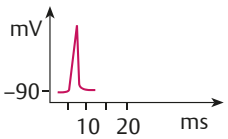
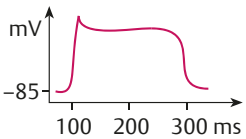
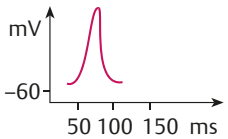
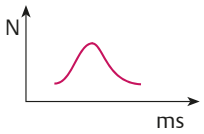
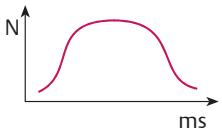
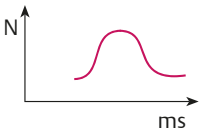
Table 6.1 Overview of morphological and functional differences between the muscle types of mammals.

	Skeletal muscles	Cardiac muscle	Smooth muscles
Cell shape	Longitudinal cylindrical	Longitudinal cylindrical	Spindle-shaped
Length (µm)	up to 200 000	100–150	50–500
Number of nuclei/cell	Up to 100	1	1
Nucleus location	Marginal	Central	Central
Cross-striping through sarcomere arrangement	Yes	Yes	No
Mitochondria	Few to many (depending on fibre type)	Many	Few
Sarcoplasmic reticulum	Strongly developed	Moderately developed	Weakly developed
T-tubule system	Yes	Yes	No
Gap junctions	None	Yes	Yes (single unit)
Pacemaker cells	No	Yes (fast)	Yes (slow) (single unit)
Motor endplate	Yes	No	No
Vegetative varicosities	No	Yes	Yes
Action potential			
Duration (ms)	5	200–400	50–100
Course (mV)			
Contractions (N)			
Refractory time (ms)	2–4	50–300	50–100
Regulatory proteins	Troponin, tropomyosin	Troponin, tropomyosin	Calmodulin, caldesmon
Tetanic contraction	Possible	Not possible	Possible

6.4.1 Morphology

In contrast to skeletal muscle cells, striated cardiac muscle cells do not have complete electrical insulation from each other. Cardiac muscle cells are conductively connected to each other by **nexus** or **gap junctions**, as is also found in smooth muscle cells of the single-unit type. Thus, the heart muscle also works as a single unit and is called a **functional syncytium**. The ability of all cells of the cardiac muscle to be excited as a unit and thus to contract as a unit is the main prerequisite for the physiological action of the heart. In contrast, the single-unit type in smooth muscle is usually limited to only parts of an organ. The cardiac muscle cell, like the smooth muscle cell, has only one central nucleus, whereas the skeletal muscle cell is a multinucleated syncytium. The high number of mitochondria in cardiac muscle cells reflects the high oxidative metabolism of this type of muscle. The sarcoplasmic reticulum is less developed in cardiac muscle cells than in skeletal muscle, but is more distinct than in smooth muscle. As in the other muscle types, it serves as a Ca^{2+} store when the cell is excited.

IN A NUTSHELL !

The cardiac muscle is a functional syncytium and therefore contracts as a unit, which is necessary for coordinated heart action.

6.4.2 Excitation

While the single cells of skeletal muscle and the multi-unit type cells of smooth muscle depend on excitation by a fibre of an α-motoneuron or a vegetative nerve fibre to contract, cardiac muscle has **autonomous** excitation generation (p. 174) similar to that found in single-unit smooth muscle. As in smooth muscle, the heart muscle contains pacemaker cells which are organised in the form of the **sinus node in the right atrium**. In contrast, in smooth muscle the pacemaker cells are diffusely distributed. The

sinus node cells continuously generate action potentials that lead to a depolarization of cardiac muscle cells with a long-lasting **plateau phase**, resulting from Ca^{2+} influx from the extracellular space. The resulting action potential of heart muscle, with a duration of 200–400 ms, lasts much longer than that of the skeletal muscle cell with 5 ms or a nerve cell with 1 ms. The smooth muscle cell, on the other hand, can have action potential lengths of 1–100 ms, depending on the type of muscle. As in single-unit-type or multi-unit-type smooth muscle, the autonomic nervous system (p. 114) plays an important role in **regulating** the **contraction processes** of the heart. The Ca^{2+} influx during the plateau phase is not only responsible for the maintenance of the action potential, but also induces a release of Ca^{2+} stored intracellularly in the sarcoplasmic reticulum (**Ca^{2+}-induced Ca^{2+} release**).

IN A NUTSHELL !

The cardiac muscle is autonomously excited by pacemaker cells. The autonomic nervous system regulates the actions of the heart in a superordinate way.

6.4.3 Electromechanical coupling and contraction

While Ca^{2+}-troponin in striated muscle enables the contacts between actin and myosin, in smooth muscle this is controlled by the Ca^{2+}-dependent activation of calmodulin. In cardiac muscle, the contraction lasts 200–400 ms and occurs almost simultaneously with the action potential. In skeletal muscles, the duration of contraction depends on the composition of the fibre types of the muscle. In type IIB fibre-rich muscles, contraction lasts 10–30 ms, in type I fibre-rich muscles 40–70 ms. The contraction duration in smooth muscles can range from 200 ms to 3000 ms depending on the type, but continuous contractions are also possible. However, the contractions in both skeletal and smooth muscles always occur after the action potential has expired. In the case of high-frequency stimulation of skeletal muscles and smooth muscles, a tetanic contraction occurs in both these muscle types, i.e. individual twitches merge into a single, more powerful contraction. This is due to the fact that the contraction starts **after** the action potential and thus during the time of electrical re-excitability of the muscle cells. With the continuous accumulation of free Ca^{2+} in the cell during frequent excitation, relaxation does not occur, and the muscle force rises. This is different in cardiac muscle, where action potential and contraction occur almost simultaneously. The cell can only be excited again when the contraction has also ended. The heart muscle is therefore not tetanisable, which is a prerequisite for the change between diastole and systole.

IN A NUTSHELL !

The cardiac muscle cannot be tetanised by high-frequency stimulation like skeletal muscle and certain smooth muscles.

Suggested reading

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Circulatory and respiratory system

7 Heart

Gerhard Breves

7.1 Functions of the heart

ESSENTIALS

The **heart** is an **autonomous organ**, the function of which is made possible by specialised muscle cells, for generation and conduction of excitation, along with other cells of the myocardium.

