Heart Rate, Synchrony and Arterial Hemodynamics

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Abstract

Heart rate is a conventional index quantifying the pulsatile action of the heart and is a basic parameter used throughout medical history and practice. However, modern science often places relatively little emphasis on heart rate in relation to the oscillatory nature of blood flow in the circulatory system, and the unyielding cyclic stress on the heart and blood vessels. Heart rate is relevant not only as an elemental measure, but also as a statistical entity and a possible confounding factor when considering its interaction with vascular hemodynamics. Pulse pressure amplification from the central aorta to peripheral arteries increases with heart rate. This has significant implications when assessing vascular function based on peripheral (brachial) pressure measurements, as the pressure changes at the central aorta with changes in arterial stiffness (as occurs with age) can be markedly different from changes at the peripheral site at different heart rates. Similarly, heart rate is a significant parameter when assessing cardiac and vascular implications of anti-hypertensive drug treatments. Heart rate, itself an independent parameter of cardiovascular risk, should also be considered in the statistical treatment of cardiovascular risk factors in large epidemiological studies. Disturbance in the regular pulsatile action of the heart due to altered synchrony of the cardiac chambers leads to heart failure, which can be treated with resychronization therapy. Cardiovascular models show that arterial stiffness can significantly affect the modification of parameters associated with cardiac resynchronization therapy. Thus, pulsatile hemodynamic parameters play a significant role when associated with both regular heart rate and with disturbed synchrony of the contracting heart chambers affecting the pump function of the heart.

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Introduction

Rhythmic contraction of the heart is the most basic evidence of life. Heart rate is an elementary clinical sign for physicians, having heralded the sphygmomanometer, the sphygmograph, and the stethoscope. Heart rate is a parameter often ignored in modern science, but is a basic parameter in the history of medicine and in medical practice.

This chapter addresses the relevance of heart rate in relation to the pulsatile aspects of hemodynamics in the context of the overall theme of blood pressure and arterial stiffness in cardiovascular prevention. Factors that determine arterial blood pressure and arterial stiffness, as well as their epidemiological relevance to hypertension and cardiovascular risk, are treated in other sections of this volume. Specifically, this chapter examines the association of heart rate with arterial stiffness and its impact on pulse pressure and parameters derived from pulse wave analysis. The importance of pulse pressure amplification between central and peripheral locations related to heart rate is highlighted with respect to proper assessment of arterial hemodynamics by peripheral pressure measurement. In addition, by use of cardiovascular models, the relationship of arterial stiffness and synchrony between the heart chambers is examined in relation to optimizing cardiac output; aspects that have particular relevance to biventricular pacing and cardiac resynchronization therapy.

In general, this chapter highlights the importance of heart rate as a significant parameter that needs to be taken into account when treating physiological, experimental and epidemiological data with regards to quantifying cardiovascular risk, both as a statistical entity and also in terms of measurement of blood pressure when using pulse waveform analysis.

Allometric Nature of Heart Rate

In physiological systems, there are parameters that are related to body weight, for example, heart rate, metabolic rate, heart size, and cardiac output. Other haemodynamic parameters are not related to body weight, for example blood pressure and arterial stiffness. The dependency of a parameter on body weight can be described by an allometric relation as described in Eq. 22.1, where x is the parameter of interest, W is body weight, and A and k are constants.

$$x = A \cdot W^k \tag{22.1}$$

The heart rate in mammals is approximately proportional to the cubic root of weight, with small mammals having a high resting rate (e.g. 600 beats/s for mice), and large animals a low resting rate (e.g. 15 beats/min for whales). The reverse relationship of heart rate to length of mammals probably denotes optimization of ventricular-vascular interactions with respect to cardiac diastolic duration and return of wave reflection in the arterial system, as well as to physiological fundamentals of muscular relaxation and contraction.

In an elegant study relating vascular parameters to functional correlates across animal size spanning a range of body weights from the rat (0.2 kg) to the elephant (3,500 kg), Westerhof and Elzinga [1, 2] illustrate the possible mechanism as to why pulse pressure is essentially similar over the whole range of animal body size and weight. Heart period (T) is taken as the characteristic cardiac time and the time constant of the exponential diastolic decay (τ) of the arterial pressure pulse as the characteristic arterial time. It was found that both T and τ increase with body weight with a similar exponent of approximately 0.25 [1]. Hence, the ratio τ/T is essentially independent of animal size.

