Dopexamine hydrochloride does not modify hemodynamic response or tissue oxygenation or gut permeability during abdominal aortic surgery

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Purpose: To assess the effects of intraoperative infusion of dopexamine (a DA-1 and B2 adrenoreceptor agonist) on hemodynamic function, tissue oxygen delivery and consumption, splanchnic perfusion and gut permeability following aortic cross- clamp and release.

Methods: In a randomised double blind controlled trial 24 patients scheduled for elective infrarenal abdominal aortic aneurysm repair were studied in two centres and were assigned to one of two treatment groups. *Group I* received a dopexamine infusion starting at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintaining a stable heart rate; *Group II* received a placebo infusion titrated in the same volumes following induction of anesthesia. Measured and derived hemodynamic data, tissue oxygen delivery and extraction and gut permeability were recorded at set time points throughout the procedure.

Results: Dopexamine infusion (0.5 -2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was associated with enhanced hemodynamic function (MAP 65 ± 5.5 *vs* 92 ± 5.7 mm Hg, $P = < 0.05$) only during the period of aortic cross clamping. However, during the most part of infrarenal abdominal aortic surgery, dopexamine did not reduce systemic vascular resistance index, mean arterial pressure nor oxygen extraction compared with the control group. The lactulose/ rhamnose permeation ratio was elevated above normal in both groups (0.22 and 0.29 in groups I and II respectively).

Conclusions: Dopexamine infusion (0.5 -2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) did not enhance hemodynamic function and tissue oxygenation values during elective infrarenal abdominal aortic aneurysm repair.

Objectif : Évaluer les effets d'une perfusion peropératoire de dopexamine, un agoniste des adrénorécepteurs DA-1 et B2, sur l'hémodynamie, l'apport et la consommation d'oxygène tissulaire, la perfusion splanchnique et la perméabilité intestinale à la suite d'un clampage total de l'aorte et de son retrait.

Méthode : Il s'agit d'un essai randomisé, contrôlé et à double insu auprès de 24 patients, provenant de deux centres et répartis en deux groupes, qui ont subi la réparation d'un anévrysme aortique abdominal sous-rénal. Le groupe I a reçu une perfusion de dopexamine amorcée à 0,5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, augmentée à 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, maintenant une fréquence cardiaque stable; le groupe II a reçu une perfusion placebo de même volume après l'induction de l'anesthésie. Les données hémodynamiques mesurées et dérivées, l'apport et la consommation d'oxygène tissulaire et la perméabilité intestinale ont été notés à des moments de mesure déterminés au cours de l'intervention.

Résultats : La perfusion de dopexamine (0,5 -2$\mu g \cdot kg^{-1} \cdot min^{-1}$) a stimulé la fonction hémodynamique (TAM 65 ± 5,5 *vs* 92 ± 5,7 mm Hg, $P = < 0,05$) pendant le clampage aortique seulement. Cependant, pendant la majeure partie de l'intervention aortique abdominale sous-rénale, la dopexamine n'a pas réduit l'indice de résistance vasculaire générale, la tension artérielle moyenne ou la consommation d'oxygène, ces données étant comparées avec celles du groupe témoin. Le ratio de dissémination de lactulose / rhamnose s'est élevé au-dessus de la normale dans les deux groupes (0,22 et 0,29 dans les groupes I et II respectivement).

Conclusion : La perfusion de dopexamine (0,5 -2$\mu g \cdot kg^{-1} \cdot min^{-1}$) n'a pas amélioré l'hémodynamie ni haussé les valeurs d'oxygénation tissulaire pendant la réparation d'un anévrysme aortique abdominal sous-rénal.

