

## Catecholamine-induced Changes in the Splanchnic Circulation Affecting Systemic Hemodynamics

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THIS article focuses on the effects of catecholamines on the splanchnic circulation that influence systemic hemodynamics (particularly venous return and cardiac output) under normal physiologic conditions. Because of its required brevity, this article could not address other important hemodynamic effects of catecholamines, such as those that result from metabolic alterations, effects on the circulatory system that do not involve the splanchnic organs, and those that accompany major pathophysiologic states, such as sepsis or congestive heart failure.

### Anatomy and Blood Supply

The splanchnic system receives nearly 25% of the cardiac output through three large arteries (fig. 1): the celiac artery (which typically has three major branches: hepatic, splenic, and gastric) and the superior and inferior mesenteric arteries. Roughly one fourth of the splanchnic arterial flow goes directly to the liver *via* the hepatic artery; the remaining three fourths reaches the liver after perfusing the preportal organs. The preportal veins anastomose to form the portal vein. The portal vein and hepatic artery enter the liver at its hilum and ramify into progressively smaller vessels before emptying into the hepatic sinusoids. Postsinusoidal blood flows through venules, sublobular and lobular veins, and the hepatic veins, which drain into the inferior vena cava.

The hepatic artery and the arteries of the preportal splanchnic organs have mean pressures of approximately 90 mmHg. The portal venous pressure is 7-10 mmHg, which is only slightly higher than the pressure in the sinusoids (fig. 2). Most of the intrahepatic vascular resistance is distal to the sinusoids<sup>1,2</sup>; possible locations of this resistance include one or more of the following sites: the sublobular veins, upstream to the larger veins, or at the junction of the hepatic veins and inferior vena cava.<sup>2</sup>

### Distribution and Function of Adrenergic Receptors

Although knowledge of the various adrenoceptor subtypes has expanded dramatically during the past decade, much uncertainty remains about the distribution and functional importance of these receptors in the splanchnic vasculature.<sup>3</sup> Pure  $\alpha$ -adrenergic agonists (*e.g.*, phenylephrine) constrict hepatic arterial smooth muscle, increase arterial resistance, and reduce hepatic arterial blood flow (table 1). Pure  $\beta$ -adrenergic agonists (*e.g.*, isoproterenol) dilate hepatic arterioles, decrease vascular resistance, and increase flow through the hepatic artery; these effects are blocked by nonselective  $\beta$ -adrenergic antagonists (*e.g.*, propranolol) but not by selective  $\beta_1$ -antagonists (*e.g.*, atenolol). Therefore, the hepatic artery contains  $\alpha$ -adrenergic and  $\beta_2$ -adrenergic receptors.<sup>4</sup> The arterial supply of the preportal splanchnic organs is densely populated with  $\alpha_1$ -,  $\alpha_2$ -, and  $\beta_2$ -adrenergic receptors.<sup>4</sup>

Preportal (intestinal) capacitance vasculatures have both  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptors but lack  $\beta_2$  receptors.<sup>5</sup> The portal vein contains  $\alpha$ -adrenergic but not  $\beta_2$ -adrenergic receptors.<sup>4</sup> Capacitance vessels of the liver (including sinusoids) have  $\alpha$ -adrenergic receptors, and hepatic veins contain both  $\alpha$ - and  $\beta_2$ -adrenergic receptors.<sup>4</sup> In the splanchnic venous system overall,  $\alpha_1$ - and  $\alpha_2$ -adrenergic receptor stimulation leads to venoconstriction, which decreases venous capacitance and increases venous resistance, whereas  $\beta_2$  receptor activation decreases hepatic venous resistance. It seems that the density of  $\alpha$ -adrenergic receptors is the highest in the splanchnic (preportal) arteries.

### The Splanchnic Blood Reservoir

Normovolemic healthy male adults have a blood volume of approximately 70 ml/kg body weight. Splanchnic organs constitute 10% of the body weight, but they contain 25% of the total blood volume.<sup>1,6</sup> Nearly two thirds of the splanchnic blood (*i.e.*, > 800 ml) can be autotransfused into the systemic circulation within seconds (table 2). The liver and intestines each provide between 300 and 400 ml of the blood; the spleen only contributes approximately 100 ml, but the hematocrit of this blood often approaches 75%. Therefore, the splanchnic vasculature serves as an important blood reservoir for the circulatory system.