The arterial system can be modeled in terms of a Windkessel [3, 4], where the exponential diastolic decay of pressure can be expressed in terms of the peripheral resistance (R) and the central aortic compliance (C, Eq. 22.2). For low values of late systolic augmentation due to wave reflection, compliance is largely related to the ratio of stroke volume (SV) and pulse pressure (PP, Eq. 22.3) [5]. Since mean arterial pressure (MAP) can be expressed as the ratio of stroke volume and resistance to heart period (Eq. 22.4), it follows that the ratio PP/MAP is inversely proportional to the ratio τ /T, and is therefore independent of body size. In fact, the ratio τ /T could be considered as a basic coupling parameter between the heart and the arterial system and forms the basis of the interaction between heart rate ($1/T$), pulse pressure and arterial stiffness [1, 2, 5]. Similar matching phenomena across a range of species have been described in terms of impedance spectra normalized for resting heart rate [6, 7]. Milnor's concepts of relating physical body dimensions to wave transmission phenomena in terms of aortic wavelength were further expanded by Iberal [8] and O'Rourke [9] to encompass the earlier work on optimal design proposed by Taylor [10] and McDonald [4].

$$\tau = R \cdot C \tag{22.2}$$

$$C = \frac{SV}{PP} \tag{22.3}$$

$$MAP = \frac{SV \cdot R}{T} \tag{22.4}$$

Heart Rate, Cardiac Function, and Arterial Hemodynamics

The interaction between the ejecting ventricle and the systemic load is described as the coupling between cardiac parameters, such as source impedance [11, 12], myocardial contractility indices [13] and arterial elastance [14]. Since the heart is essentially a self-energizing pump, the output is necessarily intermittent. Power delivery occurs during only a fraction of the periodic cardiac oscillation in which the ventricles are almost emptied of their blood content during systole and are filled during diastole for ejection in the subsequent contraction.

The energy supply to the myocardium is delivered by coronary blood flow occurring predominantly during diastole. Changes in heart rate result in changes in cycle time, which are in turn affected largely by changes in diastolic time with relatively smaller changes in systolic ejection times [15]. The relatively greater effect on the duration of diastole has direct effects on the time available for ventricular filling, hence affecting stroke volume through the Frank-Starling mechanism [13], and also on the time available for diastolic run-off of arterial blood. The rate of run-off is determined by the value of peripheral resistance and the stiffness of the arterial wall. Hence, for a given stroke volume, this mechanism, in addition to the wave reflection phenomenon, will determine the pulse pressure.

The steady state operating point is determined by the properties of the heart in terms of stroke volume, the elastic properties of the large distributing arteries, and the level of peripheral resistance at the microcirculation. Although arterial pressure undergoes instantaneous variation with time, the interaction of the generally periodic nature of the beating heart and the arterial load can be considered to operate at an arterial pressure having a steady component (mean pressure during the cardiac cycle determined by the peripheral resistance) and a superimposed oscillatory component (pulse pressure, determined by the stiffness of the large conduit arteries) [3, 4, 16]. These concepts could explain some of the differences between acute and long-term effects of changes in heart rate on pulse pressure. Acute changes, as seen with pacing studies [17], are essentially passive effects due to changes in diastolic time and so affecting minimum (diastolic) pressure during the cardiac cycle. These short-term changes are different to the long-term changes seen in population studies that may involve sustained effects due to sympathetic or vagal activation. The interaction between heart

rate, pulse pressure and arterial stiffness is complex. It involves a closed-loop system with a combination of feedback and feed forward loops, where a change of a parameter in one direction can influence others in the same or opposite direction.

