Cardiovascular system

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Content

Those structures, such as the heart, or pumping mechanism, and the arteries, veins, and capillaries, which provide channels for the flow of blood. The cardiovascular system is sometimes called the blood-vascular system. The circulatory system includes both the cardiovascular and lymphatic systems; the latter consists of lymph channels (lymphatics), nodes, and fluid lymph which finally empties into the bloodstream. This article discusses the cardiovascular system under the following major headings: comparative anatomy, comparative embryology, functional development of the heart, human fetal circulation at term, postnatal circulation, and comparative physiology. *See also:* **Blood (/content/blood/087600)**; **Lymphatic system (/content/lymphatic-system/393200)**

Comparative Anatomy

All vertebrates feature a closed system of branched vessels, a ventral heart, and a basic pattern of organization that ranges from the single system in most fishes to the double system in land forms.

Heart

The hearts of vertebrates differ from those of animals in the lower phyla in their ventral rather than dorsal location. Blood is pumped anteriorly through arteries and forced to the dorsal side. The greater part then courses posteriorly through arteries which terminate in capillaries in various parts of the body. The blood returns to the heart through veins. *See also:* **Heart**

(vertebrate) (/content/heart-vertebrate/309900)

Phylogeny

In lower vertebrates the heart is located far forward in the body, but there is a gradual backward shifting as the vertebrate scale is ascended. The heart lies in a pericardial cavity which is surrounded by an investing membrane, the pericardium. The pericardial cavity is a portion of the coelom which has been separated from the remainder of the body cavity. In elasmobranchs, the separation is incomplete and the two portions of the coelom are connected by a pericardio-peritoneal canal. A thin serous membrane, the epicardium, covers the surface of the heart. It is continuous with the lining of the pericardial cavity.

The heart is primarily a pulsating tube, the lining (endocardium) of which is derived from fusion of two vitelline veins. Its muscular wall (myocardium) and the epicardium originate from surrounding splanchnic mesoderm. It becomes divided into chambers called atria and ventricles. In addition, two accessory chambers, called the sinus venosus and conus arteriosus, respectively, may be present. Cyclostomes and most fishes have two-chambered hearts with one atrium and one ventricle. A sinus venosus connects with the atrium and a conus arteriosus leads from the ventricle. Dipnoans and amphibians have three-chambered hearts with two atria and one ventricle. The three-chambered heart of most reptiles is similar to that of amphibians, but an incomplete partition appears in the ventricle. In crocodiles and alligators this becomes complete, forming a four-chambered heart with two atria and two ventricles. Birds and mammals have four-chambered hearts. Valves are present to regulate the direction of blood flow.

Circulation in the heart

Vertebrates with two-chambered hearts have the single type of circulation (**Fig. 1**) in which only unoxygenated blood passes through the heart, which pumps it to the gills for aeration. The double type of circulation (**Fig. 2**) exists in three- and four-chambered hearts through which pass two streams of blood, one oxygenated and the other unoxygenated or partly oxygenated. Even in three-chambered hearts these streams do not mix to any appreciable extent. Partitioning of the heart has been associated in evolution with development of pulmonary circulation accompanying the appearance of lungs.

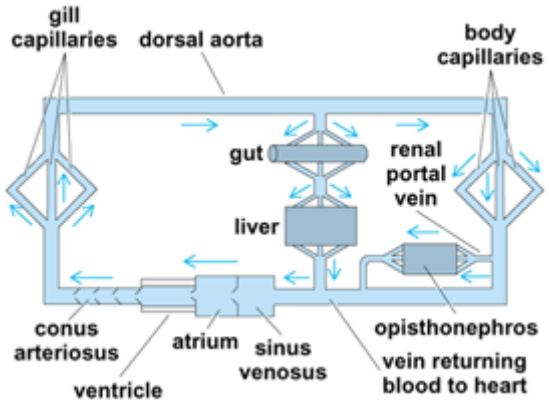

Fig. 1 Single type of circulatory system. ***(After C. K. Weichert, Anatomy of the Chordates, 3d ed., McGraw-Hill, 1965)***

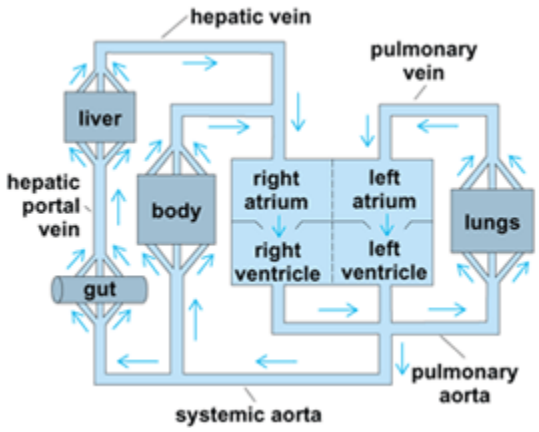

Fig. 2 Double type of circulatory system in a vertebrate having a four-chambered heart (ventral view). ***(After C. K. Weichert, Anatomy of the Chordates, 3d ed., McGraw-Hill, 1965)***

The conus arteriosus no longer exists as such in adults of higher forms; it is split into trunks leading to the aorta and lungs, respectively.

In those forms having two-chambered hearts unoxygenated blood from all parts of the body is collected by the sinus venosus which joins the atrium. In the three-chambered hearts of dipnoans and amphibians the sinus venosus has shifted its position and joins the right atrium. A large sinus venosus is present in certain reptiles, but in most it is very small or is lacking. Birds and mammals possess a sinus venosus only during early embryonic development. In vertebrates having three- or four-chambered hearts, unoxygenated blood is returned to the heart through the sinus venosus or directly to the right atrium, as the case may be.

Arterial system

Although the arterial systems of various adult vertebrates appear to be very different in arrangement, a study of development reveals that all systems are built upon the same fundamental plan.

Ventral and dorsal aortas

In lower vertebrates the conus arteriosus leads forward to a ventral aorta. During early development this vessel divides anteriorly into two aortic arches which course dorsally in the mandibular region. These continue posteriorly as the paired dorsal aortas. Additional pairs of aortic arches then appear, forming connections between ventral and dorsal aortas on each side. They appear in sequence in an anteroposterior direction, each coursing through the tissues between adjacent pharyngeal pouches. The typical number of aortic arches to form in vertebrates is six pairs (**Fig. 3***a*), although there are certain discrepancies among lower forms. The paired dorsal aortas unite posterior to the pharyngeal region to form a single vessel. This single dorsal aorta continues posteriorly into the tail as the caudal artery.

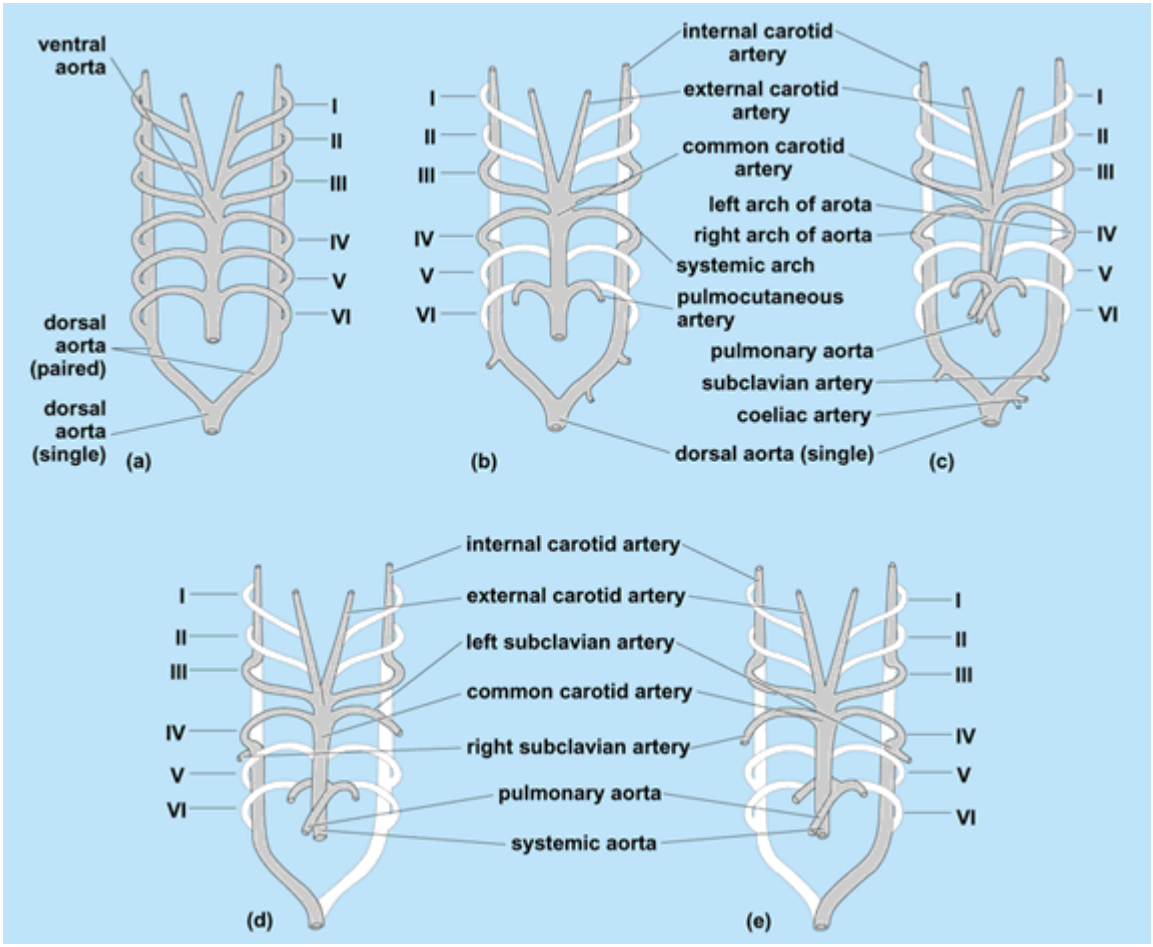

Fig. 3 Modifications of aortic arches in vertebrates, ventral views. (*a*) Typical condition in vertebrate embryos. Six pairs of arches connect dorsal and ventral aortas. (*b*) In anuran amphibians. (*c*) In reptiles. Ventral aorta has split into three vessels, right and left systemic trunks and a pulmonary trunk or aorta. (*d*) In birds. (*e*) In mammals. *(After C. K. Weichert, Anatomy of the Chordates, 3d ed., McGraw-Hill, 1965)*

Various paired and unpaired arteries arise along the length of the dorsal aorta to supply all structures of the body posterior to the pharyngeal region. Anterior continuations of the ventral aorta and the anterior remnants of the paired dorsal aortas supply the head and anterior branchial regions. Although the vessels arising from the dorsal aorta are fairly uniform throughout the vertebrate series, the aortic arches undergo profound modifications. The changes are similar in members of a given class.

Blood, pumped anteriorly by the heart, passes to the aortic arches. These vessels then carry the blood to the dorsal aorta or aortas from which it goes either anteriorly to the head or posteriorly to the remainder of the body.

Aortic arches

Changes in the aortic arch region constitute the chief differences in the arterial systems of the separate vertebrate classes. A progressive reduction in the number of aortic arches occurs as the evolutionary scale is ascended. In cyclostomes and in most fishes, in which gills are used in respiration, the aortic arches break up into afferent and efferent portions connected by numerous gill capillaries in which blood is oxygenated.

The changes in this region involve primarily a routing of the blood through certain preferred aortic arches with a consequent atrophy or disappearance of those which are no longer used, and a splitting of the conus arteriosus and ventral aorta, particularly in reptiles, birds, and mammals, in such a manner that systemic and pulmonary trunks are established (Fig. 3*b*–*e*). The systemic trunk, coming from the left ventricle (or left side of the ventricle), distributes oxygenated (or partially oxygenated) blood to the body in general. The pulmonary trunk, coming from the right ventricle (or right side of the ventricle),

carries blood to the lungs. Oxygenated blood returns through veins from the lungs to the left atrium. Vessels which carry blood from the heart to the lungs and back constitute the pulmonary circulation. Branches of the sixth pair of aortic arches give rise to the pulmonary arteries.

Coronary arteries, supplying the tissues of the heart itself, arise as branches of certain aortic arches or of the systemic trunk near the point where it emerges from the heart.

Somatic arteries

The arteries supplying the body proper are usually paired structures which clearly show evidences of segmental arrangement (metamerism). They spring from the dorsolateral regions of the dorsal aorta. Fusion of two or more segmental arteries may take place, obscuring the fundamental metameric arrangement.

Visceral arteries

Arteries supplying the viscera are of two kinds, paired and unpaired. The paired arteries, usually restricted to certain regions, are segmentally arranged. They supply structures derived from the part of the embryo from which the urogenital organs and their ducts arise.

Unpaired visceral arteries supply the spleen and digestive tract. There are usually three such vessels in vertebrates. The celiac artery supplies the stomach, spleen, pancreas, liver, and duodenum; the superior mesenteric artery supplies most of the intestine and a portion of the pancreas; and the inferior mesenteric artery goes to the posterior part of the large intestine and rectum. Variations from this condition are accounted for by fusions or separations.

Venous system

A comparison of veins in the various vertebrate groups shows that they too are arranged according to the same fundamental plan and that the variations encountered form a logical sequence as the vertebrate scale is ascended. In its development the venous system of higher forms passes through certain stages common to the embryos of lower forms.

Sinus venosus

The accessory chamber present in the hearts of lower vertebrates through which blood from all over the body is returned to the heart is the sinus venosus.

In cyclostomes and fishes the sinus venosus typically receives a pair of common cardinal veins, or ducts of Cuvier, formed by the union of anterior and posterior cardinals, a pair of small inferior jugular veins from the ventrolateral part of the head, and a pair of hepatic veins coming from the liver. In lower fishes a lateral abdominal vein also joins each duct of Cuvier. Each lateral abdominal vein receives a subclavian vein from the pectoral fin and an iliac vein from the pelvic appendage (**Fig. 4**). In some fishes the inferior jugular veins are lacking; in others they have fused. Teleost fishes lack lateral abdominal veins; rather, the subclavians enter the common cardinals. In the dipnoan *Epiceratodus*, the lateral abdominal veins fuse to form a single anterior abdominal vein which joins the sinus venosus directly.

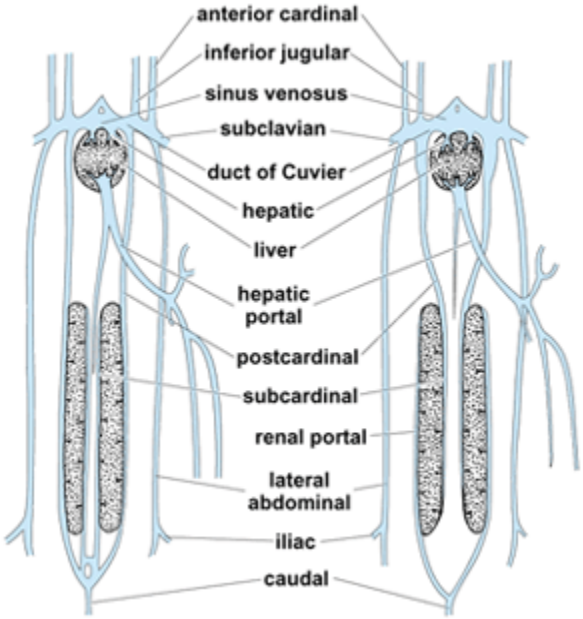

Fig. 4 Changes over the primitive condition which occur in the venous system of lower fishes, ventral view. ***(After C. K. Weichert, Anatomy of the Chordates, 3d ed., McGraw-Hill, 1965)***

The sinus venosus in amphibians is conspicuous. The ducts of Cuvier have consolidated to form two precaval veins, each of which, in addition to the usual vessels, receives a large musculocutaneous vein from the skin and body wall before joining the sinus venosus. A postcava, derived partly from the sinus venosus and partly from the vitelline veins, joins the sinus venosus posteriorly.

A large sinus venosus is present in turtles; in most reptiles, however, it has been greatly reduced and much of it may be incorporated within the wall of the right atrium. In such reptiles and in adult birds and mammals which lack a sinus venosus, precaval and postcaval veins enter the right atrium directly. Valves that are present where veins enter the right atrium represent vestiges of the sinus venosus.

Cardinal veins

Anterior cardinal, or jugular, veins are prominent in cyclostomes and fishes. In amphibians, reptiles, birds, and mammals they receive internal and external tributaries before joining the precaval veins. In some mammals a single precava is present, an anastomosis having developed between the two original vessels.

Postcardinal veins, which originally course along the lateral borders of the kidneys, at first carry blood away from the kidneys. In fishes they separate into anterior and posterior portions. The posterior sections terminate in the kidneys to become the renal portal veins. The anterior sections connect with a new pair of vessels, the subcardinals, which appear along the medial borders of the kidneys. These now carry blood from the kidneys to the heart. In caudate amphibians and a few salientians the condition is similar to that of fishes, but in most salientians the anterior portions of the postcardinals disappear, and the blood from the kidneys reaches the sinus venosus by way of the postcava. In reptiles and birds the renal portal veins have lost most of their significance, and in mammals they disappear entirely. A remnant of the anterior end of the right postcardinal of mammals becomes the azygos vein, a branch of the right precava which drains the intercostal muscles.

Abdominal veins

The lateral abdominal veins of amphibians and reptiles, like those of the lungfish *Epiceratodus*, have fused to form a single anterior abdominal vein. Instead of entering the sinus venosus, however, it joins the hepatic portal vein. In reptiles, birds, and

mammals the lateral abdominal veins are represented during embryonic life by allantoic or umbilical veins which lose their direct connections with the sinus venosus when the liver develops. In adult birds the anterior abdominal vein may possibly be represented by the coccygeomesenteric vein or the epigastric vein. It disappears entirely in all mammals, with the exception of the echidnas.

Portal systems

A portal system is a system of veins that breaks up into a capillary network before the blood which courses through it is returned to the heart. All vertebrates have a hepatic portal system in which blood collected from the digestive tract and spleen passes through capillaries (sinusoids) in the liver before reaching the heart. The embryonic vitelline (subintestinal) vessels are represented in adults by the hepatic portal vein and its tributaries. The renal portal system of lower vertebrates has already been mentioned. Another small but important portal system is found associated with the blood vessels draining the pituitary gland. *See also:* **Liver (/content/liver/387400)**

Miscellaneous

Coronary veins draining the tissues of the heart enter the sinus venosus in lower forms or the right atrium in higher vertebrates. Pulmonary veins, found in amphibians, reptiles, birds, and mammals, first appear in the dipnoan fishes, where their function is to drain the swim bladder. They enter the left atrium. *See also:* **Respiratory system (/content/respiratory-system/583600)**; **Swim bladder (/content/swim-bladder/672500)**

Charles K. Weichert

Comparative Embryology

The cardiovascular system in vertebrates arises from the splanchnic mesoderm, with the first blood and vessels formed in the wall of the yolk sac.

Heart

The heart of each species attains its characteristic morphology through an orderly series of changes which begin in early embryonic life. Although the details of development differ for different animals, there are a number of basic principles which apply to all species. Emphasis will be placed on the general principles first, and species characteristics will be noted subsequently.

