

The Pathophysiology of Aortic Cross-clamping and Unclamping

[Medical Intelligence Article]

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THE aorta at the thoracic or abdominal levels is cross-clamped during surgical procedures for trauma and sometimes for resuscitation; more often, however, it is cross-clamped for surgical treatment of abdominal, thoracic, or thoracoabdominal aneurysm or of peripheral vascular disease complicated by ischemia of the lower extremities, kidneys, or intestines.

Recent studies analyzed the results of thoracoabdominal aneurysm repair and reported discouraging results. Overall 30-day mortality ranged from 8% to 35%. [1-3] The incidence of complete or partial paraplegia was 16-38%; myocardial infarction, 11%; respiratory failure, 36%; renal failure, 18-27%; and gastrointestinal complications, mainly hemorrhage, 7%. Multivariate analysis showed that preoperative renal or pulmonary insufficiency or coronary artery disease increased the rate of complications. [2] Furthermore, this study demonstrated that the duration of aortic cross-clamping also affects the overall results of this surgical intervention. The rate of complications associated with the repair of an abdominal aortic aneurysm is lower and also depends in part on concomitant coronary, pulmonary or renal disease. [4] For example, data on complications of abdominal aortic reconstructive surgery published between 1966 and 1983 demonstrate an overall mortality rate ranging from less than 1% to 15%. [5] In cases of ruptured aortic aneurysms, the mortality rate is 20-42%. [6].

These high complication rates result in part from pathophysiologic disturbances that occur during cross-clamping and unclamping of the aorta. The level of aortic cross-clamping, the species, the baseline condition of the heart, and the anesthetic management during surgery and experiments, with their effects on myocardial status and vascular tone--all of these factors alter the hemodynamic responses to aortic cross-clamping and unclamping. Nevertheless, many responses are identical and conceptually do not depend on the level of occlusion or the species.

Therefore, to avoid repetition, this review presents the details of confounding factors only when they are important for understanding the concepts. The purpose of this review is to facilitate an understanding of the pathophysiologic derangements occurring during aortic clamping and unclamping and to provide a basis for rational therapy to decrease the complications and improve the outcome of aortic surgical procedures. Therapeutic interventions and analysis of complications and outcome of aortic surgery are beyond the scope of this article.

I. Hemodynamic Response to Aortic Cross-clamping

A. Primary Variables

In general, the hemodynamic response to cross-clamping of the aorta consists of increases in arterial pressure and systemic vascular resistance with no significant change in heart rate. [7-10] In most instances, cardiac output decreases. [8,11-18] Changes in filling pressures are inconsistent: no change [8,10] or an increase [7,12,15,19-30] has been reported. Information regarding changes in cardiac output also is contradictory. Substantial evidence supports the common belief that cardiac output decreases during aortic cross-clamping, [8,11-18] although numerous studies have failed to demonstrate such a decrease. [7,19-21,31-34] The reasons for inconsistent and contradictory observations lie in differences in degrees of changes in afterload, preload, blood volume redistribution, coronary blood flow, myocardial contractility, and other factors.

B. Afterload, Preload, and Blood Volume Redistribution

Arterial hypertension is the most dramatic and consistent component of the hemodynamic response to aortic cross-clamping. Most texts attribute this sign to a sudden increase in impedance to aortic flow and an increase in afterload. Increases in left ventricle end-systolic wall stress and systemic arterial pressure. [32,33] are consistent with this notion. The first clear documentation of this possibility was provided in 1935 by Barcroft and Samaan, [31] who, using a cardiometer, recorded an enlargement of cardiac dimensions that they attributed to increased afterload. In the same study, however, the authors observed that cross-clamping of the thoracic aorta was associated with an increase in "systemic flow" (cardiac output). This increase was attributable, they believed, to "blood transference" from the lower to the upper part of the body.

They wrote: "The inferior vena cava must be kept open to allow blood from the collapsing vessels in the trunk to pass into the upper part of the vascular system." A majority of the following clinical studies demonstrated a decrease in cardiac output, whereas animal studies showed an increase in blood flow through the proximal part of the body and no significant change in cardiac output during cross-clamping of the thoracic aorta. [19-21,33,35,36].

Fundamental work by Caldini et al. [37] suggested possible blood flow redistribution between two compartments with short and long time constants. According to their model, clamping of the thoracic aorta increases cardiac output by diverting blood away from the area with long time constants, presumably the splanchnic vasculature. In other words, the splanchnic venous vasculature collapses when intramural venous pressure decreases; the decrease in venous pressure results from a decrease in blood flow from the arterial to the venous vasculature with a subsequent decrease in venous capacitance, caused by an elastic recoil. Splanchnic venous collapse, in turn, results in an increase in venous return and cardiac output.

Important studies in this area were performed at the University of Oslo. The investigators simultaneously occluded the aorta and various large veins in dogs. [35,36] Occlusion of the inferior caval vein prevented increases in arterial pressure and in end-diastolic myocardial segment length, whereas occlusion of other, smaller veins modified the increases to different degrees, presumably reflecting different amounts of blood volume translocated from various veins, thereby affecting venous return, preload, and the degree of arterial hypertension. The authors concluded that blood volume shift from the nonsplanchnic region maintains cardiac output during infraceliac aortic occlusion, whereas during occlusion of the thoracic aorta, drainage from the splanchnic area accounts for about 70% of the increase in end-diastolic myocardial segment length. [36] Cross-clamping of the thoracic aorta is associated with almost a twofold increase in blood flow through the upper part of the body, [19-21] more than a threefold increase in blood flow through the muscle proximal to the clamp, [33] and a dramatic decrease in canine hind-leg volume as determined by mercury strain-gauge plethysmography. [38] The decrease in volume reached a plateau within 30 s.

These observations are consistent with (but do not prove) the hypothesis of blood volume redistribution. Using whole-body scintigraphy with technetium 99m-labeled plasma albumin we demonstrated that aortic cross-clamping at the diaphragmatic level is associated with a significant increase in blood volume in the organs and tissues proximal to the level of occlusion. [39] In a study in which a balloon inserted into the inferior caval vein was inflated during cross-clamping, arterial hypertension was prevented [40] apparently as a result of a decrease in blood volume redistribution and a lesser increase in preload. The effectiveness of the measure was examined in dogs, but to our knowledge the method has not been used in humans. Thus, the data presented provide evidence that blood volume shifts from the lower to the upper part of the body during aortic cross-clamping.

Many published observations concerning the hemodynamic response to aortic cross-clamping can be explained, at least in part, by blood volume redistribution. For example, filling pressures (central venous pressure, pulmonary capillary wedge pressure, or left ventricular end-diastolic pressure) in animals and humans often increase during cross-clamping of the thoracic aorta. [19-29] A study using two-dimensional transesophageal echocardiography demonstrated a substantial (28%) increase in end-diastolic area during cross-clamping of the supraceliac aorta. [14] These data are consistent with but do not necessarily support the notion of an increased venous return. An increase in filling pressures and left ventricular end-diastolic volume during cross-clamping of the aorta may result from blood volume redistribution from the venous vasculature in the lower part of the body to the upper part of the body, or it may represent an increase in afterload with subsequent increase in the amount of blood remaining in the left ventricle at the end of systole. End-diastolic volume during each subsequent cycle would be larger than that during the preceding one.

The substantial differences in hemodynamic responses observed after aortic cross-clamping at different levels [14] may result in part from different degrees and patterns of blood volume redistribution. Occlusion of the supraceliac aorta in humans was associated with dramatic increases in mean arterial pressure, filling pressures, and end-diastolic and end-systolic ventricular volumes (determined as end-diastolic and end-systolic areas by two-dimensional transesophageal echocardiography). [14] During supraceliac aortic cross-clamping, venous capacitance below the clamp decreases, expelling blood from the splanchnic and nonsplanchnic vascular beds toward the heart. Preload then increases substantially, as manifested by increases in filling pressures and the end-diastolic area of the left ventricle. Infraceliac aortic cross-clamping, in contrast, reportedly has inconsistent effects on preload. [7,12,15,33,41,42] A pulmonary artery catheter

equipped with a fast-response thermistor to measure right ventricular volume by the thermodilution technique was used in two studies that demonstrated a decrease in right ventricular end-diastolic volume during cross-clamping of the infrarenal aorta. [43,44] The observations of a decreased preload during aortic infrarenal cross-clamping might be viewed as a contradiction to the theory of blood volume redistribution. However, compression of the inferior vena cava during surgical manipulations may interfere with a "normal" volume redistribution response to the aortic cross-clamping. In addition, and possibly more important, blood volume from the infraplanchic vasculature may shift to the compliant splanchnic vasculature rather than to the heart (Figure 1).

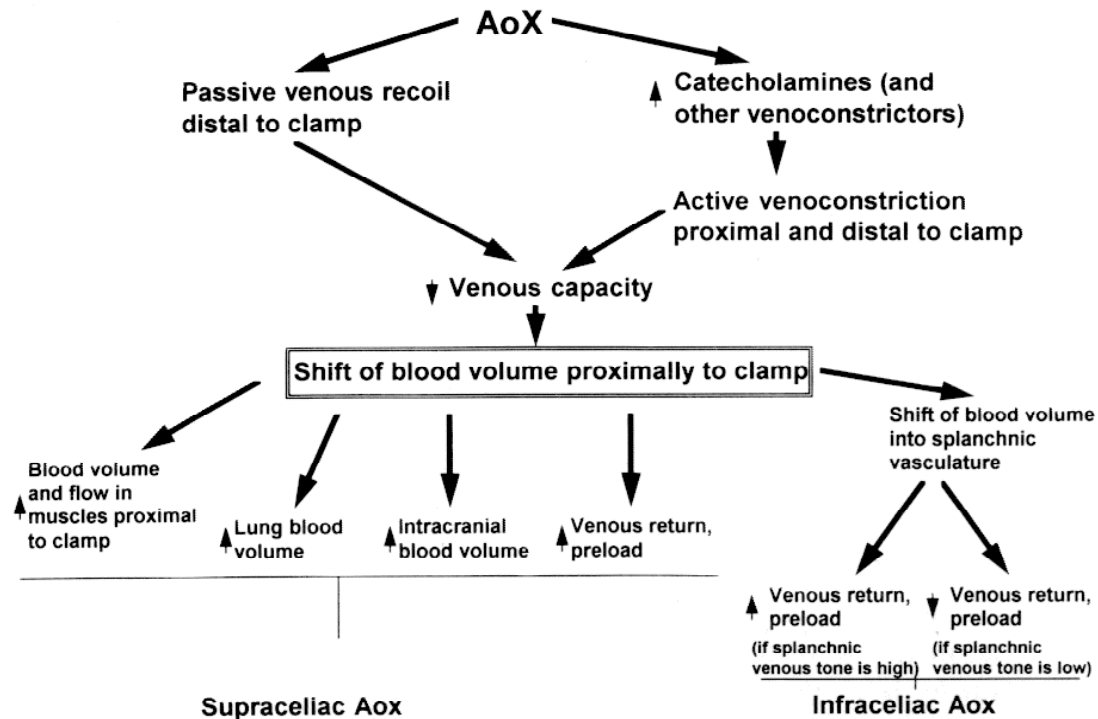


Figure 1

Figure 1. Blood volume redistribution during aortic cross-clamping. This 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 of other tissues proximal to the clamp. The distribution of this blood volume between the splanchnic and nonsplanchnic vasculature determines changes in preload. AoX - aortic cross-clamping; [arrow up] and [arrow down] - increase and decrease, respectively.

Variation in the blood volume status or splanchnic vascular tone, resulting from differences in fluid load, depth of anesthesia, pharmacodynamics of an anesthetic, and other factors may affect the degree and pattern of blood volume redistribution. For example, during infraplanchic aortic occlusion, the blood volume redistributed from the vasculature below the occlusion may travel to the heart, increasing preload and inducing central hypervolemia, or it may travel to the compliant splanchnic venous vasculature. The distribution of volume between the heart and the splanchnic system would probably depend on the sympathetic discharge to the splanchnic system. This distribution of blood volume determines the alterations in cardiac output at any particular moment.

Cross-clamping of the thoracic aorta is associated with an expected decrease in blood flow distal to the aortic occlusion and a substantial increase in blood flow above the occlusion. [19-21,33,35,36] Oxygen consumption in the part of the body distal to the aortic occlusion decreases and, paradoxically, so does oxygen uptake in tissues above the occlusion. [20] Our experiments with phosphorus 31 nuclear magnetic resonance surface coil spectroscopy to measure serial changes in the high-energy phosphate of the deltoid

muscle demonstrated a decrease in skeletal muscle creatine phosphate, an increase in glycolytic intermediates, and a decrease in intracellular inorganic phosphate. [45] These changes are consistent with skeletal muscle hypoxia. The reasons for the reduced oxygen consumption in the muscle tissue above the level of aortic occlusion are unclear. A decrease in oxygen uptake in the tissues above the level of aortic cross-clamping [20] and a decrease in deltoid muscle creatine phosphate (and some other variables obtained during experiments with nuclear magnetic resonance spectroscopy [45]) started virtually immediately after application of the aortic clamp. These observations make it unlikely that an accumulation of endotoxin or other mediators from ischemic tissues distal to the aortic occlusion play a key role in this event. Cross-clamping of the aorta is associated with a substantial increase in sympathoadrenal discharge (see below), which may by itself constrict arterioles and decrease capillary flow (possibly in combination with an increased total and shunt flows) to the tissues proximal to the aortic cross-clamping. It has been demonstrated that sympathetic stimulation and norepinephrine infusion decrease capillary density, tissue oxygen extraction, and oxygen uptake. [46,47] Substantial arteriovenous shunting through the upper part of the body during aortic cross-clamping has also been demonstrated [48] and could be responsible at least in part for oxygen deprivation in the muscle tissue above the aortic cross-clamp. Also, an increase in blood volume in the tissues proximal to the aortic clamp [39] may cause dramatic dilation of the vasculature above the aortic occlusion. Proximal hypervolemia, vasodilation, and increase in flow through the tissues proximal to the aortic clamp may result in microcirculatory disturbances to the extent of jeopardizing oxygen exchange. It has been shown that adenosine (which more than likely accumulates in ischemic tissues below the aortic occlusion and is washed out into the tissues above the occlusion) increases total tissue blood flow but decreases capillary density, oxygen extraction, and oxygen uptake. [49] The depressant effect of adenosine on tissue oxygen uptake has been attributed to selected vasodilation in one regional circulation, with redistribution resulting in blood flow reduction in the other regions. [49] It seems reasonable that similar changes in tissue oxygen supply at microcirculatory levels can be induced by aortic cross-clamping, hypervolemia, and passive vasodilation in a fashion similar to that induced by active vasodilation. However, this speculation remains unproven. Additional studies may explain the unexpected and paradoxical observation of a moderate hypoxia in tissues proximal to the aortic clamp.

