Point:Counterpoint: Active venoconstriction is/is not important in maintaining or raising end-diastolic volume and stroke volume during exercise and orthostasis

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 the content, 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 The number of references to publications is also limited to 30, and citation of unpublished findings is prohibited.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: ACTIVE VENOCONSTRICTION IS IMPORTANT IN MAINTAINING OR RAISING END-DIASTOLIC VOLUME AND STROKE VOLUME DURING EXERCISE AND ORTHOSTASIS

We bipeds, who tend to pool blood in our lower body and legs while standing (orthostatic hypotension), have evolved “active venoconstriction.” During severe exercise, venoconstriction is also important for maintaining or increasing the end-diastolic volume (EDV). Experimental proof of active venoconstriction in humans is sparse, because conclusive evidence requires major invasive techniques.

Venoconstriction reduces the venous unstressed volume. From a plot of the venous volume-to-pressure relationship (V/P)—the capacitance—this unstressed volume is a virtual volume computed by extrapolating a linear portion of the capacitance relationship over the normal operating range to zero transmural pressure (see Fig. 1) It cannot be directly measured, but it is defined as the difference between the total contained volume—the capacity—and the stressed volume, which is the product of the compliance and pressure at a specific transmural pressure (14). Active venoconstriction results from activation of the vascular contractile elements, such as smooth muscle. Passive reduction in venous volume results from a decrease in distending pressure. A mathematical model explains these relationships (16).

About 80% of the blood in mammals is in the venous compartments (Ref. 17, Table 2 and Ref. 11, page 103), and about one-half of the venous blood is in the 20- to 50-μm venules and small veins (17). Only ~30% of the total blood volume is in the stressed volume compartments (Ref. 15, page 1295). In humans, the liver is the most important controllable blood reservoir in the body, and the “control of hepatic capacitance could well have a pivotal role in cardiovascular homeostasis, particularly during exercise and orthostatic stress” (Ref. 13, page 521).

The mean circulatory pressure (Pmcf) is the equilibrium pressure if the blood flow is zero and the blood volume is redistributed so that the pressures are equal throughout the body before any reflex compensation (7-9, 14). By definition of compliance, the Pmcf is the ratio of the total stressed volume in the body to the total vascular compliance. Thus the total unstressed volume equals the total circulating blood volume minus the product of total vascular compliance times the Pmcf (14).

Guyton and Hall (6) have stated “Note that at a blood volume of about 4000 ml the mean circulatory pressure is close to zero because this is the ‘unstressed volume’ of the circulation, but at a volume of 5000 ml, the filling pressure is the normal value of 7 mm Hg. Similarly, at still higher volumes, the mean circulatory filling pressure increases almost linearly.” Maximal sympathetic stimulation increases the Pmcf from 7 mmHg to ~17 mmHg and reduces the unstressed by ~600 ml, whereas complete inhibition of the sympathetic nervous system reduces the Pmcf to ~4 mmHg and increases the total stressed volume by ~350 ml (Ref. 6, page 239–240 and Fig. 20–10).

An adequate cardiac output is a sine qua non for survival during severe stress. However, an increase in cardiac contractility can only reduce the ESV from a normal ejection fraction (SV/EDV) of ~0.70 to 1. Furthermore, at high HR, the EDV is limited, because the duration of systole then greatly limits the time available for filling. Thus, maintaining the EDV in orthostatic hypotension, and increasing the EDV in exercise, is crucial. Enhanced atrial contraction aids diastolic filling, as does the skeletal muscle pump while running. Redistribution of the blood volume (16) is also important.

