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RESEARCH ARTICLE

Frank–Starling mechanism and short-term adjustment of cardiac flow

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ABSTRACT

The Frank–Starling law of the heart is a filling–force mechanism (FFm), a positive relationship between the distension of a ventricular chamber and its force of ejection, and such a mechanism is found across all the studied vertebrate lineages. The functioning of the cardiovascular system is usually described by means of the cardiac and vascular functions, the former related to the contractility of the heart and the latter related to the afterload imposed on the ventricle. The crossing of these functions is the so-called 'operation point', and the FFm is supposed to play a stabilizing role for the short-term variations in the working of the system. In the present study, we analyze whether the FFm is truly responsible for such a stability within two different settings: one-ventricle and two-ventricle hearts. To approach the query, we linearized the region around an arbitrary operation point and put forward a dynamical system of differential equations to describe the relationship among volumes in face of blood flows governed by pressure differences between compartments. Our results show that the FFm is not necessary to give stability to an operation point. Thus, which forces selected and maintained such a mechanism in all vertebrates? The present results indicate three different and complementary roles for the FFm: (1) it decreases the demands of a central controlling system over the circulatory system; (2) it smooths out perturbations in volumes; and (3) it guarantees faster transitions between operation points, i.e. it allows for rapid changes in cardiac output.

KEY WORDS: Cardiovascular system, Dynamical system, Filling–force mechanism, Frank–Starling law, Heart, Stability analysis

INTRODUCTION

The Frank–Starling law, or heart law, has a long history, and Starling himself is not its main discoverer: indeed, the length–tension relationship from which it is derived was known at the beginning of 1830 (Katz, 2002). The Frank–Starling law is a relationship between the filling of a ventricle and the force of contraction it develops (e.g. Holubarsch et al., 1996). In this way, it is also known as the heart filling–force relationship (Katz, 2002; Saks et al., 2006). Despite the fact that many fishes regulate cardiac output mainly by changes in stroke volume, whereas mammals and birds control it mainly by heart rate, the filling–force mechanism (FFm) is found across all vertebrate classes (Shiels and White, 2008).

The relationship between cardiac muscle fiber length and force resembles the same relationship that occurs in skeletal muscles. However, the steepness of the curve obtained for the heart suggests that, beyond myofilament overlapping, there should be other mechanisms involved in the phenomenon. At the cellular level, the still-unknown mechanism is the length-dependent activation (Solaro, 2007) [also known as stretch-activation/calcium-activation (Campbell and Chandra, 2006)], and, indeed, a calcium-activation process is fundamental for the increase in force due to an increase in length (e.g. Moss and Fitzsimons, 2002; Niederer and Smith, 2009; Saks et al., 2004). Be that as it may, it is important to note that the FFm is inherent to the heart cells themselves, without the participation of extrinsic, such as neural or hormonal, controls. As stated in the opening of the review by Shiels and White (Shiels and White, 2008), 'The Frank–Starling mechanism is an intrinsic property of all vertebrate cardiac tissue'.

Guyton and co-workers conceived an invaluable static approach to address the functioning of the cardiovascular system (e.g. Guyton et al., 1957). We qualitatively illustrate this approach in Fig. 1A, where the abscissa axis is the central venous pressure and the ordinate axis is the cardiac output. Two linearized curves are shown: the cardiac function (the ascending one) and the vascular function (the descending one).

The cardiac function ultimately represents the FFm discussed above, because an increase in central venous pressure would elicit an increase in ventricular volume during the diastolic phase of the cardiac cycle, which, in turn, would increase the contraction force, resulting in increased cardiac output. The vascular curve is, in fact, plotted the other way around to as it is truly obtained (the experimental procedure is to cause changes in flow and measure the resulting pressure), and represents the relationship between central venous pressure and blood flow (for details and insightful discussions of this subject, see Brengelmann, 2003 and Levy and Pappano, 2007). The crossing of the two curves is the so-called 'operation point' (OP) of the cardiovascular system.

Now, many textbooks and papers consider, implicitly or explicitly, the OP as a stable equilibrium point, and that the FFm is responsible for such a stability. Let us give some examples: '… [OP] represent the stable values of cardiac output and central venous pressure at which the system tends to operate. Any perturbation … institutes a sequence of changes in cardiac output and venous pressure that restore these variables to their equilibrium values' (Levy and Pappano, 2007, p. 187); '[Frank–Starling mechanism] … applies in particular to the coordination of the output of the two ventricles. Because the ventricles beat at the same rate, the output of the two can be matched only by adjustments of the stroke volume' (Antoni, 1996, p. 1814); 'The heart maintains

