■ MEDICAL INTELLIGENCE ARTICLE

Julien F. Biebuyck, M.B., D.Phil., Editor

Anesthesiology
82:1026–1060, 1995

J. B. Lippincott Company, Philadelphia

The Pathophysiology of Aortic Cross-clamping and Unclamping

*Simon Gelman, M.D., Ph.D.**

CONTENTS

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

* Professor and Chair.

Received from the Department of Anesthesia, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. Submitted for publication March 17, 1994. Accepted for publication December 5, 1994.

Address reprint requests to Dr. Gelman: Department of Anesthesia, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115.

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 infrasplanchnic vasculature may shift to the compliant splanchnic vasculature rather than to the heart (fig. 1).

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 infrasplanchnic 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 mag-

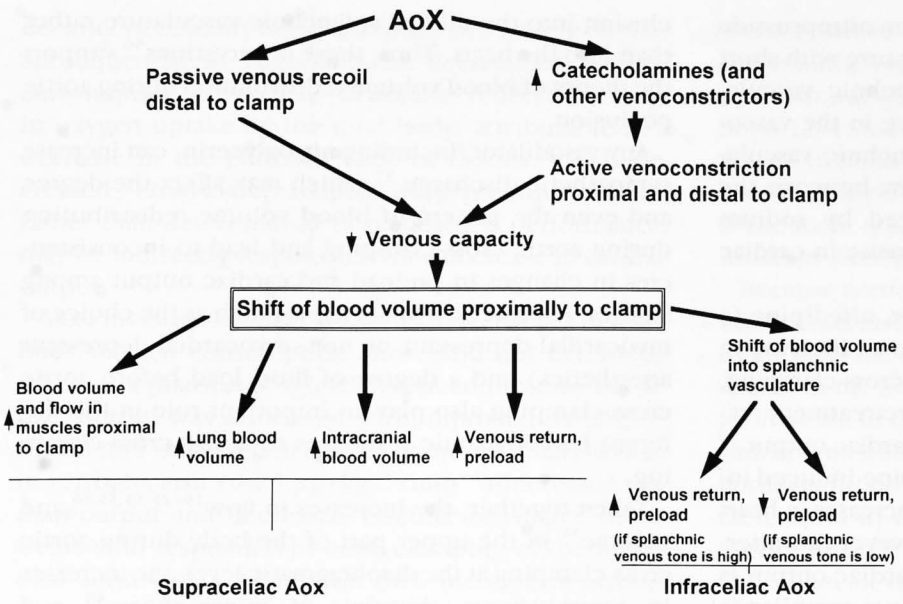

Fig. 1. Blood volume redistribution during aortic cross-clamping. This scheme depicts the reason for the decrease in venous capacity, which results in blood volume redistribution from the vasculature distal to aortic occlusion to the vasculature proximal to aortic occlusion. If the aorta is occluded 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; ↑ and ↓ = increase and decrease, respectively.

netic 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 simulation 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.[17,50] 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 ($0.25\ \mu g \cdot kg^{-1} \cdot min^{-1}$) 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 phosphoroorganic compounds and intracellular *p*H 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 vol-

ume.[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 β-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.

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 suprarenal infraceliac 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.

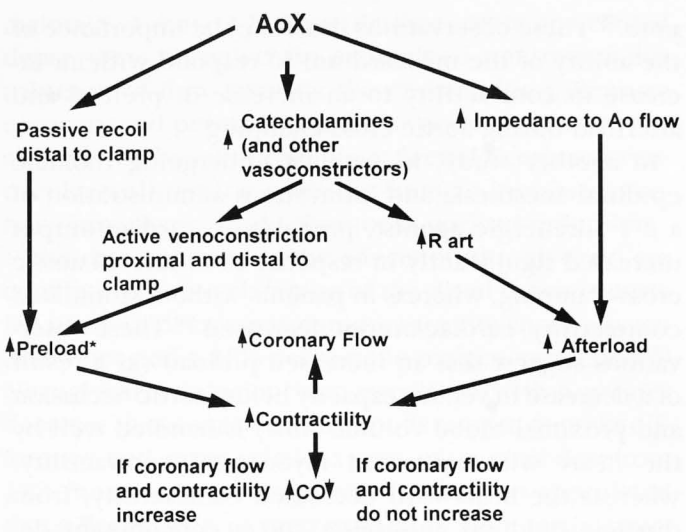

Fig. 2. Systemic hemodynamic response to aortic cross-clamping. Preload does not necessarily increase. If during infrarenal aortic cross-clamping blood volume shifts into the splanchnic vasculature, preload does not increase (fig. 1). AoX = aortic cross-clamping; Ao = aortic; R art = arterial resistance; ↑ and ↓ = increase and decrease, respectively. *Different patterns are possible; refer to figure 1.

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 (fig. 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]

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 im-

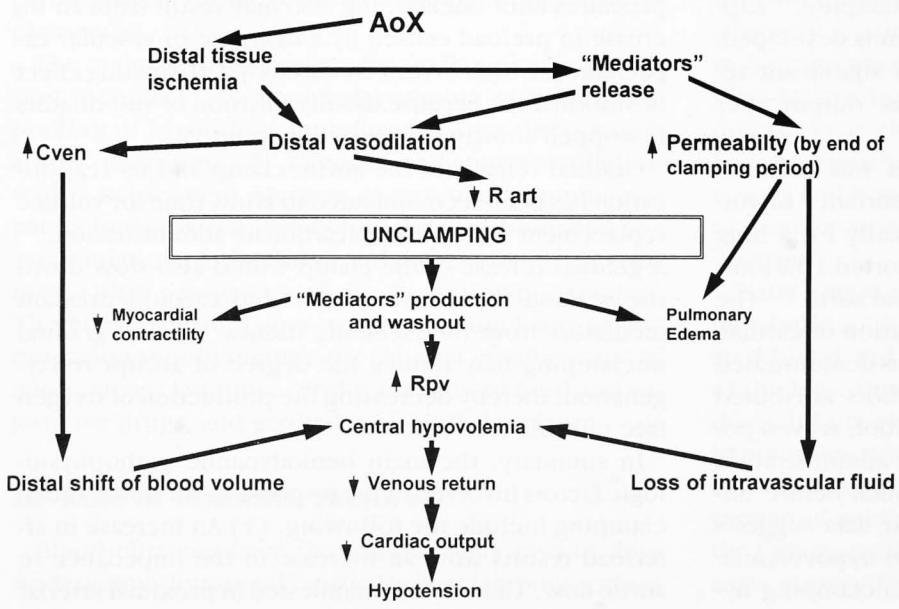

Fig. 3. Systemic hemodynamic response to aortic unclamping. AoX = aortic cross-clamping; Cven = venous capacitance; R art = arterial resistance; Rpv = pulmonary vascular resistance; ↑ and ↓ = increase and decrease, respectively.

portant 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 preclamping 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 preload (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 β-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 α-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 α-adrenergic antagonist not only prevented an increase, but actually decreased vascular resistance in the isolated limb.[148] Pretreatment with α- and β-adrenergic antagonists (phenoxybenz-

amine and propranolol) was associated with an increase in vascular resistance apparently attributable to angiotensin.[98] Only the combination of α- and β-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 α_1-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 *p*H 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 oxireductase 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 I_2) 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 F_1 (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 F_1 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 F_1 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 role of this mediator is not crucial in the development of unclamping arterial hypotension.

A concentration of thromboxane B_2 (TxB_2, a stable metabolite of a powerful vasoconstrictor, thromboxane A_2 [TxA_2]) 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. An increase in TxB_2 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 TxB_2 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 TxB_2 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 *p*H 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 antioxidase 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 ($0.2\ g \cdot kg^{-1}$) 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 TxB_2 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 hyperosmolarity 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 osmolarity.[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 Bengston and Heideman[213] and Bengston *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]

† Wallis J, Moses JW, Borer JS, Weksler B, Goldberg HL, Fisher, J, Kase M, Tack-Goldman K, Carter J, Calle S: Coronary blood flow in coronary artery disease: Heparin-induced potentiation caused by prostacyclin release (abstract). Circulation 66(suppl):II-263, 1982.

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 β-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 E_1 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 E_1.[249] Another vasodilator, sodium nitroprusside, led to no improvement in pulmonary function,[67] suggesting that effects of prostaglandins other then vasodilation are involved in pulmonary morbidity. The beneficial effect of prostaglandin E_1 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 TxA_2 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 cmH_2O 4–8 h after surgery.[211] Furthermore, the inhibition of thromboxane synthesis or the blockade of thromboxane receptors prevented pulmonary hy-

pertension, 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 TxA_2, resulting in neutrophil and platelet activation, and pulmonary dysfunction.[212,253]

Pretreatment with mannitol (0.2 g/kg) modified the increases in TxB_2 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 in-

crease 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 β-adrenergic antagonist.[141,286] However, the beneficial effect of the drug may be related to the well-documented inhibition of renin–angiotensin system by β-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 cerebrospinal 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 (fig. 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.

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.

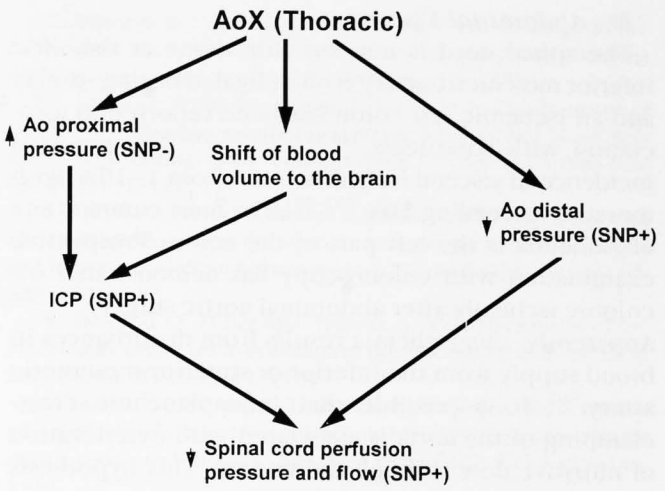

Fig. 4. Spinal cord blood flow and perfusion pressure during thoracic aortic occlusion, with or without sodium nitroprusside (SNP) infusion. The changes (arrows) represent the response to aortic cross-clamping *per se*. SNP+ = SNP aggravates the effect of cross-clamping; SNP− = SNP counteracts the effect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

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 infrasplanchnic 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-μm spheres.[48] We also have demonstrated that lack of entrapment of 9-μm 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.

