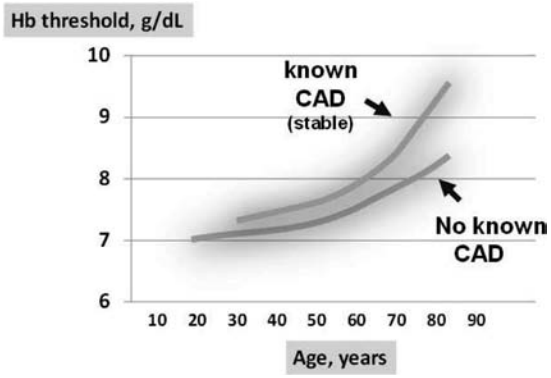

Figure 2. A schematic representation of hemoglobin thresholds based on the patient's age and the presence of coronary artery disease (*CAD*). This scheme is based primarily on clinical experience, rather than on hard data.

have the same blood transfusion requirements as an elderly patient with coronary artery disease. Transfusing all patients at the same threshold level, whatever that level is, will therefore likely harm some patients but be of benefit to others. The current paper by Park et al (8) should encourage us once again to rethink our transfusion practice. Decisions to transfuse need to be based on individual patient characteristics, including age and the presence or risk of coronary artery disease (Fig. 2). A transfusion threshold of 9 or 10 g/dL will not be appropriate for everybody, but neither will a threshold of 7 g/dL: the challenge is to balance the risks of anemia and the risks of transfusion to determine the correct transfusion trigger for each individual patient.

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Good old physiology in a modern jacket*

William Harvey (1578–1657) was the first to demonstrate the continuity of the circulation with the heart as its "pump," which he published in his book, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, in 1628. Harvey also discovered that the heart received blood from the venous side of the circulation to generate cardiac output. These physiologic concepts form the cornerstone of modern cardiovascular physiology, but were at the time of publication widely received with skepticism because of the dominant "Galenian" thinking, i.e., assuming two distinct circulations with the heart just as a generator of heat. Built on the concepts of Harvey, Otto Frank and Ernest Starling demonstrated more than three centuries later the dependency of stroke volume on cardiac filling, hereby further enhancing our physiologic knowledge (1, 2). The main question in cardiovascular physiology, however, was still unanswered: what drives the circulation? It was not until the fifties of the 20th century that Arthur Guyton (3, 4) could give a reasonable and conclusive answer. In his concepts about the regulation of cardiac output, not the cardiac pump itself but three other factors determine cardiac output (5):

- Venous return to the heart (VR)
- Cardiac function
- The degree of vascular filling

Here, blood flow depends on VR, which in turn is determined by the pressure difference of the right atrium and

*See also p. 3146.

Key Words: cardiac output; cardiovascular physiology; mean systemic filling pressure; norepinephrine; venous return

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the venous side of the circulation and the resistance to flow. Theoretically, if pressure difference of the right atrium increases to an extent that blood flow finally stops, pressure in both the arterial and venous side of the circulation would equilibrate to a static value, the mean systemic filling pressure (P_{MSF}; the upstream pressure of VR) (6). Subsequently, Guyton plotted his famous "venous return curves," showing the dependency of VR on pressure difference of the right atrium and P_{MSF} (7). In clinical medicine, Guyton's physiologic concepts almost seem forgotten, and the validity and exact characteristics of these concepts under various states of disease, such as in septic shock, are still unknown. At first, this is explained by the continuing debate about the validity of Guyton's concept of cardiac output regulation, i.e., the correctness of the interpretations derived by Guyton's experimental model as well as the model itself (6, 8). The interested reader is referred to an interesting and very detailed point–counterpoint discussion (8). At second, the concept of VR has been disputed simply because, according to Harvey's observation that the blood flows in a closed circle, VR to the right heart must equal cardiac output of the left heart, at least on average. Third, the concepts of Guyton cannot be easily validated in the human body with an intact circulation, as the traditional determination of P_{MSF} requires cardiocirculatory arrest. Recently though, a method was developed to estimate P_{MSF} with revolutionary ease under clinical circumstances in patients with a beating heart and intact circulation (9). During inspiratory hold maneuvers in sedated and mechanically ventilated patients, paired measurements of cardiac output and central venous pressure (as a surrogate for pressure difference of the right atrium) are plotted in a VR-curve where P_{MSF} is defined as the zero flow intercept (comparable to the Guyton curves). This new approach using heart–lung interactions might stimulate a revival of studying the concepts of good old cardiovascular physiology.

The endogenous catecholamine norepinephrine is a well-known pharmacological agent, which has been used for decades as a vasopressor since it stimulates α_1-adrenoceptors and hereby causes arterial vasoconstriction. Furthermore, it may improve cardiac function by $ß_1$ and some α_1 stimulation. Based on these characteristics, norepinephrine belongs to the first line agents in the treatment of septic shock according to current guidelines (10). Nevertheless, little research has been spent to elucidate the characteristics of this commonly used agent on the venous side of the circulation.