- The **cardiac cycle** consists of **systole** (isovolumetric contraction phase and ejection phase) and **diastole** (relaxation and filling phase). At the beginning of systole, the first heart sound is produced, with the second heart sound following at the beginning of diastole.
- The **work of the heart** is adapted to changing loads by the extent of mechanical muscle prestretching (**Frank-Starling mechanism**) and the influence of the autonomic nervous system. The heart works as a **pressure-suction pump** and consists of two atria and two ventricles, each connected in series. The direction of blood flow is controlled by inlet valves (atrioventricular valves) and outlet valves (aortic and pulmonary valves). The right heart drives the pulmonary circulation, the left heart the systemic circulation. Cardiac output is the product of heart rate (HR) and stroke volume (SV).
- The basis for the **contraction of myocardial cells** is the ability to generate action potentials. Muscle contraction is controlled by an influx of Ca^{2+} into the myocardial cell from the extracellular space and an intracellular release of Ca^{2+} from the sarcoplasmic reticulum.
- **The autorhythmia of** the **heart** is initiated when an action potential arises in the primary pacemaker (sinus node, sinoatrial node) through spontaneous depolarization which propagates via the conduction system to the myocardium. The sympathetic nervous system can increase the heart rate (positive chronotropic action), the conduction velocity in the AV node (positive dromotropic action) and the force of contraction (positive inotropic action). The parasympathetic nervous system decreases the heart rate (negative chronotropic action).
- The rhythmically changing **electrical activity of** the **myocardium** generates an electrical field that is conducted via the extracellular fluid to the surface of the body. There, the time-dependent potential differences can be registered as an electrocardiogram (**ECG**) by means of electrocardiography with electrodes. The standard recording points are on the limbs (limb leads according to Einthoven or Goldberger) or on the chest wall (Wilson's leads).

7.2 Heart as a pump

The cardiovascular system forms a self-contained system in which blood is constantly transported through the systemic and pulmonary circulations to all regions of the body. These circulations are vascular transport systems composed of arteries, arterioles, capillaries, venules and veins (**Fig. 8.1**). At the centre of these transport systems is the heart as a combined **pressure-suction pump** which drives the continuous outflow and return of blood to the heart. The heart is surrounded by a connective tissue sac, the **pericardium**. It consists of an outer layer (parietal pericardium) and an inner layer (visceral pericardium, **epicardium**). A thin, liquid-filled space is present between the two sheets. The epicardium is the outer layer of the heart wall with the **cardiac muscle** as the contractile element. The innermost of the three layers of the heart wall is the **endocardium**. It lines the chambers of the heart and the valves. Functionally, the muscular hollow organ heart is divided into two parts, the left and right heart, which are separated by the interatrial and interventricular septum. Both parts of the heart consist of an **atrium** and a **ventricle**. Between them, are the two **atrioventricular valves** (right heart **tricuspid valve**, left heart **bicuspid valve**, **Fig. 7.1 a**). The cranial and caudal **vena cava** directs blood flow into the right atrium, as does a large cardiac vein, which carries venous blood from the heart muscle into the right atrium (**coronary sinus**). These three veins transport oxygen-poor blood to the heart. Four veins arising from the lungs lead arterial, oxygen-rich blood into the left atrium. The blood

supply to the cardiac muscle is provided by the coronary vascular system (right and left **coronary artery**). The coronary arteries originate from the aorta just above the **aortic valve**.

The four heart valves are located in the **atrioventricular valve plane** (**Fig. 7.1 b**). Their function is to partially separate the cardiac chambers and to serve as inlet and outlet valves. Thus, a directed flow of blood through the heart is achieved. The inlet valve between the right atrium and the right ventricle is the **tricuspid valve**. The **bicuspid valve** (also called the mitral valve from Latin: mitre, bishop's mitre) is the inlet valve between the left atrium and the left ventricle. The **pulmonary artery** arises from the right ventricle, while from the left ventricle the main artery is the **aorta**. The **pulmonary valve** is located between the right ventricle and the pulmonary artery; the **aortic valve** is between the left ventricle and the aorta. Both act as outlet valves. Whereas the aortic and pulmonary valves each consist of three semilunar cusps (**semilunar valves**), the tricuspid and bicuspid valves form the **atrioventricular valves**. The first consists of three leaflets (= tricuspid) and the second has two leaflets (= bicuspid). The leaflets are limited in their range of movement by **chordae tendineae** (tendinous cords, heart strings). The chordae tendineae are connective tissue–like, delicate structures between the leaflets and the protrusions of the ventricular muscles, the **papillary muscles**. The chordae tendineae maintain the position of the atrioventricular valves and their tension; they prevent a reflux of blood into the atria during ventricular systole.

IN A NUTSHELL !

The heart is the pump that generates pressure and thereby provides the energy to move blood. The heart valves act as inlet and outlet valves to ensure that the blood flow is directed.

7.2.1 Heart action in four-quarter-beat

The structure of the heart is that of two functional pumps, running in parallel and simultaneously (right and left heart), each with an atrium and a ventricle. Each ventricular pump works separately in a four-quarter mechanical cycle. The cycle begins with the **isovolumetric contraction phase** (first beat, **Fig. 7.2 a**), followed by the **ejection phase** (ejection, second beat) and the **isovolumetric relaxation phase** (relaxation, third beat). The cycle concludes with the **filling phase** (fourth beat). During each **cardiac cycle** ("heartbeat"), the isovolumetric contraction phase and the ejection phase constitute the **systole**, while the isovolumetric relaxation phase and the filling phase are called **diastole**. In the **electrocardiogram** (ECG), which will be discussed in detail later, the electrical activity of the heart from the R wave to the end of the T wave corresponds to the mechanical ventricular activity of systole. The interval from the end of the T wave to the R wave corresponds to diastole (**Fig. 7.2 b**). During the isovolumetric contraction

