Role of short-term cardiovascular regulation in heart period variability: a modeling study

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Ursino, Mauro, and Elisa Magosso. Role of short-term cardiovascular regulation in heart period variability: a modeling study. Am J Physiol Heart Circ Physiol 284: H1479–H1493, 2003. First published December 19, 2002; 10.1152/ajpheart.00850.2002.—A mathematical model of short-term cardiovascular regulation is used to investigate how heart period variability reflects the action of the autonomic regulatory mechanisms (vagal and sympathetic). The model includes the pulsating heart, the systemic (splanchnic and extrasplanchnic) and pulmonary circulation, the mechanical effect of respiration on venous return, two groups of receptors (arterial baroreceptors and lung stretch receptors), the sympathetic and vagal efferent branches, and a very low-frequency (LF) vasomotor noise. All model parameters were given on the basis of physiological data from the literature. We used data from humans whenever possible, whereas parameters for the regulation loops are derived from dog experiments. The model, with basal parameter values, produces a heart period power spectrum with two distinct peaks [a high frequency (HF) peak at the respiratory rate and a LF peak at ≈0.1 Hz]. Sensitivity analysis on the mechanism gains suggests that the HF peak is mainly affected by the vagal mechanism, whereas the LF peak is increased by a high sympathetic gain and reduced by a high vagal gain. Moreover, the LF peak depends significantly on the reactivity of resistance vessels and is affected by noise, amplified by the sympathetic control loop at its resonance frequency. The model may represent a new tool to study alterations in the heart period spectrum on the basis of quantitative physiological hypotheses.

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In the present study, as in our previous models, we assumed that heart period is the regulated quantity instead of heart rate (HR). In fact, as pointed out by Hainsworth (20), HR is not the appropriate quantity to quantify autonomic effects, because of the gross nonlinearity of the relationship linking HR to the efferent vagal and sympathetic activities [see Levy and Zieske (27)]. Conversely, these nonlinear relationships are naturally converted to linear if pulse interval is used instead of HR (see Ref. 48 for more details).

Through a sensitivity analysis of model parameters, the present work aspires to clarify the conditions that may lead to clear LF oscillations in the heart period spectrum and to analyze the relationships between the LF and HF rhythms.

QUALITATIVE MODEL DESCRIPTION

The present model differs from a former model, described in Ref. 48, as to the following points.

Simplifications

Each feedback mechanism loop is described in a simpler way, without a definite distinction between the afferent and efferent neural activities. This simplification allows us to work with a more conceptual model, without any evident alteration in the overall regulatory response.

Improvements

The mechanical effect of respiration on venous return and cardiac output is included, and the action of lung stretch receptors on cardiovascular parameters has been taken into account. These two improvements have been introduced to obtain a physiological HF component in the heart period spectrum. In fact, both mechanisms introduce spectral components in cardiovascular quantities at the respiratory rate.

In the following description only the main aspects of the model are presented in qualitative terms. Model equations are given in the APPENDIX.

Heart and Vessels

The description of the heart and vessels is similar to that used in a previous report (48); hence, only a few details are given here. The right and left sides of the heart are modeled by means of a passive atrium (described through a linear compliance) and an active ventricle. Contractility of the ventricle is simulated by means of a time-varying elastance in series with a time-varying resistance. Shifting from the end-diastolic to the end-systolic values is governed by a pulsating activation function, which mimics the cardiac pacemaker.

The vascular system comprehends a separate description of the pulmonary and the systemic circulation. The latter, in turn, contains the parallel arrangement of the splanchnic circulation and of the other, extrasplanchnic systemic vessels. Hemodynamics in each district (pulmonary, splanchnic, and systemic extrasplanchnic) is reproduced by means of resistive, capacitive, and inertial terms, as described previously (48) (see Fig. 1). In particular, blood volume stored in capacitive terms is the sum of an unstressed volume and a stressed volume, the latter being computed as the product of compliance and transmural pressure. A further compartment, not included in the previous work, represents the large systemic veins inside the thorax, carrying venous return to the right heart (see subscript tv in Fig. 1). A separate decription of thoracic veins has been adopted to achieve a more accurate description of the effect of respiratory changes on venous return and cardiac output.

The mechanical effect of respiration on cardiovascular quantities has been simulated by using time-varying expressions for intrathoracic pressure ($P_{thor}$, which is extravascular pressure for all compartments located inside the thorax; see APPENDIX for more details). In the present study we assumed that the subject breathes with a constant respiratory cycle 5 s long.

Finally, respiratory volume (which is an input for lung stretch receptors) has been computed as a linear function of $P_{thor}$. Parameters of this pressure-volume relationship were
chosen to attain physiological values of tidal volume, minute ventilation, and end-expiration volume in humans (34, 49).