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AORTIC cross clamping reduces or abolishes blood flow to the pelvis and lower extremities distal to the clamp.[1] The cardiovascular changes occurring during aortic cross clamping have been well described.[2–4] In general, the hemodynamic responses to aortic cross clamping consist of an increase in arterial pressure and systemic vascular resistance with no change in heart rate.[5] Enhanced impedance to aortic flow and increased left ventricular end- systolic wall stress have been implicated in post aortic cross clamp hypertension.[6–7] Various investigators have reported unchanged[8] or increased cardiac filling pressures.[9] Increases in right and left sided filling pressures during aortic cross clamping may result from blood volume distribution from the central vasculature in the lower part of the body to the upper body or may represent an increase in afterload, with subsequent increase in the volume of blood remaining in the left ventricle at the end of systole.[10]

The substantial differences in hemodynamic responses observed after supra- celiac *vs* infra-renal aortic cross clamp may result, in part, from different degrees and patterns of blood volume redistribution.[11] If the aorta is occluded below the splanchnic system, blood may shift into the splanchnic system or into other tissues proximal to the clamp. The distribution of this blood between the splanchnic and nonsplanchnic vasculature may determine changes in cardiac preload. Variations in blood volume status or splanchnic vascular tone resulting from differences in fluid load, depth of anesthesia, pharmacokinetics of the anesthetic agents and other factors may effect the degree and pattern of blood volume redistribution.[10]

Increasing duration of cross clamp may be associated with the release and accumulation of vasoactive substances and may play a role in the time-dependent reductions in cardiac output and increases in systemic vascular resistance during aortic cross clamping.[12] Attention has recently focused on the adequacy of splanchnic bed perfusion during acute changes in cardiac output.[13] Gut ischemia increases the permeability of the gastrointestinal mucosa and thereby allows bacteria and endotoxin within the gut lumen to enter the systemic circulation, resulting in sepsis syndrome and ultimately multiorgan failure.[14] Relative hypoperfusion of the liver, gut and related organs is the putative mechanism of multiple organ dysfunction following abdominal aortic surgery.[15–16]

Infrarenal aortic cross clamping may be associated with decreases in splanchnic blood flow if cardiac output is reduced. Decreases in splanchnic and gastrointestinal blood flow may result in tissue hypoxia, anaerobic glycolysis and acidosis. Dopexamine, a dopaminergic (DA-1) and beta-2 adrenoreceptor agonist has been reported to increase splanchnic blood flow in patients with chronic congestive heart failure.[17] This effect is achieved primarily through splanchnic vasodilatation, although a mild positive inotropic effect may be exerted indirectly at beta-1 adrenoreceptors.[18] Inhibition of neuronal re-uptake of endogenous noradrenaline has also been suggested.[19]

The objectives of this study were to assess the effects of dopexamine infusion on hemodynamic function, tissue oxygen delivery and consumption and gut permeability following aortic cross- clamp and release.

Methods and materials

Following institutional Ethics Committee approval and informed patient consent, 24 patients scheduled for elective infrarenal abdominal aortic aneurysm repair (ASA physical status II-IV) were studied in two centres - Beaumont Hospital, Dublin and St. James's Hospital, Leeds. The study was carried out according to the instructions of the Ethics Committee. Twelve patients were recruited in each centre. The study design was prospective, randomized and double-blinded. An assistant randomly selected the agent to be used (dopexamine hydrochloride or placebo) by drawing a piece of paper from an envelope. Exclusion criteria included a history of gastrointestinal pathology and pre-operative hemodynamic instability (mean arterial pressure < 70 mmHg).

Preoperative cardiac status was assessed by physical examination, resting 12-lead ECG, chest roentgenogram, and echocardiographic determination of left ventricular ejection fraction. Patients were randomly assigned to two treatment groups. Based on previous work,[13,17] we elected to use an infusion of dopexamine hydrochloride commencing at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ that was increased up to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ while a stable heart rate was maintained.

Patients in *Group I* received a dopexamine infusion following induction of anesthesia commencing at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and increased by 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 15 min up to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until the end of surgery. Those in *Group II* received a saline infusion titrated in the same volumes and at the same time intervals. Measured and derived hemodynamic data, tissue oxygen delivery and extraction and gut permeability were recorded at set time points throughout the procedure.

