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REVIEW

Guyton's venous return curves should be taught at medical schools (complete English translation of Japanese version)

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Abstract Guyton's most significant contributions are the exploration into the development of venous return and circulatory equilibrium. Recently, several physiologists challenged the validity of venous return as a function of venous pressure. Guyton's experiment in effect controlled venous pressure by changing cardiac output. Thus, critics claimed that cardiac output is the determinant of venous return. This claim is true, but in the presence of constant stressed volume, venous return and venous pressure have a fixed reciprocal relationship. Thus, it is meaningless to argue which one is the independent variable. We fully support Guyton's venous return and in particular circulatory equilibrium. Guyton's framework should be taught at medical schools worldwide.

Keywords Venous return curve · Venous return surface · Circulatory equilibrium · Stressed volume · Cardiac output curve

Introduction

Guyton proposed the venous return and circulatory equilibrium framework more than half a century ago. While Guyton's physiology appeared to be accepted by the scientific community at one time, criticism started to emerge around 2000, sparking a flurry of debates in scientific journals. This article introduces the most important points of argument among the various controversies, and explains the views of the authors. Based on this background, the latest development of Guyton's physiology will be commented. Some terms that appear frequently in this article may be unfamiliar to some readers. For the benefit of those readers, Memos are added to explain these terms in simple language. For those readers who already know the definitions of these terms, they may skip these Memos and continue to read on. Moreover, many equations are used to explain how the basic concept proposed in Guyton's physiology has been extended in modern time to new concepts of the venous return surface and circulatory equilibrium. Readers who find these equations difficult to understand may also skip them, although we believe that following the derivation of these equations will allow readers to acquire fundamental understanding of the concept.

Guyton's venous return

In the 1950s when Guyton was engaged in research on the venous return and circulatory equilibrium, Otto Frank [2, 3] and Ernst H. Starling [4–6] had already established the preload dependence of cardiac output. However, despite understanding of the basic characteristics of the cardiac pump function, the mechanism by which cardiac pump function determines hemodynamics remained unknown.

With this historical background, Guyton hypothesized that ejection does not occur without return of the blood to the heart, and attempted to elucidate the properties of blood returning from the vein to the heart. He hypothesized that

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when central venous pressure (hereinafter venous pressure) increases, the blood returning to the heart decreases [7–11]. To prove the relationship between venous pressure and venous return flow, he performed several important experiments. In his most fundamental experiment [7], he drained blood from the superior and inferior vena cavae, fixed the venous pressure via a circuit containing a Starling resistor (see Memo), and at the same time returned the collected blood to the aorta or pulmonary artery using a pump (Fig. 1, left). In this experiment, venous pressure could be changed by altering the height of the Starling resistor. Guyton initially fixed the venous pressure, and resistance. He focused on the pressure when venous return becomes zero, and defined this pressure as the mean circulatory filling pressure. Mean circulatory filling pressure is the blood pressure when venous return (cardiac output) becomes zero, and has the same value in the whole blood circulatory system [8, 9]. Mean circulatory filling pressure is determined by the ratio of the stressed volume to the total compliance of blood vessels including the heart (see Memo). Although he observed that while venous return increases when venous pressure is lowered, venous return no longer increases when venous pressure is in the negative pressure range.

Memo

Starling resistor (see diagram on the left in Figure 1): When a part of the hard tube within the extracorporeal blood circuit is replaced with a tube made of soft material, the lumen pressure in the soft tube approximates the atmospheric pressure. Utilizing this property, by arbitrarily setting the Starling resistance at different height, the hydrostatic pressure changes and it is possible to arbitrarily change the venous pressure.

Memo

Mean circulatory filling pressure describes the pressure when circulation is arrested and the intravascular pressure becomes uniform. This pressure is obtained by dividing the stressed volume by the compliance of the whole circulatory system, and includes the compliance of the heart. Mean systemic filling pressure describes the intravascular pressure when systemic circulation is arrested and there is no inflow to or outflow from the systemic circulatory system. This pressure is calculated by dividing the stressed volume in systemic circulation by the total compliance of the systemic circulation. Since both compliance and blood volume are overwhelmingly higher in systemic circulation, not only is mean systemic filling pressure but also mean circulatory filling pressure are determined by the stressed volume of systemic circulation and the total compliance of systemic circulation. Both values are known to approximate 7 mmHg.

then adjusted the flow of the pump; i.e., cardiac output, such that the volume of blood in the blood vessel did not change at that particular venous pressure. In this experiment, cardiac output inevitably corresponds to venous return. Guyton plotted venous return along the vertical axis, and venous pressure decided by Starling resistance on the horizontal axis. In other words, he obtained the so called venous return curve. As shown in Fig. 1 (right), venous return decreases when venous pressure is increased. Guyton defined the reciprocal of the gradient of the curve that has dimension of resistance as venous return

Venous return, stressed volume, and mean circulatory filling pressure

Guyton conducted experiments to examine how fluid infusion changes venous return. His experiment showed that when fluid infusion is performed to increase the stressed volume, mean circulatory filling pressure increases and the venous return curve is shifted upward in an almost parallel manner (Fig. 2, dotted line). Conversely, when blood is drained, the venous return is shifted downward (Fig. 2, dashed line). From these experiments, Guyton