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Received from the Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Boston, Massachusetts. Submitted for publication December 19, 2002. Accepted for publication August 22, 2003. Support was provided solely from institutional and/or departmental sources.

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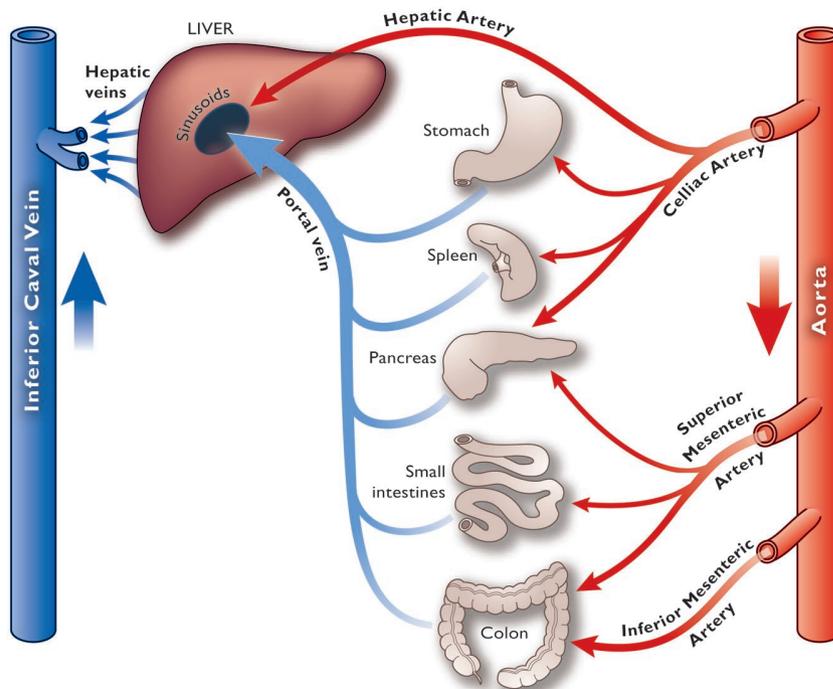


Fig. 1. Schematic representation of the splanchnic circulation.

**Regulation of the Splanchnic Reservoir Volume**

The capacity of catecholamines to increase cardiac output is dependent, in part, on the compliance, capacitance, and blood volume of the splanchnic vasculature. With normovolemia, the volume of blood in the splanchnic capacitance vessels varies in a manner that is approximately linearly related to the transmural pressure in this vasculature.<sup>7-9</sup> That is, under physiologic conditions, a change in splanchnic arterial flow leads to a proportional change in the pressure within splanchnic capacitance vessels.<sup>7</sup> When arterial flow decreases, the blood volume and therefore the pressure within the veins decrease. These veins recoil around the decreasing pressure, mitigating the reduction in pressure. This phenomenon, referred to as *elastic recoil*, maintains the intramural pressure at a level sufficient to provide a driving force for expulsion of intravenous volume to the systemic circulation.

Sympathoadrenal stimulation causes sympathetic nerve terminals and the adrenal medulla to release catecholamines, which play a major role in regulating the tone of the arterial resistance vessels and venous capacitance vessels (fig. 3). Catecholamines can cause splanchnic arterial constriction or relaxation; the net effect depends on the specific catecholamines involved, their concentrations at adrenergic receptors, and the densities of the adrenoceptor subtypes within the vasculature. The major effect of catecholamines on splanchnic capacitance vessels is venoconstriction, which increases the pressure in capacitance vessels. This mechanism can actively expel splanchnic blood into the systemic circulation, even when splanchnic arterial flow has been markedly reduced.

Active (venoconstriction) and passive (elastic recoil) mechanisms work in concert to shift splanchnic blood volume to the systemic circulation. Both mechanisms make

