Editorial: Importance of Scintigraphic Measurements of Human Splanchnic Blood Volume

An understanding of the hemodynamic importance of variations in splanchnic blood volume (SBV) in humans has awaited development of techniques that would permit quantitative measurements without the major difficulties attending the old (and rarely used) invasive method (*1*). The stimulus for this editorial is a recent paper by Robinson and colleagues (*2*), who used quantitative equilibrium blood-pool scintigraphy (EBPS) to determine changes in blood volume within a specified region of intestinal veins in humans. They measured the rise in venous volume associated with vasodilation (by nitroglycerin) and increased blood flow in humans and extended their investigation to include analogous measurements on dogs whose splanchnic blood flow (SBF) was also increased by nitroglycerin and then decreased by angiotensin. The expected changes in SBV occurred and in the dogs were related to changes in portal vein pressures. In effect, quantitative EBPS was used as a form of plethysmography.

The potential value of this approach relates to the paucity of quantitative information concerning splanchnic vascular capacity in humans and to the great hemodynamic importance of this region. Splanchnic organs receive ~25% of the cardiac output and hold 20%–25% of the total blood volume or specifically, 1200–1500 ml of which 400–600 ml is in the intestinal circulation. The ability of the splanchnic region to rapidly transfer blood from its veins to the heart may be its most important hemodynamic function. Quantitatively, the liver is of greatest importance because it receives all of the SBF and its specific vascular compliance (ml/kg of tissue/mmHg) is ten times greater than either intestinal or total systemic vascular compliance, both of which are ~2.5 ml $mmHg^{-1}$ kg^{-1}.

Historically, the splanchnic vasculature has been viewed as the "venosector and blood giver of the circulation" (Jarisch and Ludvig, 1927). In 1884, Dastre and Morat predicted that any increase in skin blood flow (a second region of high capacity and compliance in humans) must be compensated for by a decrease in blood flow to visceral organs. In 1905, Müller reinforced this idea by measuring heat- or cold-induced shifts in the weights (volume) of various body segments in people horizontally suspended on a series of weighing scales. In 1912, August Krogh provided a simple conceptual model of the circulation which he divided into two parallel circuits, one compliant (e.g., splanchnic) and one noncompliant (e.g., skeletal muscle). His message was that the volume of blood available for the heart is determined by the distribution of blood flow between such vascular beds. Krogh saw the splanchnic circulation as the principal regulator of blood supply to the right atrium (see Reference *3*).

Along with the advent of intravascular catheterization and indicator dilution techniques came the first measurements of SBF in 1945 and of SBV in 1953 by Bradley's group (*1,4*). Their volume technique required determination of average tracer (^{131}I-HSA) concentrations in blood entering and leaving splanchnic organs via the hepatic veins, multiplied by total SBF during equilibration. This yielded the amount of tracer dispersed within the splanchnic vessels at equilibrium which, divided by equilibrium concentration, yielded total SBV. Splanchnic blood flow had to be determined by constant infusion of bromsulfalein and, of course, arterial and hepatic venous sampling (Fick principle).

Measurements of SBV proved to be technically difficult and for this reason have been made only rarely in humans. In his original studies, Bradley showed that the decrease in SBF during exercise was accompanied by marked reductions (30%–40%) in SBV, and this was confirmed in 1956 by Wade et al. (*5*). Price et al. (*6*) showed that nearly one-half of the blood loss during removal of 15%–20% of total blood volume in humans came from the splanchnic circulation. Surprisingly, despite the 40% fall in SBV, SBF did not fall during hemorrhage as it did during exercise. For this reason it has been assumed that the fall in SBV during hemorrhage is due to *active* expulsion of blood whereas during exercise, SBV could simply fall as a *passive* result of reduced flow.

Subsequently, rough estimates of directional changes in liver dimensions (or volume) were made from x-rays of human subjects exposed to heat and a 420-ml blood loss, both of which reduced liver dimensions, and then to cold, which increased them (*7*).