In this issue of *Critical Care Medicine*, Persichini and coworkers (11) elegantly combine these two aspects by incorporating modern pharmacotherapy with the classical cardiovascular physiology using the aforementioned experimental model to measure P_{MSF}.

They studied the effects of norepinephrine on P_{MSF} and VR in patients suffering from septic shock (n = 16) and found that when the dosage of norepinephrine was decreased P_{MSF} decreased to a larger extent than resistance to VR, resulting in a net decrease in VR and thus cardiac output. The authors correctly point out that the observed decrease in VR after decreasing the norepinephrine dosage might be caused by decreased α^1-adrenergic stimulation, resulting in a decreased intravascular pressure on the venous side of the circulation. Here, "unstressed" blood volume (i.e., the blood volume necessary to "fill" blood vessels without generating an intravascular pressure) is increased while the "stressed" blood volume (generating intravascular pressure, resembling P_{MSF} in case of no-flow) is decreased. Another striking observation in the current study is that of a more pronounced increase in cardiac output with passive leg raising *after* norepinephrine was decreased, feeding the hypothesis of an increased unstressed blood volume after decreasing norepinephrine dosages. With this approach the authors put Guyton's concepts of cardiovascular physiology into a modern jacket.

However, this concept does not take possible alternative explanations into account: one might argue that norepinephrine influences the distribution of venous blood, e.g., in the lower extremity, due to different adrenoceptor-concentrations between vessels (12). The authors have also raised this point and acknowledge that the current study design detains the alternative hypothesis to be tested. Nevertheless, the results of the current study are intriguing; it further elucidates the characteristics of norepinephrine on the venous side of the circulation during real-life situations, which was until recently impossible to measure. These results are encouraging and open the field for further investigations under circumstances other than septic shock. Ultimately, more knowledge about our pharmacological agents might enhance their clinical use and improve patients' outcome! It took a long time from Harvey's anatomical cardiovascular perception to Guyton's physiological concepts. In the end, all models are inaccurate, and the best model for studying the human body's physiology is the human body itself. We should focus on studies such as the one from Persichini and co-workers and appreciate the derived information demonstrating important characteristics of one of the most frequently used pharmacological agents in patients with septic shock.

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Diagnosis of ventilator-associated pneumonia: Do we need surrogate parameters?*

There is no doubt that ventilator-associated pneumonia (VAP) is a frequent life-threatening complication of endotracheal intubation and mechanical ventilation. The reported raw prevalence of VAP ranges from 10% to 25% in patients who undergo mechanical ventilation for >24 hrs, and its prevalence density rate ranges between 9 and 15 cases per 1,000 days of mechanical ventilation (1). These figures usually include patients with and without microbiologically confirmed pneumonia.

For many years, the prevalence of VAP has been reported using only clinical signs of infection, irrespective of microbiological confirmation. When microbiological cultures are applied to the diagnosis, the prevalence decreases. A recent article by Morris et al (2) showed that using specific diagnostic methods (bronchoalveolar lavage) and quantitative cultures, the prevalence of VAP decreased by 76% and the prevalence density rate fell from 11 to 6 per 1,000 days of mechanical ventilation. In line with these results (personal communication, 2012), we recently compared patients with suspected VAP and hospital-acquired pneumonia with and without microbiological diagnosis. In the group of patients without microbial diagnosis, we did not include those patients who had received antibiotic treatment before respiratory sampling, in order to avoid confounding biases. The 90-day mortality was lower in patients with suspected VAP without microbiological diagnosis, clearly suggesting that some of the patients with clinically suspected VAP ultimately did not present pneumonia.

It is obvious that the clinical definition of VAP released by the Centers for Disease Control and Prevention is not of much help (3) because some of the components are not very specific. The latest American Thoracic Society/Infectious Disease Society of America (4) definition of clinically suspected VAP included radiographic infiltrate that is new or progressive, along with clinical findings suggesting infection, which include new onset of fever, purulent sputum, and leukocytosis or leucopenia. Fundamental studies demonstrated 30% of false-positive and false-negative results using postmortem quantitative cultures of lung samples, which is normally considered the gold-standard for diagnosing VAP (5).

All these problems in the diagnosis of VAP have lead to a search for surrogate and more objective parameters as it is the case of the study by Klompas et al, published in this issue of *Critical Care Medicine* (6).

The authors should be commended for the extensive amount of work done to demonstrate that deteriorating ventilator settings are strongly associated with worse outcomes. The novel definition "ventilator-associated complication" opens up new fields of research into improve morbidity and mortality in tracheally intubated and mechanically ventilated patients.

Nevertheless, the authors' choice to associate this new surveillance definition with VAP is highly debatable and a matter of great concern in this field of research. The primary potential consequence of this new definition of VAP is an inappropriate over-inflation of the reported prevalence.

In the study by Klompas et al (6), authors attempted to define VAP in a large tracheally intubated and mechanically ventilated population (>8,000 patients) using a combination of three different thresholds for respiratory deterioration, associated with two different thresholds for stability prior to respiratory deterioration, systemic signs of respiratory infection, and purulent pulmonary secretions with or without a pathogenic culture.