The prospective heart rudiment, that is, the tissue which eventually differentiates into the heart, can be located by experimental procedures (exploration, transplantation, vital dyes, and autoradiographs) before morphological differentiation is observable. The rudiment consists of bilateral areas of splanchnic mesoderm located near the blastopore in the early amphibian gastrulae and near the pharyngeal arches just prior to initial morphological differentiation. *See also:* **Autoradiography (/content/autoradiography/065200)**

The heart field, the mesoderm with potency for heart development, is more extensive than the prospective rudiment which normally forms the organ. For example, a normal heart can develop in amphibians after complete removal of a visibly differentiated primordium. This results from migration of mesoderm from the periphery of the field to the region of extirpation.

The heart field, like the prospective rudiment, is bilateral. The potency for cardiac development is greatest at the center of the field and least at the periphery. The limits of the fields have been determined precisely in chick embryos by studies on the fates of small areas transplanted to the chorioallantoic membrane. *See also:* **Fate maps (embryology) (/content/fate-**

maps-embryology/251500)

Induction

The prospective rudiment in amphibian embryos becomes destined (determined) for heart development at the time of gastrulation through an inductive effect exerted by tissue adjacent to the blastopore. Endoderm has a further inductive role on the heart-forming mesoderm at the neurula stage, as evidenced by lack of heart development following extirpation of the endoderm. *See also:* **Embryonic induction (/content/embryonic-induction/230200)**

Determination and self-differentiation

The prospective rudiment is determined early, as outlined above. This is tested by transplantation to abnormal positions and by explantation as in tissue culture. The rudiment is described as self-differentiating when it attains the ability to develop in a foreign environment.

Polarity

Polarity or axial determination occurs at different times for the different axes. For example, when the anteroposterior axis is changed by 180° in neurula-stage amphibians, the heart develops with reversed morphology and beat. When the early rudiment is rotated around the long axis, altering only the dorsoventral and ventrolateral axes, the heart develops normally.

Totipotency

The ability of part of an organ rudiment to develop the whole organ is called totipotency. Experiments on amphibians, birds, and mammals show that either of the bilateral rudiments is capable of developing a complete organ. Furthermore, a whole organ may form from less than one-half; that is, several hearts can form from one rudiment.

Tubular heart formation

The heart is usually described as tubular during its early morphological differentiation, although it is saccular in shape in most species.

Mesenchymal cells arising from the splanchnic mesoderm of the heart rudiment differentiate into endocardium continuous with the subintestinal blood capillaries. The endocardial channels are bilateral at first; they eventually fuse into a single median tubular endocardium (**Fig. 5***a* and *b*).

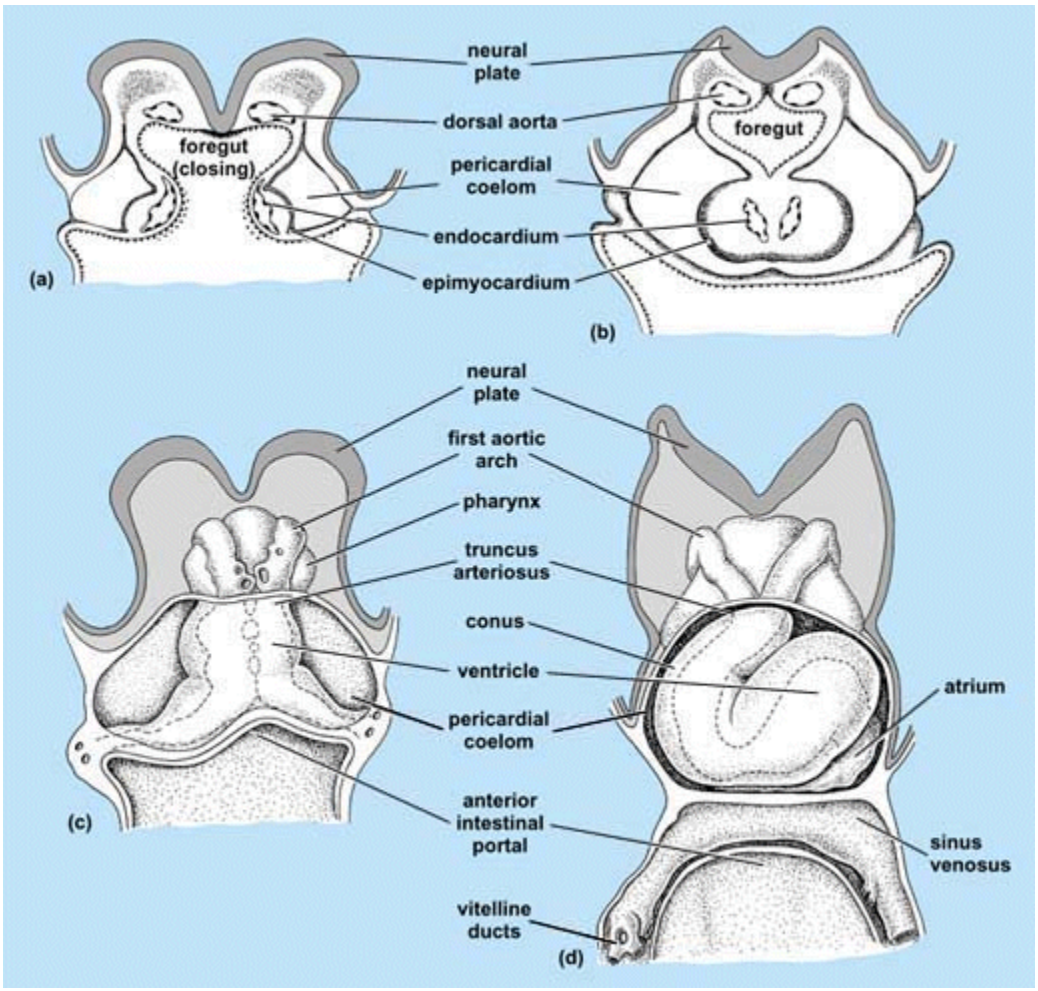

Fig. 5 Stages in development of the human heart. The organ is depicted as translucent, with the endocardium (broken lines) visible through the myocardium. (*a*) Cross section from a four-somite embryo. (*b*) Cross section at seven somites. (*c*) Ventral view at four somites. (*d*) Ventral view at thirteen somites.

The ventral portion of the splanchnic mesoderm of each bilateral heart rudiment thickens and differentiates into epimyocardium around the endocardium (Fig. 5). A space between endocardium and myocardium during early development is filled with homogeneous material known as cardiac jelly. It is eventually replaced by connective tissue uniting the endocardium and myocardium.

The space between the splanchnic and somatic mesoderm of the heart rudiment becomes the pericardial cavity, and a part of the somatic mesoderm differentiates into parietal pericardium.

The bilateral portions of the tubular heart approach the midline and unite to form a single tubular or saccular heart (Fig. 5). Fusion progresses in a cephalocaudal direction. Likewise, structural and functional differentiation of the chambers progresses cephalocaudally. These chambers, beginning with the most caudal one, are the sinus venosus, atrium, ventricle, and bulbus cordis (conus). The sinus venosus receives the blood from the veins; the bulbus empties into the truncus arteriosus and thence into the aortic arches.

The amount of morphological differentiation seen in the bilateral heart rudiments when they reach the midventral region of the body differs for different species. For example, the bilateral rudiments of the amphibian heart are only slightly differentiated at this time, whereas those of birds and mammals show considerable differentiation prior to union in the midline (Fig. 5*a* and *c*). This is because the heart of birds and mammals develops relatively early, while the mesoderm is spread out over the yolk sac. The two sides cannot come together until the head end of the body grows and folds off from the yolk sac. An early

development of the circulatory system is particularly important in mammalian embryos since they have very little yolk and come to depend very early upon metabolic exchange with the mother through a placental circulation. It is significant that the heart is the first organ to function.

Cardiac loop and regional development

The tubular heart is attached by its vascular trunks and by a continuity of visceral pericardium with the serous portion of the parietal pericardium at its venous and arterial ends. It is attached by a dorsal pericardium for only a brief period.

The heart becomes curved primarily due to its rapid growth. The heart increases in length so much faster than the cavity in which it lies that it first makes a U-shaped bend to the right and is then twisted into a loop. This moves the venous end cephalically and the arterial end caudally until the entering and exiting vessels approximate the same level in mammals (**Figs. 6***e* and **7***f*).

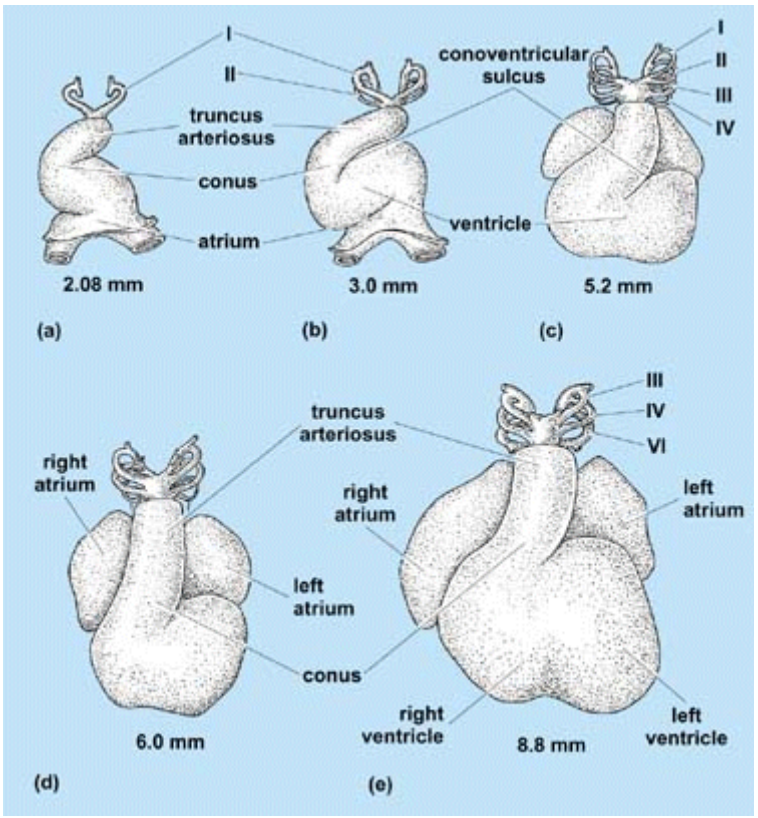

Fig. 6 Ventral views (*a*–*e*) of the human embryonic heart, showing the bending of the cardiac tube and the establishment of its regional divisions. The roman numerals I to VI indicate the aortic arches of corresponding numbers. (*After T. C. Kramer, Amer. J. Anat., 71(3):343–370, 1942*)

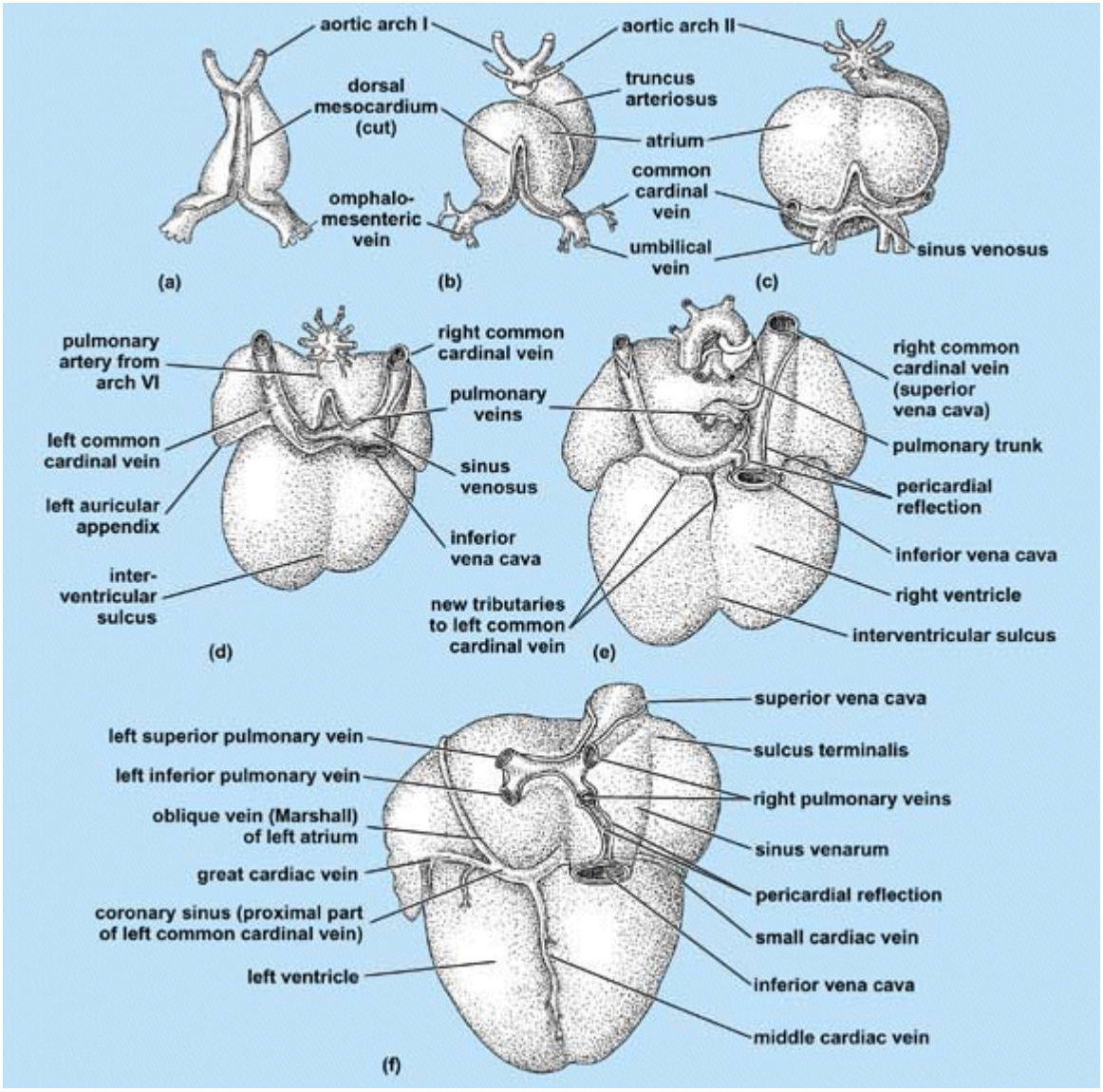

Fig. 7 Six stages in development of the heart, in dorsal aspect to show changing relations of the sinus venosus and great veins entering the heart. (*a*) 2.5 weeks (8–10 somites). (*b*) 3 weeks (12–14 somites). (*c*) 3.5 weeks (17–19 somites). (*d*) 5 weeks (6–8 mm or 0.24–0.31 in., crown-rump). (*e*) 8 weeks (about 25 mm or 1 in.). (*f*) 11 weeks (about 60 mm or 2 in.). (*After B. M. Patten, Human Embryology, 3d ed., Blakiston–McGraw-Hill, 1968*)

With the formation of the cardiac loop during the fifth week of human gestation, the primary regional divisions become clearly recognizable (Fig. 6). This is a result of the curvature and of different intrinsic growth rates in different regions. Blood flow also plays a part in the regional differentiation.

The sinus venosus is the thin-walled most caudal chamber into which the great veins enter (Fig. 7*c*). The atrial region is established by transverse dilation of the heart just cephalic to the sinus venosus, and the ventricle is formed by the bent midportion of the original cardiac tube (Figs. 5, 6, and 7). Between the atrium and ventricle, the heart remains relatively undilated to form the atrioventricular canal. The conus is distinguishable as a separate region prior to its later incorporation into the right ventricle. The most cephalic part of the cardiac tube undergoes the least change in appearance, persisting as the truncus arteriosus connecting the conoventricular region to the aortic arches (Figs. 5 and 6).

Studies on amphibians, birds, and mammals show that initial cardiac contractions begin in the ventricular region. The heart at this time is just slightly less developed than that illustrated in Fig. 6 for a human embryo 0.08 in. (2 mm) long (beginning of fourth week of development). With further cardiac differentiation in a cephalocaudal direction, the atrium and sinus venosus acquire the ability to contract, each with a successively higher intrinsic rate which dominates its predecessor.

Innervation of the heart occurs subsequent to the time when the sinus differentiates and takes over the pacemaker function. The fact that the embryonic heart pulsates rhythmically and carries on circulation prior to innervation indicates the beat is myogenic rather than neurogenic in origin.

The myocardium shows cytological differentiation relatively early. Electron micrographs of developing heart muscle cells show randomly oriented myofilaments (actin and myosin) prior to the time when striations appear due to the alignment of the filaments in register in myofibrils. A compact, well-oriented arrangement of myofibrils, each composed of many myofilaments, occurs earlier in the ventricle than in the atrium. The sinus venosus (shown in **Fig. 8** for the tadpole heart just prior to the time of innervation) retains an irregular arrangement in adult amphibians. In mammals, where the sinus venosus becomes incorporated into the right atrium, the sinoatrial node is composed of cells which have sparse randomly oriented myofibrils, like those which are found in the amphibian sinus venosus. The irregular arrangement is one of the characteristics of pacemaker cells. *See also:* **Heart (invertebrate) (/content/heart-invertebrate/309800)**; **Muscle (/content/muscle/439700)**

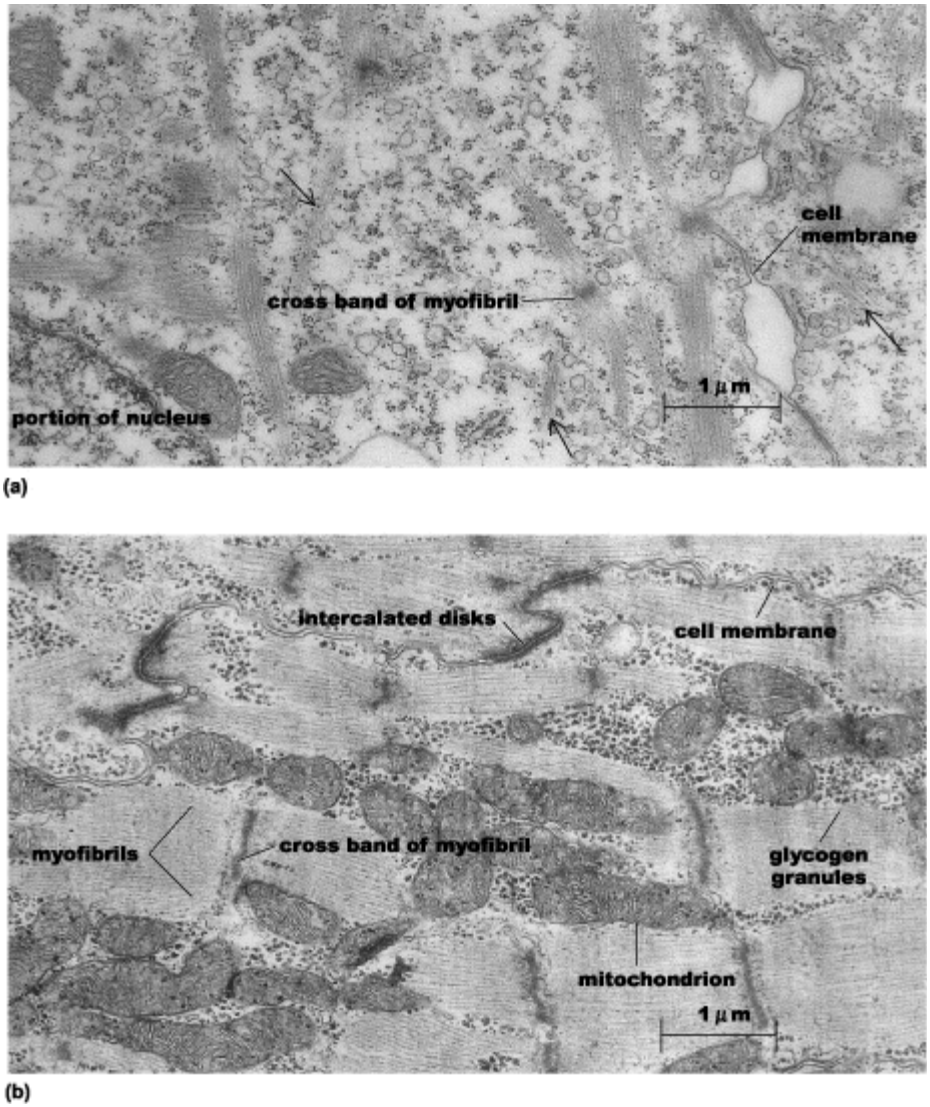

Fig. 8 Electron micrographs of cardiac muscle at different stages of development. (*a*) Section of sinus venosus from the heart of a tadpole just before the feeding stage. (*b*) Section of ventricle of adult frog. Note that the tadpole sinus has irregularly arranged myofilaments (at arrows) and poor alignment of filaments into myofibrils with only a few cross bands.