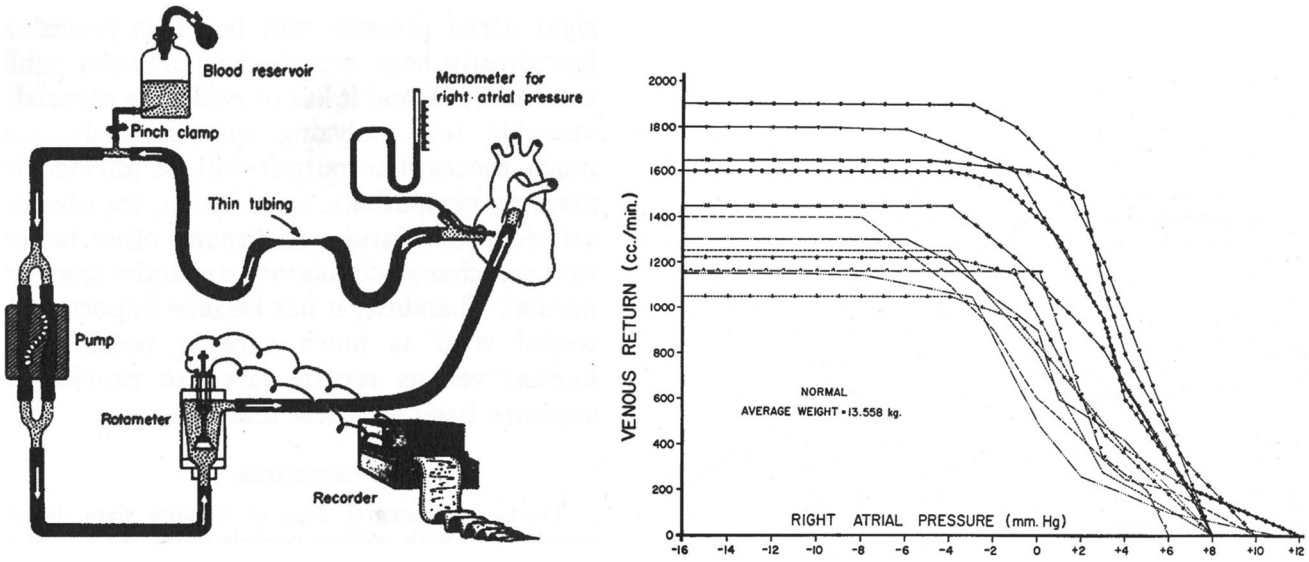

Fig. 1 Guyton's experimental model with a Starling resistor (*left*) and venous return curves (*right*), cited with permission from Guyton et al. [7]

hypothesized that venous return is determined by driving the venous return resistance by the pressure gradient between mean circulatory filling pressure and venous pressure.

Modeling of venous return by electrical circuit

To render this hypothesis more robust, Guyton performed a theoretical analysis using a simple electrical circuit [9]. Figure 3 shows the six elements in the electrical circuit

Memo

Stressed volume and unstressed volume: Guyton clearly differentiated the total blood volume in blood vessels from the stressed volume. Under the situation when blood flow is arrested, the blood vessel is simply a closed sac. When blood is introduced into this sac, up to a certain blood volume, the blood pressure in the vessel does not increase. When a certain threshold is exceeded, the intravascular pressure begins to increase. The blood volume until the threshold is reached is termed the unstressed volume, and the volume after the threshold is reached the stressed volume. The sum of unstressed volume and stressed volume is the total blood volume in blood vessel. In general, approximately one-quarter of the total blood volume is considered to be the stressed volume. The vascular compliance per kg body weight is estimated to be 2.72 ml/mmHg [12]. When mean circulatory filling pressure is 7 mmHg, the stressed volume is $2.72 \times 7 \approx 20$ ml/kg. The unstressed volume is considered to be around 60 ml/kg. An increase in sympathetic tone increases the tone of vascular smooth muscles, especially the venous smooth muscle tone, resulting in marked decrease in unstressed volume and a concomitant increase in stressed volume to a maximum of 8.7 ml/kg [12,13]. This implies that in an individual weighting 60 kg, activation of the sympathetic nerve would increase the stressed volume by over 500 ml. In this case, it is known that vascular compliance hardly changes. As a result, the increase in stressed volume due to sympathetic activation increases the mean circulatory filling pressure. Increase in mean circulatory filling pressure causes an upward shift of the venous return curve.

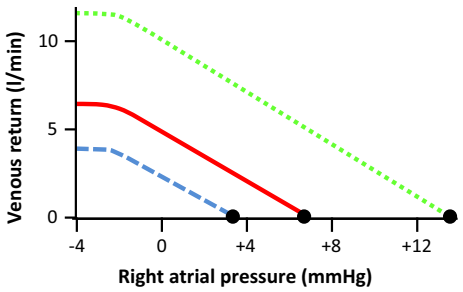

Fig. 2 Venous return curves and stressed volume solid line, a normal curve for mean circulatory filling pressure of 7 mmHg

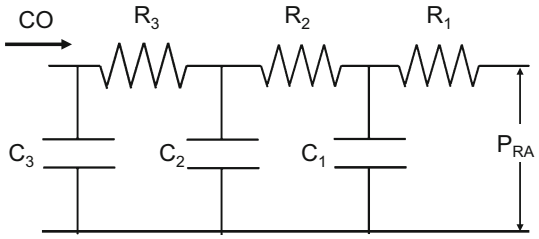

Fig. 3 Simple vascular model used by Guyton in theoretical analysis

used by Guyton. Using this circuit, Guyton obtained the relations between venous return (CO), venous pressure (P_{RA}), and stressed volume (V).

$$CO = \frac{V - C\,P_{RA}}{R_1C_1 + (R_1 + R_2)C_2 + (R_1 + R_2 + R_3)C_3}, \quad (1)$$

where $C = C_1 + C_2 + C_3$. With mean circulatory filling pressure (P_m) = V/C, substituting this into Eq. (1) yields the following:

$$CO = \frac{\dfrac{P_m - P_{RA}}{R_1C_1 + (R_1 + R_2)C_2 + (R_1 + R_2 + R_3)C_3}}{C} = \frac{P_m - P_{RA}}{R_v}. \quad (2)$$

This is Guyton's venous return equation. The denominator shows venous return resistance. Venous return resistance is not real resistance that exists physically, but represents functional resistance comprising resistance and compliance. This parameter in fact caused various confusions, which will be discussed later. On the other hand, the numerator shows the pressure gradient by subtracting venous pressure from mean circulatory filling pressure. Guyton advocated that this pressure gradient drives the venous return resistance, which gives rise to venous return. At the same time, this analysis also validated the intuitive interpretation that mean circulatory filling pressure is the value obtained by dividing stressed volume by total vascular compliance.

