arrangement in strictly water-breathing fishes. *B:* Air-breathing organ derived from pharyngeal and/or opercular mucosa (for example, *Monopterus, Electrophorus, Periopthalmus, Anabas*). *C:* Gills, buccal mucosa, or elaborations of opercular cavity serving as air-breathing organs (for example, *Clarias, Saccobranchus*). *D:* Gastrointestinal tract used as air-breathing organ (for example, *Hoplosternum, Plecostomus, Ancistrus, Misgurnus*). *E:* Relatively simple air bladder used as air-breathing organ (for example, *Polypterus, Amia, Lepisosteus*). *F:* Lung, structurally similar to that of amphibians, used for air breathing (for example, lungfishes *Protopterus, Lepidosiren*). Note that these fishes show major enhancement of the gas-exchange circuit in the form of a pulmonary vein leading directly back to the heart (from ref. 327).

the burden of gas exchange to the air-breathing organ (70, 327). Because complete mixing of oxygen-rich blood from the air-breathing organs and oxygen-poor blood from the systemic tissues occurs before reaching the heart, there has been no evolutionary selection pressure for a partially or fully divided atrium or ventricle capable of maintaining separation of distinct blood flows through the heart.

The central circulation of the Dipnoi (lungfishes) represents an important divergence (and increase in complexity) from this pattern. Foremost, systemic and pulmonary venous returns reach the heart separately. The circulatory systems of *Protopterus* and *Lepidosiren* return blood directly from the lung via pulmonary veins rather than via the central venous circulation. The development of pulmonary veins was a crucial preadaptation for division of the heart. With oxygen-rich and oxygen-poor blood entering into separate regions of the atria, there now existed a strong selection pressure for the evolution of anatomical and physiological mechanisms to preserve the identity of these separate streams of blood as they passed through the chambers of the heart, the ventral aorta, and on to the branchial circulation. Indeed, the atrium, ventricle, and bulbus cordis have partial septal divisions in all three extant genera of lungfishes, with the South American lungfish *Lepidosiren* showing the greatest degree of separation and the Australian lungfish *Neoceratodus* showing the least. Blood perfusing the lung is derived mainly from the efferent branchial arteries perfusing the two most posterior arches, while blood perfusing the systemic circulation is derived mainly from blood perfusing the two most anterior arches, a pattern consistent with other air-breathing fishes.

The atrium of the Dipnoi is partially divided into a larger right side, receiving largely oxygen-poor blood from the systemic veins, and a smaller left side, into which the pulmonary veins empty their oxygen-rich blood (see ref. 84 for a detailed review of heart structure in the Dipnoi). The major structure dividing the atrium is the pulmonalis fold, a partial septum arising from a deformation of the atrial wall produced by the overlying pulmonary vein. The ventricle of all three lungfish genera, which is highly trabeculate, is also partially divided by a vertical septum arising from the dorsal and ventral walls of the septum. Oxygen-poor blood from the right side of the atrium is directed to the right side of the ventricle, while oxygen-rich blood (originating in the lungs) is directed to the left. Effective separation of these streams of oxygen-rich and oxygen-poor blood within the heart is maintained through the cardiac cycle, and relatively distinct streams of blood are ejected into the bulbus cordis. The bulbus cordis itself has anatomical specializations to maintain these separate streams. The inner walls of the bulbus cordis of *Neoceratodus* bears several proximal rows of small conal valves (Fig. 4.7). In *Lepidosiren* and *Protopterus*, which show the greatest degree of bulbus cordis specialization, a bulbar or spiral fold arises from the ventral row of conal valves. More distally, a second fold arises from the wall opposing that of the spiral fold, and most distally these two folds are fused to form a complete division into two channels of the bulbus cordis. The bulbus cordis and the spiral fold within it rotate about 270° before generating the afferent arteries.

The afferent branchial arteries perfusing gill arches I and II of the lungfish are derived from the ventral channel in the distal region of the bulbus cordis, which conveys primarily oxygen-rich blood flowing from the left side of the heart. The afferent branchial arteries perfusing gill arches III and IV are derived from the

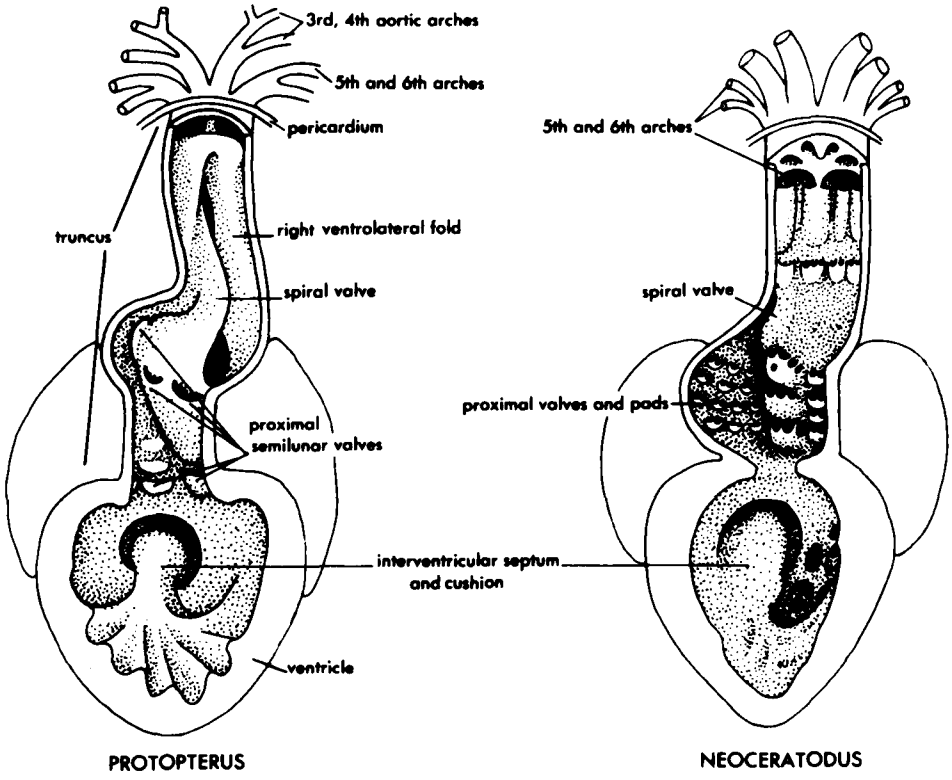

FIG. 4.7. Sagittal sections (ventral aspect) through heart and truncus of the African lungfish *Protopterus* and South American lungfish *Neoceratodus* (from ref. 335, and ref. 239).

dorsal channel in the distal region of the bulbus cordis, which conveys primarily oxygen-poor blood flowing from the right side of the heart. Thus, highly derived anatomical features have evolved in the atrium, ventricle, and bulbus cordis to direct oxygen-poor blood preferentially to the lungs. The potential loss of oxygen from blood to severely hypoxic water passing over the gills, a danger when afferent branchial blood is partially oxygen-rich, as mentioned above, is minimized in lungfish by a strong morphological dichotomy between anterior and posterior gill arches. The anteriormost arches tend to be small and mostly devoid of gill filaments, with presumably little true surface area for gas exchange in either direction. The posteriormost gills, which receive oxygen-poor blood from the right side of the heart, are well endowed with filaments (332) and secondary lamellae. If oxygen in water passing over the gills is high, then branchial exchange will contribute to the elevation of oxygen in efferent branchial blood. Most of this blood is shunted to the systemic circulation, with relatively little flowing to the lungs. However, when water oxygen levels are low, efferent branchial blood from arches III and IV remains low in oxygen (having been unable to become fully saturated in passing through the lungs), and this blood is preferentially shunted into the pulmonary circulation (see *Blood Volume and Its Regulation*, below).

Regardless of the anatomical nuances of the central circulation of air-breathing fishes, the air-breathing organ lies in parallel to the systemic circulation, which means that all of the cardial output does not go to the air-breathing organ and that, in fact, blood flow to the air-breathing organ can be regulated to a large degree independently of systemic blood flow. This "cardiovascular flexibility" was likely, and continues to be, of great survival value.

Amphibians: A Dedicated Gas-Exchange Circuit. The cardiovascular systems of extant amphibians share several general characteristics (77, 215, 328, 346, 561). In almost all species, the heart consists of an anatomically divided left and right atrium receiving blood from the lungs and systemic venous circulation (Fig. 4.8). Blood from the atria enters a highly trabeculate, undivided ventricle. The trabeculae, which form deep, blind-ended pockets that collect and hold blood during diastolic filling, provide a mechanism which appears to permit partial separation of left and right atrial blood during the filling phase of the ventricle and even while blood is ejected from the ventricle during systole (561).

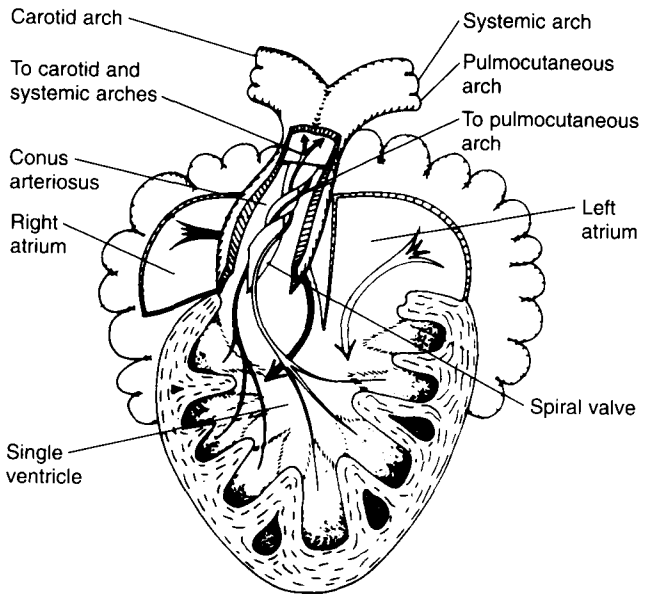

FIG. 4.8. Functional morphology of typical anuran heart. Flow of oxygen-rich blood shown by *open arrows;* flow of poorly oxygenated blood shown by *black arrows* (from ref. 561).

Blood ejected from the heart passes through semilunar cusp valves into a large conus arteriosus containing a complex spiral valve. In a way similar to that described above for the central arterial circulation of the Dipnoi, the spiral valve channels separated streams of oxygen-rich and oxygen-poor blood along the length of the conus arteriosus, which terminates with another set of semilunar cusp valves. Oxygen-poor blood is channeled preferentially into the arteries conveying blood to the lungs (and skin, in the case of anurans), whereas oxygen-rich blood is channeled preferentially into the systemic arteries. Pulmonary venous blood returns from the lungs to the left atrium via distinct pulmonary veins, while systemic venous blood returns to the sinus venosus and then directly into the right atrium.

While this general pattern applies to amphibians, there has been an unfortunate tendency to ascribe the detailed morphological characteristics of the anuran circulation to all amphibians. In fact, important differences occur between amphibian families (77). In the anurans, the conus arteriosus terminates into left and right pulmocutaneous and systemic arches. Distally, the pulmocutaneous arch splits into a large pulmonary artery and a smaller cutaneous artery (Fig. 4.9, *top*). The pulmonary artery carries poorly oxygenated blood to the lungs, while the cutaneous artery carries poorly oxygenated blood to the skin. The skin of anurans also receives a regular systemic supply of oxygen-rich blood from the vertebral arteries. Thus, the skin of anurans receives a mixed supply of poorly and well-oxygenated blood. The cutaneous arteries are most abundant in the dorsal surface and flank (447), and consequently these regions of the skin receive a greater proportion of oxygen-poor blood and make a disproportionately greater contribution to cutaneous gas transfer, both oxygen uptake and carbon dioxide elimination.

Urodeles differ from anurans in several respects. Perhaps most importantly, urodeles lack a cutaneous artery arising from the pulmonary arterial circulation, so the skin receives a homogenous blood supply from the vertebral arteries (Fig. 4.9, *bottom*). Cardiac struc-

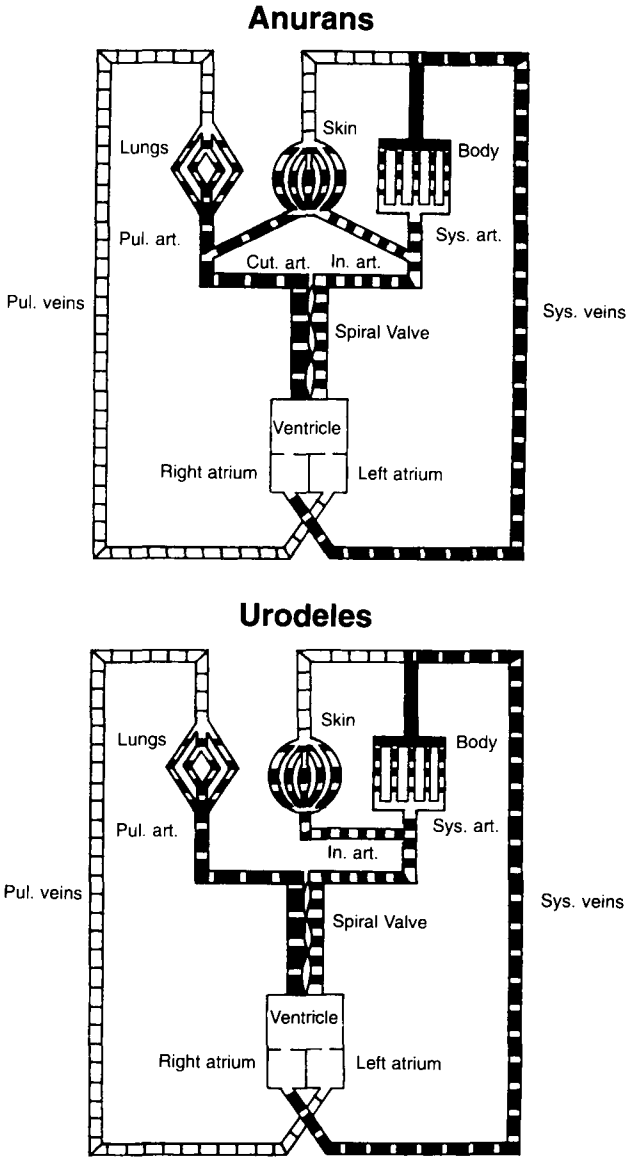

FIG. 4.9. Schematic diagram of anuran and urodele amphibian circulation. The major difference between the two is the presence in anurans of a cutaneous artery arising from the pulmocutaneous arch, which results in dual skin supply from pulmonary (pulmocutaneous artery) and systemic vertebral arteries.

ture also differs in several urodele genera. The ventricle of *Cryptobranchus alleganiensis* (505), *Siren intermedia* (474, 503), and *Necturus maculosus* (504) is partially divided by a vertical septum. The prominence of this septum varies between genera. The effects of this structure on either intracardiac blood pressures or the channeling of oxygen-rich and oxygen-poor blood through the heart are unknown but deserve physiological examination.

A final variation in central vascular structure is evident in urodeles that lack lungs as adults—*Chioglossa, Salamandrina, Rhyacotriton,* and the entire family Plethodontidae. The pulmonary artery, present in other urodeles, is either completely absent or highly reduced in these lungless groups, and the interatrial septum is either incomplete or missing (see ref. 76 for references). Lungless salamanders have been quite successful in both tropical and temperate climates, suggesting that total dependence upon cutaneous gas exchange is a viable alternative for relatively small animals in certain niches.

The circulation of the Apoda has received little attention, and the few physiological and anatomical observations that have been made are on only distantly related species within this family. In the semiterrestrial *Siphonops annulatus* from Brazil, the interatrial septum is incomplete and fenestrated (428, 545). Since the spiral valve characteristic of other amphibian families is also absent, the ability of this apodan to separate effectively oxygen-rich and oxygen-poor bloodstreams within the central circulation is unclear. However, in the aquatic *Typhlonectes compressicauda,* also from Brazil, the two atria are anatomically separate and there is a prominent spiral valve that actually divides the conus into two distinct channels (609). Physiological measurements indicate a considerable degree of separation of oxygen-rich and oxygen-poor blood during flow through the central circulation. Anatomical observations of many apodans indicate that the ventricle is partially divided by prominent muscular trabeculae (see ref. 504 for references). Clearly, a more systematic and comprehensive approach to the cardiovascular form and function in apodans is required to determine primitive and derived features of the circulation.

Reptiles: Masters of Intracardiac Shunting. The inherent anatomical complexity of the heart and central circulation of reptiles that places the systemic and pulmonary circuits in parallel, combined with the physiological consequences of an intermittent breathing pattern either in terrestrial activities or associated with diving in aquatic species, has led to much investigation of reptilian cardiovascular anatomy and physiology (for reviews, see refs. 73, 247, 279, 328, 491, 554, 563a, 623, 639, 640, 648, 650, 651). As is evident for the amphibians, the cardiovascular systems in the class Reptilia show numerous distinctions both between and within families. Major differences are found between the major groups—squamate reptiles (excepting varanid lizards), varanid lizards, and crocodilians.

Squamates. Although anatomical variations are found between and within snakes, lizards (excepting varanid lizards), and chelonians (turtles and tortoises) (see, for example, refs. 623, 640), a general cardiovascular pattern can be described for the squamate heart. The squamate heart historically was described as having a "partially divided" ventricle due to an "interventricular septal defect," clearly a perspective of those studying mammalian hearts. In fact, the squamate heart (indeed, the hearts of all reptiles) represents a highly derived condition that affords a high degree of flexibility for the control of central blood shunting. The squamate heart has three distinct chambers, or *cava* (Fig. 4.10*A*). The cavum arteriosum receives pulmonary venous return but has no direct output into the systemic circulation. Blood from the cavum arteriosum travels around a muscular ridge and the cusps guarding the atrial orifices into a second, much larger chamber called the cavum venosum. The cavum venosum also receives systemic venous blood ejected directly from the right atrium. Despite the potential for a large degree of mixing of left and right atrial blood within the cavum venosum, physiological studies (discussed under *Breath Holding and Diving* below) indicate that a high degree of separation of these bloodstreams can be achieved through both the filling and contraction phases of the ventricle. When the cavum venosum contracts, it ejects blood directly through orifices guarded by semilunar valves into left and right aortic arches. At least in chelonians, the brachiocephalic artery originates at the very base of the right aortic arch as it emerges from the heart. A single set of valves guards this systemic ejection pathway from the heart, but distal to the valves the orifices of the brachiocephalic and right aortae lay side by side. This has led to some confusion in the literature over the exact number of systemic arches arising directly from the heart (see ref. 279 for discussion). Functionally, the brachiocephalic artery and right aorta receive blood from the same region of the cavum venosum. During ventricular contraction, blood ejected into the right side of the cavum pulmonale from the right atrium is preferentially directed over a prominent muscular ridge into the third chamber of the heart, the cavum pulmonale. This chamber, which receives all of its blood from the cavum venosum (that is, there is no direct atrial input), ejects blood directly into the base of a single pulmonary trunk. In chelonians and lizards, the pulmonary trunk soon di-

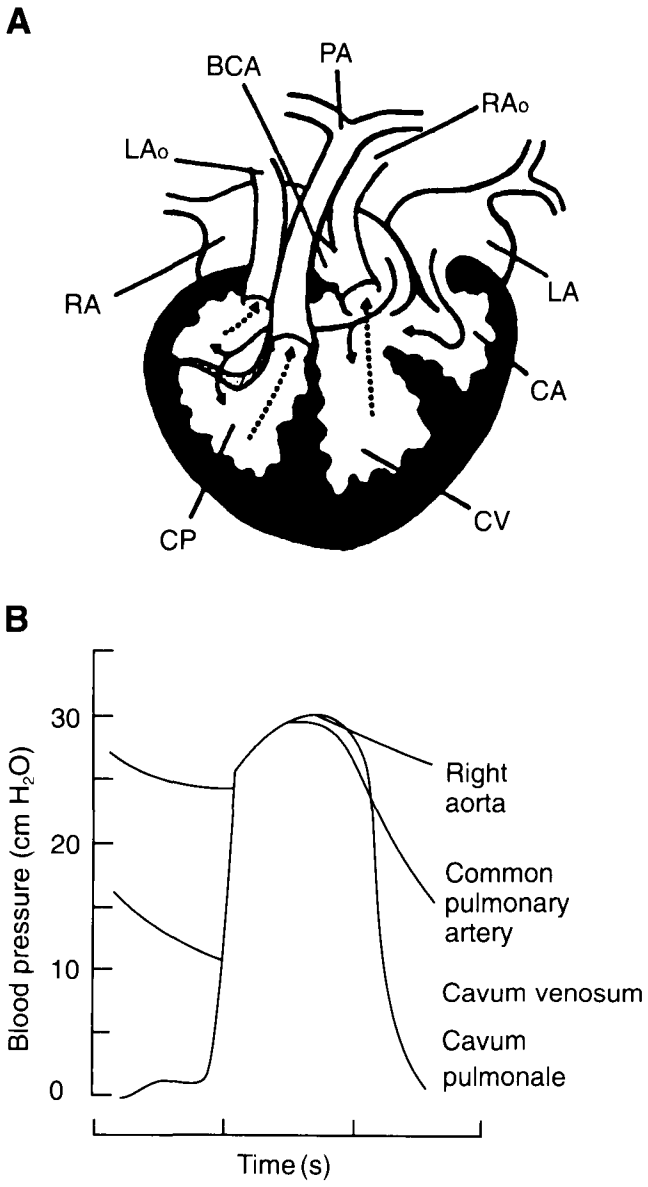

FIG. 4.10. Circulation in squamate reptiles. *A:* Highly schematic diagram of heart of freshwater turtle *Chrysemys scripta*. Pathways for blood flow from ventricular cava to arterial arches indicated by *solid arrows* (modified from ref. 562). *B:* Simultaneously recorded intracardiac and arterial pressures in anesthetized *Chrysemys scripta* (modified from ref. 562).

vides into separate left and right pulmonary arteries supplying each lung. In those snakes that have only a single functional lung, the pulmonary trunk nonetheless divides into anterior and posterior branches, depending on the species and the position of the vascular lung with respect to the heart.

As is evident in Figure 4.10*B*, pressures measured in each of the three ventricular cava are superimposable during the entire cardiac cycle in chelonians (562) and snakes (67). Thus, despite the ventricle's anatomical complexity and two distinct atria, the squamate heart (with the exception of that of varanid lizards) functions as a single pump ejecting blood into both pulmonary and systemic circulatory systems, located in parallel. The distribution of cardiac output between these two circuits in squamates is, however, highly variable depending on the balance between systemic and pulmonary resistance (see *Breath Holding and Diving*, below).

The peripheral circulation of the squamate reptiles essentially reflects the pattern common to all tetrapod vertebrates.

Varanid lizards: a special squamate case. The genus *Varanus*, with more than 30 species, represents an extremely interesting variant on the squamate cardiovascular pattern. Relative to the condition in other squamates, the varanid heart has an enlarged cavum arteriosum and a reduced cavum venosum (Fig. 4.11*A*). The arterial arches derive from the same locations, but the rearrangement of the cava arteriosum and venosum gives the ventricle the appearance of greater bilateral symmetry.

Physiologically, the performance of the varanid heart is qualitatively different from that of other squamates. While the cavum arteriosum and cavum pulmonale are patent during diastole, during systole the prominent muscular ridge defining the boundaries of the cavum pulmonale and cavum venosum presses tightly against the opposing interior surface of the heart. As a result, the cavum pulmonale becomes anatomically separated during systole from the cavum arteriosum, as is evident in the much higher pressures developed in the cavum arteriosum compared to the cavum pulmonale (Fig. 4.11*B*). Thus, the varanid ventricle should be viewed as a dual pump, perfusing the systemic circulation at a higher pressure (60–100 cm H_2O) than the pulmonary circulation (10–30 cm H_2O). Intracardiac mixing must still occur during diastole, however, as the cavum pulmonale derives all of its blood from the cavum venosum, presumably during ventricular diastole.

The condition in varanids is clearly a highly derived one. Many of the varanids are large, very active predators with a high aerobic metabolic rate. The ability of the ventricle to generate high systemic blood pressures to support high blood flow (and thereby a higher capillary density) while at the same time keeping the lungs "dry" by perfusing them at only a low pressure may be an important component supporting the high activity levels of varanids. The functional division of the ventricle in *Varanus* suggests an intermediate condition between that of other squamates, with an anatomically and physiologically undivided ventricle, and the crocodilians, with an anatomically completely divided

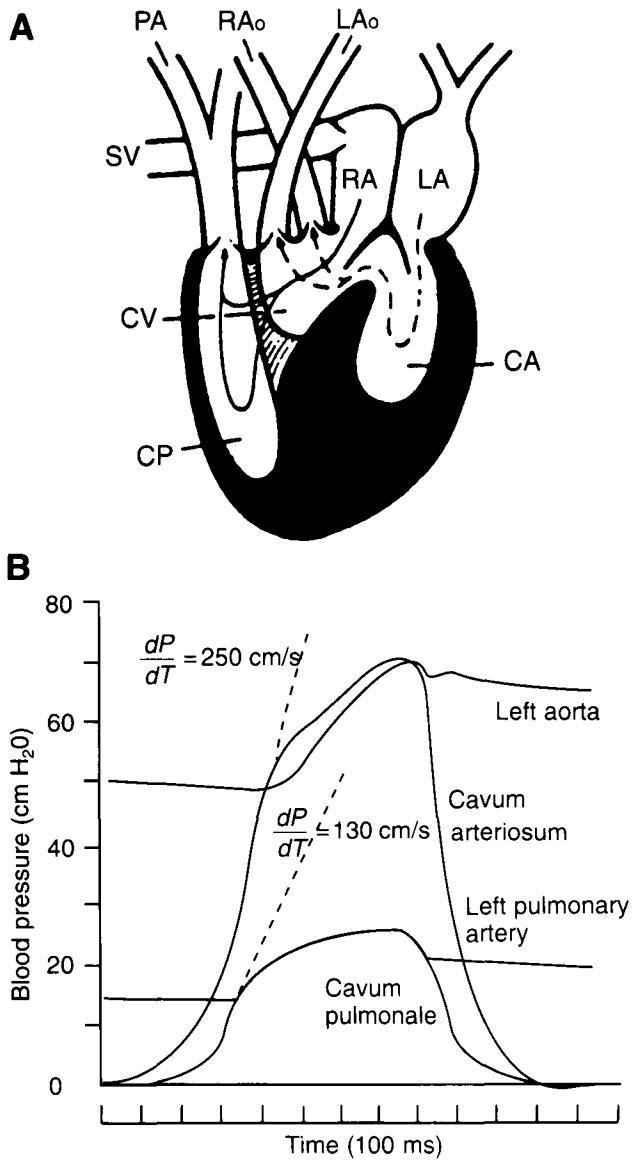

FIG. 4.11. Circulation in varanid lizards. *A:* Heart of *Varanus*. *Dashed arrows* indicate intracardiac diastolic pattern of flow of oxygen-rich blood from left atrium; *solid arrows* show flow of oxygen-poor blood from right atrium (from ref. 265). *B:* Simultaneously recorded intracardiac and arterial pressures in anesthetized savannah monitor lizard, *Varanus exanthematicus* (from ref. 83).

ventricle. While *Varanus* certainly does not represent a phyletic intermediary between these two groups, the existence of a dual pump in the form of a squamate heart with anatomically patent chambers shows that this type of intermediate arrangement is indeed feasible and has selective advantages for more active squamates, and consequently a similar sort of heart may have existed in the ancestors of the Crocodilia (78).

Crocodilians. The crocodilian circulation interested early anatomists (480, 532) and has been investigated intensively from a physiological perspective (23, 246–248, 491, 563a–564a, 639, 647, 649). In a review of the central cardiovascular anatomy and function in Crocodilia, Grigg (247) states: "Among the vertebrates, crocodilians have the most complex anatomy of the heart and outflow channels. Their cardiovascular anatomy may also be the most functionally sophisticated, combining as it does the best features of both reptilian and mammalian (and avian) systems." These rather strong statements (strong, that is, to those who investigate strictly mammalian systems) have a sound factual basis.

The crocodilian heart is anatomically equivalent and can have a functional equivalence to that of birds and mammals, with two separate atria and completely separated right and left ventricles (Fig. 4.12). The left ventricle, like that of mammals, is more thickly walled than the right and generates higher blood pressures. Some of the great versatility in performance of the crocodilian circulation arises from the origination sites of the arterial arches, as in mammals. The right aorta arises from the left ventricle and supplies blood to the head and pectoral girdle (by way of the carotid and subclavian arteries) and to the musculature of the trunk and tail (by way of the dorsal aorta). Similarly, the pulmonary artery arises from the right ventricle and, after branching, proximally supplies both lungs. Unique to the crocodilians, however, is a left aortic arch that arises from the right ventricle, medial to the base of the pulmonary artery. Even so, blood ejected from the right ventricle does not necessarily enter the left aorta. This is because the bases of the right and left aortic arches share a common wall and are in direct communication through the foramen of Panizza, which is partially blocked by a semilunar valve at the base of the right aortic arch (247). Distally, the left and right aortic arches are connected by a small communicating vessel, with the left aorta continuing on to supply blood to the viscera.

The complete division of the crocodilian heart obviously precludes the intracardiac mixing of pulmonary and systemic venous return common to other reptiles and amphibians, but central cardiovascular shunting occurs outside of the heart. Right-to-left shunting can be achieved if blood enters the left aortic arch from the right ventricle. However, because all blood entering the pulmonary circulation is derived from the right ventricle, there is no potential for a left-to-right shunt as in other reptiles. The left aortic arch can also be perfused potentially from the right aorta via the foramen of Panizza.

How does this complex heart function? Several physiological studies have reexamined the circulatory pat-

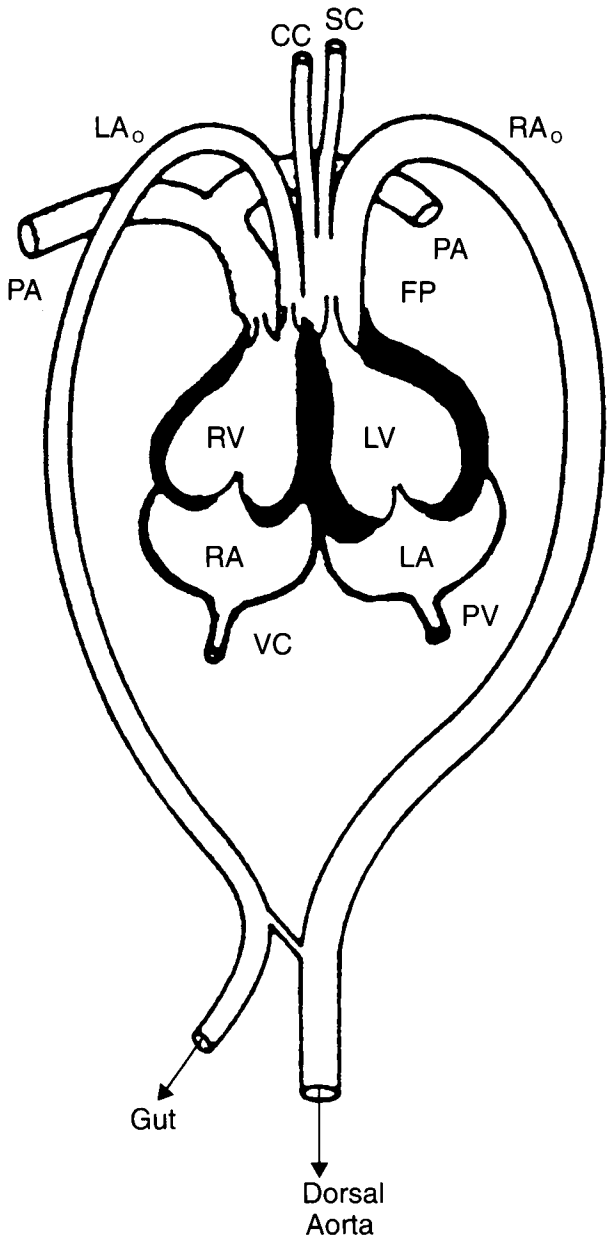

FIG. 4.12. Schematic diagram of crocodilian heart and major artiers. Outflow channels of heart have been untwisted 180° to clarify the relationship with ventricles. *CC*, common carotid artery; *FP*, foramen of Panizza; *LAo*, left aorta; *PA*, pulmonary artery; *LA*, left atrium; *LV*, left ventricle; *PV*, pulmonary veins; *RA*, right atrium; *RAo*, right arota; *RV*, right ventricle; *SC*, subclavian artery, *VC*, vena cava (after ref. 247).

terns of crocodilians (23, 246–248, 491, 563a, 639, 647, 649). While there is still some uncertainty, the following description, first offered by White (649), appears to apply generally to all crocodilians examined. During periods of free access to air, the systolic pressures on the systemic side of the circulation are much higher than those on the pulmonary side. Even though the right aorta arises from the right ventricle, the high pressure of blood on the distal side of the bicuspid valves guarding the left aortic orifice keeps these valves from opening at any time during the cardiac cycle. Under these circumstances, the crocodilian circulation operates as a mammalian or avian heart, with no central cardiovascular shunting and systemic arterial pressure being elevated relative to pulmonary arterial pressure. The amount of blood flowing through the foramen of Panizza from the right to the left aortae is uncertain. Shelton and Jones (563a) indicated that this passageway has no significant effect on the central arterial circulation of *Alligator*. Grigg (247) and Pettersson et al. (491) estimate that the flow through the foramen of Panizza may be small, making the left aortic flow only about 10% of that in the right aorta. Grigg (247) explains different findings as likely to result from the ability of crocodilians to vary the caliber of the foramen of Panizza and thus the amount of blood flowing through it.

This circulatory pattern can change profoundly when pulmonary vascular resistance increases substantially, as it does during periods of apnea such as during diving or fright. When pulmonary resistance rises, right ventricular systolic pressure rises sharply. Indeed, systolic pressure in the right ventricle apparently rises high enough to open the valves at the base of the left aorta and to eject blood into this systemic vessel rather than into the pulmonary artery. Any blood from the right ventricle entering the left aorta constitutes a right-to-left shunt.

Ventilatory state (breathing, apnea) has been the major variable in cardiovascular studies of crocodilians. However, the fact that the left aorta preferentially perfuses the gut and that any change in gut function might demand a change in left aortic flow suggests that feeding state should be included as a variable in future studies on crocodilian cardiovascular function.

Mammals and Birds: Dedicated Systemic and Pulmonary Circuits. At the gross anatomical level, both mammals and birds have a completely divided circulation, with a dedicated pulmonary circuit perfused by the right ventricle via the pulmonary trunk at low pressure and a systemic circuit perfused by the left ventricle via the aorta at high pressure. The heart itself has an apex formed by the left ventricle, with the apex pointing to the left. The pattern is so well documented that the reader is referred to standard anatomical/physiological textbooks for additional information.

However, as Goodrich (239) observed when looking at anatomical details of the sinus venosus, cardiac valves, chordae tendineae, and other cardiac structures of the adult heart, as well as the embryonic patterns

of development: "The resemblances of the 'four-chambered' avian heart to that of the mammal are superficial and misleading, and the clue to its structure and origin must be sought in the crocodilian heart." Van Mierop and Kutsche (623) make similar assertions. Comparisons of cardiovascular anatomy between genera and families have been made for both birds and mammals (239, 452, 530). Body mass influences mass-specific heart mass, with smaller animals having proportionately larger hearts (452, 490, 550). Heart shape and central vessel length in mammals also appear to be dictated in part by chest shape, animals with elongate chests having more elongate hearts and central arteries and veins (452).

FUNCTIONAL PROPERTIES OF VERTEBRATE HEARTS

Overview

The vertebrate heart is a muscular pump consisting of a series of chambers that reciprocally fill during *diastole* (a period of muscular relaxation) and empty during *systole* (a period of muscular contraction). As described in the previous section, the anatomy of the cardiac chambers varies tremendously between vertebrates. Likewise, some of the functional aspects of the hearts vary widely. Heart rate varies over two orders of magnitude for endotherms and is generally higher than that in ectotherms. Arterial blood pressure varies over two orders of magnitude among vertebrates. The hearts of some lower vertebrates are very tolerant of hypoxia and even the basic process of excitation–contraction (*E*-C) coupling differs in a fundamental way among vertebrates. There are, nevertheless, a number of functional features common to all vertebrate hearts. Thus, the challenge of this section is to outline these general features and, at the same time, to provide insight into the range of diversity that exists among vertebrates.

The vertebrate heart is a remarkable organ in that it can beat rhythmically and generate flow and pressure without any extrinsic input, provided sufficient metabolic fuels are available. In contrast to most invertebrate hearts, cardiac cells in vertebrates are myogenic; that is, they are capable of self-generated contractions. Understanding the myogenic heartbeat requires consideration of the electrical properties of, and the E-C coupling in, cardiac cells. As will become clear in the section *Mechanical Properties of Cardiac Muscle,* an important difference between cardiac muscle and skeletal muscle is that, through the intrinsic mechanical properties of cardiac muscle, the force generated by each heartbeat can be altered independently of, as well as in conjunction with, extrinsic modulators.

The function of the heart is to generate sufficient blood flow to satisfy the varying internal blood convection needs of the animal. Cardiac output, therefore, must be regulated. The various factors involved in the control of f_H and SV are detailed in subsequent sections with a special consideration of major phylogenetic groupings. As shown in Figure 4.13, f_H is set by an intrinsic pacemaker rate and modulated by neural and humoral factors; SV is set primarily by the degree of cardiac filling and myocardial contractility, both of which are modulated by physical, neural, and humoral factors.

For the heart to pump blood through vessels, it must also generate sufficient pressure to overcome the resistance imposed by the architecture of the blood vessels and by the viscosity of the blood. Thus, by generating flow and pressure in a cyclic fashion, the heart performs a work cycle with each heartbeat (stroke work, mJ/g ventricular mass). Over time, the cumulative work performed by the heart (J/s) is termed *myocardial power output* (mW/g ventricular mass). Myocardial power output is therefore a useful comparative measure of the overall performance of the heart. The mechanical work performed by the heart is usually fueled aerobically. Therefore, in addition to supplying O_2 to other tissues, the heart needs its own O_2 supply to support cardiac work. As will be described, the routes for myocardial O_2 supply in lower vertebrates are more complex than those in mammalian hearts.

Electrical Properties of Cardiac Cells

A description of the electrical properties of cardiac cells is central to a basic understanding of linkages between electrical events, the movement of ions, and the contractile event. This in turn helps explain why heart cells beat spontaneously, how f_H is controlled, and how a collection of cardiac cells can collectively and effectively function as a blood pump.

Contraction of cardiac muscle, like skeletal muscle, begins with electrical activity, the basis of which is the action potential. However, close comparison of cardiac and skeletal muscles reveals features unique to cardiac muscle:

1. Cardiac cells develop their own action potentials because the resting potential is not stable (a pacemaker potential). Thus, cardiac cells depolarize with time. A consequence of this myogenic property is that cardiac innervation is diffuse and modulatory; it does not produce discrete postsynaptic potentials.
2. Efficient pumping requires that all cardiac muscle cells of a heart chamber contract approximately in unison. The prolonged plateau phase of the cardiac

action potential and the electrical coupling between cardiac cells are specializations that permit simultaneous contraction of cardiac cells. In addition, for sequential contraction of the heart chambers, each cardiac action potential has a refractory period which prevents tetanic contraction. Also, propagation of the action potential is delayed between chambers.

Cardiac Pacemaker and the Action Potential. All cardiac muscle cells can develop action potentials. However, the exact nature, frequency, and rhythmicity of the action potential are distinguished by the anatomical location of the cardiac cell. There are five functionally and anatomically separate types of cell. The sinoatrial node, atrioventricular node, and His-Purkinje conduction system are characterized by having a pacemaker behavior (a regular, self-induced action potential characterized by a progressive depolarization and a short plateau phase). In contrast, atrial and ventricular cardiac cells (the working cardiac cells) have a true resting potential and a prolonged plateau phase.

Since cardiac cells are electrically connected into large functional syncytia, the cells with the fastest rate of spontaneous action potentials are the ones that stimulate the whole heart; that is, these pacemaker cells set the intrinsic f_H. A group (node) of specialized cells, located in either the sinus venosus (when present) or the atrium, are collectively termed the *sinoatrial node*. The cells of the sinoatrial node have the fastest intrinsic rate of action potentials and are, as a result, the cardiac pacemaker.

The cardiac action potential is divided into five phases which last around 300 ms in the resting human heart (note, however, that the action potential duration decreases significantly during activity when f_H is elevated). Phase 0 corresponds to the upstroke, phase 3 the repolarization, and phase 4 the resting potential during diastole. Phases 1 (early repolarization) and 2 (plateau), which are not found in skeletal muscle, show different configurations in the different regions of the mammalian heart. Notably, the plateau phase is reduced in the pacemaker and, to some extent, in the atrium. In addition, the resting potential of the sinoatrial node is unsteady.