Whereas the normal cardiac output is ~5 l/min with a heart rate of 72 beats/min and a stroke volume of 69 ml, well-trained athletes can attain a maximum cardiac output of 36.0 ± 1.6 l/min with a heart rate of 190 ± 3.6 beats/min and a stroke volume of 189 ± 6.6 ml (3). Pentathletes on a treadmill and using 99mTc ventriculography, showed a significantly increased EDV and decreased ESV (22). Human subjects on a bicycle at maximal oxygen update showed a 10% increase EDV and a 19% decrease in abdominal blood volume measured via 99mTc-labeled erythrocytes (4). Hainsworth (12) concluded that humans do not have a large spleen and so are unlikely to mobilize more than 5 ml/kg to lead to increase cardiac output by 50%. However, this amount “may be sufficient to maintain cardiac output in an adequate although reduced level in the upright position” (page 254). See also Ref. 11.

Shoukas and Sagawa (24) provided evidence of active venoconstriction during changes in carotid sinus pressure (ISP). The total blood volume shifted from the body was ~7.5 ml/kg from changing carotid sinus pressure between 75 and 200 mmHg. Because changes in ISP did not significantly change vascular compliances, they concluded that the blood came from the unstressed volume and that a 25 mmHg change in ISP can
cause a 30–40% change in cardiac output via venoconstriction. In another study using constant perfusion, changing carotid sinus pressures between 50 and 200 mmHg caused a 4.7 ml/kg change in splanchnic volume. They concluded that the splanchnic vascular bed contributes a major part of the blood mobilized by the carotid sinus reflex (1).

In the second edition on Human Cardiovascular Control, Rowell (21) devoted four chapters to the problems of orthostatic hypotension in humans. We agree (Rowell’s pages 72–73) that passive elastic recoil of the venous bed related to the reduction in cardiac output is somewhat more important than active venoconstriction (18).

In another dog study, extrapolating the data to zero Pmcf required a hemorrhage, before reflex activity could occur, of ~17 ml/kg body wt (18% of the total blood volume). With reflexes intact, the hemorrhage to reduce the Pmcf to zero was ~25 ml/kg, by 2 min. The difference (8 ml/kg) estimates the magnitude of venoconstriction (2).

Rowell (21, pages 73–74) claimed that active venoconstriction, causing a reduction in volume, will simultaneously cause a proportionally much larger change in resistance to flow. This will cause a passive increase in upstream pressure and distended volume if the inflow does not decrease. However, whereas the vasculature as a whole may be highly compliant, the compliance of the capillaries and venules, because of their extremely small size and collagen fiber walls, may be relatively noncompliant (10, 23). Because of the huge number of venules and small veins and huge total cross-sectional area, the resistance is minute (17). To measure liver volume changes in response to norepinephrine infused via the portal vein at ~8 μg·min⁻¹·kg body wt⁻¹, Rothe and Maass-Moreno (19) used servo-null micropipettes to measure the pressure in ~50-μm diameter hepatic venules of anesthetized rabbits. They measured lobe thickness to estimate liver volume changes (5) and used an ultrasound flow probe to measure total hepatic blood inflow. The liver volume decreased 8%. The norepinephrine, which was not fully extracted by the liver, caused the systemic arterial pressure to increase 23%. Heart rate decrease 8%, portal venous pressure increased 3.4 mmHg, and hepatic flow increased 2%. The hepatic venous pressure, just downstream from the hepatic sinusoids, significantly increased 1.6 mmHg. Because the liver lobe thickness decreased significantly although hepatic flow and hepatic venular pressure increased, they concluded that norepinephrine causes active venoconstriction of the hepatic capacitance vessels (19, 20).

In conclusion, active venoconstriction provides a rapid, self-contained blood transfusion to the stressed volume in exercise and orthostasis.

REFERENCES


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COUNTERPOINT: ACTIVE VENOCONSTRICTION IS NOT IMPORTANT IN MAINTAINING OR RAISING END-DIASTOLIC VOLUME AND STROKE VOLUME DURING EXERCISE AND ORTHOSTASIS

Veins were considered merely as passive conduits of blood until Mellander (13) reported that stimulation of sympathetic nerves supplying the cat’s hindquarters resulted in a decrease in regional blood volume. This and other work led Folkow and Mellander (4) to assert that veins were “at least as active and well controlled as other elements in the circulation and had an important role to play in cardiovascular regulation.” Since then it has been assumed that the control of veins provides a major mechanism for maintaining cardiovascular homeostasis. It is this that we question in this article.