None of the 24 patients received H_2 antagonists preoperatively. A standardised general anesthetic technique was used for all patients. Fentanyl, 5-10 $\mu g \cdot kg^{-1}$, followed by 3-4 $mg \cdot kg^{-1}$ thiopental, was administered to

induce anesthesia. Vecuronium, 0.1 mg·kg^{-1}, was given to facilitate tracheal intubation. Controlled normocapnic ventilation was commenced with N_2O / O_2 and isoflurane 0.5-1.0% with incremental doses of fentanyl. Pulmonary artery occlusion pressure was maintained between 10 and 15 mmHg with crystalloid or colloid infusions. Hypertension >25% of baseline was controlled by nitroglycerin infusion. Blood loss >15% of the estimated blood volume or documented hematocrit <26% were treated with red cell concentrate infusions.

A radial arterial catheter was inserted under local anesthesia before induction of general anesthesia. A pulmonary artery catheter was inserted through the right internal jugular vein following induction of anesthesia. The pulmonary and radial arterial catheters were measured with reference to the mid-axillary line. Heart rate was measured by the electrocardiogram (Merlin, Hewlett Packard, Blacknell UK). Central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and mean arterial pressure (MAP) were measured using standard pressure transducers and monitors (Hewlett-Packard M1166A, Andover, Mass) and were recorded at end-expiration.

Baseline cardiac index (CI), oxygen delivery index (DO_2) and oxygen consumption (VO_2) were calculated under stable non operating conditions after induction of anesthesia and at specific time points throughout the procedure using the following formula;

$DO_2 = CI \times CaO_2 \times 10$: $VO_2 = CI \times CvO_2 \times 10$:
$OER = CaO_2 - CvO_2 / CaO_2$
$CaO_2 / CvO_2 = ([\text{Hemoglobin}] \times 1.34 \times \%\ O_2\ \text{Saturation}) + (PO_2 \times 0.003)$

Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$) was measured by thermodilution in triplicate (ice cold 10 ml bolus of dextrose 5%) after withdrawal of arterial and mixed venous blood samples. Arterial and mixed venous blood samples were withdrawn anaerobically and used for the measurement of oxygen and carbon dioxide tensions (Instrumentation Laboratory 1312 blood gas analyser, Warrington, England), and oxygen saturation and hemoglobin concentration (Instrumentation Laboratory 282 cooximeter).

Hemodynamic and oxygen transport variables were obtained from measurements after arterial and pulmonary artery catheterization at the following times: T1- following induction of anesthesia; T2- five minutes before aortic cross clamp; T3- 30 min following aortic cross clamp; T4- 60 min following aortic cross clamp; T5- five minutes after aortic cross clamp release; T6- 30 min after aortic cross clamp release; T7 and T8, one, and two hours after aortic cross clamp release respectively.

All patients received a 5 g bolus of lactulose and a 1 g bolus of L-rhamnose via the naso-gastric tube at the end of surgery. The urine bag was emptied and the collection begun. The total urine volume for five hours was noted and a 20 ml sample preserved with methiorlate was collected for further sugar concentration analysis. The percentage recovery of each sugar was calculated. The percentage recovery lactulose to L-rhamnose ratio was also calculated. Percentage recovery = sugar concentration × urine volume ×100 times the amount of sugar given enterally. The normal range of the percentage recovery of lactulose to L-rhamnose ratio is 0-0.05.

Results are expressed as mean ± standard deviation or as group percentages. Comparisons of differences between groups were made using the two-tailed Student t test for unpaired data. A P value < 0.05) was considered significant.

Results

The mean age of patients in Groups I and II was 75 ± 5 yr and 73 ± 4 yr respectively. Mean body surface area was similar in both groups. The male / female ratio was 10 / 2 in Group I and 11 / 1 in Group II. Preoperative cardiac evaluation indicated that three patients in each group had a previous history of myocardial infarction and, similarly, three patients had a history of congestive cardiac failure. Ten patients in Group I and nine patients in Group II had resting left ventricular fractions greater than or equal to 40 % (Table I).

The mean duration of surgery for patients in Groups I and II was 224 (± 88) and 241 (± 109) min respectively (Table II). There were no differences between the two groups in terms of duration of cross clamp, volumes of intravenous fluid administered and blood volume transfused. One patient died in each group within 48 hr of surgery - one in the control group, with a history of previous myocardial infarct, sustained a myocardial infarction with severe left ventricular failure two days after surgery and a patient in the dopexamine group, with severe pre-existing lung disease, died as a consequence of postoperative respiratory and multisystem organ failure.