**Regulation Mechanisms**

The description of short-term regulation mechanisms includes arterial baroreceptors and lung stretch receptors. The information from these receptors modulates various cardiovascular parameters: systemic peripheral resistance (both in the splanchnic and extrasplanchnic vascular beds), venous unstrained volume (both in the splanchnic and extrasplanchnic vascular beds), heart contractility (i.e., the end-systolic elastance in the left and right ventricles), and heart period. The first three control actions are purely sympathetic in nature and are described according to the general block diagram in Fig. 2. It is worth noting the presence of two different input stimuli coming from arterial baroreceptors (sensitive to arterial pressure changes) and lung stretch receptors (sensitive to changes in respiratory volume). These input stimuli are multiplied by the respective mechanism gain and summed up. Finally, the effector response includes a sigmoidal static relationship (which accounts for the existence of upper and lower limits for the response), a pure delay, and a first-order low-pass dynamic. The last two terms reproduce the main aspects of the response time pattern.

The heart period control is more complex, involving a balance between vagal and sympathetic activities. In particular, dynamics of the vagal and sympathetic mechanisms are different: the vagal control is characterized by a rapid response, which is completed within two or three cardiac beats, whereas sympathetic control requires many seconds (20, 22, 32). Accordingly, heart period regulation in the model is described through the more complex diagram in Fig. 3. Worth noting is the existence of different gains and different dynamics for the vagal and sympathetic paths, whereas the sigmoidal relationship still describes the upper and lower limits of the effector response. Of course, some of the gains in Figs. 2 and 3 can be equal to zero (see Assignment of Model Parameters) if the corresponding mechanism plays a negligible role on the specific effector response.

Finally, the existence of other LF sources of noise (such as those caused by humoral and thermal control or vasomotion) has been accounted for in an empirical manner, by superimposing a LF (<0.12 Hz) uniformly distributed noise (zero mean value and assigned variance) on the expression of peripheral extrapulmonary systemic resistance. The power spectrum of noise used in the simulations decreases quite linearly between 0 and 0.12 Hz.

**Assignment of Model Parameters**

All parameters in the heart and vessels have been given according to the previous work (48) to simulate normal human cardiovascular dynamics. The parameters that characterize the gains and static curves of feedback regulation mechanisms in Figs. 2 and 3 have been assigned by the steps described below. Because most experiments have been carried out on dogs, all quantities were normalized to the basal level, assuming that regulation mechanisms cause the same percentage changes in humans and animals.

First, a value for the gains of the lung stretch receptor mechanism on HR and resistance has been given on the basis of experimental data obtained in the dog (14, 19). These authors measured the changes in HR and in total systemic resistance during steady-state variations in pulmonary inflation pressure and/or pulmonary volume (see Fig. 4). Moreover, according to Ref. 1, we assumed that the effect of lung stretch receptors on HR is exclusively mediated by the vagus. Finally, we are not aware of any effect of lung stretch receptors on heart contractility and on venous unstrained volumes; hence, the corresponding mechanism gains were set to zero.

Second, a preliminary value for the gains of all sympathetic mechanisms activated by the arterial baroreflex [i.e., parameter G_{sb} in Fig. 2] and the upper and lower limits of the sigmoidal relationships (with the exception of the relationship for heart period, which is described below) have been given to simulate the results of open-loop experiments performed in vagotomized dogs (5, 9, 12, 13, 38, 42, 44). In these experiments the carotid sinuses are isolated from the rest of the circulation and their pressure is changed in steps. However, because the vagus is cut, neither the efferent vagal activity nor the afferent activities from aortic baroreceptors and lung stretch receptors concur with the observed responses. Hence, all vagal gains and lung stretch receptor gains on peripheral resistances were set to zero during these simulations. The results are shown in Fig. 5.

Third, to complete the calculation of the arterial baroreflex, we must assign the gain of the vagal control on HR. Moreover, the possible role of the extracarotid (mainly aortic) arterial baroreceptors must be assessed. In this regard, some authors have observed that these baroreceptors play a major role in the control of HR in humans and that they significantly contribute to the increase in sympathetic activity to resistance vessels (17, 40, 41). Accordingly, the vagal and sympathetic gains that characterize heart period control by the arterial baroreceptors have been reassigned to reproduce...
the changes in heart period observed in young, healthy men (25) during pharmacological changes in arterial pressure (see Fig. 5). To account for the possible role of extracarotid baroreceptors, the gain of the sympathetic control of HR exhibits a higher value compared with the value inferred from experiments in vagotomized dogs. Similarly, the gain of the sympathetic control on systemic arterial resistances has been increased, to account for the possible effect of extracarotid baroreceptors. We assumed a ratio of extracarotid versus carotid sympathetic control on resistance and heart period as large as 2.5, which approximately agrees with data by Ferguson et al. (17).

Mechanism dynamics. All dynamic parameters in the control loop have been assigned on the basis of dog experiments. The time constant and time delay of the control of contractility (elastance; $E_{\text{max}}$) have been given to reproduce the frequency dependence of the open-loop transfer function from carotid sinus pressure to end-systolic elastance (26). The time constant and pure delay of the resistance control have been given according to data reported previously (16). The time constant and pure delay of the venous unstressed volume control are higher than those of the resistance control: in fact, $\sim 1$ min is required before the accomplishment of complete active venoconstriction (45). The time constants and pure delays of the HR control have been assigned considering that the effect of vagus stimulation on heart period is completed within two or three beats, whereas the sympathetic control is characterized by slower dynamics (a few seconds) (20, 22, 32).