Formation of definitive heart

The morphological changes which occur in the heart while it differentiates from a tubular structure to its definitive adult form

vary for different classes and species of vertebrates in correlation with different functional requirements. The changes in elasmobranch fishes are few and simple. The heart retains all its primitive chambers in sequence (sinus, atrium, ventricle, and conus) and each chamber remains unpartitioned.

In adult amphibians the heart attains an external form and curvature beyond that illustrated in Fig. 5 for a mammalian embryo, but it retains the chambers in sequence. In urodele amphibians there is a partial division of the atrium into right and left sides; in anuran amphibians the atrial division is complete, but other parts remain undivided.

The heart of reptiles has the atrium divided completely into right and left chambers while the ventricle is divided only partially.

In birds and mammals the sinus venosus is incorporated into the right atrium, which is divided completely from the left atrium; the primitive ventricle is completely divided into right and left chambers; the conus is incorporated into the right ventricle; and the truncus arteriosus is divided into right and left sides to form the roots and proximal portions of the pulmonary artery and aorta.

The fusion of the sinus venosus with the right atrium is somewhat more complete in most mammals than in birds. In mammals specialized tissues develop in certain areas of the original sinus region to form the sinoatrial and atrioventricular nodes. The sinoatrial node, located near the entrance of the superior vena cava, serves as the cardiac pacemaker.

Complete division of the heart into right and left sides, that is, a complete separation of respiratory and systemic circulations, is achieved only in birds and mammals. This supplies a higher arterial pressure on the systemic side and distributes oxygenated blood to the tissues more rapidly than in animals with partial separation (reptiles and amphibians) or those with no separation (fishes).

Partitioning of mammalian heart

The division of the heart into right and left sides has been studied in detail in humans and in a number of other mammals. The following account applies primarily to the human heart, but the general plan of partitioning is similar in other mammals. It should be noted that the partitioning of the embryonic heart involves more than its structural division into parts. The process is beset by striking functional exigencies. Cardiac partitioning in the human embryo does not begin until about the fifth week of development, 0.2 in. (6 mm) long, when the heart (Fig. 6*d*) is already maintaining a circulation essential for embryonic life. All of the complex changes in partitioning must be made without interruption of the blood supply to any part of the growing embryo. Starting with a stage when the blood is flowing through it in an undivided stream, the heart, by the time of birth, must become converted into an elaborately valved, four-chambered organ, pumping from its right side a pulmonary stream which is returned to its left side to be pumped out again over the aorta as the systemic bloodstream. Moreover, at the end of gestation, the vascular mechanism must be prepared for air breathing. At the moment of birth the lungs, their blood vessels, and the right ventricle (which pumps the pulmonary circuit) must be ready to take over from the placenta the entire responsibility of oxygenating the blood.

The systemic part of the circulation must also be prepared. During intrauterine life the left side of the heart receives less blood from the pulmonary veins than the right side receives from the vena cavae. Immediately after birth the left ventricle is called on to do more work than the right ventricle. It must pump sufficient blood through the myriad peripheral vessels of the systemic circulation to care for the metabolism and continued growth of all parts of the body. These are just some of the striking functional situations which the growing heart must encounter before it can attain its adult condition.

Division of atrium and ventricles

Almost from their earliest appearance, the atrium and ventricle show external indication of their impending division into right and left sides. A distinct median furrow appears at the apex of the ventricle (Figs. 7*d* and *e* and 6*c*–*e*). The atrium meanwhile bulges out on either side of the midline (Fig. 7). Its bilobed configuration is emphasized by the manner in which the truncus arteriosus compresses it mid-ventrally (Fig. 6*c*–*e*). These superficial features suggest the more important internal changes.

As the wall of the ventricle increases in thickness, it develops internally a meshwork of interlacing muscular bands, the trabeculae carneae. Opposite the external furrow these muscular bands become consolidated as a partition which projects from the apex of the ventricle toward the atrium. This is the interventricular septum (**Fig. 9**).

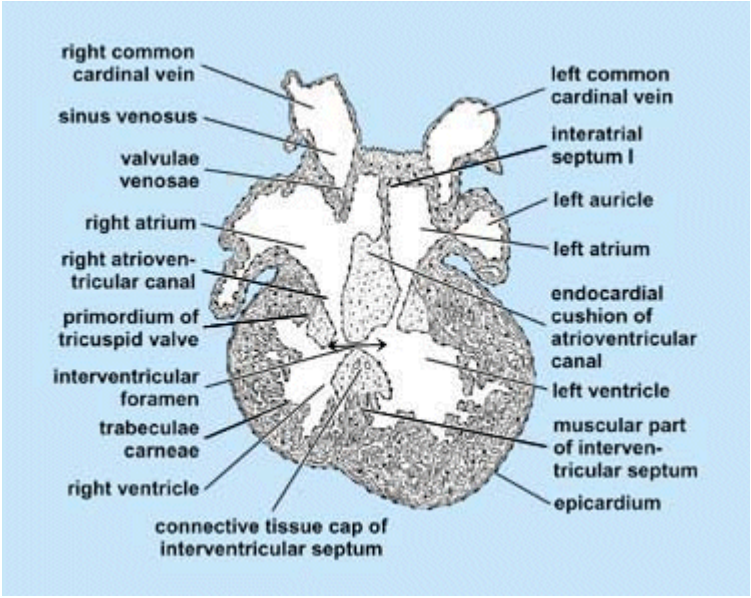

Fig. 9 Section through heart of a 9.4-mm (0.37-in.) pig embryo. Stage of development corresponds to that in a human embryo of the sixth week. (*After B. M. Patten, Foundations of Embryology, 2d ed., McGraw-Hill, 1965*)

Meanwhile, two conspicuous masses of the loosely organized mesenchyme called endocardial cushion tissue develop in the walls of the narrowed portion of the heart between the atrium and ventricle. One of these endocardial cushions of the atrioventricular canal is formed in its dorsal wall (**Fig. 10***b*). A similar one is formed opposite it on the ventral wall. When these two masses meet, they divide the atrioventricular canal into right and left channels (**Fig. 11**).

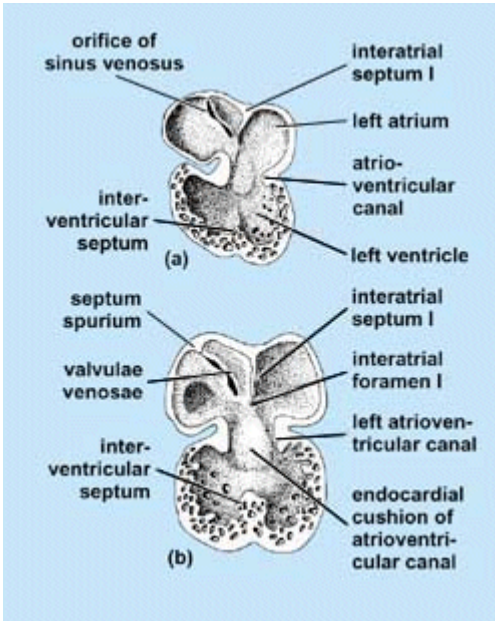

Fig. 10 Interior of heart showing initial steps in its partitioning. (*a*) Cardiac septa in human embryos early in fifth week, showing primary relations of interatrial septum primum. Based on original reconstruction of heart of a 3.7-mm (0.15-in.) pig embryo and on Tandler's reconstructions of corresponding stages of the human heart. (*b*) Cardiac septa in human embryos of sixth week. Note restriction of interatrial foramen primum by growth of interatrial septum primum. Based on original reconstructions of the heart of 6-mm (0.24-in.) pig embryo, on Born's reconstructions of rabbit heart, and Tandler's reconstructions of corresponding stages of the human heart. (*After B. M. Patten, Human Embryology, 3d ed., Blakiston–McGraw-Hill, 1968*)

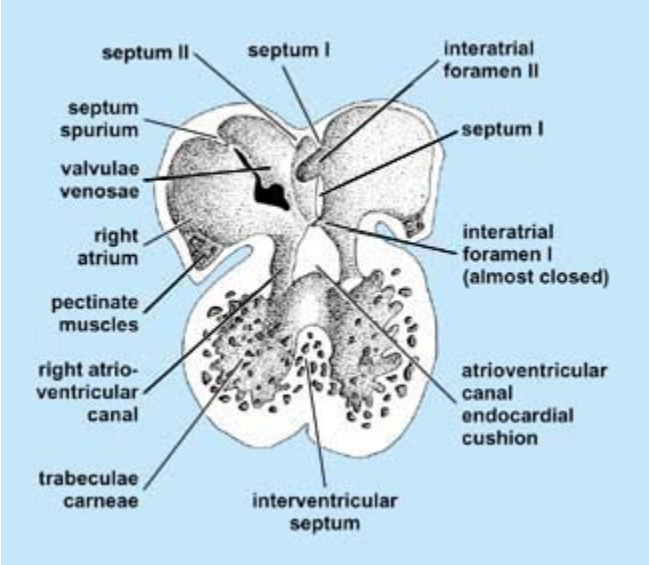

Fig. 11 Interior of heart showing start of interatrial septum secundum and appearance of interatrial foramen secundum in septum primum. Based on original reconstructions of the hearts of pig embryos and on Tandler's reconstructions of the heart of human embryos of the seventh week. (*After B. M. Patten, Human Embryology, 3d ed., Blakiston–McGraw-Hill, 1968*)

Septum primum

Concurrently, a median partition appears in the cephalic wall of the atrium. Because another closely related partition will form adjacent to it later, this is called the first interatrial septum or septum primum. It is composed of a thin layer of young cardiac muscle covered by endothelium. It is crescent-shaped, with its concavity directed toward the ventricle. The apices of the crescent extend to the atrioventricular canal where they merge, respectively, with its dorsal and ventral endocardial cushions (Fig. 10). This leaves the atria separated from each other except for a diminishing opening called the interatrial foramen primum (Fig. 10*b*).

While these changes have been occurring, the sinus venosus has been shifted out of the midline so that it opens into the atrium to the right of the interatrial septum (Fig. 7). The heart is now in a critical stage of development. Its original simple tubular form has been altered so that the four chambers characteristic of the adult heart are clearly suggested. Partitioning of the heart into right and left sides is well under way, but there are still open communications from the right to the left side in both atrium and ventricle. If partitioning were completed now, the left side of the heart would be left almost literally dry, because the sinus venosus, into which systemic, portal, and placental currents all enter, opens on the right of the interatrial septum. Not until much later do the lungs and their vessels develop sufficiently to return any considerable volume of blood to the left atrium. The partitions in the ventricle and in the atrioventricular canal do progress rapidly to completion (Figs. 10, 11, and **Fig. 12**), but an interesting series of events takes place in the interatrial septal complex which assures that an adequate supply of blood will reach the left atrium and thence the left ventricle.

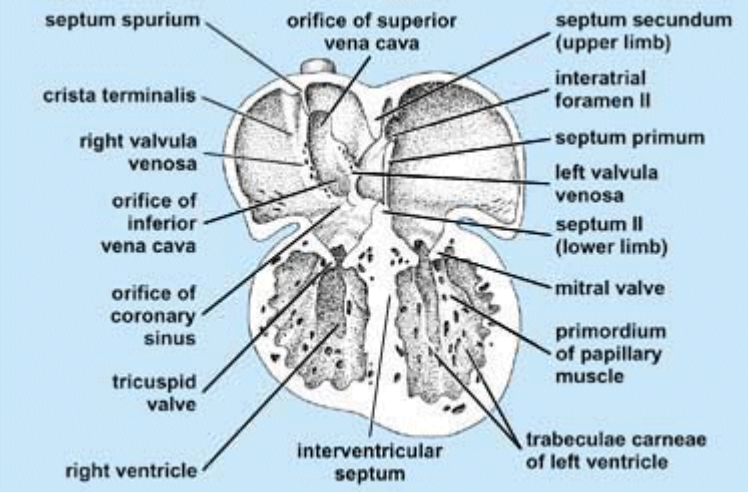

Fig. 12 Heart of third-month human embryo. Resorption has begun in valvulae venosae and septum spurium as indicated by many small perforations in their margins. Left venous valve is coming to lie against and fuse with septum secundum; it usually leaves no recognizable traces in the adult, but occasionally delicate lacelike remains can be seen adhering to septum secundum, and more rarely, extending a short distance onto the valvula foraminis ovalis. (*After B. M. Patten, Foundations of Embryology, 2d ed., McGraw-Hill, 1964*)

In the sixth week, just when the septum primum is about to fuse with the endocardial cushions of the atrioventricular canal, thus closing the inter- atrial foramen primum, a new opening is established. The more cephalic part of the septum primum becomes perforated, at first by multiple small holes. These soon coalesce to form the interatrial foramen secundum, thus keeping a route open from the right to the left atrium (Fig. 11).

Septum secundum

During the seventh week the second interatrial partition makes its appearance just to the right of the first. Like the septum primum, the septum secundum is crescent-shaped. The concavity of its crescent is, however, differently oriented. Whereas the open part of the septum primum is directed toward the atrioventricular canal, the open part of the septum secundum is directed toward the lower part of the sinus entrance which later becomes the opening of the inferior vena cava into the right atrium (Figs. 11 and 12). This difference in the direction of growth in the two interatrial septa is of vital functional significance because it means that as the septum secundum grows, the opening remaining in it is carried out of line with the interatrial foramen secundum in the septum primum (Fig. 12). The opening in the septum secundum, although it becomes relatively smaller as development progresses, will not be completely closed but will remain as the foramen ovale.

The flaplike persisting portion of the septum primum overlying the foramen ovale constitutes an efficient valvular mechanism between the two atria. When the atria are filling, some of the blood returning by way of the great veins can pass freely through the foramen ovale merely by pushing aside the flap of the septum primum. When the atria start to contract, pressure of the blood within the left atrium forces the septum primum against the septum secundum, effectively closing the foramen ovale against return flow into the right atrium. Without some such mechanism to afford a fair share of blood to the left atrium, the fetal left ventricle would receive a low blood volume, and as a result its muscular wall would not develop adequately to carry its postnatal pumping load. The strength of cardiac muscle and other muscles in the body depends on the work the muscle is called upon to do.

Division of the truncus

While these changes are going on in the main part of the heart, the truncus arteriosus is being divided into two separate channels. This process starts where the truncus joins the ventral roots of the aortic arches. Continuing toward the ventricle, the division is effected by the formation of longitudinal ridges of plastic young connective tissue of the same type as that

making up the endocardial cushions of the atrioventricular canal. These ridges, called truncus ridges, bulge progressively further into the lumen of the truncus arteriosus and finally meet to separate it into aortic and pulmonary channels (**Figs. 13** and **14**). The semilunar valves of the aorta and the pulmonary trunk develop as local specializations of these truncus ridges. Toward the ventricles from the site of formation of the semilunar valves, the ridges are continued into the conus of the ventricles (**Fig. 15**). The truncoconal ridges follow a spiral course through the truncus and extend down into the ventricles, where they meet and become continuous with the margins of the interventricular septum. This reduces the relative size of the interventricular foramen but does not close it completely. Its final closure is brought about by a mass of endocardial cushion tissue from three sources. Bordering the interventricular foramen ventrocaudally is the interventricular septum, the crest of which, above its main muscular portion, is made up of endocardial cushion tissue (Fig. 9).

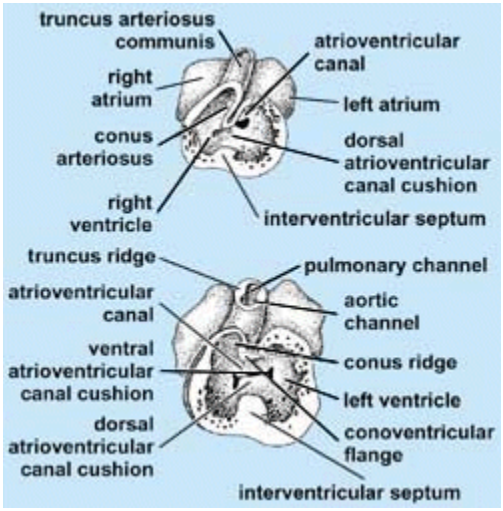

Fig. 13 Dissections of developing hearts in frontal aspect to show relations of importance in establishing aortic and pulmonary outlets. (*After T. C. Kramer, Amer. J. Anat., 71(3):343–370, 1942*)

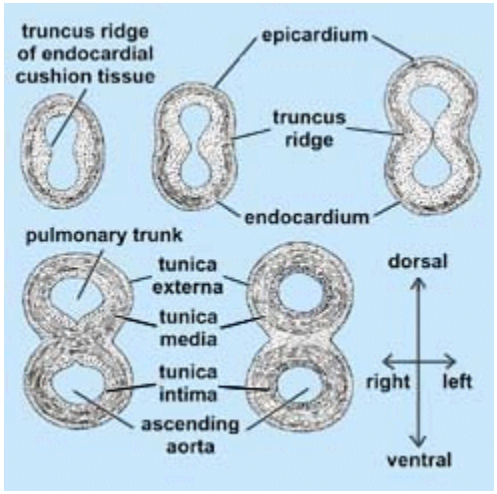

Fig. 14 Partitioning of the truncus arteriosus to form the ascending aorta and the pulmonary trunk. (*After S. E. Gould, Pathology of the Heart, Charles C. Thomas, 1953*)

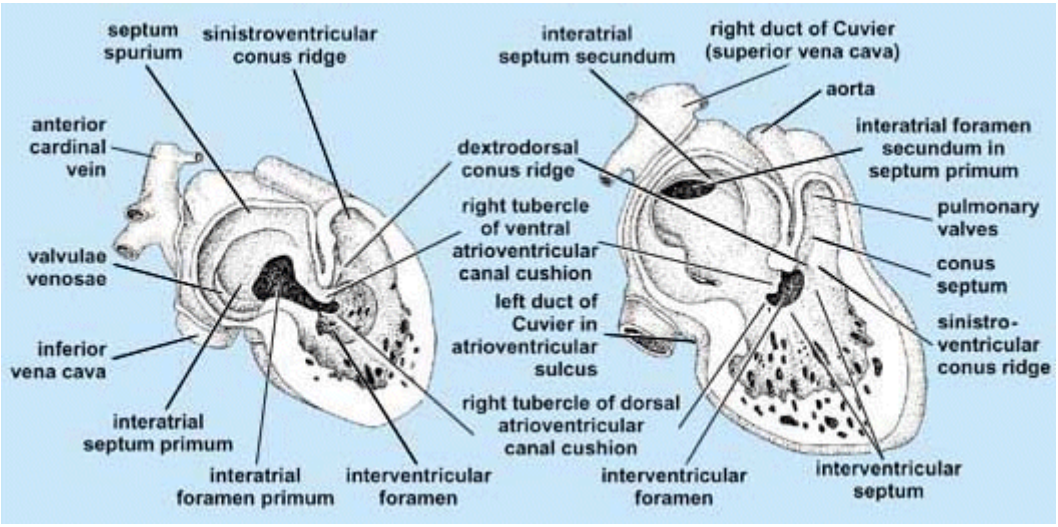

Fig. 15 Lateral dissections showing the relations of the various septa in the developing heart. (*After B. M. Patten, Human Embryology, 3d ed., Blakiston–McGraw-Hill, 1968*)

Toward the atrioventricular canal lie the masses of endocardial cushion tissue which were responsible for its partitioning (Fig. 15). In the conus outlet are the ridges that were just considered. From all three of these adjacent areas, endocardial cushion tissue encroaches on the opening. About the end of the seventh week, the interventricular foramen is completely plugged with a loose mass of this young, readily molded connective tissue. Later this mass differentiates into the membranous portion of the interventricular septum and the septal cusps of the atrioventricular valves. When the interventricular septum has thus been completed, the right ventricle leads into the pulmonary trunk and the left leads into the ascending aorta. With this condition established, the heart is completely divided into right and left sides except for the interatrial valve at the foramen ovale which must remain open throughout fetal life until after birth, when the lungs attain their full functional capacity and the entire volume of the pulmonary stream passes through them to be returned to the left atrium.

