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Short-term autonomic control of the cardio-respiratory system: a summary with the help of a comprehensive mathematical model

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***Abstract*—The system which provides short-term cardiovascular regulation has a very complex structure, resulting from the non-linear interaction among several different mechanisms: they include baroreceptors, peripheral chemoreceptors, lung-stretch receptors, a direct CNS response to hypoxia and hypercapnia, local vessel response to changes in blood gas content. Furthermore, during dynamic exercise a feedforward mechanism anticipates cardiovascular requirements, and interacts with the respiratory and muscle pumps. Aim of this work is to summarize the complexity of this system, and to point out the role of individual mechanisms and their mutual relations, with the help of a comprehensive mathematical model developed by the authors in previous years. Examples of system response are discussed during various acute cardiovascular perturbations (pressure changes, changes in blood gas content, dynamic exercise) and model results compared with existing data in the literature. These examples emphasize the great complexity, richness and variability of the autonomic cardiovascular control system. Simulations suggest that mathematical models and computer simulation techniques may represent essential tools to comprehend and deepen our understanding of complex, multifactorial systems, the behaviour of which cannot be fully revealed by simple qualitative analysis. Models play an important role in modern physiology as a repository of knowledge and to integrate disparate data inside an integrative coherent structure.**

I. Introduction

Aim of this Review work, is to describe the main aspects of a short term cardiovascular regulation model, that we developed in recent years [1]-[5], laying emphasis on the interaction among the different mechanisms which participate in the control of the cardiovascular system under various acute perturbations. First, we will start with a description of the baroreflex control, which is ubiquitously present and modulates all other control actions. Then, we will move to the control of the blood gas content, describing the main interactions that take place during changes in oxygen and CO_2 concentration. Finally, some hypotheses will be formulated on the cardiovascular control during dynamic aerobic exercise, and their consequences tested with the mathematical model.

II. The Controlled System

Throughout the present work, we will use a simplified hydraulic model of the cardiovascular system, depicted in Fig. 1. With the terminology of the automatic control theory, this model represents the system under control, or "plant", i.e., the system on which the regulatory actions take place.

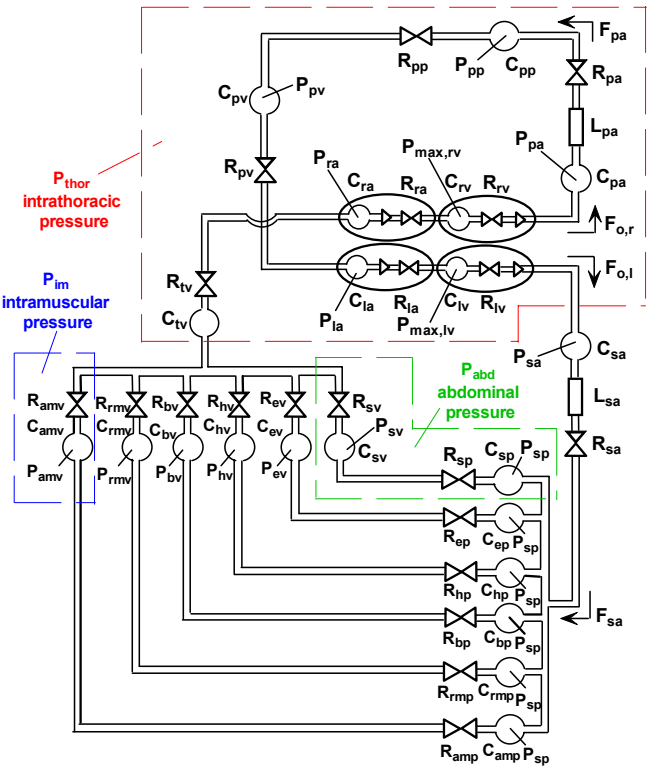

Fig. 1. Hydraulic analog of the overall circulation, used in the present model (see [2], [5] for the meaning of symbols).