A list of all model parameters (both in the vagotomized experiments and in intact conditions) can be found in Table 1. The meaning of symbols is also explained in the Appendix.

RESULTS

Figure 6A shows a segment of the heart period time pattern, simulated with the model using the basal parameter values as in Table 1. Figure 6B reports the power spectral density computed from a longer simulated signal (1,000 s) with the Welch averaged periodogram method (2). The sequence was first detrended to eliminate frequencies close to zero; then several overlapping sections (60-s duration each, windowed by means of the Hanning window) were used to compute the averaged periodogram. The results clearly show the presence of two peaks in the power spectral density. The HF peak (0.2 Hz) reflects the respiratory activity, transmitted to the cardiovascular system both via the extravascular thoracic and abdominal pressures and via action of the lung stretch receptors. The LF peak represents a resonance of the control loops, located around 0.1 Hz. Quite evident in the spectrum also is the effect of the additional noise at very low frequencies.

To clarify the role of the vagal and sympathetic mechanisms in the genesis of the power spectrum, we performed a sensitivity analysis on the strength of the sympathetic and vagal branches. This is summarized in Fig. 7. Figure 7, A and B, shows the effect of increasing or decreasing the gains of all sympathetic mechanisms (working on heart period, peripheral resistance, venous unstressed volume, and heart contractility) by $\pm 20\%$ of their basal value. Simulations show that even a moderate increase in the sympathetic gains causes a
significant increase in the LF component, whereas the HF component exhibits just a mild decrease (Fig. 7A). By contrast, a moderate reduction in the sympathetic gains strongly attenuates the LF component (which becomes almost indistinguishable from noise) with a small increase in the HF component.

Figure 7, C and D, shows the effect of a moderate change (±20%) in the vagal gains (that is, the vagal gains on heart period from both arterial baroreceptors and lung stretch receptors). Increasing the vagal gains induces a large increase in the HF component, whereas the LF component is reduced (although the sympathetic gains were still set at their basal value). The opposite effect (significant decrease in the HF band with an increase in the LF band) occurs when the vagal gains are reduced.

The previous results are summarized in Fig. 7E, where the sympathetic gains were increased by 20% and the vagal gains simultaneously decreased (−20%). The effect is a dramatic rise in the LF component of the spectrum, with a reduction of the HF peak.

Furthermore, to analyze the effect of VLF noise (such as that induced by thermal or hormonal regulation) on the spectrum, the simulation was repeated, with basal parameter values, by reducing the amplitude of the random noise by 50% of the initial value. The results, shown in Fig. 7F, attest that the presence of this VLF noise is important in the production of a clear LF component. The resonance in the control loops amplifies the existing noise at ~0.1 Hz, thus resulting in a more evident peak compared with the case with almost no noise.

In conclusion, sensitivity analyses in Fig. 7 point out that the HF peak mainly reflects the strength of vagal control (in fact, it is only mildly affected by the sympathetic gains), whereas the LF peak exhibits a more complex dependence on sympathetic and vagal mechanisms and on additional noise. In fact, this peak is affected both by a change in sympathetic strength and by a change in the vagal component. Moreover, the LF peak is also influenced by the level of superimposed noise.

The simulation results in Fig. 7 summarize the role of the sympathetic and vagal efferent branches, and of noise, on heart period variability. However, the strength of oscillations not only depends on efferent activity but also on any other component within the control loops. In particular, any change in the sensitivity of the different effectors to efferent activity may cause a change in the oscillation strength. This point is usually ignored in the physiological literature, whereas the amplitude of the LF and HF peaks is ascribed merely to efferent activity, by neglecting the role of the other components in the loop.

To analyze this aspect, we performed a sensitivity analysis on each effector response separately from the others. To this end, we selectively changed the central slope of the sigmoidal relationship for each effector (systemic peripheral resistance, venous unstressed volume, heart contractility, and heart period) by maintaining the sensitivity of all other effectors at the basal value. The slope of each effector was modified by ±50% compared with the normal level, and the effect on the LF and HF peaks was evaluated.

The results are shown in Fig. 8, with reference to a modification of the response of peripheral resistances (Fig. 8, A and B) and heart period (Fig. 8, C and D). The results concerning a modification of the response for venous unstressed volumes and contractility are not shown because a change in these effectors did not cause any appreciable change in the strength and position of the LF and HF peaks.

The results in Fig. 8, A and B, show that the response of arterioles (which are the effectors for the resistance control) plays a pivotal role in the genesis of the LF wave. In fact, if the resistance response is depressed, the LF peak almost completely disappears, whereas a strong resistance response manifestly increases the LF peak. Moreover, as well expected, the resistance sensitivity has no effect on the HF peak.