Heart Rate and Arterial Stiffness

Acute Effects

Arterial blood pressure is only a relative measure of arterial function as it is determined by the interaction of cardiac and arterial factors. However, arterial stiffness is entirely determined by vascular characteristics [4]. Of the many indices of arterial stiffness that can be measured non-invasively [18, 19], pulse wave velocity (PWV) has been accepted as an easily measurable parameter and used as a surrogate for arterial stiffness [19]. However, it is important to consider the underlying assumptions. For a uniform arterial segment of a given length, PWV is related to the stiffness of the wall material (Young's Modulus, E), vascular dimensions (radius R, wall thickness, h), and blood density (ρ) by the Moens-Korteweg relation (Eq. 22.5) [3, 4].

$$PWV = \sqrt{\frac{Eh}{2\rho R}} \tag{22.5}$$

It can also be expressed in terms of changes in pressure (ΔP) and volume (ΔV) in closed vessels, as described in the Bramwell-Hill relation (Eq. 22.6) [20].

$$PWV = \sqrt{\frac{\Delta P \cdot V}{\Delta V \cdot \rho}} \tag{22.6}$$

These relations (Eqs. 22.5 and 22.6) essentially express the velocity of the forward going pressure pulse (ΔP) using assumptions of an infinitely long, thin-walled, elastic tube with isotropic elastic properties and containing incompressible fluid. They do not contain terms related to the frequency dependency of the parameters, which would elicit some dependence on heart rate. However, the interaction of the cellular and extracellular matrix components of the arterial wall make it a viscoelastic material [21, 22], thus making the elastic modulus a complex quantity with frequency (ω) dependence (Eq. 22.7) [3, 4, 21, 22] and not a static modulus of elasticity (|E|).

$$E(\omega) = |E| \cdot \exp(j\varphi) \tag{22.7}$$

$$\varphi = arctan(\omega \Delta E) \tag{22.8}$$

This was elegantly demonstrated by Bergel in the early 1960s, using canine arteries cycled at various frequencies, where the stiffness of the vessel (E) was shown to depend on the cycling frequency below 2 Hz [23, 24]. The implication of this is that the frequency dependency of the elastic modulus produces subsequent frequency dependency of PWV (from Eq. 22.5). However, this is not similar in all arteries. From Bergel's classic experiments [23, 24], linear extrapolation from 0 to 2 Hz gives the following average increase in relative dynamic elastic modulus: carotid artery, 30 %/Hz; femoral artery, 16.5 %/Hz; abdominal aorta, 9 %/Hz; thoracic aorta, 3.5 %/Hz. These values indicate that muscular arteries have an increased frequency dependency. Indeed, studies suggest a "smart damping" role of smooth muscle in the artery wall due to viscoelasticity [25]. This is different to the frequency dependency of phase velocity, where the low frequency components have an apparent velocity due to a finite distance of wave propagation in relation to wavelength [4].

Findings from in-vitro experiments are not entirely consistent with some other observations. Accurate pulse transit time measurements in isolated canine carotid arteries showed that over a range of sinusoidal frequency pulses of 1–20 Hz and pressure range of 50–150 mmHg, PWV was independent of frequency and dependent only on pressure [26]. Furthermore, the propagation velocity of the significant harmonic components of the pulsatile pressure waveform did not change for heart rates up to 120 beats/min. Studies of heart rate and arterial stiffness in rats and humans using cardiac pacing found a variety of relations between the parameters [27–31]. The explanation for these findings may be multi-factorial,

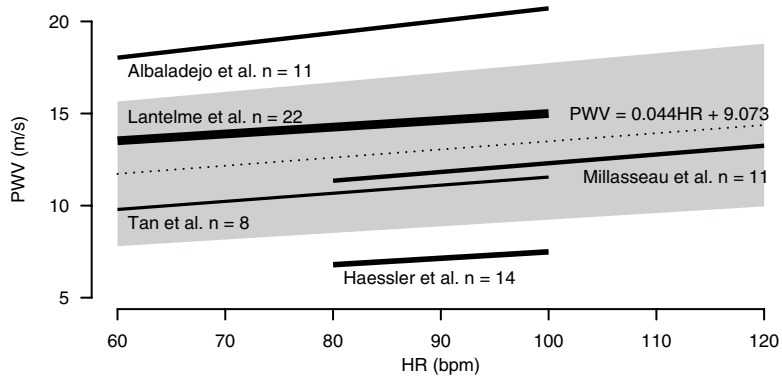

Fig. 22.1 A summary of studies investigating the effect of heart rate on carotid-femoral PWV. The sample size (n) is also indicated by the weight of the lines. The weighted average line (*dashed line*) is plotted, showing a relationship of 0.044 m/s/beat/min. The *shaded area* gives the region ± one standard deviation (Average lines are from Albaladego et al. [17], Haessler et al. [34], Lantelme et al. [27], Millaseau et al. SphygmoCor results [35], and Tan, Butlin, and Avolio [unpublished data]. PWV has not been corrected for any increases in blood pressure with heart rate)