The above briefly overviewed Guyton's venous return. Based on the venous return curve, Guyton developed the concept of circulatory equilibrium that explains how the heart and blood vessels interact to determine cardiac output.

Circulatory equilibrium

Both the cardiac output curve that describes the relationship between venous pressure and cardiac output and the venous return curve that describes the relationship between venous pressure and venous return use the same variables (venous pressure and cardiac output). Therefore, the intersection of these two graphs should depict the operating point when cardiac output and venous return reach equilibrium. Figure 4 (left) shows a superimposed plot of the cardiac output curve and venous return curve. Guyton called the intersection point "circulatory equilibrium", and proposed circulatory equilibrium as the physiological mechanism that determines cardiac output [10, 11]. This concept of circulatory equilibrium is able to explain the mechanism that determines cardiac output by opening the circulatory loop at the vein, and was a revolutional achievement in the history of circulatory physiology.

Figure 4 (left) shows the response to fluid infusion. When fluid is infused, mean circulatory filling pressure increases accompanying an increase in stressed volume. Therefore, venous return increases at all the venous pressures [Fig. 4 (left): venous return curve; solid line to dotted line]. Even in the absence of any change in the cardiac output curve, cardiac output at the intersection point (closed circle) increases, and venous pressure also increases. On the other hand, even though the cardiac output curve becomes markedly steeper due to increases in heart contractility and heart rate [Fig. 4 (left): cardiac output curve; solid line to dotted line], because venous pressure is already low, further decrease in venous pressure does not increase venous return, and cardiac output hardly increases (open square). In fact, it has been shown experimentally that modifying the cardiac output curve alone does not increase cardiac output, which corroborates the physiological observations. From these findings, Guyton concluded that physiologically, cardiac output is not determined by the heart but by venous return which is a vascular characteristic. In exercise, activation of sympathetic nerve increases stressed volume resulting in marked increase in mean circulatory filling pressure. Additionally, the cardiac output curve becomes steep due to decrease in vascular resistance, increase in contractility, or increase in heart rate. As a result, while cardiac output increases markedly, venous pressure shows little change (closed square).

Furthermore, Guyton mentioned the hemodynamics in heart failure, as shown in Fig. 4 (right). In heart failure,

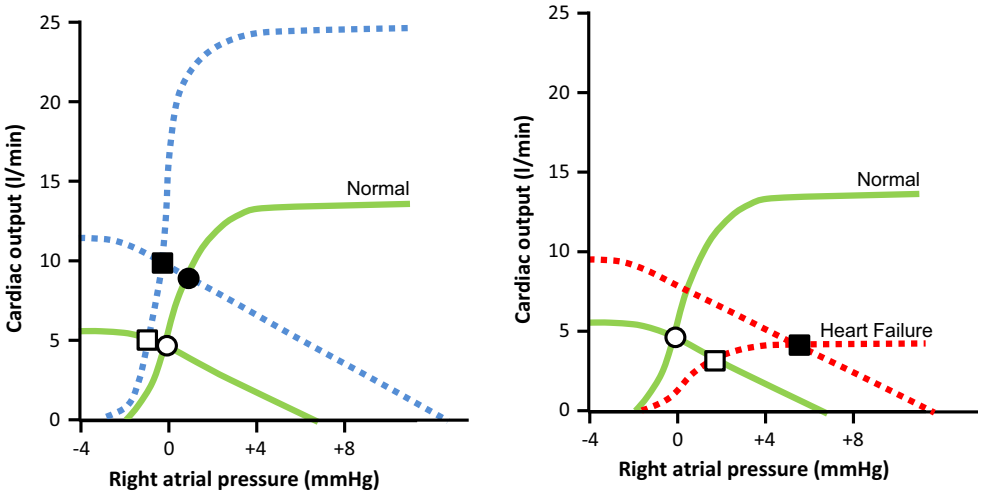

Fig. 4 Circulatory equilibrium in infusion, cardiac stimulation and exercise (*left*), and in heart failure (*right*)

because the slope of the cardiac output curve decreases, cardiac output is lowered (open square). The reason why cardiac output is relatively preserved in most patients with heart failure is that increased stressed volume increases venous return, consequently preserving cardiac output (closed square). At the same time, venous pressure increases, which does not contradict the hemodynamics of heart failure.

The venous return framework, and furthermore the circulatory equilibrium framework advocated by Guyton dramatically advanced the understanding of circulatory physiology. As a result, Guyton's book on circulatory physiology became a bestselling medical book, and began to be used as teaching material in medical schools worldwide. This is due to the common recognition that Guyton's venous return and circulatory equilibrium concepts are indispensable for the understanding of hemodynamics. However, Guyton's physiology is fundamentally difficult, and it is easy to imagine that medical students, or even lecturers, do not necessarily acquire a deep understanding of this field. Then, nearly half a century since Guyton proposed venous return and circulatory equilibrium, open opinions began to emerge in authoritative physiology journals, with comments that Guyton's physiology only confuses students, and that it should not be taught at medical schools. The arguments will be summarized below.