The results in Fig. 8, C and D, reveal that a strong sensitivity of the cardiac pacemaker (and hence of
Fig. 5. Summary of open-loop responses of arterial baroreflex in vagotomized conditions. A: systemic arterial pressure. B: cardiac output. C: heart period changes. D: systemic resistance. E: splanchnic unstressed volume. F: extrasplanchnic unstressed volume. Continuous thick lines are model simulation results. To simulate open-loop conditions, pressure at baroreceptors was given a constant nonpulsating value different from arterial pressure, changed in steps from 35 to 155 mmHg. To simulate vagotomy, pulmonary receptor gains ($G_p$ in Figs. 2 and 3) and baroreflex vagal gain ($G_aTv$ in Fig. 3) were set at zero. Model results are compared with experimental data in the vagotomized dog in open-loop conditions. To compare model data with data in the dog, the corresponding quantities were normalized or expressed per unit weight. Experimental points are from Refs. 5, 9, 12, 13, 38, 42, and 44. Only in the case of heart period changes (C) has the simulation been repeated (dashed line) by including the baroreflex vagal gain as well as pulmonary receptor gains to reproduce results of phenylephrine infusion in young human volunteers (Ref. 25). Moreover, during the last simulation, baroreflex sympathetic gain on heart period ($G_{aTs}$ in Fig. 3) and on peripheral resistances ($G_{aRep}$ and $G_{aRsp}$ in Fig. 2) have been enhanced to account for the role of aortic baroreceptors (17, 40, 41). The 3 experimental lines in E and F (unstressed volume control) are means ± SD.
heart period response) to efferent activity results in a higher HF peak, but this sensitivity has a modest effect on the amplitude of the LF peak. As well expected, a scarce sensitivity of the sinus node causes a depression of both LF and HF peaks.

These results stress that the amplitudes of the HF and LF peaks represent not only the variations in efferent activity but also the sensitivity of the effectors (mainly arterioles and sinus node). In particular, the LF peak is especially affected by the strength of the sympathetic control (which depends both on variations in sympathetic efferent activity and on the reactivity of resistance vessels) whereas the HF peak is especially expressive of the vagal control on heart period and of sinus node reactivity.

**DISCUSSION**

The present work investigates the role of some short-term regulatory mechanisms on the genesis of HRV.
Fig. 7. Results of sensitivity analysis on sympathetic and vagal gains. A and B: effect on the PSD of increasing (A) and decreasing (B) the gains of all sympathetic mechanisms (working on peripheral resistances, venous unstressed volumes, heart period, and heart contractility) by 20% of their basal values. C and D: effect of increasing (C) and decreasing (D) vagal gains (i.e., the vagal gains on heart period from arterial baroreceptors and the lung stretch receptors) by 20% of their basal values. E: combined effect of increasing sympathetic gains by 20% and decreasing vagal gains by 20% (i.e., the simultaneous occurrence of the two situations depicted in A and D); F: effect of decreasing the amplitude of the very low-frequency random noise by 50%. For comparison, the basal power spectrum is reported in each panel (dashed lines).
with the use of mathematical modeling and computer simulation techniques. Although various models have been presented in recent years for the study of HRV, the present model introduces several new aspects and overcomes previous limitations.

The idea that the arterial pressure control loop can cause oscillations in cardiovascular quantities has been portrayed in the physiological literature for many decades [see Guyton and Harris (18); see also Koepchen (24) for an ample review]. Kitney (23) first proposed a nonlinear model that involves a negative feedback loop, a pure time delay, and a switching element to theoretically analyze the oscillatory behavior of the blood pressure control system. A popular model of HRV was proposed by deBoer et al. (15) in the late 1980s. It consists of a set of difference equations describing the baroreflex control, the input impedance of the systemic arterial tree, the contractile properties of the myocardium, and the mechanical effect of respiration. With that model, the authors were able to explain the presence of a LF peak in the HR spectrum, ascribing it to a resonance of the baroreflex control loop, mainly due to the sympathetic time delay. However, these models are based on a very simplistic description of the cardiovascular system and of the heart, and they include just a few features of the pressure control loop. Hence, their value lies more in the analysis of the mathematical properties of the equations than in physiological soundness.

A simple model of HRV, which may exhibit chaotic behavior, was recently presented by Cavalcanti and Belardinelli (11). In this case, too, however, the emphasis is more on the mathematical route leading to chaos than on physiological reliability. “Reduced” models, oriented to the analysis of a simple feedback loop, have also been presented (10, 39).