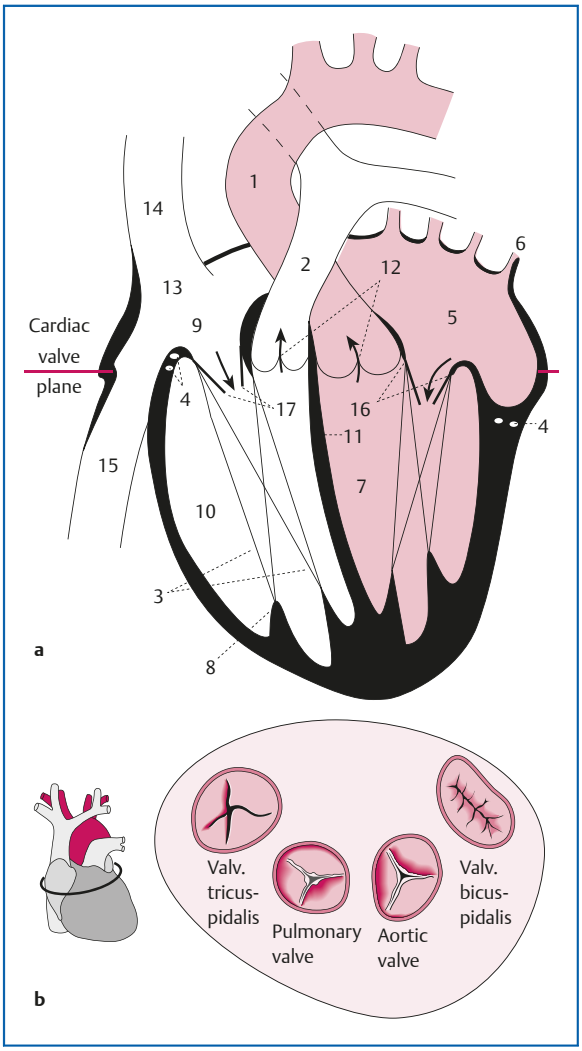

Fig. 7.1 a Schematic of the mammalian heart showing the two atria (9 right atrium, 5 left atrium) and the two ventricles (10 right ventricle, 7 left ventricle). The ventricles are separated by the interventricular septum (11). The interatrial septum is connected to the aorta (1) and the pulmonary artery (2). Between the atrium and the ventricle are the valvula tricuspidalis (17) and valvula bicuspidalis (16). The inlet valves are also commonly called atrioventricular (AV) valves. The leaflets are connected to papillary muscles (8) by chordae tendineae (3). This mechanism prevents the valves from opening during ventricular systole. During diastole blood flows from the cranial (14) and caudal (15) veins through the right atrium into the right ventricle. In the left heart, arterial blood (pink) from the pulmonary veins (6) enters the left atrium. During the following systole, the stroke volume (SV) of the right ventricle is ejected via the pulmonary valve into the pulmonary artery ((2), pulmonary circulation). The SV of the left ventricle is pumped into the aorta via the aortic valve ((1), systemic circulation). The outlet valves are also called semilunar valves (12).
b Cross section through the heart showing the atrioventricular valve plane schematically from above. It is formed by inlet and outlet valves. Note: The ventricular myocardium of the left ventricle is much thicker than that of the right ventricle because a higher systolic ventricular pressure must be generated in the systemic circulation than in the pulmonary circulation. The sinus node (13) in the venous sinus of the right atrium is the primary pacemaker of the heart. The blood supply to the heart is via coronary vessels (4).

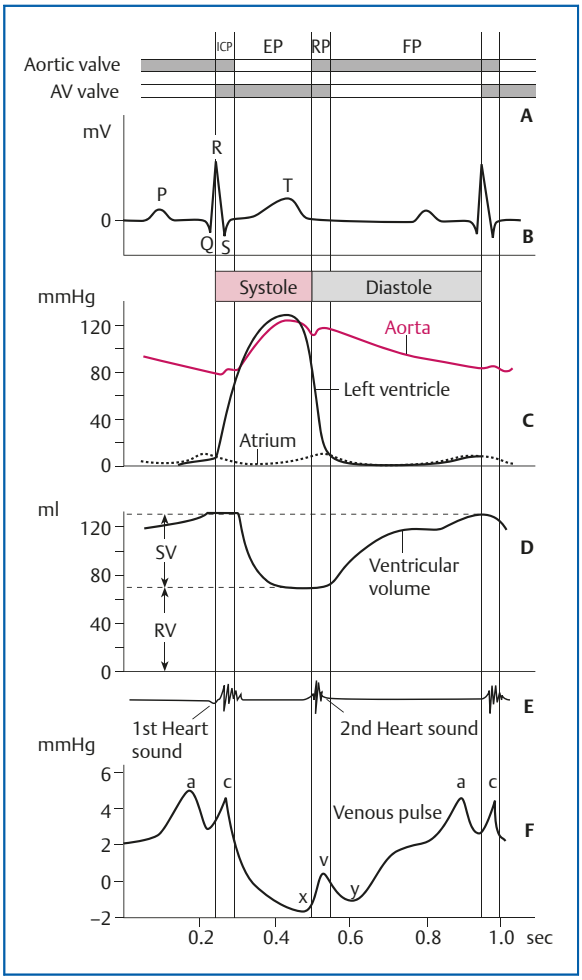

Fig. 7.2 Mechanical and electrical activity of the heart action in individual phases of a pig weighing about 70 kg.
A The four phases of the cardiac cycle: **Systole** (ICP: isovolumetric contraction phase, and EP: ejection phase), **diastole** (RP: isovolumetric relaxation phase, and FP; filling phase). The aortic valve (left heart as an example) is open (white) during EP, otherwise always closed (grey). The atrioventricular valves are open (white) during filling, otherwise always closed (grey).
B Associated **electrocardiogram** (ECG, schematic) showing the propagation of the electrical activity during the cardiac cycle. The meaning of the characteristic waves (P, Q, R, S, T) will be explained later, see ch. ECG analysis (p. 185).
C Pressure curve during systole and diastole in the left atrium and **left ventricle** and in the **aorta**. Note: The pressure amplitude in the aorta is considerably attenuated by distensibility of the vessels ("Windkessel function" (p. 196), **Fig. 8.7**, **Fig. 8.19**).
D During systole, the ventricles are never fully emptied. At rest, the **stroke volume** (SV) is even smaller than the remaining **reserve volume** (RV).
E The heart's action in four phases produces two main heart sounds (p. 169), which can be visualised in a phonocardiogram. The first heart sound is associated with the closing of the AV valves. The second heart sound is produced by the vibration of the blood column in the vessels immediately after closure of the semilunar valves. Note the incision (p. 197) (notch in the pressure curve) during the R phase.
F Pressure curve in the cranial vena cava (venous pulse). The deflections are generated by: a = atrial contraction, c = tightening phase of the right ventricle, protrusion of the AV valve, x = lowering of the cardiac valve plane, v = raising of the cardiac valve plane with the AV valve still closed, y = filling of the right ventricle.

and the isovolumetric relaxation phases, when no blood flows in the ventricles, all valves are closed. During **ejection**, the **pulmonary** and **aortic valves** (semilunar valves) are open, while the **atrioventricular valves** (bicuspid and tricuspid valves, AV valves) are closed. During the **filling phase**, the process is reversed, the AV valves are open, and the pulmonary and aortic valves are closed. These **heart valves** regulate blood flow by passive closing and opening, depending on changes in pressure. This process is supported by the anatomical arrangement of the valves in the so-called **atrioventricular valve plane** (**Fig. 7.1 a, b**). This is a stiffened plate of connective tissue which, due to fixation of the pericardium to the diaphragm at the cardiac apex (apex cordis), shifts depending on the state of contraction. In this way, it has a decisive influence on haemodynamics (**atrioventricular plane displacement**). By the shortening of the ventricular myocardium during systole, the cardiac valve plane moves towards the apex of the heart and causes the relaxed atria to dilate. This results in suction which, at the beginning of diastole, causes the rapid **inflow** of blood from the **atria** into the **ventricles**. During diastole, the increase in length of the ventricular myocardium shifts the cardiac valve plane back towards the base of the heart. The AV valves open and the blood is redistributed from the atria to the ventricles. Together with atrial contractions, the ventricles fill rapidly with blood.