References

1. Cox GS, O'Hara PJ, Hertzer NR, Piedmonte MR, Krajewski LP, Beven EG: Thoracoabdominal aneurysm repair: A representative experience. J Vasc Surg 15:780–788, 1992

2. Svensson LG, Crawford ES, Hess KR, Coselli JS, Safi HJ: Experience with 1509 patients undergoing thoracoabdominal aortic operations. J Vasc Surg 17:357–370, 1993

3. Golden MA, Donaldson MC, Whittemore AD, Mannick JA: Evolving experience with thoracoabdominal aortic aneurysm repair at a single institution. J Vasc Surg 13:792–797, 1991

4. Johnston KW: Multicenter prospective study of nonruptured abdominal aortic aneurysm: II. Variables predicting morbidity and mortality. J Vasc Surg 9:437–447, 1989

5. Roizen MF, Ellis JE: Anesthesia for vascular surgery, Clinical Anesthesia. Edited by Barash PG, Cullen BF, Stoelting RK. Philadelphia, JB Lippincott, 1992, pp 1059–1094

6. Scott A, Baillie CT, Sutton GL, Smith A, Bowyer RC: Audit of 200 consecutive aortic aneurysm repairs carried out by a single surgeon in a district hospital: Results of surgery and factors affecting outcome. Ann R Coll Surg Engl 74:205–211, 1992

7. Carroll RM, Laravisco RB, Schauble JF: Left ventricular function during aortic surgery. Arch Surg 111:740–743, 1976

8. Meloche R, Pottecher T, Audet J, Dufresne O, LePage C: Haemodynamic changes due to clamping of the abdominal aorta. Can Anaesth Soc J 24:20–34, 1977

9. Neglen P, Carlsson C, Eklof B, Gustafson I, Thomson D: Skeletal muscle metabolism and central hemodynamics during temporary incomplete ischemia induced by aortic clamping in man. Acta Chirurgica Scandinavica 146:323–331, 1980

10. Shenaq SA, Casar G, Chelly JE, Ott H, Crawford ES: Continuous monitoring of mixed venous oxygen saturation during aortic surgery. Chest 92:796–799, 1987

11. Perry MO: The hemodynamics of temporary abdominal aortic occlusion. Ann Surg 168:193–200, 1968

12. Attia RR, Murphy JD, Snider M, Lappas DG, Darling RC, Lowenstein E: Myocardial ischemia due to infrarenal aortic cross-clamping during aortic surgery in patients with severe coronary artery disease. Circulation 53:961–965, 1976

13. Dunn E, Prager R, Fry W, Kirsh MM: The effect of abdominal aortic cross-clamping in myocardial function. J Surg Res 22:463–468, 1977

14. Falk JL, Rackow EC, Blumenberg R, Gelfand M, Fein IA: Hemodynamic and metabolic effects of abdominal aortic crossclamping. Am J Surg 142:174–177, 1981

15. Roizen MF, Beaupre PN, Alpert RA, Kremer P, Cahalan MK, Shiller N, Sohn YJ, Cronnelly R, Lurz FW, Enrenfeld WK, Stoney RJ:

Monitoring with two-dimensional transesophageal echocardiography: Comparison of myocardial function in patients undergoing supraceliac, suprarenal-infraceliac, or infrarenal aortic occlusion. J Vasc Surg 1:300–305, 1984

16. Farrand EA, Horvath SM: Cardiovascular and hemodynamic functions in dogs subject to prolonged aortic occlusion. Arch Surg 76:951–955, 1958

17. Gelman S, McDowell H, Varner PD, Pearson J, Ebert J, Graybar G, Proctor J: The reason for cardiac output reduction following aortic crossclamping. Am J Surg 155:578–586, 1988

18. Silverstein PR, Caldera DL, Cullen DJ, Davison JK, Darling RC, Emerson CW: Avoiding the hemodynamic consequences of aortic crossclamping and unclamping. ANESTHESIOLOGY 50:462–466, 1979

19. Gelman S, Rabbani S, Bradley EL Jr: Inferior and superior vena caval blood flows during crossclamping of the thoracic aorta in pigs. J Thorac Cardiovasc Surg 96:383–391, 1988

20. Gregoretti S, Gelman S, Henderson T, Bradley EL: Hemodynamics and oxygen uptake below and above aortic occlusion during crossclamping of the thoracic aortic and sodium nitroprusside infusion. J Thorac Cardiovasc Surg 100:830–836, 1990

21. Gregoretti S, Henderson T, Parks DA, Gelman S: Haemodynamic changes and oxygen uptake during crossclamping of the thoracic aorta in dexmedetomidine pretreated dogs. Can J Anaesth 39: 731–741, 1992

22. Bahnson HT, Spencer FC: Excision of aneurysm of the ascending aorta with prosthetic replacement during cardiopulmonary bypass. Ann Surg 151:879–890, 1960

23. Hug HR, Taber RE: Bypass flow requirements during thoracic aneurysmectomy with particular attention to the prevention of left heart failure. J Thorac Cardiovasc Surg 57:203–213, 1969

24. Connolly JE, Wakabayashi A, German JC, Stemmer EA, Serres EJ: Clinical experience with pulsatile left heart bypass without anticoagulation for thoracic aneurysms. J Thorac Cardiovasc Surg 62: 568–576, 1971

25. Lawrence GH, Hessel EA, Sauvage LR, Krause AH: Results of the use of the TDMAC-heparin shunt in the surgery of aneurysms of the descending thoracic aorta. J Thorac Cardiovasc Surg 73:393–398, 1977

26. Vasko JS, Raess DH, Williams TE Jr, Kakos GS, Kilman JW, Meckstroth CV, Cattaneo SM, Klassen KP: Nonpenetrating trauma to the thoracic aorta. Surgery 82:400–406, 1977

27. Stokland O, Thorvaldsson J, Ilebekk A, Kiil F: Contributions of blood drainage from the liver, spleen and intestines to cardiac effects of aortic occlusion in the dog. Acta Physiol Scand 114:351–362, 1982

28. Molina JE, Corordan J, Einzig S: Adequacy of ascending aorta-descending aorta shunt during cross clamping of the thoracic aorta for prevention of spinal cord injury. J Thorac Cardiovasc Surg 90: 126–136, 1985

29. Akins CW, Buckley MJ, Daggett W, McIlldUff JB, Austen WG: Acute traumatic disruption of the thoracic aorta: A ten year experience. Ann Thorac Surg 31:305–309, 1981

30. Harpole DH, Clements FM, Quill T, Wolfe WG, Jones RH, McCann RL: Right and left ventricular performance during and after abdominal aortic aneurysm repair. Ann Surg 209:356–362, 1989

31. Barcroft H, Samaan A: The explanation of the increase in systemic flow caused by occluding the descending thoracic aorta. J Physiol 85:47–61, 1935

32. Brunsoni B, Colombo A, Merlo L, Marchetti G, Longo T: Hemodynamic and metabolic changes induced by temporary clamping of the thoracic aorta. Eur Surg Res 10:206–216, 1978

33. Kien ND, White DA, Reitan JA, Eisele JH Jr: The influence of adenosine triphosphate on left ventricular function and blood flow distribution during aortic crossclamping in dogs. J Cardiothorac Anesth 1:114–122, 1987

34. Gelman S, Reves JG, Fowler K, Samuelson PN, Lell WA, Smith LR: Regional blood flow during cross-clamping of the thoracic aorta and infusion of sodium nitroprusside. J Thorac Cardiovasc Surg 85: 287–291, 1983

35. Stokland O, Miller MM, Ilebekk A, Kiil: Mechanism of hemodynamic responses to occlusion of the descending thoracic aorta. Am J Physiol H423–H429, 1980

36. Stokland O, Molaug M, Thorvaldson J, Ilebekk A, Kiil F: Cardiac effects of splanchnic and non-splanchnic blood volume redistribution during aortic occlusions in dogs. Acta Physiol Scand 113:139–146, 1981

37. Caldini P, Permutt S, Waddell JA, Riley RL: Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. Circ Res 34:606–623, 1974

38. Strandness DE Jr, Parrish DG, Bell JW: Mechanism of declamping shock in operations on the abdominal aorta. 50:488–492, 1961

39. Gelman S, Khazaeli MB, Orr R, Henderson T: Blood volume redistribution during crossclamping of the descending aorta. Anesth Analg 78:219–224, 1994

40. Kainuma M, Katsuragawa K: An attempt to avoid changes in blood pressure resulting from aortic clamping or declamping, by the use of a balloon catheter placed in inferior vena cava. Japanese Journal of Anesthesiology 34:94–99, 1985

41. Lunn JK, Dannemiller FJ, Stanley TH: Cardiovascular responses to clamping of the aorta during epidural and general anesthesia. Anesth Analg 58:372–376, 1979

42. Dauchot PJ, DePalma R, Grum D, Zanella J: Detection and prevention of cardiac dysfunction during aortic surgery. J Surg Res 26:574–580, 1979

43. Van Der Linden P, Gilbart E, Engelman E, deRood M, Vincent JL: Determination of right ventricular volumes during aortic surgery. J Cardiothorac Anesth 3:280–285, 1989

44. Vandermeer TJ, Maini BS, Hendershott TH, Sottile FD: Evaluation of right ventricular function during aortic operations. Arch Surg 128:582–585, 1993

45. Balschi JA, Henderson T, Bradley EL, Gelman S: The effects of crossclamping of the thoracic aorta on the high-energy phosphates of myocardium and skeletal muscle: A 31P NMR study. J Thorac Cardiovasc Surg 106:346–356, 1993

46. Shepherd AP, Pawlik W, Mailman D, Burks TF, Jacobson ED. Effects of vasoconstrictors on intestinal vascular resistance and oxygen extraction. Am J Physiol 230:298–305, 1976

47. Shepherd AP, Mailman D, Burks TF, Granger HJ: Effects of norepinephrine and sympathetic stimulation on extraction of oxygen and 86Rb in perfused canine small bowel. Circ Res 33:166–174, 1973

48. Gelman S, Patel K, Bishop SP, Fowler KC, Smith LR: Renal and splanchnic circulation during infrarenal aortic crossclamping. Arch Surg 119:1394–1399, 1984

49. Shepherd AP, Riedel GL, Maxwell LC, Kiel JW: Selective vasodilators redistribute intestinal blood flow and depress oxygen uptake. Am J Physiol 247:G377–G384, 1984

50. Zaidan JR, Guffin AV, Perdue G, Smith R, McNeill DC: Hemodynamics of intravenous nitroglycerin during aortic clamping. Arch Surg 117:1285–1288, 1982

