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Effects of intraoperative angiotensin-converting enzyme inhibition by quinaprilat on gastric mucosal blood flow during cardiopulmonary bypass in humans

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Abstract

Laser Doppler flow (LDF) assessment and regional carbon dioxide measurements by air tonometry were performed to estimate the changes in gastric mucosal blood flow after angiotensin-converting enzyme (ACE) inhibition in patients undergoing cardiopulmonary bypass (CPB).
Patients scheduled for elective CABG were prospectively assigned to group A (quinaprilat 0.02 mg/kg, n = 10), group B (quinaprilat 0.04 mg/kg, n = 10), or group C (control, n = 10). Baseline values were measured after induction of anesthesia (T0) and repeated during steady state CPB (T1). Thereafter either quinaprilat, a non-sulphydryl ACE inhibitor, (group A and B) or saline solution (group C) were given as an intravenous bolus. The LDF measurements were performed after 5 (T2), 10 (T3), 15 (T4) minutes during CPB as well as 5 minutes after weaning off CPB (T5) and at the end of surgery (T6). The tonometric measurements were repeated at T4, T5 and T6.
During hypothermic CPB LDF decreased in all groups. In group B only, LDF returned to baseline after application of quinaprilat. At the end of surgery (T6) LDF returned to baseline in group A and C, too. In group B LDF was significantly higher at T3, T4, T5 and T6 compared to control ($p < 0.05$). No difference between the groups as well as over the time course could be seen with regard to carbon dioxide tension of the gastric mucosa.
The results of the LDF measurements suggests a selective increase in gastric mucosal blood flow after ACE inhibition.

Key words: laser doppler flowmetry, tonometry, angiotensin-converting enzyme inhibition, quinaprilat, cardiac surgery, cardiopulmonary bypass, gastric mucosal blood flow

Introduction

Because failure of gastrointestinal function has been implicated in the development of systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), sepsis and multiple organ failure (MOV) (1) (2), reduced gastrointestinal blood flow during cardiopulmonary bypass (CPB) is discussed to promote a complicated and prolonged recovery after cardiac surgery (3). Regional blood flow is regulated by many factors influencing the circulation directly and indirectly. However the renin-angiotensin system (RAS) appears to be an important factor regulating intestinal blood flow during CPB (4). It has been reported that activation of the renin-angiotensin system is associated with

an increase in systemic vascular resistance during non-pulsatile CPB (5). Furthermore it has been shown that angiotensin-converting enzyme (ACE) inhibitors can protect the intestine from ischemic injury after hemorrhage and cardiogenic shock (6, 7). Quinaprilat is the active metabolite of the non-sulphydryl ACE inhibitor quinapril. Its onset time after i.v. application is within 15 min and its duration of action is at least 12 h (8). Recent data suggest that quinaprilat in contrast to enalaprilat improves endothelium-mediated vasodilation (9). Therefore we used quinaprilat to evaluate the effects of intraoperative ACE inhibition on gastric mucosal blood flow during moderate hypothermic CPB in patients undergoing cardiac surgery. Our hypothesis is that quinaprilat will improve gastric mucosal blood flow during cardiac surgery with CPB. The primary outcome variable to prove this is a change in LDF.

