Physiology of Heart Rate

7

T. Alexander Quinn and Sheldon Magder

One might wonder about the need for a chapter on heart rate. A change in heart rate is one of the most basic ways that the heart regulates cardiac output. Rapid heart rates also often trigger clinical interventions. However, there is a much more basic reason for examining heart rate in more detail. The 'periodicity' that comes with rhythmic beating of the heart creates important restrictions on the cardiovascular system. It sets the fixed time available for ejection of stroke volume from the left ventricle and the time available for the stroke return to the right heart. Because of these fixed times, the rate of return and rate of ejection are important determinants of how much blood flow can leave and return during each cycle and how much the rate of blood flow needs to accelerate to reach its target. The fixed period of each cycle also means that the ratio of ejection time to the return time (i.e. diastole) is an important determinant of cardiac output. At faster heart rates, both of these are shortened, but the proportions of time for each can vary. We will start with the concept of time constants and their importance for the discussion of the periodicity of cardiac contractions. We will then review the complex membrane processes in the heart's intrinsic pacemaker that determine heart rate, as well as the factors that determine the length of the ventricular action potential. The length of the action potential is important because it sets the amount of time for the entry of calcium ions (Ca^{2+}) to produce the contraction phase. We follow with a discussion of basic mechanisms involved in regulation of the intrinsic heart rate, and heart rate during exercise which gives insight into the regulation of heart rate at the extremes. This is followed by the significance of the fixed filling times for normal function and in pathological considerations. Finally, we review the implications for changes in heart rate on the supply and demands of the heart for oxygen. Some of these issues have been covered previously (Magder 2012).

Time Constants and Volume Constraints

To appreciate the significance of the periodicity of cardiac output, it is first necessary to understand the concept of a time constant. When there is a step change in the flow or pressure in a system that has stretchable walls, a proportion of the initial increased input volume stretches the walls of the vessels and does not contribute to distal

T. A. Quinn
Dalhousie University, Department of Physiology & Biophysics, Halifax, NS, Canada
e-mail: alex.quinn@dal.ca

S. Magder (✉)
Royal Victoria Hospital (McGill University Health Centre), Departments of Critical Care and Physiology McGill University, Montreal, QC, Canada
e-mail: sheldon.magder@mcgill.ca

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flow (Fig. 7.1). Once the force across the wall matches the new pressure, a new steady state in flow is reached and what goes in is matched by what goes out. In a vessel, the time taken to reach a new steady state is determined by the amount of volume the vessel takes up with the change in pressure, which is based on the compliance of the vessel wall, and how easily volume flows out of the vessel, which is determined by the downstream resistance. Mathematically, this is described by an exponential raised to the power of the product of downstream compliance and resistance divided by time (Fig. 7.1). The product of the compliance and resistance gives a time constant, which indicates the time taken to get to 63% of the new steady state. The greater the downstream resistance, or the greater the compliance of the vessel, the longer it takes to get to a new steady state. The significance of this in a pulsatile system is that when the duration of each pulse is less than the time constant, the change in flow for a change in pressure may be less than predicted from just the change in peak pressure because there is not enough time to reach the steady state (Fig. 7.2). This is especially an issue on the venous side because the change in pressure for a change in flow is so low. At faster heart rates, blood must come back faster to allow an increase in return and increase in cardiac output. The primary process allowing this is a decrease in venous resistance because the compliance vessels do not change, but during exercise compression of peripheral veins by the contracting muscles likely gives the equivalent of a decrease in venous compliance and resistance (Magder 1995; Magder et al. 2019).

A consequence of increased heart rate is that if the duration of systole remains constant, diastolic time must become progressive shorter. This reduces diastolic filling time and the limit for return per beat (stroke return). The heart thus has to reach the peak end-systolic elastance (end-systolic pressure volume line – see Chaps. 3 and 4) faster at higher heart rates, and accordingly, the action potential needs to shorten. Ventricular relaxation time also must shorten to allow more time for diastole.

Cardiac Rhythmicity at the Cellular Level

Sinoatrial Node Control

Excitation of the heart is initiated in the sinoatrial node (SAN), the natural pacemaker of the heart. It is located adjacent to the *crista terminalis* at the junction of the right atrium and the superior

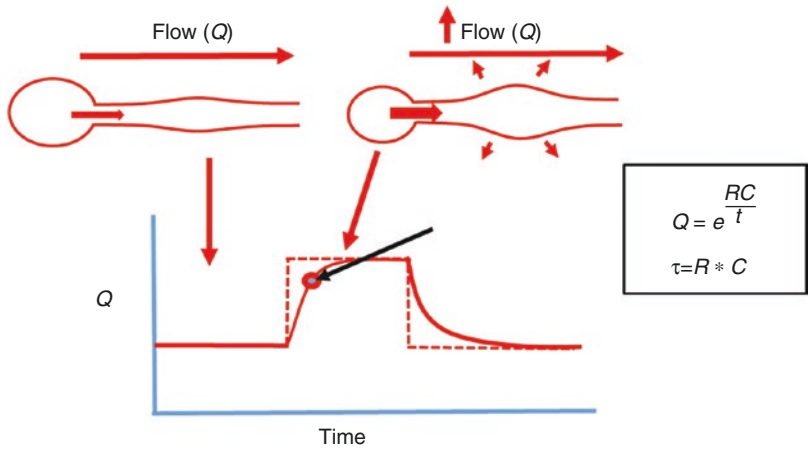

Fig. 7.1 Concept of a time constant (τ). When a step (square) change is made in a tube with a compliance, initially some of the added volume is taken up by stretching the walls and flow does not immediately reach the steady state. The small circle indicates the time taken to reach 63% of the new steady state (= τ the time constant) as indicated by the equation in the figure. Q refers to flow, R resistance, C compliance of the chamber, and t time

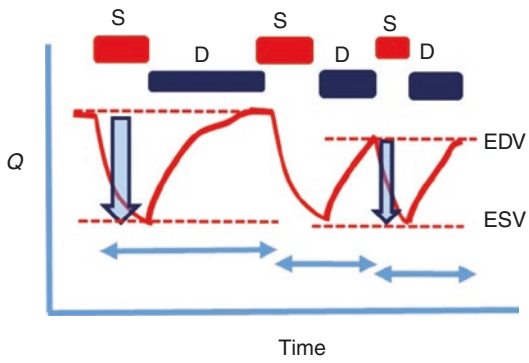

Fig. 7.2 Importance of time constant for RV filling and stroke volume. An increase in heart rate reduces the time for diastolic filling and if the rate of filling does not increase, stroke returns, and thus stroke volume must fall

vena cava. The SAN spontaneously generates action potentials (AP) in a rhythmic pattern, which propagate through the myocardium and the heart's specialised conduction system. This spontaneous, cyclic firing of the SAN (automaticity) is what determines heart rate (HR) and ultimately results in cardiac contraction, making the SAN fundamental to survival. Because of its critical importance, multiple overlapping mechanisms exist to ensure proper SAN function. These are highly regulated to allow for rapid adaptation of HR to large changes in physiological demand (Irisawa et al. 1993).