Criticism and support of Guyton's venous return

The criticisms are focused on the following two points. The first counterpoint is that in Guyton's experiment on venous return, venous pressure is not an independent variable. As mentioned above, in that experiment, although it was stated that venous pressure was determined by Starling resistance and then the pump flow rate was adjusted, in effect, however, venous pressure was determined with respect to the pump flow rate. In a later experiment using simple right cardiac bypass and did not include a Starling resistor [14, 15], a cardiac output–venous pressure relationship similar to that obtained using Guyton's venous return curve was obtained. These findings therefore suggest that venous pressure changes only because cardiac output is changed; in other words, venous pressure is a dependent variable and pump flow rate is an independent variable [14–17]. Considering the content of the experiment, such interpretation is valid. Consequently, researchers who advocate this theory claim that cardiac output which is an independent variable should be plotted on the horizontal axis, and venous pressure which is a dependent variable should be plotted on the vertical axis. In this regard, supporters of Guyton's physiology also express opinion of agreement [18].

The second counterpoint is disagreement with Guyton's view that venous return is driven by the difference between the mean circulatory filling pressure and the venous pressure. These critics claim that venous return is only possible because the heart ejects, and therefore Guyton's view that the pressure gradient between mean circulatory filling pressure and venous pressure drives venous return is not correct [16, 19, 20]. They accept that mean circulatory filling pressure is determined by the ratio of stressed volume to total compliance of the vascular bed. However, regarding Guyton's claim that mean circulatory filling pressure drives venous return, they contradict that mean circulatory filling pressure is only an abstract quantity in the world of mathematics and does not exist as a physiological driving pressure. Furthermore, they argue that although venous return resistance has a resistance unit, such resistance does not exist in the vein and the quantity is abstract. Consequently, teaching medical students about this topic will only confuse the students [17].

On the other hand, the biggest argument of supporters who advocate that Guyton's physiology should be taught at medical schools is that the concept of circulatory equilibrium can be derived by accepting the venous return curve [18, 21]. As a result, it is essentially possible to use simple graphs to describe the cardiac output and venous pressure in various disease states encountered clinically. They claim that this point is the greatest feature of Guyton's physiology, and the most important clinical model in educating medical students.

Author's view regarding Guyton's venous return

Regarding the first counterpoint against Guyton's venous return as mentioned above, the view that venous pressure is a dependent function of cardiac output is certainly true. However, the most important point here is that the experiment was done under the condition of constant stressed volume. Under this condition, venous pressure and venous return are mutually dependent; when one is fixed, the other is definitively determined. Thus, the two bear a linear relationship. Therefore, the idea that one is an independent variable and the other a dependent variable is not valid. We believe that the discussion of which of them is an independent variable is futile, and the argument itself is meaningless.

The second counterpoint is the stance that venous return is being driven by the pressure gradient between mean circulatory filling pressure and venous pressure. In actual fact, mean circulatory filling pressure does not exist physically as a source of pressure. Under the condition of constant stressed volume, venous return behaves as if venous return resistance is driven by the difference between the mean circulatory filling pressure and venous pressure, as shown above. The mean circulatory filling pressure is only an amount calculated from the ratio of stressed volume to vascular bed compliance, and such pressure source does not physically exist in the vascular bed. Venous return resistance is determined by a complex combination of vascular resistance and compliance (details to be described below), and no such viscous resistance exists physically. However, when the circulatory system, described by a combination of compliance (amount of blood stored proportional to pressure) and resistance (blood flow proportional to pressure), is driven at constant stressed volume, the relation between venous pressure and venous return is a mathematical inevitability with no room for debate. Our view is that if such concept deepens knowledge, then the concept together with the physiological characteristic quantities derived from adopting the concept should be utilized without hesitation.

Guyton's view that the pressure gradient between mean circulatory filling pressure and venous pressure drives venous return resistance to determine venous return explains an inevitable relationship only under the condition of constant stressed volume. We therefore see no problem with Guyton's idea. As mentioned earlier, there is no mistake that venous return is generated because the arterial pressure is higher than the venous pressure. However, to maintain a constant stressed blood volume, a reciprocal relationship exists between venous pressure and venous return, and this relationship is determined explicitly. This is equivalent to Ohm's law that states with resistance once decided, the voltage–current relation is unequivocally determined. Hence, the argument of which is an independent variable and which is a dependent variable makes no sense. Although blood is actually not driven by mean circulatory filling pressure, such relationship is valid in functional (mathematical) terms. If adopting functional resistance would provide reasonable explanations for circulatory equilibrium, universality will emerge despite the abstract nature of this parameter, and will result in better understanding of venous return.

Limitations of Guyton's venous return and their resolution

Having explained the usefulness of Guyton's venous return, we also need to point out that there are serious limitations. The biggest limitation in our opinion is that Guyton's venous return curve and circulatory equilibrium alone do not describe the preload of the left cardiac system. Therefore, these concepts impede discussion of the circulatory equilibrium in the setting of left heart failure, which is the most problematic clinical issue. To overcome this limitation of Guyton's venous return, we opened the circulation loop not only at the right atrial level but also at the left atrial level, and experimentally confirmed the effects by theoretically inducing a relationship between venous pressure and venous return. We introduce our work below with the aim to deepen the understanding of venous return [22–24].

