A mathematical model of the interaction between arterial and cardiopulmonary baroreceptors during acute cardiovascular stress

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Abstract

A mathematical model of some mechanisms involved in the short term arterial pressure control is described. The model considers two main baroreceptor systems (arterial and cardiopulmonary), the pressure-volume characteristics of the systemic and pulmonary circulations, their hydraulic resistances, and the dependence of cardiac output on afterload and preload. In this work, the possible role of cardiopulmonary baroreceptors, and their interaction with the arterial baroreceptors is investigated during mild haemorrhage or lower body negative pressure (LBNP). Model simulations suggest that the cardiopulmonary baroreflex control acting on systemic resistance and venous unstressed volume plays a pivotal role in buffering mild changes in blood volume, whereas its role becomes progressively less important during more severe volume displacements.

1 Introduction

The existence of low-pressure baroreceptors, located in the heart and the lungs, has been known for more than one century (see Mark and Mancia [1] for a review). Nevertheless, the physiological significance of these receptors, and their possible involvement in the regulation of the cardiovascular system has been receiving adequate attention only in recent years. There is now strong evidence that the cardiopulmonary receptors in humans may cause reflex vasoconstriction, and an increase in total systemic resistance during moderate lower body negative pressure or mild non-hypotensive haemorrhage [1]. Both perturbations do not provoke evident changes in systemic arterial pressure, hence cannot trigger sino-aortic baroreceptors located in arterial vessels. Furthermore, Price et al. [2] indicated that moderate haemorrhage may decrease splanchnic capacity in humans in the absence of significant arterial pressure
reduction, thus suggesting a possible involvement of cardiopulmonary receptors in the control of systemic veins.

The previous results indicate that the role of the baroreflex system during blood volume perturbations cannot be properly understood without considering the complex interactions between different groups of receptors, some located in the arteries others in the veins, which simultaneously participate to the short term cardiovascular control.

Aim of this work is to develop a mathematical model of the systemic and pulmonary circulations in humans, which incorporates the control actions exerted by two distinct baroreflex systems: the sino-aortic baroreceptor-neuroeffector system [3], and the low-pressure receptor reflex [1]. With this model, the author analyses the possible role of the cardiopulmonary baroreceptors during lower body negative pressure manoeuvres or mild haemorrhage. Model applications to other physiological and clinical problems are then pointed out and discussed.

2 Qualitative model description

According to the electric analogue of Fig. 1, the cardiovascular system is described by the series arrangement of six distinct compartments, which reproduce pressure losses and blood volume storage in the systemic arteries, the systemic veins and the right atrium (systemic circulation), and in the pulmonary arteries, the pulmonary veins and the left atrium (pulmonary circulation). The capacity of each compartment includes the unstressed volume (i.e., the blood volume contained at zero pressure) and the stressed or filling volume. The latter quantity is equal to the product of transmural pressure and compliance. Cardiac outputs from the left and right ventricles depend both on the upstream atrial pressure (preload) and on the downstream arterial pressure (afterload). The first dependence reproduces the well-known Frank-Starling mechanism for the heart.

Several different feedback mechanisms work on the cardiovascular system to regulate systemic arterial pressure and cardiac output. A block diagram describing the main relationships between hemodynamic quantities and feedback regulatory actions is shown in Fig. 2. The sino-aortic baroreflex is assumed to operate by modifying systemic arterial resistance, systemic venous compliance and unstressed volume, and heart frequency. While the first three mechanisms are mainly mediated by the sympathetic system, the latter is determined by a balance between the inhibitory effect of the vagus nerve, and the excitatory effect of the sympathetic nerves (sympatho-vagal balance [4]).

According to various experimental results (most summarised in [1]) we assumed that the cardiopulmonary low-pressure baroreflex significantly modulates systemic arterial resistance, whereas it probably plays little or no physiological role in the control of heart rate in humans. A controversial problem concerns the role of the cardiopulmonary baroreflex in the control of systemic veins. Two distinct cases are then considered in this work. In the first, we assumed that low-pressure receptors act merely on peripheral arteries, hence
on systemic arterial resistance. In the second, a significant control on systemic venous unstressed volume was also hypothesised. The latter assumption agrees with the observations by Price et al. [2].