As it is clear from Fig. 1, the model includes the two pulsatile cardiac chambers, the pulmonary circulation and the systemic circulation. The latter is subdivided into five distinct districts arranged in parallel (brain, coronary, skeletal muscle (further divided in exercising and resting muscles), splanchnic and the remaining extrasplanchnic vascular beds). This distinction is necessary since, as it will be described below, autonomic and local regulatory factors exert a different action on each compartment. According to Fig. 1, the different compartments include hemodynamics in the large arteries (systemic and pulmonary), the peripheral circulation, and the venous circulation. Three main kinds of lumped parameters are used in building the model: inertances, which account for inertial forces in blood (these are relevant in large arteries only); resistances, which account for pressure energy losses (this parameter is especially important in the peripheral circulation) and capacities, which represent the blood volume stored in each

compartment (this parameter is especially relevant in the venous circulation). Volume, in turn, is divided in an unstressed volume, which does not stretch the vessel wall, and a stressed volume (which causes stress in the wall, hence is associated with the increase in internal pressure). Finally, the pulmonary circulation is subjected to an extravascular pressure equal to the thoracic pressure (which oscillates with respiration), the splanchnic circulation is subjected to the abdominal pressure (oscillating with the respiratory period too) and the exercising muscles are subjected to intramuscular pressure (caused by rhythmic muscle contraction) The reader can find more details in former publications [1]-[5].

Short term regulatory actions work by modifying several parameters of the plant: the peripheral resistances and unstressed venous volumes in several vascular beds, heart contractility and heart period. It is well established that the autonomic neural system modulates the previous parameters via the action of two major efferent neural branches, i.e., the sympthoadrenergic and the vagal. Moreover, resistances are also modulated by local metabolic factors.

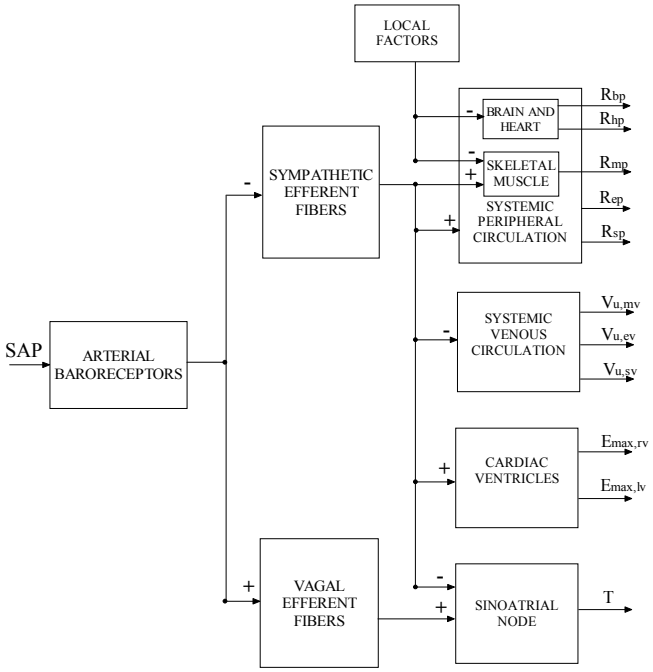

Fig. 2. Block diagram describing the relationships among afferent baroreceptor activity, efferent sympathetic and vagal activities and effector responses (see [2]).

A simple block diagram which summarizes the efferent portion of the autonomic cardiovascular control is depicted in the right part of Fig. 2. As it is shown in this figure, vagal stimulation rises heart period. Sympathetic stimulation causes vasoconstriction in arterioles and veins (thus increasing peripheral resistances and decreasing venous volumes), raises heart contractility, and induces cardioacceleration (i.e., it lowers heart period). However, as depicted in Fig. 2, not all vascular districts in the systemic circulation are equally affected by the sympathetic drive. Just some vascular beds (such as the splanchnic circulation, the skeletal muscle circulation and circulation in a few other extrasplanchnic districts, such as the renal one) are greatly sensitive to sympathetic stimulation. Conversely, other vascular beds (especially the cerebral and coronary circulation, which must warrant sufficient oxygen delivery to preserve vital functions) are largely independent of the autonomic control mechanism, and predominantly obeys to local factors (such as the actual correspondence between oxygen delivery, CO_2 removal and tissue oxygen consumption rate).