ranging from measurement techniques to determine the fiducial points for transit time measurement to modes of pacing [29, 30]. Spontaneous effects due to sympathetic stimulation of muscular arteries being associated with increased heart rate and arterial stiffness may also play a role [32, 33]. In addition, and this could be an important consideration in clinical measurements in human subjects, measurements over large path lengths may involve different segments with different frequency dependency of the wall elastic modulus.

Figure 22.1 gives relationships between carotid-femoral PWV and heart rate obtained from a number of human studies [17, 27, 34, 35], where heart rate was altered acutely through pacing. The average relationship across the studies gives a change of 0.44 m/s in PWV for every 10 beat/min rise in heart rate. However, in all but the study by Lantelme et al. [27], the paced increase in heart rate was accompanied by a significant rise in arterial pressure, indicating that the mechanism behind the rise in PWV was at least in part, if not entirely, due to changes in distending pressure.

Estimates of expected increases in PWV when transit time measurements are made between the carotid and femoral artery sites may be obtained from values of dynamic modulus change with frequency by Bergel et al. [23, 24]. By applying weights to the slopes according to the respective relative path lengths, the expected increase in PWV is of the order of 5 %/Hz. (that is, a 5 % increase in PWV for heart rate between 60 and 120 beats/min). This is much lower than the average value obtained from the regression equations in Fig. 22.1, ranging from 16 to 35 % increase between heart rate of 60 and 120 beats/min. This indicates that the change in arterial pressure is driving changes in PWV beyond the viscoelastic effect, and again supports the theory that the changes in PWV seen are blood pressure dependent and that the heart rate effect is small.

Chronic Effects

A population regression-based study of carotid-femoral PWV found that age, systolic pressure, weight, and heart rate were predictive of PWV in men, with the relationship between heart rate and PWV being linear. In women, however, only age and systolic pressure were found to be covariates [36]. Another study established a relationship between arterial stiffness and heart rate for both men and women, though heart rate was slightly less predictive in women [37]. Studies to date relating heart rate to PWV within individuals have not been suitably powered to detect differences between males and females [17, 27, 34, 35], though such a study might provide more information on this relationship. An additional chronic effects of heart rate might be related to

the cumulative effects of cyclic stress. This has been shown to be associated with the fatiguing effects of cyclic stress on the structural integrity of elastic lamellae in the aortic wall [38].

Heart Rate and Pulse Pressure

Heart rate is measured routinely in conjunction with blood pressure as a conventional procedure. In addition to being a cardiac rhythm parameter, heart rate is related to pulse wave transmission through the frequency characteristics of the arterial propagation system [39, 40]. The transfer function of the brachial arterial system has a monotonic increase in transmission ratio up to around 4 Hz, with a peak ratio of around 3 Hz [39, 40]. Therefore, for an increase in heart rate, or an increase in the frequency of the harmonics of the arterial pulse, the amplification of the pulse pressure increases. Thus, similar values of pulse pressure measured in the arm correspond to different values of pulse pressure at the central aorta. Studies using a brachial transfer function and atrial pacing showed that pulse amplification between the central aorta and radial artery was estimated as 39 % for a heart rate of 65 beats/min and 95 % for 120 beats/min [41]. This amplification ratio is also age dependent, with decreasing amplification with age [42, 43].

Implications of Heart Rate and Pulse Pressure Amplification in Population Studies

There is greater variation of normal resting heart rate in the general population at any age than for blood pressure, yet less notice is taken of heart rate than blood pressure in epidemiological, clinical, and pharmaceutical trials. The arterial vasculature exhibits amplification of the propagating arterial pressure pulse [34] as a function of heart rate. When brachial pulse pressure is used as a surrogate for central, aortic pulse pressure itself, or in determining indices of distensibility for central arteries (carotid artery, proximal aorta), any changes in heart rate can produce profound differences in the results when compared with calculations performed with the central, aortic pulse pressure.