It is worth noting that there is no set point for HR (i.e. a 'targeted' value). Thus, function of the SAN is not *regulated*, but rather is *controlled* (Cabanac 1997) – engineering logic which has applications to physiology going back at least as far as Arthur Guyton's classic *Textbook of Medical Physiology* (Guyton 1956). For a system to maintain a variable within a narrow range around its set point, sensory feedback is needed for regulation. This occurs by changes in controlled variables that are allowed to vary widely (Modell et al. 2015). In the cardiovascular system, blood pressure is a critically *regulated* variable (with a clear set point). Changes in the set point are sensed by baroreceptors. Cardiac output and systemic vascular resistance are adjusted accordingly, but they also are determined by metabolic activity. HR and SAN activity, though, are affected by multiple factors. These are both external and intrinsic to the heart. Extrinsic control is primarily through the central nervous system but also by circulating factors in the blood. Intrinsic control is within the heart itself and acts primarily through intracardiac nerves but also through release of local paracrine factors and changes in mechanical load. Both processes ultimately control HR by affecting the mechanisms responsible for SAN automaticity (Quinn and Kohl 2012; MacDonald et al. 2017, 2020; Mangoni and Nargeot 2008).

Mechanisms of SAN Automaticity

Unlike cells of the working myocardium, which have a stable negative resting membrane potential (V_m) in diastole, SAN cells spontaneously depolarise in the diastolic phase of the cardiac cycle ('diastolic depolarisation'). This depolarisation drives V_m towards the threshold for excitation and is responsible for automaticity in the SAN. Two major systems regulate V_m. These are the 'membrane-clock', which is dependent upon ion channels in the cell membrane of SAN cells, and the 'calcium-clock', which is driven by intracellular calcium (Ca^{2+}) cycling (Fig. 7.3a).

Membrane Clock

One of the principal systems driving diastolic depolarization is a collection of membrane ion channels that are responsible for inward, depolarising currents, collectively known as the membrane clock (Maltsev et al. 2006). In the initial portion of diastole, depolarization is primarily driven by cations moving out of the cell. This creates a non-specific current called the 'funny' current, (I_f). These ions pass through channels that open as the cell membrane becomes more hyperpolarised (i.e. more negative) and begin to reverse the depolarized state. They are called hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels. There are four isoforms of HCN; HCN4 is the most prominent in humans (Chandler et al. 2009; DiFrancesco 2010). I_f decreases with depolarisation of V_m and at the next stage in diastole, Ca^{2+} begins to enter the cell and this current begins to contribute to diastolic

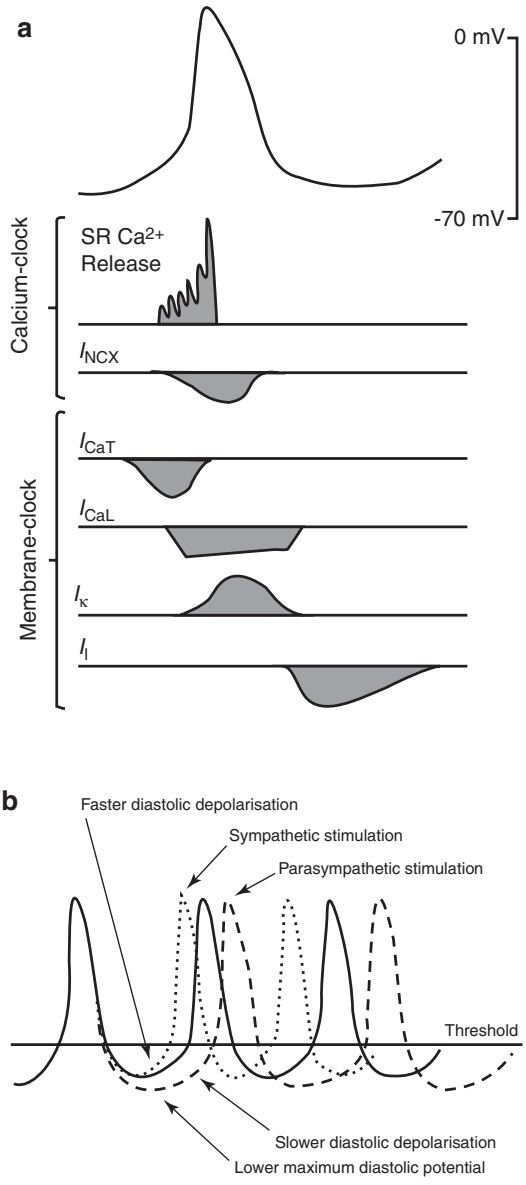

Fig. 7.3 (**a**) Sinoatrial node cell action potential and associated ionic fluxes. (**b**) Effect of sympathetic and parasympathetic stimulation on sinoatrial node cell action potential. Ca^{2+} calcium, I_{CaL} long-lasting L-type calcium current, I_{CaT} transient T-type calcium current; sodium-calcium exchanger current, I_f "funny" current, I_K repolarising potassium current, I_{NCX} sodium-calcium exchanger current, SR sarcoplasmic reticulum

depolarisation. The influx of Ca^{2+} first occurs through transient T-type current Ca^{2+} (I_{CaT}), which is created by $Ca_v3.1$ channels, and then by a long-lasting L-type current Ca^{2+} (I_{CaL}) created by $Ca_v1.3$ which takes over (Mangoni and Nargeot 2008; Bartos et al. 2015). Once the threshold for $Ca_v1.2$-mediated I_{CaL} is reached at ~−40 mV, $Ca_v1.2$ channels are activated, SAN cells are excited, and an AP occurs. This process differs from that of the working cardiac myocytes in which a fast sodium (Na^+) current (I_{Na}) passing through $Na_v1.5$ channels is responsible for excitation (Mesirca et al. 2015). SAN also express $Na_v1.5$ channels, but these have only a minor, indirect action on HR (Lei et al. 2007), as do a few other currents (Zhang et al. 2002; Ju et al. 2007).

Another important consideration for SAN and the determination of HR are the currents that are responsible for repolarisation of SAN cells. Unlike working cardiac myocytes, SAN have few Kir2.1 channels so they do not have the robust inward rectifier potassium (K^+) current (I_{K1}) to maintain the resting V_m (Chandler et al. 2009). However, similar to working cardiac myocytes, repolarisation occurs primarily through rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifier K^+ currents, along with minor contributions from currents activated late in the AP upstroke. These include the transient outward K^+ current (I_{to}), the ultra-rapid delayed rectifier K^+ current (I_{Kur}), and an inwardly rectifying chloride current (I_{Cl}). Ultimately, these currents determine the maximum diastolic V_m (MDP), which is the most negative membrane diastolic potential occurring during the cardiac cycle (Mangoni and Nargeot 2008; Bartos et al. 2015). Importantly, the magnitude of these repolarising currents continuously decays after maximal activation. This allows inward currents to drive diastolic depolarisation.