The action potential has an ionic basis. Thus, the electrical activity of cardiac cells centers around the combined and synchronized activity and density of various membrane channels, exchangers, and ion pumps. As a result of changes in the state (open and active, open and inactive, closed) of ion-specific membrane channels, there are changes in the membrane permeability (P) (or conductance [G]) to specific ions which result in various transmembrane currents (I). During diastole, potassium channels are open, whereas selective channels for sodium, chloride, and calcium are closed. Thus, the conductance for potassium (G_K) is high and those for G_{Na}, G_{Cl}, and G_{Ca} are low. The changing states of ion channels responsible for the action potential are well documented for amphibians and mammals (61, 351, 617). To what extent this description characterizes the events in other vertebrate hearts is unclear at this time because patch-clamping techniques have not been applied extensively to lower vertebrate hearts.

The spontaneous depolarization of pacemaker cells results from the unsteady resting potential. A steady, inward Na^+ current produces a slow depolarization, the pacemaker potential, which proceeds until a threshold potential is reached, whereupon an all-or-none action potential is initiated. In the frog, the pacemaker potential is about 15 mV and the threshold potential is -55 mV. The action potential arises from a rapid, brief, voltage-gated increase in Na^+ conductance. The fast Na^+ channels responsible for the action potential then remain closed until repolarization is partially completed, thereby preventing tetanic contraction. It should be noted that the mammalian and amphibian pacemaker is a node consisting of numerous cells. All nodal cells do not have the same rate of spontaneous depolarization. In the toad, the left side of the ventral part of the sinus venosus has the fastest rate.

The cardiac action potential has a characteristic plateau which results from an increase in Ca^{2+} conductance and the slowly developing and prolonged increase in K^+ conductance. The increase in Ca^{2+} conductance produces an influx of Ca^{2+}, which is a critical step in E-C coupling. The increase in K^+ conductance ultimately brings about repolarization of the cell. Ionic balance between the interior and exterior of the cell is restored by an Na^+–K^+ ATPase and an Na^+–Ca^{2+} exchanger located in the sarcolemma (SL) (Fig. 4.14).

Atrial and ventricular cells have a slower and less regular rate of spontaneous action potentials than the pacemaker. Also, the action potentials of atrial and, more so, ventricular cells have a more pronounced plateau phase so that the action potential persists for a considerable portion of the interval between heartbeats. The duration of the plateau is dependent on the sustained increase in Ca^{2+} conductance, an increase in Na^+ influx into the cell through slow Na^+ channels, and the slow increase in K^+ conductance. While the use of patch-clamping techniques has identified many of the numerous currents that contribute to the overall action potential, many (but not all) of the specific currents have been assigned to specific changes in ion permeability through the use of various pharmacological tools. Important species differences exist in the exact nature of the vertebrate action potential; how-

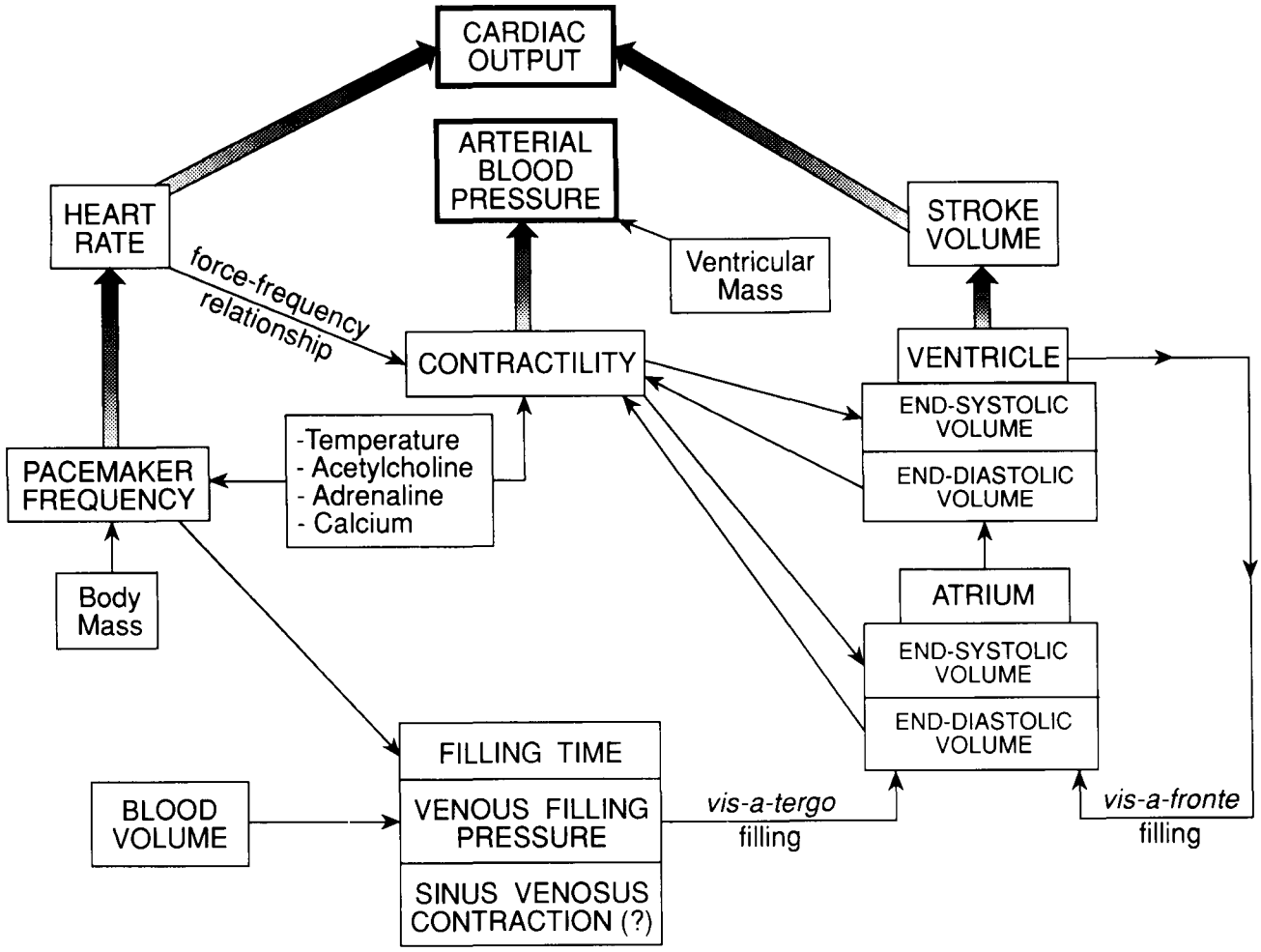

FIG. 4.13. Major factors influencing cardiac output and pressure generation in vertebrate hearts.

ever, our understanding of the mechanistic basis for these differences is incomplete. Much of our knowledge is based on work with rabbits, rats, and amphibians. This has led to two models: the sinus venosus model of the amphibian (the SV model), and the sinoatrial node model of the mammal (the SAN model). The most significant distinctions between the two models are the roles of $I_{Ca,t}$, I_f, and sarcoplasmic reticular (SR) Ca^{2+}. (The reader is directed to refs. 36, 108, 216, and 514 for detailed reading and references in this area.) What follows is a brief description of the major ion currents identified so far in cardiac cells, identifying their importance in the action potential and the distinctions between the amphibian SV and mammalian SAN models.

1. I_{K1}—an inwardly rectifying potassium current. In working (atrial and ventricular) cardiac cells, I_{K1} is the major background current and is responsible for the generation and stabilization of the resting potential. The density of I_{K1} (and hence I_{K1} current) is substantially lower in both SAN and SV cells. Thus, in the absence/reduction of I_{K1}, only small currents are required to generate the pacemaker potential.

2. I_b—presumed to be an inward background current carried mostly by Na^+. It is predicted to be extremely important in the diastolic depolarization of pacemaker and conducting cells. The only reliable measurements are from SV cells (108).

3. I_f—a voltage-gated, time-dependent current. I_f slowly activates upon hyperpolarization and more rapidly deactivates upon depolarization. The present thinking is that I_f is a channel-mediated, mixed cation current that is carried by both Na^+ and K^+. I_f has been observed in all single cardiac pacemaking preparations (including *Rana esculenta*), except for the SV cells from *Rana catesbeiana*. Thus, while I_f is generally regarded as the pacemaker current in SAN cells (108), this may

not be entirely true for lower vertebrates. In view of the effects of ACh, adrenaline, and adenosine on I_f, I_f may have an important modulatory effect on f_H and on the amplitude and duration of the action potential, rather than being an essential component of the pacemaker current.

4. I_{Ca}—a large, inward, time- and voltage-dependent calcium current. Two types of I_{Ca} have been identified in cardiac cells. All cells contain the L-type ($I_{Ca,l}$) current, which rapidly activates and relatively rapidly inactivates. $I_{Ca,l}$ is generally considered to be important in diastolic depolarization, action potential duration, and the early phases of repolarization. The upstroke of the action potential is initiated by $I_{Ca,l}$ during the latter third of diastolic depolarization. Incomplete inactivation of $I_{Ca,l}$ results in the sustained plateau of the action potential. Because of its involvement in action potential duration, the role of $I_{Ca,l}$ differs between working and pacemaking cardiac cells. A second, T-type ($I_{Ca,t}$), current has been identified in SAN cells but not in amphibian SV cells. $I_{Ca,t}$ rapidly activates at 10–20 mV more hyperpolarized than $I_{Ca,l}$ and rapidly inactivates.

In the amphibian SV model, over 95% of Ca^{2+} entry into cardiac cells is thought to be buffered by troponin and calmodulin. Thus, in the SV model, all Ca^{2+} entry into the cytoplasm is from the extracellular space. In contrast, in the SAN model, a significant proportion of the Ca^{2+} entry is involved in Ca^{2+}-activated Ca^{2+} release from the SR.

5. I_K—a large, outward, time-dependent, voltage-dependent, delayed rectifier potassium current. I_K has a slow sigmoidal activation. The kinetic properties may be more complex in SAN than in SV cells. I_K is central to repolarization.

6. $I_{Na/K}$—an electrogenic, ATP-dependent current (Na/K pump). The stoichiometry of the pump is believed to be $3NA^+:2K^+$. The pump is likely to be active throughout the action potential and maintains and restores the Na^+ and K^+ gradients across the SL.

7. $I_{Na/Ca}$—an electrogenic Na^+/Ca^{2+} exchanger current. The coupling ratio for Na^+/Ca^{2+} ions is thought

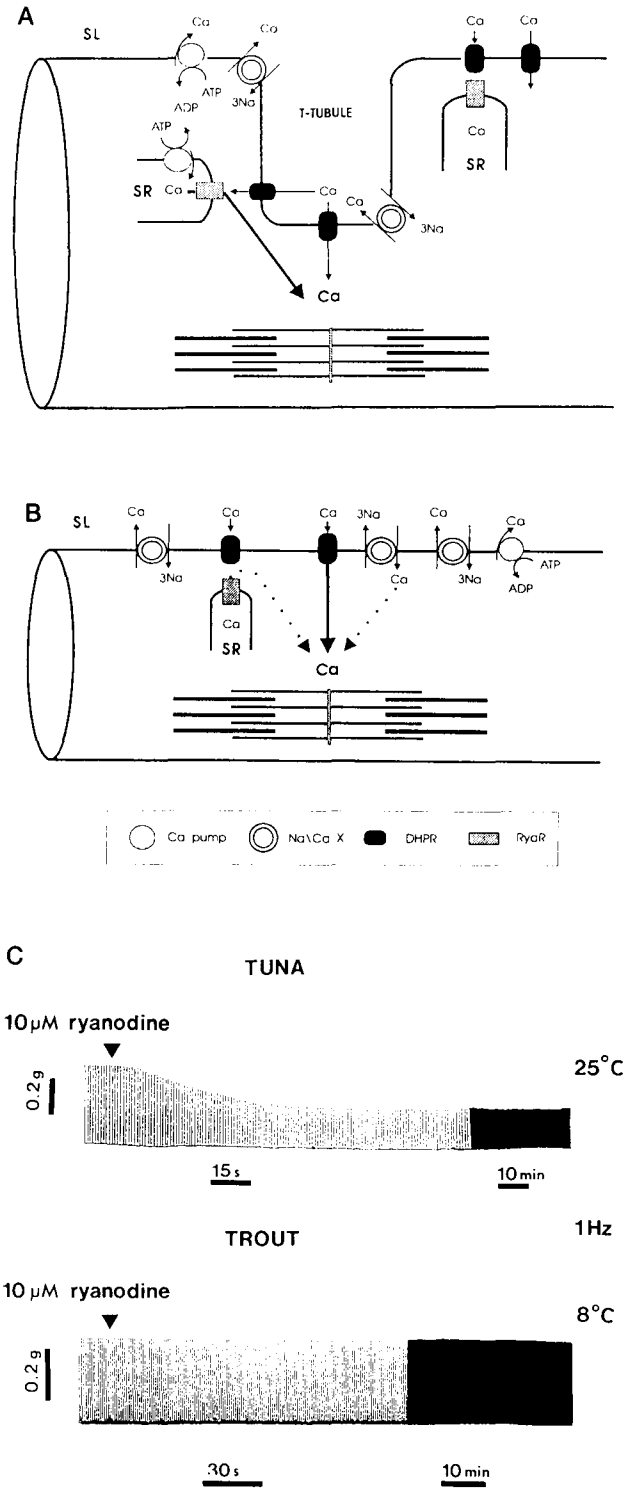

FIG. 4.14. Two proposed schemes for Ca^{2+} movements during excitation–contraction coupling of vertebrate cardiac muscle. The major difference between the mammalian scheme *(A)* and the fish/amphibian scheme *(B)* is the absence of a significant role for sarcoplasmic reticulum *(SR)* calcium release in fish and amphibians. Relative intensity of *arrows* indicates relative roles of Ca^{2+} released from SR (60%–80%) and transcarcolemmal influx (20%–40%) in mammals. *Dashed line* in the fish/amphibian scheme suggests a possible physiological role for SR Ca^{2+} release under certain conditions and in certain species, such as tuna. For example, panel C shows that whereas ryanodine, a blocker of the SR calcium release channel, is without effect on ventricular strips from rainbow trout, contractility of atrial strips from skipjack tuna is reduced by ryanodine in a manner similar to that seen with mammalian cardiac muscle (with permission from refs. 352, 353, 607). *SL*, sarcolemma.

to be 3:1. The magnitude and polarity of $I_{Na/Ca}$ depends largely on $I_{Na/Ca}$, which varies during the action potential cycle. $I_{Na/Ca}$ is outward and significant during plateau and repolarization. It is likely the major contributor to restoring Ca^{2+} homeostasis between the cytoplasm and the extracellular space.

Modulation of Pacemaker Rate and Control of Heart Rate. Four factors have major modulatory effects on the pacemaker rate: body mass, temperature, adrenaline, and ACh (Fig. 4.13).

The intrinsic pacemaker rate shows important species differences which relate to body mass, phylogeny, and to some extent the ability to perform exercise. An allometric relationship with an exponent equal to -0.25 exists between body mass and both resting and maximal f_H in birds and mammals (Fig. 4.15). This relationship reflects the large difference in f_H between the smallest birds (1,500 bpm) and the largest mammals (20 bpm). Differences of such magnitude must be based in part on differences in the Na^+ conductance setting the slope of the pacemaker potential. Although data are few, an allometric relationship with a similar exponent exists interspecifically within snakes (553) and intraspecifically within frogs (W. Burggren, unpublished observations). Determining allometric relationships for f_H in these animals is problematic because of variable body temperatures and a nonsteady-state f_H associated with arrhythmic ventilation. Also, there are difficulties in generating a universal definition of "resting" for lower vertebrates because of very different activity states. In fishes, intrinsic f_H is generally higher in more active species (179).

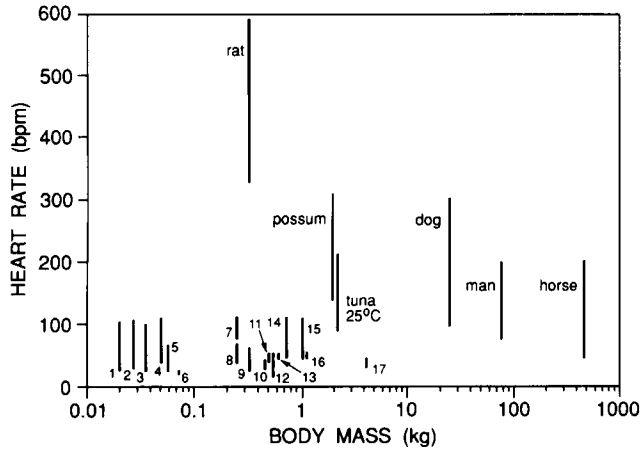

FIG. 4.15. Resting and maximum heart rates for selected adult vertebrates. Resting and maximum heart rates for mammalian species show an allometric relationship. In contrast, maximum heart rate for lower vertebrates, with the exception of tuna, shows an upper limit of around 120 bpm, which is independent of body mass. The bottom of each bar is resting value and the top is maximum value. Lower vertebrates (fishes, amphibians, and reptiles) are identified numerically. Key for lower vertebrates and experimental temperatures:

1. Scaphiopus, 24°C; *2, Bufo,* 25°C; *3, Xenopus,* 25°C; *4, Rana,* 25°C; *5, Natrix,* 25°C, *6, Myxine,* 11°C; *7, Bufo, 20°C; 8, Salmo,* 20°C; *9, Ophiosaurus,* 25°C; *10, Rana,* 20°C; *11, Salmo,* 10°C; *12, Testudo,* 25°C; *13, Gadus,* 10°C; *14, Iguana,* 35°C; *15, Varanus,* 35°C; *16, Hemitripterus,* 10°C; *17, Ophiodon,* 10°C (from ref. 180).

Maximum f_H, however, can be universally compared among lower vertebrates. Based on limited data, it appears that maximum f_H for the majority of lower vertebrates is around 120 beats per minute (bpm) (Fig. 4.15; 181). Tuna are the only known exception to this generalization, with maximum f_H reported to be over 200 bpm (66, 353). This upper limit for maximum f_H in lower vertebrates appears to be independent of body mass, reflecting instead a phylogenetically related constraint on pacemaker rates or on the modulatory mechanisms. Because of the recognized scaling of f_H to body mass, the highest f_H values are likely to be found during early development when the animal is quite small. The limited information on the development changes in f_H in lower vertebrates (see *Development of Cardiovascular Systems,* below) also supports the idea of a maximum f_H of around 120 bpm.

Resting f_H is rarely the intrinsic rate of the pacemaker. The two principal mechanisms for modulating f_H are cholinergic inhibition and adrenergic excitation. In general, modulation of f_H at the level of the pacemaker cell is achieved by altering the rate of change of the pacemaker potential (for example, it is reduced by ACh and increased by adrenaline), hyperpolarizing the pacemaker cell (for example, an action of ACh), and changing the duration of the action potential (for example, the length of the plateau phase is inversely related to temperature). Neurohumoral agents, however, may have different effects on nonpacemaker cardiac cells. For example, in carp, whereas adrenaline affects the self-excitation rate of pacemaker cells by increasing the slope of the pacemaker potential, atrial and ventricular cells have a longer plateau, unchanged beat frequency, and stronger contraction (311).

Most vertebrate hearts studied so far experience simultaneous cholinergic and adrenergic modulation. Often, but not always, this "push–pull" type of modulation creates a resting f_H that is slower than the intrinsic pacemaker rate because cholinergic inhibition is greater than adrenergic excitation. Thus, increases in f_H (tachycardia) can result from a removal of cholinergic inhibition as well as from an increased adrenergic excitation.

Adrenergic excitation of f_H is possible through three means: *(1)* endogenously by means of catecholamine stored in chromaffin tissue in the heart; *(2)* exogenously

by means of catecholamine stores outside the heart in chromaffin tissue and in the adrenal medulla, which are released by humoral or sympathetic controls; and *(3)* neurally through adrenergic nerve fibers that reach the heart via either the vagus nerve or separate sympathetic nerves. These three mechanisms have phylogenetic groupings with a semblance of evolutionary progression. Exogenous catecholamine stores are common to all vertebrates, but adrenergic cardiac innervation is absent in cyclostomes and elasmobranchs. Cyclostomes and dipnoans, however, have endogenous catecholamine stores, and in hagfish, at least, these stores are clearly important in the regulation of f_H (see *Cardiac Output and Cardiac Performance,* below).

Adrenergic excitation is usually mediated via stimulation of β-adrenoceptors, which through a stimulation of cyclic AMP production increase the probability of opening Ca^{2+} channels. Even though β-adrenergically mediated tachycardia is possible in lower vertebrates, it is often of lesser importance than the release of a vagal inhibitory tone in bringing about tachycardia (15, 501). This is especially true at low temperature, when the resting cholinergic inhibitory tone can be considerable (16). Thus, from an evolutionary perspective, adrenergically mediated tachycardia seems to have taken on greater significance in birds and mammals. α-Adrenergically mediated bradycardia is present only in a few of the lower vertebrate species so far examined.

Abrupt decreases in f_H (bradycardia) characteristically reflect increased cholinergic inhibition. Cholinergic inhibition of f_H is mediated by muscarinic cholinoceptors, effected by the cardiac branch of the vagus nerve, and is found in all vertebrates except cyclostomes. (Hagfishes have no cardiac vagal innervation, and changes in f_H are very gradual, whereas lampreys have nicotinic cardiac cholinoceptors that produce tachycardia.) The cardiac response to vagal stimulation and applied ACh is bradycardia. In mammalian hearts, bradycardia is mediated by changes in at least three different ion channels (351). In brief, these are *(1)* an activation of the potassium channel in the sinoatrial node, which increases the resting potassium current and hyperpolarizes the sinoatrial cells; *(2)* an inhibition of the sodium channel, which decreases the pacemaker current and slows diastolic depolarization, resulting in a longer pacemaker potential; and *(3)* a reduced probability of Ca^{2+} channel opening, which reduces the depolarizing currents. The effects of ACh on sodium and potassium channels are through muscarinic receptors, which activate an inhibitory G_i protein that inhibits cyclic AMP production. Negative chronotropic effects of adenosine act through A_1 receptors in the same way. Inhibition of the calcium current is an indirect effect mediated through the decrease in cyclic AMP levels. Acetylcholine applied to amphibian and mammalian cells causes hyperpolarization, whereas ACh released as a result of vagal stimulation does not, suggesting different coupling mechanisms (297).

Temperature has a profound effect on f_H in three ways. First, temperature directly affects the intrinsic pacemaker rate. In general, the pacemaker rate has a temperature coefficient (Q_{10}) of around 2.0–3.0 for a variety of vertebrates. In frog pacemaker cells, for example, both the slope of the pacemaker potential and the action potential duration (APD) have Q_{10} values greater than 2.0 (60). Second, temperature acclimation can alter the pacemaker rate. For example, at the same test temperature, a higher pacemaker rate is reported for cold-acclimated than for warm-acclimated fish (180). This change represents a partial temperature compensation. Finally, temperature acclimation can change the relative importance of adrenergic and cholinergic modulation of f_H. For example, cholinergic inhibition of f_H has greater importance in turtles during overwintering (321) and in rainbow trout and dogfish after cold acclimation (594, 664). However, cholinergic inhibition is reduced in the common eel *(Anguilla anguilla)* with cold acclimation (568). In frogs, β-adrenergically mediated chronotropy is more pronounced at higher temperatures, whereas presynaptic α-adrenergic control of f_H is found only at low temperature.

Jensen (323) claimed that all vertebrate hearts have an intrinsic, stretch-dependent mechanism for regulating f_H and that through this mechanism, which increases venous return and cardiac filling, they could produce tachycardia. This claim was based on a series of studies on isolated hearts having unusually slow spontaneous beats. Subsequent work with hearts beating at physiologically more relevant rates led Farrell (174, 180) to conclude that stretch-dependent modulation of f_H has very little overall significance in elasmobranchs and teleosts since stretch induced a change of only a few beats per minute in in situ perfused hearts. In addition, the observation that saline infusions into the caudal vein of *Myxine glutinosa* produced a 10%–20% increase in f_H when cardiac output was low (20) led to the idea that mechanical stretch can "kick start" the hagfish heart in this condition. Thus, with the possible exception of cyclostomes, this intrinsic, mechanical modulation of f_H has been superseded by neurohumoral control of pacemaker rate. Indirect, in vivo evidence for stretch-dependent modulation of f_H exists for larval (V–VII) and adult bullfrogs *(R. catesbeiana).* Increased venous return produces an increase in f_H in the intact heart even in the face of combined cholinergic and β-adrenergic blockade (80). In perfused hearts from turtles [*Chrysemys scripta* (185), *Emydura*

signata (217)] and the crocodile [*Crocodylus porosus* (218)], changes in f_H in association with increased filling pressure were either insignificant or less than 5%. In mammalian hearts, although the stretch-dependent mechanism is well established, the overall change in f_H is still relatively small. For example, Lu et al. (410) reported an increase of up to 18% over the intrinsic rate of isolated nodes from cats and up to a 6% increase in in situ nodes of anesthetized dogs. These effects are thought to occur via direct membrane actions that decrease the membrane potential difference.

Transmission of the Action Potential. Effective heart pumping is dependent on the ability of cardiac cells to act as a syncytium, with each heartbeat involving the contraction of all cardiac muscle fibers. Contraction is initiated at a focal point, so prolonged contraction (related to the APD) and rapid transmission of the action potential between cells are required for simultaneous contraction of cardiac muscle cells.

Intercalated disks connect neighboring cardiac cells and provide for low-resistance electrical connection, allowing rapid intercellular transmission of the action potential. Thus, electrical transmission between cardiac cells is influenced by the resistance of these connections and the capacitance of individual cells. Resistance, which is inversely related to the number of desmosomes, is likely to be high in fish. There are fewer and poorly developed desmosomes in teleost hearts (671) compared with mammals; desmosomes have yet to be identified for hagfishes (139). Whether or not desmosome number and structure contribute to the upper limit for maximum f_H in lower vertebrates requires further study. Capacitance is affected by cell surface area. The relatively small size of fish and amphibian cardiac cells (see below) creates a large cell surface area relative to cell volume and could in itself result in a correspondingly high capacitance. However, the absence of a T-tubular system in the myocytes of these animals reduces the cell surface area and probably the capacitance.

There is a delay between the contraction of each of the cardiac chambers, and these delays are particularly important to ensure appropriate emptying of one chamber before contraction in the next one starts. The delays in electrical transmission between each of the cardiac chambers result from specialized junctional fibers and are revealed by ECG. For example, the P–Q interval is a measure of the delay in electrical conduction between the atrium and ventricle (AV delay). The AV delay is critical in lower vertebrates, where atrial contraction may be the sole determinant of ventricular filling. A-V conduction is slower at low temperatures and may even become disrupted in certain fish species (for example, rainbow trout) unless tonic adrenergic stimulation is present (242).

Contraction of the mammalian ventricle begins at the apex and then spreads back toward the aortic valves. This requires rapid conduction of the action potential from the AV junction to the apex by specialized conducting fibers called Purkinje tissue. Ventricular contraction in fish such as rainbow trout also appears to proceed from the apex. However, specialized conduction fibers are not found in lower vertebrates. In the turtle, *C. scripta,* and the tortoise, *Testudo graeca,* the spread of depolarization across the surface of the ventricle is dependent on the animal's state of breathing (69). During apnea, conduction is almost 50% faster than during ventilation and conduction spreads from the region of the cavum arteriosum, unlike during ventilation when it spreads from the region on the opposite side of the ventricle, the cavum pulmonale. This remarkable shift in regional conduction is perhaps related to intracardiac shunting, and its basis may be a vagal modulation of a rudimentary conduction system (69). Vagal stimulation and applied ACh slow cardiac conduction velocity in these chelonians. Also, conduction velocity is significantly slower at lower temperatures (16 cm/s at 27°C. vs. 10 cm/s at 18°C, frog ventricular strips). The coordinated and perhaps regulated conduction pattern of lower vertebrates in the apparent absence of extensive specialized conduction fibers warrants attention.

Even though atrial and ventricular contractions are the principal events in cardiac pumping, other cardiac chambers may contribute. In some fishes and frogs, the contraction of muscle in the sinus venosus is signalled by the V-wave of the ECG, which follows the T-wave (ventricular repolarization) and precedes the P-wave (atrial depolarization). Similarly, contraction of cardiac muscle associated with the outflow tracts (for example, the conus arteriosus in elasmobranchs) and the bulbus cordis of amphibians and reptiles is signaled by the B-wave of the ECG.

Excitation–Contraction Coupling

Excitation-contraction coupling is the linkage between the action potential and the initiation of muscle contraction that involves Ca^{2+} binding to troponin C (TnC). An appreciation of E–C coupling is in turn important to an appreciation of the involvement of Ca^{2+} in the mechanical properties of cardiac muscle.

The pioneering work of Ringer (519) with frog hearts established that cardiac contraction has a requirement for extracellular Ca^{2+}. It has since been shown for all vertebrate hearts that the influx of Ca^{2+}

across the SL during the rapid depolarization and plateau phases of the action potential is critical to the coupling of the events associated with excitation and cardiac muscle contraction. Furthermore, the generation of force is predicated on, and regulated by, the amount of Ca^{2+} binding at the single, low-affinity Ca^{2+}-specific site on TnC. The fundamental requirements for E–C coupling are, therefore, the entry of Ca^{2+} into the myocyte in association with the action potential, the binding of Ca^{2+} to TnC to initiate cross-bridge formation between the myofilaments, and the removal of Ca^{2+} from the myocyte across the SL to complete relaxation (Fig. 4.14).

The anatomical arrangement and coupling between the SL and the SR is critical in mammalian cardiac muscle and all skeletal muscle for two reasons. First, it is the site of translation of the action potential into a trigger for Ca^{2+} release. Second, the SR is the site of storage and release of activator Ca^{2+}. A general feature in mammalian heart muscle is that the SL and junctional SR are arranged in such a way that the radius for diffusion of Ca^{2+} is greatly reduced. The junctional gap between the SR and the inner surface of the SL is 10–15 nm, and the junctional SR is typically situated less than 1 μm from the I-band of the muscle filaments. Moreover, these junctional processes are most clearly defined in birds and mammals that have very fast heart rates, such as mice, bats, and passerine birds (581). Compared to mammals, junctional processes are more difficult to find in the hearts of lower vertebrates and the gap width is more inconsistent.

There are two generalized models for E–C coupling in vertebrate hearts (Fig. 4.14). The major difference between the two models is that one involves a significant release of Ca^{2+} from the SR. Ryanodine, which blocks the release of SR Ca^{2+}, has been useful in evaluating the role of SR Ca^{2+} in E-C coupling. Ryanodine typically is without effect on fish (Fig. 4.14) or amphibian hearts under physiologically relevant conditions (for example, a normal beat frequency). Consequently, the influx of Ca^{2+} through the calcium channels in the SL of fishes and amphibians is largely responsible for Ca^{2+} binding to TnC. Thus, the source of the regulatory calcium for contraction in lower vertebrates is extracellular rather than intracellular. In contrast, ryanodine significantly reduces tension developed by ventricular and atrial strips from mammalian hearts. An influx of Ca^{2+} through calcium channels in the SL of birds and mammals triggers a much larger intracellular release of Ca^{2+} from the SR via the ryanodine-sensitive calcium release channel. This mechanistic distinction is supported by anatomical observations. The SR and T-tubular systems of the SL are rudimentary in cardiac cells of lower vertebrates. The percentage of the cell volume occupied by SR is around ten times lower in fish and amphibian myocytes compared with mammalian myocytes (0.5% in frog vs. 7.3% in rat) (475). Furthermore, the T-tubular system, which propagates the action potential to the interior of the mammalian myocyte, is absent in fishes and amphibians (475, 539). In the absence of a T-tubular system, diffusion distance from the SL to the innermost myofibril is minimized in fishes and amphibians because myocytes in these vertebrates have a much smaller diameter (187, 475, 539), so the surface area to volume ratio of myocytes is substantially greater (five to ten times) than in mammalian myocytes (607). In addition, the myofibrils of certain fish myocytes are located around the periphery of the cell, with mitochondria having a more central location (671). Even so, the APD is typically at least twice as long in amphibians compared with mammals (607).

Among vertebrates as a whole, the involvement of SR Ca^{2+} in E–C coupling is likely quite variable, with these two models for E–C coupling representing only two extremes. The effect of ryanodine does vary in intensity between atrial and ventricular tissues, between species, and between adults and neonates. For example, the rabbit and guinea pig are much less sensitive to ryanodine than the rat. In contrast to all other fishes tested so far (156, 308), the atrial tissue of tuna has a significant ryanodine sensitivity under physiologically relevant conditions (Fig. 4.14).

Tibbits et al. (607, 608) have suggested that temperature is a key factor in predetermining the SR involvement in E–C coupling in fish. At low temperatures, the SR calcium release channel of the mammalian heart remains in an open state and, as a result, Ca^{2+} cannot be sequestered properly in the SR during relaxation. Furthermore, they note that the ryanodine receptor is apparently present in the heart tissue of most lower vertebrates even though ryanodine has little influence on contractility under physiological conditions. (Ryanodine effects can be observed only at very low beating rates.) Thus, they propose that in ectotherms at a low temperature the SR cannot be adequately loaded with Ca^{2+} because of an SR calcium-release channel locked in an open state. However, Keen et al. (355) showed little change in ryanodine sensitivity between temperatures of 8°C and 18°C in rainbow trout atrial strips, indicating only a minor role for SR-mediated Ca^{2+} release even at the higher range of thermal tolerance of this species. In contrast, in tuna atrial strips at 26°C, ryanodine reduced maximum isometric tension as well as maximum contraction frequency (353). More work on the role of SR-mediated Ca^{2+} release, especially with ectotherms at temperatures between 20°C and 37°C, is clearly needed to resolve this point. It may be that there are significant interspecific and developmental differences in both the sensitivity to ryanodine

and the functional role of SR calcium, as is known to be the case in mammals.

To initiate contraction there must be a rise in cytosolic [Ca^{2+}]. The pivotal role of the SL influx of Ca^{2+} in E-C coupling of all vertebrate hearts is regulated by the voltage-gated L-type Ca^{2+} channel (also termed the dihydropyridine-sensitive Ca^{2+} channel). The level of cytosolic Ca^{2+} required to fully saturate TnC is estimated as 10 μmol/l cell water. This concentration is at least 100-fold lower than the level of free ionized calcium in the extracellular fluid (about 1 m*M*) but about one order of magnitude higher than the cytosolic calcium concentration of the resting heart during diastole (about 0.2 μmol/l). With such a large transsarcolemmal calcium gradient, control of the L-type Ca^{2+} channel is central to the I_{Ca} and the rise in cytosolic [Ca^{2+}]. A larger rise in cytosolic [Ca^{2+}] provides for greater delivery of Ca^{2+} to TnC and a greater force development. Also, up to a point, an action potential of longer duration results in a greater I_{Ca} and a larger increase in tension. The L-type Ca^{2+} channel is regulated by cAMP and G proteins in mammalian, amphibian, and fish hearts (353, 517). Thus, β-adrenergic agonists, through this type of regulation, improve contractility by increasing the probability of Ca^{2+} channels being open and augmenting I_{Ca}.

The I_{Ca} density is apparently quite similar for amphibian and mammalian species (415, 517, 607). Clearly then, with the same current density, the higher surface area to volume ratio of amphibian and fish myocytes should result in a greater rise in cytosolic [Ca^{2+}], as might be expected because of the noninvolvement of SR Ca^{2+}.

Temperature has a profound effect on the maximum Ca^{2+}-activated force (C_{max}) in amphibian and mammalian myocytes with the SL chemically removed (skinned) to allow free access of extracellular calcium to the myofilaments (259–261). C_{max} can change almost fivefold over the temperature range of 1°–22°C. This temperature sensitivity appears to be related to the properties of TnC. Even though the frog heart is considerably less temperature-sensitive than the rat heart, the effects of temperature acclimation on cardiac calcium sensitivity in ectothermic vertebrates have yet to be explored in depth.

A prominent cardiac response to low temperature acclimation in fish is to increase ventricular mass (190). Relative ventricular mass can almost double with cold acclimation in rainbow trout (243), and Antarctic fishes have relatively large hearts (302). Thus, in a general sense, the increase in ventricular muscle mass compensates to some degree for the temperature-related decrease in force developed per unit heart mass as calcium sensitivity is reduced.

The acidosis sensitivity of most vertebrate hearts is related to cytosolic [Ca^{2+}] (228). Acidosis decreases the affinity of TnC for Ca^{2+} by severalfold, so force of contraction is inversely related to intracellular pH (607). The ameliorative effects of applied adrenaline and extracellular Ca^{2+} during extracellular acidosis in many lower vertebrate hearts likely reflect a compensatory increase in cytosolic Ca^{2+} (175, 226, 321). Cardiac tissue from certain lower vertebrates such as *Caiman, C. scripta, Rana pipiens, A. anguilla,* and *Pleuronectes platessa* are considered acidosis-tolerant in that tension developed by muscle strips is restored within several minutes despite a prevailing acidosis. This recovery may be related to the release of Ca^{2+} from mitochondrial stores (227, 228).

Relaxation of cardiac muscle requires a decrease in cytosolic [Ca^{2+}]. Removal of cytosolic Ca^{2+} to the SR and SL is dependent on the SR Ca^{2+} pump and the SL Na^+–Ca^{2+} exchanger (Fig. 4.14). The Ca^{2+} ATPase located in the SL apparently plays a minor role in beat-by-beat Ca^{2+} fluxes. Given the dependence of lower vertebrates on the Na^+–Ca^{2+} exchanger and their variable body temperature, comparative studies of the functional properties of the Na^+–Ca^{2+} exchanger might be worth studying. In line with this, the Na^+–Ca^{2+} exchanger has a lower temperature sensitivity in both frog and rainbow trout, as well as a lower pH sensitivity in rainbow trout compared with the mammalian exchanger (607, 608).

Mechanical Properties of Cardiac Muscle

To increase SV requires a more forceful contraction. Likewise, to maintain SV when vascular resistance and arterial blood pressure increase also requires a more forceful contraction. Thus, the mechanical properties of cardiac muscle are those which relate to the degree to which the heart can generate tension to either maintain or vary SV.

The mechanical properties of cardiac muscle are usually studied by measuring the contractility of isolated muscle. "Cardiac contractility" is a term which expresses the vigor of contraction or, more precisely, the change in developed force at a given resting fiber length. Contractility is usually measured as maximum isometric tension. An increase in fiber length in itself also increases the force of contraction but not contractility. Thus, the force of contraction of cardiac muscle can be varied with or without external influences. In this way, an increase in force of contraction which results from a greater filling of the heart (the Frank-Starling mechanism) can be distinguished from that which results from increased contractility, say through β-adrenergic stimulation.

Before describing the various factors which increase (positive inotropy) and decrease (negative inotropy)

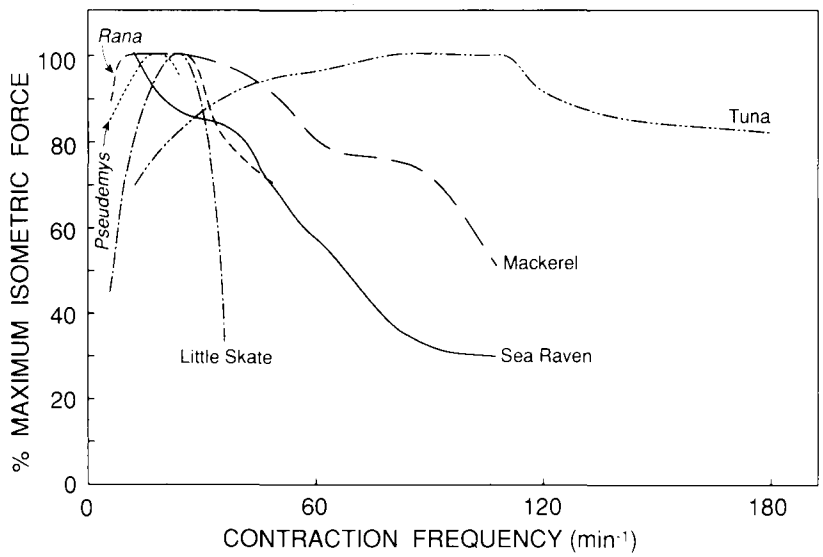

FIG. 4.16. Force–frequency relationships for isolated ventricular and atrial strips (tuna only) from selected vertebrate hearts. As contraction frequency is increased, contractility either increases to an apex (for example, elasmobranchs, tuna, and frogs) or decreases (for example, teleosts except tuna) (adapted from refs. 155, 156, 353).

cardiac contractility, it is important to mention the large phyletic differences that exist for cardiac contractility as measured in vivo. Measurement of contractility in vivo is less precise because the rate of change in pressure (dP/dt) during isometric ventricular contraction is used as an index. Nevertheless, a clear phylogenetic ranking of cardiac contractility in vivo is evident. The dP/dt values for mammals and tuna are about five times higher than those for teleost fishes (370–480 mm Hg/s), whereas values for cyclostomes (22 mm Hg/s) and sharks (30 mm Hg/s) are a further ten times lower (190). Intermediate values are reported for the varanid lizard *Varanus exanthematicus* [95–180 mm Hg/s (83)] and the anuran amphibians *R. catesbeiana* and *Bufo marinus* [60 mm Hg/s and 110 mm Hg/s (291)]. The cellular basis for this large range in contractility is not understood.