The authors then applied these definitions to retrospective clinical data to assess the potential VAP prevalence density rate and their associations with adverse outcomes using multivariate regression models for cases. Thus, using increasing thresholds for respiratory deterioration, they found a VAP prevalence density rate of 15.6, 12, and 8.4/1,000 ventilatory days; whereas, using the three respiratory deterioration thresholds with clinical signs of respiratory infection, the prevalence density rate drastically decreased to 1.7, 0.6, and 0.5. Interestingly, when the authors used only purulent pulmonary secretions and positive respiratory-secretions cultures, the prevalence density rate was 11.3, a value that closely matches the currently reported data in the literature. To calculate several parameters of outcome, cases were matched to controls on the basis of hospital, department, age, Charlson score, and duration of mechanical

***See also p. 3154.**

Key Words: diagnosis; hospital-acquired pneumonia; intensive care unit–acquired pneumonia; quality processes; ventilator-associated pneumonia

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Point:Counterpoint: The classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct

PURPOSE AND SCOPE OF THE POINT:COUNTERPOINT DEBATES

This series of debates was initiated for the *Journal of Applied Physiology* because we believe an important means of searching for truth is through debate where contradictory viewpoints are put forward. This dialectic process whereby a thesis is advanced, then opposed by an antithesis, with a synthesis subsequently arrived at, is a powerful and often entertaining method for gaining knowledge and for understanding the source of a controversy.

Before reading these Point:Counterpoint manuscripts or preparing a brief commentary on their content (see below for instructions), the reader should understand that authors on each side of the debate are expected to advance a polarized viewpoint and to select the most convincing data to support their position. This approach differs markedly from the review article where the reader expects the author to present balanced coverage of the topic. Each of the authors has been strictly limited in the lengths of both the manuscript (1,200 words) and the rebuttal (400). The number of references to publications is also limited to 30, and citation of unpublished findings is prohibited.

POINT: THE CLASSICAL GUYTON VIEW THAT MEAN SYSTEMIC PRESSURE, RIGHT ATRIAL PRESSURE, AND VENOUS RESISTANCE GOVERN VENOUS RETURN IS CORRECT

What makes the blood go around? This must be one of the most fundamental questions in cardiovascular physiology. It at first seems intuitively obvious that the heart must be the primary source of energy. Indeed it has been argued that the pressure gradient from the aorta to the right atrium determines the flow (14, 24, 25). However, it is evident that the pressure generated by the heart bears no relationship to total flow in the system (13). For example, cardiac output can increase more than five-fold during exercise with only moderate changes in arterial pressure and double in septic patients with a fall in blood pressure. Arthur Guyton advanced our understanding of the determinants of steady-state blood flow by analyzing the dual roles of right atrial pressure (Pra): *1*) as the determinant of the filling of the right heart in Starling's law of the heart and *2*) as the back pressure to the blood flow from the circuit (3).

A key element in Guyton's analysis is the role of the elastic recoil pressure of the circuit. The flow of water out of a bathtub provides a useful analogy for understanding the role of this elastic force (15, 19). The rate of emptying of a bathtub is determined by the height of water above the bottom and the drainage characteristics of the tube draining the tub, which include the resistance to flow and downstream pressure. Inflow from the tap only affects outflow by increasing the height of water in the tub. Importantly, the force or pressure coming out of the tap does not affect outflow, only the volume filling the tub provides the "elastic" energy for emptying the tub. When the tub is filled, the initial rate of emptying through the drain is the same whether the tap is on or off.

Similarly the volume that fills and stretches the elastic structures of the vasculature produces a pressure that provides the potential energy for the system. This pressure is determined by the volume and total compliance of the vasculature and is called mean systemic filling pressure (MSFP). Its importance was first recognized by Weber in the 19th century (see Refs. 3 and 26) and later by others (2, 9). Total vascular compliance is determined by the sum of the regional compliances. Venules and veins contain ~70% of blood volume at a low pressure and thus their compliance (Cv) dominates the characteristics of the vasculature and acts much like a bathtub.

When the pressure downstream of a bathtub is the same as the pressure in the tub, the tub does not empty. Similarly, when the pressure downstream to the venules and veins (i.e., Pra) is equal to MSFP, there is no flow. Flow only occurs when Pra is lowered relative to MSFP. The heart has two roles in this process. Cardiac contractions lower Pra and allow greater emptying of the circuit. Second, the heart provides a crucial "restorative" force. That is, it pumps the blood back into the systemic circulation and maintains the initial elastic recoil pressure. Of importance, the heart cannot significantly increase MSFP. This is because the volume that the heart pumps comes from the region of MSFP and there is no other substantial source of volume that the heart can use to augment MSFP except for small amounts from the pulmonary circuit and large veins (21).

Guyton showed that the return of the blood to the heart (VR) is approximated by the equation $VR = (MSFP - Pra)/Rv$, where Rv refers to the cumulative resistance in the venous system (12). Steady-state cardiac output must equal VR and visa versa and the overall flow from the heart is regulated by adjustments in the mechanical characteristics of the circuit and the heart (18). Because Pra is the determinant of venous return that is regulated by the heart, it is appropriate to consider Pra as the independent variable for venous return when venous resistance, compliance, and stressed volume are constant. Accordingly, Arthur Guyton developed his very elegant graphical analysis of the interaction of cardiac and return function by placing Pra on the *x*-axis and flow on the *y*-axis (Fig. 1; Ref. 10).