A discussion of various pharmacologic interventions for therapeutic purposes is beyond the scope of this article. However, many observations related to the effects of drugs (for example, arterial or venous vasodilators) on the hemodynamic response to aortic cross-clamping provide additional support for and can be explained by the notion of blood volume shift to the vasculature proximal to the aortic clamp. For example, vasodilators often reverse the cross-clamping-induced decrease in cardiac output. [47,50] The most plausible explanation for the increase has been that therapy with vasodilators is associated with decreases in peripheral vascular resistance and afterload and subsequent increases in ejection fraction and cardiac output. However, a change in the distribution of blood flow between the two vascular compartments with long and short time constants during sodium nitroprusside infusion [51] could be responsible for an increase in preload. In other words, in Caldini et al.'s model, [37] sodium nitroprusside could decrease resistance in the vasculature with short time constants (presumably nonsplanchnic vasculature) to a greater extent than resistance in the vasculature with long time constants (splanchnic vasculature). This redistribution of blood flow between the two vascular compartments is induced by sodium nitroprusside [51] and may lead to an increase in cardiac output.

Pretreatment with another vasodilator, nifedipine (a calcium channel antagonist) also led to an increase in cardiac output during infrarenal aortic cross-clamping, whereas dogs without nifedipine pretreatment responded with no significant change in cardiac output. [52] The authors speculated that the nifedipine-induced increase in cardiac output resulted from increases in heart rate and myocardial contractility. However, an alternative explanation for an increase in cardiac output is possible. Nifedipine does not affect venous compliance much, [53] and calcium channel antagonists are often associated with baroreceptor-mediated increases in sympathetic discharge. [54,55] An increased sympathetic tone and lack of a venodilating effect of nifedipine are consistent with splanchnic vasoconstriction and subsequent increase in preload and cardiac output, resulting from a distribution of blood volume not only from nonsplanchnic but also from splanchnic vasculature toward the heart.

A recent study demonstrated that cardiac output and total body oxygen delivery were greater and the arterial venous oxygen content difference lower in patients undergoing infrarenal aortic cross-clamping and treated with an arterial vasodilator urapidil than in patients treated with a venodilator, isosorbide. [56] The authors suggested that because cardiac output and oxygen delivery were greater in the urapidil group, arteriolar vasodilators offer certain advantages. However, the authors did not determine body oxygen consumption or

other indicators of the adequacy of oxygen supply. Therefore it is unclear whether such an increase in cardiac output was useful: an increase in cardiac output and a decrease in arteriovenous oxygen difference without an increase in body oxygen uptake were demonstrated during infrarenal aortic cross-clamping and nitroglycerin administration (apparently in doses leading to venous and to arterial vasodilation). [17] Arterial vasodilation may increase cardiac output [17,56] without improving nutritive flow, [17] whereas venodilation per se does not increase cardiac output because of blood volume shifts from the vasculature distal to aortic occlusion into the dilated splanchnic vasculature rather than into the heart. Thus, these observations [56] support the theory of blood volume redistribution during aortic occlusion.

Any vasodilator, including nitroglycerin, can increase sympathetic discharge, [57] which may affect the degree and even the pattern of blood volume redistribution during aortic cross-clamping and lead to inconsistencies in changes in preload and cardiac output among studies. Anesthetic management (such as the choice of myocardial-depressant or non-myocardial-depressant anesthetics) and a degree of fluid load before aortic cross-clamping also play an important role in the different hemodynamic responses to aortic cross-clamping.

Taken together, the increases in flow [19-21,33,35,36] and volume [39] in the upper part of the body during aortic cross-clamping at the diaphragmatic level, the increases in arteriovenous shunting of microspheres [48] and blood [58] proximal to the clamp, the increase in mixed venous oxygen content, [10,17] an increase in cardiac output during arterial vasodilation, [50,51] and absence of such an increase during venodilation [56] support the hypothesis of blood volume redistribution from the tissues below aortic occlusion to the vasculature above the clamp.

Rational therapeutic approaches to decrease the harmful effect of aortic cross-clamping include phlebotomy, inotropes, and coronary vasodilators (see below) but should be focused primarily on measures that decrease afterload (vasodilators, predominantly arteriolar dilators) and normalize preload (appropriate fluid load and use of vasodilators, predominantly venodilators).

C. Total Body Oxygen Consumption

Decreased oxygen consumption, consistently observed during aortic cross-clamping, is often attributed to decreased cardiac output. [10,16] However, an increase in mixed venous oxygen saturation and content, which also is observed during aortic cross-clamping, [10,17] contradicts this notion because inadequate cardiac output should be associated with an increase in oxygen extraction in conjunction with a decrease in mixed venous oxygen content. Consequently, another explanation is warranted. We have observed an increase in arteriovenous shunting of microspheres in tissues above the level of aortic cross-clamping. [48] Shunting of microspheres reflects arteriovenous shunting of blood. [58] Therefore, an increase in mixed venous oxygen content does not necessarily imply adequacy of tissue perfusion. Subsequently, we suggested that decreases in oxygen consumption and cardiac output may reflect a decrease in oxygen uptake by the total body, attributable to a decrease in the perfused mass of tissues. [17] This decreased "cross-clamp adapted oxygen consumption," rather than deterioration of myocardial performance, may be indirectly responsible for a decrease in cardiac output.

Most investigators have not measured changes in total-body oxygen consumption and could not determine whether a pharmacologically induced increase in cardiac output was associated with improved tissue perfusion and oxygen delivery to tissues. A small dosage of nitroglycerin (0.25 micro gram *symbol* kg sup - 1 *symbol* min sup -1) increased cardiac output and decreased vascular resistance in patients who responded to cross-clamping of the infrarenal aorta with a more than 50% increase in arterial pressure or 50% decrease in cardiac output. [50] Oxygen extraction was greater in patients who received no nitroglycerin. The authors speculated that nitroglycerin improved oxygenation in peripheral tissues. We also have observed an increase in cardiac output during nitroglycerin infusion; however, the nitroglycerin-induced increase in cardiac output was associated with no increase in total-body oxygen consumption, suggesting that the observed increase in total blood flow (cardiac output) was related neither to a real increase in nutritive blood flow nor to an improvement in tissue oxygenation. [17] The increase in flow proximal to the aortic clamp could occur through arteriovenous anastomoses and other nonnutritive vessels (thoroughfare channels, for example) rather than through capillaries; this possibility has been demonstrated in our laboratory in dogs. [48] This observation is not surprising because ischemia in the tissues below occlusion is probably associated with virtually the maximum arterial vasodilation and an increase in capillary density in the hypoxic tissues. The addition of any vasodilator, including nitroglycerin, probably could not produce further significant dilation, increased nutritive flow, or any subsequent improvement in tissue oxygenation.

D. Coronary Blood Flow and Myocardial Contractility

Blood volume redistribution and an increase in preload and afterload, require appropriate adjustments in myocardial contractility and coronary blood flow. A large end-diastolic volume combined with low myocardial contractility favors a decrease in stroke volume, whereas stroke volume increases during an increase in aortic blood pressure with high myocardial contractility. [59] An adequate coronary blood flow is of crucial importance for adequate contractility. Therefore, analysis of the changes in coronary blood flow and myocardial contractility that occur during cross-clamping of the aorta, is important in the understanding of cardiac function during aortic cross-clamping.

Because aortic cross-clamping is associated with substantial increases in preload and afterload, both leading to an increase in myocardial oxygen demand, the response of the intact coronary vasculature is predictable: an increase in demand is met by an increase in supply. Indeed, most studies demonstrated such an increase in coronary blood flow. [32,60-66] Cross-clamping of the thoracic aorta in one set of experiments was associated with a greater than 65% increase in coronary blood flow. [32] Use of vasodilators was associated with a further increase in coronary blood flow. [60,67] An increase in coronary blood flow probably represents coronary blood flow autoregulation and reflects increases in myocardial oxygen demand and consumption, [32,68] Myocardial oxygen consumption gradually decreased during cross-clamping of the thoracic aorta, in parallel with cardiac output, [16] possibly reflecting preservation of coronary blood flow autoregulation. Lactate concentration in the myocardium and lactate-pyruvate ratio in the coronary sinus blood increased, but lactate uptake by the myocardium also increased, suggesting that no severe myocardial ischemia occurred during cross-clamping of the thoracic aorta. [60] Further, no evidence for subendocardial ischemia (no change in endocardial-epicardial flow ratios) was observed during cross-clamping of the thoracic aorta. Left ventricular biopsy specimens showed preservation of myocardial high-energy phosphate stores and an essentially normal ultrastructure. [60] However, even in a heart with normal coronary vasculature, an increase in myocardial oxygen demand is not always adequately met by an increase in myocardial oxygen supply. Using ^{31}P nuclear magnetic resonance spectroscopy, we have observed a significant decrease in phosphoorganic compounds and intracellular pH in the myocardium during cross-clamping of the thoracic aorta in normal dogs. [45].

Inconsistencies in these data may result from differences in myocardial contractility, degree of upper body hypervolemia, the ability of coronary flow to autoregulate, and the degree of increase in left ventricular end-diastolic pressure, which by itself may decrease (or prevent an increase in) coronary blood flow.

In 1912, Anrep observed that sudden aortic constriction resulted in left ventricular dilation followed by partial recovery, even when arterial blood pressure was maintained at a constant increased level. [69] Other studies have confirmed that an abrupt increase in aortic pressure leads to an initial increase in end-diastolic volume and pressure; then, despite maintenance of systolic left ventricular pressure at the increased level, both end-diastolic volume and pressure return toward control values thereby manifesting a positive inotropic response that has been termed "the Anrep effect." [70-74] Such an increase in contractility was attributed to "improved nourishment" of the myocardium [70,71] or to an intrinsic property of cardiac muscle and autoregulation of myocardial function. [75-78] It has also been suggested that the Anrep effect is a manifestation of recovery from subendocardial ischemia by autoregulation of the coronary vascular bed. [73] Coronary blood flow increases, along with an increase in systolic left ventricular pressure, [79] reinforcing the notion that the Anrep effect reflects a recovery from myocardial ischemia. A regional redistribution of blood flow from epicardial to endocardial tissue [73,79,80] also supports the notion that an increase in endocardial blood flow is the main mechanism of the Anrep effect: an increase in myocardial contractility is associated with an increase in myocardial blood and oxygen supply.

Patients requiring aortic surgery often have concomitant coronary artery disease and limited coronary reserve. [81-83] Therefore, it is not surprising that the response to even relatively minor insult of infrarenal aortic cross-clamping differs in patients with or without coronary artery disease. In patients with coronary artery disease, filling pressures increased, whereas in patients without coronary artery disease central venous and pulmonary capillary wedge pressures decreased. [12,84] An increase in filling pressures in patients with coronary artery disease may be explained by left ventricular decompensation in response to an increase in afterload and preload, facilitated by impaired coronary autoregulation and inability of the heart to generate the Anrep effect: namely, an inability to increase subendocardial blood flow in response to an increase in intraventricular pressure.

Aortic cross-clamping in animals with pentobarbital-induced myocardial impairment was associated with a decrease in myocardial blood flow and in endocardial-epicardial blood flow ratios. [64] Although nitroglycerin did not prevent a decrease in total myocardial blood flow, endocardial-epicardial flow ratios could be maintained above 1. [64] Thus, despite severe myocardial depression, nitroglycerin maintained transmural distribution of flow favoring the endocardium. Because coronary and peripheral vascular resistances were not altered, the benefit probably reflected decreased ventricular wall tension resulting from an increase in venous capacitance and subsequent preload reduction.

The data concerning the effects of nitroglycerin are conflicting. Cross-clamping of the distal thoracic aorta led to a 33% decrease in coronary arteriovenous oxygen difference and a 10% decrease in oxygen extraction. [85] Nitroglycerin infusion was associated with a greater decrease in coronary arteriovenous oxygen content difference and myocardial oxygen extraction despite a 12% increase in cardiac work. The authors speculated that a decrease in oxygen extraction after aortic cross-clamping is accentuated by nitroglycerin, inducing or aggravating myocardial ischemia. Nitroglycerin may increase coronary vascular resistance despite augmentation of large vessel flow [86] because nitroglycerin dilates only the large conducting vessels. [87] Thus, the main beneficial effect of nitroglycerin may be related to a decrease in preload, allowing a more favorable stretch-contraction relation.