Effect of Contraction Frequency on Contractility. In atrial and ventricular strips from hagfish *(M. glutinosa)* and a variety of teleost species, maximum isometric tension (T_{max}) decreases with increasing frequency of electrical stimulation (12, 155, 632). This inverse relationship between contraction frequency and T_{max} (Fig. 4.16) is referred to as a "negative staircase." In ventricular tissue from mammals, frogs (60), and several elasmobranch species (156) and in atrial tissue from skipjack tuna (353), there is an additional positive relationship at low pacing frequencies. Thus, the force–frequency relationship has an apex (Fig. 4.16). Interestingly, the apices occur at contraction frequencies which correspond to a resting f_H in vivo (0.3–0.4 Hz in elasmobranchs, 0.5 Hz in the frog *Rana temporaria,* and 1.4–1.6 Hz in skipjack tuna). Likewise, the maximum pacing frequency of isolated muscle strips corresponds to the maximum f_H measured in vivo (for example, 2 Hz in frog and 3.4 Hz in skipjack tuna). The negative staircase effect is characterized by APD and time to maximum tension (T'_{max}) becoming progressively shorter as well as T_{max} becoming lower (60, 62, 632). This positive relationship between the APD and T_{max} is central to interpreting the responses to temperature and adrenaline which affect both contraction rate and contractility.

Effect of Temperature on Contractility. APD and T'_{max} decrease with increasing temperature, both having a Q_{10} of around 2.0 in paced ventricular strips from ranid frogs and rainbow trout (12, 13, 60). In fishes, relaxation time is also shorter with increasing temperature (31, 632). With spontaneously beating cardiac muscle strips, contraction frequency also increases with temperature, again with a Q_{10} of around 2.0–2.3. Consequently, T_{max} is reduced at a high temperature as a result of the shorter APD. Nonetheless, a higher maximum contraction frequency is possible at high temperature because of a shorter active state and a less pronounced negative staircase effect.

Effect of β-Adrenergic Stimulation on Contractility. β-adrenergic stimulation of frog and fish cardiac strips

increases T_{max} severalfold (12, 353, 354, 632). There are concomitant increases in APD and T'_{max}. The positive inotropic effect of β-adrenergic stimulation is directly related to increasing the influx of calcium across the SL. This is mediated by β-adrenergic stimulation, increasing the probability of SL calcium channels being in an open state. Signal transduction linking the binding of the agonist to the β-adrenoceptor with the phosphorylation of the calcium channel is well described for the frog *R. temporaria* (517, 628) and partially described for rainbow trout (353).

In the frog *(R. esculenta)*, rainbow trout *(O. mykiss)*, and flounder *(Platichthys flesus)*, the degree of positive inotropy is dependent on contraction frequency (12). In fact, the decrease in T_{max} associated with temperature-dependent tachycardia can be more pronounced after adrenergic stimulation. Even so, T_{max} at a given temperature is always higher with than without adrenergic stimulation. Thus, even though β-adrenergic stimulation has positive chronotropic as well as inotropic effects, there will always be a net increase in contractility. In atrial strips from skipjack tuna, the positive inotropic effect of adrenaline is conspicuously independent of contraction frequency (353).

Effect of Extracellular Calcium on Contractility. By increasing extracellular $[Ca^{2+}]$, the gradient for Ca^{2+} across the SL is increased and more Ca^{2+} enters the cell with each action potential. Thus, increasing extracellular $[Ca^{2+}]$ in the range of 1–9 m*M* typically results in a severalfold increase in T_{max} of vertebrate cardiac muscle (155, 156). Nevertheless, it seems unlikely that a change in extracellular Ca^{2+} (for example, ref. 531) is a functional mechanism for modulating cardiac contractility in vivo. Effective calcium homeostasis generally maintains extracellular levels around 1.5–2.0 m*M*, and increases in extracellular Ca^{2+} above this level in perfused fish hearts have only limited effects (191).

Hagfish are unusual in that the heart is relatively insensitive to changes in extracellular Ca^{2+} (267). It appears that the hagfish myocyte has an unusually thick glycocalyx which traps Ca^{2+} near the SL and thereby "protects" the myocyte (500).

Other Inotropic Agents. Many other inotropic agents are known, but their relative importance in vivo is not always clearly defined. Negative inotropic effects can occur with hypoxia, acidosis (174, 228), ACh, α-adrenergic stimulation, and purinergic agents. Positive inotropic effects are reported for arginine vasotocin, adenosine, prostacyclin, and histamine. In addition, the sensitivities of atrial and ventricular tissues are often different. A good example of this is the observation that Atlantic cod atrial tissue is more sensitive than the ventricle to ACh (304), implying that vagal innervation is confined largely to the atrial region. Sensitivity of a single tissue type (for example, pacemaker, atrial muscle, or ventricular muscle) can also change during development in larval bullfrogs (81, 357, 486).

Arterial Blood Pressure and Homeometric Regulation. There is a wide range of systemic arterial blood pressures among vertebrates, which likely reflects differences in the intrinsic ability of the heart to generate pressure. Generally, arterial pressures are correlated with cardiac anatomy and ventricular mass. *Homeometric regulation* is the ability of cardiac muscle to maintain flow relatively independent of pressure development; that is, the end-systolic volume of the ventricle is relatively unaffected by arterial pressure. Homeometric regulation is well documented for various perfused fish hearts from different phylogenetic groups ranging widely in their performance characteristics (Fig. 4.17). The range of pressures over which the fish heart intrinsically maintains SV is species-specific and corresponds well with the in vivo range for arterial blood pressure (180, 190). Similar findings are now available for reptilian hearts [*C. scripta*, (185), *E. signata* (217), *C. porosus* (218)]. Interestingly, the homeometric ability of the turtle heart is lower than that of the rainbow trout heart. Collectively these data support the idea that an intrinsic property of cardiac muscle may be the primary reason why SV is often unaffected by changes in vascular resistance despite the accompanying change in cardiac work.

Homeometric regulation typically breaks down near maximum in vivo arterial blood pressure: end-systolic volume increases and SV decreases. Changes in cardiac contractility obviously affect homeometric regulation. For example, whereas the positive inotropic effect of adrenaline increases the maximum arterial pressure generated by the perfused fish heart, the negative inotropic effects of hypoxia and acidosis reduce it (191, 192, 194). In the turtle heart, decreased temperature and anoxia both have profound effects on homeometric ability. Implicit in the finding of species-specific variability in homeometric regulation is that there will be considerable variability in central arterial blood pressure between species and the sensitivity of reflex mechanisms that regulate blood pressure. These differences are considered under *Arterial Blood Pressure and Its Regulation* below.

The Frank-Starling Mechanism and Control of SV. Changes in SV can be brought about through various intrinsic or extrinsic mechanisms (Fig. 4.12). The Frank-Starling mechanism, a fundamental property of all vertebrate cardiac muscle, represents an intrinsic control which

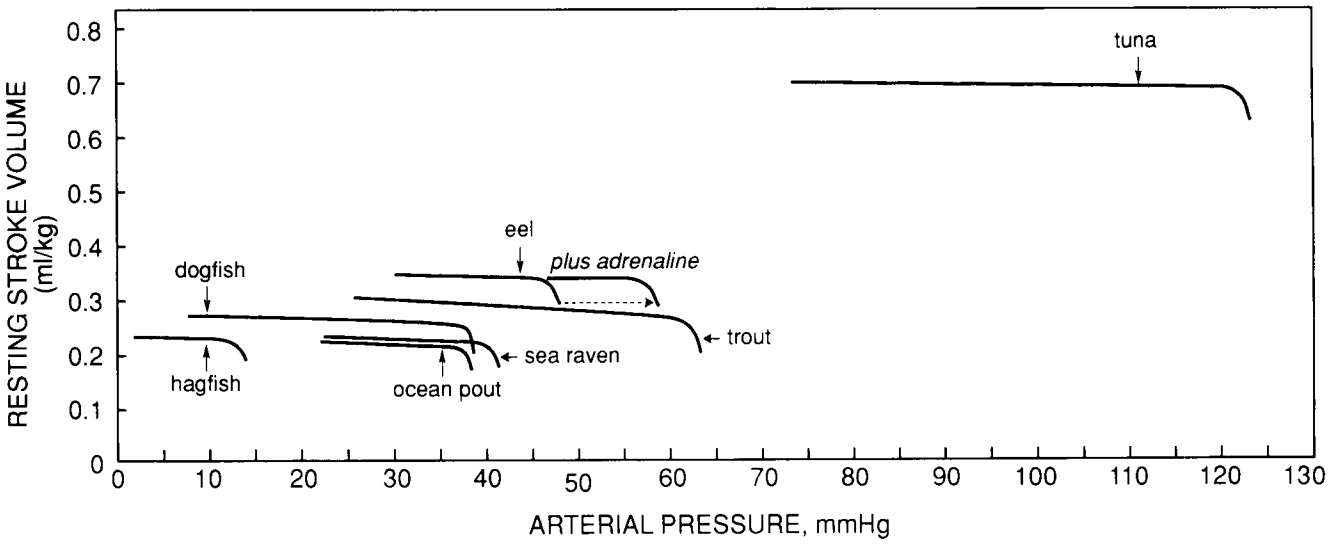

FIG. 4.17. Homeometric regulation in isolated perfused hearts from selected fishes. As demonstrated by these examples for fish, hearts in general are able to intrinsically maintain resting stroke volume (with heart rate constant) despite being required to generate higher arterial pressures as vascular resistance is increased (adapted from refs. 180, 184, 220).

ensures that when venous filling pressure increases, the additional stretch of the myofibrils resulting from the additional filling of the cardiac chamber produces a more forceful contraction. According to the Frank-Starling mechanism of the heart, the energy of contraction is a function of the length of muscle fibers. Thus, SV is directly related to cardiac filling pressure. In fact, relationships between SV and cardiac filling pressure (Starling curves or ventricular function curves) have been established for all major vertebrate groups (Fig. 4.18) (185, 217, 218). The fish heart is probably the most sensitive to filling pressure. The right side of the crocodile heart is more sensitive than the left side, though both sides have a similar maximum SV (217). Similarly, the mammalian right ventricle is more sensitive to filling pressure than the left ventricle. Whether

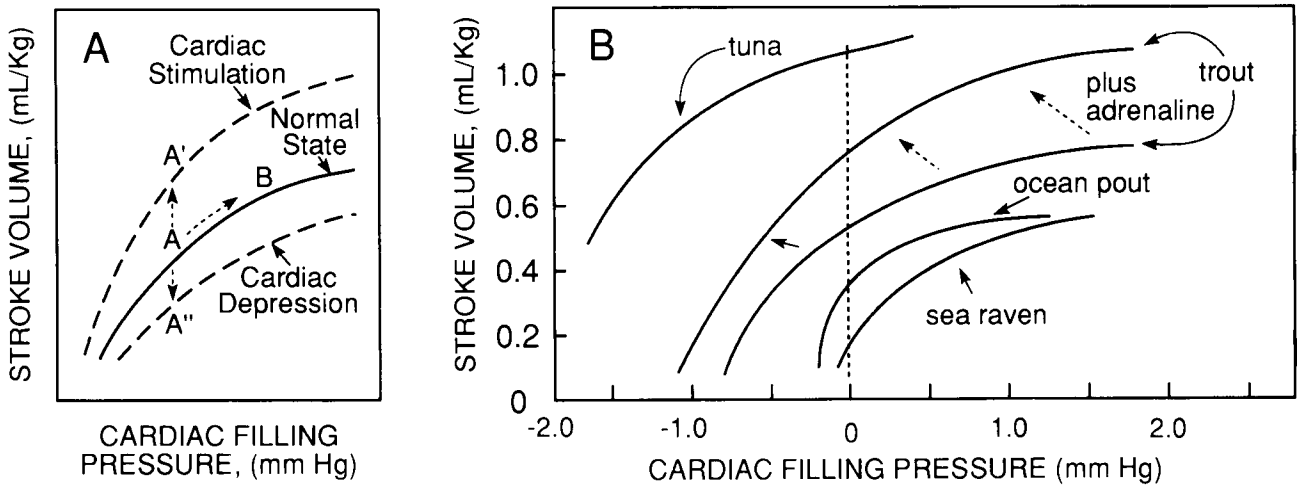

FIG. 4.18. Intrinsic and extrinsic regulation of cardiac stroke volume. *A:* In its normal state and without extrinsic input, an increase in cardiac filling pressure results in an increased stroke volume through the Frank-Starling mechanism. Extrinsic mechanisms of cardiac stimulation and cardiac depression result in a family of curves such that stroke volume can be changed by moving between curves (for example, from *A* to *A'* or from *A* to *A"*) as well as moving along a curve (for example, from *A* to *B*). The importance of the Frank-Starling mechanism in the regulation of stroke volume in fishes is illustrated in panel *B*, which summarizes experiments where filling pressure was varied in perfused heart preparations. Typically, the filling pressure required to elicit physiological stroke volume is low and, because it is subambient in some species, a *vis-a-fronte* filling mechanism is indicated (adapted from refs. 179, 180).

right and left differences in cardiac sensitivity to filling pressure exist in amphibian and noncrocodilian hearts (perhaps to assist intracardiac shunting) is unknown.

Extrinsically, inotropic agents can alter cardiac contractility. The two most universal such agents are adrenergic (neural and humoral) and cholinergic (neural). Changes in contractility create a family of Starling curves. Positive inotropic stimulation with adrenaline shifts the Starling curve upward and to the left, making the heart more sensitive to filling pressure. The negative inotropic effect of ACh shifts the curve downward and to the right, making the heart less sensitive to filling pressure. This means that changes in SV can be brought about by changes in either cardiac contractility or filling pressure or some combination of these. An increase in contractility and a decrease in filling pressure could also result in no change in SV. It is not clear at this time to what degree these two mechanisms are used either in isolation or in combination by lower vertebrates to bring about changes in SV. We can, however, make some general statements regarding the extent to which SV is regulated in the various vertebrate groups.

Amphibians, reptiles, birds, and mammals generally increase f_H to a much greater degree than SV (179). Small increases in SV (10%–30%) are typically observed when humans exercise; thoroughbred horses are exceptional in that a doubling of SV and a tripling of f_H produce up to a sixfold increase in cardiac output (603). For species in which SV does not increase appreciably with exercise, the heart likely operates on the upper arm of the Frank-Starling curve during resting, eupneic conditions. The Frank-Starling mechanism also ensures a long-term balance between the output from the right and left ventricles in the mammalian heart (94). Some exercising amphibians and reptiles show slight decreases in SV associated with increases in f_H (234, 286). The most profound changes in SV in reptiles and amphibians are the decreases associated with apnea. Clearly, for many vertebrates the many factors that affect SV (Fig. 4.12) are probably more important to the maintenance of SV in the face of external perturbations, than to bringing about substantial increases in SV.

Various fishes, including cyclostomes, elasmobranchs, and teleosts, in contrast to other vertebrates, increase SV as much as twofold during exercise. Clearly, the Frank-Starling mechanism has functional importance in terms of this increase (174, 507). In fact, fishes seem to rely upon volume modulation of the heart to a greater degree than frequency modulation in bringing about the increases in cardiac output accompanying aerobic exercise (180, 190).

This evolutionary switch away from a volume-modulated cardiac pump in fish to a frequency-modulated cardiac pump in other vertebrates may be related to a variety of factors:

1. Greater sympathetic control of f_H in mammals. This may result in a larger range over which f_H can change.
2. The atrium becoming less sensitive to filling pressure. Fish hearts are almost one order of magnitude more sensitive to filling pressure than mammalian hearts (that is, 1–2 mm Hg vs. 10–20 mm Hg for a maximum response), and this in turn may be related to the anatomically separate, thinner walled, and more distensible atria of fishes (190).
3. A greater degree of sympathetic control of wall tension in veins. This means that the large reservoir of blood in the veins can be better maintained.
4. The control of intracardiac shunting in amphibians and noncrocodilian reptiles. Intracardiac shunting may require tighter regulation of ventricular dimensions, thereby constraining SV but not f_H.
5. A more efficient shortening distance. For hearts in which SV varies slightly, the muscle presumably operates over a smaller length of shortening (relative to its resting length). This may be more efficient and in itself permissive for higher f_H.

The volume of blood pumped by a heart chamber is equal to the end-diastolic volume (EDV) minus the end-systolic volume (ESV). Since contraction does not normally empty the mammalian ventricle (the ejection fraction is around 50%), SV can increase through changes in both EDV and ESV (Fig. 4.19). Fish hearts function differently. The ventricular ejection fraction in rainbow trout is normally near 100% (220) and that in the leopard shark 80% (382). Thus, the substantial increases in SV that occur in fish are a result of increases in EDV. Quantitative information on the ejection fraction of amphibian and reptilian hearts is lacking, but angiocardiographic evidence (328) and blood pressure measurements (329) indicate that ventricular systole occupies more than 50% of the cardiac cycle, potentially leading to small ESVs. A small ESV will have important consequences for intracardiac shunting (264, 265).

Whereas cardiac EDV is regulated primarily by the atrial transmural pressure, the extent of cardiac filling is limited by *(1)* the time available for filling, *(2)* the volume of the cardiac chamber, and *(3)* the distensibility of the cardiac chamber (Fig. 4.12). A reduced cardiac filling time may explain the observed reduction in maximum SV at high f_H in perfused rainbow trout hearts (194). Similarly, an increase in f_H from 120 bpm to 180 bpm in dogs has little effect on cardiac output because of reduced SV (431).

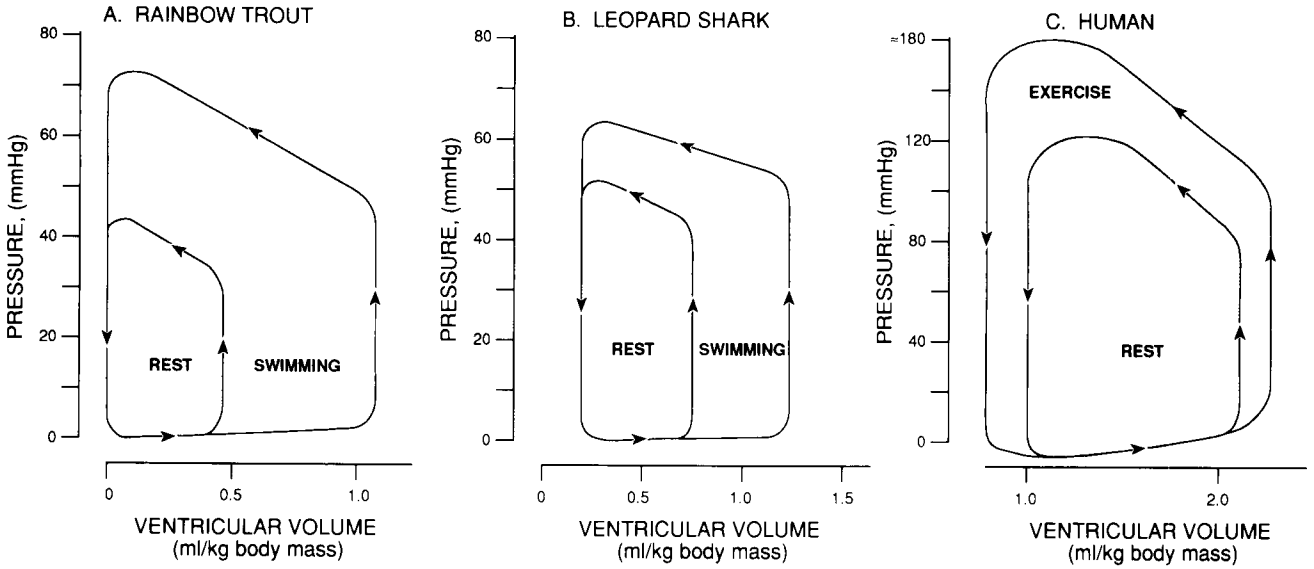

FIG. 4.19. Pressure–volume loops for rainbow trout *(A)*, leopard shark *(B)*, and human *(C)* ventricles during resting and exercise states. Differences in the extent to which stroke volume increases during exercise are quite evident. Furthermore, the mechanism by which stroke volume increases may be different. In fish, there are increases in end-diastolic volume. In humans, upright exercise increases end-diastolic volume, whereas supine exercise increases end-systolic volume (adapted from ref. 179).

Surprisingly, the maximum SV in various fishes and mammals is not that different (around 0.5–1.5 ml/kg body mass). This rather small range may reflect an anatomical constraint. Hearts with a larger volume need a disproportionately thicker wall to maintain the same wall tension (law of Laplace). However, a thicker heart wall creates problems in terms of O_2 diffusion (see below). Thus, it is most likely that maximum SV is set by a compromise between generating wall tension and providing an adequate myocardial O_2 supply. Consistent with this idea is the observation that animals with a large SV have a low arterial blood pressure. For example, SV for amphibian and noncrocodilian reptile hearts is larger (3–5 ml/kg body mass) than for fish and mammals. Also, the heart of Antarctic fishes has an exceptionally high SV (2–10 ml/kg body mass) (180, 190) and a very poor homeometric ability (613).

Cardiac Filling and the Role of the Pericardium. Most vertebrates exhibit vis-a-tergo (force from behind) cardiac filling, so the central venous blood pressure is the critical determinant of cardiac filling and, hence, SV (Fig. 4.12). In mammalian hearts, atrial and ventricular filling occur simultaneously as a result of the favorable pressure gradient between the central veins and the cardiac chambers. Therefore, venous filling pressure is the primary determinant of both atrial and ventricular filling. Atrial contraction per se contributes around 25% of ventricular filling, with a small proportion of filling due to elastic recoil of the ventricle.

Cardiac filling in lower vertebrates is different. The consensus, with the exception of the leopard shark (381), is that atrial contraction is the primary determinant of ventricular filling (179, 328, 329, 507). Evidence for this comes from angiographic images that show no filling of the ventricle prior to atrial contraction and from blood pressure measurements that show an unfavorable pressure gradient for ventricular filling either directly from the *sinus venosus* or directly from the veins during atrial diastole. In this way, the pressure gradient across the atrial wall (atrial transmural pressure equals venous filling pressure minus intrapericardial pressure) is the primary determinant of atrial filling. The degree of atrial filling, through the Frank-Starling mechanism, sets atrial SV, which in turn sets ventricular filling.

Contraction of the sinus venosus, as revealed by the V-wave of the ECG in some fish and amphibians, should theoretically supplement the pressure gradient between the central veins and the atrium. However, sinus contraction intuitively would appear to be rather ineffective at propelling blood only into the atrium given the absence of an ostial valve to guard the entrance of the sinus and to prevent retrograde flow of blood into the major veins.

Some vertebrates use the energy of ventricular contraction to distend directly the atrium and assist atrial filling, that is, vis-a-fronte filling. Elasmobranchs and certain active fishes (for example, rainbow trout and tuna) have the necessary anatomical arrangement (a

functionally rigid pericardial cavity) to allow intrapericardial pressure to be subambient during ventricular contraction. Even though central venous blood pressure can be subambient in these fishes (111, 176), subambient intrapericardial pressure creates a favorable atrial transmural pressure gradient. Furthermore, because the fish heart is much more sensitive to filling pressure than the mammalian heart (179, 180), only relatively small subambient intrapericardial pressures are necessary for effective vis-a-fronte filling.

The possible advantages and disadvantages of vis-a-fronte filling have been discussed extensively (179, 180, 188, 190, 219). Vis-a-fronte filling may be useful in promoting faster cardiac filling, higher myocardial power output, and a lower stressed venous blood volume because of the lower central venous blood pressure. Vis-a-fronte filling, however, imposes the problem of a finite pericardial volume, which could theoretically prevent substantial increases in SV. This is not the case, however, in elasmobranchs because an increase in SV can be accommodated within the rigid pericardial cavity through pericardial fluid moving into the peritoneum via a valved pericardio–peritoneal canal (381, 558). Teleosts do not have a pericardio–peritoneal canal and instead probably rely on changes in the ESV of the atrium and sinus venosus to accommodate the increase in SV (180, 213). This physical restriction on SV may explain why vis-a-fronte filling in fishes is used only for the lower range for SV; vis-a-tergo filling is needed to attain maximum SV.

Cardiac Output and Cardiac Performance

By definition, cardiac output is the total output of blood from a single ventricle. The total output of the fish heart is therefore equal to cardiac output, whereas the total output of the avian and mammalian hearts is equal to twice cardiac output because of the dual ventricles. In amphibians and noncrocodilian reptiles, the total output of the single ventricle is also equal to cardiac output; however, a variable proportion of cardiac output goes to the systemic circulation and the remainder goes to the pulmonary circulation. The situation in crocodiles is complex, and, as described subsequently, total output from the heart and cardiac output do not have a simple, fixed relationship.

Since the general aspects relating to the control of SV and f_H have already been described, this section focuses on the extent to which, and the means by which, cardiac output is regulated within the major phyletic groupings.

Cyclostomes, Dipnoans, and Phyletically Ancient Fishes. Our understanding of the cardiovascular system of hagfishes has benefited from in vivo studies with *M. glutinosa* (20) and *Eptatretus cirrhatus* (209–212) as well as in vitro heart perfusions (207, 208). (These and earlier studies are summarized in references 209 and 543). There is a dearth of in vivo cardiovascular information for lampreys.

The hagfishes *M. glutinosa* and *E. cirrhatus* are capable of resting cardiac output values similar to other sluggish fishes (8–15 ml/min/kg body mass) (Table 4.1). However, they are distinguished by having the lowest blood pressures of any vertebrate. In fact, their hearts are incapable of generating pressures much beyond 1.5 kPa (20 mm Hg) and of beating at rates greater than around 35 bpm at 17°C (20, 209). Cardiac output can increase by two- to threefold, reaching 25–30 ml/min/kg body mass largely as a result of increased SV.

Largely because of the low Pva, hagfish have the lowest myocardial power output of any vertebrate, ranging from 0.08 to 0.28 mW/g ventricular mass in *M. glutinosa* and from 0.15 to 0.68 mW/g ventricular mass in *E. cirrhatus*. The low myocardial power output means that anaerobic adenosine triphosphate (ATP) generation can keep pace with the normal energy requirements of the heart (see below). This explains why the hagfish heart continues to function during severe hypoxia. Acute exposure to severe hypoxia is tolerated in *M. glutinosa* with little change in cardiac output (20), and cardiac output actually increases somewhat in *E. cirrhatus* during hypoxic exposure as a result of increased SV (211).

The absence of cardiac innervation in hagfish precludes the rapid, beat-to-beat changes in f_H typical of other vertebrates. Heart rate rarely changes by more than 20% in hagfishes and then only slowly over several minutes. In contrast, changes in SV can be much larger (maximum SV = 0.7 ml/kg body mass) and more rapid than chronotropic changes. Changes in SV are presumably mediated by the Frank-Starling effect and changes in cardiac contractility (207).

Catecholamines, which are stored in large intracardiac quantities in endogenous chromaffin cells, appear to have an important role in the chronotropic control of hagfish hearts. Marked decreases in f_H occur after injection of β-adrenergic antagonists (20, 50, 51, 211), indicating a tonic control of f_H that may be related to cardiac catecholamine stores. Catecholamine injections can also produce positive chronotropy and inotropy (209). Lampreys stand apart from all other vertebrates in that ACh accelerates, rather than inhibits, the heart (455).

Few measurements of cardiac output and its relation to f_H and SV have been made in air-breathing fishes. Cardiac output in the African lungfish *Protopterus*

aethiopicus is typically about 20 ml/min/kg at 25°C (332). Cardiac output in the air-breathing *Hoplerythrinus unitaeniatus* is around 30 ml/min/kg at 28°C and does not change significantly with air breaths (172). These cardiac output values fall within the range for teleost fishes. The distribution of this cardiac output between the branchial vascular bed, the dorsal aorta, and the lung of lungfish and the air bladder of *H. unitaeniatus* is variable and regulated (see *Breath Holding and Diving,* below)

Elasmobranchs. Butler and Metcalfe (99) have reviewed the cardiovascular information in elasmobranchs, and Satchell (543), Farrell (180), and Farrell and Jones (190) have presented information on elasmobranchs in more general reviews of fish cardiac physiology. (Additional information from in vitro perfused hearts is provided in refs. 138 and 140.)

Measurement of cardiac output is particularly difficult in elasmobranchs because there is no single outflow vessel onto which a flow probe can be attached, and cardiac output values obtained with the Fick principle may be in error (99). Resting cardiac output values range from 19 to 53 ml/min/kg body mass in a variety of elasmobranchs at water temperatures ranging from 6 to 24°C (190). Resting SV is typically 0.7–1.2 ml/min/kg body mass and f_H is between 20 bpm and 50 bpm, depending on the water temperature and species

TABLE 4.1. *Cardiovascular Variables and Their Factorial Scope during Rest (R) and Maximum Exercise (E) in Selected Vertebrates*

	Myocardial Power Output (mW/g)		Central Aortic Pressure (kPa)		Cardiac Output (ml/min/kg)		Heart Rate (bpm)
	R	E	R	E	R	E	R
Scyliorhinus stellaris[a] (19°C, 2.8 kg)	1.43 (1.72×)	2.46	3.24 (1.06×)	3.45	52.5 (1.70×)	89.2	46 (1.12×)
Triakis semifasciata[b] (14°–24°C; 1.9 kg)	1.71 (1.71×)	3.30	6.20 (1.20×)	7.50	33.1 (1.70×)	56.2	51.3 (1.07×)
Atlantic cod[c] (10°C; 1.4–0.8 kg)	1.77 (1.86×)	3.29	4.90 (1.26×)	6.20	17.3 (1.47×)	25.4	43 (1.19×)
Hemitripterus[d] *americanus* (11°C; 0.67–1.4 kg)	1.16 (2.69×)	3.13	3.77 (1.24×)	4.68	18.8 (1.64×)	30.9	37.3 (1.32×)
Rainbow trout[e] (11°C; 1.0 kg)	1.53 (4.59×)	7.03	5.2 (1.54×)	8.0	17.6 (2.97×)	52.6	38 (1.34×)
Pagothenia borchgrevinki[f] (0°C; 0.064 kg)	(1.90×)	1.05	2.00 (1.0×)	3.64	3.64 (1.75×)	29.6	51.8 (1.85×)
Bufo marinus[g] (22°C; 0.25 kg)	1.99 (2.32×)	4.62	3.14 (1.13×)	3.56	144[k] (1.67×)	240	26 (1.81×)
Rana catesbiana[h] (21°C; 0.45 kg)	4.52 (1.42×)	6.34	4.1 (1.04×)	4.28	99[k] (1.34×)	133	28 (1.46×)
Iguana[i] (35°C; 0.7 kg)	3.82 (1.92×)	7.33	5.7 (1.12×)	6.4[l]	201 (1.71×)	343	50 (2.20×)
Varanus[i] (35.0°C; 1.0 kg)	4.96 (3.41×)	16.9	9.3 (1.14×)	10.4[l]	112 (3.04×)	341	48 (2.29×)
Rat[j] (37°C; 0.33 kg)	8.38 (3.51×)	29.4	11.0 (1.72×)	19.0[l]	269 (2.03×)	547	427 (1.49×)
Man untrained[j] (37°C; 75 kg)	3.31 (5.70×)	19.2	12.0 (1.74×)	20.9	66 (3.34×)	221	70 (2.64×)
Man (trained)[j] (37°C; 70 kg)	3.15 (9.08×)	28.6	12.0 (1.69×)	20.3	66 (5.38×)	355	55 (3.64×)
Thoroughbred horse[j] (37°C; 470 kg)	2.34 (7.91×)	18.5	14.9 (1.25×)	18.6	80 (6.3×)	506	45 (4.4×)

Numbers in parentheses indicate factoral scope *Total cardiac output estimated as twice the systemic blood flow. †Estimated value. Data were obtained or calculated from the following sources: [a]Piiper et al., 1977; [b]Lai et al., 1989; [c]Axelsson and Nilsson, 1986; [d]Axelsson et al., 1989; [e]Jones and Randall, 1978; [f]Axelsson et al., 1992; [g]Withers et al., 1988; [h]Hillman et al., 1987; [i]Gleeson et al., 1980; [j]Thomas and Fregin, 1981; Versteeg et al., 1983; Gleeson and Baldwin, 1981; and Farrell, 1991.

(Table 4.1). Pva is typically 3.0–4.0 kPa, but a higher value is reported for the leopard shark (6.3 kPa) (380, 382). Cardiac output can increase as much as twofold with exercise, but the change in f_H is only 10% (381, 382, 494). The maximum value for cardiac output (34.2 ml/min/kg body mass) and maximum output pressure (4.5 kPa) determined in perfused dogfish hearts *(Squalus acanthias)* at 17°C (140) correspond very well with in vivo values.

Teleost Fishes. Both in vivo measurements and in vitro perfused heart studies have contributed to our understanding of cardiac performance in teleosts. Farrell (174, 180) and Farrell and Jones (190) have reviewed the cardiac physiology of teleost fish. Brill and Bushnell (66) have discussed specific aspects peculiar to tuna. Also, work on Antarctic fishes (16, 613) is enlightening because of the cardiovascular adaptations of these fishes.

Resting cardiac output values in temperate water teleosts typically range from 6 to 45 ml/min/kg body mass at water temperatures of 4°–26°C (190). High cardiac output values are associated with a warm temperature and with more active fishes. Some anomalously high resting cardiac output values (60–100 ml/min/kg body mass) are based on Fick principle measurements at temperatures of 15°–20°C. Cardiac output can increase two to three times with aerobic exercise (Table 4.1). Resting SV is usually around 0.3–0.4 ml/min/kg body mass and can increase two- to threefold (up to 1.1 ml/min/kg body mass in some species). Resting f_H ranges from 20 bpm to 120 bpm depending on water temperature and can increase by 50% with swimming. A decrease in water temperature results in a slower f_H, a decrease in cardiac output, and in some species a small increase in SV. Pva usually ranges from 4.5 kPa to 6.0 kPa.

Active teleosts in general tend to have a higher resting cardiac output, a higher Pva, a greater factorial scope for increasing cardiac output, and a larger ventricular mass compared with more sluggish species. Tuna are among the athletic elite of teleost fishes, and this is reflected in their exceptionally high cardiac performance (66, 190). They have the largest ventricles (3–4 g/kg body mass), the fastest f_H (90 bpm–240 bpm), the largest cardiac output (50–130 ml/min/kg body mass), and the highest Pva (12.0 kPa) of all fishes (Table 4.1). However, SV is not unusually large (1.3 ml/kg body mass). Theoretically, the maximum cardiac output needed to meet the maximum O_2 demand in exercising skipjack tuna is 150–200 ml/min/kg body mass (66). In exercising tuna, f_H (around 200 bpm) can be twice the resting f_H (66, 184). Thus, exercising tuna may increase cardiac output primarily by increasing cardiac frequency. Tuna are, therefore, more like mammals than temperate water teleosts in terms of their cardiac regulation and their high level of cardiac work.

Farrell (181) and Farrell and Jones (190) used estimates of myocardial power output to compare cardiac performance in fishes. It was estimated that maximum power output for tuna is 15–18 mW/g ventricular mass as compared with 7.2 mW/g ventricular mass for rainbow trout, 3.5 mW/g ventricular mass for sea ravens, 3.3 mW/g ventricular mass for leopard sharks, and 0.27 mW/g ventricular mass for *M. glutinosa* (Table 4.1). Moreover, when power output is expressed as a function of body mass, the importance of a large ventricular mass in tuna is apparent; resting power output in tuna is 26 mW/kg body mass, a value that is more than ten times that in rainbow trout (2 mW/kg body mass).

Antarctic fishes show unusual cardiac specializations. The adaptations are qualitatively similar in both the red-blooded and hemoglobin-free Antarctic fishes. However, the hemoglobin-free fishes, such as *Chionodraco hamatus* and *Chaenocephalus aceratus,* show adaptations that are quantitatively more extreme (268, 302, 613). Antarctic fishes have a large ventricle (up to 3.9 g/kg body mass) that can pump a very large SV (up to 10 ml/kg in *Chionodraco*) but only at a low arterial blood pressure (<3.0 kPa) because the ventricle is thin-walled (190). Thus, even though f_H is generally slow (6 bpm–20 bpm at 0°C), the high SV permits a high cardiac output (20–120 ml/min/kg body mass). The high cardiac output partially compensates for the low O_2-carrying capacity of the blood. Antarctic fishes, therefore, have a low rate, high volume, and low-pressure cardiac-pumping strategy. Consequently, cardiac stroke work (4.0–6.6 mJ/g ventricular mass) is among the highest for all fishes, even though myocardial power output (0.8–2.0 mW/g ventricular mass) is relatively low (190).

The Antarctic fishes *Pagothenia borchgrevinki* and *Pagothenia bernacchi* maintain a very low f_H with an exceptionally high inhibitory cholinergic tone. As a result, when *P. borchgrevinki* swims, cardiac output and f_H both double, with little change in SV (16).

Amphibians. Direct measurement of cardiac output in amphibians is usually based on flow measurements in one systemic and one pulmonary artery, and assumptions are made regarding blood flow distribution between the numerous outflow vessels. Therefore, cardiac output values for most amphibians are approximations. Another problem is that cardiac output varies considerably as a function of the state of ventilation.

Cardiac output measurements during eupnea range between 60 and 240 ml/min/kg body mass in the anurans *Xenopus laevis, R. catesbeiana, R. temporaria,*

R. pipiens, and *B. marinus* at temperatures around 20°C and a f_H of 26 bpm–43 bpm (291, 292, 559, 563, 598, 659). In the urodeles *Amphiuma tridactylum* and *Ambystoma tigrinum,* cardiac output during eupnea ranges between 30 and 106 ml/min/kg body mass (310). Resting SV (1–9 ml/min/kg body mass) is generally higher than in fish, but systemic blood pressure (3–4 kPa) is lower (Table 4.1). Resting eupneic myocardial power output is 3.0–4.5 mW/g ventricular mass.

Exhaustive exercise in frogs and toads produces a 1.6- to 1.8-fold increase in cardiac output exclusively through tachycardia (286). Tachycardia is mediated predominantly through a release of cholinergic inhibition (80, 391). Myocardial power output also doubles because systemic blood pressure, like SV, changes very little (Table 4.1). The absence of a major increase in either SV or systemic blood pressure is, in fact, a characteristic of amphibians exposed to a variety of experimental perturbations (336, 638).

The intermittent breathing pattern of amphibians is accompanied by bradycardia and up to a 50% decrease in cardiac output during apnea (for reviews, see refs. 86, 561, 645). Generally, bradycardia becomes more pronounced as the apneic period progresses. In *R. pipiens* and *X. laevis,* pulmonary flow represents more than 50% of cardiac output during eupnea. However, it decreases to 33% of a reduced cardiac output during apnea (560).

Terrestrial and semiterrestrial life also impose a challenge with respect to water balance. Dehydration leads to a reduced cardiac contractility (due to a hyperosmotic effect) and a lower maximum blood flow (due to a hypovolemic effect) in anurans (284, 286, 288, 293). Predictably, tolerance of dehydration is greater in the more terrestrial *B. marinus* than in the semiaquatic *R. catesbeiana.* This relates, in part, to the higher blood volume in *B. marinus,* which permits plasma volume to be better defended during dehydration (286). Hillman (283) reports that terrestrial lifestyle is associated with a larger ventricular mass and blood volume. The ventricular mass of *Bufo cognatus* and *Scaphiopus couchii* is 2.4–3.1 g/kg body mass compared with 1.8 and 1.2 g/kg body mass for the aquatic *X. laevis* and the semiaquatic *R. pipiens,* respectively. Blood volumes are also up to twice as high (15.7%–19.4% vs. 7.0%–11.2%).

Amphibians are subjected to diurnal and seasonal changes in environmental temperature; some species even survive freezing during the winter (495). In anurans, Q_{10} values of around 2.0 are typical for both f_H and cardiac output (286).