![Diagram of the cardiovascular system](image)

**Figure 1 - Electric analogue of the cardiovascular system.** $R_{sa}$, $R_{sv}$, $R_{pa}$, and $R_{pv}$: hydraulic resistances of systemic arteries, systemic veins, pulmonary arteries and pulmonary veins, respectively. $C_{sa}$, $C_{sv}$, $C_{pa}$, and $C_{pv}$: compliances of the same compartments; $p_{sa}$, $p_{sv}$, $p_{pa}$, and $p_{pv}$: intravascular pressures of the same compartments; $p_{la}$ and $p_{ra}$: left and right atrial pressures; $C_{la}$, $C_{ra}$: compliances of the left and right atrium; $q_l$ and $q_r$: cardiac output from the left and right ventricles; $C_{low}$: venous compliance of the lower extremities; LBNP: negative pressure applied externally to the lower extremities.

The dynamics of the feedback mechanisms have been described by means of first order transfer functions with a pure delay. The static characteristics have a sigmoidal shape, i.e. they exhibit lower threshold and upper saturation. When two different feedback mechanisms work on the same effector simultaneously (this is the case of the simpatho-vagal balance on heart rate, and of the interaction between the arterial and cardiopulmonary reflexes on systemic arterial resistance and on systemic venous unstressed volume, see Fig. 2) we assumed that the two actions are linearly summed, and then flattened by the sigmoidal characteristic of the effector. Furthermore, according to physiological textbooks [4], we assumed that the vagal and sympathetic control on heart rate are characterised by different thresholds, the first mechanism working at higher pressure levels, and the second when pressure is decreased.

Parameters in the model have been taken with reference to the normal male whenever clinical data were available (see [5]), whereas data drawn from animal experiments were used to better characterise feedback regulatory actions ([3, 4, 5 and 6]).
Fig. 2 - Block diagram of the main relationships between hemodynamic and regulatory quantities.
3 Results

Fig. 3 shows the percentage changes of the main hemodynamic quantities (systemic arterial pressure, cardiac output, total systemic resistance and heart frequency) computed with the model in the steady state conditions following various lower body negative pressure manoeuvres of increasing severity. In performing these simulations we assumed that venous compliance of the lower extremities is about 1/12 of the entire venous systemic compliance (see also Fig. 1). Three distinct simulations have been performed for each level of lower body negative pressure. In the first we assumed that only the arterial baroreflex works on the cardiovascular system, whereas the low-pressure reflex does not play any significant functional role. In the second it is hypothesised that, beside the arterial baroreflex, the cardiopulmonary reflex also works on systemic arterial resistance, but its effect in the control of venous unstressed volume is negligible. Finally, the third simulations concern the case in which low-pressure baroreceptors participate to the control both of the arterial and venous systemic circulations. Of course, the three simulations have been mathematically characterised by using different values for the strength of the cardiopulmonary feedback mechanisms.

Figure 3 - Pattern of the main hemodynamic quantities computed with the model in the steady state conditions following different lower body negative pressure manoeuvres. *: absence of the cardiopulmonary reflex (i.e., only the arterial baroreflex is working); +: cardiopulmonary reflex working only on systemic arterial resistance beside the arterial reflex; o: cardiopulmonary reflex working both on systemic resistance and systemic venous unstressed volume. Continuous lines represent experimental results from [1].
As is clear from Fig. 3, the action of the arterial baroreflex alone cannot explain the excellent maintenance of arterial pressure which is observed in humans during moderate lower body negative pressure. Furthermore, inclusion of a low-pressure reflex working only on systemic arterial resistance results just in a modest improvement of the arterial pressure control. In this condition one can observe a sharp increase in total systemic resistance well above the one observed experimentally. However, the high value of systemic resistance, coupled with a reduction in mean circulatory filling pressure, causes a dramatic fall in cardiac outflow, which prevents adequate arterial pressure restoration.

The role of the cardiopulmonary baroreflex becomes much more relevant if one assumes that this system works not only on systemic arteries, but also on systemic veins. Vasoconstriction of the venous segments, in fact, allows maintenance of an adequate filling pressure for the heart, thus resulting in consistent values of cardiac output and in almost perfect restoration of the systemic arterial pressure level. In this condition, heart frequency remains close to the basal level during mild LBNP, when action of the cardiopulmonary reflex dominates, but it starts rising significantly when the level of LBNP overcomes -30 to -40 mmHg. In this range, the arterial baroreflex becomes the main responsible of the regulation.