The importance of myocardial contractility has been demonstrated in many experiments with the use of interventions affecting the contractility. Patients treated with aminophylline demonstrated some increase in cardiac output during infrarenal aortic cross-clamping, despite similar degrees of arterial hypertension. This increase in cardiac output was probably attributable to increased contractility. [88] Different degrees of inotropy induced by administering propranolol and isoproterenol were associated with differences in response to aortic occlusion. Cross-clamping of the thoracic aorta increased or did not change stroke volume in control experiments whereas it significantly increased in conditions of isoproterenol therapy, despite associated tachycardia. [89] This observation suggests that different degrees of inotropy probably plays a more important role in the response to the cross-clamping than accompanied changes in vascular tone and heart rate. The authors also demonstrated that an increase in preload with saline infusion in intact animals was associated with an expected increase in stroke volume when afterload was not changed but with a decrease in stroke volume when afterload was increased by cross-clamping of the aorta. However, experiments with similar increases in preload and afterload during isoproterenol therapy were associated with an increase in stroke volume. [89] These observations illustrate the importance of the ability of the myocardium to respond with an increase in contractility to an increase in preload and afterload during aortic cross-clamping.

In another study, in patients undergoing thoracic epidural anesthesia and intravenous administration of a beta-1 adrenergic agonist, prenalterol, cardiac output increased significantly in response to infrarenal aortic cross-clamping, whereas in patients without stimulated contractility, cardiac output decreased. [90] These observations suggest that an increased preload (as a result of a decrease in venous capacity below aortic occlusion and proximal blood volume shift) is handled well by the heart with increased myocardial contractility; whereas the heart with decreased contractility, from thoracic epidural anesthesia and a concomitant decrease in sympathetic discharge, decreased its cardiac output. This hypothesis is indirectly supported by a studies demonstrating that thoracic epidural anesthesia during abdominal surgery may be associated with an increase in arteriovenous oxygen content difference and a decrease in oxygen content in mixed venous blood. [91] These changes reflect an increase in oxygen extraction and imply a possibility of an inadequate tissue perfusion during thoracic epidural anesthesia.

An increase in preload (pulmonary capillary wedge pressure), induced by volume redistribution or increased afterload, without a concomitant increase in cardiac output during infrarenal aortic cross-clamping, has been reported by many observers [13,84,92,93] and suggests lack of a required increase in myocardial contractility. Observations with nuclear ventriculography showed that myocardial performance (evaluated as the relation between cardiac index and diastolic volume index) and systolic function (evaluated as the relation between systolic blood pressure and systolic volume index) were depressed during cross-clamping of the abdominal aorta, but returned to baseline values after unclamping. [94] This response demonstrates a temporary decrease in myocardial contractility during cross-clamping of the infrarenal aorta. On the other hand, diastolic compliance evaluated as the relation between pulmonary capillary wedge pressure and diastolic volume index decreased only after unclamping. The authors interpreted this observation as myocardial ischemia. This interpretation may be correct; however, the authors used isoflurane and did not characterize the depth of anesthesia. Therefore, the effect of isoflurane on myocardial function possibly

masked the effect of clamping and unclamping of the aorta. Myocardial-depressant factor(s) [95] (see below) also may decrease contractility and are not necessarily associated with myocardial ischemia. An increase in the concentrations of catecholamines during and immediately after aortic cross-clamping [96-98] (see below) may counteract the effect of cardiodepressant [96] and vasodepressant [99] factors released from ischemic tissues.

Constriction of the aorta and a concomitant increase in mean aortic pressure were associated with increased concentrations of adenosine, inosine, and hypoxanthine in myocardial tissue. [68] Accumulation of adenosine and inosine in the myocardium may be responsible in part for increases not only in myocardial blood flow, but also in myocardial contractility. [100] Inosine is a degradation product of tissue adenine nucleotides that is produced in myocardial cells by both deamination of adenosine and dephosphorylation of inosine monophosphate. [101] Inosine is released from the heart exposed to oxygen deprivation when adenosine triphosphate breaks down. [102-105] Inosine increases myocardial blood flow [106-108] and contractility of normal [106-110] and of ischemic heart muscle. [110,111] Thus, an increased release of both endogenous inosine and catecholamines may represent a mechanism for an increase in myocardial contractility, needed to compensate for an increase in preload and afterload.

Many studies have demonstrated a beneficial effect of vasodilators on myocardial function in patients undergoing aortic cross-clamping. [7,12,18,50,88,112] Nitroglycerin administration during infrarenal aortic cross-clamping was associated with an increase in cardiac output and a decrease in vascular resistance. [112] These changes were particularly dramatic in dogs with impairment in left ventricular function. Thus, the beneficial effect of vasodilators can be attributed to the following mechanisms: a decrease in preload resulting from an increase in venous capacitance; a decrease in afterload resulting from dilation of resistive vessels; dilation of the coronary vasculature; an increase in coronary blood flow; and facilitation of the Anrep effect.

Volatile anesthetics decrease the ability of the myocardium to increase its contractility in response to aortic cross-clamping, [113] Also, anesthetics may dampen the circulatory reflexes, preventing an increase in contractility in response to an increased afterload. [8] Thus, contractility per se may increase as a physiologic response to an increase in preload and afterload, or decrease as a result of an inadequate increase (or even a decrease) in coronary blood flow or the effects of volatile anesthetics. The overall scheme of hemodynamic response to aortic cross-clamping is depicted in Figure 2. Currently, strategies for myocardium preservation during and after aortic cross-clamping consist of decreasing afterload and normalizing preload, coronary blood flow, and contractility.

Figure 2

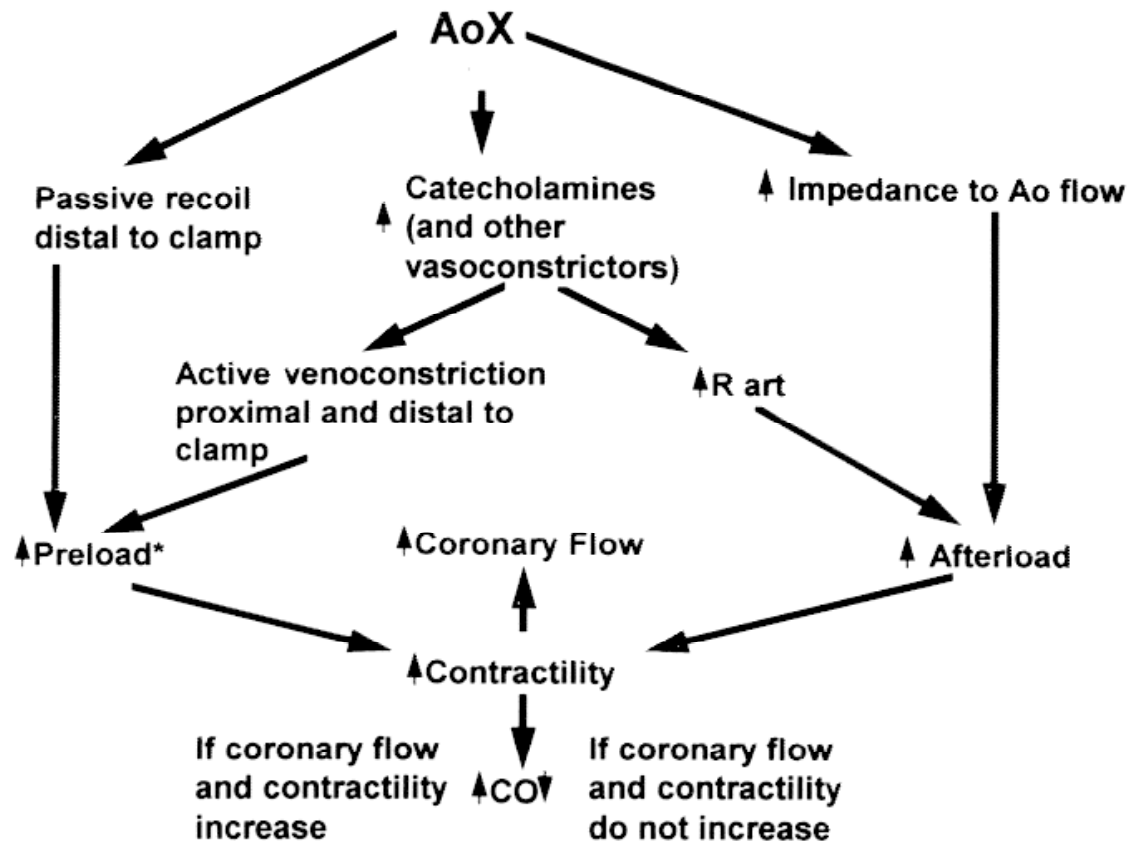


Figure 2. Systemic hemodynamic response to aortic cross-clamping. Preload does not necessarily increase. If during infrarenal aortic cross-clamping blood volume shifts into the splanchnic vasculature, preload does not increase (Figure 1). AoX = aortic cross-clamping; Ao = aortic; R art = arterial resistance; [arrow up] and [arrow down] = increase and decrease, respectively. *Different patterns are possible; refer to Figure 1. E. Level of Occlusion, Duration of Clamping, and Aortic Disease

The level of aortic cross-clamping plays an important role in the degree and even the pattern of the hemodynamic response. Changes in mean arterial blood pressure, filling pressures, end-diastolic and end-systolic left ventricular areas, ejection fraction, and wall motion abnormalities, assessed by two-dimensional transesophageal echocardiography, were minimal during infrarenal aortic cross-clamping but were dramatic during supraceliac aortic cross-clamping. [15] In the latter group of patients, mean arterial pressure increased by more than 50%, filling pressures by 40%, and end-diastolic and end-systolic areas by 28% and 70% respectively, whereas ejection fraction decreased by almost 40%. Left ventricular wall motion abnormalities were not observed in patients who underwent infrarenal aortic cross-clamping, but occurred in 33% of patients during supraceliac aortic occlusion, and in 92% of patients who underwent supraceliac aortic cross-clamping. [15].

With increasing duration of cross-clamping, systemic vascular resistance increases and cardiac output decreases. [7,16,114] The reasons have not been established, but cross-clamping may induce an increase in proximal aortic pressure and subsequently in the pressure gradient across the tissue-capillary membrane in the upper part of the body, leading to a shift of fluid from the intravascular to the interstitial space with an associated decrease in circulating blood volume and an increase in systemic vascular resistance. Release and accumulation of vasoactive substances (see below) also may play a role in the time-dependent changes during aortic cross-clamping, including increases in systemic vascular resistance.

The hemodynamic response to cross-clamping and unclamping of the aorta in patients with aortic occlusive disease is less prominent than the response in patients undergoing abdominal aortic aneurysm repair. [9,13,115-118] Furthermore, some investigators [8,95,119] needed to infuse nearly twice as much fluid in patients undergoing abdominal aortic aneurysm repair than in patients with aortic occlusive disease to

prevent unclamping hypotension. Thus, these two patient populations (patients with aortic occlusive disease and patients with abdominal aortic aneurysms) appear to differ markedly in their hemodynamic response to aortic cross-clamping. The reasons for these differences probably lie in the differences in aortic collateral vessels, which modify the response to cross-clamping.

F. Hemodynamic Response Distal to the Aortic Occlusion

Aortic pressure below a cross-clamp is decreased and is directly dependent on proximal aortic pressure. [34] Sodium nitroprusside decreases both proximal and distal aortic pressures. [34] Blood flow through the tissues distal to the aortic occlusion, which occurs through existing collateral vessels, is pressure-dependent and decreases many-fold; a strong association ($R^2 = 0.92$) between aortic pressure distal to the occlusion and renal blood flow was found. Furthermore, blood flow distal to the occlusion did not increase when preload (fluid infusion) and cardiac output were increased, [34] indicating that blood flow through the tissues distal to the clamp depends on perfusion pressure and not on cardiac output or volume load. A clinically relevant message from these findings [34] is that during cross-clamping of the thoracic aorta, which subjects vitally important organs (liver, kidneys, and spinal cord) to severe ischemia, proximal and distal aortic pressures should be maintained as great as the heart can withstand. Of course, other modalities, such as a temporary shunt, reimplantation of arteries supplying distal tissues (i.e., the spinal cord), or hypothermia would change the goals and end points of treatment. However, these therapeutic considerations are beyond the scope of this article.

A decrease in arterial and, subsequently, capillary pressure below aortic occlusion results in absorption of interstitial fluid into the vascular bed and bloodstream, which is reflected in significant decreases in specific gravity and protein content in the blood obtained from the femoral vein. [120] This absorption may be associated with a further increase in venous return and circulating blood volume above aortic occlusion. On the other hand, hypothetically, the fluid may shift from the intravascular bed to the interstitial space proximal to the aortic occlusion because of an increase in capillary hydrostatic pressure that may result from an increase in arterial or venous pressure. The clinical significance of these shifts is unknown.

G. Response to Unclamping

Unclamping of the thoracic aorta (Figure 3) is associated consistently with substantial (70-80%) decreases in vascular resistance and arterial blood pressure. [60,96] The rate of change in left ventricular pressure abruptly decreased by 42% compared with baseline values and by 60% compared with values during clamping. [32] Cardiac output may decrease, [11,32,90] increase, [60,96,120] or remain unchanged. [121] Left ventricular end-diastolic pressure decreases and myocardial blood flow increases. [60] Blood flow through the carotid arteries decreases to approximately 50% of preclamping values, [122] Flow through the terminal aorta and femoral arteries increases, [122-124] four- to fivefold compared with the values observed after infrarenal aortic cross-clamping. [122].