Changes in heart rate (HR) and mean arterial pressure (MAP) following induction of anesthesia, aortic cross clamp and release are included in Figures 1 and 2. The horizontal arrow in each of the figures provided indicates the duration of dopexamine / saline drug infusion. The rectangular areas represent periods of aortic cross clamping. The mean arterial pressure was lower in the dopexamine group (Group I) than in the control (Group II). This MAP reduction was statistically significant during the cross clamp period (65 ± 5.5 *vs* 92 ±

TABLE I Patient demographic data and past cardiac medical history (mean (SD or range) or number). No significant difference in patient and demographic data.

	Group I (n=12)	*Group II (n=12)*
Age; yr	75 (68-84)	73 (66-79)
BSA; m^2	1.8 (1.5-2.1)	1.8 (1.5-2.4)
Sex; M / F	10:2	11:1
Echocardiographic left ventricular fraction		
>40%	10	9
< 40%	2	3
Previous Myocardial Infarction	3	3
Congestive Cardiac Failure	3	3

BSA = Body Surface Area.

TABLE II Perioperative surgical details, fluid administration and patient outcome. Results are expressed as mean ± SD [range].

	Group I (n=12)	*Group II (n=12)*
Duration of cross clamp (min)	61 ±29 [30-125]	86 ±58 [40-225]
Crystalloids administered (Litres)	4 ±0.86 [2.5-5]	4.25 ±0.78 [3-5]
Colloid administered (500 ml units)	1.6 ±0.4 [1-2]	1.3 ±0.8 [0-3]
Units of blood transfused	5.6 ±1.5 [2-7]	5 ±2.8 [0-12]
Duration of surgery (mins)	224 ±88 [120-450]	241 ±109 [120-495]
Morbidity / mortality within 48 hr of surgery		
	Deaths 1	1

TABLE III Sugar studies. Saccharide recovery (in urine) from groups I and II, expressed as a percentage of the enterally administered dose. Results expressed as means (SD). No significant differences between the two groups. The lactulose / rhamnose ratios were markedly elevated above normal mean values.

Sugar	*Group I*	*Group II*	*Normal mean*
Lactulose %	0.3 ± 0.33	0.32 ± 0.27	0.315
Rhamnose %	3.3 ± 3.6	1.36 ± 0.8	11.88
Lactulose / rhamnose ratio	0.22 ± 0.21	0.29 ± 0.18	0 - 0.05

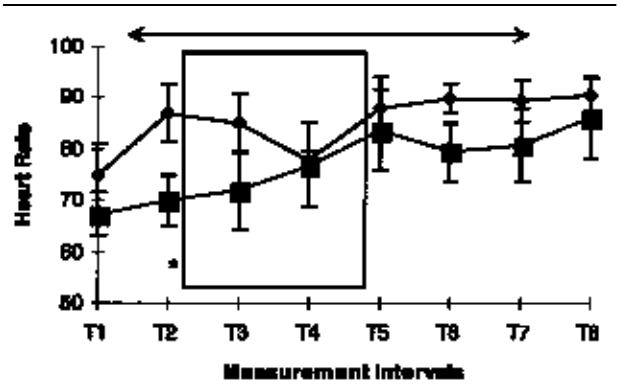

FIGURE 1 Changes in heart rate in Groups I and II throughout the study period. Dopexamine / saline drug infusion is given by the horizontal arrow. The rectangle represents the period of cross clamping. ◆= Group I and ■ = Group II. * $P < 0.05$. Data are mean (sem).

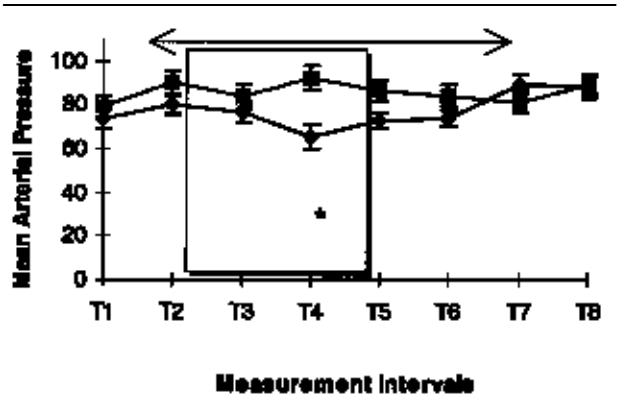

FIGURE 2 Changes in mean arterial pressure in Groups I and II throughout the study period. Dopexamine / saline drug infusion is given by the horizontal arrow. The rectangle represents the period of cross clamping. ◆ = Group I and ■ = Group II. * $P < 0.05$. Data are mean (sem).