51. Hoka S, Siker D, Bosnjak ZJ, Kampine JP: Alteration of blood flow distribution and vascular capacitance during induced hypotension in deafferented dogs. ANESTHESIOLOGY 66:647–652, 1987

52. Derrer SA, BAstulli JA, Baele H, Rhodes RS, Dauchot PJ: Effects of nifedipine on the hemodynamic response to clamping and declamping of the abdominal aorta in dogs. J Cardiothorac Anesth 3: 58–64, 1989

53. Low RI, Takeda P, Mason DT, DeMaria AN: The effects of calcium channel blocking agents on cardiovascular function. Am J Cardiol 49:547–553, 1982

54. Serruys PW, Brower RW, Ten Katen HJ, Bom AH, Hugenholtz PG: Regional wall motion from radiopaque markers after intravenous and intra-coronary injections of nifedipine. Circulation 63:584–591, 1981

55. Theroux P, Waters DD, DeBaisieux JC, Szlachcic J, Mizgala HF, Bourassa MG: Hemodynamic effects of calcium ion antagonists after acute myocardial infarction. Clin Invest Med 3:81–85, 1980

56. Van Hemelrijck J, Waets P, Van Aken H, Lacroix H, Nevelsteen A, Suy R: Blood pressure management during aortic surgery: Urapidil compared to isosorbide dinitrate. J Cardiothorac Vasc Anesth 7:273–278, 1993

57. Needleman P, Corr PB, Johnson EM: Drugs used for the treatment of angina: Organic nitrates, calcium channel blockers, and β-adrenergic antagonists, The Pharmacological Basis of Therapeutics. Edited by Gilman AG, Goodman LS, Rall TW, Murad F. New York, MacMillan, 1985, pp 806–807

58. Gelman S, Granger DN, Fowler K, Smith LR: Clearance of 9-μm spheres and rubidium in the intestinal circulation. Am J Physiol 247:G13–G18, 1984

59. Bugge-Asperheim B, Kiil F: Preload, contractility, and afterload as determinants of stroke volume during elevation of aortic blood pressure in dogs. Cardiovasc Res 7:528–541, 1973

60. Roberts AJ, Nora JD, Hughes A, Quintanilla AP, Ganote CE, Sanders JH Jr, Moran JM, Michaelis LL: Cardiac and renal responses to cross-clamping of the descending thoracic aorta. J Thorac Cardiovasc Surg 86:732–741, 1983

61. Katz LN, Wiggers CJ: The influence of high systemic blood pressures on the right ventricle and pulmonary circuit. Am J Physiol 82:91–98, 1927

62. Gupta T, Wiggers CJ: Basic hemodynamic changes produced by aortic coarctation of different degrees. Circulation 3:17–31, 1951

63. Buckberg GD, Fixler DE, Archie JP, Hoffman JIE: Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ Res 30:67–81, 1972

64. Hummel BW, Raess DH, Gewertz BL, Wheeler HT, Fry WJ: Effect of nitroglycerin and aortic occlusion on myocardial blood flow. Surgery 92:159–166, 1982

65. Wolfe WG, Kleinman LH, Wechsler AS, Sabiston DC Jr: Heparin-coated shunts for lesions of the descending thoracic aorta. Arch Surg 112:1481–1487, 1977

66. Joob AW, Harman PK, Kaiser DL, Kron IL: The effect of renin-angiotensin system blockade on visceral blood flow during and after thoracic aortic crossclamping. J Thorac Cardiovasc Surg 91:411–418, 1986

67. Katsamouris AN, Mastrokostopoulos GT, Hatzinikolaou NS, Lappas DG, Buckley MMJ: Control of left ventricular and proximal aortic dimensional decompensation during clamping of the descending thoracic aorta. Vascular Surgery 22:316–327, 1988

68. Foley DH, Herlihy JT, Thompson CI, Rubio R, Berne RB: Increased adenosine formation by rat myocardium with acute aortic constriction. J Mol Cell Cardiol 10:293–300, 1978

69. Anrep G: On the part played by the suprarenals in the normal vascular reactions of the body. J Physiol (Lond) 45:307–317, 1912

70. Knowlton FP and Starling EH: The influence of variations in temperature and blood pressure on the performance of the isolated mammalian heart. J Physiol (Lond) 44:206–219, 1912

71. Patterson SW, Piper H, Starling EH: The regulation of the heart beat. J Physiol (Lond) 48:465–513, 1914

72. Sarnoff SJ, Mitchell JH: The regulation of the performance of the heart. Am J Med 30:747–771, 1961

73. Monroe RG, Gamble WJ La Farge CG, Kumar AE, Stark J, Saunders GL, Phornphutkul C, Davis M: The Anrep reconsidered. J Clin Invest 51:2573–2583, 1972

74. Walston A, Rembert JC, Fedor JM, Greenfield JC: Regional myocardial blood flow after sudden aortic constriction in awake dogs. Circ Res 42:420–425, 1978

75. Rosenblueth A, Alanis J, Lopez E, Rubio R: The adaptation of ventricular muscle to different circulatory conditions. Arch Int Physiol Biochim 67:358–373, 1959

76. Sarnoff SJ, Mitchell JH, Gilmore JP, Remensnyder JP: Homeometric autoregulation in the heart. Circ Res 8:1077–1091, 1960

77. Sarnoff SJ, Gilmore JP, Mitchell JH, Remensnyder JP: Potassium changes in the heart during homeometric autoregulation and acetyl strophanthidin. Am J Med 34:440–451, 1963

78. Clancy RL, Graham TP Jr, Ross J Jr, Sonnenblick EH, Braunwald E: Influence of aortic pressure-induced homeometric autoregulation on myocardial performance. Am J Physiol 214:1186–1192, 1968

79. Vatner SF, Monroe RG, McRitchie RJ: Effects of anesthesia, tachycardia, and autonomic blockade on the Anrep effect in intact dogs. Am J Physiol 226:1450–1456, 1974

80. Gamble WJ, LaFarge CG, Fyler DC, Weisul J, Monroe RG: Regional coronary venous oxygen saturation and myocardial oxygen tension following abrupt changes in ventricular pressure in the isolated dog heart. Circ Res 34:672–681, 1974

81. Hertzer NR, Young JR, Kramer JR, Phillips DF, deWolfe VG, Ruschhaupt WF III, Beven EG: Routine coronary angiography prior to elective aortic reconstruction. Arch Surg 114:1336–1344, 1979

82. Whittemore AD, Clowes AW, Hechtman HB, Mannick JA: Aortic aneurysm repair: Reduced operative mortality associated with maintenance of optimal cardiac performance. Ann Surg 192:414–421, 1980

83. Cohen JL, Wender R, Maginot A, Cossman D, Treiman R, Foran R, Levin P, DeAngelis J, Treiman G: Hemodynamic monitoring of patients undergoing abdominal surgery. Am J Surg 146:174–177, 1983

84. Gooding JM, Archie JP, McDowell H: Haemodynamic response to infrarenal aortic cross-clamping in patients with and without coronary artery disease. Crit Care Med 8:382–385, 1980

85. Scott WJ, Gewertz BL: Effect of nitroglycerin on ventricular oxygen extraction during aortic occlusion. J Vasc Surg 4:505–510, 1986

86. Vatner SF, Pagani M, Manders WT, Pasipoularides AD: Alpha adrenergic vasoconstriction and nitroglycerin vasodilation of large coronary arteries in the conscious dog. J Clin Invest 65:5–14, 1980

87. Fam WM, McGregor M: Effect of nitroglycerin and dipyridamole on regional coronary resistance. Circ Res 22:649–659, 1968

88. Pottecher T, Meloche R: The use of aminophylline for correction of haemodynamic repercussions of clamping of the aorta. Can Anaesth Soc J 24:162–174, 1977

89. Bugge-Asperheim B, Kiil F: Cardiac response to increased aortic pressure: Changes in output and left ventricular pressure pattern at various levels of inotropy. Scand J Clin Lab Invest 24:345–360, 1969

90. Reiz S, Peter T, Rais O: Hemodynamic effects of infrarenal and common iliac artery declamping in man: An approach to optimal volume loading. Acta Anaesthiol Scand 23:579–586, 1979

91. Reinhart K, Foehring U, Kersting T, Schaefer M, Bredle D, Hirner A, Eyrich K: Effects of thoracic epidural anesthesia on systemic hemodynamic function and systemic oxygen supply-demand relationship. Anesth Analg 69:360–369, 1989

92. Grindlinger GA, Vegas AM, Manny J, Bush HL, Mannick JA, Hechtman HB: Volume loading and vasodilators in abdominal aortic aneurysmectomy. Am J Surg 139:480–486, 1980

93. Hjalmarson A: Myocardial metabolic changes related to ventricular fibrillation. Cardiology 65:226–247, 1980

94. Kalman PG, Wellwood MR, Weisel RD, Morley-Forster PK, Teasdale SJ, Ivanov J, Johnston KW, McLaughlin PR, Baird RJ, Cain JP, Walker PM: Cardiac dysfunction during abdominal aortic operation: The limitation of pulmonary wedge pressure. J Vasc Surg 3: 773–781, 1986

95. Lefer AM, Martin J: Origin of myocardial depressant factor in shock. Am J Physiol 218:1423–1427, 1970

96. Symbas PN, Pfaender LM, Drucker MH, Lester JL, Gravanis MB, Zachoaropoulos L: Cross-clamping of the descending aorta. J Thorac Cardiovasc Surg 85:300–305, 1983

97. Normann NA, Taylor AA, Crawford ES, DeBakey ME, Saleh SA: Catecholamine release during and after crossclamping of the descending aorta. J Surg Res 34:97–103, 1983

98. Gelman S, Curtis SE, Bradley WE, Henderson CT, Parks DA, Cain SM: Angiotensin and adrenoceptors role in hemodynamic response to aortic cross-clamping. Am J Physiol 264:H14–H20, 1993

99. Brant B, Armstrong RP, Vetto RM: Vasodepressor factor in declamp shock production. Surgery 67:650–653, 1970

100. Czarnecki W, Noble MIM: Mechanism of the inotropic action of inosine on canine myocardium. Cardiovasc Res 17:735–739, 1983

101. Berne RM, Rubio R: Adenine nucleotide metabolism in the heart. Circ Res 35:109–120, 1974

102. Berne RM: Cardiac nucleotides in hypoxia: Possible role in regulation of coronary blood flow. Am J Physiol 204:317–322, 1963

103. Richman HG, Wyborny L: Adenine nucleotide degradation in the rabbit heart. Am J Physiol 207:1139–1145, 1964

104. Rubio R, Berne RM: Release of adenosine by the normal myocardium in dogs and its relationship to the regulation of coronary resistance. Circ Res 25:407–415, 1969