The only direct measurements of cardiac output in amphibians come from studies on embryos of the clawed toad *X. laevis,* in which microvideo imaging was used to determine the dimensional changes in the heart during its cardiac cycle, thereby allowing calculation of SV as a function of development (307). Cardiac output increased from about 0.07 μl/g/min at a body mass of 5–10 mg to about 0.7 μl/g/min in larvae weighing about 1 g (20°–22°C). This tenfold increase in cardiac output was due entirely to a ten- to 15-fold increase in SV since f_H actually decreased from about 110 bpm to 90 bpm over this same body mass range.

Chelonian and Squamate Reptiles. Cardiac output in chelonian and squamate reptiles is equivalent to the output of the single ventricle. However, this cardiac output is distributed between the pulmonary trunk and the systemic arches. The method of measuring cardiac output via the Fick principle, based on arterial and venous blood oxygen values and whole-animal oxygen consumption, is thus rendered problematic because of the difficulty in determining appropriate blood-sampling sites and because intracardiac shunts result in variable arterial and venous blood oxygen values that do not necessarily represent tissue oxygen extraction. This anatomical arrangement requires that, as in amphibians, flows be measured directly at multiple sites in the central circulation. Such data are available for freshwater turtles and iguanid and varanid lizards.

In the freshwater turtle *C. scripta,* cardiac output varies enormously at rest, primarily because cardiac activity is strongly affected by respiratory state (Fig. 4.20). During diving, f_H may fall to 5 bpm, rising to 30 bpm or more during episodes of air breathing (561). Similarly, SV increases up to fivefold. As a consequence, cardiac output may rise 40-fold, from less than 2 ml/kg/min to 80 ml/kg/min or more in these turtles (18°–22°C). These in vivo measurements are now supported by reliable in vitro estimates of maximum cardiac performance using perfused hearts [*C. scripta* (185), *E. signata* (217)]. In chelonians that show long periods of apnea, SV is clearly a major variable in cardiac output. (A more detailed discussion of changes in cardiovascular performance in reptiles during apnea is given below, see *Breath Holding and Diving*).

Cardiac performance has also been measured in iguanid and varanid lizards (233, 234; see ref. 231 for review), which tend to ventilate constantly or, at least, show very short periods of apnea. At rest, cardiac output values in the green iguana and the savannah monitor are about 150 ml/kg/min and 80 ml/kg/min, respectively, at 35°C. During exercise, these values increase to a maximum of about 300 ml/kg/min in both species (Table 4.1). Interestingly, the increase in cardiac output in iguanids is produced exclusively by

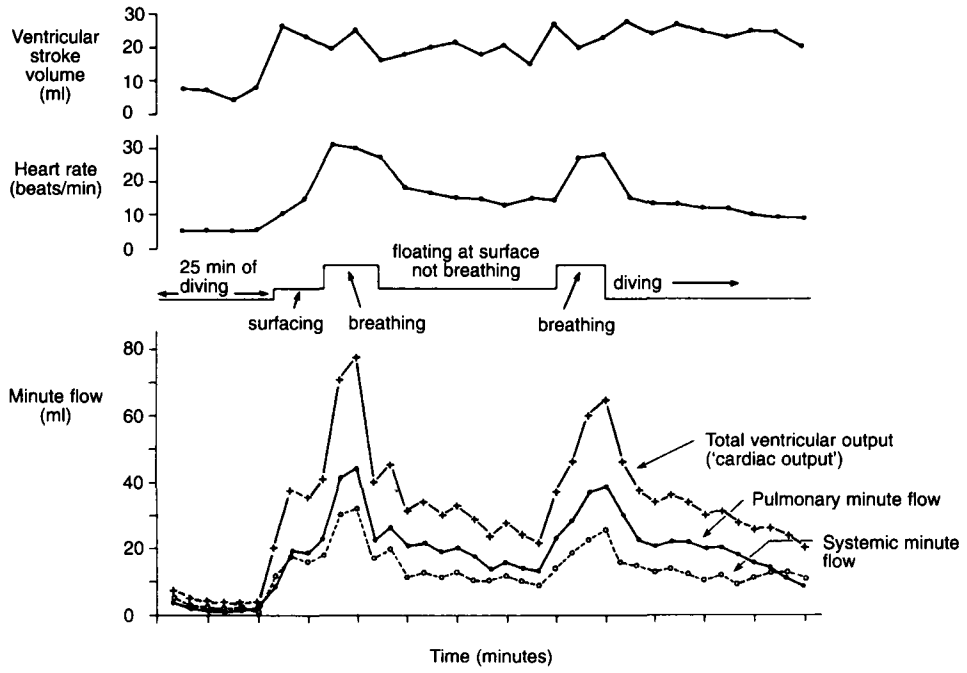

FIG. 4.20. Changes in ventricular stroke volume, heart rate, and cardiac output in an unrestrained, freely diving freshwater turtle, *Chrysemys scripta* (from ref. 328, after ref. 562).

an increase in f_H; SV actually decreases slightly during exercise. Varanids respond to exercise more like mammals, increasing SV slightly and f_H predominantly to increase cardiac output.

Crocodilian Reptiles. During periods of active lung ventilation, the pulmonary circulation is fully perfused and there is no flow from the right ventricle into the left systemic aorta. Outputs from the right and left ventricles are equal, so total output of the heart is equal to twice cardiac output. However, in the most extreme condition, in which the pulmonary circulation is completely closed, total output from the heart (that is, total output from the right ventricle) equals cardiac output. A range of intermediate conditions also exist, depending on the degree of closure of the pulmonary circulation (see *Breath Holding and Diving,* below). In these situations, the output from the right and left ventricles may be different, so, rather than defining cardiac output *per se,* it is often simpler to talk about the total output of the crocodilian heart and its systemic and pulmonary distribution, as for noncrocodilian reptiles.

Few comprehensive in vivo measurements of outflow from the crocodilian heart have been made (347, 563a). Axelsson et al. (23) and Grigg (247) provide additional information on the variable patterns of outflow from the heart. In *Alligator mississipiensis* at 25°–30°C, estimates of total pulmonary output ranged from around 15 to 50 ml/min/kg, with f_H around 50 bpm. When cardiac output is high, flow to the left aorta is around an additional 10%. Mean blood pressure in the right aorta is around 70 mm Hg and 8 mm Hg in the pulmonary artery in resting animals.

The intrinsic properties of the perfused crocodile heart *(C. porosus)* have been reported (217). At a temperature of 23°C and an f_H of 33 bpm, maximum right and left ventricular outputs were both 40 ml/min/kg body mass. The left side of the heart could generate higher pressures, however, so the maximum left ventricular power output was higher than that of the right ventricle (2.26 vs. 1.73 mW/kg body mass, with a relative heart mass of 0.28% of body mass). Homeometric regulation broke down at pressures of 75 mm Hg for the left ventricle and 45 mm Hg for the right ventricle.

Coronary Circulations, Myocardial O_2 Consumption, and Myocardial O_2 Supply

Myocardial Structure in Relation to Coronary Circulation. All lower vertebrate hearts have a muscle type termed spongiosa (also referred to as the inner, spongy, trabecular, or trabeculated layer; the subendocardium; and the endocardium). The spongiosa has an arrangement of interlacing muscle bundles (trabeculae) which span

the atrium and ventricle to form a sponge-like network. This network can create many small compartments within the heart itself. The diameter of the trabeculae in various elasmobranchs and holocephalans typically ranges between 30 and 250 μm (539). In a species of *Rana,* the mean trabecular diameter is 40 μm (60). Trabecular diameter is likely a compromise between minimizing the diffusion distance for O_2 from luminal blood and maximizing tension development. The capillary separation in frog sartorius muscle is around 60 μm. Thus, the maximum O_2 diffusion distance from luminal blood for ventricular trabeculae is between one-quarter and twice the distance in frog sartorius muscle.

The spongiosa is the only myocardial tissue type in the ventricles and atria of cyclostomes, most teleost fishes, and possibly all amphibians. In all other lower vertebrates (elasmobranchs, certain teleosts, and all reptiles), the ventricular spongiosa is encased by a layer of another myocardial tissue, the compacta. The ventricular compacta has a variable thickness. It may account for as little as 5% of total ventricular mass, as in chimaerid fish, or as much as 66%, in skipjack tuna *(Katsuwonus pelamis)* (see Table I in ref. 190). However, the compacta typically represents 20%–40% of ventricular mass when present in lower vertebrates. In birds and mammals, almost the entire ventricle is compacta. Muscle fibers of the *compacta* (also referred to as the outer, compact, or cortical layer; the subepicardium; and the epicardium) are more densely packed than those of the *spongiosa,* and the various architectural arrangements of the layers of fiber bundles within the *compacta* are well documented for fishes (180, 190, 536, 539).

The compacta is always associated with a coronary circulation. Thus, the hearts of cyclostomes, most teleosts, and amphibians are avascular; they lack a fully developed coronary circulation with capillaries within the muscle. However, the coronary circulation, when present, is not necessarily confined to the compacta. Coronary arterioles and capillaries clearly reach the spongiosa of the ventricle and atrium in all elasmobranchs and several active fishes—for example, tuna and marlins (138, 190, 539, 611).

The presence of a coronary circulation is not associated exclusively with either air breathing or terrestrial life. Air-breathing fishes, such as the bowfin *(Amia calvens),* have a coronary circulation, but amphibians and the lungfish *Neoceratodus* do not. Instead, aquatic hypoxia and a high myocardial power output appear to be important selection pressures favoring the development of a coronary circulation.

Because a greater proportion of compacta corresponds to a more developed coronary circulation, generalizations can be made about the coronary circulation by inference based on the measurements of compacta. The percentage of compacta is related to scope for activity and cardiac power output within, but not necessarily between, phyletic groupings. Endothermic sharks have more compacta than ectothermic sharks, as do endothermic teleosts compared with ectothermic teleosts. However, endothermic sharks do not have more compacta than all ectothermic teleosts (164, 190). This association probably reflects the higher pressure work performed by the hearts of endothermic fishes rather than the higher cardiac output. Hemoglobin-free Antarctic fishes, for example, have a large ventricular mass and cardiac output but no coronary circulation.

The compacta appears early in development in salmonids, increases disproportionately with growth in juveniles, and reaches a relatively fixed proportion of ventricular mass in mature fish (187, 363, 499). This development pattern is mirrored in mammals. Embryologically, mammalian hearts are trabecular and coronary vessels become incorporated as the heart is modified during development (245).

Coronary Vascular Arrangements. The following generalization can be made regarding the anatomy of the coronary circulation in lower vertebrates: it has two possible sites of origin and for both sites oxygen-rich arterial blood enters the coronary circulation, blood pressure being close to the highest possible. There is always an anterior (cranial, cephalad) origin, meaning that the origin is from postbranchial vessels in fishes and from the systemic aorta close to the heart in amphibians, reptiles, birds, and mammals. In some fishes and reptiles, there is an additional posterior (pectoral, caudal) origin that usually goes to the apex of the ventricle.

(Detailed information on the anatomy of the coronary circulation in lower vertebrates can be found in refs. 138, 190, 214, 245, 255, 416, 481, 539, and 612. The following is therefore only a brief phylogenetic overview.)

Coronaries in fishes. The majority of fish species have avascular hearts, which have no capillaries in the myocardium (Type I) (612). All elasmobranchs (including chimaerids, sharks, rays, and skates), active teleosts, chondrosteans, and some dipnoans have a coronary circulation but with varying distribution patterns.

Anterior coronary circulation in fish has its origin at the ventral ends of one or more efferent branchial arteries and reaches the ventricle on the outer surface of either the bulbus arteriosus (teleosts and chondrosteans) or the conus arteriosus (elasmobranchs). The origin of the posterior coronary circulation—for exam-

ple, in eels, marlins, rays, and skates—is associated with the coracoid branch of the subclavian artery and reaches the heart via ligaments between the pericardium and the ventricle. In both cases, coronary blood pressure is roughly equivalent to that of the dorsal aorta. The dipnoan *Protopterus* is unique in that the coronary circulation is derived from the afferent side of the branchial circulation; in contrast, *Neoceratodus* does not have a coronary artery.

In fish such as the salmonids, coronary capillaries are located only in the compacta of the ventricle (Type II) (612). In all elasmobranchs and in teleosts such as tuna and marlin, coronary capillaries and arterioles reach the spongiosa and atrium as well as the ventricular compacta. Typically, the elasmobranch version of this arrangement contains <40% compacta and is termed Type III; the teleost version has around 40% or more compacta and is termed Type IV (138, 612). The conus arteriosus of elasmobranchs also has compacta and its own coronary arteries and veins (190).

Circulation to the compacta has a discrete venous system, with large veins emptying into the atrium near the atrioventricular region. However, the coronary circulation in the muscle trabeculae of Types III and IV ventricles has no venous system (473, 630). Instead, the terminal arterioles and the few capillaries open directly to the ventricular lumen, thereby forming arteriolacunary connections analogous to the Thebesian system of the mammalian heart (612). There is no estimate of either what proportion of coronary blood flow enters the spongiosa or whether the vessels of the spongiosa are even continuously perfused. [The Thebesian system in the perfused turtle heart *(C. elegans)* accounted for less than 0.1% of the coronary drainage emptied into the ventricular cavity (63).]

Coronaries in amphibians. Urodeles and anurans have a single coronary artery which arises either at the base of the ventricle or near the right carotid artery subdivision. However, coronary vessels are located only in the outer connective tissue of the heart and not in the myocardium *per se;* no compacta is found in the ventricle (245, 255, 416, 473). The bulbus cordis has compacta and coronaries (245). Apodans do not have a coronary artery (215). Thus, it appears that the mixed venous blood in the lumen of the heart provides an adequate O_2 supply for the low cardiac work (and myocardial O_2 demand) of the amphibian heart.

Coronaries in reptiles. The origin of the reptilian coronary circulation is thoroughly described by MacKinnon and Heatwole (416). Typically, all reptiles possess either one or two anterior coronary arteries derived from the right (or sometimes left) systemicocarotid trunk at various locations near the heart. In addition, some families have a posterior supply from the coeliacomesenteric artery, which reaches the apical region of the ventricle via the gubernaculum cordis; a gubernaculum cordis is found in most reptiles but does not always contain a coronary artery.

Coronary vessels in reptiles are restricted mostly to the ventricle. In the tortoise *Emys orbicularis,* coronaries are confined to the compacta (348), but whether this is true for other reptiles is not clear from the literature. The extent of coronary development in reptiles appears to be related to the level of cardiac work and myocardial O_2 demand. For example, "fine" coronary vessels are found on the ventricle of squamate lizards, whereas the ventricle of varanid lizards, which generates higher aortic blood pressures, has larger coronary vessels and more compacta (416). Similarly, coronary circulation in the crocodile is more extensive on the left side of the heart. The absence of atrial coronaries may be directly related to the lower O_2 demand of the atrium. In varanid lizards, coronary vessels are located in the right but not the left atrium, a distribution pattern which suggests that the systemic, but not the pulmonary, venous return, may become limiting in terms of a luminal O_2 supply. Coronary circulation to the atria may become more important when reptiles grow to a large size and the atrial wall thickness increases.

Coronary O_2 Supply and Control of Coronary Blood Flow. Information on blood flow in, and vasoactivity of, coronary vessels is largely limited to studies on fish (see reviews in refs. 137, 180, 190) and a study on the *E. orbicularis* coronaries (348). This information clearly suggests that there are major differences in the control, and the role, of the coronary circulation in lower vertebrates compared with mammals.

Cardiac function in the mammalian heart is dependent on a continuous coronary blood flow. Furthermore, hypoxia, adrenaline, and increased metabolism (cardiac work) all result in a coronary vasodilation that significantly increases coronary blood flow. In this way, there is tight matching between the coronary O_2 supply and the work performed by the heart. In contrast, the lower vertebrates studied so far show coronary vasoconstriction in response to adrenaline and the control of coronary flow is less precisely matched to arterial blood pressure generated by the heart. This might be expected given the anatomical origin of the coronary arteries in fish. The origin of the coronaries is postbranchial, so the driving pressure for coronary blood flow is substantially lower than the pressure developed by the ventricle since gill resistance reduces arterial pressure by 25%–40%.

Direct measurements of coronary blood flow in resting coho salmon yield values of 0.2 ml/min/g ventricu-

lar mass (1.1% of cardiac output) (19). In burbot *(Lota lota)* and sucker *(Catastomus catastomus),* coronary blood flow was estimated at 0.56%–0.65% of cardiac output using microspheres (106). Estimates of coronary flow based on in vitro pressure–flow relationships yield higher values compared to in vivo values, perhaps because of a loss of vascular tone (for example, 0.38 and 0.67 ml/min/g ventricular mass, 1.5% and 1.9% of resting cardiac output for rainbow trout and skipjack tuna, respectively) (177, 184). By comparison, coronary flow in mammalian hearts represents a greater proportion (about 4%) of resting cardiac output. Some of this difference may reflect the smaller proportion of the fish ventricle being perfused by the coronary circulation (177).

Extravascular compression of coronary vessels during systole produces phasic flow in the coronary artery of the coho salmon (Fig. 4.21). Even though ventricular contraction attenuates flow in the main coronary artery, there is no flow reversal. In contrast, a brief reversal of coronary flow occurs in the anesthetized school shark *(Galeorhinus australis)* coincident with ventricular systole (141). This difference may reflect the different coronary distribution patterns to the compacta and spongiosa in sharks and salmonids (see above). Extravascular compression is significant in mammalian hearts (201). Moreover, because of the different radii of curvature of the thick-walled mammalian ventricle, blood flow to the inner myocardial layers is affected to a much greater degree. The differential wall tension between the inner and outer layers may, through vascular compression effects, limit wall thickness to some degree even though there is adequate vascularity.

Even though there is a resting level of blood flow to the coronary circulation, there does not appear to be an absolute requirement for coronary blood flow in salmonids during routine cardiac function. Ligation of the coronary artery does not result in immediate death of salmonids (146, 189, 196). Furthermore, salmonids with the coronary artery ligated can swim at speeds more than 50% of their normal maximum prolonged swimming speed (U_{crit}). Therefore, the luminal O_2 supply can at least partially compensate for whatever O_2 is normally supplied by the coronary circulation. In fact, in vitro perfused rainbow trout hearts can perform maximally while receiving aerated saline in the lumen and no coronary perfusion (191, 433). It is likely, however, that as fish grow the dependence upon the coronary circulation increases with increasing ventricular size and thickness.

Calculations suggest that of the O_2 normally available in luminal blood, the entire myocardial O_2 demand would deplete luminal O_2 content by only 1%–10%, even during exercise (190). In view of this, it is unlikely that the O_2 content of luminal blood limits

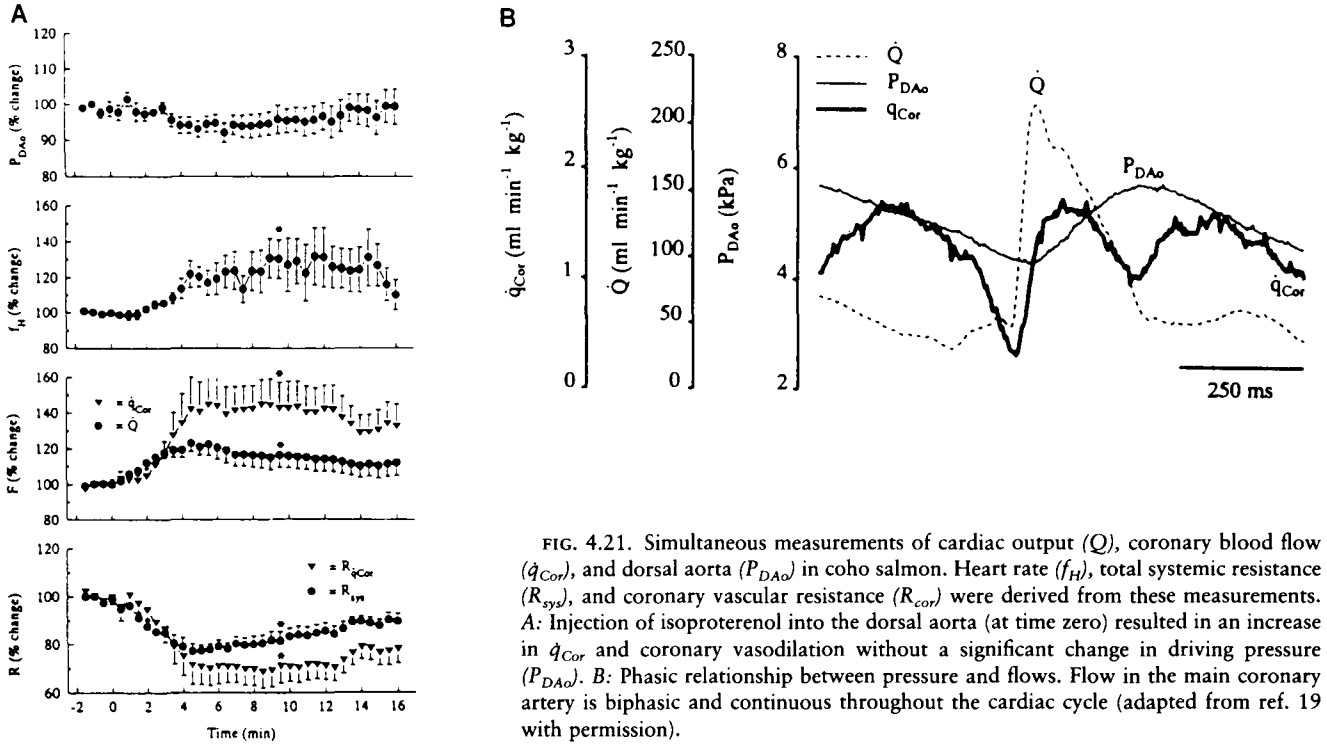

FIG. 4.21. Simultaneous measurements of cardiac output *(Q)*, coronary blood flow *($\dot{q}_{Cor}$)*, and dorsal aorta *(P_{DAo})* in coho salmon. Heart rate *(f_H)*, total systemic resistance *(R_{sys})*, and coronary vascular resistance *(R_{cor})* were derived from these measurements. *A:* Injection of isoproterenol into the dorsal aorta (at time zero) resulted in an increase in $\dot{q}_{Cor}$ and coronary vasodilation without a significant change in driving pressure *(P_{DAo})*. *B:* Phasic relationship between pressure and flows. Flow in the main coronary artery is biphasic and continuous throughout the cardiac cycle (adapted from ref. 19 with permission).

myocardial O_2 supply (137). [Note, however, that hemoglobin-free icefish are unusual in that they may use 43% of the luminal O_2 supply (138).]

Since the limitation on the venous myocardial O_2 supply route is the venous P_{O_2}, we can expect a greater reliance on the coronary O_2 supply route *(1)* in situations where venous P_{O_2} decreases (that is, the pressure gradient for O_2 diffusion is reduced) and *(2)* in animals in which the wall of the heart is particularly thick (that is, the distance for O_2 diffusion is usually larger in animals as they grow and in animals noted for a large relative ventricular mass). There is some experimental support for these ideas. During exercise and environmental hypoxia in fishes, venous P_{O_2} decreases and coronary flow not only increases (19) but maximum cardiac performance is apparently tied to adequate coronary perfusion (142, 189, 195, 196). Skipjack tuna represent an extreme in terms of the high ventral aortic pressures generated by their large heart having a thick ventricular wall. It appears that these high blood pressures are possible only if the heart is receiving O_2 via the coronary supply route, perhaps making skipjack tuna, like mammals, obligately dependent upon coronary circulation (184).

Control of coronary blood flow is achieved through changes in perfusion pressure and coronary vasoactivity. In mammals, perfusion pressure is the primary determinant of coronary blood flow (201) and is closely tied to the pressure work performed by the left ventricle. In exercising mammals, coronary blood flow can increase fivefold for a sixfold increase in cardiac work. A similar situation is likely to exist in the amphibian and reptilian coronary circulations. In rainbow trout, a roughly proportional increase in coronary blood flow accompanies a change in P_{da} (19, 177). However, P_{da} is well regulated and rarely changes by more than 30% or so during either exercise or hypoxia. This means that pressure-dependent changes in coronary flow under these two conditions do occur but are not of sufficient magnitude to account for the two-fold increases in coronary blood flow observed in coho salmon during hypoxia and exercise (19). Consequently, a coronary vasodilatory reserve is of primary importance in bringing about changes in coronary blood flow in salmon.

The basis for the coronary vasodilatory reserve in lower vertebrates is not fully understood. A number of in vitro studies in fishes have identified α-adrenergic, β-adrenergic, cholinergic, and purinergic vasoactivities in either the entire coronary circulation or the main coronary arteries (38, 136, 177, 183, 184, 186, 569). The relative importance of arterial and arteriolar control has not been addressed. An α-adrenergic constriction and a β-adrenergic dilation of the coronary circulation have been confirmed for coho salmon in vivo (19). In the tortoise, there is α-adrenergic, cholinergic, and histaminergic vasoactivity (348). An important difference in coronary vasoactivity between mammals and lower vertebrates is the coronary response to adrenaline. In the tortoise and salmonids, adrenaline increases the overall coronary vascular resistance and, therefore, by itself would reduce coronary flow (19, 177, 348). This is the opposite of the mammalian situation. Thus, it appears that α-adrenoceptors predominate in the coronary circulation of lower vertebrates, whereas β-adrenoceptors predominate in mammals.

Adrenergic-based vasoactivity is clearly not responsible for the entire vasodilatory reserve in coho salmon. Isoproterenol produces only a 40% increase in coronary flow (19). The only other potent coronary vasodilators identified are the prostaglandins I_2 and E_2 (A. P. Farrell, unpublished observations). Consequently, the vasodilatory reserve is based on either the release of a tonic vasoconstrictor mechanism or increased activity of vasodilators such as prostaglandins I_2 and E_2. Tonic α-adrenergic coronary vasoconstriction could be important in vasoconstriction, but so too could endothelin and prostaglandin $F_{2\alpha}$, which are very potent vasoconstrictors of fish coronary arteries in vitro (137, 467). What appears to be emerging is a very important role for autocoids in coronary blood flow regulation.

Myocardial Oxygen Consumption. The hearts of lower vertebrates are aerobic, and most would cease to function without an adequate myocardial O_2 supply. O_2 supply to the myocardium is provided by two circulations, the luminal and coronary. The luminal O_2 supply (the venous blood being pumped by the heart, also termed the lacunary or sinusoidal blood supply) bathes only the inner surfaces of the cardiac chambers; there are no blood vessels associated with it. Trabeculae increase the area of contact between cardiac muscle and venous blood, and, as noted above, the diameter of the trabeculae may reflect a compromise between minimizing diffusion distance for O_2 and maximizing the cross-sectional area for tension development. The coronary O_2 supply, in contrast, has arterioles and capillaries which penetrate the myocardium.

All vertebrate hearts rely upon the luminal circulation to some degree, but not all lower vertebrates have a coronary circulation. Thus, there is considerable variability in the extent to which these two circulations are utilized, and, as a consequence, there is variability in the anatomy and physiological role of the coronary circulation. Ostadal et al. (472) have suggested that development of the vertebrate coronary circulation is related to anatomical factors such as the extent of

compacta myocardium and changes in heart size during development, as well as physiological factors such as the higher metabolic turnover of endotherms and the amount of cardiac work associated with activity of the animal. In the following it will become clear that a major difference between mammals and lower vertebrates is the relative myocardial O_2 demand. Myocardial O_2 demand is related to myocardial power output.

Studies with working, perfused fish hearts have provided the basis for our understanding of myocardial O_2 consumption ($\dot{V}O_2$) in lower vertebrates. The general finding is that myocardial $\dot{V}O_2$ is directly proportional to myocardial power output under aerobic conditions (140, 190, 197, 243). The values for O_2 cost per unit power output range from 0.26 to 0.42 μl O_2/s per mW for various fish species with differing cardiac anatomies (138). Mechanical efficiency increases slightly with the work load, being 15%–20%. Since mechanical efficiency is relatively similar among all vertebrate hearts, myocardial O_2 demand can be easily compared among vertebrates by comparing values for myocardial power output. (It is much easier to measure flow and pressure generated by the heart and to estimate myocardial $\dot{V}O_2$ than to try to measure myocardial $\dot{V}O_2$ directly.) Thus, it should be fairly obvious that the high myocardial power output of mammalian, avian, and tuna hearts results in a higher O_2 demand and greater reliance on a coronary O_2 supply compared with other vertebrates. Knowing the relationship between power output and myocardial $\dot{V}O_2$, it is also possible to estimate the O_2 cost of cardiac pumping as a function of the animal's total $\dot{V}O_2$ from measurements of myocardial power output (190, 195). The O_2 cost of cardiac pumping is relatively small (between 0.5% and 5.0% of total $\dot{V}O_2$) in fish species living in temperate water. However, it may be as high as 23% of resting $\dot{V}O_2$ in *C. aceratus* as a result of the high cardiac output value and low O_2 content of these hemoglobin-free Antarctic fishes.

In general, cardiac ATP demand greatly exceeds the potential to generate ATP anaerobically; resting myocardial power output can range over three orders of magnitude (0.1–20 mW/g ventricular mass) and can increase up to fivefold with exercise. However, the ability of vertebrate hearts to generate ATP anaerobically does not vary nearly as much. Anaerobically generated ATP can and does support myocardial power output in animals in which it is either normally low or suppressed during special conditions (for example, during either winter hibernation in fishes, amphibians, and reptiles or summer estivation in air-breathing fishes). To examine the importance of anaerobic metabolism in supporting cardiac work, the cardiac ATP requirement has to be considered (515). To do this, myocardial $\dot{V}O_2$ can be estimated from myocardial power output and then converted to an ATP equivalent. In hagfish, for example, the resting myocardial output of around 1 mW/g ventricular mass can be almost completely supported by anaerobic metabolism (208, 209). In the hypoxic sea raven heart, with a myocardial power output of 0.8 mW/g ventricular mass, anaerobic metabolism can contribute 25% of the ATP requirement for resting power output (197). A power output of 0.3–2.3 mW (ventricular mass not reported) was maintained for up to 15 h (provided plasma was present in the perfusion fluid) in the severely hypoxic ($\dot{P}O_2 < 2$ mm Hg) perfused turtle heart (515). Farrell et al. (185) have shown in situ that anoxic turtle hearts are capable of generating up to 0.77 mW/g ventricular mass at 15°C. Likewise, anoxic rainbow trout hearts can generate 0.6 mW/g ventricular mass at 15°C in situ (11). Apparently, ATP generation from anaerobic metabolism can routinely fuel a cardiac work level of around 0.1–0.2 mW/g ventricular mass routinely but may not be able to fuel much more than 1.0 mW/g ventricular mass, a level quite similar in both anoxia-tolerant and hypoxia-sensitive species.

Long-term cardiac survival during anoxia clearly must be tied to two attributes (185); *(1)* the ability to reduce ATP demand to a level that can be supported by anaerobic metabolism and *(2)* the ability to further reduce ATP demand to minimize waste product accumulation and fuel reserve depletion. In the overwintering anoxic turtle at 3°C, for example, myocardial power output is around 0.03 mW/g ventricular mass [estimated from the data of Herbert and Jackson (273) and assuming cardiac output to be decreased in proportion with the 58-fold decrease in f_H]. This value is well below the 0.17 mW/g ventricular mass that can be supported by anaerobic ATP generation in anoxic perfused turtle hearts at 5°C (185). An additional adaptation for anoxic survival may be the intrinsic compensation for the negative inotropic effects of acidosis and hypoxia in anoxia-tolerant species (228, 321).

PERIPHERAL CIRCULATION AND HEMODYNAMICS

Arterial Blood Pressure and Its Regulation

Levels of Arterial Pressure. Arterial pressure can be considered as the force required to overcome vascular resistance and to maintain blood flow to body tissues. The arterial pressure at any moment is related to the volume and compliance of the vasculature, cardiac action, and the resistance to blood flow attributable to the vessel architecture and properties of blood. A sophisticated understanding of pressure regulation involving the heart and systemic circulation has been

achieved, chiefly from mammalian studies. Control of the circulation is important for adaptation to stresses, and comparative investigations suggest that regulation of arterial pressures to a homeostatic level adequate to perfuse tissues is a basic requirement of all vertebrates. At the same time, nonsteady states are important for a fuller appreciation of cardiovascular function, especially in ectothermic species.

Systemic arterial pressures range from a few to several hundred millimeters of mercury in various vertebrates (Fig. 4.22). There is, in the most general sense, an evolutionary trend toward increasing pressure as one progresses from primitive (agnathan) circulatory systems to those of endothermic birds and mammals. Such generalizations about strictly phyletic progressions of pressure are complicated, however, by environmental influence, activity of animals, temperature, and other considerations. For example, arterial pressures in amphibians are lower than those in many fishes. While development of high arterial pressures is a function of the stressed filling volume, vessel compliance, cardiac contractility, and peripheral resistance, combinations of these features to produce high levels of pressure are not limited to birds and mammals.

The lowest steady-state pressures recorded from vertebrate arterial systems are associated with the circulation of hagfish, which displays primitive features of tissue sinuses ("open" system) and accessory hearts to assist circulation (324, 543). Low pressures also occur in other fishes, some amphibians, and aquatic snakes representing taxa that have also evolved high-pressure systems. Pulmonary pressures consistently are low relative to systemic pressures in air-breathing vertebrates (328), a consequence of low resistance of the pulmonary vasculature and the requirement that gas exchangers are not compromised by excessive filtration of fluid. Given this generalization, although systemic pressures of birds and mammals are characteristically considerably higher than those of ectotherms, the pulmonary pressures of the latter animals tend to exceed those of mammals (576). Such pressure differences may reflect intermittent breathing patterns and possibly greater rates of lymph flow in the ectothermic species, notwithstanding possible differences in capillary structure and the filtration coefficient.

Pressures in the arterial system of the hagfish are on the order of a few millimeters of mercury and are supported by the independent actions of various accessory hearts on the venous side of the circulation (543). In other fishes, the highest central pressures are recorded in the ventral aorta. The ventral aorta is relatively short and, together with the bulbus arteriosus, accounts for the majority of compliance in the fish arterial system (543). Dorsal arterial pressures are lowered by gill resistance, which precedes in series that of the systemic tissues. The gills offer a significant resis-

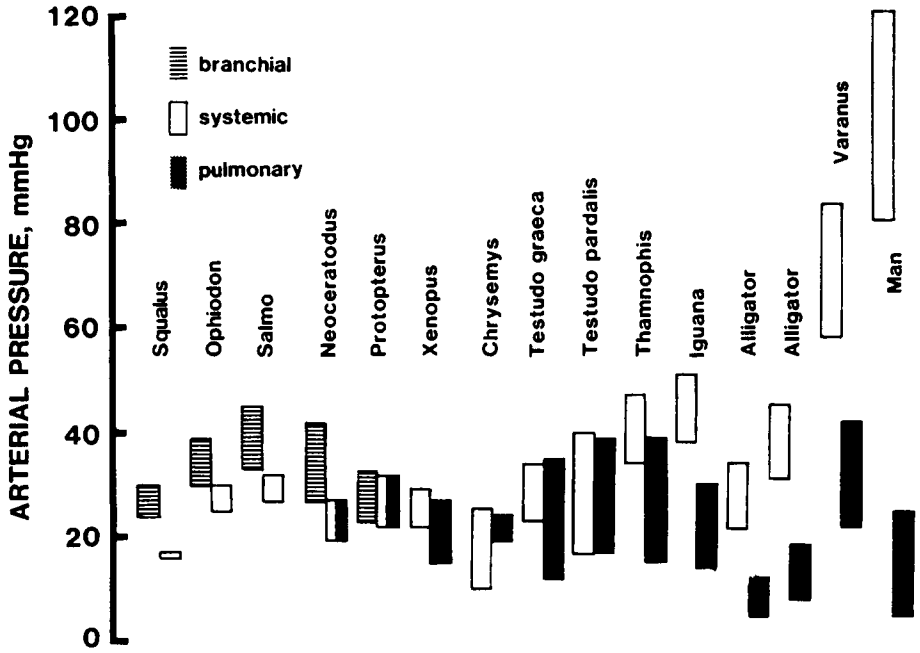

FIG. 4.22. Blood pressures in branchial *(lined bar)* v. systemic *(open bar)* and pulmonary *(stippled bar)* v. systemic *(open bar)* arteries of selected vertebrates. Height of vertical bar is equivalent to pulse pressure (from ref. 181).

tance to blood flow, and systemic pressure reductions of from 15% to 50% are commonly noted between dorsal and ventral aortae (Fig. 4.22) (173, 176, 339, 507, 646). Both pressure and flow exhibit pulsitility in the dorsal aorta, though these features are considerably dampened by reduced elasticity of the dorsal vessel and high f_H. In general, arterial pressures tend to be lower in elasmobranchs than in teleosts (507).

The amphibian heart generally does not generate pressures as high as those in most fishes (Fig. 4.22). This may be related to the fact that the single ventricle serves both the pulmonary and systemic circuits. Even though ventricular work is essentially identical for the pulmonary and systemic circuits, a significant and variable resistance protects the pulmonary circuit downstream of the outflow tract (60, 190, 325, 560). As a consequence, pulmonary arterial pressures are either lower than or equal to, but not higher than, systemic arterial pressures. Systemic arterial blood pressure and ventricular mass are greater in terrestrial amphibians (for example, *B. marinus*) compared with more amphibious species (for example, *R. catesbeiana*).

Among reptiles, the chelonians have the lowest systemic arterial blood pressures, with terrestrial species (for example, *Testudo pardalis*) having slightly higher pressures than semiaquatic species (for example, *C. scripta*) (Fig. 4.22). Resting systemic arterial blood pressure varies considerably among snakes, in part related to their diversification of exposure to gravitational forces (see below). An allometric relationship exists in snakes between arterial blood pressure and body mass (exponent = 0.15), likely because ventricular mass increases with increasing body mass (553). Resting systemic arterial blood pressures in crocodilians and varanid lizards are similar to those in mammals, and they are almost twice that in *Iguana* (Fig. 4.22). Therefore, the functional and anatomical divisions of the reptilian ventricle are associated with higher systemic arterial pressures.

Development of high arterial pressures is characteristic of, but not limited to, birds and mammals. High arterial pressures are measured in species of fish adapted for rapid swimming and high physiological performance, including endothermy. Ventricular or ventral aortic pressures can exceed 100 mm Hg in tuna and salmon (184, 524, 646). Despite differences in myocardial structure and body temperature, ventricular contractile force and tissue blood flow rates of albacore tuna approach those of mammals (646). An important conclusion from these data is that, except for agnathans, diversification of cardiovascular design during vertebrate evolution does not exert an overwhelming constraint on the evolution of high blood pressures.

High levels of arterial pressure are often associated with large cardiac output values. This relationship does not always hold, however. For example, high levels of blood flow are achieved in the hemoglobin-free antarctic icefish *C. aceratus* with lowered arterial pressures because of decreased vascular resistance in the gills and vascular beds as compared with other teleosts (269, 302). Both red-blooded and hemoglobin-free Antarctic fishes, by having conspicuously low ventral aortic pressures but relatively large ventricles, are exceptions to the generalization that a higher aortic pressure is associated with a large ventricular mass (190).

High arterial blood pressures have also evolved in relation to environmental or behavioral demands, irrespective of phylogeny or body mass. It is widely appreciated that the highest mammalian blood pressures are measured in giraffes (235, 237, 258, 620, 621). Aortic pressures of 353/303 mm Hg have been recorded in upright adult giraffes, and such levels of hypertension have been considered to be necessary for perfusion of cerebral vasculature, which may be 2–3 m above the heart (reviewed in ref. 258). Whether the high pressures are required to overcome the gravitational column of the neck vessels or merely the flow resistance of the cephalic vasculature is unresolved (28, 258, 278, 556). Cerebral vasculature aside, high levels of arteriolar resistance and tight endothelial junctions help to prevent edema in dependent tissues of the giraffe's limbs (258).

Systemic arterial pressures of snakes are correlated with the degree of arboreality or the gravitational stress to which a species is likely to be exposed (Fig. 4.23). Resting arterial pressures range generally between 15 and 30 mm Hg in sea snakes, which live in a nearly weightless environment, whereas arterial pressures in arboreal species can exceed 90 mm Hg (14, 394, 395, 400, 557). Arboreal snakes have a comparatively short heart-to-head distance (anterior heart) and are more resistant to blood pooling and edema in the dependent vasculature. Superior adrenergic control of the vasculature in arboreal species probably reflects a high peripheral vascular resistance relative to nonclimbing species, but this hypothesis remains to be investigated. Pulmonary arterial pressures in these snakes remain rather uniformly low despite species variation in the level of systemic pressures.