These and subsequent studies on nonhuman species with new and better methods raised a fundamental issue about the control of SBV. Inasmuch as 25% of the total blood volume is contained within a richly innervated venous system (only splanchnic and cutaneous veins appear to be significantly innervated in humans [*3*]), many have assumed that SBV is *regulated* by neurally induced *venoconstriction*. In contrast, others argued that release of volume from splanchnic veins could be simply a *passive* effect of *vasoconstriction* (i.e., constriction

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of arterioles rather than veins), which reduces blood flow and venous transmural pressure causing passive elastic recoil of venous walls (*3*). Although controversy on this issue is long-standing, most agree that veins offer some resistance to flow and, thus, have flow-dependent pressure gradients. When their blood flow is altered, these pressure gradients change and thereby alter transmural pressure and volume throughout the venous system (*3*). For example, increasing splanchnic vascular resistance and reducing inflow can passively expel up to 40% of the contained blood volume (*8*). Conversely, some equally compelling examples suggest an active venomotor component (*8*). Most noteworthy are those cases in which substantial quantities of blood are expelled from the region with little or no change in blood flow. Among the examples are those cited above in which hemorrhage caused major reductions in SBV without reducing SBF. Does this illustrate an active venoconstriction? The big challenges in human studies are first, to measure accurately the volumes and second, to measure venous pressures that reflect the true venous distending pressures upstream where most of the venous resistance, compliance, and volume are located.

The time is ripe for serious efforts to investigate systematically the regulation of SBV in humans. Over the past three decades, studies of the human splanchnic circulation reveal a consistent *vasomotor* response to many stresses that we now know raise sympathetic nervous activity and norepinephrine (NE) spillover in a predictable manner (*3,9*). For example, in humans under a wide variety of stresses there is a close and highly reproducible inverse correlation between SBF and both heart rate and plasma NE concentration. At the highest heart rates and NE levels, SBF is reduced by 75%–80% (e.g., severe exercise). Orthostasis, lower body negative pressure, heat stress, and exercise all reduce SBF along similar regression lines (*3,9*).

The contributions of splanchnic vasoconstriction to (a) the rise in total vascular resistance and maintenance of arterial pressure and (b) the redistribution of blood flow and oxygen to other regions have been quantified (*3*). The (passive?) translocations of SBV, which partially offset falls in central venous pressure and compensate for vasodilation and increased venous volume elsewhere (i.e., to skin during heat stress or exercise) have not been quantified. The assumption is that under all conditions in which SBF is reduced, SBV will fall as well but the amounts and their time courses are unknown. In some cases, reductions in SBF are gradual. Are the reductions in SBV equally gradual or is there a sudden (active?) expulsion of blood?

Heat stress provides an interesting example of blood volume translocation in humans (*3*). We appear to be the only mammals having two, rather than one, major vascular beds with high capacity and high specific compliance (splanchnic and cutaneous beds). Cutaneous vasodilation in humans is associated with marked splanchnic vasoconstriction, increases in cardiac output and decrements in central venous pressure. We presume a passive fall in SBV, associated with reduced flow, lessens the fall in central venous pressure and provides part of the large volume of blood translocated to cutaneous veins. Similar adjustments accompany the superimposition of heat stress on exercise. These are good illustrations of Krogh's model; namely, the volume of blood available to the heart must be controlled by regulating the fractions of cardiac output distributed between compliant and noncompliant regions. The magnitudes of the volume transfers are still unknown.

Finally, and as mentioned above, the fall in SBV without a fall in SBF in response to hemorrhage is still a puzzle (*10*). The actions of epinephrine on splanchnic venous capacity and vascular resistance may be a key. Although epinephrine is a splanchnic vasodilator, it has recently been shown in dogs to cause marked reductions in SBV (see *10*). The mechanism of β-adrenergic volume mobilization is unknown. Some have proposed a β-adrenergic venoconstriction or a β-adrenergic relaxation of hepatic venous sphincters (not present in humans). Mobilization of blood into the central circulation was recently observed by measuring the rise in central venous pressure caused by graded epinephrine infusions into awake dogs (with AV conduction block), whose cardiac outputs were kept constant by ventricular pacing (*10*). The effect of epinephrine and beta agonists in decreasing vascular capacitance and raising central venous pressure far exceeded the effects of alpha agonists or carotid artery occlusion. Volume mobilization was greatly diminished in all cases by beta blockade. So far we have only suggestive evidence that epinephrine has a similar role in humans.

The recent availability of scintigraphic techniques to quantify in humans changes in intestinal and hepatic blood volume noninvasively, and the ability to measure blood flow to some major vessels within the splanchnic region by Doppler techniques (*11*), opens the way to demonstrating for the first time the directions and magnitudes of changes in SBV and their possible causes. If measurements of pressures distending the veins could be added, we could also progress toward elucidating any active role of the splanchnic venous system in volume mobilization.

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