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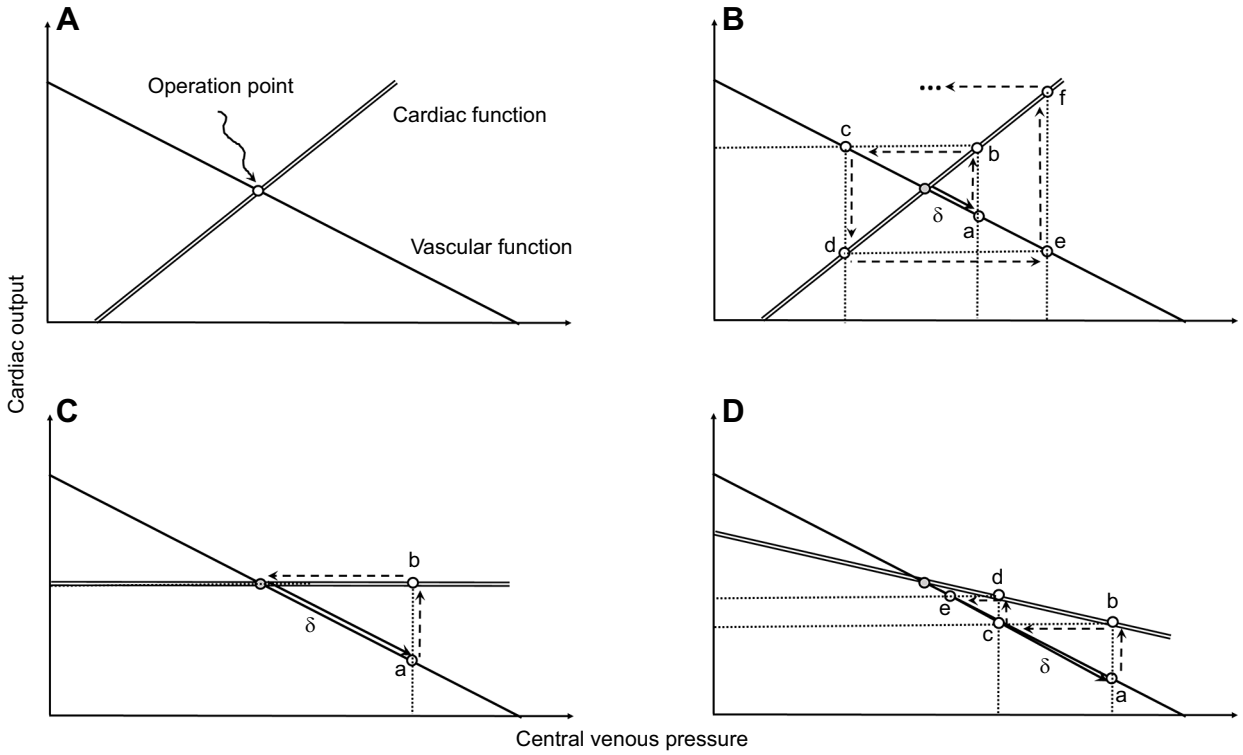

Fig. 1. Cardiovascular operation point (OP). (A) Usual (linearized) representation of the cardiac (double line) and vascular (single line) functions resulting in an OP of the heart. (B–D) Pictorial representations of putative trajectories of the system after an arbitrary perturbation under different scenarios of the cardiac function (the paths are only for illustrative purposes and based on a cobwebbing approach of discrete dynamical systems). The perturbation is indicated by the solid arrow (δ), and leaves the system at point a. Such a point corresponds to a certain central venous pressure (vertical dotted line) that, in turn, corresponds to a cardiac output over the cardiac function line (horizontal dotted line; point b). This cardiac output results in another central venous pressure to the vascular function (point c), and so forth. The dashed arrows indicate the time evolution of the system after the perturbation. (B) Here, the cardiac function is the one expected due to the filling–force mechanism (FFm). (C) Here, the cardiac function is independent of the central venous pressure. (D) Here, the cardiac function works in the opposite way as the FFm: it decreases as the central venous pressure increases. From the plots, one would be tempted to conclude that the usual FFm would render the system unstable (notice that, in B, after the perturbation the system does not return to the previous OP), whereas its absence brings stability. However, as we explain in the text, this diagram cannot be employed to draw conclusions in regard of the stability of the OP because it is not the true phase space of the system and, thus, has no vector field of temporal evolution associated to it (see Fig. 3).

normal blood circulation under a wide range of workloads, a function governed by the Frank–Starling law' (Saks et al., 2006); 'This important functional property of the heart supplies an essential regulatory mechanism by which cardiac output is intrinsically optimized relative to demand' (Asnes et al., 2006). Besides these citations, many others, one way or another, consider the OP as a stable equilibrium point owing to the FFm (e.g. Fuchs and Smith, 2001; Moss and Fitzsimons, 2002; Niederer et al., 2011).