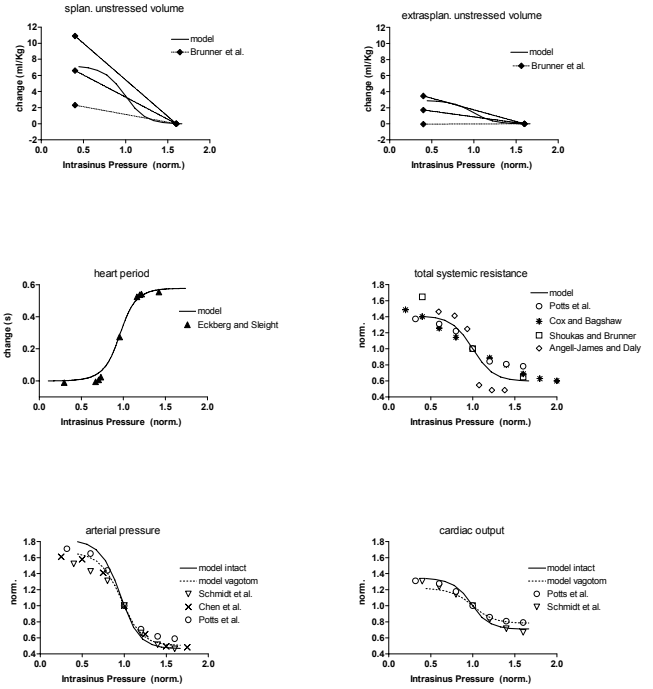

Fig. 3. Summary of arterial baroreflex response, simulated with the model, in open loop conditions.

III. THE ARTERIAL BAROREFLEX

Let us first consider a perturbation which modifies hemodynamic quantities (such as pressures, blood flows and volumes) without evident alterations in blood gas composition and metabolism. This may be the case of a dramatic perturbation, such as hemorrhage, but also of a common maneuver in human life, i.e., posture change. The main afferent information that is put into action in this case originates from the so-called arterial baroreceptors, which are located in the carotid sinuses and the aortic arch [6]. These receptors are sensitive to the mean value and the pulsating component of systemic arterial pressure, and send this information to the autonomic centres (especially located in the nucleus of tractus solitarius) via the sinus nerve and the vagus, respectively. The autonomic centres, in turn, respond to an increase in afferent activity from arterial baroreceptors with a withdrawal of sympathetic activity and an increase in vagal activity, in an effort to restore more

adequate arterial pressure levels. The resulting overall feedback loop is illustrated in Fig. 2. In our model, the afferent pathway from the baroreceptors to the central neural system (first block in Fig. 2) has been described using a linear dynamical block, which amplifies the first harmonics of the sphygmic wave in series with a sigmoid relationship, with upper and lower saturation. The effect of the efferent (sympathetic and vagal) branches on the effectors has been described via first order dynamical equations with a pure delay in series with a logarithmic relationship (which accounts for the progressive exhaustion of the effector response). An example of model behaviour in open loop conditions, compared with experimental data (see [1] for the references), is depicted in Fig. 3.

IV. Regulation to Changes in Blood Gas Content

The block diagram in Fig. 2 becomes quite more complex if we consider alternative perturbations, characterized by a change in the gas content of the arterial blood. The autonomic regulation response activated by alterations in arterial O_2 and CO_2 content, in fact, embraces many different mechanisms, which superimpose their actions in intricate ways, giving rise to synergical and antagonistic effects (see Fig. 4).