105. Olsson RA: Changes in content of purine nucleosides in canine myocardium during coronary occlusion. Circ Res 26:301–306, 1970

106. Jones CE, Thomas JX, Devous MD, Norris CP, Smith EE: Positive inotropic response to inosine in the in situ canine heart. Am J Physiol 233:438–443, 1977

107. Aviado DM: Effects of fluorocarbons, chlorinated solvents and inosine on the cardiopulmonary system. Environ Health Perspect 26:207–215, 1978

108. Jones CE, Mayer LR: Nonmetabolically coupled coronary vasodilation during inosine infusion in dogs. Am J Physiol 238:569–574, 1980

109. Juhasz-Nagy A, Aviado DM: Inosine as a cardiotonic agent that reverses adrenergic beta-blockade. J Pharmacol Exp Ther 202: 683–695, 1977

110. Thomas JX, Jones CE: Effects of inosine on contractile force and high-energy phosphates in ischemic hearts (40575). Proc Soc Exp Biol Med 161:468–472, 1979

111. Woollard KV, Kingaby RO, Lab MJ, Cole AWG, Palmer TN: Inosine as a selective inotropic agent on ischaemic myocardium? Cardiovasc Res 15:659–667, 1981

112. Peterson A, Brant D, Kirsh MM: Nitroglycerin infusion during infrarenal aortic cross-clamping in dogs: An experimental study. Surgery 34:216–223, 1978

113. Coetzee A, Fourie P, Badenhorst E: Response of the heart to acute hypertension during halothane, enflurane, and isoflurane anesthesia. Anesth Analg 66:1219–1226, 1987

114. Hong S-AH, Gelman S, Henderson T: Angiotensin and adrenoceptors in the hemodynamic response to aortic crossclamping. Arch Surg 127:438–441, 1992

115. Johnston WE, Balestrieri FJ, Plonk G, DiSouza V, Howard G: The influence of periaortic collateral vessels on the intraoperative hemodynamic effects of acute aortic occlusion in patients with aortoocclusive disease or abdominal aortic aneurysm. ANESTHESIOLOGY 66:386–389, 1987

116. Cunningham AJ, O'Toole DP, McDonald N, Keeling F, Bouchier-Hayes D: The influence of collateral vascularisation on haemodynamic performance during abdominal aortic surgery. Can J Anaesth 36:44–50, 1989

117. Powelson JA, Maini BS, Bishop RL, Sottile FD: Continuous monitoring of mixed venous oxygen saturation during aortic operations. Crit Care Med 20:332–336, 1992

118. Whalley DG, Salevsky FC, Ryckman JV: Haemodynamic and metabolic consequences of aortic occlusion during abdominal aortic surgery. Br J Anaesth 70:96–98, 1993

119. Walker PM, Johnston KW: When does limb blood flow increase after aortoiliac bypass grafting? Arch Surg 115:912–915, 1980

120. Mansberger AR Jr, Cox EF, Flotte CT, Buxton RW: 'Washout' acidosis following resection of aortic aneurysms: Clinical metabolic study of reactive hyperemia and effect of dextran on excess lactate and pH. Ann Surg 163:778–787, 1966

121. Askitopolou H, Young CA, Morgan M, Sykes MK: Some cardiopulmonary effects of infrarenal clamping of the abdominal aorta. Anaesth Intensive Care 6:44–48, 1978

122. Rader LE, Keith HB, Campbell GS: Mechanism of hypotension following release of abdominal aortic clamps. Vascular Surgery 12: 265–267, 1961

123. Fry WJ, Keitzer WF, Kraft RO, De Weese MS: Prevention of hypotension due to aortic release. Surg Gynecol Obstet 116:301–306, 1963

124. Provan JL, Fraenkel GJ, Austen WG: Metabolic and hemodynamic changes after temporary aortic occlusion in dogs. Surg Gynecol Obstet 123:544–550, 1966

125. Bayliss WM: On the local reactions of the arterial wall to changes of internal pressure. J Physiol 28:220–231, 1902

126. Folkow B: Intravascular pressure as a factor regulating the tone of the small vessels. Acta Physiol Scand 17:289–310, 1949

127. Lewis T, Grant R: Observations upon reactive hyperemia in man. Heart 12:73–120, 1925

128. Guyton AC, Carrier O Jr, Walker JR. Evidence for tissue oxygen demand as the major factor causing autoregulation. Circ Res 15:60–69, 1964

129. Barcroft H: The mechanism of vasodilation in the limbs during and after arrest of the circulation. Angiology 23:595–599, 1972

130. Campbell GS, Smiley RH: Pneumatic envelope to avoid hypertension following removal of aortic clamps. Ann Surg 160:614–621, 1964

131. Vetto RM, Brant B: Control of declamping shock. Am J Surg 116:273–279, 1968

132. Grindlinger GA, Weisel RD, Mannick JA, Hechtman HB: Volume loading and nitroprusside in abdominal aortic aneurysmectomy. Surgical Forum 29:234–236, 1978

133. Thomas TV: Aortic declamping shock. Am Heart J 81:845–847, 1971

134. Roytblatt L, Gelman S, Henderson T, Bradley E: Humoral factors and hemodynamics during crossclamping of the thoracic aorta. J Cardiothorac Vasc Anesth 5:10–14, 1991

135. Schneiweiss R, Hadsall F, Gordon HE: Prevention of hypotension following release of aortic occlusion. Surgery 60:628–632, 1966

136. Lim RC, Bergentz SE, Lewis DH: Metabolic and tissue blood flow changes resulting from aortic crossclamping. Surgery 65:304–310, 1969

137. Eklof B, Neglen P, Thomson D: Temporary incomplete ischemia of the legs caused by aortic clamping in man. Ann Surg 193: 99–104, 1981

138. Baue AE, McClerkin WW: A study of shock: Acidosis and the declamping phenomenon. Ann Surg 161:41–45, 1965

139. Akata T, Tominaga M, Sagiyama M, Taniyama T, Inaba S, Takahashi S, Yoshitake J: Changes in end-tidal CO_2 level following tourniquet deflation during orthopedic surgery. Journal of Anesthesia 6: 9–16, 1992

140. Perkins RJ, Roberts KW, Shah DM, Feustel PJ, Cohen IL: Estimation of O_2 deficit and debt resulting from abdominal aortic crossclamping in humans (abstract). ANESTHESIOLOGY 75:A113, 1991

141. Berkowitz HD, Shetty S: Renin release and renal corticol ischemia following aortic cross-clamping. Arch Surg 109:612–617, 1974

142. Gal TJ, Cooperman LH, Berkowitz HD: Plasma renin activity in patients undergoing surgery of the abdominal aorta. Ann Surg 179: 65–69, 1974

143. Grindlinger GA, Vegas AM, Williams GH, Mannick JA, Hechtman HB: Independence of renin production and hypertension in abdominal aortic aneurysmectomy. Am J Surg 141:472–477, 1981

144. Grant RP, Jenkins LC: Modification by preoperative betablockade of the renin response to infrarenal aortic cross-clamping. Can Anaesth Soc J 30:480–486, 1983

145. Kataja JHK, Kaukinen S, Viinamaki OVK, Metsa-Ketela TJA, Vapaatalo H: Hemodynamic and hormonal changes in patients pretreated with captopril for surgery of the abdominal aorta. J Cardiothorac Anesth 3:425–432, 1989

146. Kataja J, Kaukinen S, Viinamaki O: Intravenous captopril for treatment of hypertension in patients undergoing abdominal aortic surgery. Eur J Anaesthesiol 7:103–114, 1990

147. Cronenwett JL, Lindenauer SM: Distribution of intrarenal blood flow following aortic clamping and declamping. J Surg Res 22:469–482, 1977

148. Gelman S, Bredle WE, Bradley WE, Cain SM: Angiotensin and alpha-adrenoceptor activation play a role in hemodynamic response to aortic crossclamping. Am J Physiol 259:H68–H73, 1990

149. Niarchos AP, Roberts AJ, Case DB, Gay WA Jr, Laragh JH: Hemodynamic characteristics of hypertension after coronary bypass surgery and effects of the converting enzyme inhibitor. Am J Cardiol 43:586–592, 1979

150. Quintin L, Bonnet F, Macquin I, Szekely B, Becquemin JP, Ghignone M: Aortic surgery: Effect of clonidine on intraoperative catecholaminergic and circulatory stability. Acta Anaesthesiol Scand 34:132–137, 1990

151. Alexander RS: The effects of blood flow and anoxia on spinal cardiovascular centers. Am J Physiol 143:698–708, 1945

152. Pagani M, Pizzinelli P, Bergamaschi M, Malliani A: A positive feedback sympathetic pressor reflex during stretch of the thoracic aorta in conscious dogs. Circ Res 50:125–132, 1982

153. Malliani A, Pagani M, Pizzinelli P, Furlan R, Guzzetti S: Cardiovascular reflexes mediated by sympathetic afferent fibers. J Auton Nerv Syst 7:295–301, 1983

154. Lioy F, Malliani A, Pagani M, Recordati G, Schwartz PJ: Reflex hemodynamic responses initiated from the thoracic aorta. Circ Res 40:78–84, 1974

155. Andersen PT, Nielsen LK, Moller-Petersen J, Henneberg EW, Egebald K: Severe hypophosphatemia following elective abdominal aortic bypass grafting. Acta Chirurgica Scandinavica 153:641–646, 1987

156. Brawn K, Fridovich I: Superoxide radical and superoxide dismutases: Threat and defense. Acta Physiol Scand Suppl 492:9–18, 1980

157. Parks DA, Granger DN: Ischemia-induced vascular changes: Role of xanthine oxidase and hydroxyl radicals. Am J Physiol 245: G285–G289, 1983

158. Nielsen VG, Weinbroum A, Tan S, Samuelson PN, Gelman S, Parks DA: Xanthine oxidoreductase release after descending thoracic aorta occlusion and reperfusion in rabbits. J Thorac Cardiovasc Surg 107:1222–1227, 1994

159. Schoenberg MH, Fredholm BB, Hohlbach G: Changes in acid-base status, lactate concentration and purine metabolites during reconstructive aortic surgery. Acta Chirurgica Scandinavica 151:227–233, 1985

160. Bourchier RG, Gloviczki P, Larson MV, Wu QH, Hallett JW Jr, Ahlquist DA, Pairolero PC: The mechanisms and prevention of intravascular fluid loss after occlusion of the supraceliac aorta in dogs. J Vasc Surg 13:637–645, 1991