![Figure 8](http://ajpheart.physiology.org/) Results of sensitivity analysis on effector responses. A and B: effect on the PSD of increasing (A) and decreasing (B) the slope of the sigmoidal curve of the peripheral resistances (both splanchnic and extrasplanchnic) by 50% of its basal value. C and D: effect on the PSD of increasing (C) and decreasing (D) the slope of the sigmoidal curve of the heart period by 50% of its basal value. Changes in the slope of the sigmoidal curve of the other 2 effectors (heart contractility and venous unstressed volume) do not cause any appreciable alterations in the power spectrum; hence the corresponding data are omitted.
Seydnejad and Kitney (43) recently presented a more comprehensive model of cardiovascular regulation, finalized to the study of blood pressure and HRV. The model consists of a set of differential equations and includes several aspects of cardiovascular regulation, such as the afferent baroreflex, the vagal and sympathetic modulation of HR, the sympathetic control of the vasculature, the mechanical effect of respiration, and a VLF vasorhythm. However, the nonlinear dependence of blood pressure on HR, on respiration, and on sympathetic excitation (i.e., the overall circulatory response) was identified empirically, through the analysis of Volterra series expansion, without the use of a cardiovascular model. Empirical mathematical models, based on the identification of autoregressive equations, were extensively used by Baselli et al. (see Ref. 7 for a review). Although these last models represent helpful empirical tools to quantitatively analyze spectra and extract specific features from data, they do not provide a physiological underpinning for the mechanisms leading to cardiovascular variability.

The previous compendium underlines the need for a comprehensive mathematical model that carefully embodies physiological knowledge and can elucidate the possible origin of cardiovascular variability without the need for empirical learning procedures. The present model incorporates several aspects that were previously neglected, such as the control of venous unstressed volume and contractility, the lung stretch receptor reflex, heart pulsatility, the effects of intrathoracic and abdominal pressure changes on pulmonary circulation and on venous return, and a VLF vasomotor noise. Moreover, each feedback loop is separately described with its own parameter values. We are not aware of any previous model that summarizes all these aspects into a single theoretical structure. Furthermore, parameters in the model were given on the basis of physiological experiments in the literature (generally performed in open-loop conditions) and not on the basis of the final desired behavior. The pattern of HRV arises ultimately as an emergent property, when all model components are combined, and the model works in its natural closed-loop condition. This aspect strongly differentiates physiological models (like the present) from empirical models.

The primary result of the present study is that a spectrum of heart period variability, similar to that observed in human subjects, emerges spontaneously from model simulations using basal parameter values. Subsequently, the sensitivity analysis of the effect of parameter changes furnished interesting clues on the origin and physiological significance of the HF and LF spectral components.

**HF Component**

The HF or respiratory component of the spectrum is determined by two concurrent mechanisms. The first is the effect of systemic arterial pressure (SAP) changes mediated by the baroreflex. SAP exhibits respiratory fluctuations caused by the intrathoracic and abdominal pressure changes (mechanical effect) and by the lung stretch receptor reflex working on resistance (neurogenic effect). The fluctuations systematically stimulate the baroreflex at the respiratory period (0.2 Hz in the present study). At this frequency, however, the baroreflex works entirely through its strong and fast vagal component, whereas the sympathetic component is almost completely damped out because of its low-pass filtering dynamic. The second mechanism, showing the direct effect of the lung stretch receptor reflex on heart period, is also mediated by the vagus.

A common viewpoint in the literature is that the HF peak can be considered as an index of vagal activity. The previous description, and the sensitivity analysis shown in Fig. 7, confirm that the HF peak is significantly affected by the vagal gains and it is quite independent of the sympathetic gains. Hence, changes in the HF peak can be considered to be almost entirely caused by vagal control actions. However, care must be taken in considering the HF peak as an index of the strength in vagal control. In fact, the HF peak is modulated by all factors affecting the input to baroreflex and the lung stretch reflex [such as the depth and frequency of breathing (21), venous compliances in the thoracic and abdominal cavity, posture changes (47), etc.]. Moreover, as shown in Fig. 8, C and D, the HF peak depends strongly on the sensitivity of the cardiac pacemaker to efferent activity. Hence, as suggested by Akselrod (3) and Malpas (31), in different subjects and/or under different breathing conditions, the HF spectral component may be largely different even in the presence of an equivalent vagal gain.

**LF Peak**

As suggested by several authors (3, 28, 30, 31), model simulations confirm that the LF component of the power spectrum is strongly affected by the sympathetic system. A change in the sympathetic gains, in fact, causes a dramatic alteration in this component of the spectrum, leaving the HF component almost unchanged. In particular, to achieve values of LF oscillations in agreement with those observed in humans, the model requires values of sympathetic gains working on heart period and resistance much higher than those deducible from open-loop experiments in vagotomized dogs (see Fig. 5 and Table 1). These high values are justified by the presence of aortic baroreceptors (not operating in vagotomized conditions) and by the strong role of sympathetic control in humans (17, 40, 41). Actually, the present model results underscore the existence of a resonance induced by the slow sympathetic control loops around 0.1 Hz: this is congruent with the physiological considerations included in the model by Kitney (23) and deBoer et al. (15).