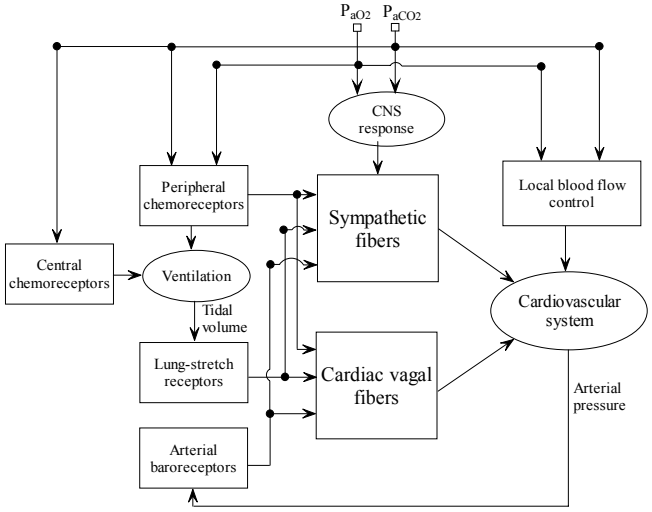

Fig. 4. Block diagram describing the interactions among arterial oxygen and CO_2 content in blood, and the different autonomic and local regulatory actions.

First, changes in O_2 or CO_2 blood content modify the activity of peripheral chemoreceptors, mainly located in the aortich arch and carotid body [7]. The arterial chemoreceptor response has also been mimicked with the series arrangement of a dynamical block and a static non-linear characteristic. The static curve relating chemoreceptor activity to arterial PO_2 during normocapnia exhibits an hyperbolic trend with an upper saturation level [8]. The static relationship linking chemoreceptor activity to CO_2 tension during normoxia exhibits a lower threshold and a monotonic increase [9]. Finally, experimental results demonstrate that hypoxia reinforces the chemoreceptor response to hypercapnia, and viceversa [9]; this behavior involves a multiplicative relationship between the individual oxygen and CO_2 static curves and a progressive shift of the lower threshold to the left during hypoxia.

The information from the arterial chemoreceptors has important effects on the autonomic regulation of cardiovascular function. First, it causes excitation of efferent sympathetic nerves directed to peripheral vessels, thus inducing vasoconstriction in arterioles and veins in the splanchnic, skeletal muscle and other extrasplanchnic vascular beds (with exception of the coronary and brain circulation), and a consequent increase in total systemic resistance and a decrease in venous volume [10]. These adjustments, of course, aim at augmenting systemic arterial pressure and favour ventricle filling, hence cardiac outflow. Moreover, further physiological data suggest that chemoreceptor activation induces a decrease in heart rate, mainly via an increase in vagal activity [10].

The former description of the chemoreflex, however, does not exhaust the complexity of the entire short-term control during changes in blood gas content. At least other three important mechanisms have to be considered.

First, activation of arterial chemoreceptors has not only important effects on cardiovascular parameters (vasoconstriction, bradycardia) but also induces a large increase in ventilation [11]. The increase in ventilation is further accentuated by the action of central chemoreceptors [11], located in the "medulla oblongata", and mainly sensitive to changes in CO_2 of the brain. The consequent ventilation increase, in turn, stimulates pulmonary stretch receptors located in the lungs: their effect on the cardiovascular system is an increase in heart rate (especially via vagal withdrawal) and a vasodilation in sympathetically-regulated vascular beds (via sympathetic inhibition) [12]. Furthermore, CO_2 and O_2 have also a direct excitatory effect on the autonomic centres: superfusion of the brain with hypercapnic fluid causes a sympathetically mediated increase in heart rate and causes vasoconstriction in peripheral vessels [13]. Hypoxia of the central neural system induces a strong sympathetic activation [14]. This mechanism represents a sort of extreme defence of the brain against neural death.

Finally, O_2 and CO_2 changes have also a local effect on some peripheral vascular beds, especially on the brain, coronary and skeletal muscle circulation. In particular, strong hypoxia may induce a threefold increase in cerebral and coronary blood flow [15]. Hypercapnia may rise cerebral blood flow up to twofold the normal [15].