Ductus arteriosus

This leaves only one of the functional exigencies of heart development still to be accounted for. If, during early fetal life and before the lungs are well developed, the vessels to the lungs were the only exit from the right side of the heart, the right ventricle would not have an outlet adequate to develop its pumping power. It is only late in fetal life that the lungs and their vessels develop to a degree which prepares them for assuming their postnatal activity, and the power of the heart muscle can be built up only gradually by continued functional activity. This situation is met by the ductus arteriosus, leading from the pulmonary trunk to the aorta. Throughout fetal life any blood from the right ventricle that cannot be accepted within the pulmonary circuit is shunted by way of the ductus into the descending aorta. Thus the right ventricle is able to develop its muscular walls by pumping throughout prenatal life its full share of the cardiac load.

The foregoing account of cardiac partitioning applies particularly to the human. There are some notable exceptions in cardiac development in the opossum, a mammal in which the young are born in a primitive stage and continue their development for several weeks in the mother's pouch. This species does not have a secondary interatrial septum or a fossa ovalis. The primary septum has multiple perforations, a few of which persist until birth. The sinus venosus remains in a more primitive stage, clearly defined from the right atrium. The left superior vena cava also persists, opening into the sinus portion of the atrium by way of the coronary sinus.

The rabbit also maintains a more primitive arrangement of the vessels and a more evident sinus region much like the opossum.

Embryogenesis of blood vessels

The endothelial lining of the earliest embryonic vessels arises from mesenchyme, with differentiation occurring first in the wall of the trophoblast and only slightly later in the body stalk and yolk sac. The mesenchymal cells with potency to form endothelium are designated as angioblasts.

According to one view (angioblastic theory), the vessels within the body of the embryo arise by migration of angioblasts from the body stalk and yolk sac. According to the local origin theory, the main intraembryonic vessels, such as the aorta, arise by in situ differentiation from vasoformative mesenchymal cells. Most experimental evidence favors the latter view.

After the main embryonic vessels have arisen, new vessels arise by vascular sprouts from preexisting vessels. Regeneration of endothelium of new vessels following injury in adult life is likewise dependent upon outgrowth from preexisting endothelium.

Angiogenesis

The earliest observable differentiation of endothelium occurs in blood islands of the trophoblast, body stalk, and yolk sac. Each island consists of mesenchymal cell clusters in which the central cells differentiate into blood corpuscles and the peripheral cells elongate and transform into endothelium. Growth and union of the isolated vascular spaces give a plexus of primitive vascular channels. Endothelium of the main vessels of the body of the embryo differentiates also but without relationship to blood islands.

Circulatory system morphogenesis

The earliest vessels are anastomosing, thin-walled tubes (capillaries) lined only by endothelium. In the course of differentiation, some of the capillaries enlarge to form arteries and veins, some remain as capillaries, and some fall into disuse and atrophy. It seems well established that the amount rather than the rate of blood flow through any given portion of a capillary plexus determines whether a vessel merely persists as a capillary enlarges to form an artery or vein. In a similar manner, alterations in vascular pathways occur after the capillary plexus stage of differentiation. For example, arteries atrophy when their blood flow is diverted to newly formed vessels.

Formation of ventral aorta

The aorta arises from bilateral primordia continuous with the bilateral cardiac primordia. The bilateral rudiments quickly fuse to form a common truncus arteriosus continuous with the bulbus cordis. By formation and fusion of two longitudinal ridges along the inner surface of the distal portion of the bulbus, the primitive aortic bulb is split into a pulmonary trunk and an ascending aorta. The latter is relatively short in mammals. It connects with the dorsal aorta by means of aortic arches which vary at different embryonic stages, and the final pattern differs in different species.

Formation of aortic arches

In mammalian embryos there are usually six pairs of arches, but these do not all function simultaneously. Furthermore, the fifth pair is very rudimentary. The arch which follows the questionable fifth one is usually called the pulmonary arch because it becomes a part of the pulmonary arterial system.

The first pair of aortic arches forms in human embryos at the beginning of the fourth week, and the remaining pairs develop in sequence during the fourth week. Transformations (**Fig. 16**) occupy the fifth to seventh weeks.

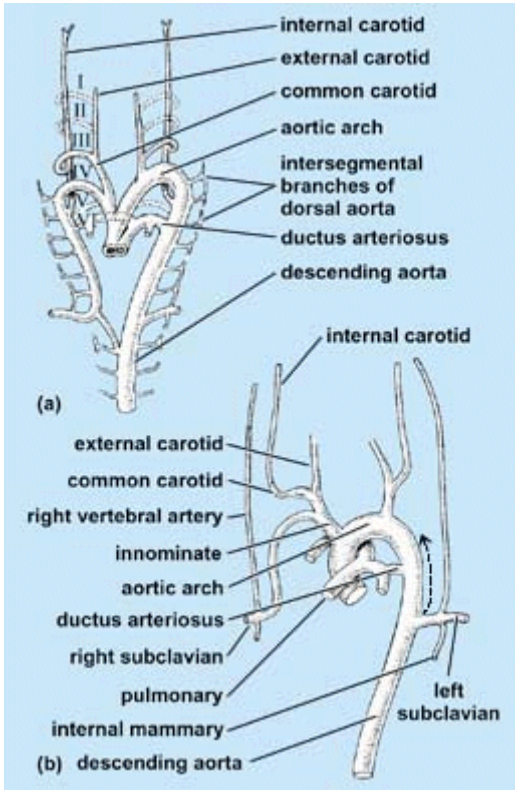

Fig. 16 Transformations of human aortic arches, ventral view. (*a*) Diagram of early stage of transformation when first, second, and fifth pairs of vessels (broken lines) have degenerated. (*b*) Adult derivatives. Diagram, from fetus, shows left subclavian arising from caudal part of arch, but shifts to a higher position at a later stage, indicated by arrow. Ductus arteriosus normally atrophies after birth.

The first and second pairs become dysfunctional and atrophy as the third and fourth pairs enlarge, and form more direct pathways from the ventral to the dorsal aortas. Following atrophy of portions of the dorsal aortas between levels of the third and fourth arches, the third arches and cephalic portions of the dorsal aortas remain as paired primitive internal carotid arteries. After the external carotid grows out from the third arch, the proximal portion is known as the common carotid.

The fate of the fourth arches differs for different classes of vertebrates. In mammals the left fourth arch persists as the arch of the aorta, whereas the right fourth arch forms a portion of the innominate artery and the proximal portion of the subclavian artery (Fig. 16). In birds the condition is the reverse, with the arch of the aorta forming on the left. In reptiles and amphibians both fourth arches retain their connection with the dorsal aorta.

Formation of dorsal aorta

The dorsal aorta arises from bilateral primordia which persist as the paired internal carotids cephalically (Fig. 16) and fuse caudally to form the descending aorta.

The aorta has dorsal, lateral, and ventral branches which are arranged serially. There are about 30 pairs of dorsal branches, which are also known as intersegmental arteries because they occur between successive body segments. Each of the intersegmental arteries divides into dorsal and ventral rami; the dorsal rami give rise to the spinal and vertebral arteries and the ventral rami form the intercostals and lumbars. The lateral aortic branches are not segmentally arranged. They form the renal, suprarenal, inferior phrenic, and internal spermatic or ovarian arteries. The ventral aortic branches develop as paired vitelline arteries to the yolk sac. They fuse when the paired aortas fuse. Later, they are reduced until they occur only at three levels, forming the celiac, superior mesenteric, and inferior mesenteric arteries.

Arteries of the extremities

Vascularization of the extremities illustrates the growth of given pathways within a plexus of vessels. At first, each extremity has a blood supply from several lateral aortic branches. Then, one lateral branch enlarges and the others fall into disuse. In the arm the main stem is the brachial artery which is a continuation from the subclavian. The extension of the brachial into the arm progresses by differential growth of pathways of a capillary plexus. At one stage, the brachial continues by the interosseous to the vessels of the hand. Later, when the median artery arises as a brachial branch and annexes the vessels of the hand, the interosseous becomes less prominent. At a still later stage, the ulnar and radial arteries develop as brachial branches and become the main vessels of the forearm.

The first axial vessel of the leg is known as the sciatic artery. Later, it is superseded by the femoral artery which is a continuation of the external iliac, a branch of the common iliac. After the femoral joins and annexes portions of the sciatic, the proximal portion of the sciatic persists merely as the inferior gluteal, whereas the distal part of the sciatic becomes the popliteal artery in continuity with the femoral.

Primitive venous system

In the early embryo there are three sets of paired veins of particular significance: vitellines carrying blood from the yolk sac to the heart, umbilicals from the placenta, and cardinals from the head and body.

Changes in vitelline veins

Changes in these vessels are correlated with the developing liver in the sense that there is a mutual intergrowth between cords of hepatic cells and endothelial sprouts from the vitelline veins. Thus the vitelline veins are interrupted by liver sinusoids. By enlargement of some of the sinusoids, a direct channel is formed between the left umbilical vein and the proximal portion of the right vitelline (the future hepatic); the channel is known as the ductus venosus.

Caudal to the liver, the right and left vitelline veins become united by three cross anastomoses. By growth of some parts and atrophy of other parts of this system, the S-shaped portal vein arises.

The segment of the right vitelline between the liver and the heart becomes the hepatic vein; the left vitelline of this level disappears.

Changes in umbilical veins

During its growth, the liver encroaches on the umbilical veins until all the umbilical blood enters the liver. Then the entire right umbilical vein atrophies, leaving the left vein which empties into the ductus venosus. The left umbilical vein and the ductus venosus persist as important vessels until birth; then they atrophy and become the ligamentum teres and the ligamentum venosum, respectively.

Plan of the cardinal veins

Paired precardinal veins from the head join paired postcardinals from the body at the level of the heart to form the common cardinals (ducts of Cuvier). During development, parts of the postcardinals are replaced and superseded by subcardinals and supracardinals. The major veins of the body arise through transformation of the cardinal system.

Changes in precardinals, common cardinals

The precardinal of each side is composed of a primary head vein and the precardinal proper extending from the head to the common cardinal. The head vein drains anterior, median, and lateral plexuses over the brain. The rostral portion of the head vein becomes the cavernous sinus; portions of the anterior plexus enlarge to become the superior sagittal sinus; and a dorsal

connection between the middle and posterior plexuses becomes the transverse sinus. The main precardinal stem of each side becomes the internal jugular vein as far caudal as the level of a shunt from the left to the right precardinal (**Fig. 17**). The shunt itself becomes the left brachiocephalic (left innominate), and the left precardinal caudal to the shunt remains as the relatively small first intercostal.

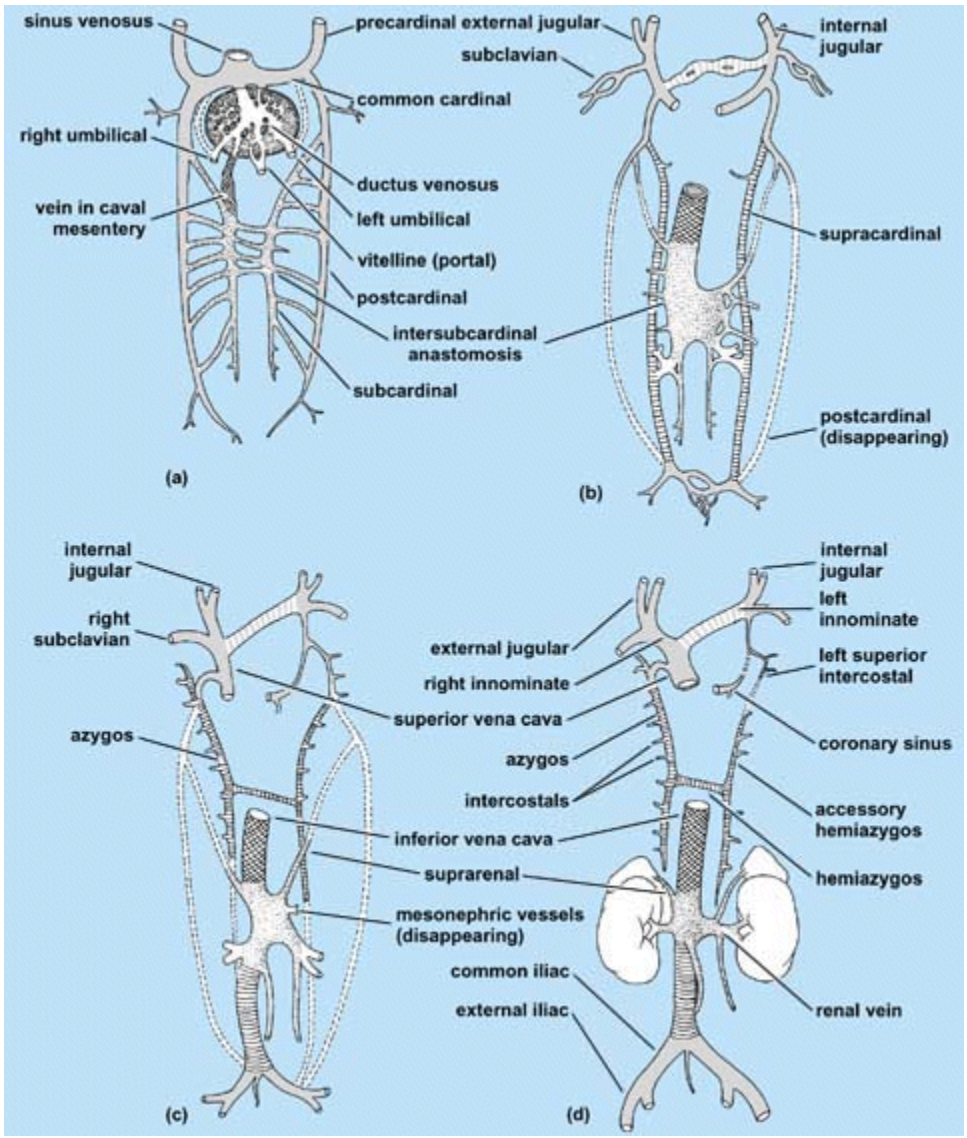

Fig. 17 Transformations of primitive veins of human embryo, ventral view. (*a*) At 5.5 weeks. (*b*) At 7 weeks. (*c*) At 8 weeks. (*d*) At term. In *a*, proximal portions of umbilicals (broken lines) have atrophied. Remainder of the right umbilical atrophies later. Vitellines (omphalomesenterics) have been interrupted by liver sinusoids. Right proximal vitelline has enlarged and will become the hepatic. Caudal portions of vitellines are transforming into the portal vein. A connection from hepatic to subcardinals via ventral mesentery will form hepatic segment of inferior vena cava. Vessels associated with liver are omitted from *b*, *c*, and *d*.

The right common cardinal with the right precardinal up to the point of intercardinal anastomosis forms the superior vena cava. The left common cardinal of humans persists as the small oblique vein of the left atrium. As a congenital anomaly, it may remain as a left superior vena cava. In some mammals and in the lower vertebrates, two superior venae cavae (left and right) occur normally.

Postcardinal system transformations

Postcardinals develop primarily as vessels of the mesonephroi and their fate in different species varies with that of the mesonephroi. In *Petromyzon* the postcardinal of each side remains, as in the embryo; in elasmobranchs the plan is modified by a renal portal system; and in humans and some other mammals the postcardinals become altered, as shown in Fig. 17.

This transformation is related to the development of subcardinal veins ventral to the mesonephroi, and supracardinals dorsomedial to the postcardinals. Parts of each of these systems contribute to the formation of the inferior vena cava (Fig. 17).

Veins of the extremities

These develop by channels within capillary plexuses, as already described for the arteries. Each extremity of an early embryo develops a peripheral or border vein. In the upper extremity the border vein persists on the ulnar side as the subclavian, axillary, and basilic veins; in the lower extremity the border vein persists on the fibular side.

Pulmonary veins

These develop from pulmonary plexuses. At one stage of development, all branches combine to open by a single stem into the left atrium. By growth of the atrium, more of the pulmonary vessel is drawn into the atrial wall until there are four pulmonary vein openings into the atrium, two from each lung.

W. M. Copenhaver

Functional Development of Heart

The heart begins to beat before all its parts have been formed. The character of the heartbeat changes with the sequential formation of the regions of the heart. The heart arises by the fusion of bilateral primordia which converge from positions on opposite sides of the embryo. In the human embryo virtually the entire development of the heart and major blood vessels occurs between the third and eighth weeks of embryonic life. In the chick embryo, one of the principal objects of experimental analysis, the bilateral primordia begin to fuse in the seven-somite stage. The first beats can be recorded in the embryo of nine somites, where the first cross striations also occur.

Contractions of the heart

The first contractions occur along the right side of the developing ventricle, the first part of the heart to form. The beat is at first slow but rhythmical and gradually involves the whole wall of the ventricle. The first contractions may be described as rhythmic but intermittent, that is, rhythmic contractions interrupted by rest periods. Next is added the atrium, which begins to contract at a higher rate than that of the ventricle, stepping up the rate of the entire heart, because the part of the tube with the highest rate of contraction sets the pace for the heart as a whole. At this time the blood is set in motion. The sinus venosus begins to contract somewhat later; again, its inclusion steps up the heartbeat. Contractions begin before any of the nerve fibers (which in their development grow out from the central nervous system), reach the heart and before the specialized system for conducting impulses in the heart is established. The nervous system secondarily assumes the regulation of the rate of the pulsations originating in the myocardium, retarding and accelerating functions being by the vagus and cervical sympathetic fibers, respectively.

Heart-forming areas

The first pulsations of the heart are foreshadowed by the localization of the heart-forming cells to well-demarcated regions of the embryo in the head-process stage, about 10 h earlier. **Figure 18** shows the position of the heart-forming areas as demonstrated by experimental tests of the histogenetic capacity of isolated fragments of the early embryo. Although cardiac muscle arises from the mesoderm, it is impossible to state whether it develops independently in the chick or whether interactions between the mesoderm and endoderm are required. Such an inductive interaction appears to be required for normal development of the heart in the salamander embryo.

