David S. Warner, M.D., Editor

Classic Papers Revisited: My Love Affair with the Venous System

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The Pathophysiology of Aortic Cross-clamping and Unclamping. By Gelman S. ANESTHESIOLOGY 1995; 82:1026–60. Reprinted with permission.

Abstract: Aortic cross-clamping (AoX) and unclamping are associated with severe hemodynamic disturbances in virtually all organs and systems. The main hemodynamic changes induced by AoX result from an increase in impedance to aortic flow, an increase in systemic vascular resistance and afterload, blood volume redistribution caused by collapse and constriction of venous vasculature distal to the aortic clamp, and a subsequent increase in preload. Preload may not increase if the aorta is clamped distal to the celiac artery; in that case, blood volume from distal venous vasculature may be redistributed to the splanchnic vasculature without associated increases in preload. Increases in afterload and preload demand an increase in contractility, which results in an autoregulatory increase in coronary blood flow. Without increases in coronary blood flow and myocardial contractility, decompensation may occur. Aortic cross-clamping is associated with the formation and release of many mediators which constitute a double-edged sword: they may mitigate or aggravate the harmful hemodynamic effects of AoX and unclamping. Injuries to the lungs, kidneys, spinal cord, or abdominal viscera are caused mainly by ischemia and reperfusion of organs distal to aortic cross-clamping. A clear understanding of the pathophysiologic mechanisms involved in these processes should help to promote rational, well-focused, and effective measures to prevent and treat homeostatic disturbances occurring during AoX and unclamping.

MY attraction to the venous system was not planned. It just happened. It was not love at first sight. It started from something not related to veins and then grew to the love of my life. Here is the story.