Generalizing from the available data for endotherms, the "average" mammal, with the exception of the giraffe, has a mean arterial pressure of about 97 mm Hg, while the "average" bird has a mean arterial pressure of about 133 mm Hg (250). Differences of pressure between these taxa appear to be attributable more to a greater cardiac output (relative to mass or metabolic rate) in birds than to differences of periph-

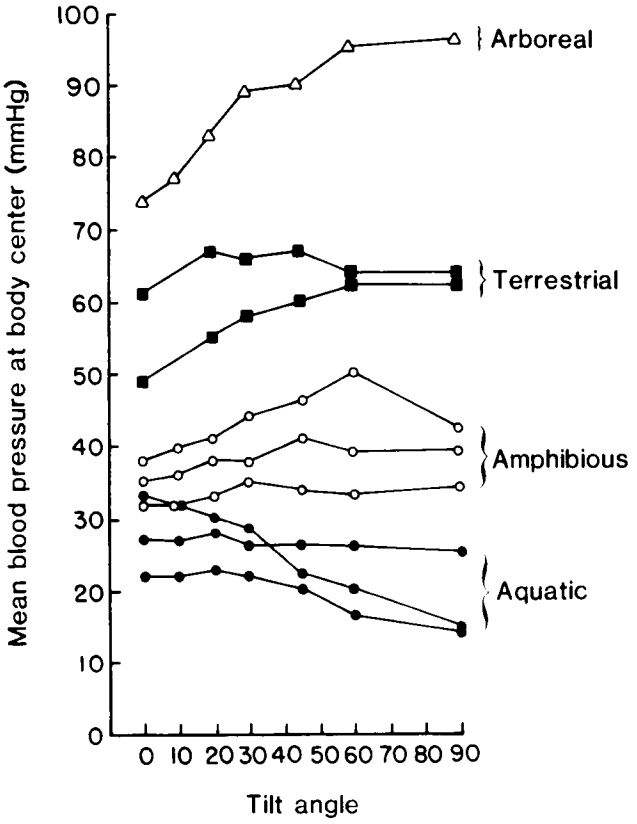

FIG. 4.23. Relationships between mean arterial pressures, measured at the body center (hydrostatic indifferent point, see text), and head-up tilt angle determined in species of snakes from different gravitational environments. Pressures at the body center are expected not to change with tilt angle if the arterial column acts as a passive system contained within a rigid tube (224) (after ref. 557).

eral resistance (250, 251). Relative to mammals, birds have larger hearts, greater SVs, lower f_H values, and greater stroke work per gram of myocardium. In probably all vertebrate embryos, blood pressure increases while peripheral resistance decreases with age and the development of a parallel system of vessels (121, 220a, 306, 590).

An increase in resting arterial blood pressure is possible in all species. Dramatic increases exceeding 50% of resting levels may occur in response to activity or exercise in fish, snakes, and mammals (Figs. 4.24, 4.25). Relatively smaller increases in arterial blood pressure are reported for exercising amphibians and lizards.

Baroreflexes and Neurogenic Regulation of Arterial Pressure. Three conceptual considerations are important to understanding blood pressure regulation: *(1)* short-term regulation; *(2)* long-term regulation, for periods exceeding hours or days; and *(3)* evolutionary adaptation

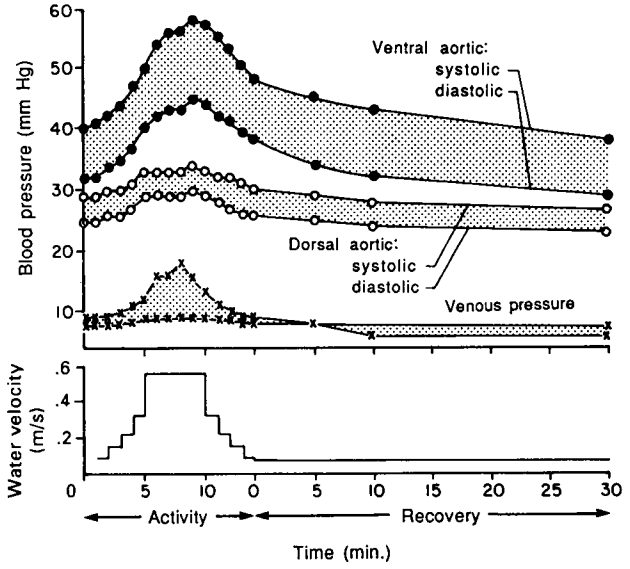

FIG. 4.24. Changes in blood pressure in ventral aorta, dorsal aorta, and subintestinal vein during and after moderate swimming activity in rainbow trout (from ref. 587).

of stabilized arterial pressure levels compatible with the morphology and activity of a species. The evolution of stabilized arterial pressures has produced in vertebrates redundant feedback controllers involving reflex neural and neuroendocrine mechanisms affecting

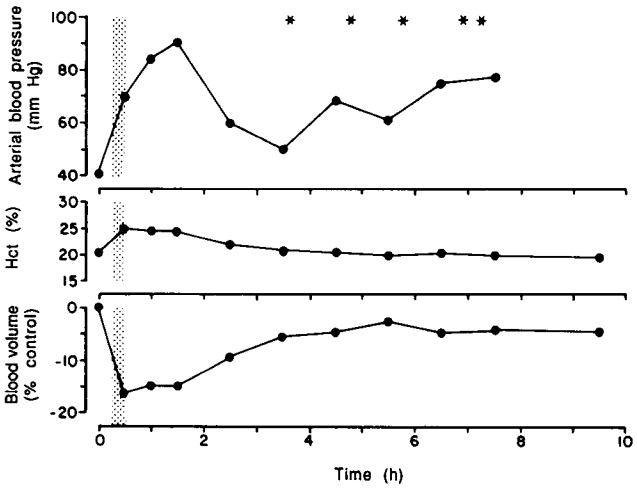

FIG. 4.25. Pattern of arterial pressure, hematocrit *(Hct)*, and blood volume in a single snake, *Elaphe obsoleta*, for an extended "recovery" period following 15 min of locomotion *(stippled bar)*. During recovery the snake was held within an acrylic tube, where it rested in an extended position but was free to move forward or backward for a distance of several centimeters. Note that the movements of the snake (*stars* in top panel) elevated arterial pressure and prevented blood volume from returning to control level measured before exercise (from ref. 404 with permission).

moment-to-moment arterial pressure. Historically, studies of cardiovascular regulation, especially those prior to the 1970s, have tended to emphasize short-term control of arterial pressure. Studies related specifically to the long-term control of pressure are relatively recent.

Two concepts are central to the current understanding of arterial pressure regulation: *(1)* shorter-term stabilization of pressure by means of cardiovascular neural reflexes and *(2)* long-term, slower adjustments of body fluid volumes mediated by physical and neuroendocrine mechanisms (130). Neurogenic reflex adjustments in cardiac output, total vascular resistance, and venous tone are integrated with humoral, metabolic, and other tissue factors to maintain arterial perfusion pressure to all organs. The implication from most mammalian literature is that these interacting processes are always homeostatic, in both design and action. Consideration of the biology of a range of vertebrate species, however, illustrates the importance of nonsteady states in understanding the full integration of cardiovascular controls.

A third important concept is that the net response of interacting cardiovascular reflexes is not a simple linear summation of the responses observed when each reflex is activated alone (1). This is because these reflexes interact, and when, for example, opposing reflexes are activated, it is difficult to predict the net response. Therefore, studies of intact organisms and responses to several simultaneously changed sensory inputs are important to a fuller appreciation of the role of cardiovascular reflexes in controlling the circulation.

The principal elements involved in short-term control of arterial pressure are mechanoreceptors (usually termed baroreceptors), their sensory feedback afferents, central integrators of the sensory information, and the autonomic effectors comprising the efferent limb of a barostatic reflex (Fig. 4.26). Mechanical stretch receptors in the walls of blood vessels and in the heart detect changes in wall tension and thereby provide sensory information related indirectly to pressure and volume changes in the circulation. As judged primarily from studies of mammals, receptors in the arterial blood vessels are important for rapid adjustments of arterial pressure through changes in volume output from the heart, whereas venous and cardiac receptors are incapable of sensing arterial pressures but play important roles in the regulation of blood volume and cardiac output.

In mammals there are multiple baroreceptor centers involving several sites in the central circulation (154). Knowledge of baroreceptors and their characteristics in nonmammalian vertebrates is far less complete than for mammals. Not surprisingly, the search for baroreceptors in a range of vertebrates has been guided by comparative anatomy and homology. Baroreceptor zones may extend from the heart and aortic arches to divisions of the arches or the truncus arteriosus (Fig. 4.27). Whereas carotid baroreceptors have received emphasis in mammalian studies, predominant baroreceptive regions in other vertebrates are associated with the aortic and pulmonary arteries (625, 645). It is important to suggest, however, that various vessels might contribute sensory information regarding their status of distension, independent of organized "centers" of baroreceptors. In mammals, there is substantial innervation of systemic vessels by unmyelinated sensory C-fibers having some degree of mechanoreceptive function (reviewed in ref. 229). The C-fiber afferents arising from these vessels mediate spinal pressor reflexes in response to mechanical stimulation. Finally, arterial chemoreceptors often are near-mechanoreceptive segments of the vasculature and can influence cardiovascular control.

The functional characteristics of cardiovascular mechanoreceptors have been reviewed elsewhere (1, 30, 46, 277, 476, 645). Arterial baroreceptors exhibit rate sensitivity and thereby produce an enhanced response to dynamic pressure stimuli. Although baroreceptors respond best to rapidly changing stimuli, slowly adapting receptors also encode the mean level of arterial pressure. Baroreceptors exhibit sensory adaptation and thereby reset to new states of wall stress equilibria, so they are thought not to participate in the long-term regulation of pressure. Indeed, destruction or denervation of the receptors may have little effect on the long-term level of arterial pressure (130, 627). It has been proposed that denervation of both arterial and cardiopulmonary baroreceptors can lead to sustained hypertension in mammals (488, 489), but this conclusion is unproven (225, 563, 564).

The distribution of baroreceptors in mammals includes the heart, the carotid sinus, several places along the common carotid arteries, the right subclavian region, the pulmonary arteries, and the intrarenal vessels (Fig. 4.27). Baroreceptor afferents consist of a heterogeneous population of neurons comprised of both myelinated and unmyelinated fibers (124, 202). Two distinct forms of mammalian baroreceptor may be distinguished on the basis of functional and morphological characteristics. Myelinated fibers have relatively low pressure thresholds and high discharge frequencies and respond to a large range of stimulation frequencies (about 10–150 Hz). Unmyelinated baroreceptors have higher thresholds and lower discharge frequencies and produce depressor responses at relatively low stimulation frequencies of 1–50 Hz (462).

Unmyelinated baroreceptors have been identified in

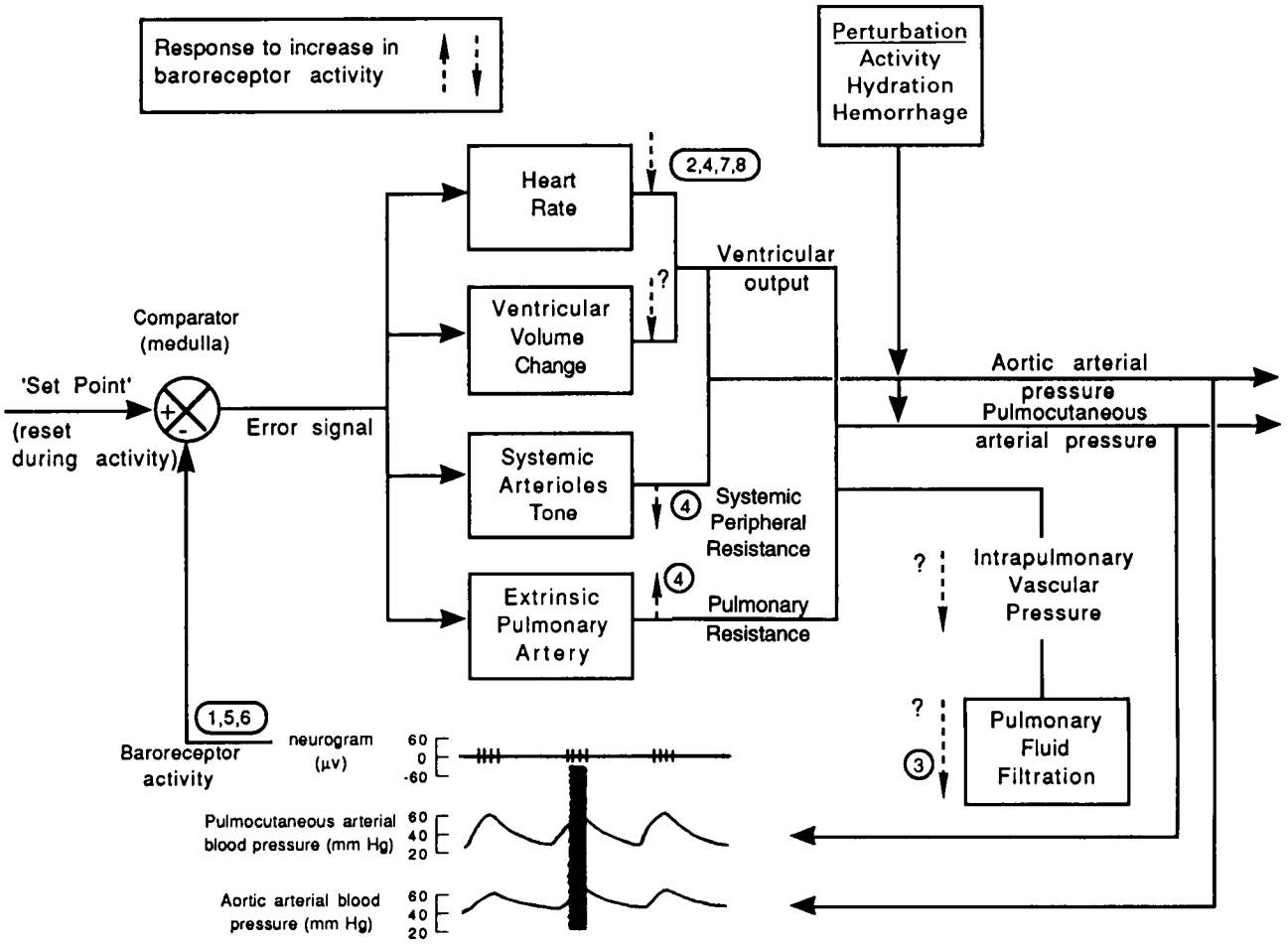

FIG. 4.26. Schematic diagram of mechanisms participating in baroreflex regulation of cardiovascular variables in *Bufo*. "Classical" representation of negative feedback, which uses a hypothesized "set point" for arterial pressure and a medullary comparator. Response of heart and systemic vasculature to baroreceptor stimulation is reduction in heart rate and systemic resistance, which opposes elevations in central arterial pressure. However, pulmocutaneous arterial (PCA) resistance increases, probably because of vagally mediated constriction of the extrinsic pulmonary artery. This opposes regulation of PCA pressure and ultimately central arterial pressure but protects the pulmonary microcirculation from pressure elevations. Some relevant references are numbered *(1–8): 1,* 319; *2,* 571; *3,* 579; *4,* 624; *5,* 626; *6,* 625; *7,* 627; *8,* 644 (modified from ref. 645).

amphibians, reptiles, and mammals, whereas myelinated baroreceptors, with thresholds well below normal arterial pressures, have so far been identified only in mammals (624–627a). Differences in the function of baroreceptors between vertebrate classes may be related to corresponding differences in circulatory function. Unmyelinated receptors may reflect a widespread need to protect the circulation from potentially damaging increases in arterial pressure, including the gas-exchange vasculature. However, low-threshold myelinated baroreceptors may be important to pressure-regulating systems of mammals which are relatively intolerant of even transient hypotension.

There is a wealth of information concerning neural regulation of arterial pressure and the role of baroreceptors in cardiovascular control of mammals. This information has been summarized in numerous reviews, and space does not allow a thorough treatment here (see, for example, refs. 1, 30, 361, 362, 373, 374, 476, 533). The following sections provide a comparative perspective by discussing neurogenic control of the circulation in non-mammalian vertebrates.

Cyclostomes, dipnoans, and primitive fishes. Responses of the heart of *Myxine* to drugs affecting the cardiovascular system are weak (see *Cardiac Output and Cardiac Performance,* above), and it is doubtful that circulating catecholamines play any role in cardiac control in these primitive vertebrates (455). It seems likely that the

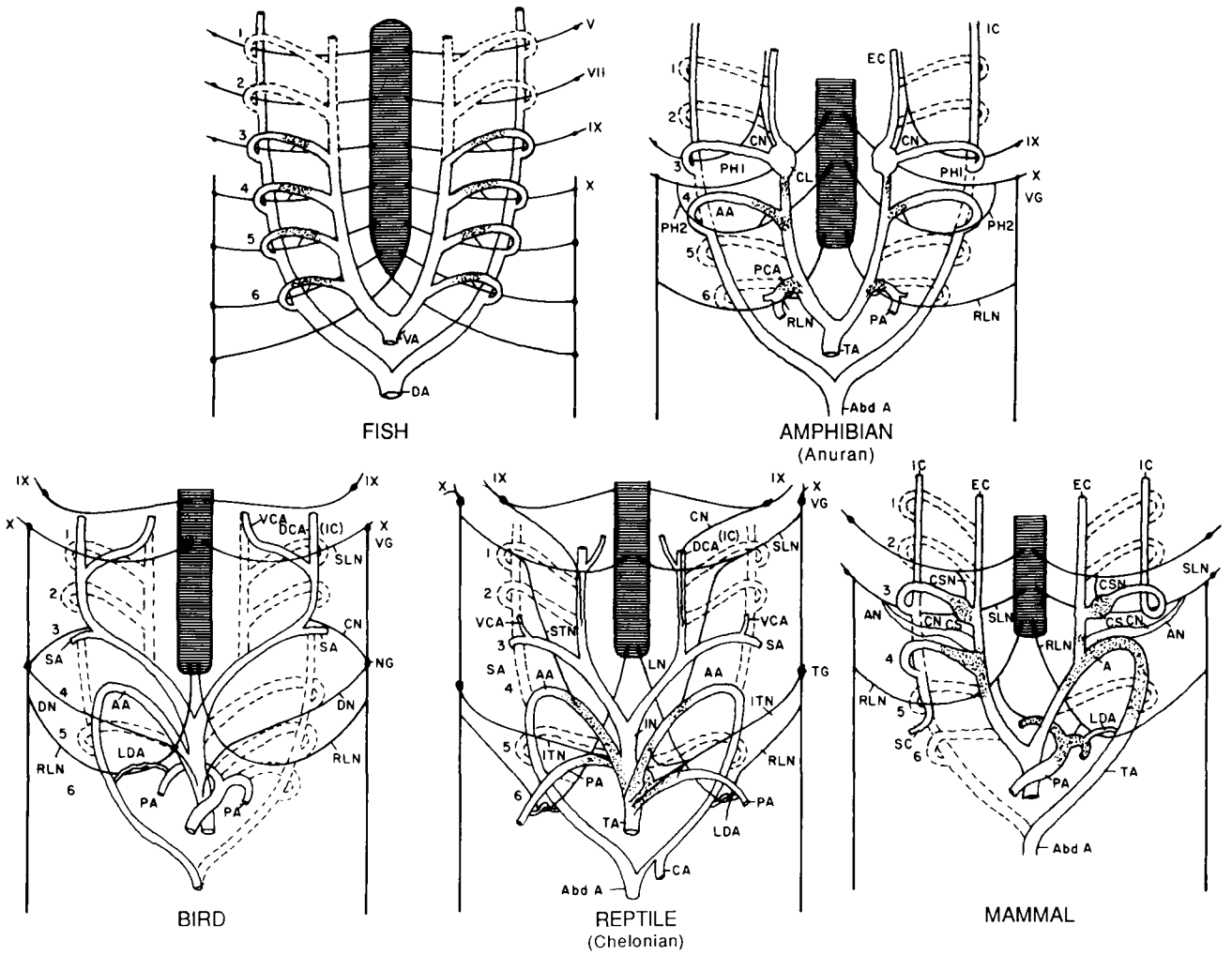

FIG. 4.27. Schematic of baroreceptor zones and their innervation in five classes of vertebrate, drawn to illustrate developmental origins from visceral arch arteries and associations with corresponding visceral arch nerves. Amphibian and mammalian examples adapted from reference 626; the remainder based on references in 30, 340, 624–627. Drawing is from Van Vliet and West (627a). Abbreviations: *A*, aorta; *AA*, aortic arch; *Abd A*, abdominal aorta; *CA*, celiac artery; *CL*, carotid labyrinth, *CN*, carotid nerve; *CS*, carotid sinus; *CSN*, carotid sinus nerve; *DA*, dorsal aorta; *DCA*, dorsal carotid artery; *EC*, external carotid artery; *IC*, internal carotid artery; *IN*, innominate artery; *ITN*, inferior truncal nerve; *LDA*, ductus arteriosus or its ligament; *NG*, nodose ganglia; *PA*, pulmonary artery; *PH1* and *PH2*, pharyngeal branches of the vagus nerve; *PCA*, pulmocutaneous artery; *RLN*, recurrent laryngeal nerve; *SC*, subclavian artery; *SLN*, superior laryngeal nerve; *STN*, superior truncal nerve; *TA*, truncus arteriosus; *TG*, truncal ganglia; *VA*, ventral aorta; *VCA*, ventral carotid artery; *VG*, vagal ganglia; *V*, *VII*, *IX*, and *X*, cranial nerves 5, 7, 9 (glossopharyngeal), and 10 (vagus); *1,2,3,4,5*, and 6, visceral arch arteries 1–6. *Stippled areas* represent functionally identified baroreceptive zones. *Shaded region* in upper midline of each figure represents larynx and pharynx.

upper level for arterial blood pressure is set by the pressure-generating ability of the heart, which appears to be quite limited (20). The chromaffin cells of dipnoans appear to be innervated by extrinsic, presumably cholinergic, fibers (547). The heart of the gar *(Lepisosteus)* is richly innervated by adrenergic fibers, and there is evidence for adrenergic control attributable to both adrenergic neurons and circulating catecholamines (454), as in more advanced fishes. Autonomic innervation of the vasculature of cyclostomes and dipnoans may be comparatively poorly developed, and adrenergic control may be primarily by means of circulating catecholamines (4, 5). Little is known about reflexogenic control of the circulation in cyclostomes, ganoids, and dipnoans, but complex regulation of blood flow patterns has obvious significance in relation to the branchial and pulmonary circuits of the lungfishes.

Elasmobranchs. The cardiovascular system of elasmo-

branchs appears to represent a primitively organized system with limited control and weak ability to withstand stress. In dogfish, baroreceptors are claimed to occur on the afferent side of the branchial arches, where increased perfusion pressures induce bradycardia (413). Bradycardia is also elicited by mechanical or electrical stimulation of several regions, including gills, heart, and the cut central ends of the first to fourth branchial nerves (413, 414). Nerve activity synchronous with cardiac systole can be recorded from branches of the branchial nerves (316). Although cardiovascular responses are elicited by nerve stimulation and autonomically active drugs (470, 471), there is little evidence of neuronally mediated control of the peripheral circulation. The cardiovascular systems of studied elasmobranchs are intolerant of tilting (464) and behave like simple pressure–volume systems in response to hemorrhage (591).

The heart of elasmobranchs is supplied by two pairs of cardiac branches of the vagus. Acetylcholine as well as stimulation of the vagus reduce f_H, and cholinergic vagal tone is considered the most important mode of nervous chronotropic regulation in elasmobranchs (455). It is generally accepted that the atrium and ventricle of elasmobranchs lack a sympathetic innervation (12). Catecholamines generally have weak positive chronotropic and inotropic effects on the heart, but responses are variable and there is evidence for a cholinergic element in catecholamine-induced inhibition (137, 386). The two naturally occurring catecholamines epinephrine and norepinephrine could conceivably mediate control of cardiac activity (111).

Most literature on the adrenergic control of elasmobranch vasculature suggests that circulating catecholamines are the most important factor in the control of blood pressure (reviewed in refs. 30, 455). The major systemic arteries of the dogfish are adrenergically innervated and contracted by epinephrine via α-adrenoceptor-mediated mechanisms (457, 458). Very little is known concerning the direct nervous control of branchial vasculature, but regulation of branchial resistance may involve the release of catecholamines from strategically located chromaffin tissue (223, 541).

The best documented cardiac reflex in elasmobranchs is the bradycardia that is induced by hypoxia in the dogfish (101, 540). Stroke volume increases during the response and is attributable to increased cardiac filling (Starling's law of the heart) and possible inotropic enhancement by circulating catecholamines (102, 103, 565, 594). Vagal cholinergic innervation comprises the efferent cardioinhibitory pathway, the reflex originating with a diffuse system of oxygen receptors in the gills (99). The significance of hypoxic bradycardia is that it maximizes respiratory gas exchange, though the mechanism is incompletely understood and appears to involve more than relative flow rates of water and blood (566, 593).

Teleosts. In teleosts, the cardiac vagi innervate the sinus venosus and atrium but do not reach the ventricle. The vagus is cardioinhibitory, as in all vertebrates except the cyclostomes, and a resting tonus has been demonstrated in some species (107, 501, 587). Although the vagus does not directly influence the ventricle, it does affect cardiac output because atrial contraction in part sets ventricular filling (Fig. 4.12; 328, 345). The importance of vagal tone in cardiac control can be temperature-dependent, such that adrenergic mechanisms predominate in cardioacceleratory actions at higher temperatures (378, 501, 664). Adrenergic innervation has been demonstrated in all parts of the teleost heart [except flounder (12)], but the density and functional importance vary from species to species (455). Levels of circulating catecholamines are sufficient to produce an adrenergic tonus on the heart in some species of fish, but a neural adrenergic tonus may be predominant (18). Comparative data suggest that both a cholinergic inhibitory tonus and an adrenergic excitatory tonus are general features of the teleost heart, during rest and at moderate levels of swimming (18).

Chemoreceptors in the gill arches cause bradycardia during hypoxia (145, 221, 493, 573, 574) except in a few species (89, 112). In salmonids and Atlantic cod, the oxygen receptors are located in the region of afferent vessels associated with the first gill arch. Oxygen receptors located elsewhere elicit a rapid increase in both ventral and dorsal aortic blood pressures, attributable to an increase in systemic vascular resistance (221). Hypoxic bradycardia could be related in part to a barostatic reflex. Hypoxia typically increases vascular resistance (95).

Rapid increases and decreases in blood pressure are brought under control by a barostatic reflex. Whereas hypertension reduces cardiac output through bradycardia to minimize the pressure excursion, it is important to note that there is a characteristic maximum pressure that a heart can generate (see section on homeometric regulation *Mechanical Properties of Cardiac Muscle,* above). Thus, if vascular resistance increases beyond the capabilities of the heart, cardiac output decreases as pressure increases (a trade-off between pressure and flow). The decrease in cardiac output results from a smaller SV and not bradycardia. Perhaps the best illustration of this phenomenon is in the Atlantic hagfish, where the efferent arm of the barostatic reflex is absent. When doses of ACh greater than 100 nmol/kg

were injected into the caudal vein, gill vasoconstriction was so great that cardiac output actually stopped as ventral aortic pressure reached 1.6 kPa (20 mm Hg) (20).

Barostatic reflexes involving cardiac inhibition and lowering of blood pressure are elicited in various teleosts by electrical stimulation of cut branchial nerves or pressure perfusion of the gill arteries (30). These depressor responses are abolished by vagotomy or atropine. The baroreceptors responsible for the reflex are located in various parts of the gills.

In the carp *(Cyprinus carpio),* reflex bradycardia is elicited by perfusion of one of the four gill arteries, but there is a progressive decrease in sensitivity of the reflex (higher perfusion pressure required) from the first to the fourth pair of gill arteries (521). This finding is of interest in view of the differential sensitivity of the mammalian carotid and aortic sinuses, which are homologous to the third and fourth gill arches, respectively. In addition to the gill arteries, pressure-sensitive receptors appear to be present in the afferent artery of the pseudobranch and possibly the carotid labyrinth (387, 468).

Further evidence for functional baroreceptors in teleosts is demonstrated by cardiac responses to increased loading of baroreceptors via either a pharmacologically or a physically induced rise in systemic blood pressure as well as to decreased loading attributable to hypovolemic lowering of arterial pressure. Injection of epinephrine elevates blood pressure by constriction of systemic vasculature in a variety of teleost species. This induces a bradycardia due to a baroreceptor reflex (450, 455, 492, 513, 520, 666). Vascular compression of the systemic circulation has also been shown to elicit a barostatic reflex (176). In both instances, the barostatic reflex is abolished by atropine pretreatment. Barostatic reflexes can be very potent in fishes and have the capability to override chemoreceptive drives (667). However, as Wood and Shelton (667) point out, the cardioacceleration effector arm of the barostatic reflex in rainbow trout may be much weaker than the cardiodepressor arm.

Beyond the barostatic reflex, there is a significant vascular tonus in resting fish which contributes to the overall pressure. Injection of the vascular smooth muscle poison papaverine causes hypotension (176). There is evidence that adrenergic control of the cardiovascular system is primarily neuronal in some species (570, 572, 665) and primarily humoral in others (635). Systemic vasoconstriction involves an α-adrenoceptor-mediated mechanism, and there appears to be appreciable adrenergic innervation of the major arteries and arterioles (360, 636). Increased levels of circulating catecholamines are evident during stressfully exhausting exercise but appear not to be important in circulatory adjustments during moderate exercise (314, 522). In cod, hypertension noted during swimming is attributable to both an increase in cardiac output and the maintenance of systemic vascular resistance by the activity of adrenergic vasomotor fibers (25). Adrenergic fibers maintain a tonic influence on the vasculature both at rest (572) and during exercise (25). Isoprenaline decreases blood pressure and vascular resistance, which suggests that α-adrenoceptors are also present in the systemic vasculature (114, 135, 266, 492, 662). Cholinergic fibers are abundant in the spinal autonomic control of various organs in teleosts, but their role in vascular control is uncertain (455).

Further indirect evidence for reflexogenic control is the observation of Mayer waves or low-frequency oscillations of the arterial pressure independent of ventilatory frequency (661). Such oscillations in mammals are considered to reflect feedback regulation of arterial pressure involving vascular smooth muscle activity in the resistance vessels. Tolerance of bluefish *(Pomatomus saltatrix)* to head-up tilt with maintenance of arterial pressure to angles of 60° from horizontal provide additional evidence for active regulation of vascular smooth muscle (464). Ogilvy and Dubois (464) speculate that the orthostatic tolerance of bluefish to posture change outside of water reflects adaptation to circulatory stresses evoked during forward acceleration and rapid carangiform swimming (see also ref. 176). These observations and the demonstration of barostatic reflexes in fishes are significant because they emphasize that reflexogenic mechanisms conferring orthostatic tolerance did not evolve de novo solely in response to strong gravitational fields experienced by terrestrial vertebrates (340).

The barostatic reflex in teleosts also shows short-term accommodation. In the sea raven, the bradycardia associated with vascular compression decays after 30–60s, with the exact period depending upon the initial level of bradycardia (176).

Amphibians. The amphibian heart is richly innervated by cardiac branches of "vagosympathetic trunks" containing fibers arising from pre- and postganglionic parasympathetic and postganglionic sympathetic efferent nerves, as well as vagal sensory fibers (455). The vagal fibers are cholinergic and produce negative chronotropic and inotropic effects in both urodeles and anurans. The intrinsic neurons (that is, postganglionic vagal neurons) of the heart of *B. marinus* contain and release both ACh and somatostatin (109). Cardiac adrenergic neurons release primarily epinephrine, as in other tissues, and produce positive chronotropic and inotropic effects on the heart of anurans. However, there is no evidence for an adrenergic innervation of

the heart of urodeles (24). All chambers of the heart, including the sinus venosus and truncus arteriosus, contain mechanoreceptors, but their function has not been demonstrated (153, 367, 369, 370, 453). The spontaneous activity of both atrial and ventricular mechanoreceptors peaks during systole, but some activity may be sustained for almost the entire cardiac cycle. The cardiac mechanoreceptor afferents include both myelinated and unmyelinated elements.

Mechanoreceptors have been identified in the carotid artery or labyrinth, the aortic arch, and the pulmocutaneous artery of anuran amphibians (Fig. 4.27) (317, 318; reviewed in ref. 645). In *B. marinus,* the pulmocutaneous receptors provide the principal sensory feedback of arterial pressure to the cardiovascular centers of the medulla, with a smaller contribution arising from the aortic arch. The physiological significance of the carotid baroreceptors is at present uncertain. Pulmocutaneous mechanoreceptors and their attendant actions in anurans are presently the most extensively characterized baroreflex in nonmammalian vertebrates (Fig. 4.26).

Pulmocutaneous baroreceptors are slowly adapting and transmit their information via nonmyelinated afferents. The mean threshold pressure for baroreceptor firing (30 mm Hg) coincides with normal systolic arterial pressures (30–32 mm Hg) of conscious toads *(B. marinus).* At pressures above threshold, feedback information from baroreceptors is increased by increased firing frequency as well as recruitment of receptors whose threshold lies above the mean. The increase in firing frequency of receptors can be up to 1.7% of their maximum, which represents a sensitivity much greater than that of mammalian baroreceptors (625). Such high sensitivity is appropriate, however, because the receptors operate over a more limited range of blood pressure than do those of mammals (645).

Feedback from the pulmocutaneous baroreceptors inhibits the cardiovascular system and results in a fall in systemic pressure. A reduction of arterial pressure can occur in the absence of bradycardia, indicating that the reflex also reduces systemic peripheral vascular resistance (644). However, pulmocutaneous vascular resistance is greatly increased in response to baroreceptor stimulation (624). Presumably, the site of increased resistance is the pulmonary vasculature because 79%–92% of pulmocutaneous blood flow passes to the pulmonary artery (329). The increase in pulmocutaneous vascular resistance concomitant with a decrease in systemic vascular resistance would tend to protect the pulmonary vasculature from excess pressures transmitted by the incompletely divided circulation whenever systemic pressures are high (626, 645). When pulmocutaneous baroreceptors are denervated, increased pulmocutaneous artery pressures produce a tenfold increase in fluid filtration from the pulmonary vasculature, as well as vascular lesions in the lungs (579, 627). Considering the available data, arterial baroreflexes of anurans appear to be adapted to protect the pulmonary microcirculation while regulating the central arterial blood pressure (645). Analyses of the open-loop gain of baroreflexes studied in toads and mammals suggest that they are surprisingly similar (645). Probably the best way of comparing the barostatic reflex between vertebrates is to calculate the normalized gain (percentage change in f_H per unit change in mean arterial pressure), even though this approach has recognized limitations (340). In fact, the normalized gain for a variety of aquatic, semiaquatic, and terrestrial vertebrates is quite similar [1.9%–6.7% for sea raven (176), 1.3% for *B. marinus* (571), and 1%–5% for the lizard and 2.7%–6.9% for dog, rabbit and human (44)].

The constrictive innervation of pulmonary vasculature is cholinergic, and, at least in some species of anuran, the most important effector unit may be a distinct sphincter in the extrinsic pulmonary artery (535). Vascular resistance in the pulmonary vessels is also varied in relation to lung ventilation, and perfusion may be reflexly limited (right-to-left shunt) during periods of apnea (560).

Adrenergic fibers innervate both arterial and venous systemic vasculature, though the innervation of major arteries is somewhat less dense than that seen in reptiles and mammals (455). The systemic vasculature is constricted by epinephrine, which elevates blood pressure as a result. In addition to adrenergic vasoconstrictor innervation, major arteries in the toad *(B. marinus)* may possess a cholinergic excitatory innervation (360, 641). Vasodilation is mediated by β-adrenoceptor mechanisms (166, 448).

While the mechanisms of autonomic regulation of blood pressure are quite extensively studied in anuran amphibians, there is little evidence that blood pressure is tightly regulated. Autonomic control of the circulation seems to be quite weak in resting *Rana* and *Bufo* (80, 634). In *Bufo,* there is no adrenergic pressor tone and cholinergic cardiac inhibition is modest. Of interest is that systolic arterial pressures of toads are often correlated positively with f_H such that increases in arterial pressure are accompanied by tachycardia rather than a bradycardia predicted solely on the basis of barostatic reflexes (627). This observation has been interpreted to indicate that cardiac interval in resting animals reflects integration of many sensory inputs to the medullary cardiovascular centers and is not determined primarily by baroreflex feedback.

Activity in anurans increases both f_H and arterial

pressure, which are initially elevated by adrenergic efferents and sustained by circulating catecholamines (127, 634). At least in toads *(B. marinus)* the cardiovascular response to exercise appears to be mediated by a psychogenic as well as an autonomic reflex component (634). In these circumstances, it is not known whether barostatic reflexes are reset or, in any case, how the reflexogenic feedback is integrated with other input–output information. There appears to be neither adrenergic innervation of the heart nor adrenergic tone on the vasculature of the mudpuppy (24, 26). In the mudpuppy, the heart is controlled by a variable cholinergic tonus combined with a variable adrenergic tonus, which is probably mediated by circulating catecholamines. During exercise, arterial pressure is elevated by increased levels of circulating catecholamines, mainly norepinephrine (26). Therefore, circulatory regulation may be quite different between urodeles and anurans.

A number of studies suggest that control of gill, skin, and lung perfusion in amphibians may be, in part, reflexly controlled by peripheral or central chemoreceptor input (645). As in other vertebrates, however, the interaction of chemo- and baroreceptors in controlling blood pressure is poorly understood. Based on available information, it seems conceivable that in amphibians, as in mammals, bradycardia can result from stimulation of peripheral chemoreceptors, receptors within the upper airways, or baroreceptors (645).

Denervation of pulmocutaneous baroreceptors has demonstrated that the pulmocutaneous baroreflex is not essential for maintenance of resting arterial pressure in *B. marinus* (627). In the long term, endocrine and renal mechanisms may adjust arterial pressure via effects on vascular tone and fluid volumes independent of the baroreflexes.

Reptiles. For reasons of convenience, phylogeny, and anatomical diversity, reptiles have been the subject of numerous studies of cardiovascular dynamics and control. Like amphibians and fishes, reptiles display wide variation in levels of blood pressure attributable to species differences, environmental stresses, and nonsteady states arising from a variety of causes. Nonetheless, like mammals, some reptilian species exhibit precise control of arterial pressure.

Resting blood pressures of reptiles are generally quite stable in the absence of external disturbance but may vary with temperature, activity, or state of wakefulness (588). However, arterial pressure in resting tiger snakes *(Notechis scutatus)* does not vary significantly over a range of body temperatures at which this species is normally active, implying adjustments of peripheral resistance and/or cardiac output as f_H increases logarithmically over the same range (402). Arterial pressures usually increase with locomotor activity and may remain elevated for long periods (1–2 h) after activity ceases (404, 589) (Fig. 4.25). Activity-induced increases of arterial pressure are partly attributable to autonomic activation and partly to augmentation of venous return.

The potency of baroreflexes in squamate reptiles has been well illustrated by studies of responses to tilt, hemorrhage, and pharmacological agents. Postural disturbance during head-up tilt displaces a significant proportion of the blood volume posteriad and immediately reduces cardiac output and central arterial pressure. Partial or full recovery of pressure is achieved by reflexogenic increases in both f_H and peripheral resistance during a compensatory period in which events are basically similar to those seen in mammals (300, 400, 402).

Responses to tilt vary considerably among species of snake (Fig. 4.23). Aquatic and some ground-dwelling species are unable to maintain arterial pressure during head-up tilt, and cerebral blood flow diminishes as a result (401, 405, 557). However, arboreal species are tolerant of tilting, and arterial pressures at head level are maintained generally within 80%–100% of pretilt (horizontal) values (394; H. Lillywhite, unpublished data). Reflex activation of vascular smooth muscle is more important than either cardiac chronotropic or inotropic effects in controlling arterial pressure; indeed, pressure is regulated even though cardiac output is reduced by 50% or more (400, 402). Increases in peripheral vascular resistance occur principally in visceral organs, posterior skin, and muscle and are blocked by α-adrenoceptor antagonists (400, 402). Control of this magnitude must involve venous constrictory mechanisms as well as arteriolar vasoconstrictory mechanisms. In the elapid snake *N. scutatus*, both the magnitude and the rapidity of regulatory responses vary with temperature and the apparent optimal response occurs at preferentially selected body temperatures (402).

Qualitatively similar autonomic adjustments of f_H and peripheral vascular resistance occur when reptiles are subjected to hemorrhage (300, 577, 578). Regulation of arterial pressure during hypovolemic states is dependent on barostatic reflexes and compensatory transcapillary shifts of extravascular fluid into the circulation. Remarkable abilities to regulate arterial pressure are again illustrated by arboreal snakes, from which more than 100% of the initially measured blood volume (not subtracting compensatory fluid shift) can be withdrawn before arterial pressure falls precipitously (403). Investigations have demonstrated extensive colocalization of neuropeptides in perivascular nerves innervating larger arteries and veins of rat snakes (143). These data provide evidence for the importance of parasympathetic nerves in controlling cir-

culation, particularly the regulation of venous capacitance.