Calcium Clock

Intracellular Ca^{2+}-cycling contributes to diastolic depolarisation through a system known as the calcium clock (Maltsev et al. 2006). Late in diastole, a small amount of Ca^{2+} is released from the sarcoplasmic reticulum (SR) in SAN cells via ryanodine receptors (RyR). This can occur spontaneously or be triggered by $Ca_v1.3$-mediated I_{CaL} (Torrente et al. 2016). Some of the Ca^{2+} is removed from the cell by the Na^+-Ca^{2+} exchanger (NCX), which extrudes one Ca^{2+} ion while

bringing in three Na^+ ions, thus generating a net inward current (I_{NCX}) that causes SAN depolarisation. The remainder of the Ca^{2+} is returned to the SR by the sarco/endoplasmic reticulum Ca^{2+}-ATPase, SERCA, pump (Lakatta et al. 2008). Diastolic SR Ca^{2+} release also occurs in cells of the working myocardium but the release is enhanced in SAN cells due to a higher basal level of cyclic adenosine monophosphate (cAMP), which through a number of downstream processes, results in a higher uptake of Ca^{2+} by SERCA, and therefore, the potential for greater SR Ca^{2+} release (Vinogradova et al. 2006; Li et al. 2016).

It is still much debated whether diastolic depolarization of the SAN is driven primarily by the membrane or calcium clock (Rosen et al. 2012; DiFrancesco and Noble 2012; Maltsev and Lakatta 2012). However, because the sarcolemmal-bound NCX plays a critical role in the Ca^{2+}-clock by generating the required transmembrane depolarising current, these two 'clocks' are intricately linked. It is now generally accepted that overlapping and redundant mechanisms combine to cause SAN automaticity by forming a coupled system (Rosen et al. 2012; Lakatta et al. 2010) which is under tight extrinsic and intrinsic control.

Extrinsic SAN Control

Central Nervous System

The primary extrinsic mediator of SAN activity is the central nervous system, which acts through direct extracardiac sympathetic and parasympathetic innervation of intracardiac neural circuits and SAN cells (Gordan et al. 2015). Postganglionic sympathetic neurons that project from sympathetic ganglia directly to SAN cells release norepinephrine. This stimulates sarcolemmal $G\alpha_s$-coupled β-adrenergic receptors (β-AR) and increases intracellular cAMP levels. By binding to the C-terminals of HCN channels and increasing their phosphorylation by PKA, cAMP increases HCN channel open probability, increases I_f, and thereby increases the rate of diastolic depolarisation and HR (Larsson 2010). β-AR stimulation also has effects on other components important for SAN automaticity, all of which will increase the rate of diastolic depolarisation and thus HR (Fig. 7.3b).

In contrast to sympathetic neurons, preganglionic parasympathetic neurons project from brainstem vagal motor nuclei to postganglionic parasympathetic neurons within the heart. These release acetylcholine, which stimulate intracardiac neurons that project to SAN cells to also release acetylcholine, which activates sarcolemmal $G\alpha_{i/o}$-coupled cholinergic M_2 muscarinic receptors. Stimulation of these receptors results in reduced intracellular cAMP concentration, as well as rapid $G_{\beta\gamma}$ subunit activation of an acetylcholine-activated K^+ current (I_{KACh}) through G-protein-regulated K^+ (GIRK) channels, which negatively shift MDP, reduce the rate of diastolic depolarization, and decrease HR (Accili et al. 1998; Renaudon et al. 1997) (Fig. 7.3b).

Circulating Factors

SAN function also is affected by circulating biogenic amines such as norepinephrine, epinephrine, histamine, serotonin, thyroid hormone (Gordan et al. 2015). Circulating catecholamines released by the adrenal glands (epinephrine, norepinephrine, and dopamine, when converted to epinephrine or norepinephrine) bind to α- or β-ARs and cause an increase in HR through similar mechanisms to neurotransmitters released by sympathetic neurons. Histamines are released primarily from mast cells in the heart, but also from basophils, and cause an increase in HR by activating G protein-coupled receptors that increase intracellular cAMP and PKA levels. It also acts as a neuromodulator by stimulating the release of norepinephrine from sympathetic nerves (Kevelaitis et al. 1994). The response to serotonin (5-HT) is complex. It binds to many different receptor types (Saxena and Villalon 1990), both directly on cardiac tissue and also on autonomic nerve terminals. Thus, it can cause both an increase or a decrease in HR (Linden et al. 1999; Villalon

and Centurion 2007; James 1964; Centurion et al. 2002; Gothert et al. 1986). Thyroid hormones act on nuclear hormone receptors and alter expression of cardiac ion channels. They influence HR over a longer timescale. High thyroid hormone levels cause an increase in HR by increasing I_f by increasing HCN channel expression (Renaudon et al. 2000; Pachucki et al. 1999; Gloss et al. 2001). Similarly, parathyroid hormone, synthesized by the parathyroid gland, acts on parathyroid receptors to increase intracellular cAMP and PKA (Potthoff et al. 2011; Chorev 2002), which increases the amplitude of I_f (Critchley et al. 2010), and thus the rate of diastolic depolarization and HR (Shimoni 1999).

In summary, HR is influenced by multiple extrinsic factors, some of which increase HR, primarily by increasing I_f and diastolic depolarisation through enhanced cAMP and PKA production, and some which decrease HR, primarily by lowering MDP and inhibiting diastolic depolarization. Together, these processes maintain HR at closely controlled levels.

Intrinsic SAN Control

Intracardiac Nervous System

As is the case with extrinsic control of the SAN, intrinsic control occurs partly through neuronal mechanisms, mediated by the intracardiac nervous system (ICNS). The ICNS comprises a collection of efferent, interconnecting, and afferent neurons within the heart (Ardell and Armour 2016). Functional and anatomical data have shown that the ICNS not only receives input from extrinsic efferent neurons, but also from local interneurons and afferent neurons from other locations within the heart. It thus forms intracardiac circuits, which are important for the internal processing and reflex control of cardiac function (Beadling et al. 1999; Gagliardi et al. 1988). As a result, even after acute (Gagliardi et al. 1988) or chronic (Hodgin et al. 2001) isolation of the heart from the central nervous system (decentralization), the ICNS remains responsive to changes in the cardiac environment. It has been estimated that less than 20% of intracardiac neurons receive direct inputs from extrinsic nerves, and instead act as interconnecting neurons (Armour 2008).

Myogenic Peptides

Locally released peptides from cardiac myocytes, fibroblasts, and endothelial cells within or in close proximity to the SAN can modulate HR by paracrine or autocrine actions. They often are released as neurotransmitters and act in conjunction with the autonomic nervous system as neuropeptides, neuromodulators, or neurohormones (Beaulieu and Lambert 1998). For instance, vasoactive intestinal polypeptide (VIP) is a neuropeptide co-released with acetylcholine from parasympathetic neurons. It has the opposite effect of acetylcholine and thus moderates its effect. VIP binds to GPCRs that activate G_s-protein cascades that increase cAMP and PKA and which shifts the activation curve of I_f. The result is increase in the rate of diastolic depolarisation and HR (Hoover 1989; Chang et al. 1994; Accili et al. 1996). Release of VIP potentially could be a factor in the persistent tachycardia often seen in patients with pancreatitis without being related to volume status. Another example is the calcitonin gene-related peptide (CGRP), a neuromodulator that increases HR by blocking vagal stimulation (Bell and McDermott 1996), but in the presence of autonomic antagonists, also acts directly on SAN cells (Beaulieu and Lambert 1998). Another example of a locally synthesized peptide with both neuromodulatory and direct SAN cell effects is angiotensin II, which is highly concentrated at the level of the SAN artery (Saito et al. 1987). Angiotensin II can stimulate the release of catecholamines from sympathetic neurons (Torrente et al. 2016), but also stimulates type 1 angiotensin II receptors to decrease I_{CaL} and HR (Lambert 1995; Habuchi et al. 1995; Sheng et al. 2011; Kobayashi et al. 1978; Lambert et al. 1991; Sechi et al. 1992). Similarly, endothelin-1 and -3, produced and secreted by endothelial cells and acting through endothelin

receptors A and B, can cause an increase or decrease in HR (Saito et al. 1987; Ono et al. 2001; Tanaka et al. 1997; Ishikawa et al. 1988; Ju et al. 2011; Minkes et al. 1990).