IN A NUTSHELL !

- **Isovolumetric contraction phase**: All valves are closed.
- **Ejection phase**: The outlet valves are open.
- **Isovolumetric relaxation phase**: All valves are closed.
- **Filling phase**: The AV valves are open.

The **atrioventricular plane displacement** is responsible for the rapid **early diastolic filling of the ventricles**.

7.2.2 The ventricles are never completely empty

During a cardiac cycle the ventricles never empty completely. As shown in **Fig. 7.2 d**, each ventricle contains approximately 130 ml of blood at the end of **diastole** (**end-diastolic volume**, EDV; example of a 70 kg pig). During systole, under resting conditions, approximately 60 ml is ejected (**stroke volume**, SV), but 70 ml remains (**end-systolic volume**, ESV). The ratio of stroke volume to end-diastolic volume gives the **ejection fraction**, a measure of cardiac function. As can be seen in **Fig. 7.2 c**, **the left ventricular pressure** is very low at the beginning of systole. It is close to 5 mmHg in this phase. Because of the forceful contraction of the ventricular myocardium, the pressure increases very rapidly until it exceeds the aortic pressure (**isovolumetric contraction phase**). Then the aortic valve opens and the stroke volume leaves the ventricle (**ejection phase**). Because at the beginning of **systole** the ventricular volume initially remains the same (**Fig. 7.2 d**), this phase is called **isovolumetric contraction phase**. The ejection of the stroke volume is initially rapid and then slows down

when the **ventricular** and **aortic** pressures fall after reaching their maxima. When the ventricular pressure drops even further, ejection is stopped and there is a brief reflux of blood in the region of the aortic valve. The aortic valve then closes. The transition from systole to diastole produces the so-called **incisura** in the pulse pressure curve in the arteries near the heart, so that the pressure curve appears as a **dicrotic** (two-peaked) **notch** (aorta in **Fig. 7.2 c**, **Fig. 8.7**, **Fig. 8.8 a**). In **diastole**, the ventricular myocardium relaxes and the left ventricular pressure drops back to a value of about 5 mmHg (ventricular **preload**; the preload of the right ventricle is about 3 mmHg). In **Fig. 7.2 c** the pressure amplitude in the left ventricle is about 120 mmHg. The mitral valve remains closed until the ventricular pressure falls below that in the left atrium (relaxation of the myocardium). The first phase of ventricular **diastole** is called the **isovolumetric relaxation phase**. **Ventricular filling** is initially rapid (atrioventricular plane displacement (p. 167)) and then slows until an action potential is initiated by the pacemaker cells of the sinoatrial node (onset of the P-wave in ECG), triggering **atrial contractions**. As can be seen in **Fig. 7.2 d**, during diastole 80–90% of **ventricular filling** is completed before atrial contraction begins. The atrial contraction ultimately causes only the final residual filling of the ventricle (end of the **filling phase**). At the onset of ventricular systole, the atrial muscle cells begin to relax again. The processes described here for the left heart also apply to the right heart in terms of timing and blood flow rates, although the pressure conditions there are different. The maximum systolic pressure in the right ventricle is only about 20–30 mmHg.

IN A NUTSHELL !

The maximum pressure in the left ventricle is about 120 mmHg, while that in the right ventricle is only about 20–30 mmHg.

7.2.3 Heart sounds

The physiological heart action causes characteristic sounds (first and second heart sound, **Fig. 7.2 e**). They can easily be recorded and documented phonocardiographically. The **first heart sound** is a low-frequency, muffled sound that occurs during the isovolumetric contraction phase. It is caused by the ventricle rapidly tightening around the non-compressible blood, causing it to vibrate together with the AV valves. The **second heart sound** is produced when the valves of the aorta and the pulmonary artery close. It is a bright, loud, shorter tone. Occasionally, a **third heart sound** can also be detected as a very quiet sound, shortly after the second heart sound. It cannot be heard with a stethoscope in healthy animals. This third heart sound is produced during early ventricular filling by the inflowing blood.

MORE DETAILS If the heart sounds are accompanied by murmurs, these usually indicate pathological changes in the heart valves or stenoses. These are not referred to as heart sounds, but instead are called heart murmurs.

IN A NUTSHELL !

The first heart sound is produced by the isovolumetric contraction of the ventricles, and the second heart sound comes from the closure of the aortic and pulmonary valves.

7.2.4 Pumping capacity at rest

The processes depicted in **Fig. 7.2** repeat with each heartbeat. They pump a new **stroke volume** (SV) into the pulmonary artery and the aorta with each subsequent cycle. The number of heart beats per minute is called the **heart rate** (HR). The **resting heart rate** varies widely in animals, decreasing significantly with increasing body mass (**Fig. 7.3 a**). An elephant with a body mass of about 4000 kg has a resting heart rate of 24 per minute, an Etruscan shrew with a body weight of 2.4 g has a resting heart rate of 800–1200 per minute.

Cardiac output (CO) is the total ejection volume pumped out by each ventricle in one minute. It is the product of SV and HR and correlates positively with body mass (**Fig. 7.3 b**).

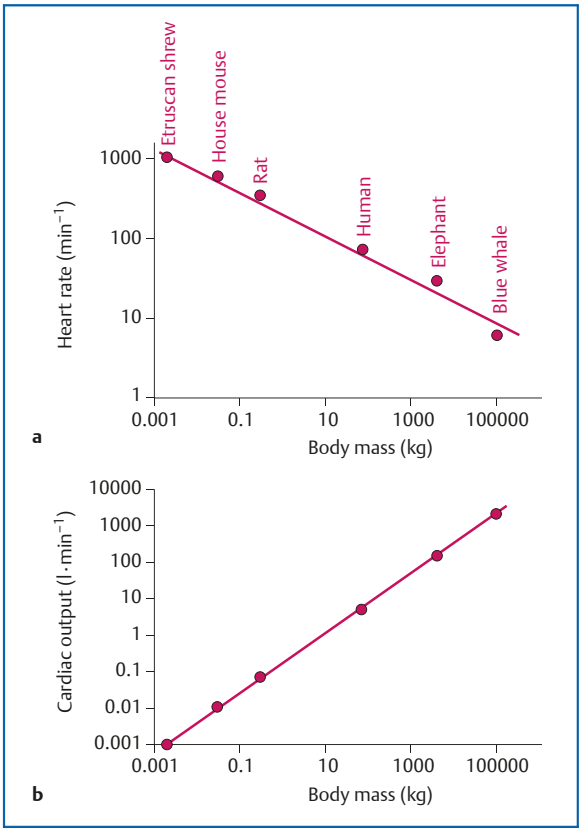

Fig. 7.3 Relationship between resting heart rate (**a**), resting cardiac output (**b**) and body mass in different mammals.