Although slightly complicated, we shall introduce the mathematical process. As shown in Fig. 5, the vascular bed is composed of a distributed system circuit with resistance and compliance sequentially connected from the artery to the vein. The blood pressure–blood flow relationship is assumed to follow Ohm's law, and the volume of blood stored in compliance is assumed to be proportional to blood pressure. This is a common assumption in the world of circulatory physiology and circulatory dynamics, and there is no major discrepancy from experimental data. We use

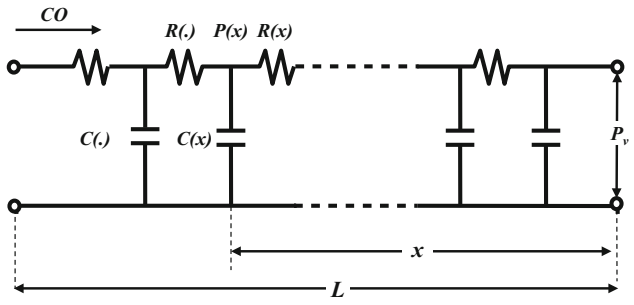

Fig. 5 Vascular model expressed by distributed system

this blood vessel model to obtain blood flow, stressed volume, mean circulatory filling pressure, venous return resistance, and other parameters. Moreover, we extend the circulatory system to systemic and pulmonary circulations to identify the characteristics of venous return of the whole circulatory system.

Let $C(x)$ be the vascular compliance at a distance x from the terminal end of the vein, $R(x)$ be the cumulative resistance from that point to the terminal end of the vein, $P(x)$ be the blood pressure at that point, and P_v be the venous blood pressure [22]. Let the cardiac output be CO. The stressed volume (V) stored in the whole blood circulatory system is as follows:

$$V = \int_0^L P(x)C(x)\mathrm{d}x. \tag{3}$$

Since $P(x) = R(x)\ \mathrm{CO} + P_v$, substituting into Eq. (3) gives:

$$V = \int_0^L \{(R(x)\mathrm{CO} + P_v\}C(x)\mathrm{d}x \tag{4}$$

Since CO and P_v that are independent of x may be a scalar of integration, Eq. (4) becomes:

$$V = \mathrm{CO}\int_0^L R(x)C(x)\mathrm{d}x + P_v\int_0^L C(x)\mathrm{d}x. \tag{5}$$

Let the compliance of the whole vascular bed be C and the distribution of normalized compliance be $C_d(x)$ (which becomes unity when integrated), the following is obtained:

$$V = \mathrm{CO}\ C\int_0^L R(x)C_d(x)\mathrm{d}x + C\ P_v \tag{6}$$

Rearranging the equation while considering $V = C\ P_m$, the equation becomes

$$\mathrm{CO} = \frac{V - C\ \cdot P_v}{C\int_0^L R(x)C_d(x)\mathrm{d}x} = \frac{P_m - P_v}{\int_0^L R(x)C_d(x)\mathrm{d}x} = \frac{P_m - P_v}{R_v}. \tag{7}$$

From Eq. (7), the pressure driving venous return is the difference between mean circulatory filling pressure and venous pressure, as shown in the numerator. Venous return resistance (R_v) is defined by the denominator. This equation implies that venous return resistance can be obtained by integrating over the whole vascular bed the cumulative resistance at every point of the vascular bed weighted by the compliance at the site. Since compliance is overwhelmingly concentrated in the vein, the actual venous return resistance is greatly influenced by venous resistance but little affected by arterial resistance. Equation (7) corresponds to Eq. (2) obtained by Guyton from his six-element electrical circuit model. This fact shows that although Guyton derived Eq. (2) using a simple model, the same result is obtained when using the more generalized distributed model. One aspect of the broad utility of Guyton's model is emerging.

This result is then extended to integrate venous return from the systemic circulation with that from the pulmonary circulation. The stressed volume, compliance and venous return resistance for systemic circulation and pulmonary circulation are expressed by the subscripts s and p, respectively. From Eq. (6), the following are obtained:

$$V_s = \mathrm{CO}\ C_sR_{\mathrm{vs}} + C_sP_{\mathrm{RA}} \tag{8}$$

$$V_p = \mathrm{CO}\ C_pR_{\mathrm{vp}} + C_pP_{\mathrm{LA}}. \tag{9}$$

Considering that the sum of stressed volume for the systemic and pulmonary circulation ($V = V_s + V_p$) is constant, and that cardiac output is same for systemic and pulmonary circulation, adding both sides of Eqs. (8) and (9) gives the following:

$$V = \mathrm{CO}(C_sR_{\mathrm{vs}} + C_pR_{\mathrm{vp}}) + C_sP_{\mathrm{RA}} + C_pP_{\mathrm{LA}}. \tag{10}$$

Since both vascular resistance and compliance of the systemic circulation are 7–8 times larger than those of the pulmonary circulation [12], the error is around 2% even if approximated by $C_sR_{\mathrm{vs}} + C_pR_{\mathrm{vp}} \approx C_sR_{\mathrm{vs}}$. Furthermore, arranging Eq. (10) for cardiac output when $V = (C_s + C_p)P_m$ gives:

$$\mathrm{CO} \approx \frac{V}{C_sR_{\mathrm{vs}}} - \left(\frac{1}{R_{\mathrm{vs}}}P_{\mathrm{RA}} + \frac{1}{\frac{C_s}{C_p}R_{\mathrm{vs}}}P_{\mathrm{LA}}\right). \tag{11}$$

This relationship is presented in Fig. 6 (left). Venous return decreases as left atrial pressure and right atrial pressure increase, constituting a venous return plane. The slope of this surface with respect to the right atrial pressure is determined by the reciprocal of the venous return resistance of the systemic circulation (R_{vs}), and the slope with respect to the left atrial pressure by the reciprocal of C_s/C_p-fold the venous return resistance of the systemic circulation (1/7–1/8 times the slope for the left than for the