Veins have floppy walls and collapse when inside pressure is less than outside pressure, which produces what is called a vascular waterfall (23). Normally collapse occurs around atmospheric or "zero" pressure and when "waterfall" conditions are present further decreases in Pra do not increase flow. Thus for a given set of circuit conditions, the maximal possible cardiac output occurs when Pra is ≤0. The heart also produces a limit to cardiac output when the plateau of the cardiac function curve is reached (17). As Guyton termed it, the heart determines "permissible" flow (11).

This allows an appreciation of the significance of the potential energy from the volume in the venules and veins. If the circulation is arrested and the veins are disconnected from the heart and allowed to drain to atmospheric pressure, there is

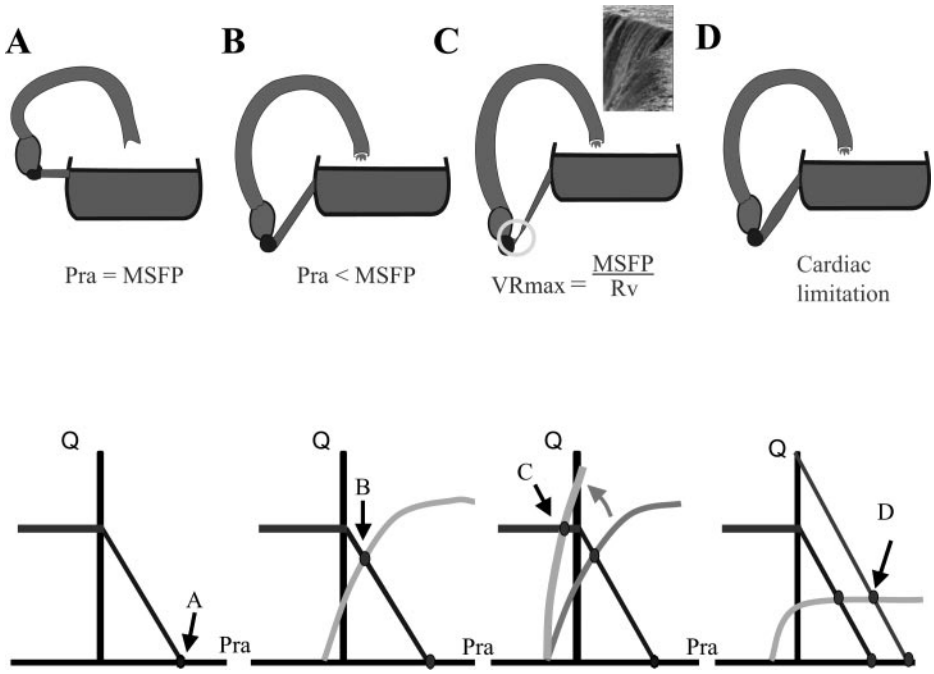

Fig. 1. Schematic model of the circulation and graphical analysis of the interaction of cardiac function and return function. *A*: right atrial pressure (Pra) equals mean systemic filling pressure (MSFP) and flow is zero. *B*: cardiac function curve intersects the return function and the 2 define the operating cardiac output, the venous return and the Pra. *C*: Pra is <atmospheric pressure and venous return is maximal ("waterfall" condition); increases of cardiac function in this range do not increase cardiac output ("return limited"). *D*: the return curve intersects the plateau of the cardiac function curve so that an increase in the return function does not increase cardiac output ("cardiac limited").

immediate flow, which is the maximal possible for the system. This maximal possible flow occurs without a heart and the heart can only get in the way by giving a Pra >0 (22)! Obviously this maximal flow is very transient, for the elastic recoil energy is rapidly dissipated and the energy must be "restored" by the work of the heart. Maximum possible flow in the system is determined by stressed volume divided by the time constant of its drainage, which is given by Rv × Cv.

The effects of small changes in downstream pressures are very evident in experimental preparations in which venous return and cardiac function are disconnected (4–8, 20). In these experiments, the vena cavae are cannulated and drain through "y" connectors, which create vascular waterfalls. Blood drains into a reservoir and is pumped back into the animal at a fixed flow rate. Adjusting the height of the y connectors can regulate venous outflow pressures. Raising the y connectors produces an immediate fall in outflow, which then returns to a new steady state after volume accumulates in the upstream vessels and increase the regional MSFP. The converse occurs when the y connectors are lowered as long as venous pressure is greater than atmospheric pressure. By design, inflow remains constant. It might be expected that the arterial pressure would rise with the increases in venous pressure (1), but it does not. This is likely due to a Starling resistor-like mechanism at the level of the arterioles, which produces an arterial vascular waterfall (16) so that regional increases in MSFP do not affect arterial flow until they exceed the waterfall pressure. The presence of a Starling resistor further strengthens the argument that the forward force from the heart does not directly regulate venous flow and arterial inflow behaves like a tap in a bathtub.