Perhaps the most important myogenic peptides in terms of their HR effects are natriuretic peptides (NP), one of the primary factors released by atrial cells (Potter and Magder 2006; Reinhart et al. 2004). Three principal NPs are present in cardiac myocytes and fibroblasts, atrial NP (ANP), B-type NP (BNP), and C-type NP (CNP), which act on three NP receptors (NPR), NPR-A, NPR-B, and NPR-C (Moghtadaei et al. 2016). NPR-A, which binds ANP and BNP, and NPR-B, which is selectively activated by CNP, are guanylyl cyclase-linked receptors and enhance cGMP signalling (Lucas et al. 2000). NPR-C, which binds all NPs with similar affinity, is coupled to inhibitory G-proteins which inhibit adenylyl cyclase and thus cAMP signalling (Rose and Giles 2008; Anand-Srivastava 2005). Among their other functions, NPs affect HR through direct effects on SAN cells (Rose and Giles 2008; Springer et al. 2012; Azer et al. 2012). By acting on NPR-A, BNP and CNP, they increase I_f and total $I_{Ca,L}$ and thus the rate of diastolic depolarisation and HR (Springer et al. 2012; Lonardo et al. 2004). In contrast, activation of NPR-C does not affect SAN activity in basal conditions, but in the presence of β-AR activation it decreases $I_{Ca,L}$ (but interestingly not I_f), the rate of diastolic depolarisation, and HR (Springer et al. 2012; Azer et al. 2012; Rose et al. 2004). Thus, NPs can modulate the SAN via activation through both stimulatory NPR-A/B and inhibitory NPR-C, which elicit opposing effects that increase HR in some conditions but decrease it in others. The net results depend on the extent of β-AR activation and the relative contribution of each NPR under varying physiological conditions (Moghtadaei et al. 2016; Azer et al. 2012, 2014).

Tissue Stretch

Cardiac function is affected by feedback from the myocardium's mechanical state to its electrical activity. This phenomenon known as mechano-electric feedback or coupling (Quinn et al. 2014; Quinn and Kohl 2016). The SAN specifically responds on a beat-by-beat basis to changes in hemodynamic load (Quinn and Kohl 2012; Quinn et al. 2011). This was first recognized as an increase in HR with atrial distension by intravenous fluid injection (Crystal and Salem 2012). Similar effects have since been observed in a wide variety of vertebrates (Pathak 1973), including human (Donald and Shepherd 1978). Stretch-induced increases in HR occur also in the isolated heart (Blinks 1956), SAN tissue (Blinks 1956; Deck 1964), and SAN cells (Cooper and Kohl 2005), indicating that the response is intrinsic to the heart. Furthermore, the response is insensitive to ablation of intracardiac neurons (Wilson and Bolter 2002), blockage of neuronal sodium channels (Wilson and Bolter 2002; Chiba 1977), as well as adrenergic and cholinergic blockade (Blinks 1956; Wilson and Bolter 2002; Chiba 1977; Brooks et al. 1966). This implies that non-neuronal mechanisms are involved. The increase in HR with stretch is associated with both an increase in MDP and the rate of diastolic depolarisation allowing for shorter time to an AP (Deck 1964). This can be explained by a mechano-sensitive whole-cell current presumably carried by cation non-selective stretch-activated channels (Cooper and Kohl 2005; Cooper et al. 2000; Peyronnet et al. 2016), although a stretch-induced increase in the current and activation and deactivation rate of HCN channels also has been observed (Lin et al. 2007; Calloe et al. 2005).

There appears to be an interaction between mechanical and autonomic HR modulation. In intact animals (Bolter and Wilson 1999; Bolter 1994) and isolated atria (Bolter 1996; Wilson and Bolter 2001; Barrett et al. 1998), an increase in atrial pressure induces both HR acceleration and a significant reduction in the percentage response to vagal stimulation. Vice versa, when HR is first reduced by vagal stimulation, the HR response with stretch is augmented which could have value for a more rapid increase in heart rate with the onset of exercise in well-conditioned persons who usually have high basal cholinergic tone.

Determinants of the Heart Rate Dependence of the Length of the Action Potential

As already discussed, if the duration of systole does not shorten at fast heart rates, diastolic filling is compromised. For systole to shorten, AP duration (APD) must shorten (Fig. 7.4). After an increase in HR, or an early excitation, there first is an immediate change in APD, followed by a slower transient change if the new faster HR is maintained, after which APD eventually reaches a new steady state. Different mechanisms account for each.

Immediate Change in APD After a Sudden Decrease in HR or a Premature Excitation

In general, the first APD after a sudden increase in HR, or a premature excitation, is shortened, an effect known as restitution. The degree of the initial change in APD depends on how soon after repolarisation of the previous AP the early excitation occurred ('coupling interval'). This is explained by considering the dynamics (activation/inactivation and deactivation/re-priming) of ion currents in cardiac cells. When there is an early excitation, ion currents that inactivate during an AP have a decreased amplitude during the early excitation. The effect on the amplitude progressively increases with an increase in coupling interval. In working myocytes, this impacts the inward I_{Na} and I_{CaL} currents, and results in faster repolarisation and thus APD shortening. In contrast, reduced amplitude of outward currents that undergo inactivation (i.e. I_{to} and I_{Kur}) prolongs APD. However, during most of the AP, other key outward currents that do not inactivate (i.e. I_{Kr} and I_{Ks}) undergo mainly activation, and do not deactivate until the diastolic phase. As a result, when a premature excitation occurs, these currents remain partly active and accumulate with the additional AP and contribute to faster repolarisation and APD shortening (Carmeliet 2004; Carmeliet 2006).