Figure 3

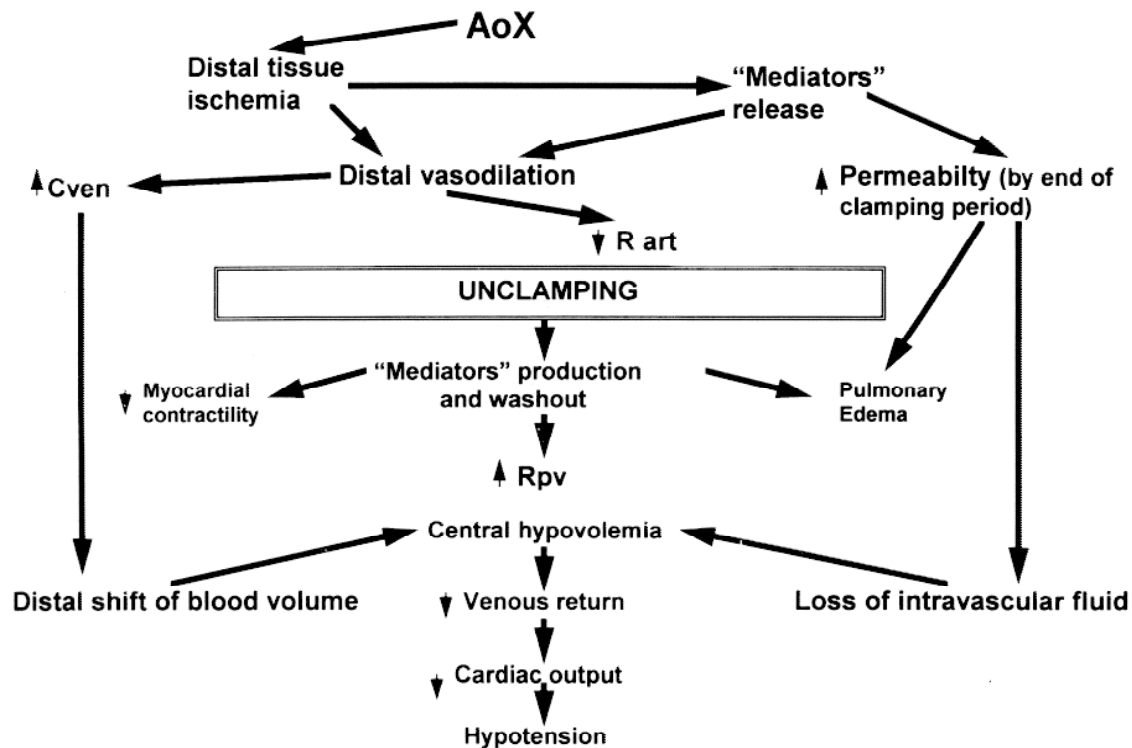


Figure 3. Systemic hemodynamic response to aortic unclamping. AoX = aortic cross-clamping; Cven venous capacitance; R art = arterial resistance; Rpv = pulmonary vascular resistance; [arrow up] and [arrow down] = increase and decrease, respectively.

Reactive hyperemia is one of the important components of the response to unclamping. Three main hypotheses have been proposed to explain this well-known phenomenon. Bayliss, in 1902, suggested that after inflation of a tourniquet and clamping of an artery, the arterial tree collapses and its smooth muscle relaxes, facilitating high flow after unclamping. [125] Indirect support for this hypothesis was provided later by Folkow, who postulated the involvement of a myogenic mechanism: passive dilation of the vasculature on removal of stimulus, namely transmural pressure. [126] The second hypothesis suggested an accumulation of vasodilating metabolites in tissues below an occlusion. [127,128] The third hypothesis, formulated by Barcroft, suggested that anoxia per se relaxes the smooth vascular muscles. This relaxation promotes increased flow after release of the occlusion. [129] These three hypotheses to explain reactive hyperemia are relevant to many of the events observed during unclamping of the aorta.

The maximum hyperemic response (maximum increase in flow distal to the site of unclamping) was observed 15 min after unclamping, suggesting an important role of metabolic or hormonal influences. However, the initial hemodynamic response to aortic unclamping (arterial hypotension and some increase in flow) was observed 10 s after the unclamping, [123] suggesting a reflex or mechanical phenomenon. A mechanical phenomenon may originate from the shift of blood volume to the tissues distal to an aortic clamp. In other words, flow would increase to fill the space that has been created by a decrease in vasomotor tone, possibly resulting from tissue hypoxia, accumulation of vasodepressant compounds produced by ischemic tissues, a myogenic response, or all three. Unclamping of the infrarenal aorta in dogs was associated with an increase in hind-leg volume measured with plethysmography that reached its maximal level within 30-60 s and exceeded the volume observed before clamping. Then, the volume gradually decreased toward pre-clamping values. The foreleg volume slightly decreased during unclamping. [38] A pneumatic envelope with an appropriate pressure (between arterial and venous pressures) applied over the legs in humans prevented blood volume redistribution and associated arterial hypotension after unclamping of the aorta. [130] The optimal counterpressure prevented unclamping hypotension, apparently because it prevented blood pooling, thereby augmenting venous return and cardiac output. Thus, sequestration of blood in the vessels distal to an aortic occlusion, and an increase in limb flow are apparently responsible for decreases in venous return, cardiac output, and mean arterial pressure during unclamping of

the aorta. Nuclear ventriculography revealed smaller diastolic ventricular volumes after unclamping, [94] supporting the notion that central hypovolemia developed. Restoration of blood volume prevents significant reductions in blood pressure and cardiac output after unclamping in dogs and humans. [11].

Despite the substantial evidence that was accumulated by the 1960s, the idea of the importance of volume redistribution was not used clinically for a long time. Even in 1968, Vetto and Brant reported 10% mortality during unclamping of the infrarenal aorta. [131] The deaths resulted from ventricular fibrillation or cardiac arrest. Their second series of observations demonstrated no mortality on unclamping. The authors attributed the improvement to the use of a leak-proof, woven polytetrafluorethylene prosthesis, and the administration of vasopressors and buffering compounds before unclamping. [131] However, analysis of their data suggests that the reason for the high mortality was hypovolemia. A decade later, studies revealed that unclamping hypotension in humans could be prevented by volume loading: if the pulmonary artery wedge pressure was maintained at 16 mmHg (compared with 11 mmHg in the control group) arterial hypotension was prevented in patients undergoing surgery on the infrarenal aorta. [18,90].

Vasoconstrictors, used systemically, may constrict the vasculature above the aortic clamp more than that below the clamp, because the former, which is nonischemic, would respond better to vasopressors than the latter, which is acidotic. This gradient may promote redistribution of blood volume from the upper to the lower part of the body, further reducing the flow above the aortic clamp. Obviously, clinical situations may dictate the use of vasopressors to maintain blood flow to the brain and myocardium. The use of vasoconstrictors regionally in the terminal aorta immediately before unclamping was associated with less redistribution of blood volume, less increase in blood volume in the tissues distal to the aortic occlusion, and less arterial hypotension. [38,123] However, these relatively old observations have not been verified and the clinical use of vasoconstrictors regionally in the terminal aorta has never been universally accepted.

Some observers have reported that vasodilators given during abdominal aortic cross-clamping, decreased cardiac output and increased pulmonary artery wedge pressure on unclamping beyond values before or during cross-clamping. [92,132] The authors suggested that vasodilators promoted release and washout of cardiodepressant substances. However, an increase in filling pressures after unclamping also may result from an increase in preload caused by a decrease in vascular capacitance, which in turn is caused by a dissipating effect of vasodilators, because usually infusion of vasodilators is stopped shortly before unclamping.

Gradual release of the aortic clamp and its reapplication has been recommended to allow time for volume replacement and sodium bicarbonate administration. [133] A gradual release of the clamp would also slow down the washout of the vasoactive and cardiodepressant mediators from the ischemic tissues. Finally, gradual unclamping may reduce the degree of abrupt reoxygenation, thereby decreasing the production of oxygen free radicals (see below).

In summary, the main hemodynamic pathophysiologic factors involved in the response to the aortic cross-clamping include the following. (1) An increase in afterload results from an increase in the impedance to aortic flow. This effect is manifested in proximal arterial hypertension and associated with an increase in contractility and maintenance of cardiac performance or an increase in end-systolic and end-diastolic ventricular volumes. (2) An increase in preload results from blood volume redistribution from the veins distal to the aortic occlusion to the proximal vasculature. This volume redistribution occurs consistently during supraceliac aortic cross-clamping. During infraceliac aortic cross-clamping, blood volume may be redistributed from the distal venous vasculature to the heart, increasing pre-load (as in a case of supraceliac aortic cross-clamping) or to the splanchnic vasculature, without an increase in preload. The distribution of blood volume between the heart and the splanchnic vasculature depends on many factors, including overall sympathetic tone. (3) Increases in afterload and preload result in an increase in contractility and, subsequently, myocardial oxygen demand, which in normal situations is met by an increase in coronary blood flow. However, if the myocardium is not able to respond with an increase in contractility or the coronary blood flow is not able to increase, then decompensation follows. The latter may be manifested by an increase in end-systolic and end-diastolic volumes and a decrease in ejection fraction. (4) Blood flow through the tissues below the aortic occlusion is dependent on perfusion pressure rather than on preload and cardiac output. Therefore, during cross-clamping of the thoracic aorta, proximal and distal aortic pressures should be maintained as high as the heart can withstand, unless other modalities (temporary shunt, hypothermia, or reimplantation of arteries supplying tissues distal to aortic cross-clamping) are implemented.

The main possible reasons for unclamping hypotension include (1) central hypovolemia caused by the pooling of blood into reperfused tissues distal to the aortic occlusion; (2) hypoxia-mediated vasodilation with a subsequent increase in vascular (venous) capacity in the extremities below the occlusion; and (3) accumulation of vasoactive and myocardial-depressant metabolites, as discussed in the following section. Therefore, the measures to prevent unclamping hypotension should include the shortest possible time of aortic cross-clamping, careful titration of fluid and vasoactive drugs, and gradual release of the clamp.

II. Role of Humoral Factors

Blood obtained from the inferior vena cava in dogs undergoing infrarenal aortic cross-clamping causes rapid and profound systemic arterial hypotension when transfused into intact animals. [99] When the serum from blood drained from the ischemic tissues was passed through a series of polyacrylamide gel columns and fractionated, a compound of 60,000 - 100,000 Da molecular weight was found to have caused the hypotension. [99] Our experiments, in which cross-circulation was used, have demonstrated that blood drained from the inferior caval vein during cross-clamping of the thoracic aorta in one rabbit led to significant hypotension in another rabbit that received the blood. [134] These observations demonstrated that compounds, formed in and washed out from ischemic tissues distal to aortic occlusion, induced vasodilation or myocardial depression and arterial hypotension. However, other studies have demonstrated the involvement of different endogenous compounds affecting vascular tone and myocardial contractility in opposite directions and to different degrees. Such compounds are formed mainly in ischemic and reperfused tissues during cross-clamping and unclamping of the aorta.

A. Acidosis

Metabolic acidosis and an increase in lactate concentration, particularly in blood drained from ischemic tissues below aortic occlusion, were demonstrated in animals and humans during cross-clamping (and to a greater extent on unclamping) of the infrarenal aorta. [11,14,131,135-137].

The degree of acidosis in humans depends on the underlying disease. For example, cross-clamping of the infrarenal aorta in patients undergoing abdominal aortic aneurysm repair was associated with dramatic increases in lactate concentration and lactate-pyruvate ratio in iliac venous blood. In patients with occlusive aortic disease such changes were less prominent. [9] The difference presumably results from developed collateral vessels and better tissue perfusion distal to arterial occlusion or stenosis in patients with aortic occlusive disease.

Many investigators have suggested that profound metabolic acidosis results from washout of deoxygenated blood and greatly expands the vascular capacity of the legs. However, the correction of metabolic acidosis did not significantly affect the degree of arterial hypotension upon unclamping of the aorta. [138] The lack of a clinically significant effect may result from the correction of acidosis in the blood, but not necessarily in the tissues, including arterial walls. Unclamping of the aorta is associated with significant, transient increases in carbon dioxide release [139] and in oxygen consumption. [140] The former may aggravate vasodilation and hypotension.

B. Renin-Angiotensin System

An increase in renin activity during cross-clamping of the aorta was observed in dogs [141] and in humans. [142-146] An increase in angiotensin concentrations during cross-clamping of the abdominal aorta has also been observed. [92] An increase in renin activity during cross-clamping of the suprarenal aorta can be easily explained by a decrease in perfusion pressure in the afferent arterioles. The reasons for an increase in renin activity during infrarenal aortic cross-clamping are less clear. The studies could not determine whether the significant increase in renin activity resulted from aortic cross-clamping per se, anesthesia, or volume changes. No correlation was found between plasma renin activity and arterial hypertension in the immediate postoperative period. [92,142,144,147] Pretreatment with beta-adrenergic antagonists was associated with a less dramatic increase in renin activity, in both animals [141] and humans. [144] Nevertheless, this was not associated with a decrease in a degree or incidence of postoperative hypertension. [144] On the other hand, our experiments in an isolated canine limb preparation demonstrated that blood drained from the caval vein during cross-clamping of the thoracic aorta causes vasoconstriction in the isolated limb perfused at a constant flow. Such an increase was blocked completely by an angiotensin-converting-enzyme (ACE) inhibitor. [148] The vasoconstricting effect of the blood drained from the caval vein in these experiments compared with vasodilating or cardiodepressant effects of such blood in other observations [99,134] may

result from different levels of aortic cross-clamping (infrarenal vs. thoracic) associated with a release of different amounts of vasoconstricting and vasodilating mediators.