In the late 1960s, I lived and worked in Leningrad, USSR, and once provided anesthesia to a local communist party official undergoing gastrectomy. Everything went well, I thought. I visited my patient an hour after surgery and almost fainted: during the gastrectomy, the surgeon inserted a red rubber tube through the nose into the stomach to unload the anastomoses. The tube had been incorrectly connected with the oxygen source and the patient was receiving 6 l/min of oxygen. I thought the patient would die and I would be arrested. I stopped the oxygen flow and before going to jail (as I expected), I decided to read something about enteral oxygen administration. I found interesting literature. In the 1920s, enteral oxygen administration was used in South Africa to resuscitate newborns. In the 1950s in Czechoslovakia, a few studies demonstrated that enteral oxygen administration temporarily improved liver function tests but found no improvement in overall outcome. The dual blood supply of the liver and especially the peculiarity of splanchnic
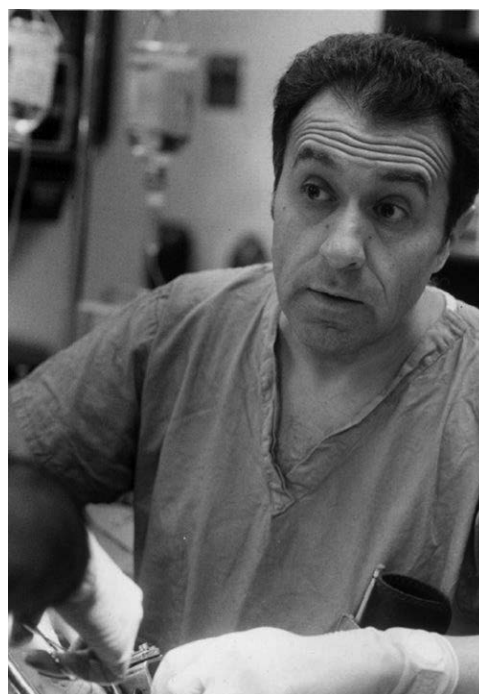
Simon Gelman, M.D., Ph.D., F.A.N.Z.C.A., in the mid-1980s conducting an experiment.
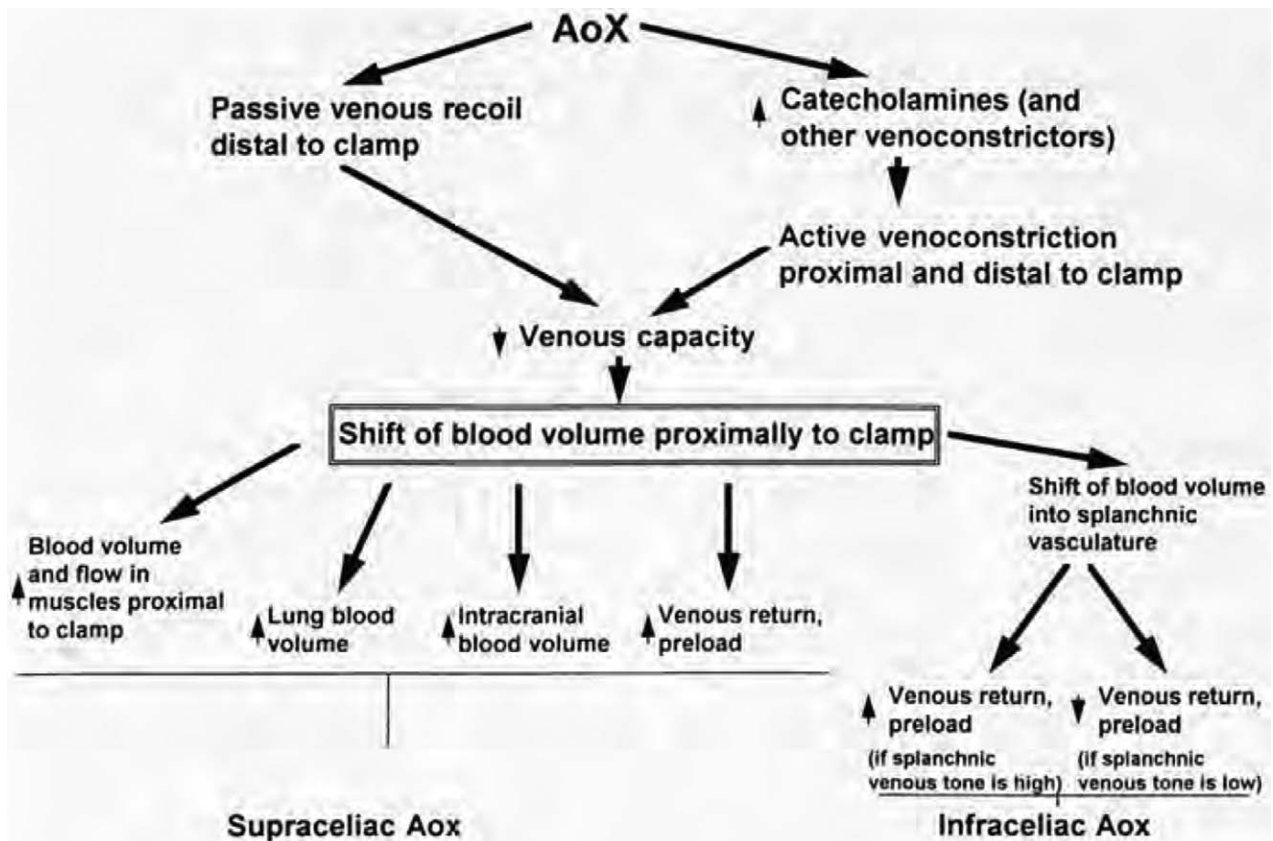
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Fig. 1. Blood volume redistribution during aortic cross-clamping. The scheme depicts the reason for the decrease in venous capacity, which results in blood volume redistribution from the vasculature distal to aortic occlusion to the vasculature proximal to aortic occlusion. If the aorta is occluded above the splanchnic system, the blood volume travels to the heart, increasing preload and blood volume in all organs and tissues proximal to the clamp. However, if the aorta is occluded below the splanchnic system, blood volume may shift into the splanchnic system or into the vasculature proximal to the clamp. The distribution of this blood volume between splanchnic and nonsplanchnic vasculature determines changes in preload. AoX = aortic cross-clamping; ↑ and ↓ = increase and decrease, respectively. Figure and legend reprinted from Gelman S: The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 1995; 82:1026–60 (fig. 1, p 1029).

and hepatic circulation intrigued me. Hepatic circulation had become[1–3] and remained, my love for the next 15 to 20 yr.[4,5]

In the early 1980s, I was working at the University of Alabama at Birmingham and was preoccupied with beginning the liver transplantation program. However, my boss, Dr. Edward Ernst, asked me to also start providing anesthesia for vascular surgery. At that time, I knew very little about aortic surgery and hemodynamic effects of aortic cross-clamping. When reading some articles and chapters in textbooks on the subject, I noticed differences in descriptions of the physiologic events between clinical settings and animal experiments. Seemingly, interventions of clinicians during surgery (*i.e.*, bleeding, replacement of blood and fluid loss, adjusting depth of anesthesia, and other pharmacologic interventions) "spoil" the normal physiologic response to aortic cross-clamping.