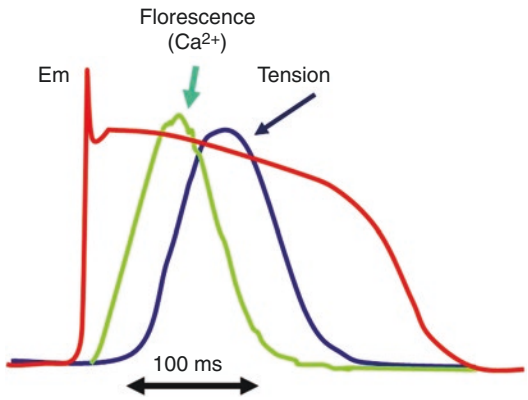

Fig. 7.4 Significance of the plateau of the myocardial action potential for cardiac contractions. Ca2+ enters myofibres, and is released from the sarcoplasmic reticulum during the plateau of the action potential and results in contraction. Ca2+ entry can be visualized by fluorescent probes, and this is seen to follow by contraction (tension) of the myofibre. The process ends when the myofiber repolarized which means that the plateau of the AP sets the limit of time for contraction and the peak force obtained during the cycle

While these are the dominant ion current changes for the immediately shortening of APD with early excitation, there also is a contribution of rapid changes in ion fluxes carried by transporters. During premature excitation, the amplitude of the inward I_{NCX} is markedly decreased because it depends primarily on the amount of Ca^{2+} released from the SR, which is reduced during early excitation because of incomplete SR refilling (Janvier et al. 1997). Similar to the decrease in other inward currents, this reduction in I_{NCX} results in a shorter AP.

In summary, with a sudden increase in HR or a premature excitation, the combined action of I_{Na} and I_{CaL} inactivation and I_{Kr} and I_{Ks} accumulation accelerate repolarisation, leading to an immediate shortening of APD (Carmeliet 2004, 2006). It should be noted, however, that the restitution process is highly species-dependent; this chapter deals with humans.

Along with the effects of increased HR or early excitation on APD being species-dependent, effects vary regionally across the heart (i.e. differences between the atria and ventricles and the sub-endocardium and -epicardium) due to differences in channels and transporters. For instance, in the ventricle, I_{to} is more highly expressed and

recovers from inactivation faster in sub-epicardial compared to sub-endocardial cells, resulting in a greater decrease in APD (Nabauer et al. 1996).

Transient Change in APD After a Decrease in HR

The initial shortening of APD when there is a sudden increase in HR generally followed by a slow, gradual decrease in APD that occurs over a few seconds to minutes although in the first few seconds oscillations in APD (alternans) can occur, due to the diastolic interval alternating in a short-long sequence before gradually reaching a steady state. The transient decrease in APD is principally driven by: (i) increased intracellular Na^+ concentration ($[Na^+]_i$, due to the increased influx of Na^+ at the increased HR; (ii) increased intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$, due to the decrease in the diastolic interval, which alters the equilibrium between Ca^{2+} influx via I_{CaL} during the AP and Ca^{2+} efflux via the NCX during diastole, as well as Ca^{2+} influx via reverse-mode NCX activity driven by the increase in $[Na^+]_i$ with the increased HR; and (iii) increased extracellular concentration of K^+ ($[K^+]_o$) (Carmeliet 2004, 2006). These changes in ion concentrations affect APD by altering the flux of ions through various channels and transporters (Carmeliet 2004, 2006).

In addition to changes in ion concentrations, transmembrane ion fluxes also are altered by the increased sympathetic nervous system activity that often drives the increase in HR. Activation of PKA by stimulation of β-ARs results in phosphorylation of RyR, and SERCA. This increases the load of Ca^{2+}in the SR which facilitates Ca^{2+} release (Carmeliet 2004, 2006). The increased SR Ca^{2+}-release causes Ca^{2+}-induced inactivation of I_{CaL} and activation of I_{Cl} and protein kinase C (PKC), which further increase I_{Kr} and I_{NaK} and inhibits the slowly inactivating (also known as the late, sustained, or persistent) Na^+ current whose magnitude is further reduced due to accumulation of intracellular Na^+ with an increase in HR (Tateyama et al. 2003). Combined, these β-AR-driven changes contribute further to more rapid repolarisation and a subsequent decrease in APD.

APD at a New Steady State

Once steady state is reached after an increase in HR, APD generally is decreased in a HR-dependent manner. This relationship, however, does not hold true at lower HRs (of around 60 beats per minute or less). In this range, little change in APD occurs with a change in HR.

Intrinsic Heart Rate

In a classic paper, Jose and Collison determined the spontaneous intrinsic beating frequency of hearts of healthy individuals without any autonomic activity (Jose and Taylor 1969; Jose and Collison 1970). To do so, they inhibited parasympathetic activity by blocking muscarinic receptors with atropine, and sympathetic activity by blocking beta-adrenergic receptors with propanol. The average heart rate in 25 year-old-subjects was 106/minute. Intrinsic heart rate declined with age at a rate of 0.057 beats/min per year. By the age of 60, intrinsic heart rate was 90 beats/min. They also found that subjects with myocardial dysfunction had an additional loss of the intrinsic rate not accounted for by age alone.

Normal resting heart rate in humans with resting autonomic activity is 70 beats/min and often lower in active individuals. This indicates that parasympathetic activity must dominate the resting state. However, there also must be resting sympathetic activity because beta-blockade lowers the resting heart rate (Jose and Taylor 1969). This is an example of nature driving with her foot on the gas and break at the same time (Magder 2012). The advantage of having opposite processes active at the same time is that it allows a more rapid change. For example, at the start of exercise, the parasympathetic output is quickly withdrawn and the sympathetic output increased so that there is a rapid acceleration of the heart rate which then can accommodate a rapid increase in venous return (Notarius and Magder 1996).

The ratio of heart mass to body weight of 0.6% is consistent throughout all mammals, including humans (Dobson 2003, Bettex 2014). Heart mass

ranges from around 0.5 kg in a normal male to 600 kg in a blue whale. Resting heart rate is inversely proportional to body size and ranges from 600 min^{-1} in a shrew (2–5 g) to 6–12 min^{-1} for blue whale (Levine 1997). Life expectancy is also related to heart rate (Levine 1997), which means that the total number of heart beats in a lifetime is relatively constant at 1.1 billion and the total body O2 consumed per body weight is also similar.

Normal Control of Heart Rate During Exercise

The importance of parasympathetic withdrawal at the onset of exercise was demonstrated by Fagraeus and Linnarsson (1976). They used combined parasympathetic and sympathetic blockade to determine the role of these systems in the change in heart rate from rest to light exercise. The increase in heart rate was primarily due to vagal withdrawal and occurred in approximately 10 s. Over the ensuing 20 s, vagal tone increased and produced some slowing of the heart rate, indicating an initial overshoot and a dynamic interaction between sympathetic and parasympathetic systems.

Maximal aerobic exercise is one of for the greatest challenges to the cardiovascular system, and the adaptations of cardiac output and heart rate provide important insights into how the system is regulated (Magder et al. 2019). Peak exercise is determined by the amount of oxygen that can be consumed by the working muscle (VO_2). VO_2 can increase 12-fold at peak performance in a healthy young males (Astrand 1976). The rise in VO_2 is associated with a linear increase in cardiac output, which can increase to 4–5 times the normal resting value (Åstrand et al. 1964) (Fig. 7.5). The relationship of cardiac output to VO_2 is so tight that if the oxygen consumption is known, and the haemoglobin is normal, the increase in cardiac output can be estimated with an accuracy of about ± 5%. This indicates that under normal physiological activity, cardiac output tightly follows the energy demands which is represented by VO_2.