As we see from the above-mentioned literature, students and physicians are led to consider the FFm as giving stability to the system. However, if we take the (apparent) stability of the cardiovascular system as *prima facie* evidence of the (supposed) stability generated by the FFm, we risk ourselves falling into a circular reasoning. Actually, the OP could well be a neutral equilibrium point or, even worse, an unstable node or focus, all compatible with the curves that describe the OP (see Fig. 1B–D as examples). In effect, during undergraduate and graduate disciplines, one of us (J.G.C.-B.) has been troubled by trying to explain the stability of the OP from the vascular and cardiac curves. If one examines with care the diagram in Fig. 1B, a perturbation in the OP would not be dampened in the following cycle(s) but instead would be amplified.

Why does this occur? It occurs because the OP diagram is not a diagram concerning the dynamical phase space of the variables. It shows a static two-dimensional (2D) relationship between a pair of variables that belong to a higher dimensional space: the curves are somehow projections of the null-clines of the whole system (note: in the case of one-ventricle hearts, as discussed later, the OP diagram is a construct from a lower dimensional space, but this is not really important here).

In plain English, the OP diagram does not, and cannot, reveal how changes in one variable (say, left cardiac output) alters the other (say, central pulmonary venous pressure) because there are missing variables. If the vascular curve refers to the vena cava, then the cardiac curve should be for the right ventricle. If the vascular curve refers to the pulmonary veins, then the cardiac curve should be for the left ventricle. However, as usually presented, the OP diagram mixes up the two sides of the heart. Once we recognize this, we understand that, for two-ventricle hearts, one needs four dimensions somehow related to the systemic pressure, the right ventricle output, the pulmonary pressure and the left ventricle output (although this obviously prevents a 2D representation). Therefore, there are two OPs: one for the left side and one for the right side of the heart.

In a more formal language, the diagram of the vascular and cardiac curves (Fig. 1) as obtained does not have an associated vector field in the phase space that represents the possible trajectories of the system given a perturbation from the OP. Thus, the conundrum is whether the OP is a stable equilibrium point due to the FFm, which, in the end, guaranties that both beat-to-beat

Journal of Experimental Biology (2017) 220, 4391-4398 doi:10.1242/jeb.167106

variation and the coordination between the ventricles can be sustained without any regulatory loop extrinsic to the heart.

The FFm is found among all vertebrate classes, as stated before. However, many vertebrates have single-ventricle hearts and so there is no match necessities between the outputs from two ventricles beating simultaneously. Moreover, exactly these vertebrates belong to the predecessor lines of the two-ventricle hearts of mammals, birds and some reptiles. Thus, in evolutive terms, the FFm precedes output-matching necessities.

Fishes regulate cardiac output mainly by systolic volume and it is considered that the FFm is responsible for the adjustment of ejection in face of large changes in ventricle volume (Shiels and White, 2008). The ascending limb of the relationship between developed tension and sarcomere length is much broader in these animals than in mammals and birds, indicating a wider range of adequate ventricular pressure responses in face of increases in chamber volume (Shiels and White, 2008). Despite the fact that these considerations seem to address the question of the stability of a given equilibrium point in fishes, in fact they are related to the transitions among operating points governed by a series of systemic changes (e.g. changes in metabolic demand, muscle contraction, autonomic tonus, etc.). Counterintuitively, the latter, transitions, does not imply the former, stability.

The present study aims to answer the questions of the role of the FFm in the stability of an OP and of the role of the FFm in output-matching. These questions are approached by the analysis of a dynamical system representing the acute and intrinsic coupling between cardiac output and central venous pressure (see the following section for details). We analyze two settings of this coupling, one concerning the single ventricle system of fishes and the other concerning the two-ventricle system of mammals, birds and some reptiles. The settings are analyzed in two different scenarios: (A) the FFm actuating the ventricular chamber; and (B) a fixed force is exerted by a ventricular chamber. These two scenarios are intended to allow for a comparison of what would happen if the FFm were absent and so, to answer the proposed questions.

MATERIALS AND METHODS

Preliminary considerations

Mechanistic description and cardiac dynamics

The functioning of the cardiovascular system is governed by a set of variables, including vascular capacitances, vascular impedances, blood rheology, total blood volume and autonomic nervous system tonus (e.g. Holubarsch et al., 1996; Hoppensteadt and Peskin, 2002). For the purposes of the present analysis, these variables would be considered as constants during the timeframe of interest. This defines what is meant by 'acute' and 'intrinsic' that we mentioned above. In other words, we are saying that there is more than one timescale to describe the system, and we shall investigate one that operates at a rate corresponding to one heartbeat interval. In doing so, we are led to consider that, in the vicinities of an OP, the system behaves linearly.

In this instance, the total volume of fluid (explicitly, blood), V_T, is constant and equals the sum of the volumes in each compartment, V_j, of the system:

$$V_T = \sum V_j. \tag{1}$$

We use the Hagen–Poiseuille model to describe flow between two points, i and j, of the circulatory system:

$$\dot{Q}_{i,j} = \frac{P_i - P_j}{R_{i,j}}, \tag{2}$$

in which $\dot{Q}$ is the flow between compartments i and j, P is the pressure in a given compartment and R is the resistance imposed to the flow between the compartments. Notice that the resistance term encloses physical constants of the system, such as mean radius and length of the vessels, viscosity of the fluid, etc.