However, the sensitivity analysis in Fig. 7 shows that other factors may modulate the LF peak considerably. First, a reduction in the vagal gains induces an appreciable increase in the LF peak, and vice versa. The model suggests that if the vagal mechanisms are
strong they can damp the alterations in heart period induced by the sympathetic loop. By contrast, if the vagal gains are reduced, oscillations in heart period induced by the sympathetic resonance can be entirely dampened, whereas the other effectors (such as venous unstressed volume or contractility) are less important. The reason for this finding is that LF fluctuations originate from oscillations in blood pressure, which are detected by the baroreflex system and transmitted to heart period fluctuations. Pressure oscillations, in turn, are directly correlated with oscillations in resistance. Hence, if the ability of resistance vessels to respond to sympathetic influences is depressed, the power of the LF spectral component will similarly decline.

The previous considerations stress that the LF peak not only reflects efferent neural activity but is also sensibly affected by vessel reactivity. As remarked by Malpas (31), the latter aspect is often ignored in the clinical/physiological literature, where the ratio LF/HF is just considered a marker of efferent neural activity, thus neglecting all other components participating to the pressure control loop.

Of course, the present model implies some simplifications and omissions, which may be the target of future improvements and extensions. The main limitations are critically discussed below.

First, in the present study we focused attention on the autonomic pressure control as the main factor affecting the LF waves, whereas other possible mechanisms have been neglected. This choice was adopted because the aim of this work was just to investigate the role of autonomic control system in the genesis of HRV. However, as discussed by Koepchen in his review (24), several other factors, and their complex nonlinear interactions, may concur with the formation of LF waves besides autonomic regulation. These include central, humoral, and vasomotor factors. Moreover, not only the strength of these factors but also their spectral distribution may be important in the etiology of LF fluctuations. A possible effect of some of these mechanisms has been included in the present study only in an empirical way, in the form of VLF noise.

Second, the present description of the autonomic loops is necessarily simplified and omits some mechanisms that may have a role. In particular, experimental evidence suggests that cardiovascular afferent sympathetic fibers (located in the cardiac structures and in large thoracic vessels) are capable of mediating excitatory reflex actions, with positive feedback characteristics (29). This reflex seems to normally participate in the neural regulation of cardiovascular system, interacting with the negative feedback mechanisms (originating in the arterial baroreceptive and vagal afferents). Sympathosympathetic circuits can play a role in the genesis of HRV and in particular in the genesis of the LF oscillations, because these mechanisms are sympathetic in origin.

The description of factors involved in HF waves is also simplified and neglects some mechanisms de-
scribed in the literature. In particular, the baroreflex system includes not only arterial (or high pressure) baroreceptors but also cardiopulmonary (low pressure) baroreceptors (located in the atria, ventricles, and pulmonary veins). Activity in these receptors may be significantly affected by changes in venous pressure induced by respiration; hence, these receptors may parallel the effect of lung stretch receptors. Moreover, several authors have hypothesized that an important constituent of HF waves may be irradiation of impulses from the respiratory centers to cardiac vagal motor neurons (central mechanism).

Furthermore, in the present simulations only metronomic breathing was simulated, with a respiratory period as great as 5 s. As a consequence, the HF peak and the changes in vagal activity are more evident than during normal respiration, because of a synchronism between all respiratory components (28). This consideration justifies why, with basal parameter values, the model predicts a HF spectral component much greater than the LF component.

Finally, the mechanical effect of respiration on cardiac output is imputable not only to venous compression (i.e., the respiratory pump included in the present model) but also to ventricular interdependence. Ventricles share a common septal wall and are situated in a space limited by pericardial constraints. Filling and emptying of one ventricle are thus directly influenced by changes in the volume or pressure in the other ventricle. As a consequence of this phenomenon, called ventricular interdependence, the inspiratory increase in right ventricle filling (due to the fall in intrathoracic pressure) results in a larger decrease in left ventricle filling from the pulmonary circulation (8, 37). Thereby, ventricular interdependence mechanically contributes to the respiratory fluctuations in systemic arterial pressure. The mechanical coupling between ventricles is increased in pericardial diseases (such as cardiac tamponade and constrictive pericarditis), producing an exacerbation of respiratory-induced hemodynamic events (pulsus paradoxus).

In the present study, the model has been validated by demonstrating that the autonomic pressure reflex may induce oscillations in heart period with physiological characteristics and by studying the size of the LF and HF components at different values of the parameters for the autonomic control. Of course, a broader validation is necessary in future works. This should include the following major items: 1) analysis of arterial pressure fluctuations and comparison of the corresponding spectra at different locations along the vascular system, 2) cross-spectral analysis among different quantities in the model, with special emphasis on phase differences among fluctuations, 3) characterization of model behavior with classic methods for nonlinear analysis (such as a study of bifurcations, computation of embedded dimensions and entrainments among oscillators). All these topics may be the target of future works.

An important aspect that deserves discussion is the choice of species used to assign the numerical parameters. Of course, the results obtained in this work depend on this choice, and scaling to other species requires caution.