The control of heart rate, though, is very different. Heart rate, too, increases relatively linearly with energy demands, but not as precisely as cardiac output. More importantly, heart rate

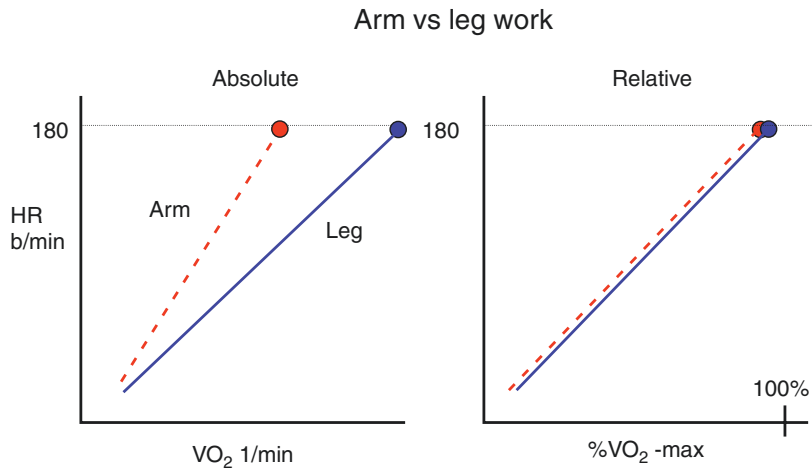

Fig. 7.5 Concept of relative work load and illustrated by arm versus leg exercise. Because legs are much larger than arms, they can generate a higher workload and thus a higher oxygen consumption (VO2). Heart rate increases linearly with VO2. However, maximum heart rate is the same with leg and arm exercise. Accordingly, the slope of the increase in heart rate with VO2 is flatter with leg exercise than arm exercise. However, if instead of the x-axis being VO2 in absolute numbers, it is instead plotted as a percent of maximal capacity of the muscle (i.e. relative capacity), the two curves overlap

increases in proportion to what is called the 'relative workload'. To understand these concepts, it first needs to be appreciated that maximum heart rate is related to age. Thus, at the same age, male and females, tall versus short, high aerobic capacity versus low aerobic capacity, and fit versus unfit persons, all have the same maximum heart rate, assuming that they are healthy. However, they obviously do not have the same aerobic capacity. Thus, at any given workload and VO_2 in L/min (not normalized to body size), the heart rate is lower in a person who has a higher maximum VO_2 than in a person who has a lower maximum VO_2 (Fig. 7.5) because the workload is a lower percent of the person's capacity. Based on this, most women have a higher heart rate at a given workload than men because they are on average smaller and have a lower maximum VO_2 max. However, if heart rate is normalized to the percent of the individual's capacity, that is, the person's work load as a percentage of their maximum VO_2, the lines of heart rate versus percent of capacity for all subjects are superimposable. The usefulness of this is that if you know your maximum heart rate, then the percent of your maximum heart rate at which you are exercising indicates what the percentage the workload is of your maximum capacity. A useful training rate is around 70% of peak aerobic capacity because that is a rate that can be sustained for more prolonged periods; above that rate, lactate increases and steady-state conditions usually cannot be sustained (Astrand and Rodahl 1977).

A likely explanation for the relationship of heart rate to the 'relative' workload is that output from the sympathetic nervous system increases in proportion to muscle effort through both central command and afferent signals from peripheral muscle (Mitchell and Shephard 1993). As discussed above, increased beta-adrenergic activity is a major factor in increasing the SAN depolarization.

There are important pathophysiological consequences of these basic concepts. Cardiac output is the product of heart rate and stroke volume. Heart rate is controlled by the relative workload and cardiac output by the VO_2. Since heart rate and cardiac output are controlled variables, it follows that stroke volume must be a dependent variable. There is no central sensor for stroke volume; changes in stroke volume occur through the Frank-Starling length–tension relationship.

The increase in heart rate is a predominant factor for the increase in cardiac output during exercise. In a young male, heart rate can increase almost threefold, whereas the stroke volume in the upright posture increases by 60–90% (Åstrand et al. 1964; Cassidy and Mitchell 1981) and only about 10% when supine (Magder et al. 1987). The increase in heart rate creates a steep rise to the cardiac function curve. As a consequence, the heart becomes much more preload responsive because every stroke volume is affected and there are more stroke volumes per minute (Fig. 7.6). The effect of heart rate on the preload responsiveness is likely a variable that should be accounted for when examining the sensitivity of predictors of fluid responsiveness. The percent change in cardiac output for the same change in preload likely is higher at higher heart rates because of the steeper slope to the cardiac function curve, although this has not been tested.

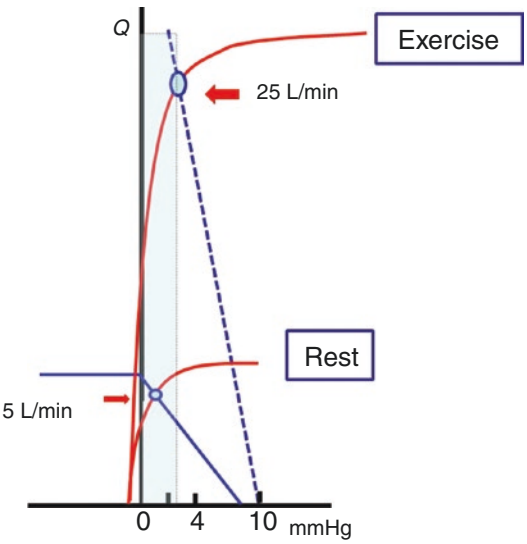

Fig. 7.6 Illustration of the dependence of the change in cardiac output for a change in preload to an increase in heart rate. An increase in heart rate makes the upslope of the cardiac function curve steeper and the plateau higher. Thus, the change in cardiac output is much large for a change in preload

Heart rate during exercise is driven by three mechanisms: central drive, baroreceptor feedback, and afferent signals from working muscle (Mitchell and Shephard 1993; McCloskey and Mitchell 1972). In addition, other central nervous system outputs (i.e. conscious thoughts), hormones, and generalized metabolic signals can change heart rate through the many currents discussed in the section on regulation of the SAN. As a consequence, based on the discussion above, changes in stroke volume are much less predictable than changes in cardiac output. Central drive describes the process by which motor signals descending to muscles from the parietal cortex and spillover into hypothalamic and medullary centres that regulate autonomic activity. This increases sympathetic output and inhibits vagal output. The initial vasodilation in the working skeletal muscle produces a large decrease in systemic vascular resistance which would markedly decrease arterial pressure except for the rapid response by the carotid baroreceptors, which decreases output from the cardio-inhibitory parasympathetic pathway and decreases the inhibition of the cardio-stimulatory centre (Raven et al. 2019). The net effect is increased sympathetic output, including direct stimulation of the sinus node. The third factor is relevant to the critically ill patient. Type III and IV thin unmyelinated afferent nerve fibres are activated by metabolic signals in working muscles (McCloskey and Mitchell 1972; Kaufman et al. 1982; Kaufman et al. 1985; Magder 2001). These signals include mechanical stretch, increased concentration of K^+ and arachidonic acid metabolites, osmolality, hypoxia, and hydrogen ions (Kaufman et al. 1982). The diaphragm and other respiratory muscles also have these afferents. When the work of breathing is increased, afferents signals from these tissues increase central sympathetic output and contribute to an increased heart rate. These afferent signals also increase the drive to breathe which produces the rapid shallow breathing associated with fatigued respiratory muscles (Magder 2001; Teitelbaum et al. 1993; Hussain et al. 1991). Adding to this the patient's mental distress and a tachycardia is inevitable. Small unmyelinated afferents in other organs, too. They are particularly dense in the region of the celiac axis. These can be activated by inflammation in this region, and also can drive an increase in heart rate. Likely, for this reason, patients with pancreatitis often have sustained high sinus rates. As discussed above, release of vasoactive peptide by the pancreas and its surrounding sympathetic fibres may also contribute (Said 1986). Their heart rates often can be in the 120–130 beats/min range, and it is important to appreciate that this does not indicate hypovolemia even though these patients often are intravascular volume-depleted.