In the textbook chapters that described anesthetic management of patients undergoing aortic surgery, there was little information on the cardiovascular response to aortic cross-clamping. However, research papers noted that aortic cross-clamping was consistently associated with an increase in

arterial blood pressure. Cardiac filling pressures were reported to become increased, decreased, or stay the same. Cardiac output (CO) was found to be decreased during aortic cross-clamping, which was attributed to increased impedance to left ventricular ejection (increased afterload), causing a decrease in ejection fraction and stroke volume. The associated decrease in total body oxygen consumption was mainly ascribed to a decrease in CO and therefore an insufficient supply of arterial blood to organs and tissues distal to the aortic clamp. The concomitant observations that mixed venous oxygen content and saturation increased during aortic cross-clamping did not support that notion because an inadequate CO must lead to an increase in oxygen extraction and a decrease in oxygen content in the venous blood. That didn't happen.

Many years ago, the young French physiologist, Claude Bernard, reportedly said, "Your textbooks are wrong, my dog is right." My own experiments on dogs showed significantly increased arteriovenous shunting in tissues proximal to the aortic clamp.[6] This partially explained why mixed venous oxygen content increased during aortic cross-clamping.
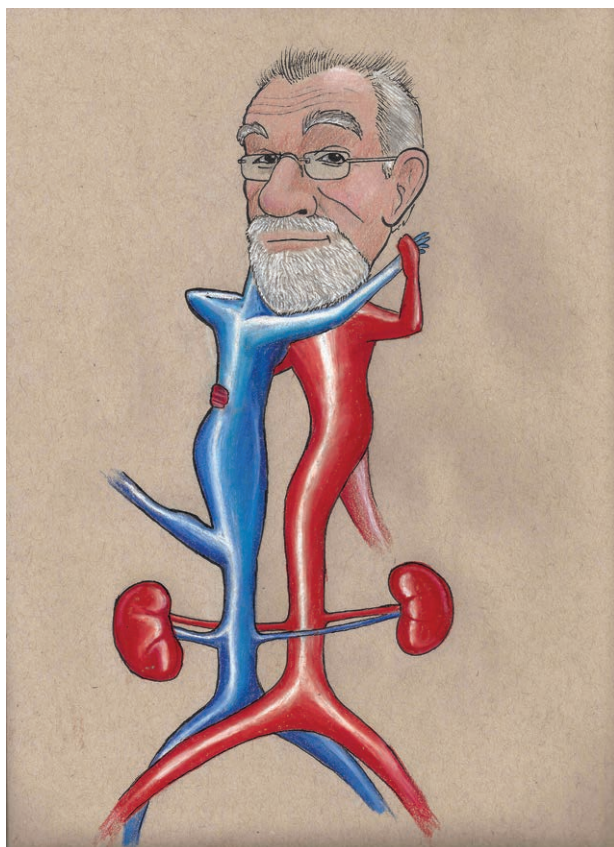
Fig. 2. Illustration of "My Love Affair with the Venous System." Illustration by Ian Riley (January 2018).

In human studies, CO consistently decreased during aortic cross-clamping while animal studies demonstrated lack of change or even increased CO.[7,8] During aortic cross-clamping at the diaphragmatic level in pigs, we observed increased blood flow through the proximal part of the body with little change in CO.[9] CO drastically decreased when the inferior cava was also clamped at the same level. This suggested that during aortic cross-clamping, volume is coming from the distal part of the body through the inferior cava into the proximal part of the body; at that time, I did not have an idea where the volume was coming from.

In 1912 August Kogh described a model of fast and slow compartments within the venous vasculature (reviewed by Gelman[10]). We posed a hypothesis that blood volume shifts from the slow compartment (mainly splanchnic circulation) to the fast compartment (the major systemic vasculature) during aortic cross-clamping because when the flow to the slow compartment decreases, the compliant splanchnic veins recoil and squeeze blood downstream into the fast compartment, increasing preload and CO. Using labeled red blood cells and clamping dogs' aortas at the diaphragmatic level, we demonstrated that, indeed, blood volume shifted from the distal to proximal part of the body during aortic cross-clamping.[11]

Thus, observations of increases in mixed venous oxygen content,[7] arteriovenous shunting,[6] and blood flow and volume in the proximal part of the body[9,12] did not support

the contention that an increase in afterload alone could be responsible for the drastic and complex changes in cardiovascular function observed during aortic cross-clamping. The shift of blood volume from the veins distal to the aortic clamp to the vasculature proximal to the clamp did.