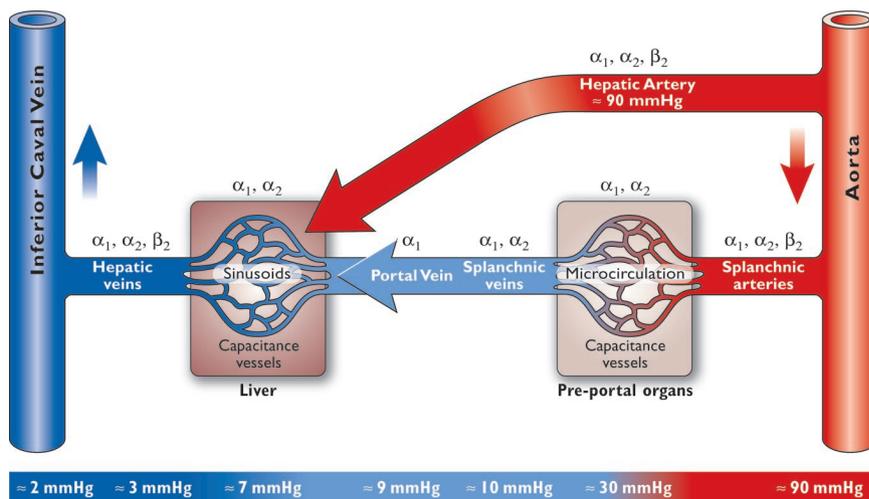


Fig. 2. Diagrammatic representation of the splanchnic vasculature. *Splanchnic arteries* represent all arterial vessels of the preportal organs; *splanchnic veins* represent the pooled venous blood from all these organs. The distribution of adrenoceptor subtypes ( $\alpha_1$ ,  $\alpha_2$ ,  $\beta_2$ ) and approximate intravascular pressures are shown for corresponding segments of the splanchnic vasculature.

Table 1.

### Distribution of Adrenoceptor Subtypes in the Splanchnic Vasculature

Receptor subtype	Vascular bed			
	Pre-portal arterial	Hepatic arterial	Pre-portal venous	Hepatic venous
$\alpha_1$	+++	+++	+++	++
$\alpha_2^*$	++	+	+	+
$\beta_2$	---	--	-?	---

+ depicts vasoconstriction; - depicts vasodilation; the number of +'s or -'s depicts the relative density of adrenoceptor subtypes; based on references 3 and 4.

Vasoconstriction decreases arterial flow, decreases venous capacitance, impedes venous outflow. Vasodilation increases arterial flow, facilitates venous outflow (see text for details).

\* refers only to peripheral  $\alpha_2$ -adrenoceptors; activation of central  $\alpha_2$ -adrenoceptors decreases sympathoadrenal tone.

equal contributions to the volume shift during activation of the sympathetic nervous system.<sup>10</sup> These processes account for the 35% decrease in splanchnic blood volume associated with mild exercise in humans.<sup>11</sup> In animals subjected to moderate hemorrhage (8–9 ml/kg), the splanchnic vessels deliver 5 ml/kg to the systemic circulation, effectively compensating for 60% of the withdrawn blood.<sup>12</sup> Studies in dogs indicate that electrical stimulation of the splanchnic (sympathetic) nerves can rapidly decrease splanchnic arterial flow while triggering a brief but substantial outflow of blood from the splanchnic vasculature.<sup>13</sup> The maximum volume expelled (15 ml/kg) was nearly 66% of the total splanchnic blood volume, and occurred in 12–15 s.<sup>13</sup>

Intrahepatic vascular resistance can affect the volume

of the splanchnic blood reservoir. By decreasing or increasing this resistance, catecholamines may either facilitate or impede the shift of blood from splanchnic capacitance vessels to the systemic circulation.<sup>14</sup> Alterations in hepatic venous resistance usually contribute less to such shifts than the degree of venoconstriction and venous recoil within the splanchnic organs. However, large increases in hepatic venous resistance can cause blood to pool within the splanchnic system and can lead to systemic hypovolemia. Histamine-related anaphylactic reactions in animal experiments provide a dramatic example of this phenomenon.<sup>15</sup> Clearly, the mechanism of the severe arterial hypotension that occurs during anaphylactic shock is complex; pathophysiologic events include

Table 2.

### Blood volume in the splanchnic reservoir that can be mobilized to the systemic circulation by sympathoadrenal stimulation\*

	Blood Volume ml	Blood Volume (ml/kg body wt)	% of Total Blood Volume*
Splanchnic system**	1225	18	25
Mobilizable from Splanchnic System to Systemic Circulation	820	12	17

\*Calculations are for a 70-kg man (total blood volume = 4900 ml, 70 ml/kg body wt) and based on the following references:<sup>6,12,32,34,35</sup>

\*\*Splanchnic blood volume varies among species, ranging between 20% and 33% of the total circulatory blood volume; for simplicity, we arbitrarily chose 25%, which is in the normal range for humans.<sup>6,35</sup>