The pressure in a given compartment (P_j) is the volume (V_j) of blood present in the compartment divided by the capacitance (β_j) of the compartment (here, we consider the capacitance as a constant in the small range of volume variations we analyze):

$$P_j = \frac{V_j}{\beta_j}. \tag{3}$$

Eqns 1–3 form the core of the subsequent models in which the time variation in the volume of a given compartment (j) is the result of the inflow and outflow of blood:

$$\frac{dV_j}{dt} = \dot{Q}_{in} - \dot{Q}_{out}. \tag{4}$$

Because total volume is constant, it follows that:

$$\sum \frac{dV_j}{dt} = 0. \tag{5}$$

As stated before, the timeframe of reference is related to one heartbeat, which is composed of two phases. During systole, the heart ejects but does not receive blood. During diastole, the reverse is true. Therefore, when we employ Eqn 4 we are referring to mean values during the cardiac cycle. To incorporate such a cycle in the mean-valued model, we consider that, during diastole, the capacitance of the ventricle tends to infinity and, therefore, the circulatory tree fills the heart against a near-zero pressure. During systole, the ventricle develops a certain pressure (force), and this pressure is related to the volume of the ventricle. This is the FFm.

The model is intended to study the behavior of the system near an OP. Therefore, we employ a simple positive linear relationship between volume and pressure (force). This means that we are neither modeling any transition between two distant OPs nor pathological conditions in which the FFm might be inverted (i.e. the greater the ventricular volume the lower the developed force, as in Fig. 1D).

RESULTS

Modeling and results: From fish …

One-ventricle hearts

Let 'H' represent the heart chamber and 'S' the vascular tree (Fig. 2).

Scenario A: the FFm actuating the ventricular chamber

The outflow from the heart (inflow to the vascular tree) and the outflow from the vascular tree (inflow to the heart) are:

$$\dot{Q}_H = \frac{F \cdot V_H - V_S \cdot \beta_S{}^{-1}}{R_S}, \tag{6}$$

$$\dot{Q}_S = \frac{V_S \cdot \beta_S{}^{-1}}{R_H}, \tag{7}$$

in which F is the linear coefficient of the relationship between ventricle volume and developed pressure (the FFm). For the sake of

Journal of Experimental Biology (2017) 220, 4391-4398 doi:10.1242/jeb.167106

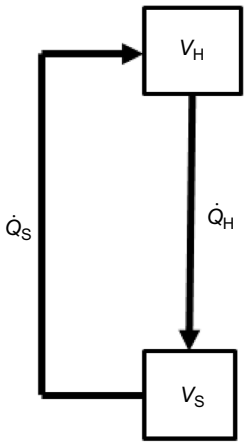

Fig. 2. Schematic diagram of the model of the one-ventricle heart system. The state variables heart volume (V_H) and systemic volume (V_S) are in boxes. The arrows indicate blood flows ($\dot{Q}$).

notation, we define:

$$a = \frac{1}{R_S \cdot \beta_S}, \tag{8}$$

$$b = \frac{1}{R_H \cdot \beta_S}, \tag{9}$$

$$f = \frac{F}{R_S}. \tag{10}$$

Coefficients a, b and f have units of pressure · volume^{-1} · resistance^{-1}. Because resistance to flow have units of time · pressure · volume^{-1}, the coefficients end up as time^{-1} (i.e. inverse of time constants).

Because the time variation in total blood volume is zero (Eqn 5), then, from Eqn 4, the system is described by the following differential equation:

$$\frac{dV_H}{dt} = (a+b) \cdot V_T - (a+b+f) \cdot V_H. \tag{11}$$

By equating dV_H/dt to zero, we obtain the value of the cardiac volume (and, consequently, the volume of the vascular tree as well) at the equilibrium point of the system, denoted by an asterisk:

$$V_H* = \frac{a+b}{a+b+f} \cdot V_T. \tag{12}$$

In fact, Eqn 11 can be directly integrated and we have:

$$V_H(t) = \frac{a+b}{a+b+f} \cdot V_T \cdot (1 - \mathbf{e}^{-(a+b+f)\cdot t}), \tag{13}$$

in which **e** is the base of the natural logarithm.