Our experiments in rats revealed that angiotensin plays an important role in the hemodynamic response to aortic cross-clamping: arterial hypertension in control animals was twice as high as that in rats pretreated with an ACE inhibitor. [114] These observations suggest that approximately half of the arterial hypertension developed during aortic cross-clamping resulted from activation of the renin-angiotensin system. In humans, pretreatment with captopril was associated with smaller increases in mean arterial pressure during aortic cross-clamping [146] and postoperatively. [149] However, ACE inhibition may be associated not only with a decrease in the concentrations of angiotensin II but also with an increase in the concentrations of bradykinin, because ACE, like kininase II, biotransforms bradykinin and generates angiotensin II. This lack of specificity of the enzyme and its inhibitors makes the interpretation of observations concerning the effects of ACE inhibition on one or another event during aortic cross-clamping difficult.

Unclamping of the aorta was associated with a significant increase in angiotensin concentration and renin activity that lasted longer than 6 h [143]; however, no correlation with postoperative hypertension was observed. The discrepancies between the data could result from different roles of the renin-angiotensin system during aortic cross-clamping and postoperatively. Also, factors other than renin-angiotensin may play a more important role in the pathogenesis of the hemodynamic response to aortic cross-clamping and could obscure the effects resulting from renin-angiotensin system activation. Such factors may include volume status, depth of anesthesia, and degree of increase in the concentrations of arginine-vasopressin [145] catecholamines, and other mediators.

C. Catecholamines and the Sympathetic Nervous System

Cross-clamping of the thoracic aorta is consistently associated with large increases in the concentrations of epinephrine and norepinephrine. [96-98] Cross-clamping of the abdominal aorta is associated with much smaller increases in blood catecholamine concentrations: epinephrine concentration increased during and particularly after cross-clamping, whereas norepinephrine increased only after unclamping. [150].

In our experiments in dogs, cross-clamping of the thoracic aorta was associated with a large increase in perfusion pressure and peripheral vascular resistance in the isolated limb perfused at a constant flow with oxygenated blood drained from the inferior caval vein. [98,148] The increase in vascular resistance could be attributed in part to norepinephrine, because the alpha-adrenergic antagonist phenoxybenzamine prevented such an increase. Furthermore, aortic cross-clamping is associated with the formation and release of not only vasoconstricting compounds such as angiotensin and norepinephrine, but also vasodilating compounds, because pretreatment with the alpha-adrenergic antagonist not only prevented an increase, but actually decreased vascular resistance in the isolated limb. [148] Pretreatment with alpha- and beta-adrenergic antagonists (phenoxybenzamine and propranolol) was associated with an increase in vascular resistance apparently attributable to angiotensin. [98] Only the combination of alpha- and beta-adrenergic antagonists and ACE inhibitor prevented significant change in vascular resistance in the isolated limb preparation during aortic cross-clamping. [98] Increases in catecholamine concentrations play a role in the overall hemodynamic response to aortic cross-clamping: our experiments in rats demonstrated that pretreatment with an alpha1-adrenergic antagonist, prazosin hydrochloride, reduced arterial hypertension during aortic cross-clamping. [114].

The increase in overall sympathetic discharge during cross-clamping of the aorta is complex and multifactorial; it includes reflex mechanisms usually observed during hypotension and shock and reinforced by direct ischemic excitation of the spinal cord and adrenal medulla. Such mechanisms have been demonstrated in a spinal cat model. [151] An increase in proximal blood pressure during aortic cross-clamping should have inhibited sympathetic activity through baroreceptor mechanisms. However, central and peripheral influences can interact with the central nervous system, depressing baroreflex function. The exact mechanisms responsible for this modulation remain elusive. Aortic distension by itself induced a potent pressor sympathetic reflex with positive feedback characteristics. [152,153] In those observations, a rubber cylinder inserted into the thoracic aorta allowed the aortic wall to stretch without obstructing blood flow. Stretch-induced reflex increased blood pressure, heart rate, and possibly contractility. The reflex travels through aortic sympathetic afferent fibers. [153,154] These responses, also found in animals after adrenalectomy, were abolished by appropriate adrenergic receptor pharmacologic blockade or by infiltration of the aortic wall with local anesthetic. [154].

From a teleologic point of view, an increase in sympathetic discharge during and immediately after aortic cross-clamping may play a compensatory role in counteracting the effects of cardiodepressant [95] and vasodepressant [99] compounds and in facilitating myocardial response (increased contractility) to increased afterload and preload during aortic cross-clamping.

D. Oxygen Free Radicals

Lactate-pyruvate concentration ratio in the muscle distal to occlusion increases, and intramuscular pH and femoral venous blood flow decrease, during aortic clamping; energy charge and creatine pools remained decreased despite a restored blood flow to the legs, [137] demonstrating severe metabolic derangement and cellular damage to the muscle induced by aortic clamping and unclamping. Patients undergoing elective abdominal aortic surgery demonstrated severe postoperative hypophosphatemia. [155] Many factors may be responsible for hypophosphatemia occurring after aortic surgery and include hemodilution and transient tubular injury associated with increased urinary phosphate excretion. These factors also include ischemia-induced intracellular depletion followed by resynthesis of high-energy phosphate compounds after reperfusion. The resynthesis may result in a shift of phosphate from the extracellular to the intracellular compartment. This process can also contribute to the development of hypophosphatemia in patients after aortic surgery.

In hypoxic conditions, the metabolism of adenosine triphosphate produces adenosine, hypoxanthine, xanthine oxidase, purines, and oxygen free radicals. [156-158] We have observed a fivefold increase in plasma xanthine oxidase concentration after unclamping of the thoracic aorta in rabbits. [158] In humans systemic hypoxanthine concentration increased threefold after infrarenal aortic unclamping, whereas the femoral venous concentration increased 20-fold; a strong direct correlation ($r = 0.85$) between the duration of aortic occlusion and hypoxanthine concentrations has been observed. [159] Hypoxanthine can cause cellular damage during reperfusion by producing oxygen free radicals. [156,157] Clamping of the supraceliac aorta for 45 min, followed by unclamping and reperfusion of ischemic tissues, resulted in fluid shifts into the interstitial space with subsequent loss into the gastrointestinal tract. [160] The fluid shifts, caused by increased permeability, were minimized by treatment with superoxide dismutase (SOD) before aortic unclamping. Allopurinol reduced (and the combination of allopurinol and SOD prevented) gastric mucosal lesions induced by cross-clamping of the thoracic aorta in baboons. [161] Moreover, Casthely et al. administered SOD 20 s before unclamping of the thoracic aorta and observed a significant decrease in systemic arterial pressure and pulmonary hypertension, and an increase in cardiac output after unclamping. [162] Acid-base balance and bradykinin concentrations (which were increased during unclamping of the aorta) were similar in the groups treated with SOD or vehicle. [162] Therefore, the differences in cardiac output, arterial hypotension, and pulmonary hypertension were probably more related to the production of oxygen free radicals than to acid-base balance disturbances or an increase in bradykinin concentration.

However, Vo et al. observed no significant effect of SOD or allopurinol or their combination on the hemodynamic response to abdominal aortic cross-clamping in dogs. [163] The reasons for this discrepancy are unclear but could be related to their cross-clamping of the abdominal aorta in contrast to the cross-clamping of the thoracic aorta by Casthely et al. [162] In addition, Vo et al. used severe hemorrhage to decrease systolic blood pressure to 70 mmHg during cross-clamping. [163] These differences could provide different windows of opportunity for the effectiveness of oxygen free radical scavengers. Also, the hemodynamic measurement times in the two studies did not coincide: Vo et al. obtained hemodynamic data only 30 min after unclamping. By dealing with a different hypoxic insult or using inappropriate timing, they might have missed the window of opportunity, to observe any effect of oxygen free radical scavengers. Contrary to others' observations (see below), Vo et al. did not notice an increase in thromboxane concentration. [163] This result casts doubt on the reliability of the methods and design of their study.

It has been demonstrated that ischemia-reperfusion injury can be significantly decreased by decreased or postponed oxygen delivery during reperfusion. For example, initial reperfusion of tissues after ischemia with anoxic blood and then with normoxic blood was associated with a decrease in postischemic microvascular injury. [164] Reduced oxygen delivery during reperfusion also significantly decreased ischemia-reperfusion injury of skeletal muscle. [165] Furthermore, when the celiac artery of a cat was pump-perfused, the splanchnic organs were made ischemic and then reperfused, severe injury to the gastric mucosa occurred. [166] Gradual reperfusion virtually prevented the damage. If these observations are extrapolated to a clinical setting, it might be assumed that gradual release of the aortic clamp and associated gradual reperfusion of the organs and tissues below the aortic clamp is associated with diminished production of reactive oxygen species and reduced tissue injury. There are no direct observations supporting this notion.

It is conceivable that an oxygen free radical-induced increase in microvascular permeability [157,167-169] and subsequent loss of intravascular volume are responsible in part for the hypovolemia and arterial hypotension observed during unclamping of the aorta. Reactive oxygen species can stimulate the generation of thromboxane by neutrophils [170] and, therefore, oxygen free radical scavengers can decrease thromboxane synthesis. [171] Thus, the interpretation of the effects of oxygen free radical scavengers is obscured by their ability to affect prostaglandin metabolism. The observation that a thromboxane receptor antagonist prevents an induced increase in pulmonary permeability after ischemia, weakens the notion of a direct role of oxygen free radicals and emphasizes an important role of prostaglandins in the pathophysiology of aortic cross-clamping.

E. Prostaglandins

Prostaglandin concentrations are increased during and after aortic cross-clamping. [172-176] However, studies examining the role of prostaglandins are difficult to interpret because almost all of them involved laparotomy or thoracotomy, anesthesia, and controlled ventilation and were associated with unavoidable disturbances in homeostasis. More important, bowel eventration and mesenteric traction during surgery on the abdominal aorta induce the release of prostacyclin (prostaglandin I₂) and subsequent vasodilation, decrease in systemic vascular resistance, and increase in cardiac output. [177,178] This response was prevented by ibuprofen. [178] The hemodynamic changes observed during bowel eventration and mesenteric traction before cross-clamping of the aorta coincided with an increase in plasma concentration of 6-keto-prostaglandin F₁ (a by-product of prostacyclin metabolism). [179,180] Cutaneous hyperemia was observed in 58% of these patients, and aspirin prevented changes in hemodynamic variables and 6-keto-prostaglandin F₁ concentration. [179] The data strongly suggest that mesenteric traction syndrome (cutaneous hyperemia and arterial hypotension) is mediated, at least in part, by a release of prostacyclin. An increase in 6-keto-prostaglandin F₁ during aortic surgery was observed during the transabdominal approach but was not observed during the retroperitoneal approach. [180] These observations support the notion that release of prostacyclin is related to mesenteric traction rather than to the manipulation of the aorta per se. An increase in prostacyclin production can also result from an increase in concentrations of angiotensin I and II. [181-183] In addition, endothelial cells subjected to cyclic mechanical deformation (cyclic stretching) increase their capacity to synthesize prostacyclin. [184,185] It is conceivable that an increased arterial pressure and increased stretching of the aorta during cross-clamping also increase the release of prostacyclin proximally to the aortic clamp.

Other vasodilating prostaglandins (prostaglandin E) are also released after unclamping of the aorta. The average increase in blood pressure during infrarenal cross-clamping was about 17% in control dogs and 65% in dogs treated with indomethacin. [173] The difference in the values of blood pressure was directly related to the change in prostaglandin E concentration. [173] However, the inhibition of prostaglandin E by indomethacin did not prevent the development of arterial hypotension, a finding that suggests that the rule of this mediator is not crucial in the development of unclamping arterial hypotension.

A concentration of thromboxane B₂ (TxB₂, a stable metabolite of a powerful vasoconstrictor, thromboxane A₂ [TxA₂]) was almost doubled 30 min after mesenteric traction. Patients pretreated with ibuprofen, the cyclooxygenase inhibitor, did not demonstrate such response. [174] Thromboxane concentration could increase in response to increased prostacyclin synthesis and vasodilation, which presumably stimulate an autoregulatory compensation and synthesis of a vasoconstrictor, namely, thromboxane. All increase in TxB₂ production during aortic surgery was suppressed by aspirin [175] and ibuprofen, [176] inhibitors of cyclooxygenase. [186] Plasma of untreated patients produced vasodilation in a cat mesenteric artery preparation, whereas the plasma from ibuprofen-pretreated patients did not. [178] These observations illustrate a complex picture characterizing prostaglandin metabolism and the relation between vasoconstricting and vasodilating prostaglandins.

Plasma from patients undergoing surgery on the abdominal aorta and pretreated with ibuprofen or aspirin did not change contractility of rat papillary muscle, whereas plasma obtained from control patients decreased contractility. [176] However, the addition of thromboxane to plasma obtained from patients pretreated with aspirin did not decrease myocardial contractility, a result suggesting that thromboxane decreases contractility not by itself but through some unknown mechanism. [176] Galt et al. observed no difference in hemodynamic response to cross-clamping of the infrarenal aorta between patients treated with placebo or ibuprofen. [187] The differences in observations have many explanations, including the use of epidural anesthesia in conjunction with general anesthesia by Galt et al. [187] in contrast to the use of only

general anesthesia in the other studies. [174,175] The vasodilating effect of epidural anesthesia could in part counteract the vasoconstricting effect of thromboxane, resulting in no difference in hemodynamic response to aortic cross-clamping between the two groups of patients. Also, ibuprofen might have been ineffective in the study by Galt et al. because the changes in TxB₂ were similar in both ibuprofen and placebo-treated patients. [187] The filling pressures in this study were lower in the ibuprofen than in the placebo group, implying that fluid load or ventricular function could have been different in the two groups. Furthermore, pretreatment with cyclooxygenase inhibitors may increase arachidonic acid metabolism by way of lipoxygenase or cytochrome P450 pathways resulting in the release of a variety of vasoactive metabolites. Finally, and most likely, the response to infrarenal aortic cross-clamping is often too small to reveal clear differences between control and experimental groups.