5.7 mm Hg, $P < 0.05$). Mean heart rates tended to be higher in the dopexamine treated group throughout the study period. This increased heart rate response was only statistically significant compared with controls prior to cross clamping (87 ± 5 *vs* 69 ± 4, $P < 0.05$).

Calculated systemic vascular resistance index (SVRI) values at the various time points are represented in Figure 3. SVRI, an indicator of left ventricular afterload,[1 2] was reduced in the dopexamine group during cross clamp (1183 ± 174 *vs* 2954 ± 403, $P < 0.05$). There was no difference in VO_2 values between the two groups. The oxygen extraction ratio (Figure 4) was lower in group I during the cross clamp period (17.2 ± 2.4 *vs* 25.1 ± 2.6, $P < 0.05$).

Gastrointestinal sugar absorption / permeability data are included in Table III. The laboratory reference values for percentage recovery of lactulose and L-rhamnose are 0.315% and 11.88% respectively. Renal rhamnose levels were markedly reduced compared with

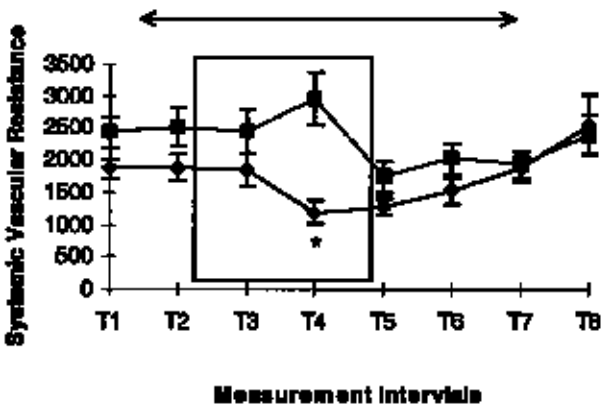

FIGURE 3 Changes in systemic vascular resistance in Groups I and II throughout the study period. Dopexamine / saline drug infusion is given by the horizontal arrow. The rectangle represents the period of cross clamping. ◆ = Group I and ■ = Group II. * $P < 0.05$. Data are mean (sem).

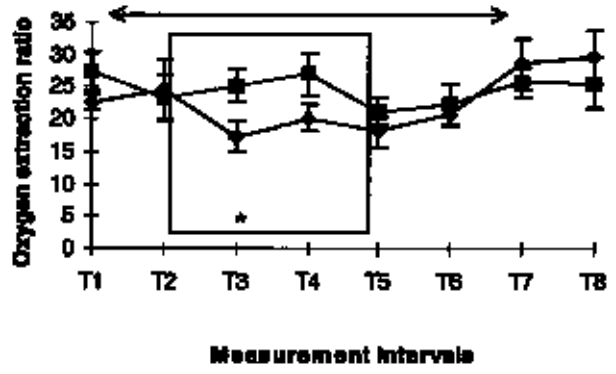

FIGURE 4 Changes in oxygen extraction ratios in Groups I and II throughout the study period. Dopexamine / saline drug infusion is given by the horizontal arrow. The rectangle represents the period of cross clamping. ◆ = Group I and ■ = Group II. * $P < 0.05$. Data are mean (sem).

reference values in the dopexamine treated and control group. However, there were no differences between the groups. The lactulose / rhamnose permeation ratio is normally 0 - 0.05. This ratio was elevated to 0.22 and 0.29 in groups I and II respectively, indicating poor gastrointestinal permeability following surgery.