Scenario B: a fixed force is exerted by a ventricular chamber

We use the subscript k to indicate the parameters and the variables in this fixed-force scenario. The outflow from the heart (inflow to the vascular tree) becomes:

$$\dot{Q}_{H,k} = \frac{F_k - V_S \cdot \beta_S{}^{-1}}{R_S}, \tag{14}$$

in which F_k is the fixed-force term. The outflow from the vascular tree (inflow to the heart) remains the same as in Eqn 6. The differential equation describing the dynamics of the system is now:

$$\frac{dV_{H,k}}{dt} = (a+b) \cdot V_T - f_k - (a+b) \cdot V_{H,k}. \tag{15}$$

Notice that the constant f_k has units of volume · time^{-1}, i.e. flow. Integrating Eqn 15 results in:

$$V_{H,k}(t) = \left(V_T - \frac{f_k}{a+b}\right) \cdot (1 - \mathbf{e}^{-(a+b)\cdot t}), \tag{16}$$

and the value of the cardiac volume at the equilibrium point is:

$$V_{H,k}* = V_T - \frac{f_k}{a+b}. \tag{17}$$

Eqn 17 shows that, if the fixed-force term (represented by f_k) is much greater than the sum of a+b, the heart chamber would become completely empty of blood.

Stability of the equilibrium point

Both Eqns 13 and 16 reveal that their respective equilibrium points are an asymptotically stable node: both eigenvalues are negative real numbers (e.g. Monteiro, 2011). Therefore, irrespective of the presence of the FFm, the one-ventricle circulatory system has a stable OP. Fig. 3 illustrates the phase portrait of the one-ventricle system with its associated vector field.

... to philosopher

[*From Fish to Philosopher* is a classical book by Homer William Smith (1959).]

Two-ventricle hearts

As stated in the Introduction, we need four state variables (shown in subscript in the equations) to describe two-ventricle hearts: left ventricle (L), systemic vascular bed (S), right ventricle (D – we use D for dextral instead of R, to avoid confusion with resistance) and pulmonary vascular bed (G; we use 'G' for 'gas exchanger organ'

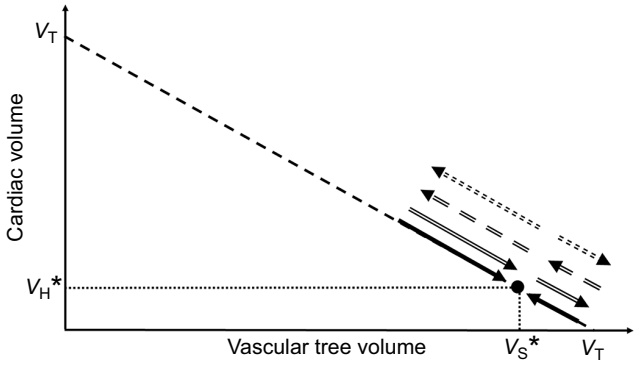

Fig. 3. Phase portrait of the one-ventricle system. The black circle indicates the pair (cardiac volume, vascular tree volume) at a given equilibrium point. The dashed line represents the total volume of the system (i.e. V_H+V_S), which is constant. The pair of solid arrows over the V_T line is the associated vector field of the system. As explained in the text, the equilibrium point is asymptotically stable. Therefore, the vector field (solid arrows) points towards the black circle, indicating that, for a given set of parameters (a, b and f, or f_k, where f_k is the fixed-force term), the system returns to this equilibrium point after a perturbation. Notice that the phase space (x- and y-axis) is not composed by 'central venous pressure' and 'cardiac output' as in the usual OP representation (Fig. 1). Instead, it is composed by the state variables 'vascular tree volume' and 'cardiac volume', and has an associated vector field that identifies the time evolution of the system. For the sake of illustration, above the V_T line we show other vector fields that would represent unstable equilibrium points.

Journal of Experimental Biology

Journal of Experimental Biology (2017) 220, 4391-4398 doi:10.1242/jeb.167106

instead of 'P', which would cause confusion with pressure) (see Fig. 4).

Scenario A: the FFm actuating the ventricular chamber

Flows are given by the following equations:

$$\dot{Q}_L = \frac{F_L \cdot V_L - V_S \cdot \beta_S^{-1}}{R_S} = f_L \cdot V_L - a \cdot V_S, \quad (18)$$

$$\dot{Q}_S = \frac{V_S \cdot \beta_S^{-1}}{R_D} = b \cdot V_S, \quad (19)$$

$$\dot{Q}_D = \frac{F_D \cdot V_D - V_G \cdot \beta_G^{-1}}{R_G} = f_D \cdot V_D - c \cdot V_G, \quad (20)$$

$$\dot{Q}_G = \frac{V_G \cdot \beta_G^{-1}}{R_L} = e \cdot V_G, \quad (21)$$

in which we employ the same short notation as in the preceding section for the sake of clarity. From the equations of flow and Eqn 5, we have the following set of coupled differential equations to describe the system:

$$\begin{cases} \frac{dV_L}{dt} = e \cdot V_G + a \cdot V_S - f_L \cdot V_L \\ \frac{dV_S}{dt} = f_L \cdot V_L - (a+b) \cdot V_S \\ \frac{dV_G}{dt} = f_D \cdot (V_T - V_L - V_S - V_G) - (c+e) \cdot V_G. \end{cases} \quad (22)$$