In conclusion, cardiac output is determined by the interaction of cardiac function and return function. The volume filling the compliant vessels of the vasculature provides an elastic recoil pressure, which is the major source of energy for the flow of blood to the right heart. Pra acts as a backpressure to this flow, and the heart can regulate cardiac output by regulating Pra. The heart also restores the volume that drains from the systemic circulation and maintains MSFP.

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COUNTERPOINT: THE CLASSICAL GUYTON VIEW THAT MEAN SYSTEMIC PRESSURE, RIGHT ATRIAL PRESSURE, AND VENOUS RESISTANCE GOVERN VENOUS RETURN IS NOT CORRECT

How mean circulatory pressure (Pms) and right atrial pressure (Pra) influence venous return (Fv) in relation to resistance of the venous system (Rven) is commonly discussed in terms that imply the balloon-like physical model illustrated in Fig. 2. The model supports characterization of Pra as a "back pressure" and assertions such as pointing out that elevating Pra to equal Pms would stop venous return (6).

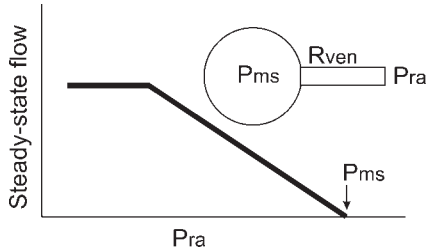

Fig. 2. Mean circulatory (Pms) and right atrial (Pra) pressures as the pressure gradient driving venous return. Implicit in typical discussions of the influence of Pra on venous return is a balloonlike model like the *inset* shown with inside pressure at Pms; a resistive outflow path representing venous resistance, Rven; and pressure at the outflow end at Pra. Outflow from the balloon would obey the relationship (Pms−Pra)/Rven. *Provided that Pms were held constant*, this expression would also describe the sloped portion of the graph of the relationship between steady-state flow and Pra, an idealized "venous return curve."

This view of Pra as the determinant of Fv in proportion to its decrement relative to Pms, which I will call the (Pms−Pra)/Rven concept, is an interpretation of findings of Guyton et al., presented in venous return curves like that in Fig. 2 (many publications by Guyton and his coworkers address our subject; for background citations, see Ref. 1). My argument is that the interpretation is wrong.

To begin with, the balloon model has a glaring defect. It would not generate the steady flow associated with any level of Pra below Pms in the venous return curve because outflow would remove volume from the elastic compartment. Inside pressure would fall along with volume according to the compliance of the compartment. Outflow rate would decline accordingly as the elastic energy stored in the compartment walls was expended. To keep Pms constant would require a pump, but then the drive for Fv comes from the pump, not stored elastic energy manifested as Pms.

Stored elastic energy was not what propelled the flow recorded for venous return curves like that in Fig. 2. Flow came from a pump whose output, recorded as Fv, passed into the aorta of the peripheral vasculature under study. The only way to change Fv was by manually resetting the pump rate or by throttling the pump by imposing a resistance in the connection to its inflow port.

Return flow was intercepted at the right atrium (where Pra was recorded) and fed through a Starling resistor to the input end of the pump. The Starling resistor functioned as a variable resistance that throttled the pump, thus changing pressures and volumes throughout the vasculature until Pra settled at the value consistent with the height of the hydrostatic column between the level of the resistor and the level of the right atrium. The beauty of this closed-loop design was that they could keep the volume contained within the vasculature constant while recording a range of steady-state levels of Fv and corresponding Pra by adjusting the height of the resistor (see, for example, Ref. 4).

So, Fv was certainly not the outflow of an elastic compartment shrinking in volume, it was recorded when flows, pressures, and segment volumes throughout the vasculature were steady.

Also, in no way was venous return recorded as distinct from the rate at which flow entered the aorta. In the investigators' view, cardiac output would be the flow seen by an observer in the aorta looking upstream. Venous return would be what the observer would see if he turned around and looked downstream, the same flow, but in the opposite sense.

Nor was Fv set by adjusting Pra. It is not generally recognized that the Starling resistor circuit was the control element in a closed feedback loop and that its variable resistance, not Pra back pressure, caused Fv changes. What Guyton et al. varied as an independent variable was resistor height, not Pra.

Writers have stressed that one cannot say Pra or Fv is the independent variable in the intact cardiovascular system (e.g., Ref. 6). The same is true of the Starling resistor + peripheral vasculature + pump system. But, when we open loops, we can identify independent and dependent variables unequivocally. Remove the Starling resistor, find some other way of keeping total circulating volume constant, and you can independently set Fv at various levels in an isolated peripheral vasculature and observe what happens to Pra [as various workers have done, e.g., Levy (5)]. Obviously, you cannot do the opposite;

Fv is the independent variable in the Fv:Pra relationship in the isolated vasculature. Without a pump, you can set Pra wherever you want but you will get no steady-state flow.