Active vs. passive changes. It is estimated that 70% blood volume is contained in veins (6, 8) and because some veins contain smooth muscle (2), venous constriction in response to sympathetic nerve activity would reduce venous volume and enhance cardiac filling. However, veins are highly distensible (30 times more so than arteries) and so their volume can also be changed by changes in transmural distending pressure. In humans, a 5 mmHg change in venous pressure would be associated with a change in venous volume of ~1 liter (9).

Changes in venous volume may be regarded as active (capacitance change) when they result directly from contraction of venous smooth muscle or passive when changes result from changes in transmural distending pressure (9). These two mechanisms are interlinked. An increase in sympathetic activity not only constricts veins but also constricts arterioles. This reduces flow of blood into veins, resulting in less venous distension and consequently a passive decrease in venous volume. These “active” and “passive” effects are difficult to separate, but it seems reasonable to assume that if blood flow to a region is forced to remain constant despite resistance vessel constriction, by isolation of the region and constant flow perfusion, any change in volume would be mainly active. We (10) compared the volume changes in the dog’s hindlimb to direct and reflex sympathetic stimulation, during constant flow and constant pressure perfusion, and found that changes occurred only during constant pressure. The conclusion, therefore, is that the circulation in the limb does not make any significant contribution to the control of vascular capacitance and that changes reported by others (1, 3) were just secondary passive effects from changes in flow.

Capacitance in the abdominal circulation. The absence of appreciable venoconstriction in musculocutaneous circulations may actually be of physiological benefit because when flow is high, as during exercise, venoconstriction would impede rather than enhance venous return. The situation in the abdominal circulation, however, is quite different. Even during exercise, increases in sympathetic activity would reduce blood flow, so both active and passive effects would reduce regional blood volume. We (11, 12) reported that changes in volume of 7.5 and 5 ml/kg were expelled from the abdominal circulation of the dog in response to direct and reflex stimulation, respectively. These occurred during constant flow perfusion and assumed to be active.

Despite the existence of active capacitance responses in the abdominal circulation, passive effects may be greater. Just decreasing blood flow to the splanchnic region resulted in a decrease in volume only a little less than that during sympathetic stimulation (14). In dogs with intact spleens, we showed that at low frequencies of stimulation the decrease in abdominal blood volume was mainly active, but at high frequencies, active and passive responses were similar. After splenectomy, the active response was greatly reduced but the passive change was unaffected (14). The estimated active capacitance responses at stimulus frequencies of 1 and 8 Hz were only 1.4 and 2.7 ml/kg. The significance of results is that humans, unlike dogs, do not possess a large contractile spleen, so to extrapolate dog results to humans we should exclude the splenic contribution.

In an attempt to determine the regions responsible for the capacitance responses, Noble et al. (15, 16) separated the circulations to the liver, gastrointestinal tract, and remainder of the abdominal circulation (excluding spleen) and found that most of the active response (average 88%) arose from the liver. The gastrointestinal tract made only a very small contribution to the active response, although the volume changed considerably with changes in flow (Fig. 2). Thus it is mainly the liver that is responsible for the active response and the intestine for the passive response.

![Fig. 2. Summary diagram showing responses calculated from splanchnic circulation to changes in carotid pressure and to changes in blood flow. Values are means ± SE from 6 splenectomized dogs. This shows that, of the total volume change in the region, the active component (during constant flow) made only a small contribution. The difference in the responses at constant flow and constant pressure was not significantly different from the change in volume occurring when flow was changed by a similar amount by altering the pump speed (reproduced with permission from Ref. 15).](image-url)