For a pig (70 kg) with a resting HR of 85 beats · min^{-1} and a SV of approx. 60 ml (**Fig. 7.2 d**), the result is 5.1 l · min^{-1}. A rough estimate of the total blood volume (p. 212) of an adult animal is obtained by multiplying the body weight by a factor of 0.07: e.g. 70 kg · 0.07 = 4.9 kg or about 4.9 litres of blood. This means that even under resting conditions the entire blood volume is transported through the lungs or heart once per minute.

IN A NUTSHELL !

The resting heart rate varies widely in different animal species, and decreases with increasing body mass. At rest, the entire blood volume is transported through the lungs or heart once per minute.

7.2.5 Adjustment of cardiac power during physical work

As already mentioned in ch. 7.2.2, the **stroke volume** (**SV**) is the **end-diastolic volume** (**EDV**) minus the **end-systolic volume** (**ESV**). The SV can be increased by (1) an increase in end-diastolic volume (e.g. by increased filling during diastole) or by (2) a decrease in end-systolic volume or by both processes simultaneously. The effects of increasing end-diastolic volume on SV are shown in **Fig. 7.4 a**. The physiological mechanisms underlying this relationship are based on the fact that stretching the ventricular musculature (prestretch (p. 152), **Fig. 6.8**) increases the force of the next contraction, and that stretching the muscles during diastole leads to increased release of Ca^{2+} from the sarcoplasmic reticulum in myocardial cells. The latter triggers the beating force, i.e. the **prestretch has a positive inotropic** effect. This effect is comparable to the so-called Bayliss effect on smooth muscle cells (see ch. Autoregulation, myogenic tone (p. 208). **Fig. 7.4 a** shows the interdependence of the end-diastolic ventricular volume and the stroke volume in a large dog. **Resting conditions** are shown approximately in the middle of the curve (dashed lines). It is clear that the SV can be proportionally adjusted upwards or downwards within a certain range of EDV changes. This raises the question of what the end-diastolic volume ultimately depends on.

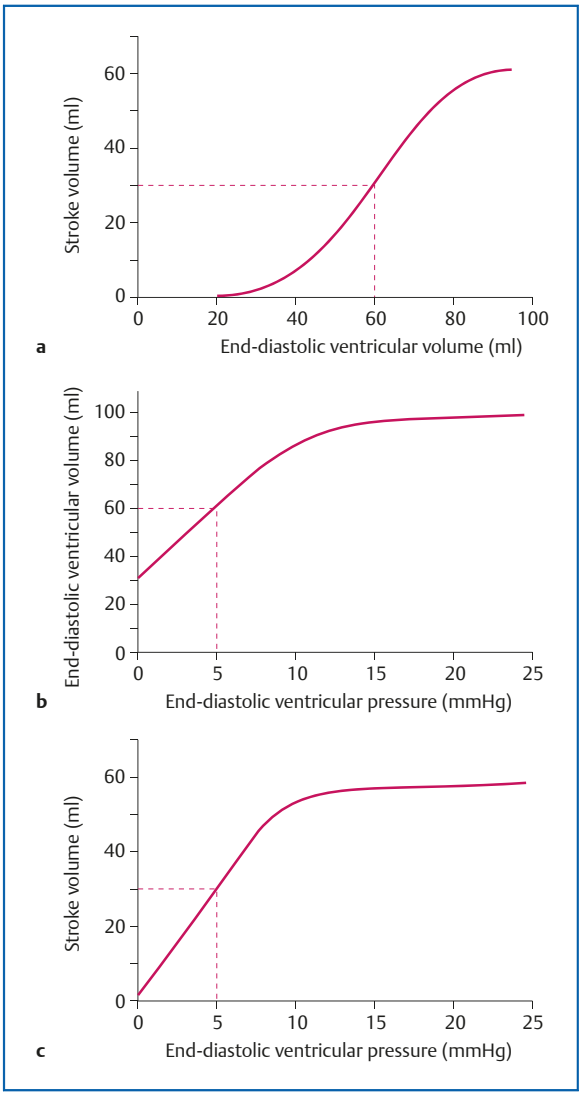

Fig. 7.4 **a** Increase in end-diastolic ventricular volume (EDV) augments stroke volume; **b** Increase in end-diastolic ventricular pressure (preload) augments EDV; **c** Combination of the functional relationships in a and b: Increase in ventricular preload augments stroke volume. In all functional relationships a maximum is reached (a-c, examples for the left ventricle of a larger dog, dashed lines indicate values at rest). With increasing EDV, the ventricular wall is stretched until it reaches the limit of its elasticity; based on data from Klein BG (ed.). Cunningham's Textbook of Veterinary Physiology Philadelphia: Elsevier; 2013

7.2.6 Frank-Starling mechanism

The **wall tension** caused by the end-diastolic ventricular volume and the resulting end-diastolic **ventricular pressure** is called the **ventricular preload** of the **heart**). End-diastolic ventricular pressure is identical to atrial pressure because the AV valves are open during diastole. Thus, ultimately ventricular preload is also influenced by processes that act on **atrial pressure** such as the pressure in the pulmonary veins. **Fig. 7.4 b** shows that, for example, an increase in preload to 5 mmHg leads to a proportional increase in EDV. Physiologically, this effect means that preload-induced increases in EDV lead to an increase in stroke volume (**Fig. 7.4 c**). Conversely, a decrease in preload can decrease stroke volume, for example, in **haemorrhagia** (bleeding).

The **autoregulation of stroke volume** as a function of the end-diastolic volume was first studied by the scientists Otto Frank and Ernest Henry Starling and is known as the **Frank-Starling mechanism**. The Frank-Starling mechanism also achieves, above all, that the **right** and **left heart** adapt to **equal ejection volumes**. If, for example, the right heart were to pump only 1 ml more blood per beat than the left, the difference would already correspond to approx. 60 ml after one minute and would lead to pulmonary oedema within a very short time. These effects of the end-diastolic ventricular volume on the stroke volume of the right and

left ventricle ensure an autoregulatory adjustment of the stroke volumes at a constant heart rate. This also allows rapid coordination of the pumping of both ventricles to rapid fluctuations in blood pressure, such as when an animal lies down or stands up.

IN A NUTSHELL !

Frank-Starling mechanism: autoregulation of stroke volume ensures that the stroke volumes of both ventricles remain equal.

In addition to preload, end-diastolic volume is also influenced by ventricular **compliance**. Compliance is a measure of the distensibility of a body structure such as the vessels (p. 196) or the lungs (p. 270). Ventricular compliance describes the increase in volume with increasing filling pressure. **Fig. 7.5** (upper curve) shows that with normal ventricular compliance there is no problem for end-diastolic filling at a preload up to approx. 5 mmHg. At a preload of 10 mmHg, the EDV would be significantly higher. With reduced compliance due to inelastic connective tissue in the ventricular wall, the EDV is significantly lower (**Fig. 7.5** lower curve). The normal EDV is reached under these conditions only with a preload of 10 mmHg (dashed line).