The heart rate effect on pulse pressure amplification can be a potentially important phenomenon in assessing ventricular load (especially peak load due to systolic pressure) for conditions where there are substantial changes in heart rate, such as exercise [44]. It is also important in large-scale studies investigating anti-hypertensive agents that also affect heart rate, as small differences in blood pressure can be statistically significant and may be due to heart rate and not inherent blood pressure changes. The result of the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) in over 9,000 hypertensive subjects followed for 4 years showed that an angiotensin receptor blocking agent (losartan) had reduced brachial blood pressure to an almost identical extent as a beta blocking agent (atenolol) [45]. For a similar reduction in blood pressure, losartan produced additional beneficial and alleged pressure independent effects such as improved regression of left-ventricular hypertrophy [45, 46]. However, atenolol caused a decrease in heart rate of the order of 6 beats/min. This meant that although brachial pulse pressure was identical for both agents, pulse pressure amplification was greater with losartan due to the higher heart rate. Hence, aortic pulse pressure would be lower with losartan. For a given diastolic pressure, and heart rate amplification characteristics [41], the difference in heart rate between the two drug treatments would cause an estimated difference in aortic systolic pressure of 3 mmHg. This, conceivably, would be significant (in a large cohort of over 5,000 subjects) in determining the pressure-related effects on the heart, such as left ventricular hypertrophy. Confirmation of this phenomenon was seen in subsequent studies (e.g. REASON [47], CAFE [48]) showing that the lowering of heart rate with a beta blocker (atenolol) resulted in a sustained higher central aortic pressure despite a similar brachial systolic pressure achieved with other antihypertensive agents.

Neglecting to account for heart rate related changes in pulse pressure amplification also has implications in the calculation of parameters of central arterial stiffness. A recent study [49] conducted in a large cohort (n = 6,484) showed that resting heart rate had an independent association

Table 22.1 Distensibility calculated using peripheral and central blood pressure values across different heart rates. Note the low slope and very low r^2 value for carotid distensibility with respect to heart rate calculated using central pressure, and the relatively similar magnitudes of slope, opposite sign and high values of r^2 for aortic distensibility compared to distensibility values calculated using peripheral pressure

			Carotid distensibility ($\times 10^{-3}$ mmHg)		Aortic distensibility ($\times 10^{-3}$ mmHg)	
Heart rate quintile	Average heart rate (beats/min)	Pulse amplification	Peripheral pressure	Central pressure	Peripheral pressure	Central pressure
1	50.9	1.18	2.70	3.19	1.90	2.24
2	58.1	1.24	2.62	3.26	1.87	2.33
3	62.9	1.28	2.55	3.27	1.85	2.37
4	68.3	1.33	2.49	3.32	1.85	2.46
5	78.1	1.42	2.22	3.14	1.70	2.41
Slope (10^{-3} mmHg/beat/min)			−0.0174	−0.0012	−0.0067	0.007
Intercept ($\times 10^{-3}$ mmHg)			3.63	3.31	2.26	1.92
		r^2	0.95	0.03	0.83	0.71

Pulse pressure amplification calculated from the data of Wilkinson et al. [50] using linear regression between heart rate and ratio of peripheral/central pulse pressure. Distensibility using peripheral pressure determined by Whelton et al. [49] using brachial pulse pressure. Distensibility using central pressure uses central pressure estimated with pulse pressure amplification values related to heart rate

with arterial stiffness, even after correction for conventional predictors of arterial stiffness, including brachial systolic, diastolic, and pulse pressure. Arterial stiffness was quantified as distensibility and determined from ultrasound measurements of carotid diameter and MRI measurements of aortic diameter coupled with the pulse pressure in the brachial artery obtained by cuff sphygmomanometry. Central aortic pressures were not used in this study. Distensibility was related to heart rate, which spanned an average range of 50.9–78.1 beats/min between the first and last quintile, respectively (Table 22.1). As so calculated, distensibility showed a marked reduction with heart rate for the carotid artery and less so for the aorta. However, with a change in heart rate, the pulse pressure associated with the measured change in vessel caliber cannot be accurately measured from a peripheral and distal location such as the brachial artery due to the amplification of the pressure pulse between the central and peripheral sites. Furthermore, the difference between central and peripheral pulse pressure increases with heart rate [44, 50].