Studies of squamates show that all parts of the systemic vasculature are densely innervated by adrenergic fibers, which, in snakes, show considerable species and regional variation (149, 455). The density of adrenergic fibers innervating systemic vessels is especially high in posterior arteries and veins of arboreal snakes, which reflects the importance of adrenergic adjustments of vascular tone in postural contexts of hemodynamic regulation (149; J. Donald and H. Lillywhite, unpublished data). Catecholamines constrict vascular beds, elevate arterial and venous pressures, and are antagonized by pharmacological blockade of α-adrenoceptors (7, 43, 360, 394, 401, 402, 516). The dense innervation of veins presumably reflects their role in active regulation of venous capacity. Central venous pressures of snakes remain constant during progressive isovolemic hemorrhage, suggesting that venomotor tone is actively regulated to maintain venous return, cardiac filling (403), and hence cardiac output.

Perivascular nerves innervating the vasculature of snakes contain a variety of neuropeptides apparently associated with parasympathetic postganglionic fibers, adrenergic fibers, and afferent sensory fibers (143). The distribution of these neuropeptides suggests considerable functional specialization within the peripheral autonomic system controlling the circulation, especially the regulation of venous capacity.

The reptilian heart is innervated by vagal cholinergic inhibitory nerves that produce negative inotropic and chronotropic effects and an extensive sympathetic adrenergic excitatory innervation that promotes positive inotropic and chronotropic responses (69, 151, 263, 455). These elements innervate both atria and ventricles, as well as the adjoining inflow and outflow vessels. (Cholinergic inhibitory nerves are vagal in origin, whereas adrenergic fibers are of spinal autonomic origin.) Adrenergic effects are mediated via β-adrenoceptors, and cholinergic receptors are muscarinic in character. The hearts of some reptiles appear to be, during resting states, under the tonic influence of both cholinergic and adrenergic fibers (263, 402). Vagal stimulation can arrest the heart for very long periods, and a "vagal escape" of the sort seen in mammals is not apparent in reptiles (435). Little is known concerning the interplay of chemoreceptors in autonomic cardiovascular responses, but oxygen-sensitive receptors in the central circulation may play a role in modulating autonomic outflow to the heart (672).

As in amphibians, somatostatin is present in the heart of rat snakes *(Elaphe obsoleta),* probably in postganglionic cell bodies and axons of intrinsic parasympathetic neurons (152). Additionally, immunohistochemical studies have demonstrated the presence of substance P–like, calcitonin gene–related peptide-like, and neuropeptide Y–like immunoreactive axons in the sinus venosus, atria, and ventricles of *E. obsoleta* (152). The extensive distribution of peptides in the cardiac nerves suggests an as yet unknown cardiovascular role.

The reptilian heart is capable of enormous cardiac output variation and its respective distribution to systemic and pulmonary circuits. The most dramatic examples of such flow variation are related to intracardiac shunts that develop in relation to intermittent breathing cycles of diving species (91, 399, 562, 654). Blood flow completely bypasses the lung for variable periods when aquatic file snakes *(Acrochordus granulatus)* are submerged and resting (399). Conversely, when the lung is ventilated during intermittent bouts of air breathing, pulmonary blood flow increases dramatically and the blood pumped from the ventricle largely bypasses the systemic circulation. The reciprocating patterns of preferential cardiac outflow reflect inverse changes in vascular resistance in the two parallel (pulmonary and systemic) circuits, such that pulmonary and systemic arterial pressures remain quite constant throughout repetitive dive cycles.

Cholinergic excitation and adrenergic inhibition of vascular smooth muscle is found in the pulmonary circulation of turtles and squamates (151, 455). The extrinsic pulmonary artery is the major site of vasoconstriction in the pulmonary circuit (68) except in snakes, in which the vasoconstrictive response occurs additionally in the extrinsic and intrinsic pulmonary vasculature (151, 399). Adrenergic and cholinergic innervation is present throughout the arterial and venous vasculature in the lungs of snakes (150, 399). In addition, various pulmonary vessels are innervated by vasoactive intestinal polypeptide–like, substance P–like, and calcitonin gene–related peptide-like immunoreactive axons (151). However, there is no information on the role of these peptides in the neurogenic control of reptilian vasculature. Isolated perfusion studies found no evidence for nonadrenergic, noncholinergic (NANC) transmission to the pulmonary vasculature in snakes (151).

Reptilian baroreceptor physiology has been summarized by Berger (42). Depressor responses are elicited by stimulation of truncal nerves that terminate in the ventricle and truncus arteriosus of squamates (59, 356). Cardiac mechanoreceptors have not been studied in reptiles, but considerable attention has been paid to the truncal region and central vessels as potential baroreceptive regions. Mechanoreceptors have been localized to the proximal pulmonary artery and bulbus cordis region of the pond turtle (171, 365) and the

truncus arteriosus of lizards (44, 45) and snakes (27, 376). Both anatomical and physiological evidence also indicate that baroreceptors are located in distal segments of the aorta and pulmonary arteries, as well as truncal regions, in two species of chelonian (317). Electron-microscopic investigations of snakes have demonstrated the presence of baroreceptor-like elements in the entire circumferential wall of the truncus at locations close to the ventricle as well as the free pulmonary artery (J. Donald, unpublished data). In brief, congruences between morphological and physiological data point to the truncal region and central outflow vessels as important baroreceptive regions in the reptilian vasculature (Fig. 4.27).

Other baroreceptive regions have also been proposed, however, and it is likely that multiple receptive fields provide sensory feedback concerning pressures in the reptilian vasculature. Anatomical investigations led Boyd (59) to conclude that cardiovascular mechanoreceptors were present in distal segments of the aorta and pulmonary artery. Seymour and Barker (555) induced pressure changes in the necks of snakes using external cuffs and suggested that baroreceptors might be diffusely distributed along the length of the carotid arteries. It remains significant, however, that physiological as well as anatomical investigations have failed to show that reptiles possess reflexogenic sites homologous to the mammalian carotid sinus.

There are few studies that attempt to characterize the activity of reptilian baroreceptor afferents (27, 171, 376). Arterial baroreceptor afferents of snakes exhibit low conduction velocities (0.3–0.65 m/s) that are characteristic of unmyelinated afferent fibers (27; corrected data in ref. 376). Single- and multi-unit activities increase with increasing pressure over a physiological range of systolic pressures, and bursts of activity are essentially confined to systolic interval pressures. Kozubowski (376) suggested that while some receptors appeared to be rate-sensitive, others might provide information about the absolute level of arterial pressure (see also ref. 171).

Birds. Very little is known concerning the neural regulation of blood pressure in birds (reviews in refs. 30, 340, 590). The avian heart is innervated by vagi in a direct sympathetic fashion (455). All parts of the heart are innervated, but fiber density is greatest at the sinoatrial and AV nodes. In contrast to the situation in reptiles and mammals, there is substantial cholinergic innervation of the ventricles. The vagi mediate negative inotropic and chronotropic effects, whereas the adrenergic nerves have positive effects via β-adrenoceptor mechanisms. Despite high f_H relative to many other vertebrates, the avian heart is under substantial cholinergic (vagal) and adrenergic tonus (333, 616). Ventricular mechanoreceptors that discharge irregularly are sensitive to CO_2, which diminishes their discharge (167).

Much of the avian vasculature has dual adrenergic and cholinergic innervation, and the pressor and depressor effects of ACh and exogenous catecholamines parallel closely those seen in mammals (455). Catecholamines produce a β-adrenoceptor-mediated relaxation of vascular smooth muscle in addition to β-adrenoceptor-mediated constriction. Both cholinergic and NANC vasodilatory fibers have been implicated in the reflexogenic control of blood flow in the avian foot. Vasodilatory fibers may be dopaminergic (39). Variation of responses may reflect adaptation to environmental requirements. For example, the wall thickness and vasoconstrictive response of mesenteric arteries are considerably greater in the duck than in the chicken, features that are undoubtedly related to requirements of diving (238).

Arterial baroreceptors have been demonstrated in birds, though various workers have established that birds lack a carotid reflexogenic zone homologous to that of mammals (590). Nor is there evidence for cephalic receptors, as was sometimes postulated earlier (425). Arterial baroreceptors are present in the walls of the ascending aorta, pulmonary artery, and common carotid artery (2, 3, 336, 359, 592, 602). Increases in atrial or ventricular diastolic pressure activate receptors that reflexly cause bradycardia and hypotension, but the physiological significance of cardiac receptors is unknown (343). Injection of catecholamines transiently raises systemic, but not pulmonary, arterial pressure and causes a concomitant bradycardia (336). Some studies indicate that reflex changes in f_H are mediated by the vagus nerve and not cardioaccelerator nerves (159, 615, 668). Reflex vasoconstriction is elicited by hemorrhage, but the response varies greatly among species (148, 497).

Part of the diving bradycardia seen in ducks is attributable to a barostatic reflex in response to chemoreceptor-induced increases in peripheral resistance (341). However, studies of ducks with denervated baroceptors indicate that intact barostatic reflexes are not a requirement for most of the cardiovascular response to forced submergence (336, 342, 392). Generally, studies of ducks have shown that activation of carotid body chemoreceptors increases peripheral vascular resistance and induces bradycardia in the absence of breathing (8, 341, 344). Some two-thirds to three-fourths of diving bradycardia is attributable to stimulation of carotid chemoreceptors by hypoxia and hypercapnia (337, 341).

Walking or treadmill exercise increases blood pressure in several species of bird, particularly at higher work levels (590). In running turkeys, much of the

increased f_H associated with exercise is attributable to increased sympathetic tone, vagal control of the heart being less important (35). Hypoxia lowers blood pressure in chickens, apparently due to a direct effect on vessels (590). Flight may have little effect on blood pressure (104).

Central Neural Control of Arterial Pressure. The CNS mediates in all vertebrates a wide range of cardiovascular responses, including those that accompany arousal, emotions, and cognitive functions. Many of these responses are acute, such as defense reactions involving tachycardia and elevation of blood pressure. Centrally mediated cardiovascular responses to a range of external sensory stimuli are probably universal among vertebrates. Central nervous mechanisms in mammals can suppress baroreceptor reflex responses during exercise (411, 423), and there is some evidence that the brain can alter the long-term set-point around which arterial pressure is controlled or stabilized (40, 348a).

In a comparative context, few generalizations regarding central mechanisms in arterial pressure regulation are possible because of the paucity of comparative literature in this area. The CNS clearly is important for central integration and the provision of sustained sympathetic output that is essential to the maintenance of peripheral vascular tone and cardiac output. If vascular sympathetic tone is absent, reflexogenic controllers cannot effectively stabilize pressure on a moment-to-moment basis. There is no evidence, however, that the CNS can detect changes of arterial pressure independent of baroreceptor mechanisms unless the central pressure decreases to levels below the cerebral autoregulatory range, thereby inducing the ischemic sympathetic discharge demonstrated in mammals. However, bradycardia associated with spontaneous activity in lingcod slightly precedes the start of the activity, suggesting an anticipatory response (173).

Blood Volume and Its Regulation

Despite the importance of barostatic reflexes to short-term regulation of arterial pressure, it is increasingly clear from studies of various vertebrates that these mechanisms may not be crucial to the long-term homeostasis of blood pressure (130, 392, 466, 627). While the nervous system is certainly involved with chronic adjustments of arterial pressure, the factor of prevailing importance is the adjustment of body fluid volumes that depend on the loss or intake of water and osmolytes. There is thus a functional coupling between mechanisms of arterial pressure control and osmoregulation. Space does not permit a thorough discussion of all factors that determine the volumes and distribution of body fluids. However, in general principle, the total fluid volume and its compartmental distribution remain within narrow limits relative to daily exchanges of water and solutes.

Measurements of whole blood volume in vertebrates range typically from a few percent to slightly over 10% of body mass. Few generalizations are possible concerning the variation. The smallest blood volumes are reported to occur in certain teleosts (1.2%), while the largest occur in cyclostomes (16.9%) and some diving mammals (15%–20%) (181). Therefore, variation among fishes nearly equals that among vertebrates, generally. There is also wide variation of blood volume among marine snakes, with a range from 3.9% in a sea snake to 13.3% in the file snake, *A. granulatus* (262, 401, 406). In other reptiles as well as amphibians, blood volume ranges generally from 5%–7%. Blood volumes in nondiving birds and mammals usually range from 7%–10% and are somewhat smaller than those found in some diving species (580). All of these measurements are presumed to reflect steady-state conditions but are, of course, subject to variation depending on hydration state, activity, hibernation, and other factors.

Regulation of the blood volume is dependent largely on the transcapillary fluid equilibrium determined by prevailing gradients of osmotic, oncotic, and hydrostatic pressures. However, there are no known mechanisms to detect the blood volume per se. None of the body fluid compartments is regulated in the sense that receptors exist to detect the absolute volume of fluid in these spaces (130). The mechanoreceptors at various locations in the circulation detect volume only in the sense that filling pressures stress the containing wall in relation to the ratio of filling volume to vascular compliance. Thus, blood volume, vascular compliance, and arterial pressure are related and cannot be considered separately. Physiologically, the proportion of filling volume that does not stress the vascular wall is undetected by known vascular receptors and, thus, is inert to hemodynamic control systems.

A variety of receptors have been identified within mammalian atria and veins whose afferent activity affects numerous neural and endocrine mechanisms affecting salt and water excretion. Receptors located in low-pressure regions on the venous side of the circulation are best suited to detect changes in the degree of filling of the circulation. (The venous system, in addition to low pressure, has vessels that are thin-walled and very compliant and contains the majority of the blood volume.) Afferent fibers innervating those regions of mammals respond to relatively small changes in pressure on the order of 1–2 cm of water (606). The responses of these receptors to volume expansion

with consequent stimulation of sensory afferents include reductions in renal sympathetic nerve activity, secretion of arginine vasopressin, and reduced activity of the renin-angiotensin-aldosterone system. These mechanisms have been thoroughly described in mammals (130) but are less well characterized in other vertebrates, especially with respect to the afferent limb of the reflex.

Renal Sympathetic Nerve Responses. Limited published information suggests that vertebrate kidneys are under both nervous and endocrine control. Innervation of the kidneys, which in mammals is exclusively sympathetic (33), provides a major link by which variations in blood volume and pressure can signal changes in renal excretion. Increased efferent nerve activity can elicit renal vasoconstriction, which in turn severely reduces renal blood flow. These responses are mediated by α-adrenoceptors, which occur on both afferent and efferent arterioles in mammals. Despite the existence of these pathways, the relevance of barostatic reflexes in the regulation of renal nerve activity and the physiological role of neurogenic renal control have been difficult to establish. Studies suggest that the principal function of mammalian renal nerves is the achievement of rapid (reflexogenic) short-term adjustments of water and sodium excretion analogous to stabilization of arterial pressure by baroreceptors (130). This view is supported by the fact that mammals, including humans, deprived of renal nerves can survive without long-term impairment of sodium and water balance.

Neural regulation of glomerular filtration may be of physiological importance in amphibians, fishes, and reptiles (133). Pang et al. (478) suggested that such neural influence is probably absent in fishes, achieved prominence in early tetrapods, then declined in importance as hormonal controls became more complete in advanced tetrapods [for example, the evolution of antidiuretic actions of arginine vasotocin (AVT)].

Endocrine and Other Factors Affecting Hemodynamics and Blood Volume. Various endocrines are involved in complex controls of water and solute balance, coupled to blood volume through direct pressor–depressor actions and baroreflexes. The afferent limbs of such reflexes are well studied only in mammals, where patterns of action are still subject to many unresolved questions. Low-pressure baroreceptors in atria and veins are almost totally unstudied in nonmammalian vertebrates.

Neurohypophyseal and other peptides. Arginine vasopressin (AVP), the mammalian antidiuretic hormone, promotes retention of water at the level of the kidney, and its physiological importance to direct effects on blood pressure is secondary. It is well established that secretion of AVP decreases in response to stretch of the atrium in dogs, in which reflex changes in plasma AVP concentrations are highly correlated with left atrial pressure (506). The release of AVP is less sensitive to atrial stretch receptors than to changes in blood osmolality, however, and may vary with species (130).

The octapeptide AVT, which is chemically similar to AVP, is the most primitive and ubiquitous of the neurohypophyseal peptides. It is found in the neurohypophysis of all nonmammalian vertebrates and fetal mammals (240). Except in the cyclostomes, other neutral peptides are present as well. AVT is vasoactive, and its primitive physiological role is thought to be related to control of blood pressure (546). As in mammals, neurohypophyseal peptides of nonmammalian tetrapods promote water conservation, and AVT is the more potent factor relative to mesotocin (MST) or oxytocin (OXY). AVT has both vasopressor and antidiuretic effects in most tetrapods but has vasopressor and diuretic effects in teleosts and lungfishes (113, 477). In fishes, osmoregulatory effects of AVT acting at the gills may also have importance for volume regulation.

AVT causes diuresis in freshwater fishes, though some species exhibit an antidiuretic effect at low doses (270). The renal effects of this hormone are variable and dependent on dose. In general, the role of neurohypophyseal peptides in water balance and volume regulation of fishes is unclear. Other hormones, for example prolactin, are also important to osmoregulation of fishes.

The actions of AVT are better studied in amphibians, in which the hormone causes pressor responses and antidiuresis (618). The renal effect is attributable largely to a reduction in glomerular filtration rate (GFR) due to vasoconstriction of afferent arterioles, which are more sensitive to the peptide than to the vasculature peripheral to the kidneys. AVT also increases tubular reabsorption of water (41). The effects of AVT are most pronounced in terrestrial amphibians, in which it also affects permeability of skin and bladder (564a). As a consequence of these several effects, dehydration and attendant decrease of body fluid volumes elicit in terrestrial species a "water balance response" (or Brunn effect) in which excretion of water is decreased while water is reabsorbed from the bladder (an important water store) and taken up more rapidly from the environment. MST apparently causes vasodilation and produces depressor effects, the significance of which is not understood. Other hormones, such as prolactin, insulin, catecholamines, aldosterone, and other peptides, also affect amphibian osmoregulation (58).

The neurohypophyseal octapeptides AVT and MST are present in reptiles and birds and appear to have physiological roles in regulating water reabsorption (518). Both OXY and MST have demonstrated depressor effects in crocodilians and squamates, while OXY has a pressor effect in turtles. Both OXY and AVT are antidiuretic in birds, but the effects of AVT are more potent. OXY is the more effective depressor agent, however. The physiological importance of cardiovascular actions is questionable, and the role of octapeptide hormones is quite variable among avian species (461). In general, the renal effects of neurohypophyseal peptides in reptiles and birds are similar to those of mammals in that antidiuresis results from water reabsorption in kidney tubules. An additional action of decreased GFR appears to be characteristic in reptiles (133).

Many teleost fishes have neurosecretory cells located in the spinal cord near the caudal vertebrae, with axonal projections to a well-developed neurohemal organ, the urophysis, located in the ventral midline. Such neurosecretory cells are diffuse in elasmobranchs and lacking altogether in cyclostomes, dipnoan lungfishes, and tetrapods. The urophysis secretes a number of peptides, called "urotensins," that appear to control osmoregulation and have pharmacological actions that increase blood pressure.

The importance of neuropeptides (bioactive peptides of about four to 40 amino acids and present in autonomic neurons as well as in neurons of the CNS) in cardiovascular control is rapidly gaining acceptance. Immunohistochemical techniques have revealed a variety of peptides within autonomic and afferent sensory perivascular nerves, often in coexistence with classical autonomic transmitters (229). Particular combinations of these neurotransmitter substances may "code" anatomically and functionally distinct populations of neurons in specific neural pathways, enabling a population of neurons to be subdivided on the basis of their transmitter complement and innervation target (222). Despite increasingly broad and detailed knowledge of the existence and colocalization of neuropeptides, there is little information regarding their functional roles in cardiovascular regulation. Nilsson and Holmgren (457) have reviewed the known cardiovascular actions in fishes. What emerges is that vasoactive intestinal peptides (VIP), bombesin, and substance P display vasoactivity in a variety of organs, but particularly mesenteric ones, in dogfish and several teleost fishes. Other studies have suggested considerable functional specialization within peptidergic innervation of both the heart and peripheral autonomic system of amphibians and reptiles (see ref. 143 and references therein). The present knowledge of the morphological distribution of neuropeptides suggests that they may be important in regulation of central cardiovascular shunts, blood flow distribution, arterial pressure, and venous capacitance.

Renin-angiotensin system. The renin-angiotensin system (RAS) is present in all vertebrates except cyclostomes and elasmobranchs. Its role in maintenance of salt and water balance has received considerable attention, but the majority of experiments have been conducted in mammals. Numerous reviews of the structure, function, and evolution of the RAS are available (21, 160, 416, 459, 460, 468, 484), and only salient features related to blood volume and pressures are given here.

The principal components of the RAS consist of a specific proteinase, renin, which hydrolyzes the decapeptide angiotensin I (ANG I) from the globulin angiotensinogen. Angiotensin-converting enzyme then hydrolyzes the carboxyl terminal end of ANG I to produce a dipeptide, ANG II, which has potent vascular, renal, adrenal, and other actions. ANG I is largely biologically inactive, while a third angiotensin, ANG III, sometimes produced in mammals, is less vasoactive than ANG II. Angiotensins can be inactivated by a variety of peptidases. Renin circulates in plasma or is bound to membranes, where it may have endocrine, paracrine, or autocrine functions. Messenger RNAs for renin and angiotensinogen have been identified in brain, heart, vascular, adrenal, and other tissues in addition to the kidney, which suggests the operation of local RASs (422).

The end product of renin secretion, ANG II, is a potent hormone involved not only with salt and water balance but also with the control of blood pressure secondary to changes in volume of the fluid compartments. Additionally, ANG II is a potent vasoconstrictor in all groups of vertebrates and directly affects blood pressure through its action on the vasculature. The role of ANG II in the maintenance of blood pressure in fish is demonstrated by drops in pressure following administration of angiotensin-converting enzyme inhibitors (466). In agnathans and elasmobranchs, the pressor responses of ANG II are mediated by a phentolamine-sensitive catecholamine release, whereas in lungfishes and a variety of teleosts only a fraction of the pressor response to ANG II is mediated by catecholamines (466). In turtles, pressor responses are shown to include a catecholamine-dependent component as well as direct vascular receptors sensitive to ANG II (585, 674). ANG II has a biphasic action in birds, wherein pressor actions appear to be related to secondary release of catecholamines and the direct effect of ANG II may be depressor. ANG II can be vasodilatory in vitro in birds and mammals, but the mechanisms appear to differ. Vascular relaxations mediated by ANG II involve cyclooxygenase/prostaglan-

din pathways, whereas those of the fowl aorta involve nitric oxide release and are not dependent on prostanoids (670). Nonetheless, the RAS is primarily a vasoactive system, and some have suggested that it evolved in response to a disturbance of homeostatic mechanisms regulating blood pressure.

In addition to direct vascular actions, ANG II has a physiological role in regulating AVP release and produces central nervous effects on blood pressure in mammals. ANG II elicits drinking and salt intake, influences tubular sodium reabsorption, and acts directly on the adrenal gland to stimulate release of aldosterone, an important mediator of sodium and water balance in mammals. There is also strong evidence for a brain RAS and many central neurons that respond to ANG II in mammals. ANG II stimulates secretion of adrenal corticosterone in turtles (538) and may have a role in sodium balance in these reptiles. Amphibians are not stimulated to drink by ANG II, but the hormone regulates behavioral water absorption responses (299), which are a functional parallel to the control of drinking in other vertebrates, including fish (421).

Mammalian studies have established that plasma renin activity and circulating ANG II are controlled partly by volume changes in atria attributable to variations in central venous filling pressures. Cardiac reflexes involving atrial stretch receptors are shown to be important in controlling renal sympathetic nerve activity, but these do not regulate renin–ANG II levels alone. Although high circulating levels of ANG II can reduce GFR, the role of the hormone in regulating GFR remains to be clarified. ANG II can stimulate prostaglandin synthesis in isolated glomeruli (549), so the constrictive actions of the peptide could be attenuated by the dilatative effects of the prostaglandins (or by nitric oxide release).

Hemorrhage and hypotension are potent stimulators of renin release in several mammals and in both birds and fish (466). In freshwater turtles, however, severe hypotension does not affect blood plasma levels of renin. Unlike other vertebrates studied, it may be inferred that turtles lack baroreceptors that control renin release, implying that the RAS does not function directly in the regulation of blood pressure in this animal (118).

Actions of the RAS are powerful, making this appear to be one of the more important hormonal systems in the long-term modulation of renal function and hemodynamics in mammals. Given the inherent complexity of the system (and its interacting modulators), much further research is needed to understand its role in the hemodynamics of other vertebrates which have been far less intensively studied than mammals.

Paracrine, Autocrine, and Other Factors Influencing Hemodynamics. Numerous factors other than classically studied hormones affect the circulatory system and are potentially quite important to the control of pressure and volume. In most cases, these have been discovered and studied most intensively in mammals. The following is a brief account of some of the more important factors that are likely to prove significant in vertebrate circulatory function generally.

Atrial natriuretic factor. This family of peptides is secreted primarily by atrial myocytes in response to local wall stress (increased intraatrial volume) and evidently is present in all vertebrates (reviewed in refs. 64, 115). Atrial natriuretic factor (ANF) has combined actions on vasculature, kidney, and adrenals which serve both acutely and chronically to reduce systemic arterial pressure and intravascular volume. Arterial pressure is reduced partly by direct relaxation of vascular smooth muscle and partly by diminished cardiac output. The active peptide also increases renal papillary blood flow, inhibits sodium transport in tubular epithelium, suppresses renal sympathetic nerve activity and renin secretion, blocks renal actions of ANG II, and inhibits biosynthesis of aldosterone, thereby inducing both diuresis and natriuresis.

Investigation of ANF (cardiac peptides) in nonmammalian vertebrates is producing an emerging picture of these hormones as present in all vertebrate classes and as playing an important role in various aspects of fluid and cardiovascular homeostasis. ANF has been shown to be vasoactive and natriuretic in fish, which have been most intensively studied among the groups of nonmammalian vertebrates (168, 169, 466). In rainbow trout, continuous infusion of ANP lowers blood volume and extracellular fluid volume to different degrees. Hypotension is the most common response to ANP infusion in dogfish and various teleost species. ANP relaxes isolated vessels from hagfish, elasmobranchs, and teleosts. ANP does not, however, affect cardiac function in perfused trout hearts, so the observed tachycardia with ANP infusion may simply reflect a barostatic reflex. The mechanism of ANF release from the perfused trout heart has been studied (A. Cousins and A. P. Farrell, unpublished observations). The majority of ANF is located in the atrium, and, as in mammals, the rate of release is dependent upon the degree of filling of the atrium (as induced by increased filling pressure). The rate of ANF release can increase threefold over the basal rate and be maintained at the elevated rate for several hours.

ANF has been characterized in both atria and the ventricle of anurans and may have a role in the production and secretion of corticosteroids (390). ANF in freshwater turtles has vasodepressive effects similar to

those observed in mammals and birds but apparently no effect on renal function (117). These findings suggest that the ANF peptide in turtles is more important in cardiovascular regulation than in controlling renal function. However, prolonged anoxic dives by freshwater turtles appear to induce a diuresis that might be secondary to increased ANF concentrations found in the blood plasma (29).

Release of ANF from mammalian atria is transient and rapidly attenuated, but repetitive stimulation can lead to sustained elevations of plasma ANF (130). Thus, prolonged expansion of the blood volume with attendant increases in atrial filling pressures can produce sustained elevations of plasma ANF. As discussed above, baroreceptor reflexes exhibit rapid resetting and therefore are unlikely to provide a sustained mechanism effective in long-term control of blood pressure. ANF, however, may prove to be an important controller in the long-term regulation of blood volume and arterial pressure due to the apparent nonadaptive nature of stretch receptor mechanisms of cardiac myocytes (130). Several studies have suggested that ANF participates in the long-term regulation of arterial pressure (244, 435, 482). This involvement must, however, be through volume effects since ANF release is in response to atrial stretch rather than changes of arterial pressure.

Unidentified natriuretic factors are suspected to be released from mammalian atrial tissue. It can be expected that novel cardiac peptides will be isolated from cardiac myocytes and endothelial and smooth muscle cells and subject to release upon stretch of the tissue. The integrative roles of these factors, if any, need to be investigated.

Eicosanoids. Prostaglandins and leukotrienes are derived from fatty acid substrates and produced in cells and tissues rather than endocrine organs. These compounds have many physiological actions and affect the cardiovascular system of vertebrates. Various prostaglandins increase or decrease blood pressure in various species and in various tissues. Prostaglandin I_2 (PGI_2) is a potent systematic vasodilator in many mammals, while $PGF_{2\alpha}$ is the most potent vasoconstrictor in some, but not all, mammalian species. Whether prostaglandins increase or decrease blood pressure, they always increase f_H in vivo. Studies of bullfrogs suggest that synthesis of prostaglandins differs depending on acclimation temperature (275). Moreover, the pressor and depressive effects of $PGF_{2\alpha}$ and PGI_2 are weakened at low temperatures, and neither factor increases f_H in cold-acclimated (5°C) frogs (275). These findings suggest that receptor sensitivity to prostaglandins is diminished at low temperatures. In fish, PGI_2 enhances inotropy of atria (6), while $PGF_{2\alpha}$ is a very potent vasoconstrictor of coronary arteries from rainbow trout (569), long-nosed skate *(Raja nasuta)* (182), and mako shark *(Isurus oxyrinchus)* (183).

Sulfidopeptide leukotrienes decrease blood pressure while increasing f_H in amphibians (274). As with prostaglandins, the cardiovascular effects of these eicosanoids are blunted at lower temperatures. Leukotrienes are capable of contracting vascular smooth muscle and increasing vascular permeability in mammals.

Endothelium-derived factors. Mammalian studies have demonstrated the release of vasoactive substances from endothelial cells that diffuse to the underlying smooth muscle (256). Such substances include numerous peptides and produce vasoconstrictive or vasodilatory effects. Endothelium-derived relaxing factors (EDRFs), including prostaglandins and nitric oxide, have been demonstrated in all vertebrate classes and can be released by ACh or the calcium ionophore A23187 (432). Endothelium-derived contraction factors (EDCFs), including endothelins, also are probably ubiquitous among the vertebrate classes (498). The localization and physiological significance of these substances in the regulation of vascular tone remain to be elucidated in mammals, as well as in other vertebrates. Fish vasculature is sensitive to endothelins (ET-1) (467, 498), but nonprostanoid EDRFs apparently are not present in trout vessels (432, 469).

Parathyroid hormone. Parathyroid hormone (PTH) reduces blood pressure in all vertebrates, apparently due to direct vasodilatory effects (479). Responses of various groups of vertebrates are not similar, however. PTH has positive inotropic and chronotropic effects on isolated atria of bullfrogs (274).

Other factors. Various autocrine or paracrine factors are present in cells and affect the vertebrate cardiovascular system. Histamine is released from injured tissues and has variable vasomotor actions in different taxa and species. It relaxes arterioles and constricts venules when sympathetic tone is absent in skeletal muscle. Vasomotor actions vary with species, but these results must be considered in relation to variable doses used in the different investigations (for example, ref. 507). Serotonin produces vasoconstriction following vascular injury but also dilates arterioles, affects adrenergic neurotransmission, and produces variable pressor and depressive effects in vivo.

Coronary responses to histamine, bradykinin, and serotonin were either weak or absent in the rainbow trout, skate, and mako shark (137, 138, 569). In contrast, serotonin produces marked constriction of the branchial circulation in Atlantic cod and eel, resulting in increases and decreases, respectively, in ventral and dorsal aortic blood pressures (456). Constrictions of coronary arteries were commonly observed with vari-

ous purinergic agents [adenosine, ATP, and adenosine diphosphate (ADP)] in teleosts and elasmobranchs (138), though high concentrations of ADP and ATP produced relaxation in elasmobranchs. ATP produces systemic vasoconstriction in rainbow trout (663), but adenosine is without effect (125). Adenosine dilates the branchial vasculature of *M. glutinosa* (20) but constricts the branchial vasculature of rainbow trout (125).

Numerous regulatory peptides having vascular or cardiac effects have been described from autonomic nerves or endocrine cells of all vertebrate groups (456). There is also evidence that plasma of all vertebrate groups contains components of the kallikrein-kinin system found in mammals (126, 466). Bradykinin or kinin peptides have pressor or depressive actions in various species and may have physiological importance in the regulation of cardiovascular functions. These conclusions are tentative, however, and further work is required to elucidate the significance of such peptides in vertebrate circulatory systems. Evidence suggests that kinins formed in the mammalian kidney influence tubular reabsorption by modifying papillary blood flow (525).

In mammals, a circulating factor, related to or identified as ouabain, increases peripheral resistance and elevates arterial pressure during acute blood volume expansion (130). Studies in rats indicate that the factor is independent of central neural control (including neurally mediated release of factors from the CNS) (296). Other new or novel factors no doubt remain to be discovered and their physiological role or significance elucidated in various vertebrates.

Integrative Responses to Blood Volume Changes. Responses to hypo- or hypervolemia have been investigated in a number of vertebrates. Hypervolemic states have been useful as a means to elucidate excretory mechanisms and are problematic for freshwater vertebrates, especially amphibians. However, depletion of blood and body fluid volumes is the more common natural perturbance for most species in terrestrial (dehydration through evaporation) and marine (dehydration through osmotic imbalance) environments.

Acute hypovolemia is conveniently studied by experimental hemorrhage, which elicits a suite of physiological responses that arise in the interest of maintaining or restoring tissue perfusion. Short-term volume restitution is accomplished by absorption of fluid from interstitial or intracellular compartments and is generally the major determinant of survival. Reflex adjustments of cardiac performance and vascular tone maintain perfusion pressure during transient hypovolemic states. Long-term recovery involves adjustments in water and osmotic balance and replacement of plasma cells and proteins.

Both tolerance and responses to hemorrhage vary considerably among vertebrates. Mammals generally are less tolerant of blood loss than are other vertebrates. Fish (157), amphibians (288, 429, 658), reptiles (397, 403, 577, 578), and birds (148, 375, 548) can withstand a greater degree of hemorrhage and mobilize compensatory fluid more rapidly than mammals. Snakes, for example, are especially tolerant and can withstand acute volume depletion exceeding their initial blood volume without significant loss of arterial pressure (403). Responses may show marked species variation, however. Whereas trout withstand volume depletion similarly to snakes (157), bluefish are more like mammals and do not survive 27% blood loss (465).

The single most important factor to survival of hemorrhage is restoration of the circulating fluid volume and, ultimately, blood pressure. The source of fluids that are mobilized may differ quantitatively in different species. Thus, lymph mobilization is important in amphibians and venous and splenic blood stores are important in trout, both according to their volume and lability. Transcapillary absorption of interstitial fluid is probably an important route in all vertebrates. It may account for all of the fluid restoration during acute recovery of large hemorrhaged volumes in reptiles which appear to have comparatively large interstitial compartments (577, 578). The contributions of lymph (which may be considered as part of the interstitial volume) to hypovolemic recovery in reptiles is presently unknown but likely to be substantial. Intracellular water is mobilized in a variety of vertebrates and may be coupled to an increase in plasma glucose (some mammals, birds) or plasma ions (some fish, amphibians).

Recovery of plasma volume is assisted by the restoration of plasma protein, which can be accomplished by direct absorption across the capillary wall or by lymph return. Posthemorrhage decreases in the reflection coefficient appear to assist volume recovery in the dog (32) and perhaps trout (157).

The hypovolemic unloading of baroreceptors activates sympathetic reflexes that are expressed as improved cardiac output, increased peripheral resistance, and constriction of the capacitance vessels. There is evidence that in trout blood flow decreases to less vital organs to insure adequate perfusion of more critical tissues (157). There is also evidence in amphibians for perfusion redistribution with hypovolemic and dehydrational stress (287). These reflex cardiovascular adjustments affect not only arterial pressure but also the intracapillary pressures which can be regulated in the

interest of fluid reabsorption. In mammals, ducks, some fish, and probably snakes, reflex vasoconstriction tends to maintain arterial pressure while increasing the pre- to postcapillary resistance ratio, which in turn lowers intracapillary pressures. Secondary activation of β-adrenoceptors interacts with a concomitant α-adrenergic constrictor influence to relax precapillary sphincter vessels, leading to an increase in capillary surface area available for fluid exchange (252, 281, 412). The absorption process is further facilitated by a relatively more pronounced dilator interaction in post- than in precapillary resistance, which decreases capillary pressures. These mechanisms preferentially occur in skeletal muscle, which contains a large fluid reservoir, especially in the duck. The microvascular effects in skeletal muscle evoked by β_2-adrenoceptors are to some extent neurally mediated but largely accountable to catecholamines released from the adrenal medulla. The latter were shown to account for about 70% of the cumulative fluid absorption from skeletal muscle to blood (280, 282).

Reflex vasoconstriction coupled with β-adrenergic control of microvasculature favors fluid volume restoration with concomitant regulation of arterial pressure; that is, arterial pressure is maintained by vasomotor tone in the face of decreased cardiac output. An alternative mechanism that allows rapid restoration of blood volume independent of increased peripheral adrenergic control is seen in some species [for example, chicken (496), bluefish (465), probably some snakes and turtles (401, 577)]. The fall of arterial pressure which would occur with hemorrhage is argued to allow rapid volume absorption and restoration of cardiac output (157). It is not possible to say at present which response to hemorrhage is the more effective, especially in view of species variability in capillary permeability. It has been argued that a fall in arterial pressure is usually "less efficient" because precapillary autoregulation tends to minimize the fall in capillary pressure if there is no reflex adjustment of the resistance vessels (148, 463). Evidently, considerable hemorrhage tolerance and blood volume regulation can be achieved by either mechanism in different species.

Amphibians are interesting with respect to volume control because rapid increases and decreases of blood volume are natural stresses in aquatic and terrestrial environments, respectively. Amphibians exhibit rapid responses and interspecific variation in their capacity to compensate for volume stress, though generally their tolerance for stress and abilities to regulate volume are very great. Hypervolemic stress appears to be compensated primarily by transcapillary filtration into lymphatic spaces which are generally capacious, especially in anurans (564a). Renal compensation during acute responses, mediated by pressure diuresis and hormones, is secondarily important. Of course, production of dilute, voluminous urine is essential to long-term volume control.

The primary mechanism important to restoration of blood volume in hypovolemic states appears to be lymphatic mobilization assisted by increased lymph heart activity, while transcapillary shifts may be secondary (37, 285). Dilute bladder water is also mobilized by hormonally induced changes of permeability and osmotic reabsorption. Data from anurans indicate that loss of plasma volume during uncompensated dehydration stress is the principal factor diminishing cardiac output, while reflexogenic vasoconstriction may reduce blood flow secondarily (285). Studies of amphibians suggest that cardiovascular transport is the rate-limiting step to maximal oxygen consumption; therefore, blood volume regulation can be an important physiological adaptation affecting aerobic capacity (657). This is certainly thought to be the case in human athletes.

Environmental challenges and the activities of vertebrates produce variation in blood volume and a rather common occurrence of non-steady states. Activity, for example, enhances transcapillary filtration of plasma from the vascular compartment to interstitial space (55, 404, 614). Measurements indicate that blood volume can be reduced 20%–25% during locomotor activity in snakes (Fig. 4.25), which reinforces the inference that these animals possess a compliant extravascular space and a blood volume that is potentially quite labile (404). Postural edema due to gravity-driven capillary filtration is another behavioral circumstance that potentially leads to transient changes in circulating blood volume (393). Clearly, variations in capillary permeability and Starling forces affecting transcapillary fluid equilibria may promote considerable variability in the moment-to-moment fluid distribution between the vascular and extravascular fluid compartments of lower vertebrates.

Autoregulation. Stabilization of arterial pressure by rapid reflex mechanisms following acute changes in blood volume may result in temporarily inadequate or excess perfusion of tissues. Regional tissue perfusion is adjusted, however, by local (autoregulatory) vasomotor adjustments appropriate to the local requirements (334, 377). Adjustments of vascular arteriolar tone are attributable to either myogenic (pressure) or metabolic signals. It appears that changes of vascular tone with reductions of blood volume are best explained by metabolic theory (131), though either mechanism may be operative in different circumstances (130). Both large and small arteries can exhibit increased active tone in

response to elevations of transmural pressure. Various vasodilatory or constrictive substances are produced by endothelial cells, including nitric oxide, adenosine, ammonia, EDRF (vasodilatory), eicosanoids, endothelin or other peptides, and serotonin (vasoconstrictive). Considerations of mechanisms for release of endothelial factors suggest that vascular smooth muscle and endothelial cells are sensitive to shear stress and may possess stretch-activated or shear-stress-activated ion channels (383, 449, 551). The significance of these considerations is the emerging concept that both pressure and flow can directly signal responses in vasculature.