161. Svensson LG, Von Ritter C, Oosthuizen MMJ, Fimmel CJ, Rickards E, Hunter SJ, Robinson MF, Hinder RA: Prevention of gastric mucosal lesions following aortic cross-clamping. Br J Surg 74:282–285, 1987

162. Casthely PA, Dluzneski J, Jones R, Goodman K, Redko V, Cottrell JE, Yoganathan T, Fiordalisi J: Superoxide dismutase and hemodynamic changes following aortic crossclamp release. J Cardiothorac Anesth 2:450–454, 1988

163. Vo NM, Dunbar J III, Stanton PE: Hemodynamic changes secondary to aortic occlusion and shock are not mediated by oxygen free radicals. Vascular Surgery 20:353–358, 1986

164. Korthuis RJ, Smith JK, Carden DL: Hypoxic reperfusion attenuates postischemic microvascular injury. Am J Physiol 256:H315–H319, 1989

165. Walker PM, Lindsay TF, Labbe R, Mickle DA, Romaschin AD: Salvage of skeletal muscle with free radical scavengers. J Vasc Surg 5:68–75, 1987

166. Perry MA, Wadhwa SS: Gradual reintroduction of oxygen reduces reperfusion injury in cat stomach. Am J Physiol 254:G366–G372, 1988

167. Del Maestro RF, Thaw HH, Bjork J: Free radicals as mediators of tissue injury. Acta Physiol Scand Suppl 492:43–57, 1980

168. Del Maestro FR, Bjork J, Arfors KE: Increase in microvascular permeability induced by enzymatically generated free radicals: I. In vivo study. Microvasc Res 22:239–254, 1981

169. McCord JM: The superoxide free radical: Its biochemistry and pathophysiology. Surgery 94:912–917, 1983

170. Segal ML, Fertel RH, Kraut EH, Sagone AL: The role of reactive oxygen species in thromboxane B2 generation by polymorphonuclear leukocytes. J Lab Clin Med 102:788–794, 1983

171. Kaufman RP Jr, Klausner JM, Anner H, Feingold H, Kobzik L, Valeri CR, Shepro D, Hechtman HB: Inhibition of thromboxane (Tx) synthesis by free radical scavengers. J Trauma 28:458–464, 1988

172. Graham LM, Stanley JC, Gewertz BL, Zelenock G, Fry WJ: Prostaglandin F2a attenuation of aortic declamping hyperemia and hypotension. J Surg Res 20:413–419, 1976

173. Rittenhouse EA, Maixner W, Knott HW, Barnes RW, Jaffe BM: The role of prostaglandin E in the hemodynamic response to aortic clamping and declamping. Surgery 80:137–144, 1976

174. Utsunomiya T, Krausz MM, Dunham B, Mannick JA, Allen PD, Shepro D, Hechtman HB: Maintenance of cardiodynamics with aspirin during abdominal aortic aneurysmectomy (AAA). Ann Surg 194:602–608, 1981

175. Krausz MM, Utsunomiya T, McIrvine AJ, Allen PD, Levine L, Mannick JA, Shepro D, Hechtman HB: Modulation of cardiovascular function and platelet survival by endogenous prostacyclin released during surgery. Surgery 93:554–559, 1983

176. Huval WV, Lelcuk S, Allen PD, Mannick JA, Shepro D, Hechtman HB: Determinants of cardiovascular stability during abdominal aortic aneurysmectomy. Ann Surg 199:216–222, 1984

177. Seeling W, Heinrich H, Oettinger W: Das Eventerationssyndrome: Prostacyclinnnfreisetzung und akuter paO2-Abfall durch Dunndarmeventeration. Anaesthesist 35:738–743, 1986

178. Seltzer JL, Goldberg ME, Larijani GE, Ritter DE, Starsnic MA, Stahl GL, Lefer AM: Prostacyclin mediation of vasodilation following mesenteric traction. ANESTHESIOLOGY 68:514–518, 1988

179. Gottlieb A, Skrinska VA, O'Hara P, Boutrous AR, Melia M, Beck GJ: The role of prostacyclin in the mesenteric traction syndrome during anesthesia for abdominal aortic reconstructive surgery. Ann Surg 209:363–367, 1989

180. Hudson JC, Wurm WH, O'Donnell TF Jr, Kane FR, Mackey WC, Su YF, Watkins WD: Ibuprofen pretreatment inhibits prostacyclin release during abdominal exploration in aortic surgery. ANESTHESIOLOGY 72:443–449, 1990

181. Gimbrone MA, Alexander RW: Angiotensin II stimulation of prostaglandin production in cultured human vascular endothelium. Science 199:219–220, 1975

182. Hsuch W, Isakson PK, Needleman P: Hormone selective lipase activation in the isolated rabbit heart. Prostaglandins 13:1073–1091, 1978

183. Dusting GJ, Mullins EM, Doyle AE: Angiotensin-induced prostacyclin release may contribute to the hypotensive action of converting enzyme inhibitors, Advances in Prostaglandin and Thrombosis Research. Volume 7. Edited by Samuelsson B, Ramwell PW, Paoletti R. New York, Raven Press, 1980, pp 815–819

184. Sumpio BE, Banes AJ: Prostacyclin synthetic activity in cultured aortic endothelial cells undergoing cyclic mechanical deformation. Surgery 104:383–389, 1988

185. Koller A, Sun D, Kaley G: Role of shear stress and endothelial prostaglandins in flow- and viscosity-induced dilation of arterioles in vitro. Circ Res 72:1276–1284, 1993

186. Roth GJ, Majerus PW: The mechanism of the effect of aspirin on human platelets: I. Acetylation of particulate fraction protein. J Clin Invest 56:624–632, 1975

187. Galt SW, Bech FR, McDaniel MD, Dain BJ, Yeager MP, Schneider JR, Walsh DB, Zwolak RM, Cronenwett JL: The effect of ibuprofen on cardiac performance during abdominal aortic cross-clamping. J Vasc Surg 13:876–884, 1991

188. Stallone RJ, Lim RC, Blaisdell FW: Pathogenesis of the pulmonary changes following ischemia of the lower extremities. Ann Thorac Surg 7:539–549, 1969

189. Blaisdell FW, Lim RC, Stallone RJ: The mechanism of pulmonary damage following traumatic shock. Surg Gynecol Obstet 130: 15–22, 1970

190. Beal SL, Heimbach D, Chi E, Reynolds L: Physiology and histology of the pulmonary micro-embolism syndrome. Surgical Forum 35:37–39, 1984

191. Anner H, Kaufmann RP Jr, Kobzik L, Valeri CR, Shepro D, Hechtman HB: Pulmonary hypertension and leukosequestration after lower torso ischemia. Ann Surg 206:642–648, 1987

192. Goldman G, Welbourn R, Rothlein R, Wiles M, Kobzik L, Valeri CR, Shepro D, Hechtman HB: Adherent neutrophils mediate permeability after atelectasis. Ann Surg 216:372–380, 1992

193. Welbourn R, Goldman G, Kobzik L, Paterson IS, Valeri CR, Shepro D, Hechtman HB: Role of neutrophil adherence receptors (CD 18) in lung permeability following lower torso ischemia. Circ Res 71:82–86, 1992

194. Saliba MJ, Covell JW, Bloor CM: Effects of heparin in large doses on the extent of myocardial ischemia after acute coronary occlusion in the dog. Am J Cardiol 37:599–604, 1976

195. Fegen JP, Albert DJ, Persky L: The role of heparin in prolonging acute renal ischemia time. Investigative Urology 9:16–20, 1971

196. Smith DR, Ducker TB, Kempe LG: Temporary experimental intracranial vascular occlusion: Effect of massive doses of heparin on brain survival. J Neurosurg 30:537–544, 1969

197. Hobson RW, Wright JG, Fox D, Kerr JC: Heparinization reduces endothelial permeability and hydrogen ion accumulation in a canine skeletal muscle ischemia-reperfusion model. J Vasc Surg 7: 585–591, 1988

198. Engleberg H: Actions and functions of heparin, Heparin: Metabolism, Physiology and Clinical Application. Springfield, Charles C. Thomas, 1963, pp 42–63

199. Jaques LB. Heparin: An old drug with a new paradigm. Science 206:528–533, 1979

200. Rent R, Nylrman R, Fiedel BA, Gewurz H: Potentiation of CI esterase inhibitor activity by heparin. Clin Exp Immunol 23:264–271, 1976

201. Hiebert LM, Jaques LM: The observation of heparin on the endothelium. Artery 2:26–37, 1976

202. Mahado J, Hiebert L, Jaques LB: Vascular sequestration of heparin. Thromb Res 12:79–90, 1977

203. Glimelius B, Busch CH, Höök M: Binding of heparin on the surface of cultured human endothelial cells. Thromb Res 12:773–782, 1978

204. Schell RM, Cole DJ, Schultz RL, Osborne TN: Temporary cerebral ischemia: Effects of pentastarch or albumin on reperfusion injury. ANESTHESIOLOGY 77:86–92, 1992

205. Nielsen VG, Weinbroum A, Samuelson PN, Gelman S, Tan S, Baldwin S, Matalon S, Parks DS: Hetastarch decreases lung injury after descending thoracic aorta occlusion and reperfusion in rabbits (abstract). ANESTHESIOLOGY 79:A575, 1993

206. Zikria BA, King TC, Stanford J, Freeman HP: A biophysical approach to capillary permeabilty. Surgery 105:625–631, 1989

207. Webb AR, Tighe D, Moss RF, Al-Saady N, Hynd JW, Bennett ED: Advantages of narrow-range, medium molecular weight hydroxyethyl starch for volume maintenance in a porcine model of fecal peritonitis. Crit Care Med 19:409–416, 1991

208. Knudsen F, Andersen PT, Nielsen LK, Jersild C: Complement and leukocyte changes during major vascular surgery. J Cardiothorac Anesth 2:646–649, 1988

209. Welbourn CRB, Goldman G, Paterson IS, Valeri CR, Shepro D, Hechtman HB: Neutrophil elastase and oxygen radicals: Synergism in lung injury after hindlimb ischemia. Am J Physiol 260:H1852–H1856, 1991

210. Paterson IS, Klausner JM, Goldman G, Pugatch R, Feingold H, Allen P, Mannick JA, Valeri CR, Shepro D, Hechtman HB: Pulmonary edema after aneurysm surgery is modified by mannitol. Ann Surg 210:796–801, 1989

211. Paterson IS, Klausner JM, Pugatch R, Allen P, Mannick JA, Shepro D, Hechtman HB: Noncardiogenic pulmonary edema after abdominal aortic aneurysm surgery. Ann Surg 209:231–236, 1989