Using the amplification values reported by Wilkinson et al. [50], which were derived in paced patients, for the range of heart rates in the study by Whelton et al. [49], the average amplification is calculated to increase from 18 % at 50.9 beats/min to 42 % at 78.1 beats/min. Due to pulse amplification, for a given peripheral pulse pressure, the central pulse pressure would decrease with increasing heart rate. Hence, the values of distensibility calculated by Whelton et al. [49] would be increased by the amplification factor for the corresponding heart rate [51]. These values are compared in Table 22.1, showing the calculated carotid and aortic distensibility when corrected for the heart rate dependent pulse amplification. These values are used to determine a linear regression association between heart rate and the carotid and aortic distensibility (Table 22.1). These data demonstrate the significant confounding effect that pulse pressure amplification can produce. When carotid or aortic distensibility is determined from measurements of vessel caliber and peripheral (brachial) pulse pressure, distensibility is inversely related to resting heart rate. However, when distensibility is computed using the central aortic pulse pressure, determined by the specific amplification factors associated with the particular heart rate, the association virtually disappears for the carotid artery and indeed reverses for the aorta.

In the estimation of the corrected values for distensibility shown in Table 22.1, a single value of amplification was used for both carotid artery and aorta. However, this is not unreasonable as

both measurement sites are centrally located and close to the heart. In addition, the large cohort in the study of Whelton et al. [49] results in a similar mean age for all heart rate quintiles (mean range 61.8–62.9 years). This is also similar to the mean age of 63 years of the cohort of Wilkinson et al. [50] from which the heart rate dependent pulse wave amplification was determined (Table 22.1). So if peripheral pulse pressure is used as a surrogate for central aortic pressure, the best case is when there is very little or no pulse amplification, a condition that is present for very low heart rates or possibly very old age, in which case the distensibility values using brachial pulse pressure would be valid. In all other cases, even though the vessel caliber measurements using ultrasound or MRI might be accurate, the heart rate effect is overestimated when using brachial pulse pressure and could be significantly different when distensibility is computed using central aortic pulse pressure.

Heart Rate, Arterial Hemodynamics and Cardiovascular Risk

The relationship between heart rate and disease is reciprocal. The physician measures and records heart rate because it may be an indicator of disease – emotional stress, fever, thyroid over or under activity or arrhythmia, for example. In humans, heart rate is generally around 10 % higher in females who are generally 10 % shorter than males. Tall males have a greater life expectancy than shorter males. However, females with faster heart rates outlive males, indicating interaction with other factors. Additionally, change in heart rate can cause disease. Rapid pacing of the heart over a period of days is a method for inducing cardiac failure in experimental models. Tachycardia from any cause can induce dilated cardiomyopathy in humans.

In the animal kingdom, especially among mammals, there is an inverse relationship between heart rate and life expectancy [52]. In human subjects, the epidemiological association between heart rate and cardiovascular mortality was first reported in 1980 in the Chicago People Gas Company Study [53]. The study reported an association between levels of heart rate and coronary heart disease mortality and overall cardiovascular mortality. This was followed by data from a later Framingham longitudinal study showing that an association between heart rate and sudden death existed for both males and females, though it was less marked among females [54].

Other studies such as the Paris Prospective Study [55] and the CORDIS Study [56] from Israel confirmed the relationship between resting heart rate and cardiovascular disease mortality even after adjustment for several other risk factors and other confounding factors. In the CORDIS Study [56], the risk for cardiovascular death was more than doubled in subjects with heart rate greater than 90 beats/min as compared to subjects with heart rate less than 90 beats/min.