IN A NUTSHELL !

Compliance is a measure of the distensibility of a body structure, such as the vessels or lungs. The compliance of the ventricles describes the ventricular volume increase with increasing filling pressure.

In addition to preload and compliance, **filling time plays a role as a third factor in controlling end-diastolic volume**. The filling time is determined by the heart rate. An increase in heart rate is usually accompanied by an increase in contractility (p. 170). Under resting conditions there is sufficient time for filling. Ventricular filling is virtually complete when atrial systole begins (**Fig. 7.2 d**). However, if the heart rate rises sharply during heavy physical work, the duration of the diastole and thus the filling time decrease significantly (**Fig. 26.14**). Ch. 7.2.8 discusses why cardiac output does not decrease significantly with heavy work and thus with increasing heart rates.

IN A NUTSHELL !

An increase in heart rate is at the expense of diastolic filling time.

7.2.7 Ventricular contractility

Contractility is the force and velocity of myocardial contraction exerted by the cardiac muscle itself without the influence of preload or afterload. With increasing contractility, the stroke volume increases, and with decreasing contractility it decreases (**Fig. 7.6**). The contractility of the myocardium is fully influenced by the hormonal action of noradrenaline (p. 116) in control by the sympathetic nervous system (p. 178). The effect of **adrenaline**, released from the **adrenal medulla**, is comparable (**Fig. 7.13**). The ventricular wall then contracts more forcefully, faster and in a shorter time. Stroke volume (**Fig. 7.6**) and thus also cardiac output increase accordingly, which can lead to a rise in blood pressure (**Fig. 8.23**, **Fig. 8.24**).

MORE DETAILS The stimulating effect of noradrenaline and adrenaline on contractility occurs via the excitation of adrenergic β1 receptors (p. 117) in the heart (**Table 4.1**; **Fig. 4.3**). Hypertension can be treated by inhibiting the adrenergic signalling pathway with β_1 receptor blockers such as propranolol.

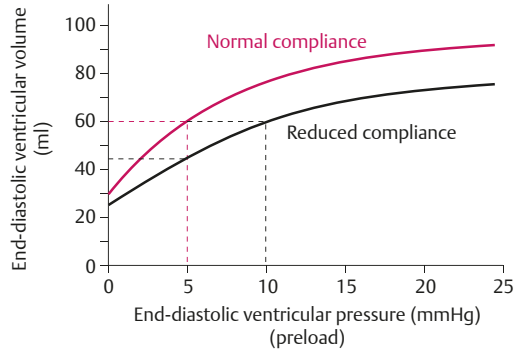

Fig. 7.5 End-diastolic ventricular volume and end-diastolic ventricular pressure. Ventricles with reduced distensibility (compliance) require a greater filling pressure (preload, e.g. 10 mmHg versus 5 mmHg) to achieve a normal end-diastolic volume (e.g. 60 ml for a dog, 30 kg); based on data from Klein BG (ed.). Cunningham's Textbook of Veterinary Physiology Philadelphia: Elsevier; 2013

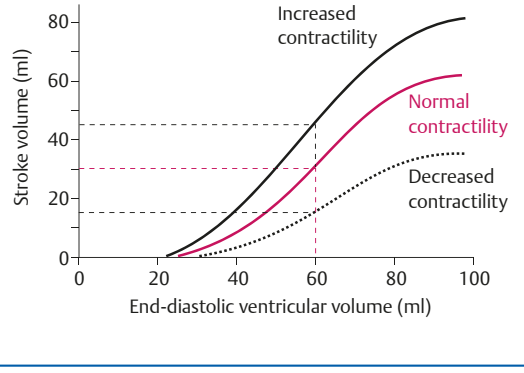

Fig. 7.6 The increase in stroke volume in a dog, as a function of end-diastolic ventricular volume (EDV) at normal (**Fig. 7.4 a**), decreased, and increased contractility. Increased ventricular contractility is shown graphically as an upward shift, decreased contractility as a downward shift of the functional curve. With normal contractility and normal EDV of 60 ml, in this example of a dog (30 kg), the stroke volume is about 30 ml. If the contractility increases with unchanged EDV, the stroke volume is increased to 45 ml. If the contractility decreases, the stroke volume is only 18 ml; based on data from Klein BG (ed.). Cunningham's Textbook of Veterinary Physiology Philadelphia: Elsevier; 2013

Ventricular contractility is the main factor in regulating end-systolic ventricular volume. In addition, arterial blood pressure influences the pumping capacity of the heart. A significant elevation of arterial blood pressure makes it difficult to eject stroke volume because left ventricular pressure must exceed aortic pressure during systole for blood to be pumped out. This aortic pressure determines the **afterload**, i.e. the wall tension that the myocardium must exert to open the aortic valve. It is mainly determined by two factors – the pressure in the aorta, which must be overcome with every systole, and the compliance of the arteries, see ch. 8.3.4 (p. 196).

7.2.8 Adjustment of cardiac output at work

Since cardiac output is the product of stroke volume and heart rate, it is to be expected that cardiac output doubles with a doubling of heart rate (**Fig. 7.7** black line; **Table 7.1**). With increasing physical exercise and the associated increase in heart rate, the ejection rate increases beyond even the expected values (**Fig. 7.7** red line). This increase occurs through a combination of increased preload (increased stroke volume) and an increase in heart rate. Crucial to these changes is the activation of the sympathetic nervous system, which increases heart rate, augments the force of contraction and causes contraction and relaxation to occur more rapidly (**Fig. 7.13**). At very high heart rates, the stroke volume decreases due to the then very short filling phase, the increase in cardiac output thus becomes smaller as the heart rate (p. 624) continues to rise, see ch. Frank-Starling mechanism (p. 170).

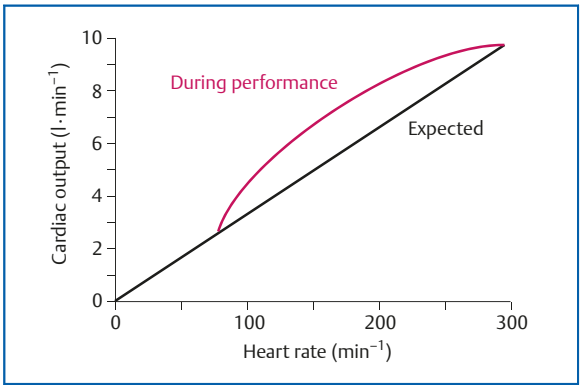

Fig. 7.7 Assuming that stroke volume remains constant, then cardiac output (CO) increases linearly with increasing heart rate (expected dependency as black line). The red line shows the increase in CO for a dog running alongside a bicycle. This increase in CO with increasing heart rate is greater than the expected linear relationship due to sympathetic influence; based on data from Klein BG (ed.). Cunningham's Textbook of Veterinary Physiology Philadelphia: Elsevier; 2013

Table 7.1 Typical adjustments of cardiac parameters in a large dog (30 kg) during physical exercise.