The cumulative effects of local autoregulation have been termed "whole-body autoregulation" and theoretically lead to constancy of blood flow (cardiac output) in the face of changes in arterial pressure (129, 253). The systemic circulation of rats possesses considerable autoregulatory capacity during blood volume reduction and expansion (294, 295). While these local mechanisms help to ensure adequate perfusion of tissue in relation to local requirements, their effects on arterial pressure and blood volume regulation must be considered together with other modulators, such as nerves and hormones.

The systemic vasculature also responds to long-term changes in blood volume, pressure, and tissue perfusion by structural changes involving medial wall hypertrophy and/or reductions of microvessel density (rarefaction). There is evidence that such structural changes are mediated by local signals rather than by circulating factors (129).

Autoregulation has been preferentially studied and is best understood in mammals. The potential for autoregulatory phenomena in lower vertebrates clearly exists, but this topic has received very little attention. One clear and emerging distinction between fish and mammals is the role of endothelium-derived factors. Whereas endothelin is a potent vasoconstrictor in fish, no prostanoid EDRFs have been found to date in fish. Autoregulation in response to PO_2, pH, and myogenic stimuli were tested in the isolated tail muscle of the ocean pout, *Macrozoarces americanus* (110). Changes in PO_2 and vascular compression to stimulate myogenic mechanisms were both without effect. However, acidosis produced vasodilation, a response consistent with the predominantly white muscle mass that comprises the tail of this fish. Whether other autoregulatory mechanisms exist in the red muscle of fish and account for the profound increase in red muscle blood flow during swimming is unknown.

The systemic vasculature also responds to long-term changes in blood volume, pressure, and tissue perfusion by structural changes involving medial wall hypertrophy and/or reductions of microvessel density (rarefaction). There is evidence that such structural changes are mediated by local signals rather than by circulating factors (129).

Long-Term Regulation of Blood Volume. Clearly, mechanisms exist for regulating blood volume in all vertebrates, and numerous studies have demonstrated short-term compensatory adjustments of volume in a range of vertebrate species. To our knowledge, there is not a single study that has been devoted to long-term blood volume regulation in nonmammalian vertebrates, though this topic has been a matter of intensive investigation in mammals.

Cowley (130) has provided an excellent review of long-term control of arterial pressure and blood volume in mammals. He concludes that a growing body of evidence supports the renal pressure–diuresis volume regulation hypothesis for long-term control of arterial pressure, which reflects the coupling between renal excretory function, blood volume, and arterial pressure regulation. The ability of the nervous system to control arterial pressure is limited to the detection and reflex correction of rapid short-term changes of arterial pressure. Clearly, the nervous system is one of many factors that influence the long-term level of steady-state pressure, but there is no evidence that the CNS detects information over sustained periods whereby it could provide adequate long-term normalization of relevant error signals. However, "the integrating nature of a pressure-driven volume control system endows it with the capability of potentially serving as a continuously operating, nonadaptive, long-term controller of arterial pressure" (130). Long-term control of arterial pressure is coupled to the regulation of body fluid volume, but there is no direct long-term relationship between total blood volume and arterial pressure. The level of arterial pressure is related to the stressed blood volume, the requirements for tissue perfusion, and the hydraulic requirements of the kidney for maintenance of fluid balance. Arterial pressure is influenced by the blood volume only in relation to cardiac output and the interaction of regional autoregulatory responses and neural and hormonal control systems required to sustain adequate tissue perfusion and an optimal distribution of body fluids (Fig. 4.28).

Much further research is required before we can expect to enhance our understanding of blood volume regulation in nonmammalian vertebrates and the evolutionary development of control mechanisms present in mammals and humans. Increasing attention should be paid to neural and endocrine control systems and their interactions with blood pressure–regulating systems, especially with regard to long-term homeostasis. The

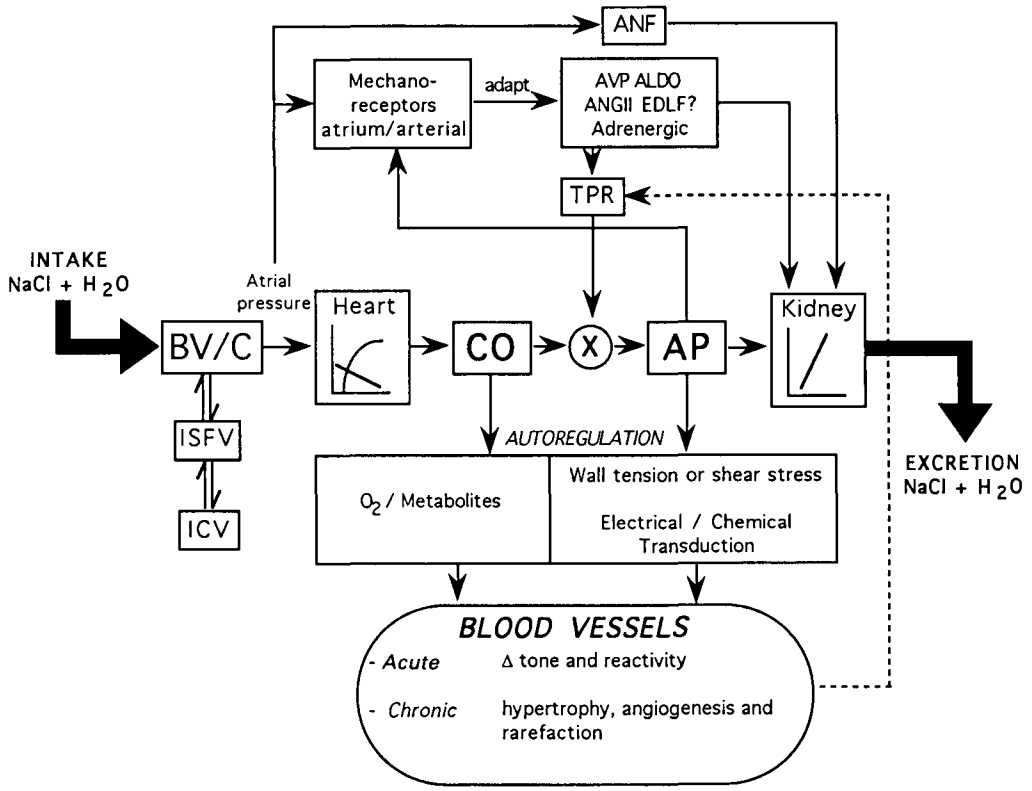

FIG. 4.28. Schematic representing NaCl and H_2O intake and excretion. Renal excretion determined by arterial pressure *(AP)* and modulated by neural and endocrine factors. Resetting of reflex control systems regulating total peripheral resistance *(TPR)* and renal excretion is indicated *(adapt)* to emphasize short-term role of these systems. Arterial pressure provides a continuous nonadaptive signal to kidney to maintain sodium and water balance. *Bottom:* Influence of changes of blood volume *(BV)* and/or vascular compliance *(C)* with resulting changes of cardiac output *(CO)* and/or arterial pressure on blood vessels and vascular resistance *(TPR)* of systemic circulation. Venous return–cardiac output (*Heart* box) and pressure–natriuresis (*Kidney* box) relationships are indicated. *ALDO,* aldosterone; *ANF,* atrial natriuretic factor; *ANG II,* angiotensin II; *AVP,* arginine vasopressin; *EDLF,* endogenous digitalis-like factor; *ICV,* intracellular volume; *ISFV,* interstitial fluid volume (from ref. 130).

concept of "normal" steady states, still prevalent in the context of mammalian studies, will have to be modified to accommodate considerations of non-steady (transitional) states, variation in body temperature, and physiological changes associated with dormancy, reproductive status, or other conditions related to season and environment.

CARDIOVASCULAR PERFORMANCE UNDER SPECIAL CONDITIONS

Aerobic Exercise

Aerobic exercise increases the demand placed on the internal O_2 convection system. Whereas O_2 consumption can increase ten to twenty times, changes in cardiac output can be much lower because tissue O_2 extraction also increases. In fact, in many instances the increases in tissue O_2 extraction and cardiac output contribute approximately equally to increased O_2 transport to the tissues. An additional response is the preferential distribution of blood flow to the working skeletal muscles. The control of these various responses is not fully understood, especially for lower vertebrates. In exercising mammals, the vasomotor center integrates afferent information from active muscle (proprioceptors), arterial and cardiac mechanoreceptors, chemoreceptors, the cortex, and the hypothalamus to ensure appropriate autonomic nervous output (373).

Information on the cardiovascular responses of exercising lower vertebrates is very limited. Most available information is for fishes (see refs. 95, 190, 508 for reviews) and, to a lesser extent, reptiles (231). Table

4.1 summarizes key cardiovascular data for selected vertebrates at rest and at maximum exercise states. A number of general points emerge from these data. The majority of vertebrates increase cardiac output during exercise by between 1.3- and 3.3-fold over resting values. Known exceptions to this are trained human athletes and thoroughbred horses (Table 4.1). Also, flying pigeons can increase f_H sixfold with no change in SV (104). The mechanism by which cardiac output is increased during exercise varies among vertebrates. Most amphibians, reptiles, birds, and mammals rely heavily on tachycardia (Fig. 4.29), with SV changing relatively little. Training in mammals does, however, increase the role of increasing SV. Fish rely on increases in both f_H and SV, with the increase in SV predominating in most species. *P. borchgrevinki* and possibly tuna are unusual in this regard by relying substantially more on tachycardia (16, 66). Tachycardia typically involves both vagal release and, where possible, adrenergic stimulation. Central arterial blood pressure increases with exercise. However, species with in-series respiratory and systemic circulations (fishes and mammals) generally show somewhat larger increases in systemic arterial blood pressure than species with an in-parallel respiratory and systemic circulation (amphibians and noncrocodilian reptiles). The extent of the hypertension is reduced because total vascular resistance is reduced. More active mammals appear to be capable of a greater factorial reduction in vascular resistance. The net effect of increased cardiac output and acute hypertension is to increase myocardial power output by between 1.4- and 5.7-fold (Table 4.1), and this, of course, requires a concomitant increase in myocardial O_2 consumption.

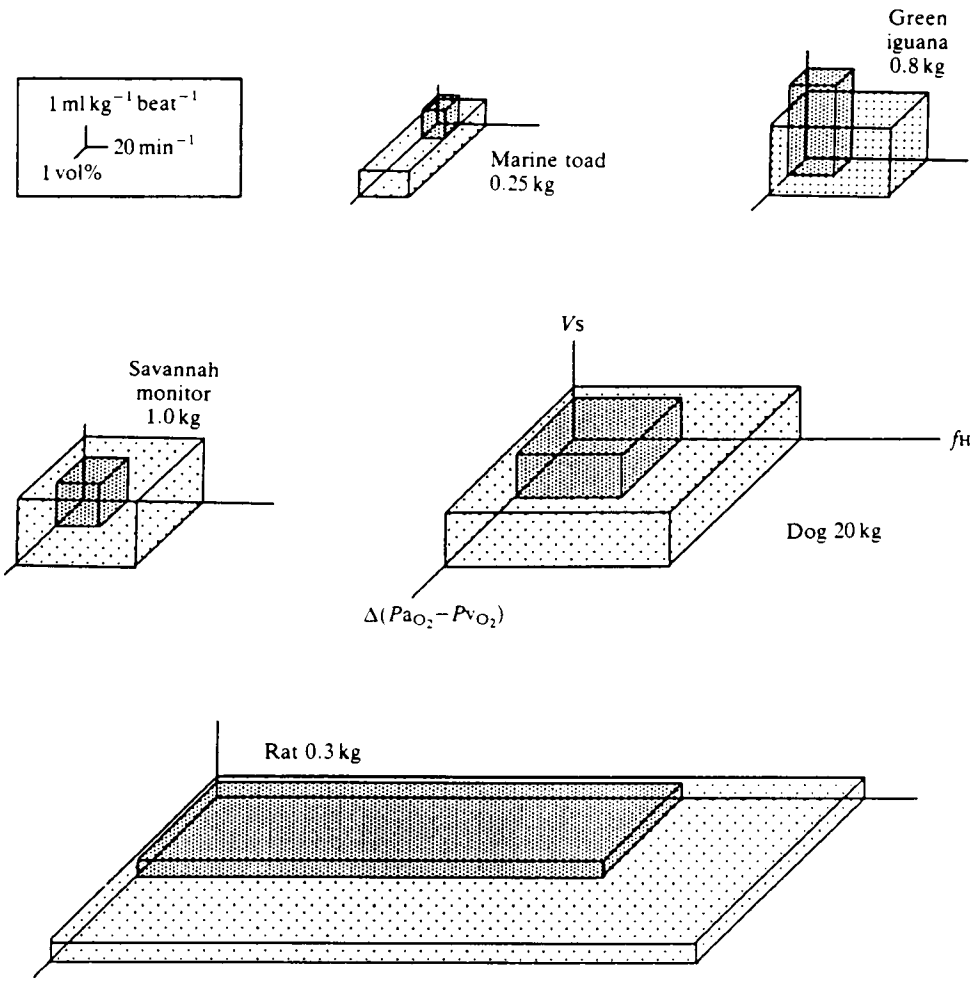

FIG. 4.29. Cardiovascular adjustments to exercise in selected vertebrates. This three-dimensional treatment deals with stroke volume (ml/kg/beat), heart rate (bpm), and arterial-mixed venous oxygen extraction (vol %). Resting conditions are heavily shaded, while exercising conditions are lightly stippled (from ref. 231).

The change in regional blood flow distribution with exercise has been measured in several species of fish. Because aerobic swimming is powered largely by red muscle, there is a dramatic increase in both the mass-specific blood flow to red muscle and the proportion of cardiac output going to red muscle. In rainbow trout and large mouth sucker, red muscle blood flow is 9% and 0.57% of cardiac output at rest, increasing to 42% and 13.2% during exercise, respectively (368, 512). At the same time as blood flow to skeletal muscle increases, that to visceral organs is reduced (605). The reduction in blood flow to the celiac, mesenteric, and intestinal arteries can be particularly pronounced, being around 30% in Atlantic cod (21) and 70% in chinook salmon (605). Because systemic resistance is reduced, the effect of skeletal muscle vasodilation must be greater than that of visceral vasoconstriction. The control of these vascular responses is poorly understood. Modulation of the systemic α-adrenergic tone is one possibility. The roles of locally produced metabolites (110) and nonadrenergic, noncholinergic fibers, especially in the gut circulation (457, 458), have yet to be thoroughly investigated.

With respect to amphibians and reptiles, changes in particular aspects of cardiovascular performance, such as f_H and blood pressure during exercise, have been investigated (56, 100, 292, 659). However, our understanding of how cardiac output is regionally distributed during activity in amphibians and reptiles is very limited. One of the few such studies measured left pulmonary and left aortic blood flows during rest and swimming in the green sea turtle *Chelonia mydas* (642). During exercise, cardiac output was presumed to increase, primarily due to an increase in heart rate from 24 bpm to 40 bpm (28°C). Both pulmonary and aortic flows increased markedly with exercise, but there was little evidence for a redistribution of cardiac output other than that typically associated with periods of intermittent lung ventilation and breath holding (see below).

Breath Holding and Diving

One of the fundamental tenets of effective gas exchange is that ventilation and perfusion of a gas-exchange organ be appropriately matched. Many animals, especially lower vertebrates, breathe only intermittently. This may be due to voluntary cessation of continuous breathing while in air or may be a result of diving. In any event, to prevent a relative hyperperfusion of gas-exchange organs during apnea, as well as to conserve limited O_2 stores during nonbreathing periods, profound changes occur in the cardiovascular system of almost every animal examined in this context. The literature on the subject is relatively extensive, initiated largely by the pioneering work of Scholander and colleagues (for reviews, see refs. 54, 74, 97, 98, 163, 198, 205, 305, 338, 371, 372, 554, 586). The literature provides conflicting data as to whether or not the classical diving response as described by Scholander and co-workers in laboratory experiments was indeed the diving response that occurs in all animals in nature. The literature on the subject, reviewed below, sometimes fails to take into account the natural history of the animal in question—that is, whether the dive durations used were those typically shown by animals and whether forced diving mimics diving in the natural habitat.

Almost all intermittently breathing animals show a similar suite of cardiovascular responses associated with periodic gas exchange. These include changes in total cardiac output, achieved through changes in SV and/or f_H, and redistribution (shunting) of cardiac output between and within tissues of the systemic and gas-exchange circuits. In addition, some diving animals are now known to use adjustments in cardiac output and blood flow to "meter out" oxygen during apneic periods. The extent of this total suite of changes will be at different levels, however, depending on the duration, stress, and/or exercise levels associated with diving.

Cardiac Output Reduction. A reduction in cardiac output during apnea is one of the most universal cardiovascular responses of intermittently breathing animals. While many species respond to the increased cardiac demands of exercise by specifically increasing predominantly one of either SV or f_H (see *Aerobic Exercise*) during breath holding cardiac output reduction is often profound, and in most species examined both SV and f_H are decreased. The rate and extent of fall in cardiac output during breath holding is related to a complex interaction between the resting oxygen demand of the animal, the O_2 stores available at the beginning of the breath hold, the duration of the breath hold, and the ability of the animal to tolerate hypoxia and hypercapnia (98). In animals like humans that are poorly adapted for breath holding, cardiac output may decrease by a maximum of 20% during voluntary breath holds of several minutes (305). Animals adapted for breath holding, most often in the form of diving, show much more profound cardiac output reduction. In experimentally submerged Weddell seals and spotted seals, cardiac output falls by about 90% during prolonged dives (162, 364, 673). Stroke volume decreases about 30%, indicating that bradycardia is the biggest component of the cardiac response to diving in these seals. Cardiovascular responses to both involuntary and voluntary diving in diving birds (especially ducks) are

similar to those for similar conditions in seals (for reviews, see refs. 98, 371, 586). During short forced submersion in the domestic mallard, for example, SV decreases by about 25% and f_H by more than 90%, leading to a fall in cardiac output of more than 90% (Fig. 4.30). Voluntary submersion in the diving freshwater turtle *C. scripta* can lead to a reduction in cardiac output of more than 95%, contributed to by profound reductions in both SV and f_H (Fig. 4.20). Similar responses have been measured in diving crocodiles and alligators (247, 491, 649). In perhaps the most extreme case, forced submersion of *Chrysemys picta* in completely anoxic water at 3°C for up to 6 months (an annoyance rather than a lethal condition for these animals) results in an f_H of about 0.4 bpm (273).

Estimates of cardiac output during diving in amphibians are few. Experiments based on microsphere distribution suggest that cardiac output falls during diving (447). Amphibians, like reptiles, show considerable reductions in f_H during diving (58, 86, 495). Measurements of systemic and pulmonary blood flows during intermittent breathing indicate that SV also falls greatly during apnea (560). Collectively, these data suggest a large fall in cardiac output associated with breath holding.

Indicating both the physiological utility and phyletic antiquity of the reduction in cardiac output during breath holding, air-breathing fishes also show this response. A decrease in f_H associated with the intervals between air breaths occurs in air-breathing fish such as the bowfin *Amia* and the gar pike *Lepisosteus* (331, 510). Most attention in this regard has been focused on the lungfishes (for reviews, see refs. 84, 85, 204, 205, 327, 328), where f_H similarly decreases. Although cardiac output has not been measured directly, blood flow in individual major vessels has been measured and indicates a reduction of stroke flow and cardiac output between air breaths. However, as discussed earlier, there is no change in cardiac output during apnea in the jeju, an air-breathing fish (172).

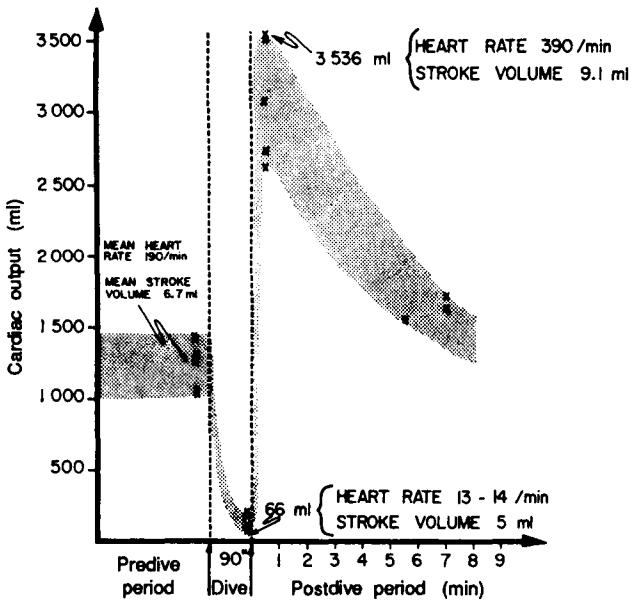

FIG. 4.30. Changes in heart rate, stroke volume, and cardiac output in the domestic mallard before, during, and after a forced dive (from ref. 206).

Shunting. Decreased cardiac output during breath holding is an important physiological response to diminished oxygen availability. However, redistribution of cardiac output between vascular beds is also an essential component of maintaining O_2 delivery to those tissues that most need it. Redistribution is of two major types: *(1)* between systemic and gas-exchange circuits (except for birds and mammals) and *(2)* between organs within the systemic circulation.

In animals with either an incompletely divided heart or non-intracardiac, central arterial shunting capabilities (crocodilians), cardiac output can be preferentially and variably distributed, or "shunted," to either the systemic circulation or the gas-exchange organ(s). Borrowing nomenclature derived from more bilaterally divided mammalian circulations, shunts are classified as either "left-to-right" (L-R) or "right-to-left" (R-L). L-R shunt is a measure of the percentage of the oxygen-rich blood returning from the gas-exchange circuit via the left atrium, which is then shunted within the ventricle (or in the central arterial circulation in the case of crocodiles) directly back into the gas-exchange circuit for a second, immediate pass through the gills, lungs, or other exchange organs. R-L shunt represents a bypass of the gas-exchange circuit in that oxygen-poor blood returning from the systemic circulation via the right atrium is shunted within the ventricle directly back into the systemic circuit without an opportunity for gas exchange. A further distinction needs to be made between a gross shunt and a net shunt. A gross shunt reflects the total quantity of blood (usually expressed as a percentage of right or left atrial flow) that is shunted in a particular direction. L-R and R-L shunts can occur simultaneously, so a net shunt and its direction are calculated from the difference between the two flows. Thus, a net R-L shunt occurs when the blood flow to the pulmonary circuit (Q_{pul}) is less than the blood flow to the systemic circuit (Q_{sys})—that is, $Q_{pul}/Q_{sys} < 1.0$—while a net L-R occurs when $Q_{pul}/Q_{sys} > 1.0$.

Central blood shunting is a carefully regulated process in all animals in which it occurs. Fortunately, the comparison of lower vertebrates with intracardiac

shunts to humans with intraventricular septal defects, where shunting is an unfortunate consequence of a pathological situation, is seen as highly flawed. Indeed, central vascular shunting in intermittently breathing animals provides a very useful way of matching perfusion and ventilation in the gas-exchange organs.

The magnitude and direction of intracardiac shunts associated with various ventilatory states is measured using blood gas contents in central arteries and veins, blood flow, or microsphere distribution. R-L and L-R shunts have been documented in air-breathing fishes (for reviews, see refs. 84, 205), amphibians (598, 610), and reptiles (90, 264, 399, 554, 562, 563a, 652, 654). For example, in the freshwater turtle *C. scripta,* during lung ventilation 60%–65% of cardiac output perfuses the pulmonary circulation, indicating a net L-R shunt of 10%–15% (90, 562). During apnea, the net L-R shunt reverses to a net R-L shunt, with about 55% of cardiac output flowing into the systemic circulation.

What purpose does central vascular shunting achieve? Several answers are possible (73). The direction and magnitude of the shunt tends to vary with the minute-by-minute potential of the aerial gas-exchange organ for O_2 uptake and CO_2 elimination. During the actual periods of air breathing and shortly thereafter, P_{O_2} in the exchanger is highest and P_{CO_2} lowest, while at the end of a prolonged period of apnea, the opposite is the case and a net R-L shunt prevails. By not perfusing the gas-exchange organ when its potential for gas exchange is low, the metabolic cost of perfusing the gas-exchange circuit is reduced. In turtles *(C. scripta)*, the metabolic saving due to R-L shunting during apnea is about 0.5% of total aerobic metabolism (73). While this seems very small, our knowledge of what constitutes a significant energetic saving in a physiological process is fragmentary at best. It may be that a small saving applied over the thousands of apneic periods in a turtle's lifetime amounts to large energetic savings. R-L shunting during apnea may also reduce plasma filtration into the lungs, which appears to correlate with level of pulmonary blood flow, at least in turtles (71) and toads (576, 579). Fewer explanations have been offered as a rationale for L-R shunting during apnea, but this may be because shunting is often examined in the context of its effects on blood O_2 transport. While the repeated recirculation of fully oxygen-saturated blood through the gas-exchange circuit makes little energetic sense vis-à-vis O_2 transport, it does in terms of CO_2 elimination. With every circuit through the lung, additional CO_2 is removed (653). Indeed, the gas-exchange ratio of the lungs of both freshwater turtles (90) and African clawed toads (57) rises progressively to values well above 1 during long bouts of breathing, suggesting that CO_2 elimination increases disproportionately over O_2 uptake when an L-R shunt is occurring.

Shunting may also have nonrespiratory effects, most predominantly on heat exchange with the environment. By recirculating blood to the non-ventilated lung (L-R shunt), blood is kept within the core and away from the peripheral systemic tissues, where it could pick up or lose heat, depending on the gradients between the animal and the environment.

Central vascular shunting in air-breathing fishes, amphibians, and reptiles is controlled by adjusting the relative peripheral resistances of the systemic and gas-exchange circuits. The lack of anatomical ventricular division (or, in the case of crocodilians, the presence of a left aorta arising from the right ventricle) essentially places the systemic and gas-exchange circuits in parallel rather than in series as in birds and mammals. Consequently, a rise in pulmonary relative to systemic arterial resistance, for example, will result in a redistribution of cardiac output from the lungs to the systemic tissues. The mechanism(s) by which this is achieved is somewhat species-specific but usually involves vasoconstriction and vasodilation of vascular smooth muscle (for reviews, see refs. 73, 76, 178, 205). Both large central and small peripheral vessels may be involved. In air-breathing fishes like the lungfish *Protopterus,* redistribution of cardiac output between the gills, lungs, and systemic tissues is achieved by a combination of vasodilation/vasoconstriction in both large central vessels and the microvasculature of the gills (205). Freshwater turtles, as well as crocodilians, have a smooth muscle sphincter at the base of the pulmonary artery that can regulate pulmonary vascular resistance and, thus, the degree of blood shunting (68). At least in turtles and tortoises, the direction and magnitude of the intracardiac shunt is regulated in part by the temporal and spatial pattern of cardiac depolarization and activation, which occurs in one of two states associated with periods of breathing and periods of apnea (69). Regulation of cardiac contraction patterns, and thus of intracardiac shunting, is under vagal control.

While mechanistically we understand how intracardiac shunting is achieved in many lower vertebrates, we know very little about the factors that regulate this active process. Given that we have yet to identify the factors that initiate and terminate the much more easily studied process of ventilation of intermittently ventilated gas-exchange organs, it will no doubt take considerable additional study to identify the role of the CNS in controlling shunting.

O_2 Metering. Oxygen stores at the beginning of a period of apnea (typically a dive) can be distributed in the blood (predominantly bound to hemoglobin), in the

tissues (predominantly bound to myoglobin), or in lung gas. Different species tend to distribute their oxygen stores in different sites (Fig. 4.31). Diving mammals and, to a lesser extent, diving birds tend to store oxygen primarily in blood and tissues; lung gas oxygen stores in these animals are relatively small (74, 98, 163, 371, 372). Birds and mammals tend to dive to much greater depths than lower vertebrates, and by minimizing lung gas stores so, too, the risk of the bends may be reduced. Reptiles and amphibians, however, tend to dive with large, fully inflated lungs, and consequently a much greater proportion of their oxygen is stored in the form of lung gas (74).

A pulmonary gas O_2 store is of benefit to animals during diving only if they can effectively transfer O_2 to the blood from these stores and distribute it to the least anaerobic tissues. Thus, while L-R shunts producing a partial pulmonary bypass are useful mechanisms for conserving oxygen during certain circumstances (see above), the ability to minimize or even reverse the shunt during apnea, enabling the temporary transfer of O_2 from pulmonary to blood stores, is crucial. Indirect evidence for such a transfer during apnea in diving frogs *(Xenopus)* and turtles *(Chrysemys)* has been recorded (53, 74) and consists of a slow decline in lung gas P_{O_2} that quickly turns into a more sharp decrease as arterial P_{O_2} actually increases. Direct evidence for transfer of O_2 from lung gas to arterial blood exists in the form of simultaneous blood gas, lung gas, and pulmonary blood flow measurements in the diving turtle *Chelodina longicollis* (91). Pulmonary blood flow appears to be carefully regulated to "meter out" oxygen during diving, maintaining arterial O_2 saturation at 90%–95% as lung P_{O_2} progressively falls, during all but the longest dives. Sharp increases in blood flow during diving result in actual increases in blood saturation (Fig. 4.32).

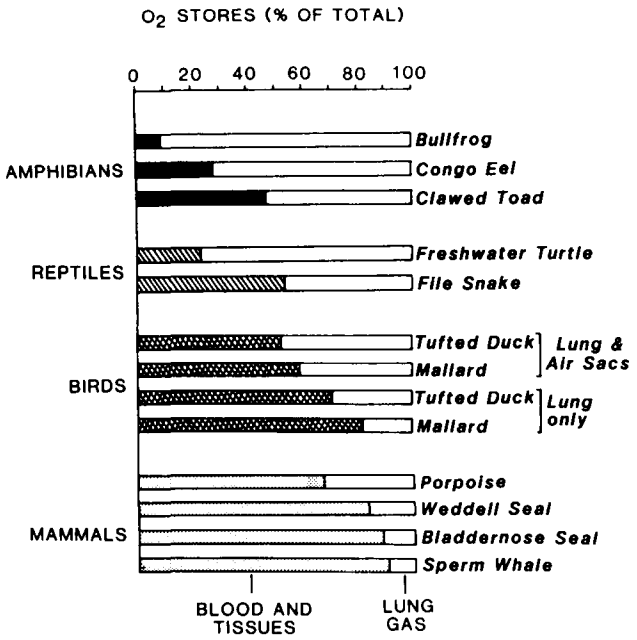

FIG. 4.31. Distribution of O_2 stores available at the beginning of a dive in a selection of amphibians, reptiles, birds, and mammals. Data are approximations derived from primary data from different studies on the same species (from ref. 74).

Little is known about how O_2 metering is regulated in amphibians or reptiles. The simple notion that there is some threshold level of blood or lung gas P_{O_2}, P_{CO_2}, or pH that might stimulate pulmonary perfusion (or any other cardiorespiratory) process is antiquated (643, 645). Additional studies are needed on amphibians and reptiles to identify what will probably be a suite of factors that modulate CNS control over shunt patterns and pulmonary perfusion.

The phenomenon of O_2 metering during apnea in air-breathing fishes has not been observed to our knowledge. The smaller size of many air-breathing fishes combined with the need to monitor constantly either blood flow or arterial O_2 levels has conspired against the type of physiological measurements that would lead to O_2 metering. However, the physiological rationale for this phenomenon applies equally well to fish intermittently breathing air.

Reduced Metabolism

Certain birds and mammals reduce O_2 consumption overnight (torpor) or over the winter (hibernation) by regulating body temperature at a lower than normal value (5°–15°C). In addition, a self-imposed state of hypoxia accompanies breath-hold diving under water. The cardiovascular responses to reduced metabolic states in birds and mammals are well documented (48, 96, 128, 163, 298, 371, 655). There are a variety of conditions under which lower vertebrates may reduce their metabolic state, but the physiological responses in general, and the cardiovascular responses in particular, are less well understood. Furthermore, more than one condition may influence the overall cardiovascular response. For example, the overwintering of frogs involves reduced temperature, submergence, and hypoxia (495). Ectotherms may either conform or acclimate to a decrease in environmental temperature (315, 528). Thus, rate functions can have a Q_{10} of around 2.0 in conformers or much larger in animals that down-regulate metabolic activity (for example, eels overwintering on the bottom of rivers). Semiaquatic vertebrates, such as *Protopterus* and *Bufo,* burrow over summer to survive drought conditions *(estivation).* During burrowing these animals take advantage of a lower environmental temperature and down-regulate

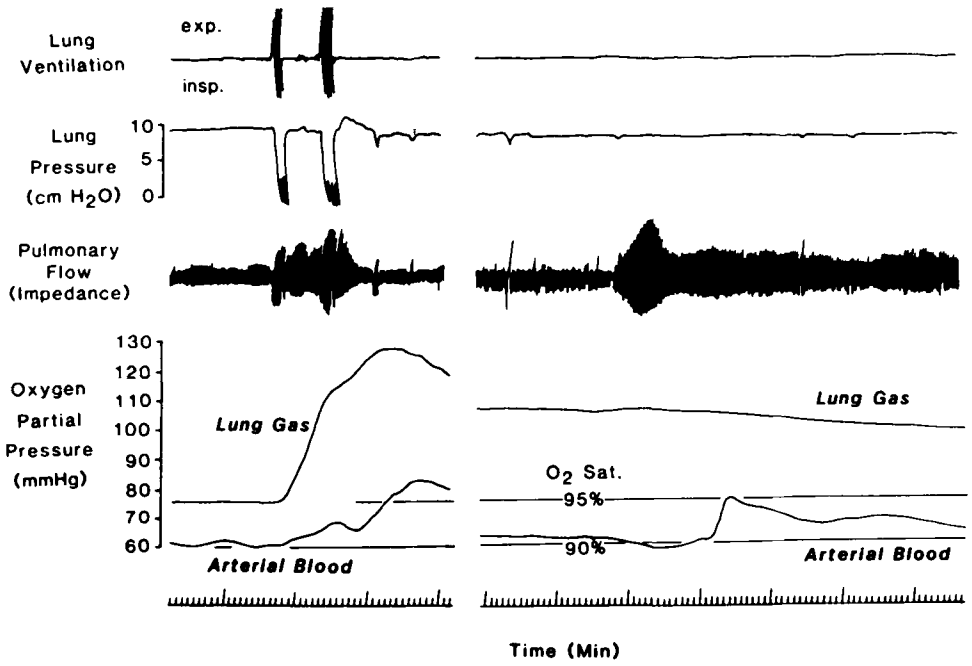

FIG. 4.32. Pulmonary oxygen metering in the turtle *Chelodina longicollis*. *Left panel* shows records of lung ventilation, intrapulmonary lung pressure, pulmonary flow, PO_2 of lung gas, and PO_2 and O_2 saturation of systemic arterial blood at termination of a dive and during two brief lung ventilation bouts. *Right panel* shows same records taken between 9 and 16 min into a voluntary dive (from ref. 91).

their metabolism. Amphibians, reptiles, and air-breathing fishes perform breath-hold dives. Aquatic vertebrates also experience environmental hypoxia.

As with reduced metabolic states in mammals, lower vertebrates typically reduce cardiac output through a vagally mediated bradycardia. This is true whether diving is performed by crocodiles, turtles, amphibians, lungfishes, or air-breathing fishes (178, 510); whether fishes are exposed to severe aquatic hypoxia (95); whether lungfishes estivate (147); and whether turtles overwinter under water (272). The extent to which bradycardia develops depends in part on *(1)* the duration and severity of the change and *(2)* other confounding inputs to the vasomotor center, such as afferent input associated with exercise during diving. Estivating lungfishes reduce f_H and arterial blood pressure over the first 70 days to 12 bpm and 14 mm Hg, respectively, and these levels are maintained for the next 180 days of estivation (147). Perhaps the most extreme example of cardiac depression during a reduced metabolic state is that of a 129-day submersion in anoxic water at 3°C by *Chrysemys:* f_H was reduced to 0.1 bpm–1.0 bpm and arterial blood pressure to 10 mm Hg (273). However, frogs that freeze over the winter must have a complete cardiac arrest.

Vascular changes also accompany reduced metabolic states in lower vertebrates. Systemic vascular resistance is reported to increase, decrease, or remain unchanged during aquatic hypoxia in fish (95). These varied responses may reflect differences between species, in the level and length of hypoxic exposure, and in the extent of accompanying motor activity. During prolonged diving by amphibians and reptiles, the most profound vascular change is the progressive reduction in pulmonary flow (559, 562). This is primarily brought about by a vagally mediated constriction of the pulmonary artery. The extent of pulmonary vasoconstriction is again a function of (1) the duration of the dive and (2) other confounding inputs to the vasomotor center. Perhaps the best example of this confounding effect is the response of the green sea turtle swimming under water; pulmonary flow is maintained even though the animal is "diving" (100, 642).

Digestive State

That metabolic rate increases following ingestion of food, a phenomenon termed specific dynamic action (SDA), has long been appreciated by both medically oriented and comparative physiologists. Metabolic increases in the postprandial period can range from 10% to up to tenfold depending on the species in question and the size of the meal. The metabolic consequences of SDA have been examined by comparative physiolo-

gists in both vertebrates and invertebrates (for a selection of references, see ref. 87). However, far less attention has been paid to the cardiovascular changes that presumably support SDA-associated increases in metabolic rate. Presumably, a large increase in metabolism associated with SDA must be supported by an increase in cardiovascular transport of nutrients to tissues experiencing the elevated metabolic rate. Indeed, circumstantial evidence for this appears in the toad *B. marinus,* where both f_H and myocardial O_2 consumption quickly double following injection of peptone into the stomach (158, 637). Feeding causes redistribution of blood flow from other systemic tissues preferentially toward the gut in mammals (170), alligators (22), and fishes (17, 21). This response is generally produced by vasodilation of mesenteric vessels; in some species, this can produce a several-fold increase in blood flow to the gut.

Unlike ambush predators and humans, some animals eat while they exercise. Thorarensen and co-workers (604, 605) have examined the cardiovascular changes related to intestinal blood flow in exercising salmonids. At rest, intestinal blood flow was 12–18 ml/min/kg body mass, and this accounted for 34% of cardiac output. Postprandially, intestinal blood flow increased by 81%, peaking 23 h after feeding. In unfed fish swimming maximally, although cardiac output was increased by 86%, intestinal blood flow was reduced by 60%–70% because of an increase in splanchnic vascular resistance. A negative linear relationship was obtained between intestinal blood flow and oxygen consumption, suggesting an association between the regulation of intestinal blood flow and the oxygen demand of locomotory muscles. The apparent tradeoff of blood flow between the intestine and working skeletal muscle was calculated to provide 14% of the total oxygen transported to the skeletal muscle during swimming. Thorarensen et al. (604, 605) further propose that an additional and perhaps more important benefit of increasing splanchnic vascular resistance is blood pressure homeostasis.

Much of the cardiovascular physiology that we know (and that is discussed in this chapter) is based on relatively steady-state conditions, often measured in animals in a fasting or otherwise steady nutritional state. Yet, nonsteady-state conditions clearly have profound effects on cardiovascular function as well as gas exchange and metabolism and deserve to be the focus of additional studies.

Responses to Gravity

Gravity affects blood circulation primarily by inducing shifts of blood volume whenever posture departs from the horizontal (396a). The effect is especially important in long or tall animals. Pooling of blood in dependent vasculature and the tendency to edema in dependent tissues are both related to the hydrostatic pressure, which in turn depends directly on the length of the vertical blood column. Gravity-dependent shifts of blood volume when posture departs from the horizontal initiate a sequence of hemodynamic changes and reflexogenic adjustments that have been thoroughly studied by numerous investigators (reviewed in refs. 49, 224, 529a, 575). Depending on the height of arterial or venous blood columns and the associated changes in hydrostatic pressure, the total pressure across blood vessel walls (that is, transmural pressure approximates the sum of blood pressure plus hydrostatic pressure) increases passively in the lower vasculature and decreases in the upper vasculature ("lower" and "upper" defined with reference to a central or near-central hydrostatic indifferent point, HIP, where pressure does not change) (224). Pooling of blood reduces cardiac outflow and thereby tends to reduce arterial pressures, which shifts the effective HIP downward in the absence of compensatory responses. However, cardiovascular reflexes which elevate arterial pressures shift the HIP upward such that the passive initial decrease of pressure in elevated vasculature tends to be compensated.