During a clinical conference I attended, an anesthesiologist reported that he had used sodium nitroprusside during aortic cross-clamping at the low thoracic level in a patient who underwent surgery after a motor vehicle accident to improve blood supply to the organs distal to the clamp (*i.e.,* splanchnic organs, kidneys). I argued it was unlikely that arterial vasculature in hypoxic tissues, already dilated by adenosine released from adenosine triphosphate metabolism, would be any further dilated by a vasodilator. A few anesthesiologists disagreed, insisting that they had successfully used sodium nitroprusside for decades in similar situations. I was prompted to undertake the shortest study in my career (two weeks); it was the only manuscript that was accepted without any revision. The editor-in-chief of the journal asked me for permission to correct a typo and told me that, being an editor for many years, he had not seen a better study than this one. However, I maintain that the study was not necessary: I knew exactly what I would get and I got it. The study demonstrated that vasodilators administered during aortic cross-clamping do not increase blood flow in tissues distal to the clamp.[13]

A few studies demonstrated that CO is decreased during infrarenal aortic cross-clamping, but when a vasodilator is given, CO is restored to baseline.[14] Many anesthesiologists in that era were using vasodilators during aortic cross-clamping for different reasons, including CO restoration. In our study,[7] we measured total body oxygen consumption and CO during infrarenal aortic cross-clamping in humans and also observed that nitroglycerine increased CO to preaortic cross-clamping levels. However, oxygen content in mixed venous blood increased while total body oxygen consumption did not change. Thus, the study showed that CO restoration by a vasodilator during aortic cross-clamping is meaningless because it does not increase tissue perfusion.

Another study in dogs demonstrated that use of a vasodilator further decreased blood flow and oxygen consumption in the distal part of the body, illustrating the fact that perfusion in hypoxic tissues is pressure dependent: lower pressure causes lower flow, which increases tissue hypoxia.[15] Oxygen consumption in the distal part of the body was significantly decreased and a vasodilator decreased it even further, apparently aggravating the existing oxygen deprivation in those tissues. We expected this. What we did not expect was that oxygen consumption in the proximal part of the body also decreased, by approximately 15 to 20%. This suggested that the proximal part of the body also was somewhat hypoxic. Was it?

Using magnetic resonance spectroscopy on dogs during aortic cross-clamping at the diaphragmatic level, we observed decreased pH and phosphocreatine in the deltoid muscle during aortic cross-clamping, which quickly recovered after the clamp was released.[11] Thus, a relatively minor degree of hypoxia probably develops in the proximal tissues

during aortic cross-clamping. Why? The increased blood volume in the proximal part of the body[12] could have led to heterogeneous perfusion of the tissues, causing some degree of tissue ischemia to occur. An explanation of the physiology causing heterogeneous perfusion still needs to be provided.

My love for and fascination with the venous system continued and resulted in an article entitled "Venous Function and Central Venous Pressure: A Physiologic Story."[10] The article analyzed the two-compartment model of the venous system—a slow, compliant compartment and a fast, less compliant compartment. The two-compartment model helps us to understand how the actions of certain medications can induce opposite effects on major hemodynamic variables (see Gelman[10] for detailed explanation).

The two-compartment venous model predicts that central venous pressure alone is often a misleading indicator of volume status. Central venous pressure is affected by pressures within the thorax (including controlled ventilation with or without positive end-expiratory pressure), abdomen, pericardium, pulmonary artery (including changes in the fraction of inspired oxygen), myocardial contractility, and obviously, blood volume, including the relationship between stressed and unstressed venous volumes. All this makes central venous pressure *per se* an unreliable indicator of the patient's volume status.

The role of the two-compartment model in the explanation of different, often opposite effects on hemodynamics can be illustrated by the following example: constriction of arteries in the main, fast compartment is usually associated with a decrease in flow, venous return, and CO. Constriction in splanchnic vasculature (slow compartment) leads to a decrease in blood flow, decreased volume and pressure within the veins, their consequent recoil, and shift of volume from that vasculature into the fast, main compartment, which is associated with an increase in preload, venous return, and CO.

My love affair matured with another publication.[16] That article suggests that changes in stressed venous volume to unstressed venous volume ratios likely contribute to the observation that up to half of the patients treated with goal-directed hemodynamic therapy do not demonstrate an increase in CO in response to fluid challenge, causing some patients to become overloaded. We justified a hypothesis that the stressed venous volume to unstressed venous volume ratio might be responsible for misinterpreted responses to fluid challenge[16]; a portion of infused fluid that ends up in unstressed venous volume does not affect hemodynamics and therefore cannot increase CO. During anesthesia, sympathetic nervous system tone may decrease, allowing unstressed venous volume to enlarge. However, during the postoperative period, when the effect of anesthetics has subsided, unstressed venous volume decreases and thereby shifts blood volume to the stressed venous volume, causing potential fluid overload. That article also explains why vasoconstrictors can have a variety of hemodynamic effects, depending on the stressed venous volume to unstressed venous volume ratio. Finally, the article suggests future directions for study

to better account for changes in the stressed venous volume to unstressed venous volume relationship.

I feel fortunate that at age 81 my passionate absorption with the venous system not only survived but still piques my curiosity. All love affairs should be so long lived.

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