212. Paterson IS, Klausner JM, Goldman G, Kobzik L, Welbourn R, Valeri CR, Shepro D, Hechtman HB: Thromboxane mediates the ischemia induced neutrophil oxidative burst. Surgery 106:224–229, 1989

213. Bengston A, Heideman M: Altered anaphylatoxin activity during induced hypoperfusion in acute and elective abdominal aortic surgery. J Trauma 26:631–637, 1986

214. Bengston A, Lannsjo W, Heideman M: Complement and anaphylatoxin responses to cross-clamping of the aorta. Br J Anaesth 59: 1093–1097, 1987

215. Mahler F, Intaglietta M, Hugli TE, Johnson AR: Influence of C3a anaphylatoxin compared to other vasoactive agents on the microcirculation on the rabbit omentum. Microvasc Res 9:345–356, 1975

216. Hugli TE: Complement anaphylatoxins as plasma mediators, spasmogens and chemotaxins, The Chemistry and Physiology of Human Plasma Proteins. Edited by Bing DH. New York, Pergamon Press, 1979, pp 255–280

217. Pavek K, Piper PJ, Smedegard G: Anaphylatoxin-induced shock and two patterns of anaphylactic shock: Hemodynamics and mediators. Acta Physiol Scand 105:393–403, 1979

218. Regal JF, Eastman AY, Pickering RJ: C5a-induced tracheal contraction: A histamine independent mechanism. J Immunol 124: 2876–2878, 1980

219. Marceau F, Hugli TE: Effect of C3a and C5a anaphylatoxins on guinea-pig isolated blood vessels. J Pharmacol Exp Ther 230: 749–754, 1984

220. Goldstein IM, Brai M, Osler AG, Weissmann G: Lysosomal enzyme release from human leukocytes: Mediation by the alternative pathway of complement activation. J Immunol 111:33–37, 1973

221. Chenoweth DE, Hugli TE: Demonstration of specific C5a receptor on intact human polymorphonuclear leukocytes. Proc Natl Acad Sci U S A 75:3943–3947, 1978

222. Hachfeld del Balzo U, Levi R, Polley MJ: Cardiac dysfunction caused by purified human C3a anaphylatoxin. Proc Natl Acad Sci U S A 82:886–890, 1985

223. Stimler NP, Bach MK, Bloor CM, Hugli TE: Release of leukotrienes from guinea pig lung stimulated by C5a des Arg anaphylatoxin. J Immunol 128:2247–2252, 1982

224. Heideman M: Complement activation in vitro induced by endotoxin and injured tissue. J Surg Res 26:670–674, 1979

225. Herzlinger GA, Bing DH, Stein R, Cumming RD: Quantitative measurement of C3 activation at polymer surfaces. Blood 57:764–770, 1981

226. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD: Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 86:845–857, 1983

227. Shepard AD, Gelfand JA, Callow AD, O'Donnell JE Jr: Complement activation by synthetic vascular prostheses. J Vasc Surg 1: 829–838, 1984

228. Roizen MF, Rodgers GM, Valone FH, Lampe GH, Benefiel DJ, Gelman S, Rapp J, Weiler JM, Ota M, Shuman A, Goetzl EJ: Anaphylactoid reactions to vascular graft material presenting with vasodilation and subsequent disseminated intravascular coagulation. ANESTHESIOLOGY 71:331–338, 1989

229. Fosse E, Mollnes TE, Ingvaldsen B: Complement activation during major operations with or without cardiopulmonary bypass. J Thorac Cardiovasc Surg 93:860–866, 1987

230. Papahadjopoulos D, Jacobsson K, Poste G, Shepard G: Effects of local anesthetics on membrane properties: I. Changes in the fluidity of phospholipid bilayers. Biochim Biophys Acta 394:504–519, 1975

231. Feinstein MB, Volop M, Perrie S, Makriyannis A, Sha'afi RI: Mechanisms of local anesthetic action on the permeability of erythrocytes, leukocytes, and liposomes containing the erythrocyte anion channel protein. Mol Pharmacol 13:840–851, 1977

232. Hammer R, Dahlgren C, Stenddahl O: Inhibition of human leukocyte metabolism and random mobility by local anaesthesia. Acta Anaesthesiol Scand 29:520–523, 1985

233. Roumen RMH, van der Vliet JA, Wevers RA, Goris RJA: Intestinal permeability is increased after major vascular surgery. J Vasc Surg 17:734–737, 1993

234. Roumen RMH, Frieling JTM, van Tits HWH, van der Vliet JA, Goris RJA: Endotoxemia after major vascular operations. J Vasc Surg 18:853–857, 1993

235. Baigrie RJ, Lamont PM, Whiting S, Morris PJ: Portal endotoxin and cytokine responses during abdominal aortic surgery. Am J Surg 166:248–251, 1993

236. Caty MG, Guice KS, Oldham KT, Remick DG, Kunkel SI: Evidence for tumor necrosis factor-induced pulmonary microvascular injury after intestinal ischemia-reperfusion injury. Ann Surg 212:694–700, 1990

237. Sterpetti AV, Cucina A, Morena AR, Di Donna S, D'Angelo S, Cavallaro A, Stipa S: Shear stress increases the release of interleukin-1 and interleukin-6 by aortic endothelial cells. Surgery 114:911–914, 1993

238. Milner P, Bodin P, Loesch A, Burnstock G: Rapid release of endothelin and ATP from isolated aortic endothelial cells exposed to increased flow. Biochem Biophys Res Commun 170:649–656, 1990

239. Antonucci F, Bertolissi M, Calo L: Plasma endothelin and renal function during infrarenal aortic crossclamping and nifedipine infusion (letter). Lancet 336:1449, 1990

240. Bolger TB, Liard F, Jaramillo J: Tissue selectivity and calcium dependence of contractile responses to endothelin. J Cardiovasc Pharmacol 15:946–958, 1990

241. Miyauchi T, Tomobe Y, Shiba R, Ishikawa T, Yanagisawa M, Kimura S, Sugishita Y, Ito I, Goto K, Masaki T: Involvement of endothelin in the regulation of human vascular tonus: Potent vasoconstrictor effect and existence in endothelial cells. Circulation 81: 1874–1880, 1990

242. Kiowski W, Luscher F, Linder L, Buhler FR: Endothelin-1-induced vasoconstriction in humans. Circulation 83:469–475, 1991

243. Svensson LG, Hess KR, Coselli JS, Sfi HJ, Crawford ES: A prospective study of respiratory failure after high-risk surgery of the thoracoabdominal aorta. J Vasc Surg 14:271–282, 1991

244. Shenaq SA, Chelley JE, Karlberg H, Cohen E, Crawford ES: Use of nitroprusside during surgery for thoracoabdominal aortic aneurysm. Circulation 70:1–7, 1984

245. Kainuma M, Nishiwaki K, Shimada Y: Rise in pulmonary arterial pressure following release of aortic crossclamp in abdominal aortic aneurysmectomy. ANESTHESIOLOGY 69:257–260, 1988

246. Bowald S, Gerdin B: Pulmonary microembolization during and after aortic cross-clamping in heparinized and non-heparinized pigs. Acta Chir Scand 146:351–356, 1980

247. Bowald S, Eriksson I, Wiklund L: The influence of heparin on haemodynamics and blood gases during abdominal aortic surgery. Acta Chirurgica Scandinavica 146:333–341, 1980

248. Mathieson MA, Dunham B, Huval WV, Lelcuk S, Stemp LI, Valeri CR, Shepro D, Hechtman HB: Ischemia of the limb stimulates thromboxane production and myocardial depression. Surg Gynecol Obstet 157:500–504, 1983

249. Hocken D, Galvin D, Pate P, McCollum C: The influence of prostaglandin E1 on systemic and pulmonary haemodynamics after aortic surgery. Eur J Vasc Surg 3:19–23, 1989

250. Nakano J: Effects of prostaglandins E1, A1 and F2a on the coronary and peripheral circulations. Proc Soc Exp Biol Med 127: 1160–1163, 1968

251. Nakano J, Change ACK, Fisher RG: Effects of prostaglandins E1, E2, A1, A2, and F2a on the canine carotid arterial blood flow, cerebrospinal fluid pressure and intraocular pressure. J Neurosurg 38:32–39, 1973

252. Klausner JM, Paterson IS, Goldman G, Kobzik L, Valeri CR, Shepro D, Hechtman HB: Thromboxane A2 mediates increased pulmonary microvascular permeability following limb ischemia. Circ Res 64:1178–1189, 1988

253. Klausner JM, Paterson IS, Mannick JA, Valeri CR, Shepro D, Hechtman HB: Reperfusion pulmonary edema. JAMA 261:1030–1035, 1989

254. Weinbroum A, Nielsen VG, Gelman S, Matalon S, Skinner KA, Bradley E, Parks DA: Liver ischemia-reperfusion increases pulmonary permeability in the rat: Role of circulating xanthine oxidase. Am J Physiol (in press)

255. Adkinson D, Hollwarth ME, Benoit JN, Parks DA, McCord JM, Granger DN: Role of free radicals in ischemia-reperfusion injury to the liver. Acta Physiol Scand 126:101–108, 1986

256. Yokoyama Y, Beckman JS, Beckman TK, Wheat JK, Cash TG, Freeman BA, Parks DA: Circulating xanthine oxidase: Potential mediator of ischemic injury. Am J Physiol 258:G564–G570, 1990

257. Blaisdell FW, Lim RC Jr, Amberg JR, Choy SH, Hall AD, Thomas AN: Pulmonary microembolism: A cause of morbidity and death after major vascular surgery. Arch Surg 93:776–786, 1966

258. Mulcare RJ, Royster TS, Phillips LL: Intravascular coagulation in surgical procedures on the abdominal aorta. Surg Gynecol Obstet 143:730–734, 1976

259. Klausner JM, Anner H, Paterson IS, Kobzik L, Valeri CR, Shepro D, Hechtman HB: Lower torso ischemia induced lung injury is leukocyte dependent. Ann Surg 208:761–767, 1988

260. Tucker A, Weir EK, Reeves JT, Grover RF: Pulmonary microembolism: Attenuated pulmonary vasoconstriction with prostaglandin inhibitors and antihistamines. Prostaglandins 11:31–41, 1976

261. Todd MH, Forrest JB, Cragg DB: The effects of aspirin and methysergide on responses to clot-induced pulmonary embolism. Am Heart J 105:769–776, 1983