The volumes at the equilibrium point of the system are (we let V_S* and V_G* be functions of V_L*):

$$V_S^* = \frac{f_L}{a+b} \cdot V_L^*, \quad (23)$$

$$V_G^* = \frac{b \cdot f_L}{e \cdot (a+b)} \cdot V_L^*, \quad (24)$$

$$V_L^* = \frac{f_D \cdot e \cdot (a+b)}{f_D \cdot e \cdot (a+b) + f_L \cdot [f_D \cdot (b+e) + b \cdot (c+e)]} \cdot V_T. \quad (25)$$

Just to check the feasibility of Eqn 25, if f_D=0, i.e. the right ventricle has no ejecting force at all, then the whole volume of blood would be retained in the right ventricle, whereas, if f_L=0, then the volume is completely retained in the left ventricle. If both f_D and f_L go to zero simultaneously, then one has a proportion of blood retained in the right side and the other in the left side, as in stagnation conditions. These extreme results are in accordance with what one would anticipate within this simplified framework of the circulatory system.

Stability of the equilibrium point in the presence of the FFm

The stability of the equilibrium point is given by setting the determinant of the Jacobian of the system to zero:

$$\begin{vmatrix} -f_L - \lambda & a & e \\ f_L & -(a+b) - \lambda & 0 \\ -f_D & -f_D & -f_D - c - e - \lambda \end{vmatrix} = 0, \quad (26)$$

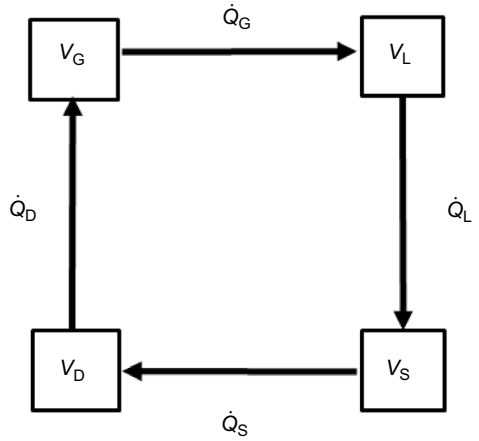

Fig. 4. Schematic diagram of the model of the two-ventricle heart system. The state variables left ventricle volume (V_L), systemic circulation volume (V_S), right ventricle volume (V_R) and gas-exchanger circulation volume (V_G) are in boxes. The arrows indicate blood flows ($\dot{Q}$).

in which λ is an eigenvalue of the system. This determinant corresponds to the following characteristic equation:

$$\lambda^3 + z_1 \cdot \lambda^2 + z_2 \cdot \lambda + z_3 = 0. \quad (27)$$

The coefficients z_i are:

$$z_1 = a + b + c + e + f_L + f_D, \quad (28)$$

$$z_2 = a \cdot c + a \cdot e + b \cdot c + b \cdot e + f_D \cdot a + f_D \cdot b + f_D \cdot e + f_L \cdot b + f_L \cdot c + f_L \cdot e + f_L \cdot f_D, \quad (29)$$

$$z_3 = e \cdot f_D \cdot a + e \cdot f_D \cdot b + e \cdot f_L \cdot b + f_L \cdot c \cdot b + f_L \cdot e \cdot b + f_L \cdot f_D + e \cdot f_L \cdot f_D. \quad (30)$$

For the equilibrium point to be asymptotically stable, the following conditions must be satisfied: (1) $z_i > 0 \ \forall \ i$; (2) $z_1 \cdot z_2 > z_3$. Because all parameters are positive, condition 1 is satisfied. Plain inspection of the coefficients shows that condition 2 is also satisfied. Therefore, the equilibrium point of a two-ventricle system in the presence of the FFm is asymptotically stable.

Scenario B: a fixed force is exerted by a ventricular chamber

The system is described by the following coupled differential equations, where the subscript k indicates the fixed force:

$$\begin{cases} \frac{dV_L}{dt} = e \cdot V_G + a \cdot V_S - f_{L,k} \\ \frac{dV_S}{dt} = f_{L,k} - (a+b) \cdot V_S. \\ \frac{dV_G}{dt} = f_{D,k} - (c+e) \cdot V_G. \end{cases} \quad (31)$$

The volumes of the compartments S and G at the equilibrium point of the system are:

$$V_S^* = \frac{f_{L,k}}{a+b}, \quad (32)$$

$$V_G^* = \frac{f_{D,k}}{c+e}. \quad (33)$$

Journal of Experimental Biology (2017) 220, 4391-4398 doi:10.1242/jeb.167106

From these values, in the equation of dV_L/dt, we obtain that the following relationship must hold in order for the system to have an equilibrium point:

$$f_{L,k} \cdot b \cdot (c+e) = f_{D,k} \cdot e \cdot (a+b). \quad (34)$$

Therefore, unless the condition in Eqn 34 is fulfilled, the system will not attain an equilibrium point at all. Also notice that the volumes of two compartments are not obtained (see below).