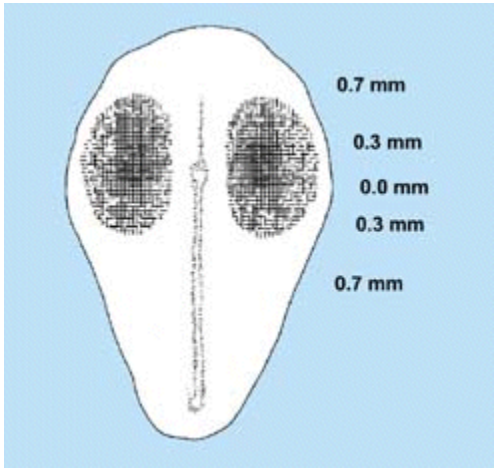

Fig. 18 Heart-forming areas in a head-process stage chick blastoderm. Numerals show distances from level of primitive pit. (*After M. E. Rawles, The heart-forming areas of the early chick blastoderm, Physiol. Zool., 16:22–42, 1943*)

Contractile proteins

The question has been raised as to what extent the early localization of heart-forming cells reflects the early differentiation of specificity in chemical composition or metabolism. It has also been questioned whether the heart-forming areas differ chemically from adjacent regions of the embryo. Immunochemical techniques employing as tools specific antiheart sera reveal that the early embryo contains macromolecules identical with or closely related to those of the adult heart, a conclusion that is supported by the additional finding that when early embryos are cultured in a medium containing antiheart serum the development of the heart is differentially suppressed. Similar techniques show time of origin and pattern of localization of the cardiac contractile proteins, myosin and actin.

Synthesis of contractile proteins

The synthesis of cardiac myosin is initiated during the formation of the mesoderm, the protein being detected first during the movement of prospective mesodermal cells through the primitive streak. As these formative movements are terminated, myosin is distributed widely in the ectoderm and mesoderm, but cannot be detected in the endoderm. At the head-process stage, cardiac myosin is restricted to the heart-forming regions of the embryo where, at the same time, the synthesis of cardiac actin is initiated. It is impossible at the present time to say whether the myosin first detected is adult myosin, or a complete myosin molecule closely related to but not identical with the adult protein, a situation that exists in the sequential formation of fetal and adult hemoglobin molecules. It is postulated that, in the formation of cardiac muscle, the contractile proteins are synthesized and subsequently aggregated to form fibrils. Although this hypothesis of stepwise organization agrees with the limited information available on the development of the fine structure of heart muscle, a note of caution must be expressed, because in skeletal muscle myosin has been detected simultaneously with the formation of the first simple muscle fibrils, and not before. *See also:* **Hematopoiesis (/content/hematopoiesis/312900)**

Action of inhibitors

In further studies of the biochemical differentiation of the heart-forming areas, it has been found that the metabolic pathways operating in the development of the brain and heart differ markedly. When early chick embryos are cultured in vitro on a medium containing traces of the metabolic inhibitor antimycin A, the development of the regions destined to form muscle is inhibited almost completely, whereas the developing brain and spinal cord remain intact. The heart is more sensitive than other mesodermal tissues. Another compound, sodium fluoride, also inhibits development of the heart. The inhibition of the embryo produced by sodium fluoride follows a clear-cut, reproducible pattern, in which the initial sites of inhibition are the

heart-forming regions. At succeeding stages in the establishment of the heart, the locations of the cells destroyed by sodium fluoride reflect the sites of highest ability to form pulsatile heart and the area of greatest capacity for the synthesis of actin and myosin. Thus the primary forces operating in the formation of the heart must be sought at the very outset of development.

James D. Ebert

Human Fetal Circulation at Term

The circulation in the mammalian fetus at term must be thoroughly understood as a basis for the consideration of postnatal circulatory changes, because the very mechanisms which ensure intracardiac balance during prenatal life maintain a balanced cardiac load during the changes to the postnatal basis. In this discussion of the fetal circulation at term, the basic conditions presented are essentially applicable to all the higher mammals. Reference to ages and to other specific details are, however, based on the conditions in humans.

By the last trimester of pregnancy all the major blood vessels have been developed in essentially their adult pattern, and all the steps in the partitioning of the embryonic heart are leading progressively closer to the final adult condition, in which the heart is a four-chambered organ completely divided into right and left sides. However, from the nature of its living conditions it is not possible for the fetus in utero to attain fully the adult type of circulation. The plan of the divided circulation of postnatal life is predicated on lung breathing. After birth the right side of the heart receives the blood returning from a circuit of the body and pumps it to the lungs, where it is relieved of carbon dioxide and acquires a fresh supply of oxygen. The left side of the heart then receives the blood that has just been aerated in the lungs and pumps it through ramifying channels to all the tissues of the body. In the last part of intrauterine life the lungs and their blood vessels are fully formed and ready to function, but they cannot actually try out their functional competence until after birth. Nevertheless, in the first minutes of its postnatal life a fetus must successfully change from an existence submerged in the amniotic fluid to air breathing with its hitherto untested lungs. Moreover, this abrupt change must be accomplished without the sudden overloading of any part of the cardiac pump.

It is in the light of these functional exigencies that the fetal circulation at term must be considered. Of primary importance is the fact that at no time during the prenatal life are the atria completely separated from each other. This permits the left atrium to receive a contribution of blood from the inferior vena cava by a transseptal flow which compensates for the relatively small amount of blood entering the left atrium directly by way of the pulmonary circuit. The routes and the relative amounts of this interatrial shunt are different at different ages. Very early in development, before the lungs have grown to any great extent, the pulmonary return is negligible and the flow from the right atrium through the interatrial ostium primum constitutes practically the entire intake of the left atrium (**Fig. 19***b*). After the ostium primum has been closed and while the lungs are but little developed, flow through the interatrial ostium secundum must provide for the major part of the blood entering the left atrium (Fig. 19*d*). During the latter part of fetal life the foramen ovale in the septum secundum becomes the transseptal route for blood (Fig. 19*e* and *f*).

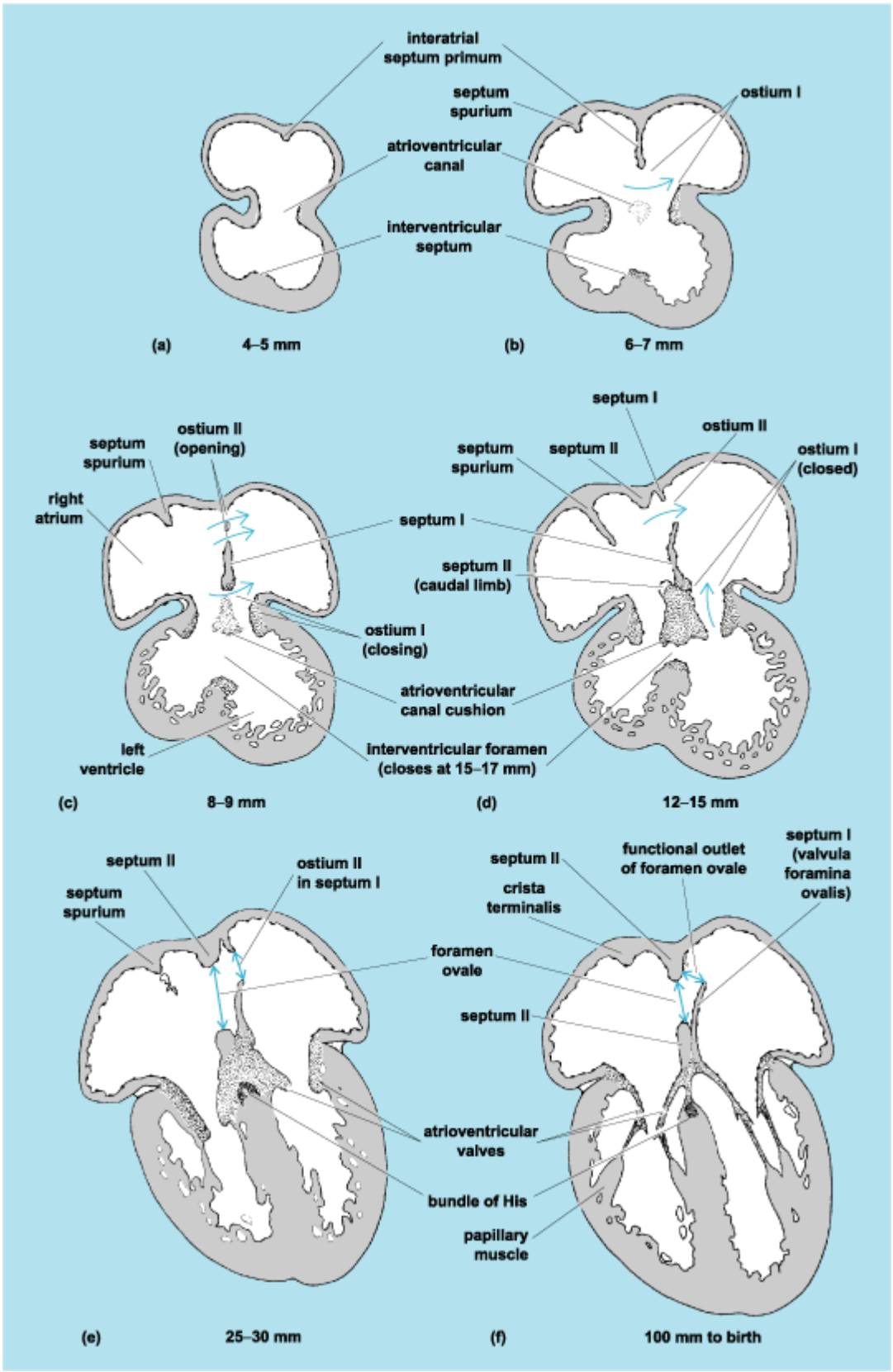

Fig. 19 Sectional plan (*a–f*) of the embryonic heart in frontal plane, showing progress of partitioning in the human embryo. The endocardial cushion tissue is indicated by stippled areas, the muscle by gray areas, and the epicardium by solid black outline. Parts *b* and *c* show the location of endocardial cushions of the atrioventricular canal before they have grown sufficiently to fuse in the plane of the diagram. (*After B. M. Patten, Developmental defects at the foramen ovale, Amer. J. Pathol., 14(2)135–161, 1938*)

Intracardiac circulatory balance

The precise manner in which this balancing transseptal flow occurs in a fetus at term and where and to what extent the various bloodstreams are mixed has long been a controversial subject. By a synthesis of the most significant of the anatomical evidence with the newer experimental evidence, the course followed by the blood in passing through the heart may be summarized as follows. The inferior caval entrance is so directed with reference to the foramen ovale that a considerable portion of its stream passes directly into the left atrium (**Figs. 20** and **21**). Careful measurements have shown, however, that the interatrial communication through the foramen ovale is considerably smaller than the inferior caval inlet. This implies that the portion of the inferior caval stream which could not pass through this opening into the left atrium must eddy back and mix with the rest of the blood entering the right atrium. Angiocardiographic studies confirm this inference.

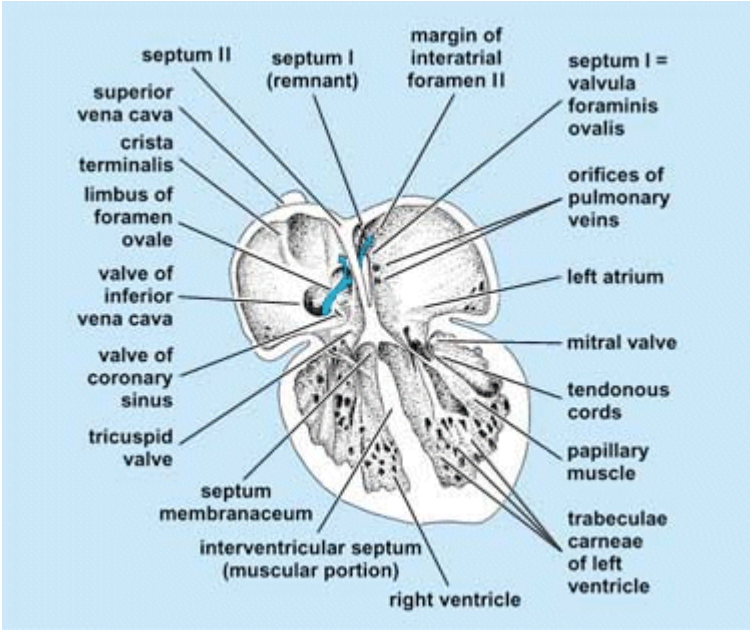

Fig. 20 Interrelations of septum primum and septum secundum during latter part of fetal life. Lower part of septum primum is situated to act as a one-way valve at the foramen ovale in septum secundum. Split arrow indicates the way a considerable part of blood from inferior vena cava passes through foramen ovale to the left atrium while remainder eddies back into the right atrium to mingle with the blood being returned by way of the superior vena cava. (*After B. M. Patten, Foundations of Embryology, 2d ed., McGraw-Hill, 1964*)

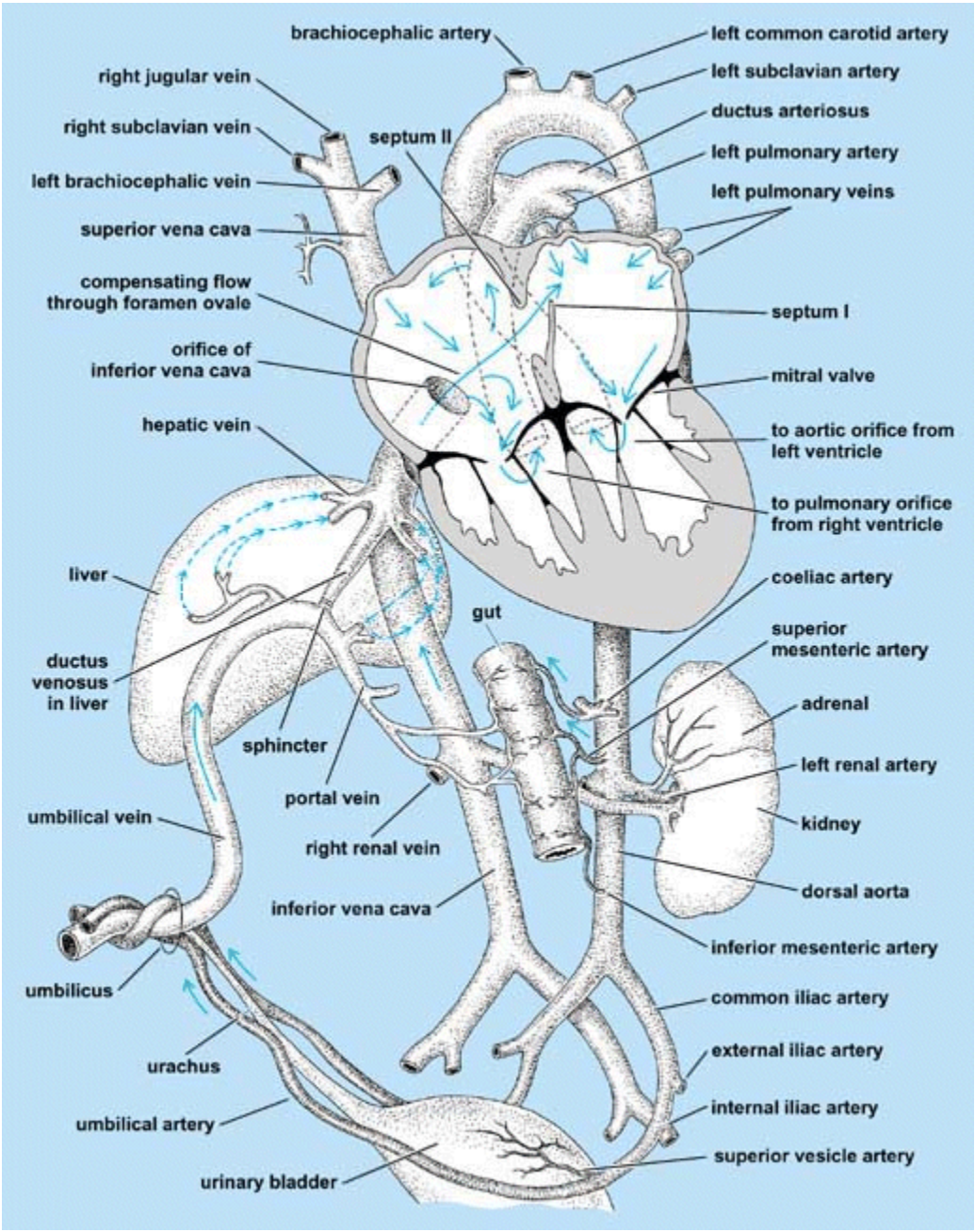

Fig. 21 Diagram of heart and major vessels of fetus just before birth. Small arrows within liver indicate alternative blood routes by way of hepatic sinusoids. (*After B. M. Patten, Human Embryology, 3d ed., McGraw-Hill, 1968*)

Prenatal pulmonary circulation

As the lungs grow and the pulmonary circulation increases in volume relatively less of the left atrial intake comes by way of the foramen ovale and relatively more from the vessels of the growing lungs. However, the circulation of the lungs, although increased as compared with earlier stages, has been shown by angiocardiographic studies to be much less in volume than the caliber of the pulmonary vessels would lead one to expect. Until the lungs are inflated, there are evidently factors, either vasomotor or mechanical or both, which restrict flow through the smaller pulmonary vessels. Therefore, even in the terminal months of pregnancy, a considerable right-left flow must still be maintained through the foramen ovale in order to keep the left atrial intake equal to that of the right.

Balancing ventricular output

The balanced atrial intake thus maintained implies a balanced ventricular intake, and this in turn implies the necessity of a

balanced ventricular output. Although not in the heart itself, there is, in the closely associated great vessels, a mechanism which affords an adequate outlet from the right ventricle during the period when the pulmonary circuit is developing. When the pulmonary arteries are formed as downgrowths from the sixth pair of aortic arches, the right sixth arch soon loses its original connection with the dorsal aorta. On the left, however, a portion of the sixth arch persists as the ductus arteriosus connecting the pulmonary artery with the dorsal aorta (Fig. 21). This vessel remains open throughout fetal life and acts as a shunt, carrying over to the aorta whatever blood the pulmonary vessels at any particular phase of their development are not prepared to receive from the right ventricle. The ductus arteriosus can therefore be called the exercising channel of the right ventricle because it allows the right ventricle to do its full share of work throughout development and thus be prepared to pump its full quota of blood through the lungs at birth.

Thus by means of intake and output shunts there is maintained, throughout prenatal development, an effective right-left balance in the pumping load of the heart. The importance of this for the attainment of normal cardiac structure is forcefully shown by the abnormalities that appear when the balancing mechanisms are in any way disturbed. The importance of these same mechanisms in accomplishing postnatal circulatory changes is discussed in the following section.

Human Postnatal Circulation

The changes in circulation following birth involve some of the most dramatic and fascinating biological processes. One of the most impressive phenomena in embryology is the perfect preparedness for these changes which has been built into the very architecture of the circulatory system during its development. The shunt at the ductus arteriosus, which has been one of the factors in balancing ventricular output throughout intrauterine development, and the valvular mechanism at the foramen ovale, which has been balancing atrial intakes, are perfectly adapted to prevent any abrupt unbalancing of cardiac load as a result of postnatal changes in circulatory routes.