262. Hyman AL, Spannhake EW, Kadowitz PJ: State of the art: Prostaglandins and the lung. Am Rev Respir Dis 117:111–136, 1978

263. Poskitt KR, Irwin JTC, Lane IF, Karacagil S, McCollum CN: Pulmonary microembolization in experimental aortic surgery. Br J Surg 75:1207–1211, 1988

264. Morgan EL, Weigle WO, Hugli TE: Anaphylatoxin-mediated regulation of the immune response: C3a-mediated suppression of human and murine humoral immune responses. J Exp Med 155:1412–1426, 1982

265. McLoughlin GA, Grindlinger GA, Manny J, Valeri CR, Lipinski B, Mannick JA, Hechtman HB: Intrapulmonary clotting and fibrinolysis during abdominal aortic aneurysm surgery. Ann Surg 190:623–630, 1979

266. McCombs PR, Roberts B: Acute renal failure following resection of abdominal aortic aneurysm. Surg Gynecol Obstet 148: 175–178, 1979

267. Noirhomme P, Buche M, Louagie Y, Verhelst R, Matta A, Schoevaerdts JC: Ischemic complications of abdominal aortic surgery. J Cardiovasc Surg (Torino) 32:451–455, 1991

268. Breckwoldt WL, Mackey WC, Belkin M, O'Donnell TF: The effect of suprarenal cross-clamping on abdominal aortic aneurysm repair. Arch Surg 127:520–524, 1992

269. Kouchoukos N, Lell WA, Karp RB, Samuelson PN: Hemodynamic effects of aortic clamping and decompression with a temporary shunt for resection of the descending thoracic aorta. Surgery 85:25–30, 1979

270. Najafi H, Javid H, Hunter JA, Serry C, Monson DO: An update of treatment of aneurysms of the descending thoracic aorta. World J Surg 4:553–561, 1980

271. Crawford ES, Walker HSJ III, Salch SA, Normann NA: Graft replacement of aneurysm in descending thoracic aorta: Results without bypass or shunting. Surgery 89:73–85, 1981

272. Carlson DE, Karp RB, Kouchoukos NT: Surgical treatment of aneurysms of the descending thoracic aorta: An analysis of 85 patients. Ann Thorac Surg 35:58–62, 1983

273. Abbott WM, Austen WG: The reversal of renal corticol ischemia during aortic occlusion by mannitol. J Surg Res 16:482–489, 1974

274. Gamulin Z, Forster A, Morel D, Simonet F, Aymom E, Favre H: Effects of infra-renal aortic cross-clamping on renal hemodynamics in humans. ANESTHESIOLOGY 61:394–399, 1984

275. Awad RW, Barham WJ, Taylor DN, Woodward DA, Bullen BR: The effect of infrarenal aortic reconstruction on glomerular filtration rate and effective renal plasma flow. Eur J Vasc Surg 6:362–367, 1992

276. Oyama M, McNamara J, Suehiro A, Sue-Ako K: The effects of thoracic aortic cross-clamping and declamping on visceral organ blood flow. Ann Surg 197:459–463, 1983

277. Myers BD, Miller DC, Mehigan JT, Olcott C, Golbetz H, Robertson CR, Derby G, Spencer R, Friedman S: Nature of the renal injury following total renal ischemia in man. J Clin Invest 73:329–341, 1984

278. Joob AW, Dunn C, Miller E, Freedlender A, Kron IL: Effect of left atrial to left femoral artery bypass and renin-angiotensin system blockade on renal blood flow and function during and after thoracic aortic occlusion. J Vasc Surg 5:329–335, 1987

279. Riley AL, Alexander EA, Migdal S, Levinsky NG: The effect of ischemia on renal blood flow in the dog. Kidney Int 7:27–34, 1975

280. Szocs E, Laszlo K, Juszko S, Balint P: Pathomechanism of postischemic renal failure in the dog induced by temporary occlusion of the renal artery. Acta Physiol Acad Sci Hung 52:323–339, 1978

281. Paul MD, Mazer CD, Byrick RJ, Rose DK, Goldstein MB: Influence of mannitol and dopamine on renal function during elective infrarenal aortic clamping in man. Am J Nephrol 6:427–434, 1986

282. Colson P, Capdevilla X, Cuchet D, Saussine M, Seguin JR, Marty-Ane C, Roquefeuil B: Does choice of the anesthetic influence renal function during infrarenal aortic surgery? Anesth Analg 74:481–485, 1992

283. Colson P, Ribstein J, Seguin JR, Marty-Ane C, Roquefeuil B: Mechanisms of renal hemodynamic impairment during infrarenal aortic cross-clamping. Anesth Analg 75:18–23, 1992

284. Alpert RA, Roizen MF, Hamilton WK, Stoney RJ, Ehrenfeld WK, Poler SM, Wylie EJ: Intra-operative urinary output does not predict post-operative renal function. Surgery 95:707–711, 1984

285. Gamulin Z, Forster A, Simonet F, Aymonn E, Favre H: Effects of renal sympathetic blockade on renal hemodynamics in patients undergoing major aortic abdominal surgery. ANESTHESIOLOGY 65:688–692, 1986

286. Stein M, James PM, Kelly J, Brown D, Shircliffe AC, Patterson WE: Renal protection during aortic cross-clamping. Am Surg 38:681–689, 1972

287. Reid IA, Schrier RW, Earley LE: An effect of extrarenal beta adrenergic stimulation on the release of renin. J Clin Invest 51:1861–1869, 1972

288. Gutmann FD, Tagawa H, Haber E, Barger AC: Renal arterial pressure, renin secretion, and blood pressure control in trained dogs. Am J Physiol 224:66–72, 1973

289. Brezis M, Rosen S, Silva P, Epstein FH: Renal ischemia: A new perspective. Kidney Int 26:375–383, 1984

290. Brezis M, Rosen SN, Epstein FH: The pathophysiological implications of medullary hypoxia. Am J Kidney Dis 13:253–258, 1989

291. Pass LJ, Eberhart RC, Brown JC, Rohn GN, Estrera AS: The effect of mannitol and dopamine on the renal response to thoracic aortic cross-clamping. J Thorac Cardiovasc Surg 95:608–612, 1988

292. Cantarovich F, Galli C, Benedetti L, Chena C, Castro L, Correa C, Loredo JP, Fernandez JC, Locatelli A, Tizado J: High dose furosemide in established acute renal failure. Br Med J 4:449–450, 1973

293. Thompson JE, Vollman RW, Austin DJ, Kartchner MM: Prevention of hypotensive and renal complications of aortic surgery using balanced salt solution: Thirteen year experience with 670 cases. Ann Surg 167:767–778, 1968

294. Bush HL, Huse JB, Johnson WC, O'Hara ET, Nabseth DC: Prevention of renal insufficiency after abdominal aortic aneurysm resection by optimal volume loading. Arch Surg 116:1517–1524, 1981

295. Colson P, Capdevilla X, Barlet H, Seguin JR, Marty-Ane C, Roquefeuil B: Effects of halothane and isoflurane on transient renal dysfunction associated with infrarenal aortic cross-clamping. J Cardiothorac Vasc Anesth 6:295–298, 1992

296. Carrel A: On the experimental surgery of the thoracic aorta and the heart. Ann Surg 52:83–95, 1910

297. Najafi H, Javid H, Hunter JA, Serry C, Monson D: Descending aortic aneurysmectomy without adjuncts to avoid ischemia. Ann Thorac Surg 30:326–335, 1980

298. Brewer LA, Fosburg RG, Mulder GA, Verska JJ: Spinal cord complications following surgery for coarctation of the aorta. J Thorac Cardiovasc Surg 64:368–379, 1972

299. Crawford ES, Rubio PA: Reappraisal of adjuncts to avoid ischemia in the treatment of aneurysms of the descending thoracic aorta. J Thorac Cardiovasc Surg 66:693–703, 1973

300. DeBakey ME, McCollum CH, Graham JM: Surgical treatment of aneurysms of the descending thoracic aorta. J Cardiovasc Surg (Torino) 19:571–576, 1978

301. Livesay JJ, Cooley DA, Ventemiglia RA, Montero CG, Warrian RK, Brown DM, Duncan JM: Surgical experience in descending thoracic aneurysmectomy with and without adjuncts to avoid ischemia. Ann Thorac Surg 39:37–45, 1985

302. Jex RK, Schaff HV, Piehler JM, King RM, Orszulak TA, Danielson GK, Pairolero PC, Pluth JR, Ilstrup D: Early and late results following repair of dissections of the descending thoracic aorta. J Vasc Surg 3:226–327, 1986

303. Laschinger JC, Izumoto H, Kouchoukos NT: Evolving concepts in prevention of spinal cord injury during operations on the descending thoracic and thoracoabdominal aorta. Ann Thorac Surg 44:667–674, 1987

304. Hollier LH: Protecting the brain and spinal cord. J Vasc Surg 5:524–528, 1987

305. McCullough JL, Hollier LH, Nugent M: Paraplegia after thoracic aortic occlusion: Influence of cerebrospinal fluid drainage. J Vasc Surg 7:153–160, 1988

306. Svensson LG, Stewart RW, Cosgrove DM, Lytle BW, Antunes MD, Beven EG, Furlan AJ, Gottlieb A, Grum DF, Hinder RA, Schoenwald P, Lewis BS, Salgado A, Loop FD: Intrathecal papaverine for the prevention of paraplegia after operation on the thoracic or thoracoabdominal aorta. J Thorac Cardiovasc Surg 96:823–829, 1988

307. Bower TC, Murray MJ, Gloviczki P, Yaksh TL, Hollier LH, Pairolero PC: Effects of thoracic aorta occlusion and cerebrospinal fluid drainage on regional spinal cord blood flow in dogs: Correlation with neurologic outcome. J Vasc Surg 9:135–144, 1989

308. Feguson LRJ, Bergan JJ, Conn J, Yao JST: Spinal ischaemia following abdominal aortic surgery. Ann Surg 181:267–272, 1975

309. Adams HA, van Geertruyden HH: Neurologic complications of aortic surgery. Ann Surg 144:574–610, 1956

310. Hands LJ, Collin J, Lamont P: Observed incidence of paraplegia after infrarenal aortic aneurysm repair. Br J Surg 78:999–1000, 1991

311. Djindjian R: Arteriography of the spinal cord. Am J Roentgenol 107:461–478, 1969

312. Kadyi H: Uber die Blutgefasse des menschlichen Ruckenmarkes. Lemberg, Gubryonwicz and Schmidt, 1889, pp 21–57

313. Svensson LG, Von Ritter C, Groeneveld HT, Rickards ES, Hunter SJS, Robinson MF, Hinder RA: Cross-clamping of the thoracic aorta: Influence of aortic shunts, laminectomy, papaverine, calcium channel blocker, allopurinol, and superoxide dismutase on spinal cord blood flow and paraplegia in baboons. Ann Surg 204:38–47, 1986