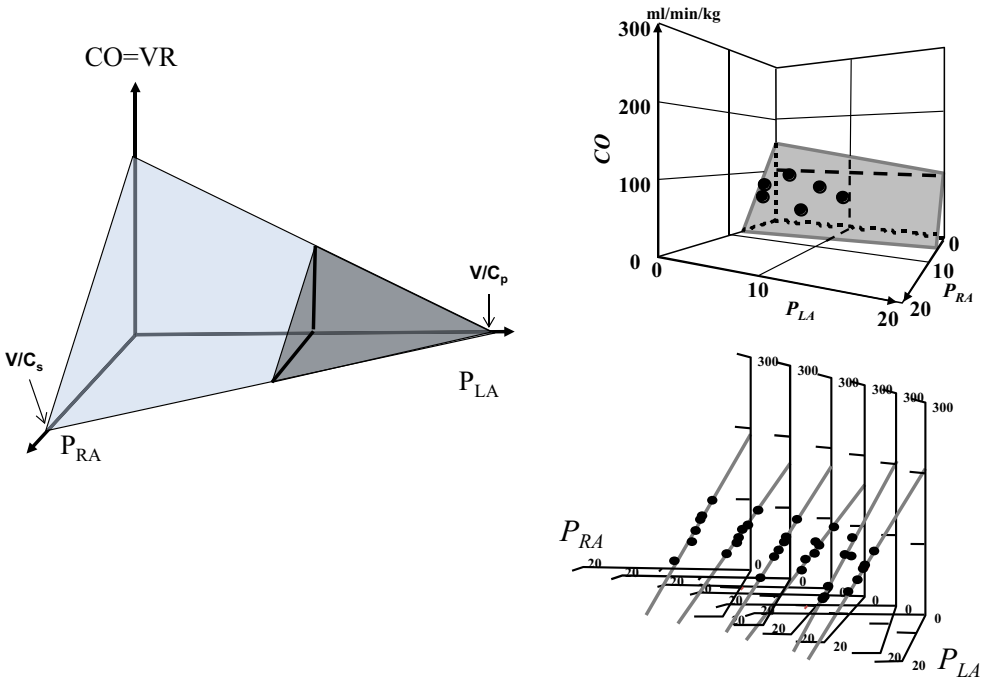

Fig. 6 Venous return surface shown on a triangular pyramid which most extends along the left atrial pressure axis (*left*), experimentally obtained venous return surface (*right*)

right). The intercept of right atrial pressure is the mean systemic filling pressure when blood flow is interrupted and all the blood is collected in the systemic circulation, and is given by $P_{\mathrm{ms}} = V/C_s$. The intercept of the left atrial pressure represents the mean pulmonary circulation filling pressure generated when all the blood is collected in the pulmonary circulation, and is given by $P_{\mathrm{mp}} = V/C_p$. Obviously, the compliance of pulmonary blood vessels is much smaller than that of systemic blood vessels, therefore $P_{\mathrm{mp}} \gg P_{\mathrm{ms}}$. The intercept of the venous return axis is obtained by dividing the systemic mean filling pressure by the systemic venous return resistance, and represents the maximum venous return for a given stressed volume. Since the actual increase in physiological left atrial pressure is limited, the physiological venous return surface assumes a shape obtained by cutting out a part of the triangular pyramid as shown in the figure. Figure 6 (left) is an extension of Guyton's venous return for systemic and pulmonary circulations under the condition of constant stressed volume, and this diagram describes universally the venous return–venous pressure relationship.

In order to theoretically derive the venous return surface, we made a loose hypothesis regarding vascular resistance and compliance. Experimental validation is obviously required to establish the correctness of the derived venous return surface. We performed experiments by bypassing both the left and the right hearts, and perfusing the systemic and pulmonary circulations using pumps. To determine the venous return surface, we fixed the stressed volume, changed the blood distribution of systemic circulation and pulmonary circulation, and investigated whether the actual operating points constitute a plane [23]. As shown on the right side of Fig. 6, venous return forms a plane with left and right atrial pressures. To verify the accuracy of the surface, we observed the distribution of operating points over the surface. If the surface is strictly planar, the operating points will be distributed on a straight line, the projection of the surface. As shown on the right side of Fig. 6, all the operating points are distributed exactly on a straight line, indicating that the venous return surface is an exact plane. Also, changing the stressed volume results in a parallel shift of the plane in an up–down direction. Thus, the features of the theoretically derived venous return plane were reproduced experimentally.

Limitations of Guyton's cardiac output curve and circulatory equilibrium, and their resolution

As mentioned above, Guyton's circulatory equilibrium ingeniously explained various disease conditions. However, it has two major limitations. The first is that the cardiac output curves of the right heart and the left heart are not depicted independently. Without this distinction, it is difficult to understand the changes in hemodynamics associated with left heart failure and right heart failure. This issue can be solved by obtaining the cardiac output curves for the right heart and the left heart separately and then drawing the integrated cardiac output curve of the two as a function of the right atrial pressure and the left atrial pressure. In Fig. 7, the graph on the left shows Guyton's