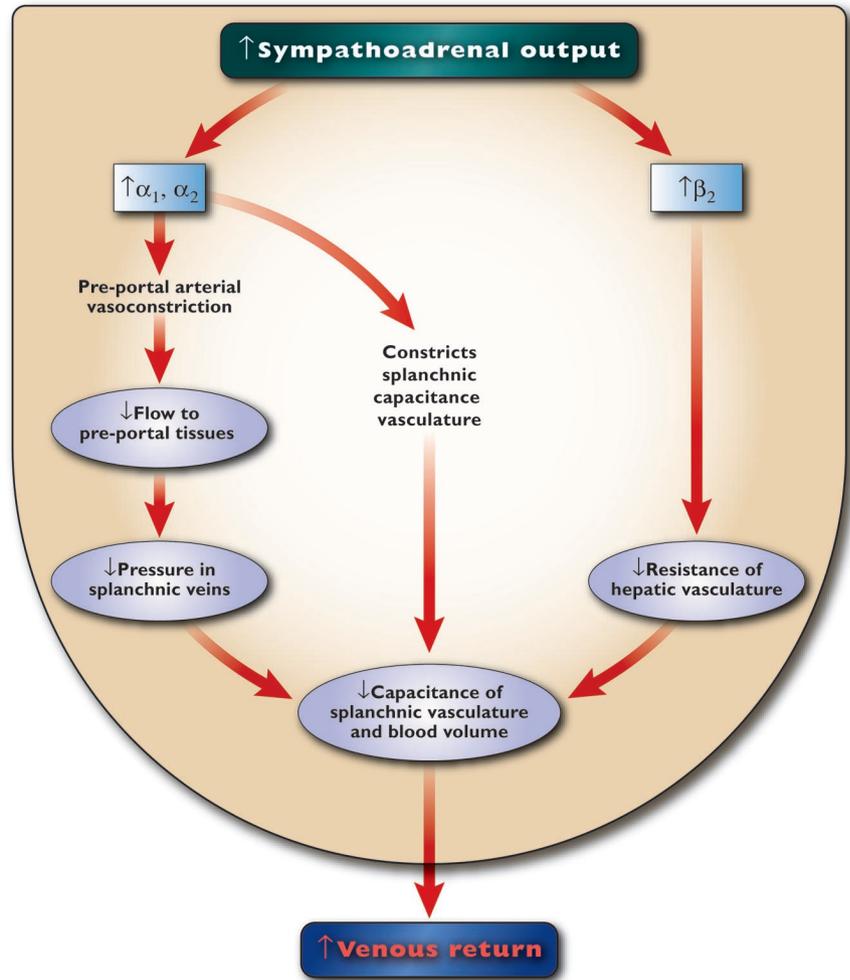


Fig. 3. Schematic representation of mechanisms by which sympathoadrenal activation can augment venous return.  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_2$  = adrenoceptor subtypes.

profound vasodilation as well as increased capillary permeability and massive transudation of fluid into the interstitial space. Epinephrine is the drug of choice for the treatment of anaphylaxis, primarily because of its efficacy to maintain arterial blood pressure; conceivably, it supports the systemic circulation in part by constricting splanchnic capacitance vessels and relaxing hepatic venous resistance vessels. Such effects would maximize the translocation of splanchnic blood to the central circulation, helping to restore venous return and cardiac output.

### Splanchnic Vasculature and Cardiac Output

Cardiac output is regulated by preload, contractility, heart rate, and afterload. Unless heart failure exists, the heart (in accordance with the Frank-Starling law) pumps out all of the blood that returns to it, leaving a small residual end-systolic volume. An increase in contractility *per se* increases stroke volume to a limited extent by increasing ejection fraction and reducing end-systolic left ventricular volume. The ability of a catecholamine to increase cardiac output is related in part to its capacity to shift splanchnic blood into the systemic circulation and

to increase venous return. An increase in flow through other organs and tissues also plays a role in the increase in venous return and cardiac output. Experimental data confirm that the mobilization of splanchnic blood volume is almost entirely the result of  $\beta_2$ - and  $\alpha$ -adrenergic receptor activation because selective  $\beta_1$  blockade does not alter the associated increase in cardiac output.<sup>16</sup>

### Catecholamines, Blood Volume Shifts, and Cardiac Output

The capacity of any particular catecholamine to affect the systemic circulation through an alteration of the splanchnic circulation is determined by numerous factors, including (1) relative densities of  $\alpha_1$ ,  $\alpha_2$ , and  $\beta_2$ -adrenoceptors throughout the splanchnic vasculature; (2) affinities of the catecholamine for the adrenoceptor subtypes; (3) plasma concentration of the catecholamine; (4) preexisting tone of the splanchnic vessels; and (5) blood volume in the splanchnic vasculature.