Figure 4 - Time pattern of systemic arterial pressure simulated with the model following a 3% haemorrhage accomplished between the instants 2s and 7s. Dotted line: absence of the cardiopulmonary reflex (i.e., only the arterial baroreflex is working); continuous line: cardiopulmonary reflex working both on systemic arteries and systemic veins. The basal level is indicated by the point-dotted line.
Fig. 4 shows the time pattern of systemic arterial pressure, simulated with the model after a 3% haemorrhage accomplished between the instants 2s and 7s. As is clear from this figure, the cardiopulmonary baroreflex plays a pivotal role in maintaining a normal arterial pressure level following mild haemorrhage. An interesting aspect of these simulations is that the time pattern of arterial pressure exhibits an overshoot in the first minute after the perturbation. Indeed, an increase in arterial pressure above normal in the early phase following modest blood losses is often reported in the literature (see, among the others, Fig. 2 in Mark and Mancia [1]). Other simulations, not reported here for the sake of brevity, suggest that the role of the cardiopulmonary reflex becomes progressively less important after a severe haemorrhage (10-15% removal of the total blood volume). In the latter conditions, the arterial baroreflex appears as the main responsible of the regulation, even though a certain contribution of the cardiopulmonary reflex is still evident.

4 Final Remarks

The present model constitutes a first attempt to investigate the importance of the cardiopulmonary vs. the arterial baroreflex, and to ascertain the complex interactions between these two regulatory systems in the short term arterial pressure control. Although the involvement of the low-pressure reflex in the regulatory response has been stressed by several authors recently, and it is thought to have significant clinical implications, we are not aware of any theoretical investigation on this subject based on mathematical models and automatic control theory.

The most important result of the present study is that action of the cardiopulmonary reflex on systemic arterial resistance can contribute significantly to the arterial pressure control only if it is paralleled by a concomitant action on venous unstressed volume. In the absence of the latter mechanism, cardiac output falls dramatically, which prevents restoration of a normal arterial pressure level. This result stresses that the relationships among hemodynamic quantities may be very complex, and that proper regulation can be achieved only by a fine balance among various synergical and antagonistic actions working simultaneously. In this regard, mathematical modelling may contribute significantly to clarify the importance and the intrinsic limitations of the various feedback mechanisms operating on the cardiovascular system, to point out their reciprocal influences, and may suggest lines for future physiological and clinical investigations.

Although the agreement between model and clinical data is rather good, one can observe that the model underestimates the excellent arterial pressure control evident in human subjects during mild LBNP (Fig. 3). A possible explanation for this discrepancy is that the model is intended to reproduce cardiovascular dynamics only in the very short period (less than 60-100 s) following acute blood volume perturbations. After a longer period, other biomechanical factors not included in the model (such as creep relaxation in the
arterial wall, and especially fluid exchange across capillaries) are put into action and contribute significantly to the arterial pressure restoration. The experimental results shown in Fig. 3 were obtained at a few minutes from the manoeuvres, hence they were probably influenced not only by active reflex adjustments, but also by passive fluid exchange across the capillary wall with slower dynamics.

Looking at the simulated time pattern of arterial pressure (see Fig. 4) one can observe that action of the cardiopulmonary baroreflex provides a perfect restoration of the arterial pressure level between 20 and 40 seconds from the perturbation. After that period, capillary fluid exchange becomes an important homeostatic mechanism. We can thus speculate that the synergical temporal superimposition of the cardiopulmonary reflex and of capillary fluid shift may warrant a constant arterial pressure level in humans for several minutes following mild blood volume changes, without a significant involvement of the arterial baroreflex. Baroreceptors in the carotid sinus and the aortic arch may become important only for blood volume losses exceeding a certain threshold.

In this work the model has been used to analyse clinical phenomena such as lower body negative pressure or mild haemorrhage. Of course, the model can also be used to study other and more severe perturbations of the cardiovascular system, often employed in physiological experiments. Among the perturbations which can be analysed, mention must be made to peripheral vasodilation, heart pacing, occlusion of systemic veins. In all these cases, significant qualitative agreement between model and experimental results has been tested.

References