In the present study, parameters of the cardiovascular system (resistances, compliances, volumes, cardiac output, etc.) have been assigned to simulate hemodynamics of a normal man (see Ref. 48 for a thorough description). By contrast, as discussed in qualitative model description, the parameters of the autonomic regulation have been assigned mainly on the basis of experiments performed in dogs. The latter choice has two main implications. First, the use of a parameter setting based on dog experiments may lead to spectra more similar to those observed in dogs than in humans. Second, as discussed by Malpas (31), the dynamic characteristics of the autonomic loops (time delays, time constants) are significantly different between animal species. As is well known from the automatic control theory, time delays are particularly important in the genesis of instability phenomena. Small animals (such as rabbits and rats) exhibit time delays shorter than those measured in the dog’s baroreflex arc: these differences determine a higher resonance frequency for the control loop. For instance, the LF band is at ~0.1 Hz in the human, 0.14 Hz in the dog, 0.3 Hz in the rabbit, and 0.4 Hz in the rat (see Ref. 31 for extensive references). Hence, we emphasize that new “ad hoc” values should be assigned for the baroreflex loop parameters (especially time delays) if one intends to use the present model to simulate experiments in smaller animals.

In conclusion, the present study demonstrates that LF and HF peaks in the heart period spectrum spontaneously emerge from a model of short-term cardiovascular regulation based on actual physiological knowledge. The model suggests that the LF peak reflects a resonance of the pressure control loop, especially connected with sympathetic regulation and with the reactivity of resistance vessels, but it is also intensified by other LF sources of noise and is attenuated by a strong vagal control. The HF peak is dominated by the vagal control of heart period. The model can be used to achieve deeper understanding of the mechanisms causing HRV, and of the significance of spectral changes, on the basis of rigorous quantitative hypotheses and physiological considerations.

APPENDIX: QUALITATIVE MODEL DESCRIPTION

Cardiovascular System

Equations for the heart and hemodynamics are formally similar to those used in the previous article (48); hence, they are not repeated for the sake of brevity. However, compared with the previous work, the present paper accounts for an extravascular pressure different from atmospheric pressure (i.e., not null) in the thoracic and abdominal cavity. As a consequence, vessel transmural pressure inside the thoracic cavity is computed as the difference between the intravascular and intrathoracic pressure (\(P_{\text{intr}}\)), whereas transmural pressure at splanchnic vessels is intravascular pressure minus abdominal pressure (\(P_{\text{abd}}\)).
Time patterns of intrathoracic and abdominal pressures during each respiratory cycle have been given to reproduce data measured by Moreno et al. (35). $P_{thor}$ falls linearly during inspiration down to $-9$ mmHg and then rises linearly during expiration to recover the steady value of the respiratory pause ($-4$ mmHg). Abdominal pressure decreases down to approximately $-2.5$ mmHg during inspiration and then rises to zero during expiration. The following equations hold

$$
P_{thor} = \begin{cases} 
-5 \cdot \frac{\alpha \cdot T_{resp}}{T_i} - 4 & 0 < \alpha < T_i/T_{resp} \\
-5 \cdot \frac{T_i + T_e - \alpha \cdot T_{resp}}{T_e} & T_i/T_{resp} < \alpha \leq (T_i + T_e)/T_{resp} \\
-4 & (T_i + T_e)/T_{resp} < \alpha < 1
\end{cases}
$$

$$
P_{abd} = \begin{cases} 
-2.5 \cdot \frac{T_{resp}}{T_i/2} & 0 < \alpha < T_i/T_{resp} \\
-2.5 & T_i/T_{resp} < \alpha < T_i \\
-2.5 \cdot \frac{T_i + T_e - \alpha \cdot T_{resp}}{T_e} & T_i/T_{resp} < \alpha \leq (T_i + T_e)/T_{resp} \\
0 & (T_i + T_e)/T_{resp} < \alpha < 1
\end{cases}
$$

where $T_{resp}$ is the respiratory period, and $T_i$ and $T_e$ denote the duration of inspiration and expiration, respectively; $\alpha$ is a dimensionless variable, ranging between 0 and 1, which represents the fraction of the respiratory cycle; $\alpha = 0$ conventionally corresponds to the beginning of inspiration. An expression for $\alpha(t)$ has been obtained by using an additional state variable $\epsilon(t)$

$$\frac{d\epsilon}{dt} = \frac{1}{T_{resp}}$$

with

$$\alpha(t) = \text{frac}(\epsilon(t))$$

where the function “fractional part” [frac($\epsilon$)] resets the variable $\alpha(t)$ to zero as soon as it reaches the value $+1$.

**Regulation Mechanisms**

The description of the cardiovascular control system includes the response of several effectors (peripheral resistances and venous unstressed volumes, both in the splanchic and extraplanchnic vascular beds, heart period, and left and right ventricular contractility) to stimuli coming from arterial baroreceptors and lung stretch receptors. Only in the control of the heart period has the autonomic division between the sympathetic and parasympathetic limbs been considered; the other effectors have been assumed to depend on sympathetic activity only.