The increased production of vasodilating prostaglandins during aortic cross-clamping and the release of vasoconstricting prostaglandins during unclamping can be viewed as compensatory responses to reduce arterial hypertension during cross-clamping and to attenuate hypotension during unclamping.

F. Platelets and Neutrophils

Cardiopulmonary complications observed after aortic surgery could be attributable to anaerobic metabolic products and microaggregates released from the ischemic tissues and then entrapped by the lungs. [188-190] Thromboxane induces neutrophil entrapment in the lungs [191]; entrapment is followed by an increase in lung microvascular permeability. [192] Neutropenic animals exhibit no increase in plasma or lung lymph TxB₂ concentrations with reperfusion [190] or in pulmonary permeability. Neutrophils are probably involved in these processes by release of vasotoxic compounds including proteases and oxygen free radicals. The neutrophil adherence receptor CD18 may play an important role in neutrophil-dependent pulmonary injury after remote ischemia and reperfusion. [193].

Infusion of dextran, heparin, or saline into the iliac artery decreased the degree of unclamping arterial hypotension, [135] The authors claimed that the beneficial effect of heparin and dextran was related to a decrease in clot formation below the aortic occlusion. Systemic administration of heparin significantly decreased ischemic injury of the heart, [194] kidney, [195] brain, [196] and skeletal muscle [197] in various animal models of acute ischemia and reperfusion. Administration of heparin during ischemia-reperfusion insult to skeletal muscle was associated with a smaller increase in permeability and necrosis and a higher pH in the ischemic muscle compared with those of animals not given heparin. [197] Indeed, the protective effect of heparin could be attributable to its anticoagulant effect. Alternatively, heparin may inactivate toxic proteins released from ischemic tissues, [198] prevent endothelial damage, [199] neutralize lysosomal cationic proteins released by leukocytes, limit activation of complement, [200] or increase the production of prostacyclin.* Heparin also has antiplatelet and antiinflammatory properties. The beneficial effect of heparin could result from the effect of large, negatively charged molecules of heparin, which could prevent the adherence of neutrophils to endothelial cells, [201-203] and the subsequent inhibition of production of inflammatory mediators. Pentastarch reduces cerebral ischemia-reperfusion injury. [204] We have observed that hetastarch decreased pulmonary damage induced by cross-clamping and unclamping of the thoracic aorta. [205] Dextran may decrease ischemia-reperfusion injury to the ischemic or remote organ by plugging the separated endothelial junctions of leaky capillaries, [206,207] by inhibiting the adherence of neutrophils to endothelial cells, or by reducing plasma antioxidant activity and oxidant stress after aortic occlusion and unclamping.

Lymphocyte count decreases, whereas leukocyte and neutrophil counts increase, after unclamping of the aorta in patients undergoing aortobifemoral bypass surgery. [208] Mannitol can inhibit the ischemia-induced neutrophil oxidative bursts and subsequent hydrogen peroxide production. [209] Pretreatment with mannitol (0.2 g *symbol* kg sup -1) inhibited thromboxane synthesis by activated platelets, reduced pulmonary damage after bilateral hind-limb ischemia, and modified the reduction in leukocyte count and the increases in the concentration of TxB₂ and mean pulmonary arterial pressure. [210] Mannitol scavenges oxygen free radicals and decreases arachidonic acid breakdown. [170,210] The effects of mannitol are unlikely to be the result of hyperosmolality or an inappropriate diuresis, because urine output and weight gain were the same in the control and experimental groups. Further, the degree of thromboxane inhibition in vitro was prominent and dose dependent when platelets were exposed to mannitol, but it remained unchanged in a dextrose solution of similar osmolality. [210,211] Thus, oxygen metabolism with production of oxygen free radicals, prostaglandin metabolism, and neutrophil activation may be closely interrelated. Therefore, the beneficial effects of oxygen free radical scavengers may be attributable not only to the scavenging of oxygen free radicals but also to the prevention of thromboxane release or neutrophil activation, which can be

thromboxane dependent. [212] The role of oxygen metabolism and the involvement of neutrophils in ischemia-reperfusion injury represent a complex interplay; mannitol, with its highly nonspecific action, may affect this process on more than one level.

G. Anaphylatoxins and Complement Activation

The concentrations of the anaphylatoxins C3a and C5a increased during abdominal aortic surgery. [213] The increases in C3a concentrations were related to the duration of aortic clamping. [214] Other investigators observed no complement activation in patients undergoing similar surgery and claimed that previous reports possibly reflected the administration of plasma during the surgical procedure. [208] These authors conducted their measurements only on patients who received no blood or blood products. On the other hand, the blood sampling in their study (before and 1, 2, and 24 h after unclamping vs. 5 min after unclamping in the studies by Bengtson and Heideman [213] and Bengtson et al. [214]) might have missed the peak complement concentration.

Anaphylatoxins are potent mediators of smooth muscle contraction in many tissues and organs, including arteries; they increase pulmonary arterial pressure and pulmonary vascular resistance and vascular permeability. [215-219] Both C3a and C5a release histamine from mast cells, and proteases and peroxidases from leukocytes, [220-222] (thromboxane) [223] and platelet-activating factor. C3a causes tachycardia, some impairment of atrioventricular conduction, and coronary vasoconstriction. [222].

The activation of complement with subsequent release of anaphylatoxins C3a and C5a can result from the introduction of foreign material. [216,224-228] Activation of complement during major vascular surgery involving the insertion of a vascular prosthesis and aortic cross-clamping has been documented. [229] Some observers have reported anaphylactic responses to an aortic prosthesis. [227,228].

Epidural anesthesia virtually prevented an increase in C5a and significantly modified an increase in C3a in patients undergoing surgery on the abdominal aorta. [161] The mechanisms responsible for these effects are unclear. Local anesthetics per se may be involved. [230-232] Release of leukotrienes can also be inhibited by local anesthetics. [223] The membrane-stabilization effects of local anesthetics also may play a role in decreasing the release of anaphylatoxins.

H. Myocardial-depressant Factor(s)

Myocardial dysfunction that develops after unclamping of the aorta also may play an important role in the overall hemodynamic response. One of the causes of myocardial dysfunction can be the formation and release of myocardial-depressant factor(s) from ischemic tissues. Occlusion of the splanchnic vasculature resulted in the elaboration of a substance in the plasma of portal venous blood, that depressed isolated papillary muscle; this substance was isolated and partially purified. [95] Occlusion of the vasculature supplying the pancreas resulted in a high plasma concentration of this myocardial-depressant factor. Pancreatectomy just before splanchnic vascular occlusion failed to yield significant amounts of the myocardial-depressant factor in portal venous blood. Therefore, it is reasonable to assume that the myocardial-depressant factor itself or an activator or precursor of this factor is produced primarily by the ischemic pancreas. [95] These observations have not yet been confirmed, and the factor has never been purified.

I. Endotoxins, Cytokines, and Other Mediators

Elective and emergency repair of infrarenal aortic aneurysm is associated with approximately equal degrees of an increase in intestinal permeability (measured by a dual sugar absorption test, with lactose and mannitol as markers). [233] Presumably, this increase in permeability resulted from ischemia-reperfusion injury of the tissues distal to the aortic clamp or intestines themselves. It is possible that infrarenal aortic cross-clamping is associated with ischemia of the colon and with a decrease in nutritive blood flow in tissues proximal to the aortic clamp, including the intestine. [48] An increase in intestinal permeability associated with aortic surgery resulted in an increase in concentrations of endotoxin. [234] However, the increases in the concentrations were moderate and not related to adverse effects observed postoperatively. Moreover, there were no differences observed between the patients undergoing elective or emergent procedures. [234] Thus, the role of endotoxins per se in homeostatic disturbances occurring as a result of aortic cross-clamping and unclamping remains unclear. However, another study demonstrated that an increase in endotoxin concentrations in the portal blood during abdominal aortic surgery was associated, as expected, with a release of interleukin-6. [235] Portal endotoxemia was detected in the majority but not in all patients during surgery, and there was no correlation between portal endotoxemia and interleukin-6 concentrations. The

lack of changes in concentrations of endotoxin and interleukin-6 may be related to the finding that the patients undergoing infrarenal aortic surgery are subjected to relatively mild hypoxic insult to the intestines. Experimental data show that 60 min of intestinal ischemia in rats is not associated with a significant increase in the concentration of another cytokine, tumor necrosis factor (TNF), whereas 120 min of intestinal ischemia and reperfusion is associated with a tenfold increase in circulating TNF concentrations. [236] Portal venous endotoxin concentrations increased before an increase in TNF concentrations, suggesting that intestine-derived endotoxin may induce TNF release. Moreover, anti-TNF antibody did not prevent pulmonary neutrophil sequestration but attenuated the increase in pulmonary microvascular permeability. These observations suggest that endotoxin and TNF play a role in the acute lung injury that follows intestinal ischemia and reperfusion.

Other cytokines may be released during aortic cross-clamping. Shear stress increases the release of interleukin-1 and interleukin-6 by aortic endothelial cells. [237] Also, aortic endothelial cells exposed to an increased flow rapidly release endothelin-1. [238] Infrarenal aortic cross-clamping in patients was associated with transient, but significant increase in endothelin-1 plasma concentrations. [239] The source and the role of endothelin-1 release remain unknown. It is noteworthy that a decrease in renal blood flow and glomerular filtration rate during infrarenal aortic cross-clamping persists for many hours postoperatively (see below), whereas an increase in endothelin-1 concentration is very brief. A vasoconstricting action of endothelin-1 depends on extracellular calcium concentration, [240] and therefore, calcium channel antagonist administration may prevent the vasoconstricting effect of endothelin-1. Experiments in vitro supported this notion. [241] Furthermore, experiments in healthy volunteers demonstrated that the vasoconstricting effect of endothelin-1, infused in the brachial artery (forearm blood flow was measured), was completely prevented by calcium channel antagonists but was not affected by sodium nitroprusside or acetylcholine, suggesting that blockade of voltage-operated calcium channels, but not cyclic guanosine monophosphate-dependent vasodilation, may be an effective tool to inhibit endothelin-1-induced vasoconstriction. [242] Thus, the exact role of endotoxins and cytokines (interleukins and TNF) in response to aortic cross-clamping, has not been accurately determined.

In summary, neutrophils, the sympathetic nervous system, the renin-angiotensin system, and other hormonal factors and mediators including prostaglandins, oxygen free radicals, the complement cascade, and others are involved in the homeostatic response to aortic cross-clamping. Therapeutic interventions that would decrease the effect of humoral factors involved in the pathogenesis of this response should include measures ensuring the shortest possible duration of cross-clamping, careful titration of fluid and vasoactive compounds against the desired hemodynamic end points, and gradual release of the aortic clamp. Future measures probably will include use of antagonists of humoral factors and mediators released during and after aortic cross-clamping. These antagonists should be specific and short-acting, because the requirements for their use may be very different during and after aortic cross-clamping. The clinical significance of different mediators is difficult to establish because their effects are often opposing and sometimes overridden by changes in main physiologic variables (such as preload, afterload, and contractility).

III. Effects of Aortic Cross-clamping on Organ Systems

A. Lungs

Pulmonary complications are observed frequently after surgery on the abdominal and particularly on the thoracic aorta. A recent study analyzed the results of 1,414 patients who underwent repair of a thoracoabdominal aneurysm. [243] Eight percent of these patients had severe pulmonary complications that required prolonged respiratory support and tracheotomy. Almost half of them died in the hospital. Another study demonstrated a 26% incidence of postoperative respiratory failure in patients undergoing thoracoabdominal aortic aneurysm repair. [3] These, and many other clinical studies did not address the pathogenesis of pulmonary injury.

An increase in pulmonary vascular resistance during and particularly after cross-clamping of the thoracic aorta in animals [31,67,162] and in humans [41,211,244] has been a common finding. Almost 60 yr ago, Barcroft and Samaan suggested that an increase in the volume of blood in the lungs may be responsible, at least in part, for such observations. [31] An increase in left ventricular end-diastolic volume and pressure may explain in part an increase in pulmonary arterial pressure. The role of the sympathetic nervous system in such events is probably minimal, because neither epidural anesthesia [46] nor beta-adrenergic antagonist administration was associated with any improvement in the pulmonary circulation. Unclamping of the infrarenal aorta in humans is also associated with increases in pulmonary arterial pressure and pulmonary

vascular resistance. [7,41,44,213,245-247] The mechanism of such increases is unclear but may involve pulmonary microembolism. [246,247].