Discussion

A dopexamine infusion, administered during elective abdominal aortic aneurysm repair, was associated with enhanced hemodynamic function only during the period of aortic cross clamping. During the most part of infrarenal abdominal aortic surgery, dopexamine did not reduce systemic vascular resistance index, mean arterial pressure or oxygen extraction compared with the control group. On a regional level, dopexamine hydrochloride did not improve splanchnic blood flow. Gastrointestinal sugar absorption / permeability assessment confirmed that renal L-rhamnose levels were reduced compared with reference values in both the dopexamine and control group.

Both groups received similar volumes of intravenous fluids and blood products intraoperatively. An increased heart rate was observed associated with dopexamine infused in the range 0.5-2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. There was no ECG evidence of ST segment depression in either group. Nonetheless, tachycardia associated with dopexamine infusion is a concern in a patient population with a high incidence of overt and covert ischaemic heart disease.[6]

Dopexamine hydrochloride is a synthetic dopaminergic (DA-1) and beta-2 adrenoreceptor agonist. As such, it has been reported to be one third as potent as dopamine in stimulating DA-1 receptors but 60 times more potent as a beta-2 adrenoceptor agonist.[18] Unlike dopamine, it has weak beta-1 adrenoreceptor agonist properties and does not stimulate vascular alpha-1 adrenoceptors in higher doses. Human studies, in both healthy volunteers and patients with hypertension, suggest that dopexamine hydrochloride in doses >0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increases cardiac output as a result of increased stroke volume and heart rate.[20]

Boyd and colleagues reported a dopexamine induced increased cardiac output and oxygen delivery in a series of sixteen high-risk surgical patients.[21] The enhanced hemodynamic function and tissue oxygenation observed in their study was attributed to vasodilatory and mild inotropic properties. In a more extensive study involving 107 high-risk surgical patients, the same investigators reported a 75% reduction in mortality and halving of the mean number of complications per patient treated with dopexamine hydrochloride.[22]

Global tissue oxygen delivery within normal or enhanced physiological ranges does not address the issue of regional variations in oxygen delivery and consumption, particularly splanchnic circulation. Permeability refers to the ease with which the intestinal mucosal surface can be penetrated by diffusion of specific constituents. Permeability remains unchanged in healthy bowel. Estimates of permeability can be made through measurements of permeation of these two markers, lactulose and L-rhamnose. Lactulose is a

nonhydrolyzable disaccharide that permeates the intercellar tight junctions, while L-rhamnose, a smaller molecule, is absorbed mainly via the transcellular route.[2,3] The integrity of the tight intercellur junctions between the enterocytes is maintained by active control of ATP-dependant intracellur mechanism. During episodes of hypoperfusion, the integrity of these junctions and thus of the mucosal barrier may become impaired. We observed a rise in lactulose absorption relative to L-rhamnose and an increase in gut permeability following abdominal aortic surgery. This increase in gut permeability following cross clamp release is similar to Sinclair's study of 20 patients following cardiopulmonary bypass.[23] They suggested that increased gut permeability was a reflection of small bowel blood supply, which is from the superior mesenteric artery, and that gastric tonometry reflected blood flow specifically to the stomach via the coeliac artery. Furthermore, the presence of atheromatous disease may contribute to the disruption of blood flow in one or other of these arteries, thereby creating local ischemia exacerbated by low systemic perfusion pressures during and after coronary artery bypass. Similarly, in our study, these changes may occur during and after abdominal aortic cross clamping. The result of such a process would be to create areas of localised ischaemia that could effect the L / R ratio. Changes in the differential absorption of ingested sugars may also reflect upper gastrointestinal mucosal damage / or impairment in the uptake, transfer or renal clearance of the monosaccharides which may be related to gastric stasis or impaired renal clearance or a combination of these factors. Our data, in patients following major vascular surgery, is in conflict with a previous study reporting protective effects of dopexamine on gut mucosa following cardiopulmonary bypass.[24]

The study suggests that dopexamine infusion (0.5-2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) does not enhance hemodynamic function in patients undergoing elective abdominal aortic aneurysm repair. Throughout most of such surgery, dopexamine did not improve hemodynamic variables and global oxygen delivery compared with the control group. The small patient population studied and the technical difficulties encountered in a two centered study preclude any possible beneficial effects of dopexamine on splanchnic circulation.

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