Stability of the equilibrium point in the presence of a fixed force of ejection

We obtain the following determinant of the Jacobian of system 22:

$$\begin{vmatrix} -\lambda & a & e \\ 0 & -(a+b)-\lambda & 0 \\ 0 & 0 & -(c+e)-\lambda \end{vmatrix} = 0. \quad (35)$$

Therefore, the system has an asymptotically stable subspace with two real eigenvalues [λ_1=–(a+b) and λ_2=–(c+e)] and a central manifold corresponding to λ_3=0. This central manifold represents the indeterminacy of the two volumes (V_L and V_D in this case). Let V_H=V_L+V_D. Because:

$$\frac{dV_H}{dt} = \frac{dV_L}{dt} + \frac{dV_D}{dt} = -\frac{dV_S}{dt} - \frac{dV_G}{dt}, \quad (36)$$

the system becomes simply:

$$\begin{cases} \dfrac{dV_S}{dt} = f_{L,k} - (a+b) \cdot V_S \\ \dfrac{dV_G}{dt} = f_{D,k} - (c+e) \cdot V_G \end{cases}. \quad (37)$$

In a very similar way to what happens in the case of one-ventricle hearts, the system is asymptotically stable even in the absence of the FFm and, considering Eqn 34, one way to write the heart volume is:

$$V_H^* = V_T - \frac{f_{D,k}}{c+e} \cdot \left(\frac{b+e}{b}\right). \quad (38)$$

DISCUSSION

The stability of the OP of the cardiovascular system is usually taken for granted as a result of the Frank–Starling law, i.e. the FFm of the heart. However, the OP diagram does not convey sufficient information to conclude that such an intrinsic mechanism of the myocardium truly would bring about stability to the system on a beat-to-beat basis.

In the present study, we approach this question by investigating the behavior of a dynamical system, representing a circulatory system, in the vicinity of an OP. In such a vicinity, the temporal variation of a set of relevant physical variables in the cardiovascular system is taken as null, i.e. we investigate the behavior of the system within a fast time scale, roughly corresponding to the heartbeat interval. In this sense, all the sympathovagal inputs to the heart are considered as constants, as well as changes in blood volume, rheological factors, etc.

The first important conclusion of the study is that both types of circulatory systems, i.e. one-ventricle and two-ventricle hearts, are asymptotically stable even in the absence of the FFm. In other words, if a given OP exists, it is stable, and the system will return to such an OP after suffering a perturbation, irrespective of the presence of the FFm and without any extrinsic regulatory loop.

Therefore, the question is now renewed. One has to understand the evolutive conservation and the role of the FFm without evoking its alleged and putative responsibility in stabilizing the OP.

Owing to the similar results between the systems with one and two ventricles, let us focus on the one-ventricle heart for simplicity. Eqns 12 and 17 describe the volume in the heart compartment for one system with and for another one without the FFm, respectively. Fig. 5 shows a plot of these functions (the 5% volume line is indicated simply as a reference to a usual value of the volume in the heart in relation to the volume of blood).

At the risk of becoming repetitive, let us put it once again: both scenarios allow for the existence of stable OPs. In addition, as already stated (see Results), if the force term tends to zero, the total blood volume tends to be retained in the cardiac chamber (left-hand side in Fig. 5). In the vicinities of the zero force, the heart volume of the system with the FFm shows a steeper relationship with force than the fixed-force system. However, from a certain volume down, the linear relationship of the fixed force becomes steeper than the asymptote of the FFm system. Thus, close to the range of reasonable heart volumes, the fixed-force system shows a higher variation in the volumes of its compartments in face of variations in force, whereas the filling-force system has a smooth response.

The effort required for control (e.g. Kirk, 2012 p. 259; Todorov and Jordan, 2002) and computational complexity (e.g. Benenti et al., 2007 p. 24; Moller and Smolka, 1965) are somehow related to energy waste and resource allocation by the controller system or the resolution algorithm in a given task. In this sense, it is now widely recognized that the processing of information in the nervous systems incurs substantial increases in energy demands of the organism, and reducing the amount of redundant information processing or eliminating predictable inputs are important selective pressures operating at diverse levels of organization (Niven and Laughlin, 2008). Considering that the resistances, capacitances and even the myocardial force itself are under adjustments regulated by the autonomous nervous system, the smoothness brought by the FFm ends up as a lower effort on the controller unit (i.e. lower energy demand and/or use of system resources).