The role of prostaglandins in pulmonary circulatory disturbances during aortic cross-clamping and unclamping has been clearly demonstrated. Ischemia generates thromboxane, [248] which increases mean pulmonary arterial pressure, induces neutrophil entrapment in the lungs, and increases pulmonary microvascular permeability. [191] Infusion of prostaglandin E1 in pigs undergoing 90 min of infrarenal aortic cross-clamping was associated with a smaller increase in pulmonary vascular resistance after unclamping of the aorta. [249] By the 3rd postoperative day, a pulmonary shunt of 10% in the control animals caused hypoxia, whereas pulmonary function was preserved with a pulmonary shunt of less than 5% in the animals treated with prostaglandin E1. [249] Another vasodilator, sodium nitroprusside, led to no improvement in pulmonary function, [67] suggesting that effects of prostaglandins other than vasodilation are involved in pulmonary morbidity. The beneficial effect of prostaglandin E1 could result in part from the inhibition of platelet aggregation and leukocyte activation and in part from systemic and pulmonary vasodilation. [250,251] Cross-clamping of the infrarenal aorta in humans was associated with an increase in TxA2 synthesis and time-related increases in mean pulmonary arterial pressure and pulmonary vascular resistance. [211] The authors also observed interstitial pulmonary edema on chest radiography, even though pulmonary arterial wedge pressure did not exceed 12 mmHg. Pulmonary dysfunction was also manifested by an increase in intrapulmonary shunt from 9% to 16% and in peak inspiratory pressure from 23 to 33 cmH₂O 4-8 h after surgery. [211] Furthermore, the inhibition of thromboxane synthesis or the blockade of thromboxane receptors prevented pulmonary hypertension, leukopenia, sequestration of leukocytes in the lungs, and an increase in lung microvascular permeability after lower-torso ischemia. [252] Neutrophils sequestered in the lungs after hind-limb ischemia probably mediate the permeability edema in the lung by release of both elastase and oxygen free radicals. [209] Thus, reperfusion of the ischemic lower torso leads to the synthesis of TxA2, resulting in neutrophil and platelet activation, and pulmonary dysfunction. [212,253].

Pretreatment with mannitol (0.2 g/kg) modified the increases in TxB2 concentrations, mean pulmonary arterial pressure, intrapulmonary shunting, and peak inspiratory pressure and the decrease in leukocyte count. [210] Mannitol could modify thromboxane-mediated activation of platelets, neutrophils or both, [210] or could scavenge hydroxyl radical. [209] Oxygen free radicals may mediate the pulmonary injury that follows remote ischemia. [167,254] SOD injected 20 s before unclamping of the aorta significantly modified an increase in pulmonary vascular resistance after unclamping of the thoracic aorta, compared with that in control animals. [162] Allopurinol, SOD, and catalase protected sheep from lung injury after hind-limb ischemia. [253] Reactive oxygen species can arise from several sources including xanthine oxidase. [157,255,256] Recently, we observed severe pulmonary damage induced by ischemia and reperfusion of the liver. The isolated liver and lung were perfused with modified Krebs-Henseleit buffer in series. Two hours of ischemia followed by reperfusion of the isolated perfused liver increased capillary filtration coefficient in the lung almost fivefold and doubled the lung wet-dry ratio. When livers were isolated from rats pretreated with allopurinol and the perfusate was supplemented with allopurinol, the pulmonary damage was virtually prevented. [254] The study demonstrated that the ischemic, reperfused liver released a large amount of xanthine oxidase into the circulation, altering capillary membrane integrity. These changes were observed in the absence of neutrophils. The interpretation of the effect of oxygen free radical scavengers is obscured by the ability of the SOD to inhibit thromboxane synthesis. [171].

Pulmonary complications described after aortic surgery were attributed to anaerobic metabolic products and to microaggregates released from the ischemic tissues and then entrapped in the lungs. [252,257-259] Neutropenic animals exhibited no increase in pulmonary permeability or in plasma or lung lymph thromboxane concentrations with reperfusion. It is possible that neutrophils release toxic compounds including proteases and oxygen free radicals. Pulmonary microembolization is also associated with a release of vasoactive (mainly vasoconstrictive) substances from lung tissues [260-262] that apparently aggravate the damage induced by neutrophils. Infrarenal aortic cross-clamping in pigs (90 min) was associated with reproducible shock and 50% mortality within 3 days. [263] Platelet and leukocyte counts decreased. Aggregate concentrations in the inferior vena caval blood were maximal at the time of unclamping. Radiolabeled platelet accumulation in the lung was associated with increases in pulmonary vascular resistance and in alveolar-arterial oxygen content difference. [263] Another study on pigs demonstrated an increase in pulmonary vascular resistance on unclamping of the aorta associated with a decrease in arterial oxygen tension. [246] The authors used labeled platelets and fibrinogen and showed that cross-clamping of the abdominal aorta for 2 h was associated with a significant decrease in plasma

fibrinogen concentration in animals not given heparin. This decrease was associated with numerous fibrin-platelet thrombi, leukocytes and platelet aggregates, atelectasis, and bleeding within the lung tissue. These changes did not occur in pigs treated with heparin (300 units/kg). [246].

The observed changes in pulmonary circulation (increased pressure and vascular resistance) can be explained in part by the increases in anaphylatoxin activity that have been demonstrated during aortic surgery. [214] Anaphylatoxins are potent mediators of smooth muscle contraction of arteries, trachea, and airway preparations. They also affect vascular permeability and respiratory function. [215-218] C3a and C5a increase pulmonary vascular tone, [219] suppress immune responses [264] and therefore may increase the risk of pulmonary infection. Angiotensin is also involved in the hemodynamic response to aortic cross-clamping. [98,114,148] An ACE inhibitor, captopril, prevented an increase in pulmonary vascular resistance during aortic cross-clamping. [146].

Not every pulmonary complication after aortic surgery is related to aortic cross-clamping and unclamping per se. Controlled ventilation in humans is associated with significantly greater fibrinolytic activity in arterial blood than in the mixed venous blood, indicating pulmonary sequestration of proteolytic activity. [265] Any major abdominal surgery is often associated with atelectasis and some degree of postoperative pulmonary dysfunction.

Thus, the pulmonary damage associated with aortic cross-clamping and unclamping is reflected in an increase in pulmonary vascular resistance (particularly on unclamping of the aorta), and an increase in membrane permeability with subsequent pulmonary edema. The mechanisms involved may include pulmonary hypervolemia and effects of various mediators, mainly prostaglandins, oxygen free radicals, the renin-angiotensin system, and the complement cascade. Pulmonary protection during aortic surgery should consist of careful titration of fluid load and the use of nonspecific (e.g., mannitol) and specific antagonists of hormonal and humoral factors formed and released from ischemic tissues during and after aortic cross-clamping. Specific antagonists may include, for instance, monoclonal antibodies and specific receptor antagonists not yet used in clinical practice.

B. Kidneys

Surgery on the infrarenal aorta may be associated with a 5% incidence of renal failure requiring hemodialysis. [266] The overall rate of renal complication after surgery on the suprarenal aorta remains high and may reach 17%. [267] One study compared the renal function in 166 patients who underwent infrarenal aortic cross-clamping with that in 39 patients who underwent suprarenal cross-clamping of the aorta. [268] Transient renal insufficiency was more frequent in the suprarenal group than in the infrarenal group (28% vs. 10%), but dialysis rates were similar (3% vs. 2%). Surgery requiring cross-clamping of the thoracic aorta is associated with a rate of renal complications as high as 51%. [3,269-272] Renal failure virtually always results from acute tubular necrosis. [273] Ischemia-reperfusion insult to the kidneys plays the central role in the pathogenesis of renal failure associated with aortic surgery.

Infrarenal aortic cross-clamping is associated with a large increase in renal vascular resistance and as much as 30% decrease in renal blood flow. [273,274] Renal hemodynamic deterioration persists after unclamping of the aorta. [274] Six months after surgery, renal plasma flow and glomerular filtration rate were still significantly decreased in patients who underwent infrarenal aortic reconstructive surgery. [275].

Cross-clamping of the thoracic aorta is associated with severe (85-94%) decreases in renal blood flow, glomerular filtration rate, and urine output. [34,60,276-278] In an experimental model with a clamped renal artery, the renal blood flow returned immediately to baseline values after release of the occlusion, [279,280] whereas unclamping of the thoracic aorta was associated with a prolonged postischemic decrease in both renal blood flow and glomerular filtration rate. [34,60,276,278] The reasons for this difference may lie in the specifics of the neurohormonal disturbances (including neutrophil activation and mediators release) that follow aortic cross-clamping, but apparently do not occur after renal artery occlusion.

A maldistribution of blood flow within the kidney, with particular decrease in renal cortical blood flow, [273] persisted for at least 60 min after the unclamping of the infrarenal aorta. Such a decrease in renal blood flow and redistribution of flow within the kidney are associated with a temporary decrease in glomerular filtration rate. [274,281] The degree of decrease does not correlate with changes in cardiac output nor with changes in mean arterial pressure. [281-283] The degree of decrease in urine output does not correlate with the degree of reduction in glomerular filtration rate, [281] and does not predict postoperative renal failure. [284].

The renin-angiotensin system is apparently involved in the pathogenesis of renal hemodynamic disturbances during aortic cross-clamping. [96,141,273] The major effect of angiotensin II is an increase in renal vascular resistance and sodium reabsorption, directly (proximal and tubular) and indirectly (by increased aldosterone production). Pretreatment with an ACE inhibitor was associated with a complete return of renal blood flow and glomerular filtration rate to baseline after the unclamping of the aorta, whereas in control animals the renal blood flow returned to only approximately 50% of baseline values. [66,278] The values of renal blood flow in animals pretreated with an ACE inhibitor were lower during aortic cross-clamping and higher immediately after unclamping compared with the control observations. [278] In other words, the protective effect of ACE inhibitors is not during, but rather after, aortic cross-clamping. The lower renal blood flow during clamping in the group treated with the ACE inhibitor was probably related to lower perfusion pressure.

Activation of the sympathetic nervous system may not play a clinically significant role in the decrease in glomerular filtration rate associated with aortic cross-clamping because epidural anesthesia, which is associated with a significant decrease in sympathetic outflow to the kidney, neither prevents nor modifies it. [285] Cortical ischemia during infrarenal aortic cross-clamping can be reversed by a beta-adrenergic antagonist. [141,286] However, the beneficial effect of the drug may be related to the well-documented inhibition of renin-angiotensin system by beta-adrenergic antagonists. [287,288].

Apparently, other mediators may play an important role in the renal vasoconstriction and decrease in glomerular filtration rate after aortic cross-clamping. For example, a significant increase in plasma concentration of endothelin has been clearly demonstrated. [239] Nifedipine, a calcium channel antagonist, could prevent the vasoconstrictive action of endothelin on the renal vascular bed. [239] Myoglobin release from the ischemic low extremities [286] may interfere with nitric oxide formation within the kidney, leading to renal vasoconstriction and a decrease in blood flow. Alterations in renal release of prostaglandins also may play a role in the intrarenal redistribution of blood flow.

The observed transient decrease in glomerular filtration rate per se is not necessarily harmful and may represent a protective response to renal hypoperfusion: a decrease in glomerular filtration rate may be associated with a decrease in reabsorption, thereby decreasing energy and oxygen requirements. [289,290].

Mannitol reduces the degree of the decrease in renal blood flow during cross-clamping of the infrarenal aorta. [273] However, after the unclamping of the aorta, mannitol, dopamine, and the combination failed to return renal blood flow to baseline values. [291] Other authors observed no beneficial effect of mannitol or dopamine on renal function during elective infrarenal aortic cross-clamping in humans. [281] However, the sample in this study was small: nine patients in each of the three groups. A contradiction between the consistent experimental evidence of the protective effects of diuretic agents against ischemic insult to the kidney, and the frequent lack of clinical evidence for such protective effects, may be related to the following three factors. First, the clinical situations are usually much more diverse than the clearly defined experimental insults. Therefore, diuretics may be used in clinical situations beyond the window of opportunity. In other words, some patients would suffer renal failure because the ischemic insult was too severe for the kidneys and nothing could have helped, whereas other patients would be subjected to an insult too mild to cause any damage even without diuretics. Second, a decrease in reabsorption and an associated decrease in renal oxygen demand is the main mechanism responsible for the protective effect of diuretics from ischemic insult to the kidneys. [289,290] In clinical studies, diuretics were used--usually in small doses--causing only minimal decrease in reabsorption and oxygen demand. The few clinical studies that have demonstrated a beneficial effect of diuretics used very large doses. [292] Third, therapy with diuretics requires close observation and adequate replacement of lost fluid and electrolytes. If fluid replacement is insufficient, the diuretic therapy can be more harmful than beneficial. Further well-designed clinical studies are required.

Anesthetic management plays an important role in the pathogenesis of renal dysfunction during aortic cross-clamping. Adequate fluid replacement substantially decreases the rate of renal complications after surgery on the infrarenal aorta. [293,294] This effect may result from volume-loading-induced inhibition of the production of certain vasoconstrictive compounds. [141] Anesthetics per se also may play a role because of their effects on the hemodynamics and release of hormones and mediators. For example, halothane anesthesia is associated with more prominent deterioration of renal function than is isoflurane, even when

used in the doses associated with similar values of arterial pressure. [282,295] The relatively greater deterioration with halothane probably results from a greater decrease in cardiac output and renal blood flow.

In summary, renal dysfunction, including renal failure, results from renal hypoperfusion and involves activation of the renin-angiotensin system, the sympathetic nervous system (to a lesser extent), and other mediators. Optimization of systemic hemodynamics, including circulating blood volume, represents the most effective measure to protect the kidneys from aortic cross-clamping-induced ischemic insult. Strong experimental evidence supports the ability of adequate doses of diuretic agents to protect the kidneys; however, the clinical data are lacking. Specific antagonists of humoral factors released during and after aortic cross-clamping have not been adequately tested to be recommended for wide clinical use.

C. Spinal Cord

Paraplegia after thoracic aortic cross-clamping was first described in dogs more than 80 yr ago. [296] The reported incidence of paraplegia in humans varies from 0.4% to 40% depending on the urgency of operation, the presence of aortic dissection, hypotension, the age of the patient, and the duration and level of the aortic cross-clamping. [3,271,297-307] Approximately half of the patients with initial paraplegia make no neurologic recovery. [308] Paraplegia is much less common after repair of infrarenal aortic aneurysm. The first case was described in 1956 [309] and the incidence has fluctuated between 0.11 and 0.90%. [310].