Pulmonary circuit and ductus

In much of the older literature, great emphasis was placed on what happened at the foramen ovale. It is now known that these changes are secondary and that the events of primary significance occur in connection with the pulmonary circuit and the ductus arteriosus. In the section on fetal circulation at term, the importance of the ductus arteriosus as an exercising channel for the right ventricle was emphasized. From the standpoint of postnatal circulatory changes, the reciprocal relation between flow through the ductus and flow through the lungs becomes the center of interest. As the lungs increase in size, relatively more of the blood leaving the right ventricle by way of the pulmonary trunk goes to the lungs, and relatively less goes through the ductus arteriosus to the dorsal aorta.

By the end of gestation the pulmonary vessels must be large enough to handle a blood volume adequate to care for oxygenating the blood. Injection preparations of fetuses clearly show that the vascular channels in the lungs are of generous size for this function well before birth. However, such postmortem material does not show that before birth these large vessels are not carrying the blood volume their size would suggest.

Prenatal pulmonary blood flow

The brilliant work of C. Wegelius and J. Lind, utilizing angiocardiographic methods on living fetuses, has shown that the flow of blood through the pulmonary circuit is actually restricted to a volume much below the potential capacity of the vessels. How much of this is the result of mechanical factors, such as the unexpanded condition of the lungs, and how much it depends upon differential vasoconstriction of the smaller vessels within the lungs remains to be determined. It is clear, however, that pulmonary channels of the requisite size have been formed and are ready to increase their blood flow radically and promptly with the beginning of respiration. Within a short time after birth, under the stimulus of functional activity, the lungs are able to

take all the blood from the right side of the heart.

Abandonment and closure of ductus

When the lungs accept all the blood entering the pulmonary trunk, blood flow through the ductus arteriosus ceases. Following its functional abandonment, the ductus arteriosus is gradually occluded by an overgrowth of its intimal tissue. This process in the wall of the ductus is as characteristic and regular a feature of the development of the circulatory system as the formation of the cardiac septa. Its earliest phases begin to be recognizable in the fetus as the time of birth approaches, and postnatally the process continues at an accelerated rate, to terminate in complete anatomical occlusion of the lumen of the ductus some 6–8 weeks after birth.

Postnatal readjustment of the circulation cannot, however, wait on this protracted structural closure. Following birth there appears to be an immediate reduction in the bore of the ductus as a result of its muscular contraction. This is accompanied by a reduced flow of blood through it. This reduction in the shunt from the pulmonary circuit to the aorta, acting together with the lowering of resistance in the vascular bed of the lungs which accompanies their newly assumed respiratory activity, aids in raising the pulmonary circulation promptly to full functional level. At the same time, the functional closure of the ductus arteriosus paves the way for the ultimate anatomical obliteration of its lumen by the active growth of its intimal connective tissue.

Closure of foramen ovale

The results of increased pulmonary circulation with the concomitant increase in the direct intake of the left atrium are manifested secondarily at the foramen ovale. Following birth, as the pulmonary return increases, compensatory blood flow from the right atrium to the left decreases correspondingly, and shortly ceases altogether. In other words, when equalization of atrial intakes has occurred, the compensating one-way valve at the foramen ovale falls into disuse and the foramen may be regarded as functionally closed. The abandonment of the shunt at the foramen ovale is indicated anatomically by a progressive reduction in the looseness of the valvula foraminis ovalis and the consequent diminution of the interatrial communication to a progressively narrower slit between the valvula and the septum.

Anatomical obliteration of the foramen ovale slowly follows its functional abandonment (**Fig. 22**). There is a highly variable interval of 3–9 months following birth before the septum primum fuses with the septum secundum to seal the foramen ovale. This delay is, however, of no functional import because as long as the pulmonary circuit is normal and pressure in the left atrium equals or exceeds that in the right, the orifice between them is functionally inoperative. It is not uncommon to find the fusion of these two septa incomplete in the hearts of individuals who have, as far as circulatory disturbances are concerned, lived uneventfully to maturity. Such a condition can be characterized as probe patency of the foramen ovale. When, in such hearts, a probe is inserted under the margin of the fossa ovalis and pushed toward the left atrium, the probe is prying behind the no longer used, but still unfastened, interatrial door.

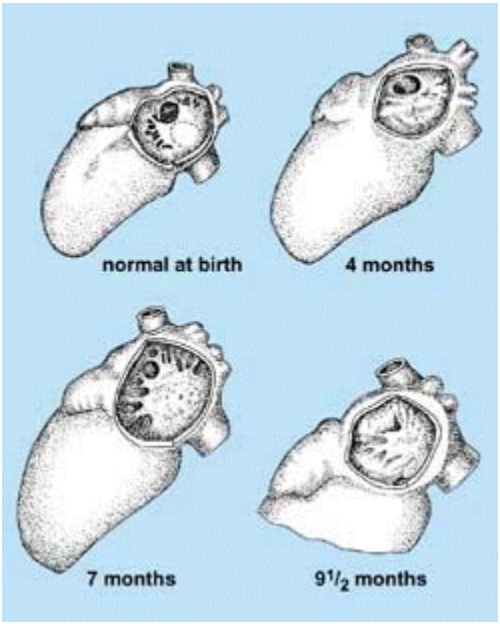

Fig. 22 Hearts with left atrium opened to show gross changes in relations of valvula during period in which foramen ovale closes anatomically. (*After B. M. Patten, The closure of the foramen ovale, Amer. J. Anat., 48:19–44, 1931*)

Physiological aspects of transition

Much yet remains to be learned concerning the more precise physiology of the fetal circulation and concerning the interaction of various factors during the transition from intrauterine to postnatal conditions. Nevertheless, it is quite apparent that the changes in the circulation which occur following birth involve no revolutionary disturbances of the load carried by different parts of the heart. The fact that the pulmonary vessels are already so well developed before birth means that the changes which must occur following birth have been thoroughly prepared for, and the compensatory mechanisms at the foramen ovale and the ductus arteriosus which have been functioning throughout fetal life are entirely competent to effect the final postnatal reroutings of the circulation with a minimum of functional disturbance. The change from living in water to living in air is crowded into a few crucial moments that in phylogeny must have been spread over eons of transitional amphibious existence.

Bradley M. Patten

Comparative Physiology

Comparative physiology describes the structure and operation of the circulation in living animals, and enquires as to how or why the circulatory system may have evolved. Comparing the circulatory system in different animal groups leads to an understanding of general principles and also to various applications of those principles, adapting animals to a wide range of habitats. The circulatory system in all vertebrates has multiple functions, but all functions are involved in regulating the internal environment of the animal (promoting homeostasis).

General physiology of circulation

In all vertebrates the circulatory system consists of a central pump, the heart, which drives a liquid transport medium, the blood, continuously around a closed system of tubes, the vascular system. The arterial portion of this system is divided into larger elastic and smaller resistance vessels (arterioles) which distribute blood to specialized regions or organs (such as muscles, gut, and lungs) where transfer of nutrients, oxygen, or waste products takes place across the walls of a fine network of microscopic capillaries. Blood from the capillaries passes through the venules (small venous vessels) into the main veins and returns to the heart (**Fig. 23**). The arterioles, venules, and capillaries make up the microcirculation, which is arguably the

most important role of the vertebrate circulatory system from a functional point of view.

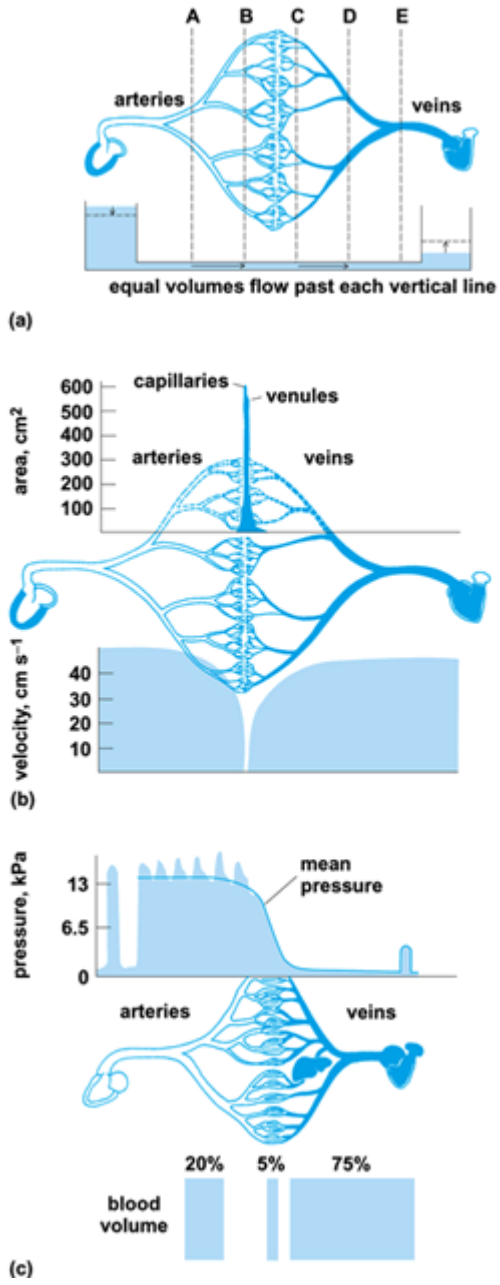

Fig. 23 Systemic circulatory system in a dog (13 kg or 28.7 lb). (*a*) Representation of the aborization of the system. All vessels of the same caliber are arranged vertically (at A, B, C, and so on). (*b*) Increase in cross-sectional area of the various segments. The velocity of blood flow (cm · s^{-1}) is inversely proportional to the cross-sectional area of the tubes through which it flows. (*c*) Pulsatile and mean pressures in the various vascular segments. At the extreme left is a representation of left ventricular pressure, while right ventricular pressure is shown at the extreme right. The boxes show the proportion of blood volume (approximately 85% of total blood volume) in the systemic arteries (including the heart), capillaries, and veins (the pulmonary circulation has about 10–15% of the total blood volume). (*After R. F. Rushmer, Cardiovascular Dynamics, W. B. Saunders, 1961*)

Blood flow in the circulation occurs from regions of high to regions of low fluid energy (or down an energy gradient). The total fluid energy consists of “pressure” energy (created by the heart) and energy contained in the blood due to its motion (kinetic energy). The latter component is small (1 to 2% of the pressure energy in main arteries) and is usually ignored. Hence, the term “pressure” has become synonymous with the total fluid energy. However, this is not always the case as pressures usually recorded in the circulation are transmural pressures; that is, pressure across the wall of the vessel.

The transmural pressure can be very misleading if it is taken as representing the energy for flow. For example, in a recumbent

person, transmural pressure in the foot arteries is 1.7 lb in.$^{-2}$ or 12 kilopascals, but in an erect person, the column of fluid between the heart and foot is subjected to the gravitational force, which means the column bears down on the foot arteries with a pressure equivalent to its height (4 ft or 1.2 m), and adds to the pressure created by the pump. Due to this hydrostatic effect, transmural pressure in the foot may be 2.4 lb in.$^{-2}$ or 24 kPa. However, this hydrostatic effect is also added to the veins so the energy gradient for flow through the vascular beds remains unchanged. In other words, in a closed circulation, flow cannot be maintained by differences in fluid level (hydrostatic pressure). Flow occurs as a result of difference in total fluid energy between two points in the circulation; if these points are at the same fluid level (central arteries and veins), then the energy difference can be measured in terms of pressure.

Energy is dissipated unevenly around the circulation, the major portion being expended to force blood through the arterial resistance vessels (Fig. 23, energy shown as pressure). Even so, loss of energy is not altogether due to friction between the vessel wall and blood but rather to overcoming the internal friction (or viscosity) of the blood. In the circulation, blood flow is usually streamlined or laminar. If blood, flowing in a vessel, is imagined as made up of a series of thin concentric tubes (or laminae), the layer of fluid next to the wall is stationary while that in the center flows fastest. Therefore, successive layers of blood slide past one another, and friction between these layers of fluid dissipates mechanical energy as heat.

The relation between mean pressures (energy) and flows in the body circulation (equally applicable in general principle to the pulmonary circulation) is shown in Fig. 23. At every division of a blood vessel the cross-sectional area of the branches always exceeds that of the parent vessel (with two branches by a factor of 1.2 to 1.3), so there is a tremendous increase in area as the capillaries are approached (Fig. 23*b*). In a closed circulation what goes in at one end must come out the other, so the total blood flow through each region must be the same, but the rate of flow will be inversely proportional to the cross-sectional area of any given region (Fig. 23*a* and *b*). Since the cross-sectional area of the veins is not much greater than that of the arteries, venous flow rates are high (Fig. 23*b*). On the other hand, mean pressure in the circulation falls from the arteries to the veins. The major pressure drop in the circulation occurs across the arterial resistance vessels which lead to the capillaries (Fig. 23*c*). Consequently, venous pressure is low, despite high blood flow rates, and this explains why blood does not spurt out when one severs a vein. The majority of the total blood volume is stored in the venous vessels (Fig. 23*c*).

Microcirculation

The microcirculation consists of arterial (arterioles) and venous (venules) resistance vessels on either side of the capillaries. The arterioles and venules constitute the pre- and postcapillary resistances respectively. A capillary is a single layer of endothelial cells enclosed by a basement membrane. Blood flow through the capillary is low (at rest, less than 1 mm · s^{-1}) and is controlled by the opening and closing activity of a short muscular region of blood vessel at the capillary entrance (precapillary sphincter). The total number of capillaries, and therefore their surface area for exchange of materials with the cells, is enormous. The systemic (or body) circulation of humans has a billion capillaries with a surface area of 10,800 ft^2 (1000 m^2). In the pulmonary (or lung) circuit there are billion capillaries with a combined surface area of 650 ft^2 (60 m^2). Lipid-soluble substances, including oxygen and carbon dioxide, and some water cross the capillary cell walls, whereas most water and all water-soluble substances are exchanged through pores either within or between the cells. The structure of capillaries is dictated by their function in the organ supplied and falls into three main types which are basically similar in all vertebrates. Fenestrated capillaries have holes through the cells permitting large and rapid exchange of solvent and solutes; the pores may be closed by a delicate membrane. This type of capillary is found in kidney, intestine, and glands. Discontinuous capillaries have large gaps between the cells of the wall, and are found where macromolecules or even red blood cells are exchanged, as in bone marrow, liver, and spleen. Continuous capillaries have an apparently continuous layer of cells and occur in muscle, lungs, and central nervous system. However, there are small-diameter pores between the cells in all tissues except the brain. The brain capillaries of all vertebrates, except those of lampreys and hagfishes, appear to present an extremely effective barrier to the transport of materials across their walls. In conjunction with the astrocytes, modified

nonnervous brain cells which invest the brain capillaries, they form an effective blood-brain barrier. Metabolites must cross the blood-brain barrier by specialized carrier systems or active transport, and this explains the abundance of mitochondria in the brain capillaries. Neurons are more sensitive than most cells to an imbalance in their environment, and homeostasis of the neuronal environment is the function of the blood-brain barrier.

Capillaries are generally about the diameter of the red blood cells (RBCs) which flow through them. Hence, in some amphibians (RBC diameter, 80 micrometers) the capillaries are far larger than, for example, in the mouse deer (RBC diameter, 1.5 micrometers). This relation between size of the RBC and capillary means that blood cells move through capillaries one at a time acting as a moving plug, sweeping unstirred fluid layers away from the capillary wall and facilitating exchange across the wall by diffusion, by reducing the diffusion distance. This is referred to as bolus flow.

Pressure and flow

The pulsatility of pressure and flow allied to the anomalous viscosity of blood greatly complicates any attempt to describe mathematically the relationship between pressure and flow in large arteries. However, in arterial resistance vessels both pressure and flow pulsations are dissipated so that a condition of steady pressure and flow is approached in the microcirculation. In large vessels, blood viscosity is high (some four times that of water) and, due to the presence of RBCs, appears to change with flow velocity (anomalous properties). In small vessels (less than 200 μm diameter) the apparent viscosity falls and, in capillaries, appears constant and similar to that of water (Fähraeus-Lindqvist effect).

Given conditions of steady pressure, flow, and viscosity, the relation between pressure and flow in the microcirculation can be described by the Hagen-Poiseuille law, Eq. (1),

$$Q = \frac{\pi r^4 \cdot [P_1 - P_2]}{8\eta L} \tag{1}$$

where Q = flow per unit time, r = radius of the vessel, $P_1 - P_2$ = pressure difference between the upstream and downstream ends of a pipe of length L, and η = blood viscosity. An important relationship emerging from the Hagen-Poiseuille law is that flow varies with the radius of the vessel raised to the fourth power. Thus, if r is halved (by constriction of a blood vessel), then flow through that vessel will be reduced to one-sixteenth [$½^4$ = 1/16] of that existing formerly for the same pressure difference.

Hagen-Poiseuille's law is often rewritten in a simplified form, Eq. (2)

$$Q = \frac{P_1 - P_2}{R} \tag{2}$$

[where R = resistance = $8\eta L/\pi r^4$], as a direct analog of Ohm's law describing the relation between electric current, voltage and resistance. This “Ohmic” relation is frequently applied to the whole circulation (not just the microcirculation) to determine total peripheral resistance (TPR) when Q = cardiac output (volume per unit time), P_1 = mean arterial pressure (kPa), and P_2 = mean venous pressure (kPa). TPR is generally expressed in peripheral resistance units (PRU; kPa · ml^{-1} · unit $time^{-1}$). To simplify comparisons between animals of vastly different sizes (or even between individual vascular beds in the same animal), cardiac output is usually expressed on a unit weight basis yielding PRU per unit weight (see **table**).

Some cardiovascular variables in selected vertebrates*

Species name (common name)	Conditions	Body mass and temp.	Heart rate, beats · min^{-1}	Cardiac output, ml · min^{-1} · 100 g^{-1}	Mean arterial pressure, kPa	Mean pulmonary pressure, kPa	Peripheral resistance of body (PRU_{100}), kPa · ml^{-1} · min^{-1} · 100 g^{-1}	Peripheral resistance of gas exchanger (PRU_{100}), kPa · ml^{-1} · min^{-1} · 100 g^{-1}
Salmo gairdneri (rainbow trout)	Unrestrained, rest	1.25 kg, 10°C	38	1.76	4†	5.06‡	2.26	0.6
	Unrestrained, exercise		51	5.26	4.8†	8‡	0.9	0.6
Xenopus laevis (clawed toad)	Restrained, rest, breathing	0.1 kg, 20°C	45	11	3.74	2.8	0.57	0.43§
	Restrained, rest, not breathing		40	6.4	4	3.7	0.56	3.2§
Pseudemys scripta (red-eared turtle)	Unrestrained, rest, breathing	1.25 kg, 21°C	23	5.7	3.74	2.4	1.73	0.65
	Unrestrained, rest, not breathing		11	2.65	2.8	2.0	1.94	1.73
Anas platyrhynchos (white pekin duck)	Restrained, anesthetized	2.5 kg, 41°C	219	22	19	2.0	0.87	0.1
	Diving, unanesthetized		30	2	18	1.67	8.33	0.17
Homo sapiens (human)	Unrestrained, rest	70 kg, 37°C	72	8	12	1.75	1.5	0.2
	Maximum exercise		193	33	14.5	2.4	0.44	0.07

*In fish the gills are in series with the body circulation, so the resistances were calculated by using the pressure difference between the ventral and dorsal aorta and the dorsal aorta and veins, respectively. In fish, amphibians, and reptiles the heart is undivided and cardiac output is the total amount of blood pumped per unit time, whereas in birds and mammals cardiac output is the output of only one ventricle or half the output of the whole heart. In all cases, central venous pressures were assumed to be insignificant, except during diving in ducks when both pulmonary and central venous pressure rise to 1.3 kPa.
†Dorsal aorta.
‡Ventral aorta.
§Includes skin.