A study of over 2,500 subjects (1,407 men and 1,134 women) without major cardiovascular disease at the time of initial examination (65–70 years of age) and followed up at 85 years of age provided evidence that heart rate had a strong predictive value for survival in men [57]. After adjustment for major risk factors (age, systolic blood pressure, smoking, physical activity), men with a heart rate greater than 80 beats/min had a more than 40 % reduction in the probability of reaching 85 years of age compared to men of the same age with a low heart rate (less than 60 beats/min). However, the results of this study [57], along with those from the Framingham Study for subjects over 55 years of age [58], indicated that heart rate was not associated with mortality and longevity in females. A study of 19,386 younger men and women (40–69 years of age) showed that heart rate was a predictor of non-cardiovascular mortality in both men and women, but a predictor of cardiovascular mortality only in men [59]. Interestingly, in men with a brachial pulse pressure greater than 65 mmHg, a high heart rate was not associated with increased cardiovascular mortality. This may be related to the effect of heart rate on aortic pulse pressure relative to brachial aortic pressure, such that for a given brachial pulse pressure, central aortic pulse pressure is lower for higher heart rates [39, 44].

Theoretically, differences between men and women could at least in part be due to the relatively smaller number of cardiovascular disease deaths in the female population, resulting in a lack of statistical power in the studies. However, other risk factors such as blood pressure have similar predictive values for cardiovascular disease and coronary heart disease mortality in both men and women. Similar results were found in a much larger population of more than 96,000 women and 125,000 men [60]. In this cohort, cardiovascular mortality was strongly associated with heart rate and pulse pressure in men. In women, only mean arterial pressure was associated with cardiovascular mortality. Thus, gender differences do not seem to be the exclusive consequence of low death rates in women.

The association of heart rate with cardiovascular disease mortality in men was mainly due to a strong association with coronary heart disease mortality and less with cerebrovascular mortality [59]. The Framingham Study also reported that the relationship between heart rate and cerebrovascular mortality was less significant [58]. The role of heart rate on cardiovascular mortality persisted even after excluding deaths during the first 2 years of the follow-up, thereby eliminating the hypothesis that heart rate was just an indicator of a severe disease [58, 59].

The relationship between heart rate and cardiovascular risk in men has been demonstrated to be linear [59]. After adjustment for age, systolic blood pressure, total cholesterol, smoking, diabetes mellitus, body mass index and physical activity, the increase in risk corresponding to an incremental rise in heart rate of 20 beats/min was 40 % [59]. This is approximately equivalent to the risk of an elevation in systolic blood pressure of 15–20 mmHg.

To date the roles of heart rate and gender-related differences have not been entirely elucidated. Women present a higher heart rate than men, on average between 3 and 7 beats/min greater [61]. Although the mechanisms for this difference are not clearly understood, it is generally believed that they are primarily related to women's average smaller height. Studies in diversified populations [62] have shown a negative relationship between height and heart rate in both genders. Despite these results however, the possibility that other mechanisms regulate heart rate differently in men and in women cannot be excluded.

Cardiac Synchrony and Arterial Hemodynamics

Electromechanical dyssynchrony of the heart chambers, a condition associated with heart failure, results in wasted workload, with internal blood flow ("sloshing") within the ventricle [63]. The dyssynchronous motion of the ventricle walls results in exaggerated sideways movement, and increased work for the same, or reduced, cardiac output. Cardiac dyssynchrony is treated by cardiac resynchronization therapy (CRT) [64, 65], the pacing of two or more heart chambers with a set delay between chamber pacing. The efficacy of CRT is determined by optimizing the appropriate synchrony of the cardiac chambers to maximize cardiac output. Setting of optimum atrio-ventricular (AV) and inter-ventricular (VV) conduction times is often done using echocardiography to maximize atrial inflow [66] and so maximizing cardiac output, or using peripheral pulse measures to maximize arterial pulse pressure [67–69]. However, even with attempts at optimizing timing parameters, not all subjects obtain benefits in terms of increased ejection fraction and improved ventricular function from the different optimal delay strategies [70].

In addition to the optimum time delays for atrial and ventricular filling and contraction to achieve maximal cardiac output, cardiac ejection is also influenced by the arterial load from both the pulmonary and systemic vasculature. The arterial load is determined by the steady component comprising peripheral resistance, and a pulsatile component related to the elastic properties of the large conduit arteries. Hence, with a given set of AV and VV delay times optimized for particular values of load parameters, CRT performance would be altered by changes in either peripheral resistance, arterial compliance, or both.