My dispute is with the (Pms−Pra)/Rven concept, not the significance of the experimental results. Knowing how Pra changes in relation to steady-state flow passing through the vasculature as an open loop subsystem of the cardiovascular system with Fv as the independent variable enabled an important advance. Guyton put this new information together with cardiac output curves [properties of the open loop cardiopulmonary subsystem, with Pra as input and flow, Fco, as output, (2)]. By doing this graphically, he could discuss steady-state equilibrium points for the closed-loop system in terms of changes in either subsystem, such as the overall elevation of a venous return curve with increased system volume.

In this technique, both open-loop relationships are plotted on one graph. Guyton chose to put flow on the *y*-axis and pressure on the *x*-axis. That meant that the peripheral vasculature dependence of Pra on Fv ended up plotted as in Fig. 2, i.e., with the independent variable on the *y*-axis. Unfortunately, the apparent proportionality between (Pms−Pra) and Fv plus the mistaken idea that Pra was actually the independent variable launched the (Pms−Pra)/Rven concept.[1]

Perhaps two other considerations contributed to persistence of the concept. *1*) (Pms−Pra)/Rven appeals to those with a Poiseuillean view who look for a pressure gradient as the cause of flow through a vascular segment and overlook the fact that pressure gradients and flow in the vasculature develop hand in hand as a consequence of pumping. *2*) The elastic compartment in the physical model in Fig. 2 has an intuitive appeal because of the importance of stored elastic energy in driving venous return as understood in the following sense. The appropriate reason for a separate term for "venous return" as distinct from "cardiac output" is that the rates at which blood is pumped into the aorta and at which flow returns to the right atrium can differ temporarily. These transient discrepancies involve transfers of elastic energy and changes of vascular volumes beyond the predictive capability of a pumpless one-chamber model.

Why then does Pra fall below Pms in proportional relation to flow? Not because Pms is a fixed pressure head at the upstream end of a fixed venous resistance, but because progressively greater flow creates a progressively steeper pressure profile around the peripheral vasculature. With no flow, pressure in all segments of the vasculature is Pms. Forcing flow through the vasculature elevates arterial pressures above Pms. Total blood volume is fixed, so the volume that expands arterial segments is displaced from venous segments where pressures therefore fall below Pms. It is this progressive reallocation of total volume among the elastic segments of the vasculature that results in decline in Pra proportional to flow.

So what does drive venous return? In the isolated peripheral vasculature setting of venous return curves, it is set by a pump. In the closed-loop cardiovascular system, it equilibrates with cardiac output at a level set by variables such as total system volume, contractility, and elastic state of the vasculature that we could discuss with the aid of cardiac output and venous return curves. In stresses that disturb cardiovascular equilibrium, it changes dynamically as volumes redistribute among the organ vasculatures, conduit vessels, and heart. Neither steady-state nor dynamic venous return is properly described as driven by Pms in proportion to the back pressure from Pra.

[1]The use of a single outflow resistance, Rven, ignores the explicit caveat of Guyton et al. that the denominator in their model equation was not the physical resistance of the venous vasculature, but an impedance that combined the resistances and capacitances of all the arterial and venous segments of the vasculature (3).

ACKNOWLEDGMENTS

Thanks to Loring Rowell for friendship and editorial assistance and for unflagging determination to understand flow and volume dynamics in the cardiovascular system.

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REBUTTAL FROM DR. MAGDER

So close yet so far apart! Dr. Brengelmann finds a "glaring" defect in the balloon model of the circulation and presumably my bathtub analogy (Brengelmann 2006). He argues that the elastic-recoil pressure in the balloon is rapidly dissipated and to "keep Pms constant would require a pump, but then the drive for Fv comes from the pump." I agree with the first part and argued that the heart provides a "restorative" force. However the heart does not "drive" venous return just as the tap filling a tub does not "drive" emptying of the tub. His argument misses Guyton's key point that the "working" cardiac output is determined by interaction of pump *function* (not cardiac output) and return *function* (3) and thus the pump is an integral part of Guyton's analysis. He also fails to deal with the flow that occurs without a pump, even if only transiently and that maximum flow is defined by the ratio of stressed volume (υ) to the time constant of its drainage, which is determined by the product of venous compliance (Cv) and resistance (Rv; Ref. 8).

In the physiological range, Cv is essentially constant so that four variables define the system: flow (Q), υ, Rv [includes the distribution of Q(1)], and right atrial pressure (Pra). A change in one requires a change in at least one of the others (1, 8). The heart only controls Q and Pra. In most of Guyton's experiments, υ and Rv were constant and changes in Pra were related to changes in Q by a changes in cardiac function (or pump in the experiments). In other studies (2, 5), a pump held cardiac output constant, and changes in Pra equivalent required changes in υ or Rv. A physiological example occurs with the rise in Pra and fall in Q with an increase in pleural pressure.

Recruitment of unstressed to stressed volume then increases MSFP and restores Q (6). During aerobic exercise, Q can increase with a constant Pra (7). This requires an increase υ or decreased Rv (4).

In conclusion, steady-state and dynamic VR are properly described by MSFP in proportion to the backpressure. However, steady state *cardiac output* is determined by the interaction of pump and return functions. The heart cannot pump out more than the flow that is determined by the drainage characteristics of the circuit. The heart provides the "restorative force" and, as per Guyton, plays a "permissive" role.