Since flow per unit time (ml · min^{-1}) through the vascular system is the same at any two points, capillary pressure (P_c) may be calculated from arterial (P_a) and venous (P_v) pressure by application of the Hagen-Poiseuille law, yielding Eq. (3),

$$P_c = \frac{P_a \cdot (R_v/R_a) + P_v}{1 + (R_v/R_a)} \tag{3}$$

where R_a and R_v are the pre- and postcapillary resistances. Since it is the ratio of these resistances which determines capillary pressure, capillary pressure is largely independent of arterial blood pressure over a wide range. For instance, an R_a/R_v ratio of 5:1 gives P_c = 1.875 kPa when P_a = 10 kPa and P_v = 0.25 kPa. Now if P_a rose to 15 kPa, an adjustment of the ratio to 8:1 would leave P_c unchanged.

Measured capillary pressures are in the range of 1.33 to 4 kPa. This raises the question of why the single layer of cells in the capillary is not disrupted by these high internal pressures. The answer is contained in Laplace's law. This law describes how the wall tension (T) which opposes the distending force of the blood pressure (P) is critically dependent on the radius of the vessel, for Eq. (4).

$$P = \frac{T}{r} \tag{4}$$

Hence, wall tension in a capillary in a human is $^1/_{10,000}$ of that in the aorta, even though the pressure within is one-fifth of that in the aorta. Not surprisingly the aortic wall is 10,000 times thicker than the capillary wall.

Fluid exchange across capillaries

Water is exchanged both across the wall of the capillary and through pores. It is driven out by the blood pressure in the vessel, which is much higher than the pressure in the fluid between cells. In fact, the extracellular fluid pressure is frequently

subatmospheric (negative). The venules (small veins), as well as capillaries, are apparently involved in this exchange because the venules are also highly permeable to water. The pressure which filters water out of the capillary (filtration pressure) is opposed by the colloid osmotic pressure (COP) of the blood; COP tends to pull water back into the blood vessel. The COP difference between the blood and the fluid between the cells (interstitial fluid) is almost entirely due to a higher concentration of relatively impermeable proteins in blood plasma; it is equivalent to a pressure of 1.3 to 4 kPa depending on the animal.

At the arterial end of the capillary there is usually a net loss of water because the blood pressure is higher than COP. As water leaves, the blood is concentrated, and its COP increases. This increase in COP, coupled with the fall in blood pressure along the capillary, causes fluid absorption at the venous end. In a human perhaps 21 quarts (20 liters) of fluid is filtered from the body capillaries each day, excluding kidney filtration. Of this filtrate, 17–19 quarts (16–18 liters) are reabsorbed, and the remainder returns to the blood by the lymphatic system. When filtration and absorption are more or less in balance, a Starling equilibrium is said to exist (named after E. H. Starling). However, the degree of equilibrium in individual tissues may vary; some may be exclusively involved in filtration, and others in absorption due to the independent regulation of capillary blood pressure in different tissues.

Obviously, capillary fluid exchange must be regulated if the volume of the blood is to be controlled. The vital importance of this control is seen when animals, such as humans, assume an erect posture. A column of fluid stretching from the heart to the feet applies an additional pressure of 12 kPa to the capillary pressure. This results in a pressure across the capillary wall (transmural pressure) of perhaps 16 kPa. This pressure is added to both arterial and venous sides of the circulation so the pressure gradient for flow across the vascular bed remains unchanged (except that flow resistance may drop because the vessels expand a bit due to the high transmural pressures). However, capillary pressure now greatly exceeds COP, and fluid should be filtered throughout the microcirculation. In fact, this is prevented by a marked reduction in the permeability of the microcirculation due, it is thought, to precapillary sphincters closing off capillaries and thereby reducing the surface area for capillary exchange.

In the brain of erect animals, the hydrostatic effect due to standing is reversed. The blood column must be lifted against gravity from the heart. Thus, in the head of an erect human, there is a negative hydrostatic pressure of 5 kPa, whereas in the giraffe it is 20 kPa. Consequently, a positive capillary pressure, even at the arterial end of the microvasculature, can only be achieved by a high arterial blood pressure. This is the explanation for the extremely high arterial blood pressure in the giraffe. However, at the venous end of the microcirculation, pressures could still be negative, causing veins to collapse. Even though the brain is enclosed within a rigid box, which would tend to prevent blood vessel collapse, many veins are tethered to surrounding skeletal structures to ensure that they remain open.

Control

Microvascular activity is coupled to local tissue function through intrinsic mechanisms which are independent of control by the nervous or hormonal systems. The arterioles, metarterioles, and precapillary sphincters are muscular vessels in which muscle fibers contract spontaneously (myogenic activity), keeping these vessels in a state of partial constriction (basal vascular tone). Increases in blood pressure stretch the vessels, causing an increase in myogenic activity in the vascular smooth muscle and a return toward their original diameter. Any tendency for vessels to close completely is prevented by the accumulation of vasodilator metabolites in the tissues as flow is reduced. Decreases in oxygen and increases in carbon dioxide, both in the blood and tissues, cause muscle relaxation and an increase in vessel diameter (vasodilation). However, in the lung circuit, low oxygen causes blood vessel diameter to decrease (vasoconstriction). This reversal of blood vessel response is related to the lung's role as a supplier, rather than user, of oxygen and has important consequences for distributing blood to areas of the lung where oxygen is available.

The arterioles and metarterioles are also subject to remote control by the nervous system. They are innervated by vasodilator and vasoconstrictor nerve fibers which modulate and sometimes dominate local control systems. In contrast, the precapillary sphincters lack innervation and can only be affected by local or blood-borne excitatory or inhibitory influences.

The endothelial (inner) layer of cells of the blood vessels makes an important contribution to regulation of resistance to flow. Physical stimuli such as stretch, flow, and pressure as well as hormonal influences cause the release of contracting and relaxing factors from the endothelial cells, which affect adjacent smooth muscle. These endothelium-dependent regulatory mechanisms integrate blood vessel responses, and may explain regional differences in responses of vascular beds to the same hormone. The most well-known relaxing factor is nitric oxide (NO), produced from L-arginine, which very rapidly loses its potency in the circulation. Contracting factors include peptides, such as endothelin and prostaglandin which remain active for a considerably longer period of time.

The efficacy of the local control system as an unaided regulator of blood supply to the tissues is remarkable. For example, blood flow to the brain can be maintained constant despite induced arterial blood pressure changes from 8 to 18 kPa. Such control, in the absence of nerves or blood-borne factors, is referred to as autoregulation.

Heart

The heart is a pump imparting propulsive energy to the blood. Primitively, the heart is a tubular structure equipped with valves to prevent backflow. In more advanced animals it is differentiated into receiving and storage chambers (sinus venosus and atrium) and pumping chambers (ventricle and conus arteriosus). During evolution, these chambers have become folded upon one another; some were incorporated into others, and some subdivided. Sharks and rays have all four chambers, whereas in birds and mammals, the sinus venosus is incorporated into the right atrium and the conus arteriosus into the outflow tract of the ventricle. In birds and mammals the two remaining chambers (atrium and ventricle) are subdivided to form two parallel circulations, one supplying the body and the other the lungs.

In all vertebrates the heart is enclosed in a double-layered membranous pericardium; a liquid-filled space separates the layers. The inner layer of the pericardium is applied to the ventricular surface. In elasmobranchs, the outer layer of the pericardium is extremely thick and is attached to surrounding skeletal structures. As a result, ventricular contraction creates a subatmospheric pressure within the pericardium which tends to stretch the thin-walled atrium so that it fills with blood by aspiration.

Cardiac cycle

In all vertebrates the period of one heartbeat, or cardiac cycle, can be divided into four phases (**Fig. 24***a* and *b*).

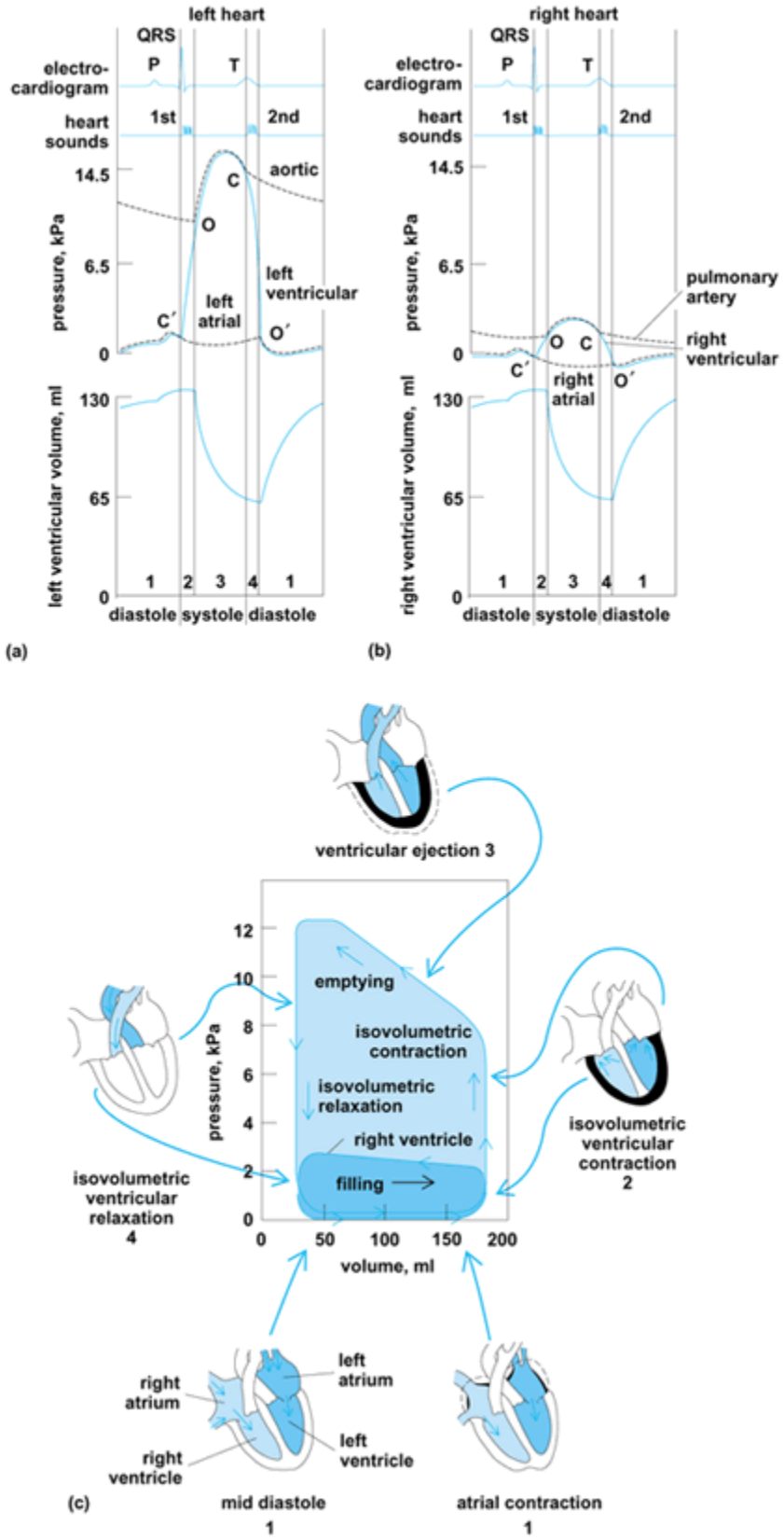

Fig. 24 Mammalian heart. Events in the (*a*) left heart and aorta and (*b*) right heart and pulmonary arteries during a cardiac cycle. In *a*: At *C'* the atrioventricular valve closes; at *O'* it opens. At *O* the aortic valve opens; at *C* it closes. In *b*: At *C'* the atrioventricular valve closes; at *O'* it opens. At *O* the pulmonary valve opens; at *C* it closes (*after A. J. Vander et al., Human Physiology, McGraw-Hill, 1975*). (*c*) Pressure-volume loops for the right and left ventricles. The area enclosed by the loop is a measure of the work done by the heart in ejecting blood. Diagrammatic representations of the heart during one cardiac cycle surround the loops and are linked by arrows with their appropriate position (in time) on the loop. The contracting portions of the heart are shown in black. The numbers (1 to 4) under each heart diagram refer to the phases of the cardiac cycle in *a* and *b* (*after R. Eckert and D. J. Randall, Animal Physiology, W. H. Freeman, 1978*)

1. Filling phase: the inflow valves are open and the outflow valves shut. Ventricular pressure at the start of this phase is low and falling; when it falls below that in the atrium, the atrioventricular valves open and blood flows rapidly into the ventricle. Flow into the ventricle is driven by the energy contained in venous blood. As ventricular pressure rises, flow slows, and atrial contraction “tops up” the ventricle. The end of the ventricular relaxation phase (diastole) is marked by the start of ventricular contraction (systole) which increases ventricular pressure and shuts the atrioventricular valves.

2. Isovolumetric contraction (contraction without a change in volume): both inlet and outlet valves are shut. The ventricular muscle contracts, developing tension, and the pressure of the contained blood increases. In hearts with large and rapid pressure generation the free edges of the atrioventricular valves have guy ropes (chordae tendineae), attached to papillary muscles of the ventricular wall; these prevent the valves being turned inside out.

3. Ejection phase: the rising ventricular pressure exceeds that in the arteries and the outlet valves open; the inlet valves remain closed. Blood is ejected rapidly, but pressure continues to rise in both ventricle and outflow tract until peak systolic pressure is reached. About two-thirds through this phase, ventricular contraction stops and pressure falls; when it falls below arterial pressure, the outflow valves shut, causing a disturbance in the arterial pressure pulse (incisura or dichrotic notch). The amount of blood pumped in this phase, by a single ventricle, is the stroke volume (ml), while cardiac output ($ml \cdot min^{-1}$) is the product of stroke volume and heart rate ($beats \cdot min^{-1}$). Backflow of blood is not necessary to shut the outflow valves. When the valve opens during blood ejection, vortices are created between the valve cusp (free edges of the valve) and the aortic wall, and the pressure distribution associated with these vortices deflects the cusps toward apposition (closure) as outflow from the ventricle decelerates. Leonardo da Vinci is credited with first describing the role of vortices in valve closure more than 100 years before W. Harvey's discovery of the circulation. Some lower vertebrates have an extra contractile chamber (conus arteriosus) on the ventricular outflow tract; the conus shuts the outflow valves when it contracts.

4. Isovolumetric relaxation: inflow and outflow valves shut and pressure falls rapidly as the ventricular muscle relaxes. Subatmospheric pressure can occur in this phase due to “elastic recoil” of the walls of the ventricle.

The plot of ventricular pressure against volume describes a closed loop circling counterclockwise with respect to time (Fig. 24*c*). The area enclosed by the loop is a measure of the work done by the ventricle in ejecting blood. Since pressures in the lung circuit of birds and mammals (see **table**) are lower than those in the body circulation, the work required to circulate the blood to the lungs is much less.

The ventricles are not divided in amphibians and noncrocodilian reptiles. Since both the lung and body circulations are connected to the same pressure source, flow in each circuit is inversely proportional to the resistance of that circuit. In amphibians such as frogs and toads, during periods of breath holding (apnea) blood can be circulated away from the lung circuit and sent to the body by increasing pulmonary flow resistance (**Fig. 25**). Hence, unlike the situation in avian and mammalian hearts, flows in lung and body circuits can be independent of one another. However, in incompletely divided hearts peak pressures during cardiac contraction have to be the same in both lung and body circuits because they are connected to the same pressure source. The peak pressure must be low; otherwise plasma will filter out of the lung capillaries into the lung and the animal will drown. Only when the heart is completely divided can pressures in lung and body circuits be independent of one another (high pressure in the body, low pressure in the lung), but the price to be paid is that flows in each circuit must now be exquisitely balanced.

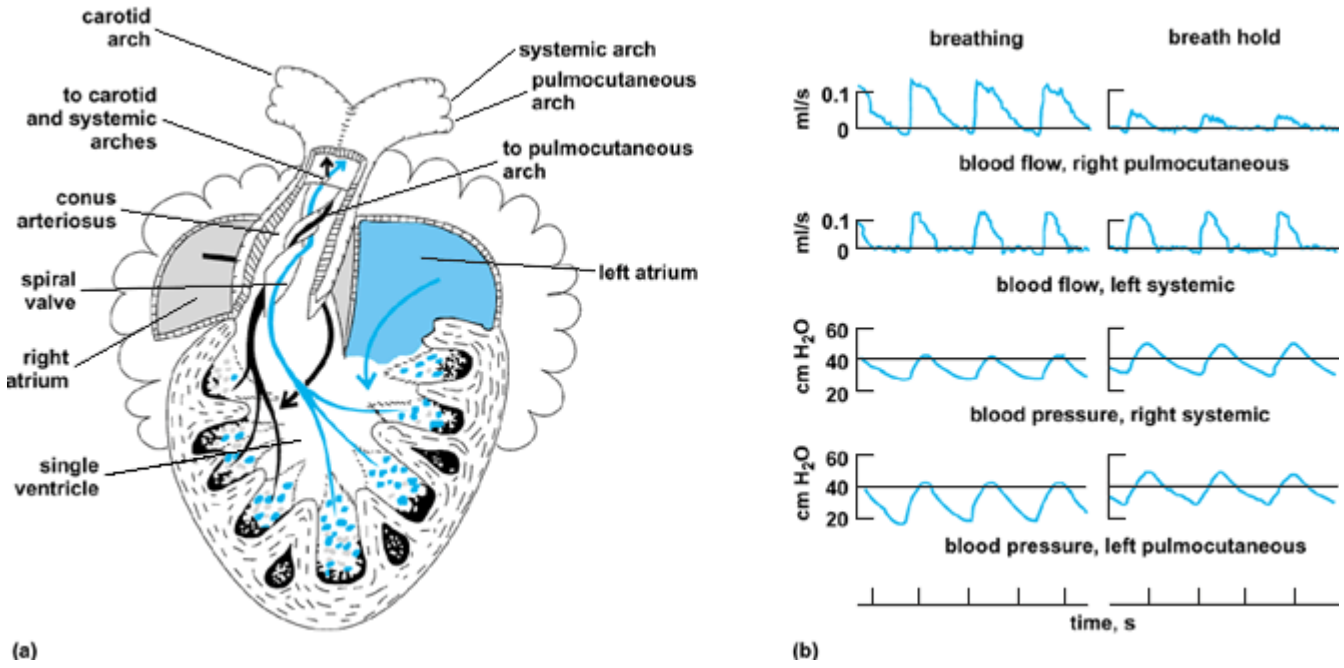

Fig. 25 Frog heart. (*a*) Ventral walls of the atria, ventricles, and conus arteriosus are removed to show flow streamlines that account for selective distribution of oxygenated blood to the head and body via the carotid and systemic arteries, and deoxygenated blood to the lungs via the pulmocutaneous arteries. (*b*) Blood pressures and flows in the blood vessels supplying the lungs (pulmocutaneous) and body (systemic) during a period of breathing and during a breath hold in the anuran amphibian *Xenopus laevis*. (*After P. S. Davies, Perspectives in Experimental Biology, vol. 1, Pergamon Press, 1976*)

Varanid reptiles (for example, monitor lizards), however, show clear pressure separation between lung (low pressure) and body circuits (high pressure), yet the varanid ventricle is morphologically undivided. This extraordinary triumph of physiology over morphology is achieved by partitioning the ventricular cavity during the contraction and relaxation phases. An interventricular partition formed by the atrioventricular valves divides the ventricle during diastole, whereas a musclar ridge within the ventricle divides it at a different site during systole. Crocodilians also have a high-pressure body and low-pressure lung circulation. The heart is completely divided by an interventricular septum, but the left aorta, supplying the body, arises along with the pulmonary artery from the right ventricle. Furthermore, the left and right aortas are joined just outside the heart by a hole in their common wall (foramen of Panizza) and again by a connection behind the heart. Hence, in the crocodilians a unique situation exists, because it is possible for venous blood to be transferred away from the lung circulation and sent back to the body through the left aorta so that both flows and pressures are independent of one another.