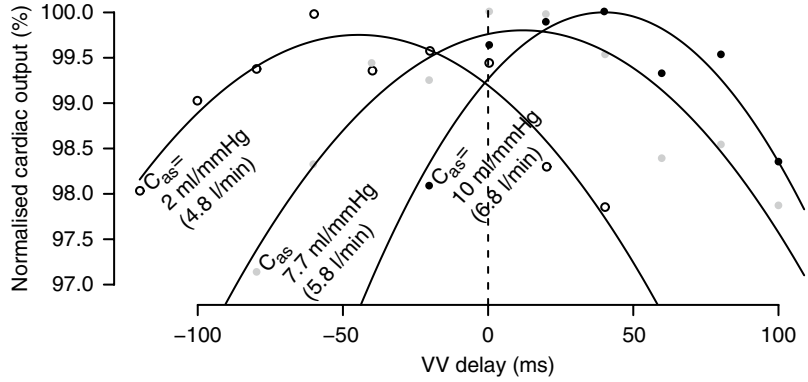

Fig. 22.2 Increase in arterial stiffness (reduction of aortic compliance, C_{as}) casues a left shift in interventricular (VV) delay (shorter delay) of maximal (optimal) cardiac output. Results from a simulation using a lumped parameter cardioavascular model of the cardiac chambers, septum and pulmonary and systemic circulation [71]. For each value of aortic compliance the cardiac output is normalized by the value in *brackets*

To investigate the relationship of changes in arterial load parameters with AV and VV delays to achieve maximal CRT performance, closed-loop computational models of the pulmonary and systemic circulation have been constructed using lumped parameter representation of the arterial load and variable elastance for the cardiac chambers and interventricular septum with incorporation of the Frank-Starling mechanism [70, 71]. Increased arterial stiffness (simulated by reduction in aortic compliance) resulted in a reduction in the VV delay for maximal cardiac output (Fig. 22.2). That is, a decrease in aortic compliance is associated with a relatively earlier activation of the left ventricle compared to right ventricular activation (a negative VV delay indicates that the right ventricle contracts after the left ventricle). This implies that for an arterial system with stiff arteries, the optimum performance of the CRT would not be obtained by the theoretical zero delay between the contraction of the left and right ventricle, but rather with an additional delay of contraction of the right ventricle in relation to the time for contraction of the left ventricle.

The models [70, 71] can be used to assess the sensitivity for maximizing either cardiac output or systolic pressure as functions of large artery stiffness or total peripheral resistance for both VV and AV delays. Simulation results show that vascular effects on AV delay are much less pronounced than that on VV delay for optimal cardiovascular function [71]. Hence, non-invasive measurements of arterial stiffness parameters (aortic pulse wave velocity) can be incorporated in patient specific simulations for synchronisation of chamber contraction by appropriate AV and VV delays so as to maximise pulse pressure or cardiac output.

Conclusions

Although changes in heart rate are inherent in cardiovascular adaptive mechanisms, there is an emerging acceptance of heart rate being associated with cardiovascular risk, high blood pressure, and all-cause morbidity and mortality. The determinants of arterial pressure are related to the interaction of the pulsating ventricle at a given frequency and the elastic and geometric properties of arteries determining arterial stiffness. Hence, a case could be made for heart rate to be considered as an integral parameter when performing the basic measurements of blood pressure and pulse wave velocity. In addition, heart rate is relevant when blood pressure is measured in a peripheral location (as is conventionally measured in the brachial artery) and making conclusion on effects of pressure on the heart since the relation between central aortic and peripheral pulse pressure depends on both the pressure pulse waveform characteristics and

heart rate. It follows, therefore, that heart rate should also be taken into account when considering cardiac effects of pharmacological anti-hypertensive agents and in statistical treatment of cardiovascular risk factors in large scale epidemiological studies.

There is also potential for the use of heart rate in other clinical interventional procedures, such as correction of irregular heart rate due to asynchrony of the contracting cardiac chambers through cardiac pacing and CRT. By use of cardiovascular models of the heart and pulmonary and systemic circulation systems, it has been shown that arterial stiffness can have a significant effect in modifying AV and VV delays for optimal CRT performance in maximizing cardiac output.

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