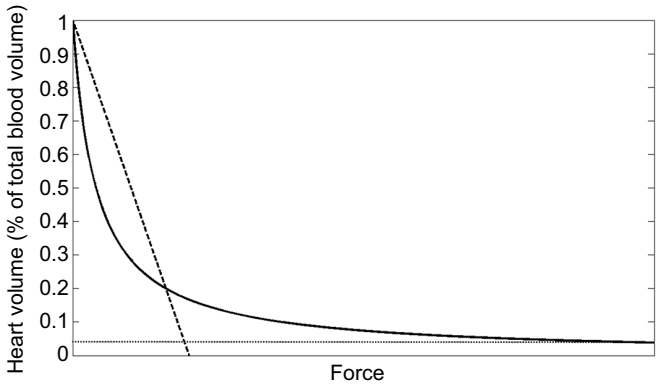

Fig. 5. Comparison between the effects of varying the force terms in the two different scenarios analyzed (Eqns 12 and 17). The *y*-axis represents the fraction of blood in the cardiac chamber in relation to total blood volume. The *x*-axis represents force, i.e. the terms *f* and f_k (it must be kept in mind that *f* and f_k have different dimensions). Continuous line: volume in the scenario with the FFm. Dashed line: volume in the scenario with a fixed-force exerted by the ventricular chamber. Dotted horizontal line: 5% of total blood volume. The sum of the terms *a* and *b* in both Eqns 12 and 17 is 1 for the simulations shown in the plot.

Inspection of Eqn 25 shows that the controller unit can operate a variation in one given parameter (say, systemic resistance in the coefficient a) and the circulatory system will self-adjust its volumes accordingly. By contrast, in the scenario with fixed-force terms, inspection of Eqn 34 shows that the controller unit must operate simultaneous variations in at least two parameters in order to guarantee the working of the system.

Thus, the second conclusion we can draw is that the FFm has a role in decreasing the controlling effort external to the circulatory system (note that this has nothing to do with the stability of an OP discussed above). The absence of the FFm does not preclude variations to be operated in the circulation, but the presence of the FFm smooths out perturbations more easily.

Then, the next inevitable question is whether the FFm plays some role in heart-rate variability. Heart rate suffers variations on a beat-to-beat basis. The most prominent are changes associated with ventilation (respiratory sinus arrhythmia), but many other factors are also interconnected with these variations, resulting in a multifaceted composition of frequencies. The beat-to-beat modulation of heart rate is due to a number of feedback loops that end in a common dual efferent path, the sympathetic and parasympathetic branches of the autonomic nervous system (e.g. Aubert et al., 2003; Stauss, 2003). Also, there might exist some intrinsic innervation in the heart itself, whose role in this process is not well established (Stauss, 2003). This modulation gives rise to the so-called 'heart-rate variability', and such a variability is an important sign of adequate functioning of the cardiovascular system (e.g. Stauss, 2003; TASK FORCE, 1996).

In this sense, the third relevant conclusion of the present study comes from the inspection of the eigenvalues of a system with the FFm and of a similar system (i.e. a system with the same set of values for the parameters of the vascular bed) with a fixed ejection force. For the one-ventricle hearts, this can be directly evaluated in Eqns 13 and 16 for the cases with the FFm and without it, respectively. Considering that the volume of blood in the heart is approximately 5% of the total blood volume, from Eqn 12 we obtain that the filling-force term would be roughly 19-fold greater than the sum of the other two terms, a and b. This results in a returning to the OP 20 times faster in the presence of the FFm than in its absence.

For the two-ventricle hearts without the FFm, the eigenvalues of the stable sub-space are shown in Eqn 35. Although we did not directly compute the eigenvalues of two-ventricle hearts when the FFm is present, we can have a glimpse of what occurs in them. Because the sum of the eigenvalues of a system equals the trace of the Jacobian matrix, then we can observe that both terms f_L and f_R, related to the FFm, take part in at least one of the eigenvalues of the system (see Eqn 26). Therefore, similarly to what happens in one-ventricle hearts, two-ventricle systems will also return to the OP faster in the presence of the FFm than in its absence.

Thus, our third conclusion is in regard to the time constant of a system: the FFm allows for a much faster return to an OP after a perturbation. In other words, despite the fact that an existing OP is stable even in the absence of the FFm, its presence guaranties the OP to be regained in a fraction of the time than if there were no such a mechanism.

Heuristically, we might consider that, when the system transits from a previous OP to a new one, the former is a perturbation in relation to the latter (notice that this is not the mathematical definition of 'perturbation'). In this sense, the transition among OPs would be sped up by the FFm. In a similar line of reasoning, this speeding up potentially contributes to non-autonomic components of heart-rate variability, particularly in the high-frequency range.

In conclusion, in contrast to the currently held view, the FFm is not necessary in order to give stability to an OP in a circulatory system, whether composed by a heart with a single ventricle or with two. Our modeling supports that the role of the FFm is related to decreases in the controlling effort over the circulatory system, to smooth out perturbations and to guarantee faster transitions between OPs.

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