In birds and mammals the heart is completely divided, and the flows in both lung and body circuits must be matched. This matching of flows is largely achieved by nervous control although an automatic mechanism, referred to as Starling's law of the heart, could play a role. Starling's law (which also applies to the hearts of lower vertebrates) states that the energy of contraction of ventricular muscle is a function of the length of the muscle fiber. Thus, if in a particular beat a ventricle is filled to a greater extent than the previous one, the next contraction would be more vigorous and a greater volume of blood (stroke volume) would be ejected. So, if there is an increase in pumping by the right heart, a few beats later more blood will return to the left heart and increase its filling, so its output will rise, maintaining a balance between flows in the two circuits without intervention of any nervous or humoral (blood-borne) control mechanisms.

Pacemaker

The cardiac rhythm is myogenic in all vertebrates, the heartbeat being initiated in a specialized group of muscle cells which form the pacemaker. From the pacemaker, a wave of electrical excitation passes across the heart, activating the contractile process in cardiac muscle. This wave of excitation may pass across the muscle tissue itself or along specialized conducting pathways (Purkinje fibers, which are modified muscle cells; **Fig. 26**). Pacemaker cells are different from other cardiac cells in

that the electrical charge across their cell membranes spontaneously and repetitively declines (depolarization). These repeated depolarizations are called pacemaker potentials. They reach a threshold, after a depolarization of some 15 mV, and an action potential is generated (a sudden reversal of the membrane electrical charge). The action potential is propagated from cell to cell, initiating muscle contraction (Fig. 26). The cycle then repeats. An unusual feature of the cardiac action potential is its long duration, compared, for instance, with the action potential in skeletal muscle. If a muscle action potential is short, then further action potentials and contractions can be generated before the muscle relaxes. Consequently, in skeletal muscle a sequence of contractions may sum. However, in the heart the shortest possible interval between two action potentials is still longer than the relaxation time of cardiac muscle. Thus, the sustained contractions (tetanus) characteristic of skeletal muscle, and due to the fusion of individual waves of contraction, cannot occur in cardiac muscle. Tetanus in cardiac muscle would, of course, be maladaptive.

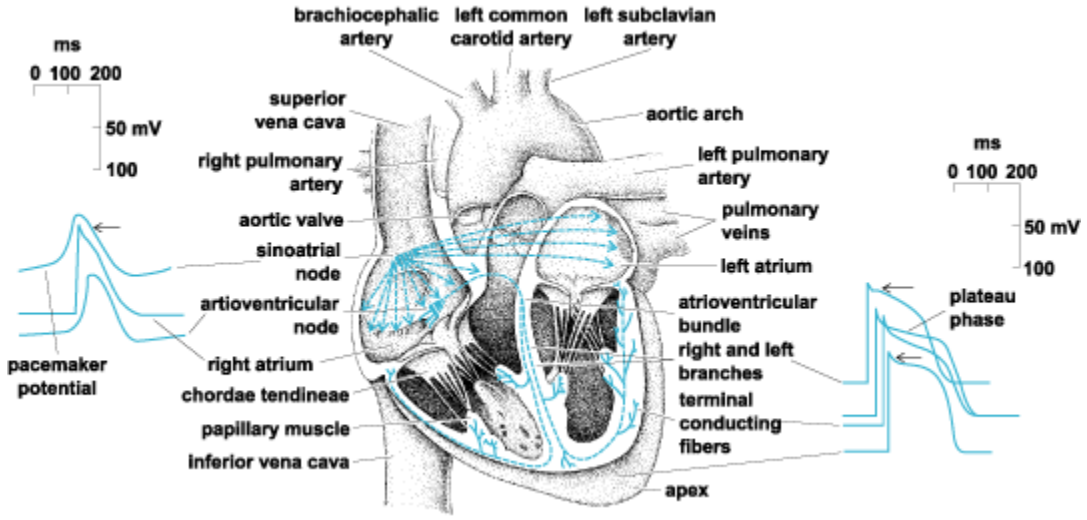

Fig. 26 Anterior view of the opened human heart, showing the pacemaker in the sinus node, the atrioventricular node, and the specialized conduction pathways of the ventricle. Intracellular action potential shapes were recorded at identified sites of the heart during one cardiac cycle. The arrows link the action potentials to the site. Time and voltage calibrations are shown at the left and right. Zero transmembrane voltage is indicated on some of the action potentials by the arrowhead. (*After J. E. Crouch, Functional Human Anatomy, Lea and Febinger, 1978*)

The sum of the electrical events occurring during the synchronous activity of all the cardiac cells can be detected as a series of small voltage changes at points all over the body (Fig. 24*a* and *b*). The record of small voltage changes is the electrocardiogram; it exhibits waves associated with atrial depolarization (P-wave), ventricular depolarization (QRS complex), and repolarization (T-wave) [Fig. 24*a* and *b*].

In all vertebrate hearts there is a hierarchy of pacemakers. This is reflected in embryonic development where the ventricle is formed and begins beating before the other parts of the heart have differentiated. The ventricular pacemaker sets a slow rate and is superseded by pacemakers, first in the atrium, and ultimately in the sinus venosus. In fish and frogs heart rate is set by the pacemaker in the sinus venosus because it beats fastest and drives the other pacemakers. In birds and mammals the sinus venous is incorporated into the right atrium, and the pacemaker zone is called the sinoatrial node (Fig. 26). The wave of excitation crosses the atrium (in some mammals specialized conducting pathways have been described) at a rate of up to 1 $m \cdot s^{-1}$, but it can only cross to the ventricle through the atrioventricular node. In the atrioventricular node, the rate of conduction slows to 0.05–0.1 $m \cdot s^{-1}$, allowing time for the atrium to complete its contraction before the ventricle is activated. From the atrioventricular node the wave of excitation is propagated rapidly (0.05–2.5 $m \cdot s^{-1}$). In birds and mammals propagation takes place through specialized conducting fibers called, in mammals, the right and left bundles of His. Lower vertebrates lack specialized conducting fibers and even a discrete atrioventricular node; in noncrocodilian reptiles there is an almost complete ring of junctional tissue between the atria and ventricle.

In all except the lowest vertebrates the pacemaker region receives innervation both from excitatory (sympathetic) and depressor (parasympathetic) nerves. The sympathetic nerves liberate catecholamines which increase the rate of spontaneous depolarization, and therefore heart rate. The parasympathetic nerves liberate acetylcholine which stabilizes the membrane potential and decreases the rate of spontaneous depolarization, so heart rate falls. The extent to which these nerves innervate cardiac muscle or other structures, such as the atrioventricular node, is variable. However, when muscle innervation is dense, catecholamines increase the force of contraction (positive inotropic effect) while acetylcholine decreases it (negative inotropic effect).

The effects of chemicals released by nerves are due to the activation of receptors on the cardiac cell which are specific for that particular chemical. For noradrenaline and adrenaline, the receptors are called α and β receptors, respectively. Adrenaline and noradrenaline increase in the circulation in response to stress and stimulate the heart. In many vertebrates, however, the effects are different from those caused by nerves. For instance, circulating adrenaline is unable to reach the same receptors which are activated neurally because the nerve ending is so closely attached to the cardiac cell. Receptors stimulated by nerves have different effects on pacemaker potentials from those accessed from the circulation.

Arteries

The arteries are the connecting tubes between the heart and the microcirculatory vessels. They are largest and most distensible just outside the heart. The arteries decrease in diameter and flexibility at every bifurcation, so the arterial tree is said to display both geometric and elastic taper. The vessels within the thorax are extremely distensible due to a much higher proportion of rubbery (elastin) to stiff (collagen) fibers in their walls. In nonthoracic arteries collagen dominates the wall composition, but its proportion remains constant as the vessels get stiffer and stiffer with their approach to the periphery.

During the ejection phase of the cardiac cycle much of the blood is temporarily stored in the central arteries as these become distended by the pressure rise. This blood is fed into the peripheral circulation, by the rebound of the stretched elastic walls, throughout diastole. Consequently, a highly pulsatile input is transformed into a more even outflow (**Fig. 27***a*). However, in a large number of animals (such as humans, dogs, and ducks) this is not the case with the pressure pulse. The pressure pulse is amplified in the peripheral vessels (peaking), and both the size and rate of rise of the pulse wave is greater than in the more central vessels (Fig. 27*a*). On the other hand, small high-frequency components such as the incisura disappear from the peripheral pulse as they are damped out (Fig. 27*a*).

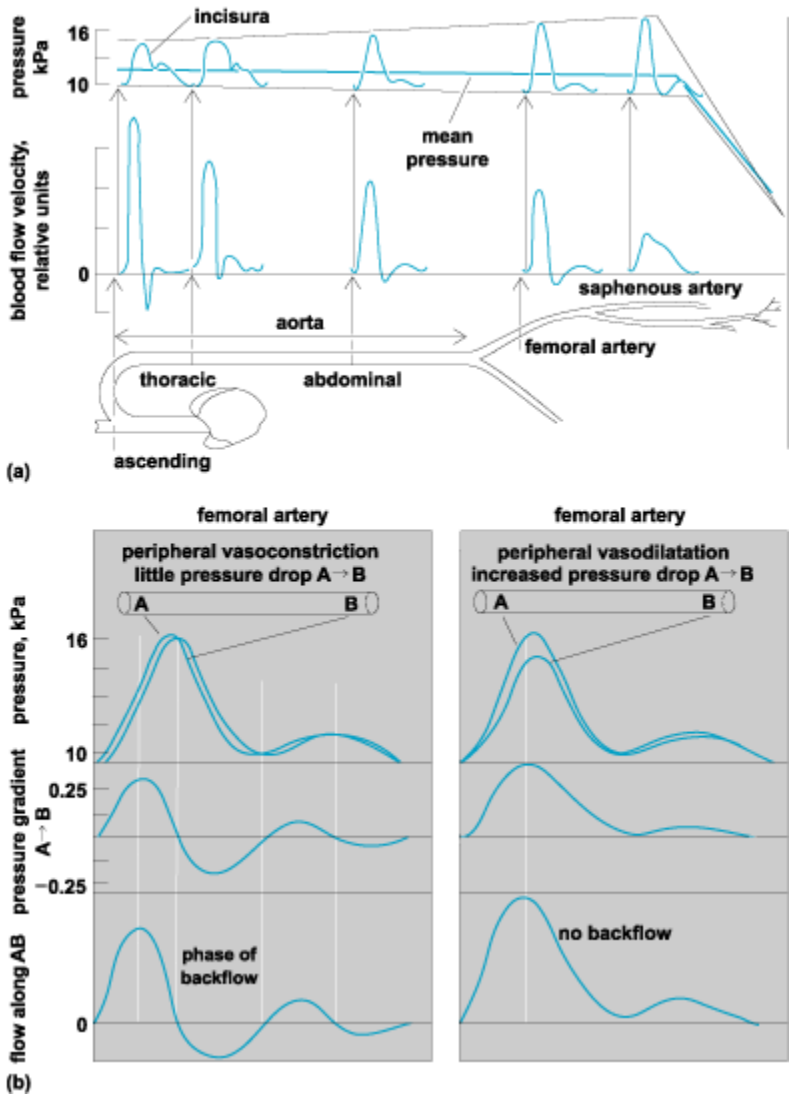

Fig. 27 Arterial circulation. (*a*) Comparison of the behavior of the pressure and flow velocity pulses from the ascending aorta until the saphenous artery. (*b*) The propagation of the pulse wave along an artery, with deduction of the pressure gradient and the phasic flow. (*After B. Folkow and E. Neil, Circulation, Oxford University Press, 1971*)

The pressure pulse wave travels through the arteries at a velocity which depends on the viscosity of the fluid and distensibility of the vessel. In humans it picks up speed, from 3 m · s^{-1} centrally, to 5–10 m · s^{-1} in peripheral arteries. At every discontinuity in the arterial tree (regions of geometric and elastic taper and, more importantly, the terminal vascular beds) the incident wave will be reflected toward the heart. At any major reflecting sites, such as the terminal vascular beds, the incident wave and the reflected wave will be almost in phase and will sum so that the pressure pulse increases in size (Fig. 27*a*). If the heart is positioned one-quarter of a wavelength back from the major reflecting sites (wavelength is the pulse velocity divided by the cycle length), the incident wave will have passed here one-quarter wavelength before (with respect to the reflecting sites) and the reflected wave will arrive here one-quarter wavelength later (with respect to the reflecting sites) so the two waves will be out of phase, by half a wavelength, and will cancel one another out. Hence, the pressure pulsations in central arteries will be reduced by wave reflection (Fig. 27*a*). In mammals about 30% of cardiac power is invested in pulsatile pressure and subsequent flow, so by reducing the pressure pulsations just outside the heart, energy can be saved. Peaking occurs only if the transit time is a significant proportion of the cardiac cycle. In humans mean pulse wave velocity is around 5–6 m · s^{-1} at a cardiac interval of 1 s, so the transit time is about a quarter of the cardiac cycle (quarter wavelength) and, as described above, pulse amplification occurs. However, arteriosclerotic individuals (be they ducks, dogs, or humans) do not show peaking of the pressure pulse since the pulse wave velocity in the “hardened” arteries is extremely fast and transit time through the circulation is greatly reduced. This lack of pulse wave amplification may contribute to the deleterious effects of

this condition on the heart. In frogs mean pulse wave velocity is around 3 m · s^{-1} at a cardiac interval of 1 s, so the transit time is about 50 ms, and the shape of the peripheral pulse in frogs is, except for damping of fast components (incisura), identical in shape to that in central arteries.

As blood is pumped through the circulation, energy is dissipated and mean pressure drops (Fig. 27*a*). Mean pressure is a steady pressure obtained by integrating the pressure pulse over one or several cardiac cycles and is somewhat lower than the arithmetic mean of systolic and diastolic pressures. When peaking occurs, the pressure pulse gets bigger but much narrower (Fig. 27*a*), and mean pressure is still lower in the peripheral arteries compared with the central arteries. Therefore, the flow occurs down the mean pressure gradient.

Unfortunately, an analysis in terms of steady pressures and flows tells little about the shapes of the pressure and flow pulses. Why does flow reverse at certain portions of the cardiac cycle? The reason is that the pulsatile pressure gradient reverses in those phases (Fig. 27*b*). The pressure pulse travels through the arterial tree with a velocity from 3 to 10 m · s^{-1}. If pressure is recorded at two sites in a vessel that are a small distance apart, then as the wave passes the upstream point, pressure will exceed that downstream and forward flow will occur (Fig. 27*b*). When the wave moves on and passes the downstream point, pressure there will exceed the pressure upstream and the flow will reverse (Fig. 27*b*). In fact, it is the pressure difference between the upstream and downstream points (the pressure gradient) which oscillates about a mean and is closely linked to the flow velocity (Fig. 27*b*).

Arterial blood pressure is controlled, at least in the short term, through the agency of arterial baroreceptors. Baroreceptors are specialized nerve endings located in the walls of major vessels; they are stimulated when the wall is expanded by the blood pressure. They have been found in the aortic arch and carotid sinus of mammals, the aortic arch of birds, and the carotid labyrinth of amphibians. Claims have been made for their existence in fishes. Blood pressure is controlled using the negative feedback principle. A rise in blood pressure stimulates baroreceptors which send electrical messages (action potentials) to the brain where they are directed to regions involved in control and adjustment of heart rate, stroke volume, and resistance in the peripheral blood vessels. In response to a rise in blood pressure, heart rate, stroke volume, and peripheral resistance are reduced. Input from mechanically stimulated receptors in the heart and lungs, and from chemoreceptors (measuring blood oxygen and carbon dioxide) in the vascular system and brain, are also involved in regulating the circulatory system.

Venous system

From the capillaries the blood passes through venules to successively larger veins and returns to the heart. Aside from being conduits for returning blood to the heart, the major function of the venous system is as a storage site for blood (Fig. 23). Veins are thin-walled, although the larger ones have a muscular coat, and are distended by small changes in pressure across their walls (transmural pressure). A pressure rise causes the veins to change from an elliptical cross-sectional profile to one that is nearly circular, greatly increasing blood storage while reducing flow resistance. Contraction of the muscles in the walls of the larger veins (venomotor activity) reverses the effects of increases in transmural pressure. Venoconstriction is under the control of the sympathetic nervous system.

In larger veins, valves appear as intimal folds and ensure that flow moves only in one direction. In humans some veins such as the vena cava, hepatic, pulmonary, and cerebral veins lack valves, a feature shared with the major veins running the length of the body in fishes. In elasmobranchs, these long veins have a unique structure; they are invested with such a thick connective tissue sheath that they are virtually incompressible tubes. Elasmobranch fishes and some seals also have a muscular venous sphincter located between the liver and heart which regulates venous return when venous pressure rises during exercise (elasmobranch) or diving (seal).

In most animals the majority of the venous reservoir is placed level with or above the heart (even in giraffes). However, in

erect animals (primarily humans) the majority of the venous reservoir is below the heart. Consequently, due to the hydrostatic effect (as described above), transmural pressure will increase in veins below the heart and will decrease in those above. Hence, when the animal is upright, leg veins distend and head veins may collapse. This hydrostatic effect has no “direct” effect on flow (aside from the fact that flow resistance will fall as vessels distend or increase if they collapse) since it is added to both arterial and venous sides of the circulation.

Venous return is caused by the forward push of the blood generated by the heart and transmitted in the form of a positive pressure across the capillaries (*vis à tergo*). In the pulmonary circulation and, on the body side in some lower vertebrates, the arterial pressure pulse may be transmitted across the capillaries. Even when these pulsations are damped out, venous pressure pulsations occur in central veins as heart movements are transmitted “backward” to these veins. In some animals venous return is promoted by a suction force (*vis à fronte*) due to subatomospheric pressures in the cardiac cavities caused either by a negative intrapericardial pressure stretching the atrium, as in elasmobranchs, or, in animals lacking a rigid pericardium, to “elastic recoil” of the ventricles, or atrial volume changes associated with ventricular relaxation. When veins with valves run through blocks of skeletal muscle, contraction of these muscles squeezes blood toward the heart (muscle pump).

The muscle pump works in all vertebrates; in some fishes, even the arteries within the muscle mass have valves to ensure unidirectional flow of blood. In animals that have a diaphragm, inspiration aids venous return; since pressure within the thorax is at subatmospheric level, the transmural pressure of intrathoracic veins increases, and they expand. At the same time, abdominal pressure rises, so the transmural pressure in extrathoracic veins will decrease and they will be compressed, thus forcing blood toward the heart. Hence, at the diaphragm a sharp drop in venous pressure occurs which is referred to as a vascular waterfall.

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