All these aspects have been included in our comprehensive model, and the overall effect on cardiovascular parameters and ventilation tested during different perturbations which affect oxygen and CO_2 content in blood: normocapnic hypoxia (i.e., hypoxia at constant

CO_2) , hypercapnic hypoxia (asphyxia) , hypocapnic hypoxia (i.e., hypoxia of aviators). In all cases a good agreement between model and real data has been verified (see [4] for more details and results). Examples of the percentage changes in cardiovascular quantities during hypocapnic hypoxia and asphyxia are shown in Fig. 5 vs. existing data.

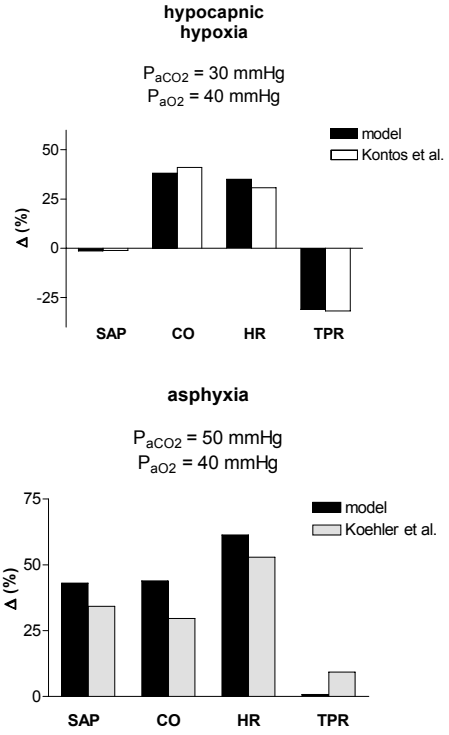

Fig. 5. Percentage changes in mean systemic arterial pressure, cardiac output, heart rate and total peripheral resistance simulated with the model in response to hypocapnic hypoxia and asphyxia, and compared with eperimental data [14], [16].

V. Regulation to Aerobic Exercise

During exercise, other local mechanisms are activated and must be taken into account to have a proper description of systemic hemodynamics.

First, one can observe a massive vasodilation and a consequent dramatic increase in blood flow in exercising muscles [17]. This is mainly a consequence of two local phenomena: accumulation of vasodilator metabolites (such as adenosine, potassium, etc..) in the perivascular space of the organs under exercise, and local tissue hypoxia. The latter phenomenon is a consequence of the increased oxygen extraction from blood, which abates mean O_2 concentration in the tissue and in the venous blood. Both metabolite accumulation and local tissue hypoxia relax vascular smooth muscle, thus explaining the enormous fall in local resistance.

Furthermore, during dynamic exercise cardiac output is improved by action of the so called "muscle pump" and "respiratory pump" [17]. These terms signify that the intermittent changes in extravascular pressure, occurring in the active skeletal muscle and in the intrathoracic circulations during exercise (as a consequence of muscle contractions and of the hyperpnoea, respectively), improve venous outflow through a periodic squeezing and refilling of the veins. This feature, in turn, may favour venous return to the heart, thus enhancing cardiac filling and cardiac output.

The previous local mechanisms, however, are unable to explain the entire cardiovascular response to exercise: heart rate augmentation, vasoconstriction in non-exercising vascular beds (splanchnic, renal,…) and hyperpnoea (i.e., the increase in tidal volume and respiratory rate). These changes require the active participation of autonomic neural mechanisms. Moreover, this autonomic regulation cannot be ascribed to the action of peripheral chemoreceptors, since (at least during aerobic exercise) gas content in blood remains quite constant, nor to the baroreflex (since the increase in arterial pressure during exercise causes the baroreflex to antagonize the increase in heart rate and vasoconstriction).