Heart Rate, Beta Blockers, and Ejection Fraction

As already noted, cardiac output is tightly related to metabolic demand. This means that venous return, too, is regulated by metabolic demand, and the heart handles this return through its heart rate and stroke volume. This has an important consequence when pharmacologically manipulating heart rate with, for example, a beta blocker. Except for perhaps some adjustments when a beta blocker is first started, cardiac output usually does not change with chronic beta blocker therapy. Thus, venous return also must be the same. If venous return is the same and heart rate is slowed, the end-diastolic volume must be increased and the stroke volume then is increased through the Frank-Starling mechanism. This normal response can happen as long as right ventricular end-diastolic volume is not limited and the heart is functioning on the flat part of the cardiac function curve. Because both stroke volume and end-diastolic volume increase, the calculated ejection fraction increases, but this does not mean that there actually was any change in cardiac function as often is argued. The increase in ejection fraction is simply a mathematical result of the changing ratio of stroke volume to end-diastolic pressure. On the other side, in distributive shock, venous return is increased but there are no central command signals to produce the usual increase in heart rate (except perhaps form the hypotension and baroreceptor activation as well as through direct cytokine activation); the myocardium often

also is depressed in sepsis. Consequently, right-sided filling pressures usually are increased and the right ventricle becomes limited at an end-diastolic volume that is not sufficient to provide the necessary higher blood pressure to match the decrease in peripheral resistance. Blood pressure then decreases.

Another important consequence of the interaction of heart rate, stroke volume, and cardiac output is the addition of the cyclic heart–lung interactions from ventilation. As discussed in the chapters on right ventricular function and heart–lung interactions, the independent respiratory effects on filling and loading of the right and left ventricles, and time delay for changes in the right ventricle to reach the left ventricle, are modified by the phasic interactions of the cardiac cycle. In the background is the return of blood, which is relatively constant over time since it is based on the metabolic activity of the body, that is, flow follows metabolic need. A modification of this is needed when there is active recruitment of abdominal muscles because the changing peritoneal pressure can alter emptying of the splanchnic venous reservoir, as well as the return of blood from the legs. The implication is that the final magnitude of the impact of ventricular and ventilator interactions cannot be studied in isolation. The dominant variable is the steady-state flow need, and moment-to-moment changes in ventricular size may be measureable but likely have only modest effects on overall oxygen delivery.

Tachycardia and Hypovolemia

Medical personnel often react to tachycardia as a sign of hypovolemia, but heart rate bears a poor relationship to hypovolemia because there are no 'volume' receptors in the system except for some mild afferent fibers in the atria and ventricles (Coleridge and Coleridge 1980). More than likely the increase in heart rate with hypovolemia is due to local receptors that are activated by the ischemia from inadequate tissue perfusion, or by direct action of the cytokines involved in inflammation acting on the cardiac excitatory centres in the brain and directly on the SAN. A number of studies have examined the sensitivity of heart rate and the blood pressure response to hypovolemia. One study compared the detection of hypovolemia by measurement of the pH in the stomach wall by gastric tonometry (pHi) to changes in heart rate and blood pressure. To do so, they removed 20% of predicted blood volume in normal subjects (Hamilton-Davies et al. 1997). In 5 of the 6 subjects, heart rate and blood pressure did not change, and in the sixth heart rate slowed because he became vasovagal. The gastric tonometer, however, detected a decrease pH in the gastric mucosa in all subjects indicating that splanchnic perfusion was impaired despite the lack of change in heart rate and blood pressure. If the subjects had stood up, though, they likely would have been tachycardic because the gravitational stress would have increased the effect of the hypovolemia and induced a baroreceptor response. These observations indicate that loss of volume has to be severe to activate an increase in heart rate in a supine patient. In trauma, pain and anxiety are more likely to be the cause of the tachycardia than hypovolemia.

An accelerated heart rate allows a more rapid increase in cardiac output. This is seen especially in racing animals, but also can be seen in humans as an 'anticipatory' response. The faster heart rate means that the diastolic volume is lower than normal and can immediately handle an increase in venous return per beat.

Bainbridge Reflex

Another factor that can increase heart rate is called the Bainbridge reflex (Crystal and Salem 2012; Bainbridge 1915; Hakumaki 1987). As discussed in the section on regulation of the SAN, stretch of atrial tissue can directly alter the rate of SAN depolarization, even in isolated SAN cells without innervation (Blinks 1956; Cooper and Kohl 2005). This unusual reflex is a feed-forward mechanism. A sudden increase in right atrial distension triggers an increase in heart rate. It also blocks normal baroreceptor activity that would have suppressed the heart rate increase. This was

made evident by showing that inactivation of the baroreceptors dos not alter the heart rate response (Vatner et al. 1975). In the intact person, a reflex pathway also is active. The mechanism for the reflex is thought to be activation of atrial type B receptors by atrial stretch (Crystal and Salem 2012; Hakumaki 1987). Afferent signals from these cells increase sympathetic discharge to the heart and decrease vagal activity. Sympathetic activity to peripheral resistance vessels also increases and maintains the increased arterial pressure. As originally proposed by Bainbridge, the reflex allows the heart rate to respond faster to a sudden increase in venous return as occurs at the onset of exercise as discussed under the rapid vagal withdrawal at the onset of exercise (Notarius and Magder 1996; Fagraeus and Linnarsson 1976; Linnarsson 1974). As will be seen later, the consequent shortened diastolic time also limits the distension of the right heart. Finally, the suppression of baroreceptor reflex prevents it from countering the increase in heart rate. The activity of this reflex likely is minor in critically ill patients receiving volume boluses. In one study, there was only an average decrease of 1 mmHg whether a colloid or crystalloid was given (Magder and Bafaqeeh 2007).

Heart Rate and the Interaction of Venous Return and Cardiac Function in the Guyton Analysis

The impact of a change in heart rate on cardiac output can be analysed with Guyton's venous return cardiac function diagram, which was discussed in Chap. 2. An increase heart rate shifts the cardiac function upward and to the left. As a consequence, the cardiac function curve intersects the venous return curve at a lower right atrial pressure and higher cardiac output. This effectively makes the heart more 'permissive', in that it allows more blood to come back. The cardiac function curve shifts because at the same right atrial pressure, that is, same preload, there are more stroke volumes per minute. An increase in heart rate also means that there are more plateaus of the action potential which results in greater intracellular calcium influx, a major determinant of cardiac contractility. This increases the peak slope of the end-systolic pressure–volume relationship (end-systolic elastance).