314. Hara M, Lipin RJ: Spinal cord injury following resection of abdominal aortic aneurysm. AMA Arch Surg 80:75/419–79/423, 1960

315. Coupland GAE, Reeve TS: Paraplegia: A complication of excision of abdominal aortic aneurysm. Surgery 64:878–881, 1968

316. Skillman JJ, Zervas NT, Weintraub RM, Mayman CI: Paraplegia after resection of aneurysms of the abdominal aorta. N Engl J Med 281:422–424, 1969

317. Grace RR, Mattox KL: Anterior spinal artery syndrome following abdominal aortic aneurysmectomy. Arch Surg 112:813–815, 1977

318. Neilsen BP: Ischaemic injury to the spinal cord as a complication to abdominal aortic surgery. Acta Chirurgica Scandinavica 151:433–435, 1985

319. Szilagyi DE, Hageman JH, Smith RF, Elliott JP: Spinal cord damage in surgery of the abdominal aorta. Surgery 83:38–56, 1978

320. Shenaq SA, Svensson LG: Paraplegia following aortic surgery. J Cardiothorac Vasc Anesth 7:81–94, 1993

321. Katz NM, Blackstone EH, Kirklin JW, Karp RB: Incremental risk factors for spinal cord injury following operation for acute traumatic aortic transection. J Thorac Cardiovasc Surg 81:669–674, 1981

322. Berendes JN, Bredee JJ, Schipperheyn JJ, Mashhour YAS: Mechanisms of spinal cord injury after cross-clamping of the descending thoracic aorta. Circulation 66:112–116, 1982

323. D'Ambra MN, Dewhirst W, Jacobs M, Burgus B, Borges L, Hilgenberg A: Cross-clamping the thoracic aorta: Effect on intracranial pressure. Circulation 78(suppl 3):198–202, 1988

324. Woloszyn TT, Marini CP, Coons MS, Nathan IM, Basu S, Acinapura AJ, Cunningham JN: Cerebrospinal fluid drainage and steroids provide better spinal cord protection during aortic cross-clamping than does either treatment alone. Ann Thorac Surg 49:79–83, 1990

325. Marini CP, Grubbs PE, Toporoff B, Woloszyn TT, Coons MS, Acinapura AJ, Cunningham JN: Effect of sodium nitroprusside on spinal cord perfusion and paraplegia during aortic cross-clamping. Ann Thorac Surg 47:379–383, 1989

326. Piano G, Gewertz BL: Mechanism of increased cerebrospinal fluid pressure with thoracic aortic occlusion. J Vasc Surg 11:695–701, 1990

327. Mutch WAC, Thomson IR, Tskey JM, Thiessen D, Rosenbloom M: Phlebotomy reverses the hemodynamic consequences of thoracic aortic cross-clamping: Relationships between central venous pressure and cerebrospinal fluid pressure. ANESTHESIOLOGY 74:320–324, 1991

328. Elmore JR, Gloviczki P, Harper CM, Murray MJ, Wu QH, Bower TC, Pairolero PC, Naessens JM, Daube JR: Spinal cord injury in experimental thoracic aortic occlusion: Investigation of combined methods of protection. J Vasc Surg 15:789–799, 1992

329. Miyamoto K, Veno A, Wada T, Kimoto S: A new and simple method of preventing spinal cord damage following temporary occlusion of the thoracic aorta by draining the cerebrospinal fluid. J Cardiovasc Surg (Torino) 16:188–197, 1960

330. Blaisdell FW, Cooley DA: The mechanism of paraplegia after temporary thoracic aortic occlusion and its relationship to spinal fluid pressure. Surgery 51:351–355, 1962

331. Wadouh F: New surgical techniques for the prevention of paraplegia during aortic surgery. Thorac Cardiovasc Surg 40:26–32, 1992

332. Murray MJ, Bower TC, Oliver WC, Werner E, Gloviczki P: Effects of cerebrospinal fluid drainage in patients undergoing thoracic and thoracoabdominal aortic surgery. J Cardiothorac Vasc Anesth 7: 266–272, 1993

333. Shine T, Nugent M: Sodium nitroprusside decreases spinal cord perfusion pressure during descending thoracic aortic cross-clamping in the dog. J Cardiothorac Anesth 4:185–193, 1990

334. Granke K, Hollier LH, Zdrahal P, Moore W: Longitudinal study of cerebral spinal fluid drainage in polyethylene glycolconjugated superoxide dismutase in paraplegia associated with thoracic aortic cross-clamping. J Vasc Surg 13:615–621, 1991

335. Qayumi AK, Janusz MT, Jamieson WRE, Lyster DM: Pharmacologic interventions for prevention of spinal cord injury caused by aortic crossclamping. J Thorac Cardiovasc Surg 104:256–261, 1992

336. Agee JM, Flanagan T, Blackbourne LH, Kron IL, Tribble CG: Reducing postischemic paraplegia using conjugated superoxide dismutase. Ann Thorac Surg 51:911–915, 1991

337. Laschinger JC, Cunningham JN, Cooper MM, Krieger K, Nathan IM, Spencer FC: Prevention of ischemic spinal cord injury following aortic cross-clamping: Use of corticosteroids. Ann Thorac Surg 38:500–507, 1984

338. Grinstein-Nadler E, Bottoms GD: Dexamethasone treatment during hemorrhage shock: Changes in extracellular fluid volume and cell membrane transport. Am J Vet Res 37:1337–1343, 1976

339. Braughler JM, Hall ED: Correlation of methylprednisolone levels in cat spinal cord with its effects on $(Na^+ + K^+)$-ATPase, lipid peroxidation and alpha motor neuron function. J Neurosurg 57:838–844, 1982

340. Hall ED, Braughler JM: Effects of intravenous methylprednisolone on spinal cord lipid peroxidation and $(N^+ + K^+)$-ATPase activity. J Neurosurg 57:247–253, 1982

341. LeMay DR, Neal S, Neal S, Zelenock GB, D'Alecy LG: Paraplegia in the rat induced by aortic cross-clamping: Model characterization and glucose exacerbation of neurologic deficit. J Vasc Surg 6:383–390, 1987

342. Pontius RG, Brockman L, Hardy EG, Cooley DA, DeBakey ME: The use of hypothermia in the prevention of paraplegia following temporary aortic occlusion: Experimental observations. Surgery 36: 33–38, 1954

343. Coles JG, Wilson GJ, Sima AF, Klement P, Tait GA, Williams WG, Baird RJ: Intraoperative management of the thoracic aortic aneurysm: Experimental evaluation of perfusion cooling of the spinal cord. J Thorac Cardiovasc Surg 85:292–299, 1983

344. Colon R, Fraizer OH, Cooley DA, McAllister HA: Hypothermic regional perfusion for protection of the spinal cord during periods of ischemia. Ann Thorac Surg 43:639–643, 1987

345. Berguer R, Porto J, Fedoronko B, Dragovic L: Selective deep hypothermia of the spinal cord prevents paraplegia after aortic cross-clamping in the dog model. J Vasc Surg 15:62–72, 1992

346. Svensson LG, Crawford ES, Patel V, McLean TR, Jones JW, DeBakey ME: Spinal oxygenation, blood supply localization, cooling, and function with aortic clamping. Ann Thorac Surg 54:74–79, 1992

347. Marsala M, Vanicky I, Galik J, Radonak J, Kundrat I, Marsala J: Panmyelic epidural cooling protects against ischemic spinal cord damage. J Surg Res 55:21–31, 1993

348. Nylander WA, Plunkett RJ, Hammon JW: Thiopental modification of spinal cord injury in the dog. Ann Thorac Surg 33:64–68, 1982

349. Michenfelder JD, Milde JH, Sundt TM: Cerebral protection by barbiturate anesthesia: Use after middle cerebral artery occlusion in Java monkeys. Arch Neurol 33:345–350, 1976

350. Demopoulos HB, Flamm ES, Seligman ML, Jorgensen E, Ransohoff J: Antioxidant effects of barbiturates in model membranes undergoing free radical damage. Acta Neurol Scand Suppl 64:152–153, 1977

351. Naslund TC, Hollier LH, Money SR, Facundus EC, Skenderis BS: Protecting the ischemic spinal cord during aortic clamping. Ann Surg 215:409–416, 1992

352. Breckwoldt WL, Genco CM, Connolly RJ, Cleveland Rj, Diehl JT: Spinal cord protection during aortic occlusion: Efficacy of intrathecal tetracaine. Ann Thorac Surg 51:959–963, 1991

353. Robertson CS, Foltz R, Grossman RG, Goodman JC: Protection against experimental ischemic spinal cord injury. J Neurosurg 64: 633–642, 1986

354. Hollier LH, Money SR, Naslund TC, Procter CD, Buhrman WC, Marino RJ, Harmon DE, Kazmier FJ: Risk of spinal cord dysfunction in patients undergoing thoracoabdominal aortic replacement. Am J Surg 164:210–214, 1992

355. Picone AL, Green RM, Ricotta JR, May AG, DeWeese JA: Spinal cord ischaemia following operations on the abdominal aorta. J Vasc Surg 3:94–103, 1986

356. Golden GT, Sears HF, Wellons HA, Muller WH: Paraplegia complicating resections of aneurysms of the infrarenal abdominal aorta. Surgery 73:91–96, 1973

357. Ernst CB, Hagihara PF, Daugherty ME, Sachatello CR, Griffen WO: Ischemic colitis incidence following abdominal aortic reconstruction: A prospective study. Surgery 80:417–421, 1976

358. Hagihara FP: Incidence of ischemic colitis following abdominal aortic reconstruction. Surg Gynecol Obstet 149:571–573, 1979

359. Ruckert RF, Buchmann P: Ischamische Colon und Rectumnekrosen nach Resektion der Aorta abdominalis. Chirurg 53:556–562, 1982

360. Schroeder T: Ischemic colitis complicating reconstruction of the abdominal aorta. Surg Gynecol Obstet 160:299–303, 1985

361. Ouriel K, Fiore WM, Geary JE: Detection of occult colonic ischemia during aortic procedures: Use of an intraoperative photoplethysmographic technique. J Vasc Surg 7:5–9, 1988

362. Jonung T, Ribbe E, Norgren L, Thorvinger B, Thorne J: Visceral ischemia following aortic surgery. Vasa 20:125–131, 1991