The sympathetic regulation mechanisms (peripheral resistances, venous unstressed volumes, end-systolic elastances) include a static sigmoidal relationship in series with a dynamic characteristic. The latter incorporates a pure delay and a first-order low-pass filter. The input to the sigmoid is the weighted sum of the information coming from the two groups of receptors. Arterial baroreceptors are sensitive to systemic arterial pressure, whereas lung stretch receptors respond to changes in lung volume. The following equations hold

$$x_s = G_{dl} \cdot (P_{sa} - P_{sum}) + G_{hl} \cdot (V_L - V_{Ln})$$

where $\theta$ represents the generic effector of the regulation ($V_{sum}, V_{uev}, R_{sp}, R_{ep}, E_{max,rv},$ and $E_{max,lv}$); $P_{sa}$ represents systemic arterial pressure, and $V_i$ is lung volume. $P_{sa, n}$ is systemic arterial pressure basal value, and $V_{Ln}$ is the lung volume at the end of a normal expiratory act. $\tau_i$ and $\Delta_s$ are the time constant and the time delay of the mechanism, and $\sigma_s$ represents the static sigmoidal relationship. $\theta_{max}$ and $\theta_{min}$ in Eq. 5 represent the upper and lower saturation levels of the effector response. The sigmoidal relationships are monotonically increasing as to unstressed volumes ($V_{sum}$ and $V_{uev}$, i.e., one must assume the $+$ sign in Eq. 5) but are monotonically decreasing ($-$ sign in Eq. 5) as to ventricular elastances ($E_{max,lv}$ and $E_{max,rv}$) and peripheral resistances ($R_{sp}$ and $R_{ep}$). The parameter $k_s$ sets the slope at the central point of the sigmoidal relationship ($S_{0}$). The following relationship holds

$$k_s = (\theta_{max} - \theta_{min})/(4 \cdot S_{0})$$

We assumed that in basal conditions the central slope $S_{0}$ is $\pm 1$; in these conditions, parameters $G_{sa, n}$ and $G_{ph}$ in Eq. 4 represent the maximal gain (i.e., the gain at the central point of the sigmoid) of arterial baroreceptors and pulmonary receptors respectively, when the other mechanism is silent. Altering the value of $S_{0}$ (see results in Fig. 8) corresponds to modifying the ability of the effector $\theta$ to respond to sympathetic activity.

In addition, to simulate the action of LF processes (such as humoral and thermal regulation), a random LF noise (with spectral contents approximately in the band 0–0.12 Hz) has been superimposed on the extraplanchnic peripheral resistance ($R_{ep}$). Hence, we can write

$$R_{ep}(t) = R_{ep, con}(t) + A \cdot R_{rand}(t)$$

where $R_{ep, con}$ is the controlled parameter resulting from Eqs. 4–6, whereas $R_{rand}$ represents a uniformly distributed random noise, ranging between $-1$ and $+1$. Hence, the multiplicative factor $A$ sets the amplitude of the superimposed noise.

The control of the heart period is different from the other controls because it involves a balance between the sympathetic and vagal activities. Hence, for each group of receptors, we used two different gain values, which reproduce the different impact of the reflex on the sympathetic and vagal control, respectively; moreover, we introduced two distinct dynamics, which account for the different temporal response of heart period to vagal and sympathetic stimulation. The equations for the heart period control are

$$v_T = G_{sv} \cdot (P_{sa} - P_{sum}) - G_{pv} \cdot (V_L - V_{Ln})$$

$$s_T = G_{sv} \cdot (P_{sa} - P_{sum}) + G_{pv} \cdot (V_L - V_{Ln})$$

$$\frac{dx_T(t)}{dt} = \frac{1}{\tau_s} \cdot [v_T(t - D_s) - x_T(t)]$$

$$\frac{dx_T(t)}{dt} = \frac{1}{\tau_s} \cdot [s_T(t - D_s) - x_T(t)]$$

$$T = T_{min} + T_{max} \cdot e^{\gamma_T x_T}$$

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where the meaning of symbols is analogous to Eqs. 4–6, the subscripts s and v denote sympathetic and vagal control, respectively, and \( k_F = (T_{\text{max}} - T_{\text{min}})/(4 \cdot \sigma_T) \). \( \sigma_T \) is the slope of the sigmoidal curve at its central point, and it is equal to +1 in basal conditions. An alteration of this value (Fig. 8, C and D) modifies the sensitivity of the sinus node to both sympathetic and vagal stimulation.

Finally, lung volume \( V_L \), which is the input stimulus for lung stretch receptors, is computed (in liters) from intrathoracic pressure \( P_{\text{thor}} \) by the following equation

\[
V_L = 1.9 - 0.1 \cdot P_{\text{thor}} \quad (A15)
\]

Hence, during the respiratory cycle, \( V_L \) ranges between 2.3 liters (which is the value at the end of expiration) and 2.8 liters (which is the value at the end of inspiration) (34, 49).

REFERENCES


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