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REBUTTAL FROM DR. BRENGELMANN

Point of agreement: the utility of combining open-loop cardiac and vascular subsystem properties in analyses of cardiovascular stability. For the heart, Pra ↑ → F ↑; for the vasculature, F ↑ → Pra ↓. Connected, they form a negative feedback system that stabilizes at the Pra that causes the heart to pump out the F that causes that Pra. Showing this graphically requires plotting one of the relationships with its independent variable on the *y*-axis.

"Waterfall" relevance? Yes, resistance of a vascular segment or Starling resistor increases as it collapses. But, the (Pms−Pra)/Rv concept applies only to the sloped segment of venous return curves, for which intravascular pressures are positive and apparent Rv is constant, i.e., no vessel collapse. About waterfalls: *1*) flow depends only on the flow arriving at the precipice edge; *2*) transport to the lower level is due to gravity; and *3*) they are not enveloped by flexible elastic walls. Why are we talking about them?

Bathtub analogous? In Magder's Fig. 1*A*, (1) we see the right atrium at the level of the water surface and Pra labeled as equal to MSFP (my Pms). But surface level pressure has to be zero, i.e., equal to atmospheric (Patm). Just as the Fig. 1*A* tub cartoon does not correspond to the pressures marked on the graph below it, the hydrostatic relationships are incorrect in the other panels (e.g., pressure at the atrium level would be greater than any in the tub). Correcting all pressures to the same level would reveal the pressure gradient associated with flow, but why pursue this? The (Pms−Pra)/Rv concept is not about blood flowing downhill, and flow in the defining experiments was certainly not driven by gravity. And that faucet? How does it know the flow needed to keep the tub full?

MSFP (Pms) energy source? Quantitatively, the elastic work that moves blood out of a compartment equals the integral of instantaneous pressure times compartment volume decrement dV. Magder's compartment at Pms, kept at constant volume for steady states, has no dV. No dV, no energy release.

To Magder's "what makes the blood go around?" (1, first sentence), I reply *not elastic energy from a compartment at Pms*; but the work manifested in the integral of P times dV for the ventricles (ignoring for the purposes of the present argument the energy input by vessel compression and expansion due to activity of skeletal and respiratory muscles).

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The following letters are in response to the Point:Counterpoint series "The classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct" that appears in this issue.

To the Editor: I believe Dr. Brengelmann's (1) criticism of the Guyton model of the interaction between the circulation and the heart in controlling cardiac output (2) is wrong as validated by clinical observation. As initially described by Mitzner and Goldberg (3) using a right heart bypass preparation, cardiac output cannot be increased by increasing the pump speed in patients undergoing cardiopulmonary bypass unless reservoir volume or fluid resuscitation simultaneously occur. Although the "bathtub" analogy of Dr. Magder (4) is overly simplistic in lumping one reservoir and a single outflow circuit, it correctly models the role that cardiac function plays in determining cardiac output. We previously showed that the cyclic change in right atrial pressure induced by positive pressure ventilation alters pulmonary flow and their relation approximates an instantaneous venous return curve (5). Furthermore, venous return physiology explains the development of acute cardiogenic pulmonary edema. If the only thing that happened with myocardial ischemia was decreased contractility, then cardiac output would decrease but filling pressure would not rise greatly because its upstream mean systemic pressure is only ~10 mmHg. What causes the acute increase in filling pressure is the associated increased sympathetic tone decreasing vascular unstressed volume, increasing mean systemic pressure for the same blood volume. This also explains why sympathetolytic agents rapidly improve cardiovascular status (6). Thus the Guyton model of the control of the circulation is strongly supported by real-life examples and explains the pathophysiology of disease and can be used to define appropriate therapy.

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To the Editor: The systemic circulation can be viewed as an elastic compartment analogous to the lungs. The respiratory physiologist has no problem in understanding the role of elastic recoil pressure as a determinant of expiratory flow, because expiration typically occurs by the passive recoil of the elastic elements of the lung. It may be difficult to visualize expiratory pressure and flow relations under isovolume conditions, because air cannot move out of the lungs at constant lung volume. It was only with the construction of expiratory pressure-flow relations under isovolume conditions (not a simple exercise!; Refs. 2, 3) that expiratory flow limitation was understood, and this resulted in an appreciation of the role of elastic recoil pressure as a major determinant of maximum expiratory flow (4, 5).

The isovolume venous return curve presents the opposite dilemma to the circulatory physiologist. How can the emptying of a balloon have any relevance in an isovolume system? Thus Brengelmann's inference that "the balloon model has a glaring defect . . . because outflow would remove volume from the elastic compartment, prohibiting the isovolume conditions of the venous return curve" (1). The conceptual necessity of continuous replacement of the draining volume of the systemic circulation obscures the role of the simultaneous mechanics of emptying (elastic recoil and resistance to venous return) that determines the maximum attainable cardiac output. The circulatory or respiratory pressure-flow isovolume curves, remarkably similar to each other, arise from the same mechanical principles and clearly reveal how flow may become independent of the activity of the pump.