Two main hypotheses can be found in the literature to justify autonomic changes occurring during dynamic aerobic exercise [17]. A first hypothesis suggests that cardiorespiratory variations during exercise are caused by a reflex (based on mechanoreceptors or chemoreceptors) located in the contracting skeletal muscle. Other studies propose the so-called "central command" hypothesis: this assumes that the same motor impulses from the cerebral cortex, which initiate movement, are also sent to cardio-respiratory control centres in the medulla, thus causing a reconfiguration of autonomic control. We examined the possibility that cardiorespiratory autonomic adjustments during dynamic aerobic exercise can be entirely explained assuming a central command reconfiguration of the efferent (sympathetic and vagal) activities (quantitative details on how this hypothesis is implemented can be found in our previous works [5]). Using appropriate patterns for the central command reconfiguration of autonomic control, the model furnishes the percentage changes of cardiovascular and respiratory quantities shown in Fig. 6. The agreement between model predictions and real data [18]-[20] is satisfactory in the overall range of aerobic exercise .

VI. Discussion

In the present work we summarized the main aspects of the short-term cardiovascular regulation, by using results obtained with a comprehensive mathematical model developed by us in a series of recent papers. Our analysis emphasizes the plethora of different factors involved in the regulation, their mutual non-linear relationships, and the complex interactions (sometimes synergical, sometimes antagonistic) which characterize natural control systems.

Different scenarios may emerge from model simulations, even in response to apparent similar perturbations, just as a consequence of the prevalence of one or another of the different factors involved. We claim that mathematical models and computer simulation techniques may represent

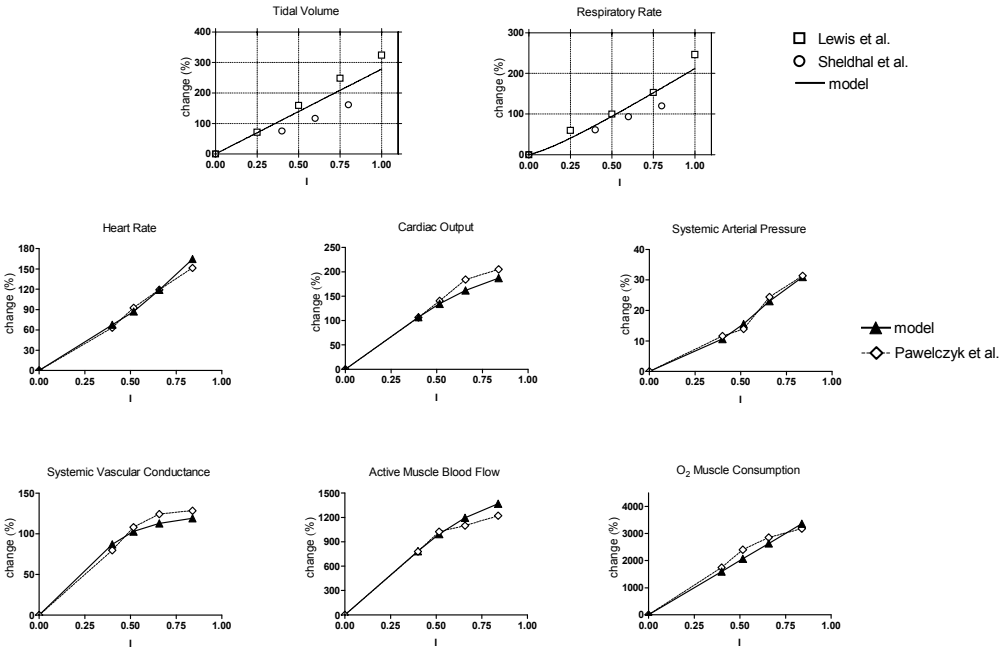

Fig. 6. Percentage changes of some hemodynamic quantities at different levels of aerobic dynamic esercise (I = 0: resting; I = 1: maximum aerobic effort): comparison between model simulation (continuous line) and experimental data [18]-[20].

essential tools to comprehend and deepen our understanding of such complex, multifactorial systems, the behaviour of which cannot be fully revealed by simple qualitative analysis. Furthermore, these models represent excellent repository for the present knowledge: they may play a fundamental role towards a synthesis of multidisciplinary expertise, are instrument to test new hypotheses, and a way to integrate new data inside an integrative coherent structure.

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