Parameter	Resting state	Physical exercise
Ventricular end-diastolic volume (ml)	60	55
Ventricular end-systolic volume (ml)	30	15
Stroke volume (ml)	30	40
Ejection fraction (%)	50	73
Heart rate (beats · min^{-1})	80	240
Cardiac output (l · min^{-1})	2.4	9.6

Based on data from Klein BG (ed.). Cunningham's Textbook of Veterinary Physiology. Philadelphia: Elsevier; 2013

7.3 Electrical activity of the heart

The heart muscle, like skeletal muscle, is a striated muscle, but as well as this similarity there are also important differences (**Table 6.1**). The electrical processes in the heart are mediated by cells of the **cardiac conduction system** (**Fig. 7.9 a**). The contraction of the myocardium is triggered by action potentials initiated by spontaneous depolarizations in specialised cardiac muscle cells. The **primary pacemaker** is the sinoatrial node. If the sinus node fails, then the **atrioventricular node** (**AV node**) can take over this function, but at a much lower frequency (**secondary pacemaker**). The AV node has the capacity for spontaneous electrical depolarization. This does, however, not normally come into play because the sinus node "imposes" its higher frequency on the AV node. The cardiac muscle forms a functional **syncytium** via **gap junctions** (**Fig. 7.8**), through which the pacemaker potential quickly spreads to every muscle cell. The cardiac action potential is very long, thus guaranteeing relaxation and refilling between heartbeats. **Noradrenaline**, released from sympathetic nerve endings at the sinus node, stimulates heart rate (positive **chronotropic effect**). Parasympathetic nerve endings reduce heart rate by the action of **acetylcholine** (negative chronotropic effect). Noradrenaline causes faster and more powerful contractions in all heart muscle cells (positive **dromotropic**, **inotropic** and **lusitropic**). The effect of the parasympathetic nervous system is limited to the sinoatrial node, the atria (negative inotropic) and the AV node (negative dromotropic).

IN A NUTSHELL !

The electrical activity of the heart is controlled by the cardiac conduction system. Dominant pacemakers are the cells with the fastest depolarization, usually the sinoatrial node cells. In principle, however, every cell of the cardiac musculature can trigger an action potential.

7.3.1 Comparison of contractile elements in cardiac muscle and skeletal muscle

The structural units of the heart are the cardiac muscle fibres (**cardiac muscle cells – cardiomyocytes**). Each cardiomyocyte contains a few hundred **myofibrils** similar to those of skeletal muscles (p. 145). In cardiac and **skeletal muscles**, each myofibril consists of many **sarcomeres** arranged in series. They form the smallest functional unit of muscle. The contractile elements of the sarcomere are **actin** and **myosin**. They are responsible for contraction and also relaxation through their interaction with ATP (**cross-bridge cycle**, **sliding filament theory**). This leads to shortening and force generation of the skeletal and cardiac muscle (p. 150) (**Fig. 6.6**; **Fig. 6.7**). Cardiomyocytes have a central nucleus and are much shorter than skeletal muscle fibres. Desmosomal end-to-end linkages (**intercalated discs**) give rise to long cell chains that function like a long muscle fibre (**Fig. 7.8a**). The cardiomyocytes branch and connect to other parallel cell strands through these branches, forming an interconnected plexus. Between the cell strands run collagen fibrous septa with small blood vessels and capillaries. Capillary density in cardiac muscle is very high (pig: 1000–1500 capillaries per mm^2, skeletal muscle 100–300 capillaries per mm^2). The end-to-end connections appear as bright lines under the light microscope and are called **disci intercalares**. They contain three types of cell junctions: 1. **desmosomes**, which closely anchor neighbouring cells to each other by means of the intermediate filaments; 2. **zonulae adhaerentes**, which fix the actin filaments of the sarcomeres to the two ends of the cells (equivalent to the Z-lines of skeletal muscles); 3. **gap junctions**, which allow the passage of excitatory electrical currents (**Fig. 7.8b**). A **stem cell population** analogous to the **satellite cells** of the skeletal muscle is only weakly developed in the cardiac muscles of mammals, so that the capacity of heart muscle to be able to regenerate is not strong.

7.3.2 Two types of cardiac muscle cells

Most **cardiomyocytes** do not generate their own, spontaneous action potential. Some cardiomyocytes, however, are specialised and can spontaneously depolarize to threshold. Thus, they initiate action potentials that can then trigger a heartbeat. Such myocytes are called **pacemaker cells**. A population of such cells is localised in the **sinus node** of the right atrial wall. Under physiological conditions, these cells depolarize in a regular rhythm. Their action potentials reach the ventricular myocardium via the electrical conduction system. The sinus node thus functions as the primary pacemaker. Consequently, the heart is able to generate through these pacemaker cells, its own muscle action potentials followed by contractions (**autorhythmia of the heart**). The heart's pumping capacity is adjusted mainly by changes in heart rate, by sympathetic and parasympathetic innervation of the sinoatrial node.

7.3.3 Cardiac muscles as a functional syncytium

An important difference between cardiac and skeletal muscles are the electrical **gap junctions** (**Fig. 7.8b**; **Fig. 6.16**, smooth muscle cell; **Fig. 1.5a**, cell-cell contacts) between cardiac muscle cells. Action potentials propagate in the longitudinal direction of a cell, through gap junctions at the end of the cell to a neighbouring cell, or through cell branches to a neighbouring cell strand. As the action potentials propagate from cell to cell through the cardiac tissue, neighbouring cells contract synchronously, quasi as one unit. They also relax simultaneously. As a result, the heart muscle behaves largely like a single cell and is referred to as a **functional syncytium**. The **gap junctions** are formed by special channel proteins called connexons (**Fig. 1.5a**); see ch. on cell-cell connections (p. 29)). Like cardiac muscle cells, smooth muscle cells (p. 161) also form gap junctions, but skeletal muscle does not. The T-tubules of cardiac muscle cells are larger than those of skeletal muscles, and they are often branched. The Ca^{2+}-storing **sarcoplasmic reticulum** is moderately developed in heart muscle (**Table 6.1**). Heart muscle cells also require extracellular Ca^{2+} for contraction. One third of a cardiomyocyte is composed of mitochondria. This indicates the high metabolic activity of cardiac muscle, see ch. Energetics of the Heart (p. 180).