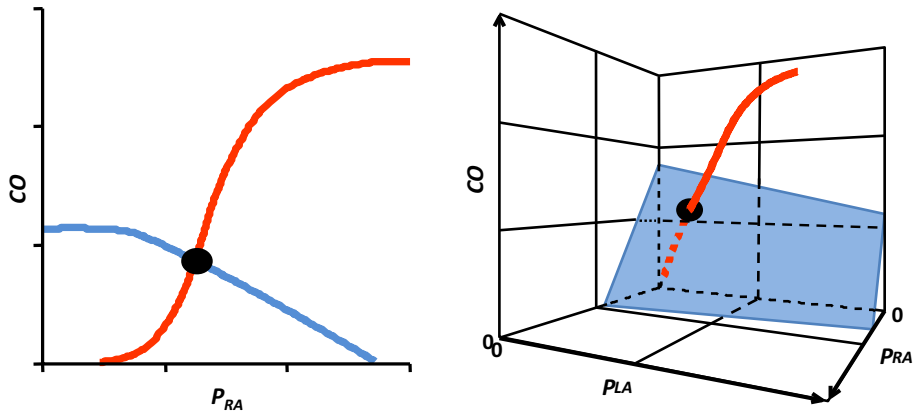

Fig. 7 Guyton's venous return curve and cardiac output curve (*left*), venous return surface and integrated cardiac output curve (*right*)

venous return and cardiac output curves, and that on the right presents circulatory equilibrium described by the integrated cardiac output curve obtained as mentioned above and the venous return surface. Using this framework, not only cardiac output but also left and right atrial pressures can be determined from the equilibrium point. In the case of left heart failure, the cardiac output curve of the left heart is depressed, consequently the cardiac output at the equilibrium point decreases while the left atrial pressure increases markedly. On the contrary, in the case of right heart failure, the right atrial pressure increases as cardiac output decreases. Therefore, by using the integrated cardiac output curve and the venous return surface, it is possible to describe the circulatory equilibrium in various pathological conditions simply with a graph, as was done by Guyton.

The second limitation is that the cardiac and vascular characteristics that affect the cardiac output curve, which had been sought since Frank-Starling, have not been identified quantitatively. To understand disease conditions, it is necessary to quantitatively know how the dynamic properties of the heart and blood vessels influence the cardiac output curve. As a point of entry to this inquiry, we established a framework of ventriculo-arterial coupling.

Quantitative representation of cardiac output curve by expansion of ventriculo-arterial coupling

In the 1980s, Suga and colleagues [25–27] demonstrated that the dynamics of the ventricle can be accurately represented by time-varying elastance. Especially, the end-systolic elastance (E_{es}) expresses the cardiac contractility in a load-insensitive manner. Using this idea, the end-systolic pressure (P_{es}), the end diastolic volume (V_{ed}), the stroke volume (SV), and volume at zero pressure (V_0) can be described by the following relationship:

$$P_{es} = E_{es}(V_{ed} - SV - V_0). \tag{12}$$

On the other hand, Sunagawa and colleagues [28–30] focused on the fact that the mean arterial pressure and end-systolic pressure have similar magnitude, and the afterload constituted by the arterial system can be approximated by the effective arterial elastance (E_a) obtained by dividing the vascular resistance (R) by the cardiac cycle (T) ($E_a \approx R/T$) (Fig. 8, left). Using this relationship, the arterial system can be expressed in terms of elastance, as follows:

$$P_{es} = E_a SV = \frac{R}{T} SV. \tag{13}$$

Solving Eqs. (12) and (13), and expressing in terms of SV yields the following:

$$SV = \frac{E_{es}}{E_{es} + E_a}(V_{ed} - V_0). \tag{14}$$

By using Eq. (14), it was confirmed that SV obtained from the ventricular and arterial characteristics very accurately concur with the actually measured values, and the framework of coupling with the arterial vessel was established. Expanding to cardiac output by multiplying Eq. (14) with heart rate gives:

$$CO = \frac{60}{\frac{60}{HR} + \frac{R}{E_{es}}}(V_{ed} - V_0) \tag{15}$$

It is known that in the heart, the actual end-diastolic volume is determined by venous pressure, and that the end-diastolic pressure–volume relationship follows a simple exponential function (especially when the ventricular volume is in the physiological range). Therefore, the relationship of end-diastolic pressure (P_{ed}) and stiffness of the heart at diastole (E_{ed}) is as follows:

$$P_{ed} = e^{E_{ed}(V_{ed} - V_u)} + P_0 \tag{16}$$

From Eq. (16), left ventricular volume within the physiological range is approximated as:

$$V_{ed} \approx \frac{1}{E_{ed}} \ln(P_{ed}). \tag{17}$$

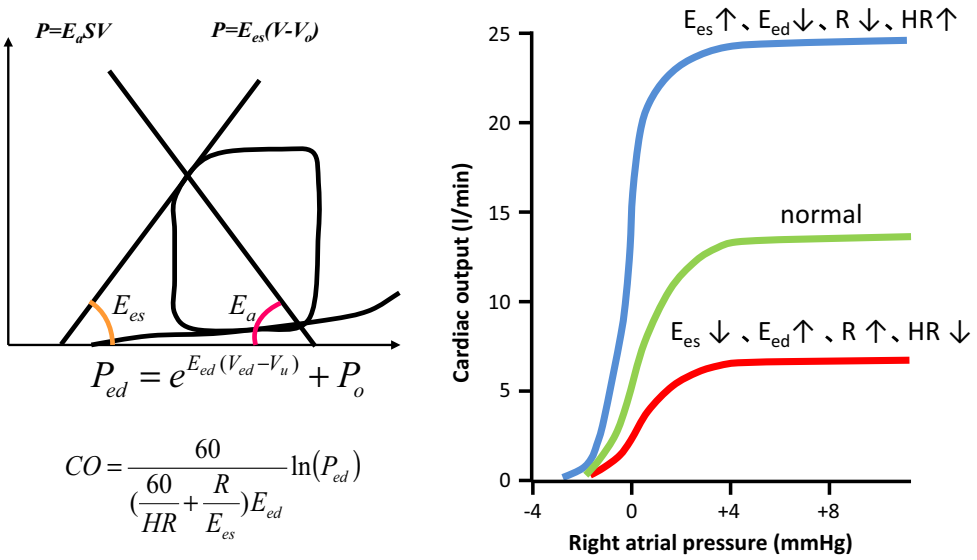

Fig. 8 Analytical solution of cardiac output curve by extending ventricular-arterial coupling framework (*left*), factors determining the cardiac output curve (*right*)