Many years ago, Imai *et al.*,<sup>17</sup> using various adrenergic antagonists, found that stimulation of  $\beta_2$ -adrenergic receptors decreased venous resistance (including splanchnic

nic venous resistance) and increased venous return, whereas activation of  $\alpha$ -adrenergic receptors increased venous resistance and decreased venous return. Activation of  $\beta_2$  adrenoceptors almost invariably enhances venous return (by increasing arterial flow and decreasing hepatic venous resistance); the situation with  $\alpha$  adrenoceptors is more complex—an increase or a decrease may occur. Generally,  $\alpha$  agonists increase venous return under normovolemic conditions, but they decrease it when used at high doses or in the presence of severe hypovolemia. Although the decrease could result from an  $\alpha$ -adrenoceptor-mediated increase in hepatic venous resistance, it is more likely the result of removing a portion of the vasculature from the systemic circulation by arterial vasoconstriction. The initial response to an  $\alpha$  agonist is usually an increase in venous return. However, if the splanchnic reservoir is depleted, further  $\alpha$ -adrenergic stimulation will no longer increase venous return and may indeed decrease it.

Epinephrine has a high affinity for all splanchnic adrenergic receptors, but it seems to exert greater effects on  $\alpha_1$ - and  $\beta_2$ -adrenergic receptors than on  $\alpha_2$ -adrenergic receptors. In the splanchnic system, norepinephrine exerts pronounced effects on both  $\alpha_1$  and  $\alpha_2$  receptors but has very little if any effect on  $\beta_2$ -adrenergic receptors. Selective  $\beta_2$ -adrenergic agonists can increase venous return by one third, entirely by increasing splanchnic blood flow and decreasing splanchnic venous resistance by more than 40%.<sup>18</sup>

The effect of dopamine on splanchnic circulation is complex, and the information in the literature is controversial. Dopamine, at low doses, stimulates dopaminergic-1 and dopaminergic-2 receptors and produces vasodilation. At higher doses, dopamine (directly and *via* conversion to norepinephrine) activates both  $\alpha_1$  and  $\alpha_2$  adrenoceptors. Infused at relatively low doses, dopamine consistently causes an increase in portal blood flow; this effect may be related to the stimulation of  $\beta_2$ -adrenergic receptors within the preportal arteries because phenoxybenzamine (an  $\alpha$ -adrenergic antagonist) augments the increase, whereas propranolol (a  $\beta$ -adrenergic antagonist) abolishes it.<sup>19</sup>

Dopamine can cause hepatic arterial blood flow to decrease, increase, or remain constant.<sup>20,21</sup> The mechanism of the decrease is unclear; it may result from the effect of dopamine on  $\alpha$ -adrenergic receptors, particularly at relatively high doses, or from the hepatic arterial buffer response,<sup>22</sup> which mediates the reciprocal relation between portal flow and hepatic arterial blood flow (*i.e.*, an increase in the former causes the latter to decrease) when lower doses are used.

The dose-related effects of dopamine on the hepatic oxygen supply-demand relation have been studied in animals. At the low end of the dose range, dopamine causes a parallel increase in hepatic oxygen supply and consumption; however, higher doses of dopamine decrease the ratio of oxygen supply to consumption.<sup>20</sup> Dopamine-induced increases in mesenteric blood flow have been associated

with decreases in oxygen extraction,<sup>23</sup> nutritive blood flow, and capillary density in the intestines.<sup>24</sup> Therefore, dopamine may divert blood flow away from splanchnic mucosa and predispose to mucosal ischemia.<sup>25,26</sup>

More than 25 yr ago, Marino *et al.*,<sup>27</sup> using a cardiopulmonary bypass model, noted that phenylephrine and dopamine increased the blood volume in the bypass reservoir, indicating that both drugs decrease venous capacitance. In such experiments, changes in bypass reservoir volume are inversely related to the changes in venous capacitance. Studies in the cardiopulmonary bypass model have also shown that dopamine produces dose-dependent decreases in venous capacitance during spinal anesthesia.<sup>28</sup> Experiments using selective receptor antagonists have demonstrated that both  $\alpha$ - and  $\beta$ -adrenergic receptor stimulation contribute to dopamine- and norepinephrine-induced increases in venous return.<sup>29</sup> Epinephrine and norepinephrine can produce equivalent reductions of splanchnic (including hepatic) blood volume.<sup>30</sup>