Regional pressure changes in the arterial system conform closely to expected hydrostatic pressures related to vertical distance. For example, pressures in mammalian appendages vary with respect to central pressures depending on whether they are elevated or lowered with reference to the heart (258, 350). In veins, however, postural changes can introduce significant nonlinearities in the distribution of intravenous pressures, partly attributable to the presence of valves. Pressures in human leg veins can be modified by venous collapse above the heart when the body is upright or by partial collapse within the legs when the head is down (49). Jugular veins in the neck and upper part of the superior vena cava may collapse in upright humans (366) and giraffes (236). However, intracranial vessels are maintained in a patent state by periosteal adhesions and hydrostatic pressure gradients in the cerebrospinal fluid.

Both neural and endocrine mechanisms interact to counter gravitational disturbance of the cardiovascular system. The principal interplay of responses entails adjustments in peripheral resistance, f_H, and venous capacity. It is generally assumed that arterial baroreceptors play the major role in regulating the acute responses to vertical posture, though cardiac and low-pressure mechanoreceptors may also be involved. The generalized vasomotor response to head-up posture entails substantial vasoconstriction mediated by decreased arterial and cardiac mechanoreceptor stimulation, coupled to reflex α-adrenergic stimulation.

Sympathetically mediated vasoconstriction affects peripheral resistance nonuniformly and is quantitatively more important than adjustments of cardiac rate or contractility. Thus, central arterial blood pressure (at heart level) is usually maintained despite significant reductions of cardiac output. Vasoconstriction affects principally splanchnic, skin, and muscle vasculature. Vasoconstriction in skin and muscle of snakes during head-up tilt is limited largely to dependent (posterior) regions in which vessels are densely innervated compared with cervical regions of the body (149, 400).

Adaptive responses elicited by head-up tilt are similar in snakes, lizards, humans, and other mammals. Central arterial pressure falls transiently immediately following head-up tilt but recovers toward or exceeds the pre-tilt level as compensatory mechanisms regulate arterial pressure. As a consequence, the band of arterial pulse pressure narrows due largely to elevation of diastolic pressure attributable to increases in peripheral resistance, while f_H increases. Progressive blood pooling, with attendant reductions in SV, secondarily reduces arterial pressure, which promotes compensatory tachycardia and increases cardiac contractility and peripheral resistance due to reduced sensory outflow from cardiovascular mechanoreceptors. The effects on f_H reflect combined β-adrenergic stimulation in combination with vagal withdrawal. Arterial pressures at head level drop by 20–30 mm Hg during standing in humans (271, 483), and such changes are comparable to the proportional reductions of arterial pressure measured during vertical posture in arboreal snakes (394). Driving pressures at the cephalic vasculature may be relatively unaffected, however, due to reductions in venous as well as arterial pressures at head level. The juxtaposition of vascular and cerebrospinal fluid columns is probably important in protecting against excessive changes in transmural pressures that are counterbalanced at all points in the cranium and spine, thereby preventing venous distension or collapse.

Endocrine responses contribute importantly to regulatory responses to gravity but have been studied only in mammals. Sympathetic stimulation and decreased renal blood flow stimulate the release of renin, which initiates a cascade leading to increases in plasma angiotensin and aldosterone. The release of renin during head-up posture can also be augmented by increases in intrarenal vascular pressures and reductions of circulating levels of ANF (132, 254). Postural changes can also produce small increases in plasma levels of AVP, which is a potent vasoconstrictor in humans (144, 537, 552). Finally, sympathetic activation tends to promote parallel increases in plasma catecholamines, which sustain the pressor response elicited by arterial baroreceptors (407, 523).

A range of possible adaptive responses to head-up posture is nicely illustrated by the behavior of central arterial pressures in various species of snake (Fig. 4.23). Arterial pressures at the body's center (approximately the HIP) either increase, show little change, or decrease depending on the species' adaptations to counteract gravitational blood pooling and to elevate arterial pressure (400, 401, 405, 557). Considering a range of species, the ability to control disturbances to arterial pressure appears to be at least somewhat graded according to the degree of gravitational disturbance normally encountered (394). Studies of arboreal snakes indicate that hemodynamic adjustments in central vessels bias systemic cardiac output in the cephalic direction and assist the regulation of carotid arterial blood flow during head-up tilt (398). Similar data for other terrestrial snakes demonstrate that carotid blood flow is not well regulated (during tilt) in nonclimbing species, suggesting adaptation of the control mechanisms in the arboreal forms (396, 405).

Circulation to the brain of giraffes *(Giraffa camelopardalis)* has attracted the interest of physiologists since the early 1950s. Various investigations have demonstrated that systemic arterial pressures near the giraffe heart are about twice that in humans, sufficient to raise blood against the arterial gravitational column and to supply additional pressure sufficient to perfuse the cranial tissues (235–237, 619–621). An average-sized giraffe stands about 5 m, and the heart is at roughly the center of this distance. Central arterial blood pressure averages about 200 mm Hg in a 3–4 m giraffe and supplies "normal" perfusion pressures (ca. 100 mm Hg) at the cranium, which is 1.2 m above the heart (258). Systolic blood pressures are reported to reach 360 mm Hg at heart level in standing giraffes (236). When the head of the giraffe is lowered, as during drinking, blood pressure measured in the carotid artery near the base of the brain may actually decrease (from 200 to 175 mm Hg) (235). It has been suggested that a rete mirabile and voluminous jugular vein both help regulate cerebral hemodynamics during head-down tilt (236).

Development of Cardiovascular Systems

The study of the ontogeny of cardiovascular system physiology has been heavily biased toward *(1)* the mammalian fetus and *(2)* the final third or quarter of gestation. The reasons for these biases are understandable. Apart from the obvious focus of most biomedical research on systems that can further our understanding of human development, large domesticated mammals have large fetuses that allow invasive measurements. Although the vast majority of studies on the development of cardiovascular systems have been made on mammalian fetuses, the positioning of the fetus within

the uterus presents significant obstacles for making physiological measurements, especially in the early fetus and embryo. Moreover, experiments that present physiological challenges to the fetal cardiovascular system to gauge regulatory ability, for example, are made more complex by the frequent need to pass this challenge indirectly to the fetus by first influencing maternal physiology and overwheiming potentially protective maternal reflexes. Notwithstanding these difficulties, the biomedical literature dealing with the development of mammalian, and particularly human, cardiovascular systems is vast and well beyond the scope of this chapter. Consequently, what follows deals primarily with the cardiovascular systems of lower vertebrates and birds.

Morphological Development. Developmental changes in the gross anatomy of the cardiovascular system have been described for many vertebrates in great detail. Early but comprehensive studies are described in Goodrich (239) for a wide range of vertebrates, which comprises one of the best overviews despite its age.

Developmental changes in the cardiovascular system are closely tied to events in the life cycle. (For many species, a more accurate way of stating this is that developmental events in the cardiovascular system permit new events in the life cycle.) Figure 4.33 compares and contrasts major developmental events in the life cycle of fishes, amphibians, birds, and mammals. Perhaps least well understood from an anatomical (and physiological) viewpoint are the ontogenetic changes in the cardiovascular system of fishes. Developmental changes have been examined primarily in strictly aquatic teleost fishes, most often salmonids (424, 526). Although there is much diversity in the state of cardiovascular development at hatching (526), in most species

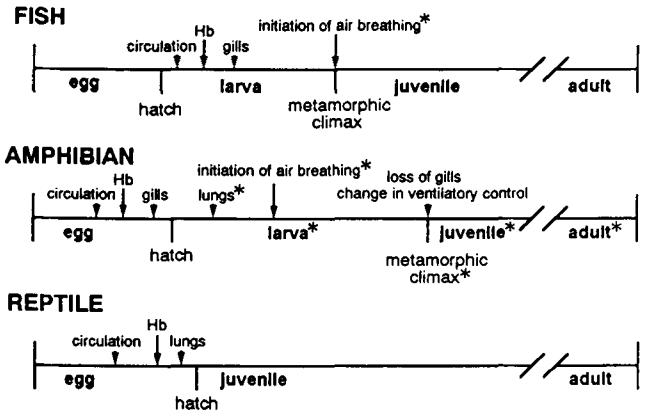

FIG. 4.33. Major cardiovascular and respiratory events during the life cycle of fishes, amphibians, and reptiles. *Developmental stages that may or may not occur within the class (from ref. 88).

the heart begins to beat only after hatching and in the first few hours or days pumps plasma devoid of red blood cells. The internal gills, mouth, and opercular slits are usually absent at this time, and plasma is circulated through external gills (if present) (85). Usually by the time the external gills have elaborated beyond simple capillary loops, red blood cells appear in the plasma. Internal gills develop quickly, and with this event the branchial vasculature is greatly expanded. Few quantitative measures of cardiovascular morphology are available for fishes, though the long-term influence of hypoxia on f_H has been noted in the Artic char, *Salvelinus alpinus* (424). In addition to the external and/or internal gills, the skin of larval fishes doubtlessly plays an important role in early phases of development (88, 527). In larvae of the air-breathing fish *Monopterus albus,* the flow of capillary blood in the skin is counter to the direction of flow of water currents over the skin's surface, forming an effective countercurrent gas-exchange organ (389). Water currents over the body's surface have been noted in larvae of several species of fish (526), though whether the cutaneous circulation develops as in *M. albus* is unknown. Of particular interest, but also of particular scarcity, are details of the development of the cardiovascular system in air-breathing fishes. Dedicated air-breathing organs require a dedicated vascular supply, but few observations have been published on the developmental events leading to their vascularization.

The development of the amphibian cardiovascular system has been extensively examined, in part because of the externally profound anatomical changes that accompany metamorphosis in many species. Morphological details of development are available for anuran (72, 349, 426, 430, 660) and urodele (418–421) amphibians. Although the cardiovascular morphology of some adult apodan amphibians has been described (609), we know of no accounts of developmental changes in this amphibian family. As is evident in Figure 4.33, the sequence of anatomical and physiological changes associated with development in amphibians is among the most complex of all vertebrates, in part because of the complex mid- to late-larval stages in which gas exchange occurs across three sites (gills, skin, and lungs) using one of two respiratory media (water or air). The circulation must be complex enough to provide arterial supply and venous drainage to all of these sites, while at the same time accommodating the inevitable developmental changes (usually tending toward simplification) leading to the adult condition. Figure 4.34 shows developmental changes in the general circulatory pathways in the salamander *A. tigrinum.* Two features are particularly noteworthy. First, in the larval tiger salamander, the gills are both in

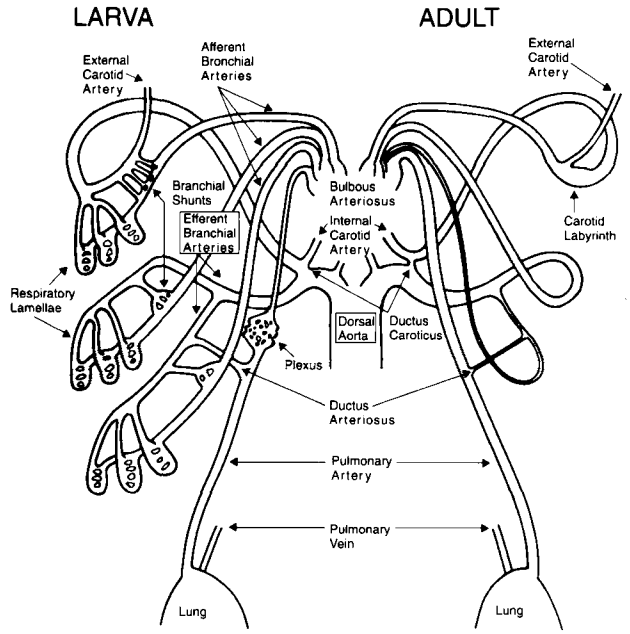

FIG. 4.34. Gross morphology of central venous circulation of larval and adult tiger salamanders *(Ambystoma tigrinum)* (from ref. 417).

series and in parallel due to the derivation of the pulmonary arch directly from the bulbus arteriosus. Urodeles are also the only amniotes to retain the fifth aortic arch as adults. This differs from the pattern in larval bullfrogs, where the lungs and that portion of the skin served by the cutaneous artery are in series and downstream from gill arch VI. The second noteworthy feature, true for both urodeles and anurans, is that the adult condition is substantially less complex than that of the larvae. This is contrary to a prevailing view that continuing development leads to continuing anatomical complexity.

In reptiles, as in birds and mammals, all structural elements of the adult cardiovascular system are essentially in place and operational at birth or hatching, with no major developmental events occurring in the circulation after assuming air breathing at birth/hatching (Fig. 4.33). The developmental cardiovascular anatomy of reptiles is scant (88) compared to that of amphibians, a surprising finding given the large literature on both the anatomy and physiology of the cardiovascular system of adult reptiles (see references in the discussion of reptiles under *Cardiovascular Patterns in Vertebrates,* above). Most general accounts of cardiovascular development refer to a (fictitious) general amniote or tetrapod condition. Very little is known about the developmental morphology of the cardiovascular system of reptiles, especially of varanid lizards and the crocodilians.

The development of the cardiovascular system of birds has been documented extensively, due to the role of the chick embryo as the major model for vertebrate development. The reader is referred to basic embryology textbooks for further information on development of the heart and blood vessels.

Physiological Development

Heart. The study of developmental changes in heart physiology in fishes has been restricted largely to the categorization of ontogenetic changes in f_H. Heart rates are, of course, temperature-dependent and vary between species. Heart rates decline, sometimes after an initial increase, during larval development in the brown trout *Salmo trutta* (249), the rainbow trout O. *mykiss* (303), the Arctic char *S. alpinus* (424), and the little skate *Raja erinacea* (485). While developmental changes in the membrane permeability of the cardiac pacemaker and/or the onset of sympathetic and parasympathetic tone could explain these developmental changes in f_H, little is known about the ontogeny of cardiac regulatory mechanisms in larval fishes.

Developmental changes in f_H in amphibians have been well documented, especially for anurans (77, 86, 93). As is evident in Figure 4.35, there is great variation

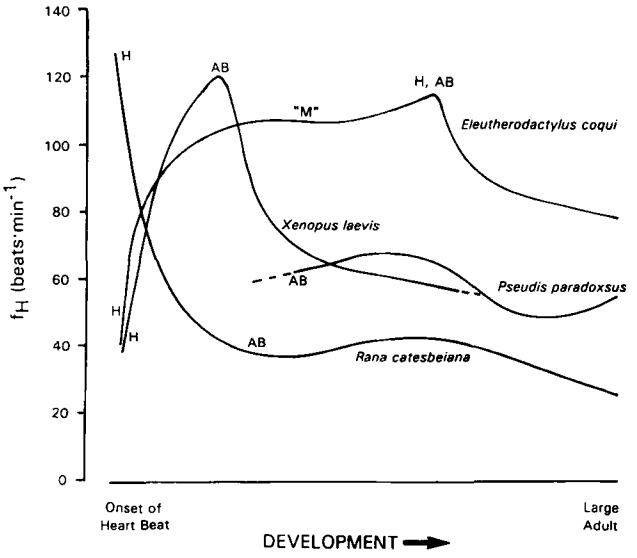

FIG. 4.35. Developmental changes in heart rate (20°–25°C) during development in four anuran amphibians. Data have been "normalized" with respect to development such that the earliest points are from when the heart first begins to beat and the last points are from the largest adults for which data are available. This distorts the abscissa such that a single vertical line at a given point on the developmental scale is not the same stage of development of all species. Major developmental landmarks indicated; *H,* hatching; *AB,* onset of air breathing; *M,* metamorphosis (from ref. 77, which provides original sources of data).

in the pattern of f_H change accompanying development in anurans (and presumably in urodeles). In some species, like the bullfrog *R. catesbeiana,* f_H has been measured over a body mass span of 40 mg shortly after hatching (about 135 bpm at 20°C) to 400 g as adults (about 20–25 bpm at 20°C). When analyzed for an allometric relationship, f_H is found to scale to body mass to the exponent −0.23, compared with a value of about −0.25 based on interspecific comparisons of adult vertebrates (88). That is, almost all of the f_H changes in *Rana* during development can be accounted for by changes in body mass rather than qualitative changes due to development. In the coqui *Eleutherodactylus coqui,* a direct-developing neotropical frog, f_H rises very rapidly from about 50 bpm to about 100 bpm (24°–25°C) in the first few days of development, then increases much more slowly during development to the adult morph within the egg, and then from hatching to maximum adult size decreases from about 120 bpm to 80 bpm. The changes prior to hatching are completely the opposite of those that would be predicted by allometric effects, suggesting that "pure" developmental effects, such as the opening of new vascular beds and the expansion of blood volume, primarily affect heart performance. After hatching, however, when presumably little additional developmental effects occur, the decline in f_H can be explained largely (but not entirely) by increasing body mass and cholinergic control.

The mechanisms behind f_H regulation in anuran amphibians (and, to a much lesser extent, urodeles) have similarly been studied in detail. β-Adrenergic and cholinergic receptors, cholinergic and adrenergic innervation, and vagal tone occur relatively early in larval development (65, 82, 357, 358, 502). Consequently, although metamorphosis results in additional modification of the central arterial circulation, there is very little additional change in cardiac regulatory mechanisms at this time. It is beyond the scope of this chapter to review these data in detail, so the reader is referred to reviews of the subject (77, 86–88). Figure 4.36 summarizes what is known of the development of cardiac regulation in the bullfrog *R. catesbeiana,* for which most is known. Qualitative and quantitative differences between the ontogeny of cardiac regulation of the bullfrog and other anurans, urodeles, and apodans doubtlessly exist and deserve further study.

Perhaps due to the small size of reptilian embryos and the fact that most are either hidden within a uterus (some snakes and lizards), enclosed in an opaque shell (virtually all egg-laying reptiles), or guarded by a parent weighing in excess of 100 kg (crocodilians), we know extremely little of the regulation of the heart of reptilian embryos. Embryos of the California black king snake *(Lampropeltis getulus nigritis)* and the American alligator *(A. mississippiensis)* at 40% of their embryonic development respond to short-term exposure to 12% ambient oxygen by changes in f_H (S. Warburton, unpublished data). However, California black king snake embryos show a reversible tachycardia (mean f_H

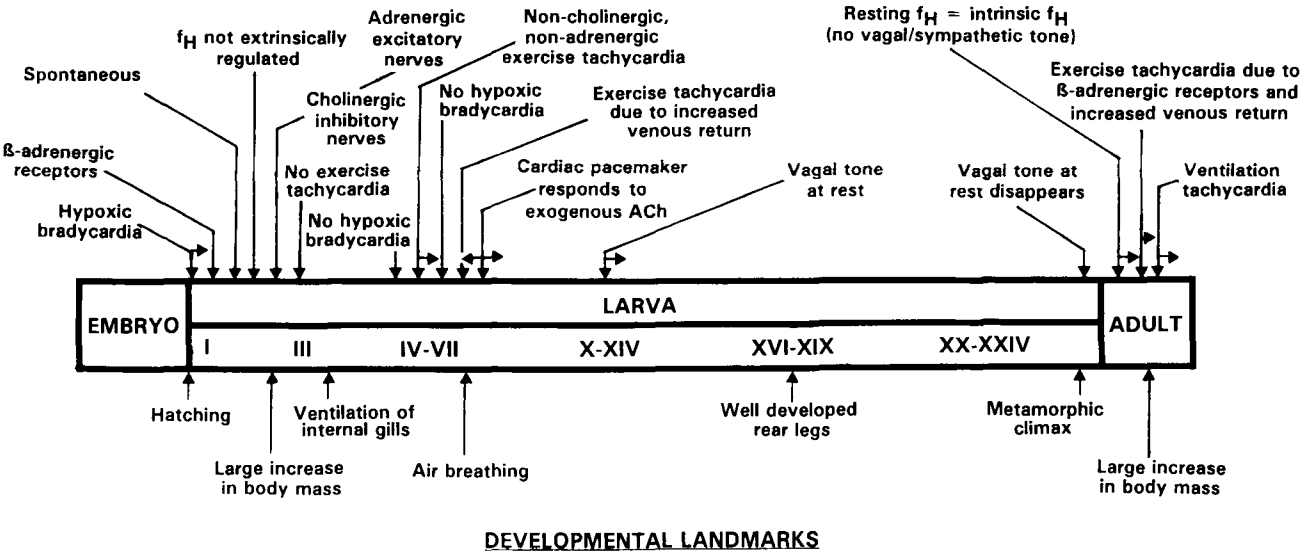

FIG. 4.36. Major developmental events in ontogeny of heart rate regulation in the bullfrog *Rana catesbeiana* (from ref. 77).

increases from 64 bpm to 71 bpm), while American alligators show a reversible bradycardia (f_H decreases from 85 bpm to 70 bpm).

Ontogenetic changes in f_H have been studied extensively in precocial birds, especially the domestic chicken (105, 121, 122, 230, 309, 312, 384, 596, 597, 600, 622, 633). Differences exist between species in the developmental patterns of f_H. Heart rate temporarily increases during the last half of the incubation period in the Japanese quail *(Coturnix coturnix japonica)* and chicken and then decreases again as pipping approaches. Variations on this general theme are observed in the turkey, duck, and goose. In the peafowl *(Pavo cristatus)*, f_H increases rather than decreases toward the end of incubation. In the semiprecocial brown noddy *(Anous stolidus)*, f_H is constant during the last several days of prepipping development but subsequently changes during the prolonged paranatal period (596).

Heart rate has been studied much less in altricial birds, where differences in developmental trajectories have been identified for O_2 consumption, thyroid development, and thermoregulatory capacity. In the pigeon *Columbia domestica* and the bank swallow *Riparia riparia*, f_H increases slowly until the final 3–6 days before external pipping, when it increases more sharply until hatching (601). Interestingly, there seems to be much more inter- than intraclutch variability in terms of daily f_H, as well as onset and length of external pipping (92). That is, siblings show greater similarity in specific patterns of f_H change during development than do nonsiblings. The reasons for this are unclear but could be due to genetic effects (that is, very specific aspects of the pattern of f_H change are heritable) or to maternal effects, in which maternal environmental experiences influence development of the embryos produced by that female.

The ontogeny of mechanisms for f_H regulation in domestic chicken embryos has been considered in some detail (119, 165, 230, 388; see for review, ref. 595). The main protocol in these experiments has been to apply autonomic agonists and antagonists and to note changes in cardiac performance. Cholinergic receptors influencing cardiac function are in place at the end of the first week (the first third of incubation), but the absence of any effect by atropine indicates that there is no vagal tone in embryos around days 13–16 (595). The absence of vagal tone does not mean that the CNS does not exert control over the heart but rather that there was no tone under the circumstances of the experiment. The lack of both parasympathetic and sympathetic neural tone is suggested by the fact that up to day 16 of incubation, destruction of the CNS causes no change in f_H (52). However, propranolol often causes a decrease in f_H in 13- to 16-day-old embryos, suggesting that circulating catecholamines may elevate f_H over its intrinsic rate by this point in development (595). Adrenergic sensitivity in the domestic chicken appears by the end of the first week of incubation (230), and both α- and β-receptors increase f_H, blood pressure, and peripheral resistance in day 13–18 embryos. The relative roles of circulating catecholamines and sympathetic innervation in regulating f_H remain to be determined. One weakness of studies using pharmacological probes is that they show the presence of receptors, not of postganglionic neurons. However, to our knowledge, stimulation of sympathetic or parasympathetic trunks to determine their effects on heart performance has not been attempted in bird embryos.

Peripheral vasculature. The two nonmammalian groups that have been studied for ontogenetic changes in peripheral vasculature regulation are the amphibians and birds.

In amphibians, detailed studies have been made of the regulation of blood flow through the elaborate branchial/pulmonary vasculature illustrated in Figure 4.34 (86, 203, 417–419, 534). In *A. tigrinum,* ACh and vagal stimulation induce vasoconstriction in the branchial vessels and the pulmonary artery, while catecholamines dilate the respiratory vessels in the gills. Catecholamines, however, have little effect on the shunt vessels that allow blood to bypass the gills. Collectively, these data indicated that cholinergic and adrenergic stimuli cause reciprocal changes in blood flow between the vascular beds of the lungs and gills.

Studies on the peripheral vasculature of bird embryos have centered around observations of the in situ effects of intravascular injection of sympathetic and parasympathetic agonists and antagonists (see refs. 120, 595 for reviews). The systemic vascular bed of the domestic chicken embryo responds to the β-adrenergic agonist isoproterenol by the end of the third day (stage 21) of the 21-day incubation period. This drug induces arteriolar constriction, reflected in increased arterial pressure, decreased cardiac output, and increased peripheral resistance (121). By days 13–16, blood pressure is increased by catecholamines (epinephrine and norepinephrine) via α-adrenoreceptors, an effect blocked by phentolamine, while β-receptors stimulated by isoprenaline mediate vasodilation (Fig. 4.37; 595). Acetylcholine induces bradycardia and hypotension. Atrial natriuretic peptide has been identified in chick embryos as early as day 2 (stages 15–21) (451), and this hormone decreases cardiac output and blood pressure through changes in cardiac SV (121).

Central hemodynamics. The measurement of central hemodynamics (cardiac output, arterial blood pres-

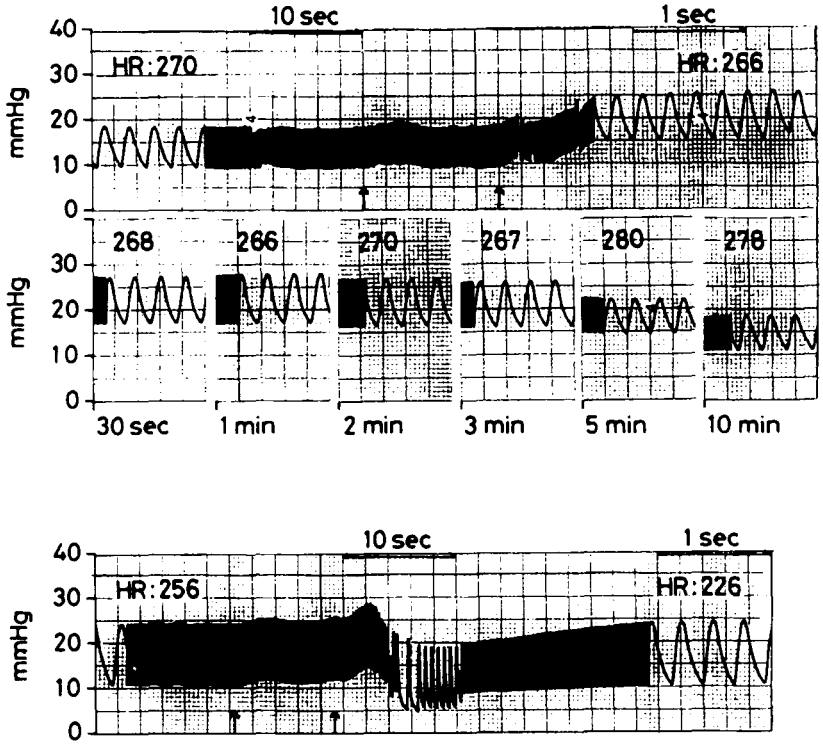

FIG. 4.37. Adrenergic and cholinergic effects on arterial blood pressure and heart rate in 15-day-old embryo of the domestic chicken. *Top panels* show influence of 1 μg of epinephrine in 10 μl of saline *(first arrow)* followed by 50 μl of saline *(second arrow)* on central arterial blood pressure and heart rate. Effects at 30 s and 1, 2, 3, 5, and 10 min are shown. *Bottom panel* shows influence of 1 μg of acetylcholine in 10 μl of saline *(first arrow)* followed by 50 μl of saline *(second arrow)* on central arterial blood pressure and heart rate (from ref. 595).

sures, peripheral resistance) in embryonic/fetal circulations has been advanced greatly by the use of servo-null micropressure systems, Doppler crystal technology, and microvideo recording of heart dimensions (82a). Once again, hemodynamic measurements during early development have been made primarily in embryos of the domestic chicken and in embryos and larvae of anuran amphibians.

Central arterial blood pressures in embryos of *X. laevis* increase sharply with development (307). Mean blood pressure in the truncus increases from only about 3.5 mm Hg at a body mass of 2 mg to about 10 mm Hg at a body mass of about 1 g. Further growth to an adult body mass of about 100 g results in a further rise in mean arterial blood pressure to about 20 mm Hg. Intraventricular and central arterial blood pressures have been measured in the anuran *R. catesbeiana* (486, 487). Strong seasonal effects independent of temperature were found in the larvae of this species, which in its northernmost ranges may overwinter twice before metamorphosis). In spring/summer larvae, blood pressure at 20°–22°C ranged between 10 mm Hg and 12 mm Hg and was not significantly affected by development from stages II to XIV (Taylor-Kollros stages). In fall/winter larvae measured at 20°–22°C, however, blood pressure in stage II was only 2 mm Hg, increasing significantly to 11–12 mm Hg by stage X. Central hemodynamics similarly showed intertwined seasonal and developmental influences. In spring/summer larvae of all developmental stages, "adult-like" hemodynamics were evident, with the ventricle generating systolic pressures that slightly exceeded those in the conus arteriosus and the truncus arteriosus. In fall/winter larvae of stage III and beyond, a similar pattern was evident. In the earliest fall/winter larvae (stage II), however, higher systolic pressures were generated by the contractile conus arteriosus rather than by the ventricle (Fig. 4.38). Ventricular systolic pressures never reached those in the conus or truncus, indicating that in these larvae the ventricle was functioning as a priming antechamber for the conus, which was at least an equivalent "cardiac" pump to the ventricle in terms of the net development of kinetic energy. The mechanisms accounting for these seasonal shifts in ventricular contractility are currently unknown.

Developmental changes in arterial blood pressure

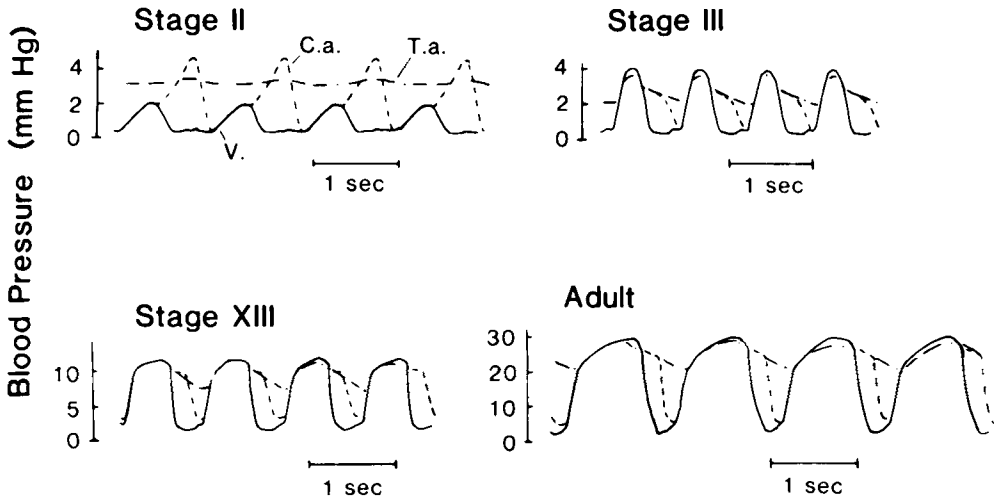

FIG. 4.38. Superimposed recordings of blood pressure from the ventricle *(continuous line)*, conus arteriosus *(broken line)*, and truncus arteriosus *(broken and dotted line)* from three larval stages and small adult bullfrogs *(Rana catesbeiana)*. Taylor-Kollros developmental stages (from ref. 486).

have also been measured in the paradoxical frog *Pseudis paradoxsus* (79). This anuran is highly unusual because, in addition to having the largest known tadpole (>150 g), it paradoxically shrinks to just 5–10 g immediately before metamorphosis. Blood pressure seems to be largely unaffected by large body mass changes either before or after metamorphosis, but a doubling of mean arterial pressure from around 15 mm Hg to 30 mm Hg accompanies the actual process of metamorphosis (Fig. 4.39). Heart rate changes little during larval development and metamorphosis.

Cardiac output has been measured using visual techniques in the embryos of *X. laevis* weighing as little as 2 mg (82a, 220a, 306, 471). By videotaping the beating

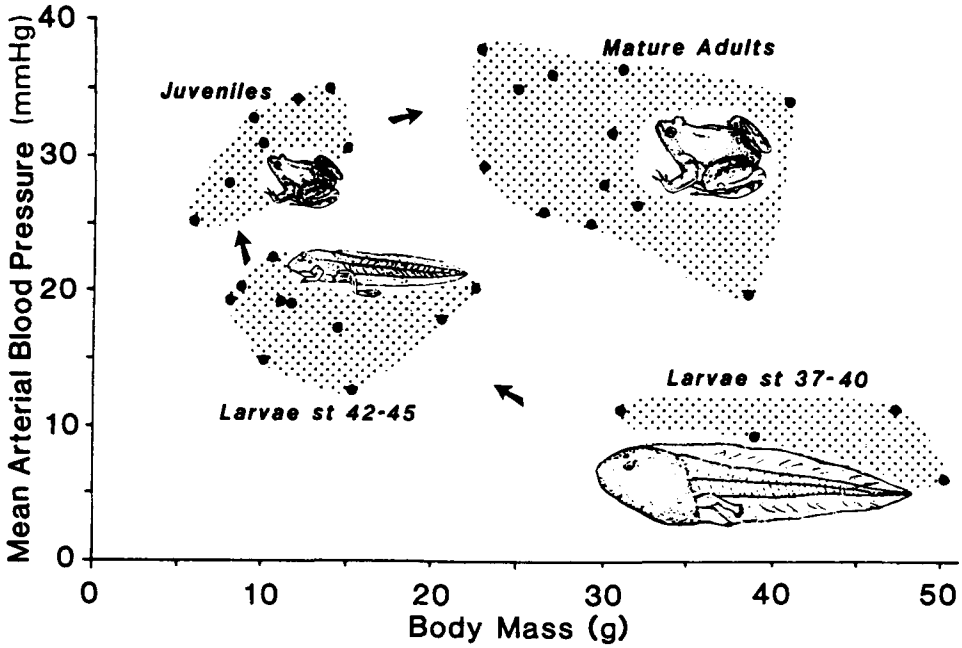

FIG. 4.39. Mean arterial blood pressure as a function of body mass and development in intact, undisturbed larvae and adults of the paradoxical frog, *Pseudis paradoxsus*. Gosner developmental stages (from ref. 79).

heart and assuming its shape to be that of a prolate spheroid, changes in two dimensions could be used to calculate cardiac output and its changes through development. Along with simultaneous measurements of central arterial pressures (306), peripheral resistance could be calculated (307). Peripheral vascular resistance decreased greatly during development and was inversely correlated with increasing body mass, suggesting a progressive rather than an intermittent growth of tissue and an attendant increase in total cross-sectional area of the arterial vasculature. Mass-specific values of SV, cardiac output, and cardiac work increased continuously during larval development, indicating the increasing demands of larval growth on the cardiovascular system.

In the domestic chick, the qualitative aspects of the hemodynamics of the simple circulation of the developing embryo are surprisingly similar to those of immediate posthatch birds (122, 123). Interestingly, even in the early stages, when there are no patent cardiac valves, the endocardial cushions at the atrioventricular sulcus and at the proximal conotruncus produce the same effects as the valves that develop later since there is a distinct dicrotic notch. Cardiac output increases with increasing embryonic mass, while vascular resistance decreases as new vascular beds are added (121; Fig. 4.40). As Clark (121) indicates, peripheral resistance as the embryonic circulation develops is influenced by a multitude of opposing factors, including changes in cardiac output and vascular reactivity, addition of new resistance vessels, increases in cross-sectional area of the systemic vascular bed, and critical closing pressures of the microcirculation.

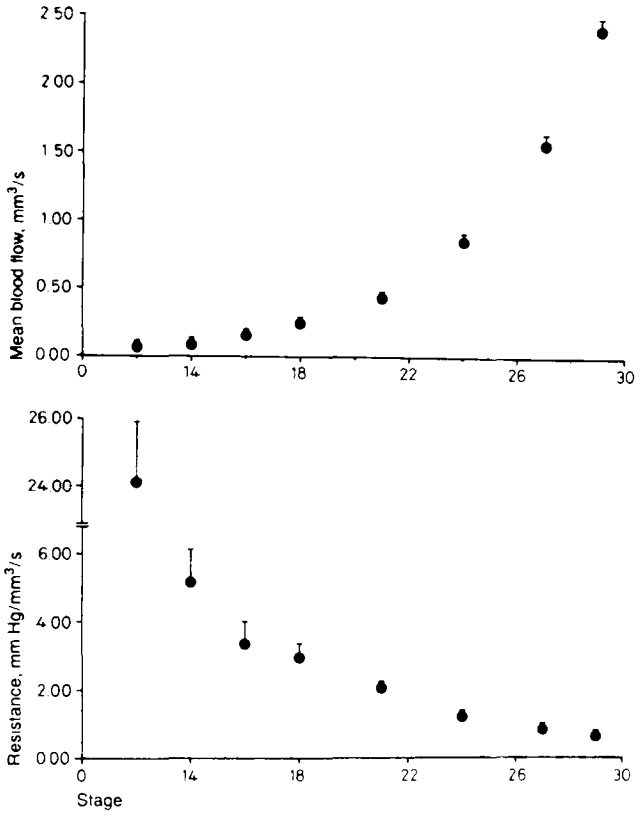

FIG. 4.40. Mean dorsal aortic blood flow *(top)* and vascular resistance *(bottom)* in stages 12–29 of chick embryo. Mean ± 1 SEM, n> 15 at each stage (from ref. 121).

The role of cardiac output in supporting oxygen consumption in the very early vertebrate embryo, when convective blood flow is just beginning, has been investigated. Counter to expectations, the elimination of convective oxygen transport by exposure of embryos to carbon monoxide (blocking hemoglobin oxygen transport), surgical removal of the heart primordia in the embryo, and use of genetic mutations producing heartless animals had little or no effect on oxygen consumption (92a, 486a). These findings indicate that heartbeat and blood flow begin well before the absolute need for blood oxygen transport, during a period when oxygen delivery by diffusion suffices. Why the heart begins to beat earlier than is absolutely required (that is, before blood flow contributes to oxygen consumption) is not yet clear. One possibility is that the heart begins to beat to generate pressurized blood that helps to force open newly forming peripheral vessels.

CONCLUSIONS AND FUTURE DIRECTIONS

Much is known about nonmammalian vertebrate cardiovascular systems, and yet many even quite basic aspects of their physiology remain but poorly known. As we assembled material for this review, each of us generated a list of new, unanswered questions and was reminded of numerous long-standing questions that beg investigation. These questions were naturally grouped around mechanistic, adaptive, integrative, and developmental themes. We finish this review by presenting these questions in the hope that they will stimulate additional research on vertebrate cardiovascular systems.

Mechanistic Unknowns

1. What are the mechanisms for long-term regulation of blood pressure and blood volume?
2. How is intracardiac blood shunting controlled, and what are the stimuli for changes in shunt patterns?
3. To what extent does blood distribution change between systemic tissues, as distinct from between the systemic and respiratory circuits?

4. What is the role of afferent neural information vs. central pattern generators in the regulation of the cardiovascular system? Where are these receptors?

5. How extensive is the peptidergic innervation of vasculature in vertebrates, and what is its importance relative to cholinergic and adrenergic innervation?

Adaptive Unknowns

1. How do cardiovascular systems function in animals at low temperature—for example hibernation, overwintering? How do physiological processes resume after their suspension during freezing or torpor?

2. How does the cardiovascular system perform during avian flight?

3. Are the functions of hormones and local chemical factors, such as ANF, prostaglandins, and endothelium-derived factors, the same in lower vertebrates as in mammals? Has their physiological role changed during evolution?

Integrative Unknowns

1. What factors/mechanisms influence the performance of the cardiovascular system when confronted with simultaneous multiple demands (for example, nutrient absorption and exercise, gas exchange, and thermoregulation)?

2. How are conflicting functional demands on the cardiovascular system (for example, water conservation vs. thermoregulation) prioritized by animals?

3. What are the roles of the lymphatic system in fluid balance, blood volume regulation, and nutrient transport? How, and to what extent, are lymphatic functions regulated?

4. What is the phyletic distribution of the secondary circulation described in fishes, and what are its physiological roles?

Developmental Unknowns

1. When do the various elements of the cardiovascular system first come under neural and hormonal control, and how does this control change with further development?

2. What are the developmental "critical windows" for cardiovascular morphology, and do they coincide with those for cardiovascular physiology?

3. What factors, in addition to hypoxia, stimulate angiogenesis and other aspects of cardiovascular development? How labile is the cardiovascular system of adults compared with immature developmental stages?

The preceding lists reflect our own biases and research interests and represent but a tiny fraction of important unanswered questions about the vertebrate cardiovascular system. As mentioned at the outset, the cardiovascular system is in many respects rate-limiting to other physiological processes. Answering fundamental questions about the cardiovascular system of vertebrates will doubtlessly pave the way for a greater understanding of vertebrate physiology as a whole.

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