CO can be approximated by substituting Eq. (17) into Eq. (15), as follows:

$$\mathrm{CO} \approx \frac{60}{\left(\frac{60}{\mathrm{HR}} + \frac{R}{E_{es}}\right)E_{\mathrm{ed}}} \ln(P_{\mathrm{ed}}). \tag{18}$$

Equation (18) shows that cardiac output increases logarithmically with increasing preload, and the manner of bending is derived from (the reciprocal of) the exponential characteristics of the diastolic characteristics. By examining the cardiac and vascular parameters in the denominator and numerator, it is possible to delineate how the cardiac output curve is modified quantitatively by these factors. The graph on the right in Fig. 8 indicates qualitatively how various properties of the ventricle and blood vessel modify the cardiac output curve. Uemura and colleagues [24] validated experimentally that the cardiac output curve can be approximated by this equation. Equation (18) can be used to define the cardiac output curve for either the left or the right heart, and the cardiac output curve that describes both at the same time is defined as the integrated cardiac output curve.

Circulatory equilibrium obtained from the integrated cardiac output curve and venous return surface

Applying the extended concept of circulatory equilibrium, Fig. 9 shows the relationship between the predicted and measured values of circulatory equilibrium in response to changes in stressed volume when the integrated cardiac output curve and venous return surface are known. Cardiac output, right atrial pressure, and left atrial pressure are found to be accurately estimated for a wide range of stressed volume [24].

The above findings show that the current circulatory equilibrium framework with the integrated cardiac output

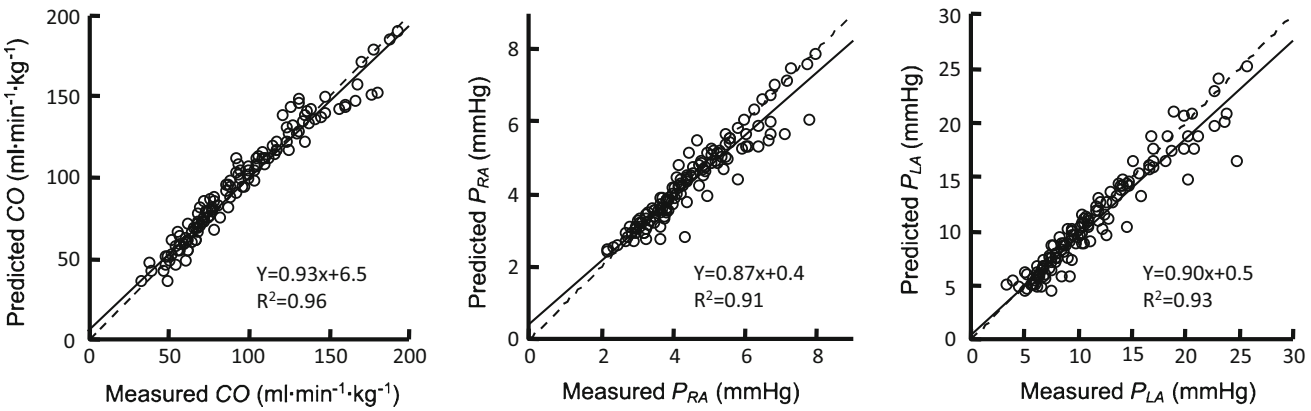

Fig. 9 Prediction of circulatory equilibrium (*left* cardiac output, *middle* right atrial pressure, *right* left atrial pressure)

curve and venous return surface, while preserving the excellent qualities of Guyton's classic circulatory equilibrium, is more generalized and takes into account the systemic circulation, pulmonary circulation, right heart failure, and left heart failure. It is an extremely powerful analytical framework that allows systematic consideration of left heart failure. Extension of the classic concept was only possible because of the existence of previous research in which Guyton opened the circulation loop at the vein and defined circulatory equilibrium by the cardiac output curve and venous return.

Conclusions

In recent years, the merits and demerits of Guyton's physiology have been widely debated. However, when we look at the arguments, none of the papers raised questions about experimental facts. Consequently, there were few questions about the most elegant outcome of Guyton's physiology; that circulatory equilibrium is depicted graphically and can be applied clinically. On the other hand, many questions were directed to interpretation of the experimental results; for example, is venous return driven by mean circulatory filling pressure, and what is venous return resistance. Although all the issues in question concern some sort of abstract quantities, the relationship between venous pressure and venous return is unambiguously established in that they bear a reciprocal relationship mathematically when stressed volume is unchanged. In our opinion, despite being abstract, if the concept contributes to more in-depth understanding, then the concept as well as the functional quantities derived from the concept (including venous return resistance and mean circulatory filling pressure) should be accepted positively. The author's generation is probably the last generation that has the opportunity to talk directly with Guyton. From personal experience through direct discussion, Guyton was a rare scholar who challenged circulatory physiology with mathematical rationality as well as exceptionally finely honed sensibility. With his undoubtedly huge research achievement, Guyton is the greatest physiologist in human history. In our views, Guyton's physiology is the foundation of circulatory physiology, with potential for extension. It should be taught in the medical school, and we believe that more comprehensive circulatory physiology will be born from generations who receive the teaching.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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