However, there are limits to these processes, and these have clinical implications. When right atrial pressure is below atmospheric pressure, and the pressure inside a floppy vein is less than the pressure outside, the vessel collapses. This creates a plateau on the venous return curve and flow does not increase when right atrial pressure is lowered further. This means that in the steady state an increase in cardiac function may lower right atrial pressure but does not increase cardiac output. Furthermore, if cardiac output does not change, and heart rate increases, stroke volume has to decrease. This is the normal state when sitting or standing, but not when moving (Notarius et al. 1998). The cardiac function curve also frequently intersects the plateau of the venous return curve in patients who are on positive pressure ventilation because the limitation to venous return occurs at pressures above atmospheric pressure. A clinical consequence of this physiological point is that when cardiac output is measured with a device that is based on a stroke volume measurement, a fall in stroke volume does not mean that there necessarily has been a fall in cardiac output; the product of heart rate and stroke volume must be examined.

At the other end of the spectrum, that is, when the venous return curve intersects the plateau of the cardiac function, giving volume cannot increase stroke volume and an increase in heart rate, an increase in contractility, or a decrease in afterload are required to increase cardiac output by shifting the cardiac function upwards. However, what is not evident with the Guyton venous return curve is that the heart rate effect can be limited if the inevitably shortened diastolic time limits venous return per beat. In this case, cardiac output falls. This would 'appear' as an increase in venous resistance.

Heart Rate and Diastolic Limitation

Heart rate is especially important when there is left ventricular diastolic dysfunction and end-diastolic pressure needs to be higher for a given end-diastolic volume. As discussed above, slowing the heart rate by beta blocker requires an increase in stroke volume to maintain cardiac output. In a heart with decreased diastolic capacity, this can significantly increase end-diastolic pressure. This is especially a problem during exercise because the stroke volume needs to increase even more. It is important to determine if a patient's dyspnea on exertion is due to myocardial ischemia, in which case limiting the heart rate is a good therapeutic option, or whether is it due to a stiff left ventricle, in which case a beta blocker will can make congestive symptoms worse.

The limit of diastolic filling in the right heart and the decline in peak heart with aging is a major factor for the decline in VO_2 with age. An estimate of the age-related peak heart rate is: Max heart = 220 − age in beats per minute. Based on this, the peak heart rate of a 20-year old is close to 200 and in a 60-year old, it only is 160 beats per minute. Normally, exercise that is prolonged for more than 5–10 minutes only can be sustained at approximately 70–80% of the person's maximum aerobic capacity; in a 60-year old male, 80% of peak heart rate is 128 b/min compared to 160 in the 20-year old.

The significance of heart rate limitation can be seen in a quantitative analysis. If the aerobic demand requires a cardiac output of 20 L/min, and the peak heart rate is only 120 b/min, the stroke volume would have to be 168 ml. However, in an average-sized person, the limit of diastolic filling is less than 140 ml so that this is not possible.

A low heart rate has different effects on the right and left ventricles. On the right side, diastolic filling pressures generally are low until the limit of right-sided filling is reached. Assuming a right ventricular end-diastolic volume of 130 ml, and a cardiac output of 5 L/min to meet metabolic needs, the lowest tolerable heart rate would be 38 b/min; a heart beat lower than this will lower the cardiac output because the stroke volume would be limited. On the left side, because of the steeper diastolic filling curve, and especially in subjects with diastolic dysfunction, a low heart rate can markedly increase end-diastolic pressure and the likelihood of pulmonary congestion.

Supply Demand of the Heart

The risk of myocardial ischemia is analysed by considering the factors determining myocardial oxygen demand and the factors affecting the supply of oxygen. Myocardial oxygen consumption (MVO_2) is determined by a baseline need to maintain cell function and the need for the work done by the heart. The three determinants of oxygen for cardiac work are heart rate, contractility, and wall tension, the latter of which is determined by the peak systolic pressure and the radius of curvature of the ventricular walls (Katz 1992). Heart rate and systolic pressure are easy to obtain, and contractility usually rises with a rise in heart rate. Thus, the product of heart rate and systolic pressure gives a good indication of MVO_2. This is the rationale behind standard exercise testing. Most of the information is given by just the heart rate but adding the systolic pressure gives what is called the rate-pressure product, which gives a pretty good indication of myocardial oxygen demand.

O_2 is supplied to the heart by coronary flow. Just as occurs in the whole body, coronary blood flow is tightly related to MVO_2. 'Rest state', means a heart rate of approximately 70 b/min, where the heart extracts about 70% of the oxygen content in the coronary blood. In comparison, only about 25% is extracted from the blood for the whole body. Because of this, the heart is especially dependent upon coronary flow. There is little reserve for more extraction and anaerobic metabolism provides too little energy to maintain the working heart. Besides coronary flow, the other factors affecting O_2 delivery to the heart are haemoglobin concentration and arterial oxygen saturation. Coronary flow is determined by the pressure difference between the aorta and a

downstream critical pressure of 25–30 mmHg (Bellamy 1978), which is dependent upon the diastolic pressure in the ventricle and activity of the heart.

The range of coronary flows in the heart is huge. Resting coronary blood flow is in the range of 80 ml/min/100 g of tissue. At peak exercise in a young male, this can increase to 500 ml/min/100 g, a greater than fivefold increase (Bellamy 1978, 1980). In comparison, flow in resting skeletal muscle is 5–7 ml/min/100 g, and at peak exercise blood flow in aerobically active muscles reaches around 200 ml/min/100 g. The implication of this is that coronary reserves are very large and as long as there is no proximal coronary artery stenosis, the myocardium can handle a large increase in heart rate. Furthermore, most of the resistance in the coronary vasculature is at the level of arterioles. Only about 5% of the pressure drop occurs in the large epicardial coronary vessels seen on an angiogram. It can be shown that it requires more than a 70% proximal stenosis of a coronary vessel to impact significantly on maximum coronary flow.

Conclusion

Control of heart rate is a complex process that is affected by the autonomic activity of the sympathetic and parasympathetic systems as well as the impact of many endogenous and other circulatory factors directly on the SAN. Under normal conditions, the heart rate increases according to the relative external workload, whereas the cardiac output increases according to the absolute workload. This means that stroke volume becomes a dependent variable based on the cardiac output venous return and the heart rate. The heart rate sets the time available for filling and ejection by the heart, which ultimately determines what the heart can pump out. When the heart rate is increased by factors not related to aerobic workload, adaptations in the return of blood to heart, and in the ratio of diastolic to systolic time, may not be adequate for optimal cardiac filling and emptying. Both ends of the spectrum of heart rates are important for cardiac output. If the heart rate is too fast for the rate of venous return, stroke volume is decreased. If the heart rate is too slow for the rate of returning blood, stroke volume becomes limited. Heart rate is the major factor for large normal increases in cardiac output but it also is a major factor in the energy needs of the heart. With normal coronary circulation, this is not a problem because of the large coronary reserves but it can be a problem when coronary oxygen delivery is limited.

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