The reasons for neurologic deficit lie in the decrease in blood flow to the spinal cord during cross-clamping of the aorta. Survival of the spinal cord depends, to a great extent, on the collateral arteries and communications. The most distal of these arteries is the artery of Adamkewicz, which arises from the lower thoracic or upper lumbar aorta. This artery usually makes an important contribution to lower spinal cord blood supply. The frequency with which it arises from the infrarenal aorta varies from less than 25% [311] to 50%. [312] If the artery of Adamkewicz arises from the part of the aorta that is cross-clamped, the pressure in the anterior spinal artery may indeed be much less than the pressure in the distal aorta. [313] Much attention has been paid to the artery of Adamkewicz with regard to the development of paraplegia after lower aortic surgery. [314-319] The anatomic details of the blood supply of the spinal cord are extremely important but are beyond the purpose of this article and are addressed elsewhere. [311,320].

Because the main mechanism of paraplegia associated with cross-clamping of the descending thoracic aorta lies in spinal cord ischemia and reperfusion, the duration of cross-clamping is influential. Studies suggest that a cross-clamping period of less than 30 min is often safe. [304,321] Some investigators have proposed that the relation between the aortic cross-clamping time and the probability of paraplegia is a function of a sigmoid dose-response curve. [302,321] The curve is shifted to the right with lower-risk aortic surgery and by protective measures that prolong the period of safety. [2].

The perfusion pressure to the spinal cord, defined by the difference between the distal aortic pressure (or, more accurately, the anterior spinal artery pressure) and cerebral spinal fluid pressure (or venous pressure, whichever is greater), apparently plays an important role in the pathogenesis of paraplegia. Cross-clamping of the thoracic aorta is associated not only with a decrease in distal aortic-anterior spinal artery pressure but also with an increase in cerebrospinal fluid pressure and a decrease in the compliance of the spinal fluid space. [322] The compliance was assessed as the relation between volume and pressure in the spinal fluid space. The most commonly cited reason for intracranial hypertension during aortic cross-clamping has been arterial hypertension above the clamp, producing engorgement of the intracranial compartment. [323-325] Volume changes in the venous capacitance beds within the dural space also have been suggested, [326] A directly measured increase in blood volume within the skull recently has been demonstrated in our laboratory. [39]. Thus, the blood volume redistribution that occurs during cross-clamping of the thoracic aorta is directly responsible for an increase in intracranial pressure. Phlebotomy reverses the increase in cerebrospinal fluid pressure induced by cross-clamping of the thoracic aorta, [327] probably by modifying the blood volume redistribution and intracranial hypervolemia. It has been suggested to increase distal aortic pressure or to decrease cerebrospinal fluid pressure by cerebrospinal fluid drainage, in order to increase spinal cord perfusion pressure and decrease the risk of spinal cord damage during surgery on the thoracic aorta. However, the measure has not been universally accepted and the issue remains controversial. In fact, cerebrospinal fluid drainage was associated with greater spinal cord perfusion pressure, increased spinal cord blood flow, diminished reperfusion hyperemia, and decreased incidence of neurologic complications, [305,307,328] including prevention of paraplegia in dogs. [305,324,329,330] However, other studies in animals [331] and humans [299,332] found no decrease in the incidence of paraplegia. The controversy may result from differences in the experimental and clinical conditions during these studies. The ischemic insult

could have been too strong or too weak (beyond the window of opportunity) to allow cere-brospinal fluid drainage to affect the overall results.

Patients who had sodium nitroprusside infused during cross-clamping of the thoracic aorta had a lower spinal cord perfusion pressure and a greater incidence of neurologic deficit compared with the control group. [325] The decrease in spinal cord perfusion pressure is caused by a decrease in the distal aortic pressure below the aortic clamp [34,325] and by an increase in cerebral spinal fluid pressure (Figure 4). [322,325,333] The latter results from cerebral vasodilation, whereas the former is caused by a direct, strong correlation between proximal and distal aortic pressures during cross-clamping. [34] Furthermore, this blood flow through the tissues below aortic occlusion, including the spinal cord, is pressure dependent and directly related to the distal aortic pressure. [34] This direct and strong relation probably results from the hypoxia-induced, almost maximal vasodilation in the tissues below the aortic clamp. Thus, drugs used to decrease proximal aortic pressure should possess minimal cerebral vasodilating properties and should be used to a minimum.

Figure 4

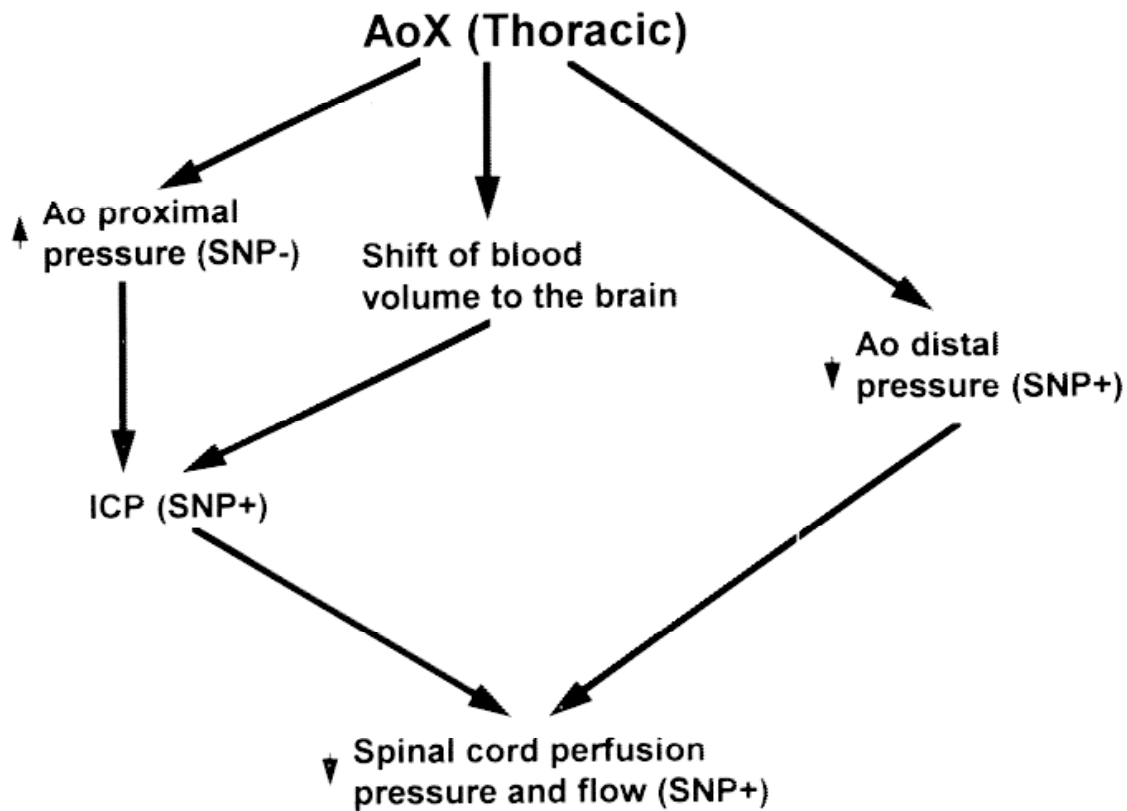


Figure 4. Spinal cord blood flow and perfusion pressure during thoracic aortic occlusion, with or without sodium nitroprusside (SNP) infusion. The changes (arrows) represent the response to aortic cross-clamping per se. SNP+ - SNP aggravates the effect of cross-clamping; SNP- = SNP counteracts the effect of cross-clamping; AoX - aortic cross-clamping; Ao = aortic; ICP = intracranial pressure; [arrow up] and [arrow down] increase and decrease, respectively.

The incidence of paraplegia was substantially decreased when a femoral vein-femoral artery bypass or external shunt from the ascending aorta was used. [65,96] The absence of harmful effects of sodium nitroprusside infusion when external shunts were used [96] is not surprising, because in such situations the distal pressure is very close if not equal to the proximal aortic pressure.

Some studies have demonstrated effectiveness of the oxygen free radical scavenger, allopurinol and SOD. [334,335] Polyethylene glycol-conjugated SOD, administered before and during occlusion of the thoracic aorta in rabbits, increased the spinal cord tolerance to the ischemic insult. [336] These studies suggest the importance of reperfusion insult and oxygen free radical production in the pathogenesis of paraplegia

associated with aortic cross-clamping and unclamping. Some studies in dogs suggested an effectiveness of corticosteroids in decreasing the incidence of paraplegia. [337] The mechanism of action of steroids can be attributed to reduction of edema of the spinal cord and stabilization of cell membranes, which decreases the release of mediators from the ischemic and reperfused tissues. [337,338] The mechanisms may include the scavenging of oxygen free radicals. [339,340] However, steroids may also induce hyperglycemia, which can exacerbate ischemia-induced spinal cord damage. [341].

Hypothermia clearly prolongs the safe ischemic time for the spinal cord, [342-345] apparently by decreasing the metabolic rate and oxygen requirements of the spinal cord. Local cooling, injection of 120 ml of cold saline solution with lidocaine into the distal aorta during aortic cross-clamping in pigs, [346] or infusion of cold saline in the epidural space in dogs, [347] prevented paraplegia.

Attempts have been made to use different anesthetics to protect the spinal cord from ischemic insult. Sodium thiopental significantly decreased the incidence of paraplegia in dogs. [348] The protective effect of barbiturates may be related to a decrease in cerebral blood flow and less engorgement of the intracranial compartment, a decrease in cerebral metabolism and oxygen consumption, [349] membrane stabilization, and a free radical scavenging effect. [350] In another study, thiopental and ketamine each decreased acute paraplegia to 17% compared with 61% in control animals. [351] The protective effect of ketamine could be related to the ketamine action on n-methyl-D-aspartate receptors. Intrathecal tetracaine also decreased neurologic injury caused by spinal cord ischemia and reperfusion after aortic occlusion in a rabbit model. [352] The suggested mechanisms for the protective effect probably lie in a decrease in neuronal cell metabolism and a neuronal membrane-stabilizing effect.

Intrathecal injection of papaverine was encouraging in animals [313] and in humans. [306] The combination of hypothermia and thiopental was effective in spinal cord protection in rabbit models. [353] Cerebrospinal fluid drainage and steroids in combination provided more protection against ischemic insult to the spinal cord than either of the interventions alone. [324] Cerebrospinal fluid drainage or aorta-femoral shunting significantly improved spinal cord blood flow and neurologic outcome. [328] Excluding the thoracic aorta by applying a second clamp at the lower level, restored oxygen tension in the spinal cord almost to the control level. [331] Other measures included the use of shunts and bypasses. This subject is beyond the scope of this article and is discussed elsewhere. [320] A combination of measures, including intercostal reimplantation whenever possible, cerebrospinal fluid drainage, maintenance of proximal hypertension during cross-clamping, reduction of spinal cord metabolism by moderate hypothermia, barbiturates and avoidance of hyperglycemia, and the use of mannitol, steroids, and calcium channel antagonists may reduce spinal cord dysfunction in patients undergoing thoracoabdominal aortic aneurysm repair from 6% to 0%. [354] It is impossible to conclude which therapeutic measures or combinations actually decreased the incidence of neurologic complications and which measures were unnecessary. Further research is needed.

D. Abdominal Viscera

The spinal cord is not the only tissue at risk. The inferior mesenteric artery is often ligated during surgery and an ischemic left colon has been reported in association with paraplegia. [316,317,319,355,356] The reported incidence of visceral ischemia varies from 1-10%, with mortality exceeding 50%. [357-361] The most common site of ischemia is the left part of the colon. Prospective examination with colonoscopy has demonstrated 6% colonic ischemia after abdominal aortic surgery. [357,358] Apparently, this ischemia results from disturbances in blood supply from the inferior or superior mesenteric artery. [362] It is possible that infraplanchnic cross-clamping of the aorta is associated with deterioration of nutritive flow through the viscera. This hypothesis is supported by our observations in dogs that infrarenal cross-clamping is associated with a large decrease in entrapment of radiolabeled 9-micro meter spheres. [48] We also have demonstrated that lack of entrapment of 9-micro meter spheres may reflect a decrease in nutritive flow [58] and, possibly, intestinal ischemia. Hypovolemia, thrombosis, cardiac insufficiency, and microembolism should also be considered in the development of bowel ischemia.

IV. Conclusions

The reviewed data demonstrate that aortic cross-clamping and unclamping are associated with severe homeostatic disturbances in virtually all organ systems in the body. The main hemodynamic changes induced by cross-clamping of the aorta result from an increase in impedance to aortic flow and an increase in systemic vascular resistance and afterload, blood volume redistribution caused by collapse and constriction of venous vasculature distal to aortic clamp, and a subsequent increase in preload. Preload may not increase if the aorta is clamped distal to celiac artery; in that case blood volume from distal venous

vasculature may be redistributed into 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. If an increase in coronary blood flow and myocardial contractility do not occur, decompensation follows. Aortic cross-clamping is associated with the formation and release of many mediators. These mediators represent a double-edged sword: they may reduce or aggravate the harmful effects of aortic cross-clamping and unclamping. Injury to the lungs, kidneys, spinal cord, and abdominal viscera is caused mainly by ischemia and reperfusion of organs distal to aortic cross-clamping (local effects) or to a release of mediators from ischemic and reperfused tissues (distant effects). 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 aortic cross-clamping and unclamping.

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