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To the Editor: Magder (5) depicted arterial inflow as a tap in a bathtub. However, in a circulatory system, there are many bathtubs. Flowing from the heart to any bathtub, blood has to travel a long journey by passing through tubes of decreasing cross sections. How to supply all bathtubs with the appropriate amount of blood becomes an important task for the heart. The heart is designed to provide enough power for blood transportation in an efficient way via pulsatile pumping.

Pulsatile pumping makes blood propagate as a wave not as a direct flow. It is the same strategy as using AC transmission line to replace DC current for long-distance electric power delivery. Pressure gradients and flow in the vasculature develop hand in hand as a consequence of pumping (1). Movement of the blood in artery is governed by a pressure wave equation (3) not by the Poiseuille's Law. In other words, left ventricular output is delivered through pressure wave, offering all bathtubs the sufficient blood and energy source for venous return. Pulse pressure is transmitted deeper into the microcirculation (2). Without a pulsatile pump, only bathtubs near the heart may get enough blood.

Heart rate control is an important regulation for proper blood supply. Frequency-matching rules (4) are the matching relations between heart rate and the natural frequencies of arterial systems or organs. Fulfilling these rules enhances the efficiency of power transportation, and these rules can be used to explain how heart rate and total blood flow change during exercise.

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To the Editor: Hydraulic resistance is customarily defined as a pressure drop divided by flow (when gravitational and temperature gradients can be ignored). The entire systemic resistance, (MAP−RAP)/CO, can be split into its serial components (e.g., Rprecap), each defined as the appropriate ΔP divided by CO. Guyton's definition of "the resistance to venous return" [Rvr = (MSFP−RAP)/VR] is unconventional because the driving pressure does not exist while blood is flowing and because Rvr cannot be identified with any particular series component of the circuit. MSFP should not be confused with the average pressure in the system or any pressure in the system while blood is flowing. Rvr is not specifically the flow resistance through the venous system. Guyton himself pointed out in his textbook that about one-third of Rvr was in arterioles and small arteries.

The concept of Rvr arose from "venous return curves" where flow increases as RAP decreases below MSFP. The obvious explanation for this relationship is that, in these experiments, the decrease in RAP and increase in VR were both caused by an experimental increase in CO, as discussed by Brengelmann.

The argument that elastic recoil force in vessel walls provides the driving force for VR (aka CO) is specious. Vessel wall tension and blood flow are both maintained by the left ventricle.

As a teacher of cardiovascular physiology, I have always avoided the fussy and misleading concept of Rvr and the notion that MSFP is the driving force. Neither concept is useful.

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To the Editor: A careful reading of Guyton's papers (2, 3) related to the mean systemic pressure (Pms) shows that the junction of his "cardiac function curve" with his "venous return curve" at a specific right atrial pressure (Pra; Ref. 3) is valid only at equilibrium conditions. It was not designed to provide the dynamic characteristic of the cardiovascular system during disturbances. Furthermore, a simple "venous resistance" (Rsv) to flow is not part of Guyton's concept. It is the "resistance to venous return," which is a complex combination of systemic resistances and compliances (2). Neither author seems to realize that a simple Rsv must be associated with a systemic peripheral venous pressure (Psv), which cannot currently be measured but can only be assumed to be similar in magnitude to the Pms. Furthermore, the Pms is a fixed pressure at a given total systemic stressed volume and total systemic compliance. The Pms is not changed by a change in cardiac output or venous return. A decrease in flow from the arteries will lead to a passive decrease in systemic venous stressed volume (because inflow is less than outflow) and a decreased Psv (because the volume is less) at a constant Pra. An increase in right ventricular function will lead to a decreased Pra and then an increase in venous return. These changes will lead to redistributions of blood volume based on the integral of inflow minus outflow for each compartment. (The principal of mass balance, see Ref. 6).

In retrospect, I wish that I had been more explicit (5).

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To the Editor: This is a most curious controversy (1, 2), seemingly so 20th Century. In fact, it is not clear what the controversy really is, because no sane person can argue with the fact that venous return must equal cardiac output in the steady state. So, if we agree to deal exclusively with the steady state, then the only question is what are the hemodynamic relations that exist in the peripheral circulation? In this regard, Dr. Brengelmann seems to have misinterpreted the question. Of course there is no steady-state flow if the heart is dead, but because even the most powerful heart cannot generate blood, in the steady state the heart's ability to pump blood is limited to what comes back to it. The blood flow returning to the heart is driven by the difference between the elastic recoil pressure of the peripheral circulation and the pressure at the input to the heart, i.e., the right atrium. This is fact—hardly something to be debated on expensive journal pages. What can be discussed is how best

to model this peripheral circulation, and given the highly nonlinear pressure-volume properties of the peripheral vasculature with its complex parallel vascular pathways, this is still not entirely understood. Nevertheless, the bottom line is the same as it was well before Guyton (or anyone else) even thought about it, that steady-state flow back to the heart is always determined by a mean pressure gradient divided by an effective equivalent resistance, properly designated as the resistance to venous return.

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