## Clinical Implications for Hypovolemia

Hypovolemia leads to an activation of sympathetic nervous system and an increase in circulating catecholamines. As a result, blood is translocated from blood reservoirs (primarily splanchnic capacitance vessels) of the body into the systemic circulation, which partially compensates for the decreases in circulating blood volume. In a recent study in dogs, hemorrhage sufficient to decrease mean aortic pressure by 50% was associated with a 50% reduction in cardiac output and nearly a 90% reduction in intestinal blood volume.<sup>31</sup> Although the induction of moderate hypovolemia or hypovolemia did not substantially affect cardiac output, it markedly altered the intestinal blood volume.<sup>31</sup> When intestinal blood volumes ranged between 95% and 135% of the baseline values, cardiac output remained constant. Outside this range, constriction or dilation of intestinal vessels caused large increases or decreases in venous pressure and cardiac output.<sup>31</sup> Therefore, these observations confirm the notion that splanchnic venous vasculature moderates changes in cardiac output during acute volume loading and hemorrhage, thereby maintaining cardiac output relatively constant over a wide range of total vascular blood volume.<sup>6,12,31,32</sup>

The effects of catecholamines administered during hypovolemia depend on the volume of blood in the splanchnic reservoir. When hypovolemia is severe, the homeostatic mechanisms involved in blood pressure and cardiac output regulation have already emptied the splanchnic reservoir. That is, the capacity of exogenous catecholamines to improve systemic hemodynamics by modulating the splanchnic circulation decreases progressively in the setting of increasing sympathoadrenal outflow and increases in the plasma concentrations of endogenous catecholamines and other vasoconstrictors

(e.g., angiotensin II, vasopressin/antidiuretic hormone, endothelin-1). After depletion of the splanchnic reservoir, large doses of catecholamines may still be able to increase blood pressure by further elevating arterial resistance in splanchnic and other vascular beds. Such effects might be essential for maintaining perfusion pressure and blood flow to the heart and brain. However, the intense vasoconstriction can be detrimental to the splanchnic organs by producing severe ischemic injury, which could subsequently lead to multiorgan failure. Therefore, when treating hypovolemia-induced hypotension, the use of exogenous catecholamines should be limited to a brief period and should not be viewed as a substitute for the immediate replacement of blood volume.

**Summary**

Nearly 25% of the total blood volume in humans resides within the splanchnic venous vasculature. In healthy normovolemic adults, sympathoadrenal stimulation can almost instantaneously transfuse approximately 2 units of whole blood from the splanchnic to the systemic circulation (table 2).  $\alpha$ -Adrenoceptor stimulation actively expels blood from splanchnic capacitance vessels, producing a rapid increase in venous return.<sup>33-35</sup> This volume mobilization occurs because of active venoconstriction as well as passive elastic recoil of the splanchnic veins secondary to decreased arterial inflow. The initial increase in venous return may be counteracted by other  $\alpha$ -adrenergic effects, such as an increase in hepatic venous resistance (which impedes expulsion of blood from the splanchnic to the central circulation) and a significant decrease in splanchnic arterial flow (which pharmacologically removes a portion of the systemic circulation). The degree to which an  $\alpha$ -adrenergic agonist affects venous return and cardiac output is therefore dependent on many factors, including baseline myocardial contractility, blood volume, and sympathetic tone.

Pure  $\beta$ -adrenergic agonists (e.g., isoproterenol) augment cardiac output primarily by increasing venous return, which results from increases in splanchnic blood flow due to lowered resistances in splanchnic arterial vessels and hepatic veins. In general, a drug that stimulates both  $\alpha$ - and  $\beta$ -adrenergic receptors would be expected to more effectively maintain systemic hemodynamics than one that activates either  $\alpha$ - or  $\beta$ -adrenergic receptors. When simultaneously stimulated,  $\alpha$ - and  $\beta$ -adrenergic receptors act in concert to maximally shift blood from the splanchnic vasculature into the systemic circulation by producing vasoconstriction, decreasing splanchnic vascular capacitance, and decreasing (or minimizing the increase in) intrahepatic vascular resistance.

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