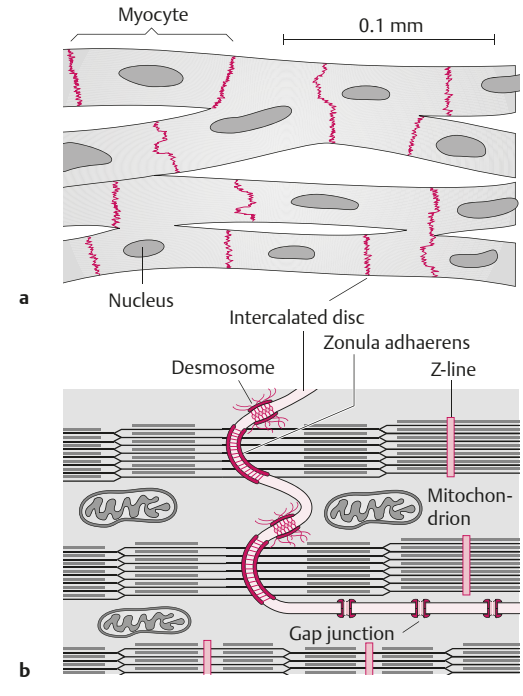

Fig. 7.8 a Basic structure of the myocardium with the branched transverse connections, central nucleus and striation (schematic). The muscle cells adhere to each other at the intercalated discs (disci intercalares).
b Enlarged area of an intercalated disc. There are three types of cell contacts: (1) **desmosomes**, which attach the cell membrane of adjacent fibres to each other, (2) **zonulae adhaerentes**, which are not only cell-cell connections but also bind to the actin filaments, and (3) the electrically conducting **gap junctions**. The cardiomyocyte contains numerous mitochondria.

IN A NUTSHELL !

The cardiac muscle consists of a network of myocytes that form a functional syncytium at the cell borders (intercalated discs) through electrically conducting gap junctions.

7.3.4 Generation and conduction of electrical impulses

The **cardiac conduction system** is formed by the **sinus node**, the **atrioventricular node** (AV node, Aschoff-Tawara node), the **His bundle** (AV bundle), the **Tawara branches** (bundle branches) and the **Purkinje fibres** (**Fig. 7.9 a**). Each heartbeat begins with a spontaneous action potential from one of the pacemaker cells in the sinoatrial node (**Fig. 7.9 a**). It then propagates from cell to cell in the atrial muscles of the right and left atrium (**internodal pathways**). This is followed by contraction of the atria. The **action potential** then travels to the atrioventricular node and then to the start of the His bundle at the septum. The AV node is the only way for the action potential to propagate from the atria to the ventricles because without this connection the atria are separated from the ventricles by a non-excitable layer of connective tissue within the **atrioventricular plane**. The conduction of excitation from the beginning of the AV node to the beginning of the His bundle is slow in comparison with the ventricular conduction of excitation ("**snail path**"). This slow conduction creates the necessary delay between atrial and ventricular contractions (**Fig. 7.9 b**). After the slow conduction from the AV node and the subsequent first part of the His bundle, the action potential then continues rapidly towards the cardiac apex ("**racetrack**"). The second part of the His bundle consists of specialised muscle cells that can conduct excitation very quickly. The action potential is distributed to the two Tawara bundles, which run in the septum, up to the apex of the heart. There, the bundles branch into a network of **Purkinje fibres** that conduct the action potentials to the inner sides of both ventricles. Thus, the action potentials are first distributed to the subendocardial muscle cells. From there, they propagate very rapidly from cell to cell through the cardiac wall towards the pericardium. Since the action potential spreads extremely quickly in the millisecond range from the distal part of the His bundle to the outer part of the ventricular myocardium, there is an almost synchronous **contraction of cardiac muscle cells in both ventricles**. With the subsequent atrial and ventricular relaxation and the filling phase, the cardiac cycle is completed.

IN A NUTSHELL !

A small number of specialised cardiac muscle cells form the electrical conduction system of the heart. This consists of the sinoatrial node, the atrioventricular node (AV node), the His bundle, the right and left Tawara bundles and the Purkinje fibres.

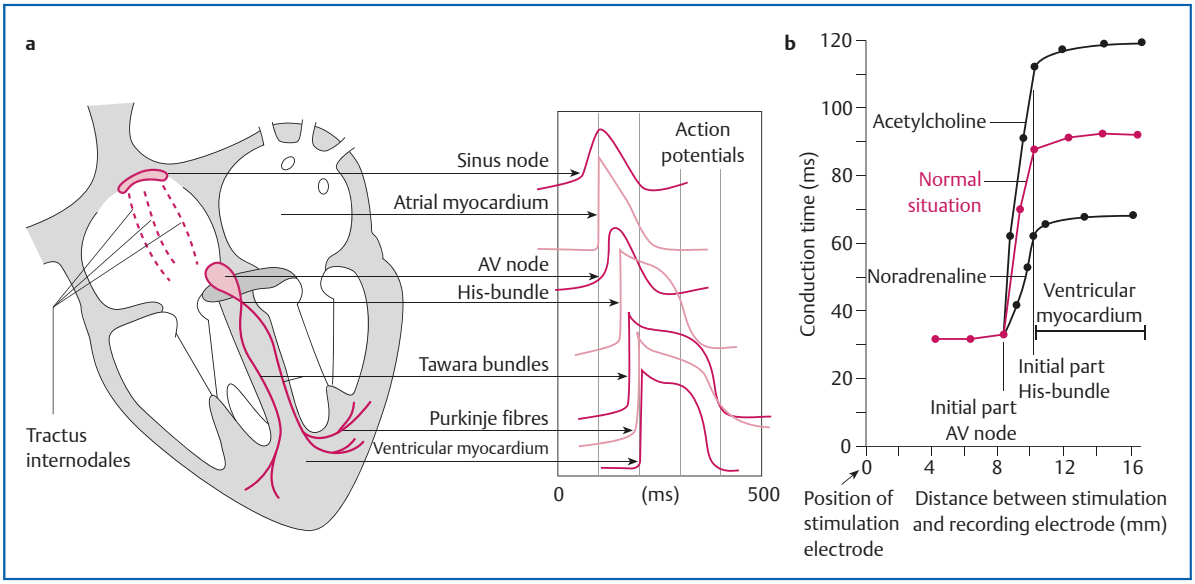

Fig. 7.9 a Shape of a characteristic action potential in different regions of the heart. Action potentials of the **pacemakers** (primary pacemaker (sinus node), secondary pacemaker (AV node)) as well as the other parts of the **cardiac conduction system** (His bundle, Tawara bundle, Purkinje fibres) appear as solid red lines. The action potentials of the atrial myocardium and the ventricular myocardium are dashed in red. The temporal shift corresponds to the sequence of excitation during cardiac action.
b Dependence of conduction time on the distance between the stimulus site and the recording electrode under control conditions and under the influence of acetylcholine and noradrenaline. The neurotransmitters only influence the conduction time in the region of the AV node. An increase in conduction time means a decrease in conduction velocity.