Methods

Patients, anesthesia and cardiopulmonary bypass

Thirty consecutive eligible patients undergoing elective CABG have been included in a placebo controlled study. After approval by the Local Ethics Committee, written informed consent was obtained from the patients. Patients with preexisting cardiac failure (ejection fraction < 50 % as estimated by ventriculography), renal insufficiency (serum creatinine > 2.0 mmol/l) or impaired liver function (GOT > 30 U/l, GPT > 30 U/l), and patients who took ACE inhibitors in their history or had previous unacceptable side effects from ACE inhibitors were excluded from the study. Three patients, refusing the informed consent, were not enrolled in the study. Using a randomized sequence, the patients were prospectively assigned to group A (quinaprilat 0.02 mg/kg, n = 10), group B (quinaprilat 0.04 mg/kg, n = 10), or group C (control, n = 10). Preoperative treatment such as nitrates, beta-adrenergic blockers and calcium channel blockers was continued until the day of surgery. Anesthesia was similar in all patients. The morning of surgery the patients received flunitrazepam 2 mg and morphine sulfate 30 mg for oral premedication. Intravenous induction was performed using sufentanil (0.2 to 0.3 µg/kg), midazolam (0.05 to 0.1 mg/kg) and pancuronium bromide (0.1 mg/kg). For maintenance of anesthesia every 30 min sufentanil 25 µg, and every 45 min midazolam 5 mg were given. Prior to cardiopulmonary bypass (CPB) anesthesia was supplemented with nitrous oxide. CPB was instituted using a single two-stage venous and aortic cannulation. CPB was performed in moderate hypothermia (rectal temperature ≥ 33° C) using non-pulsatile perfusion (2.4 $l \cdot min^{-1} \cdot m^{-2}$) with membrane oxygenators (Sorin 41; Sorin, Torino, Italy). Priming of the extracorporal circuit consisted of 2000 ml of Ringer´s solution and 250 ml of 5 % albumin solution and electrolytes. HTK (histidine tryptophane ketoglutarate) solution was used for cardioplegic arrest. In all patients rewarming began using the integral heat exchanger of the oxygenator when the final distal anastomosis was started. The acid-base management followed the alpha-stat methodology. During CPB norepinephrine was given to keep mean arterial pressure (MAP) above 50 mm Hg. When MAP was > 100 mm Hg during CPB sufentanil 0.2 µg/kg and midazolam 0.1 mg/kg were given additionally followed by a vasodilator when necessary. All patients receiving vasodilators or vasoconstrictors at any time during the study period were removed from the study. During CPB the hematocrit was held between 20 and 30 %. Arterial (Left mammarian artery) and autologous venous grafts were used in all patients. No calcium-blocking drugs were given to prevent arterial spasm. The reperfusion period before weaning from CPB was one third of the aortic cross-clamping time. Weaning from CPB was performed by optimizing preload and successively reducing pump flow without routine use of catecholamines or other inotropes.

Measured parameters and data points

The following hemodynamic variables have been recorded: Heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was measured by thermodilution (mean value of three measurements; CO-Set, Baxter Healthcare Corp, Irvine, CA). Pressures were measured with reference to the midaxillary line. Oxygen delivery (DO_2I) and Oxygen consumption (VO_2I) were calculated using the following formula: $DO_2I = CI \times CaO_2 \times 10$; $VO_2I = CI \times (CaO_2 - CvO_2) \times 10$, where CI is the cardiac index, CaO_2 is the arterial oxygen content and CvO_2 is the mixed venous oxygen content. Microcirculatory blood flow was studied using laser Doppler flowmetry (MBF 3D, Moor Instruments Ltd., Devon, UK). To measure gastric mucosal blood flow a probe designed for endoscopic measurements (P6b, Moor Instruments Ltd, Devon, UK) was used. After calibration with a Moor instruments Ltd. motility standard kit the probe was inserted through the lumen of a standard gastric tube. After induction of general anesthesia and positioning of the patient on the operating table the gastric tube was entered orally and sited in the stomach. The correct placement of the gastric tube was confirmed by instilling air into the gastric tube and auscultating over the epigastricum and by aspirating gastric contents. Thereafter the laser Doppler flow (LDF) probe was inserted through the gastric tube, and the mean red blood cell flux was displayed on the monitor. The correct position of the probe was verified by observing the typical pulse-synchronous oscillations. When the laser Doppler signal was stable the probe was fixed by tape at the nasogastric tube. The laser Doppler signal was continuously monitored to detect any loss of contact between probe and gastric mucosa. The frequency band used throughout the study was 14.9 kHz. The LDF data collection was automatically at a rate of 2 Hz. The last minute of each measurement period (120 data points) was averaged off-line by a blinded observator (M.M.). Steady state baseline measurements after induction of anesthesia were recorded, and subsequent measurements were expressed as a percentage of this value. A nasogastric tonometer catheter (TRIP NGS-Catheter, Tonometrics Division, Instrumentarium Corp.) in combination with an automated tonometric measurement device (Tonocap TC 200, Tonometrics Division, Instrumentarium Corp.) was used to assess the carbon dioxide tension of the gastric mucosa ($P_{muc}CO_2$). The PCO_2 gap was defined as the difference between mucosal and arterial PCO_2.

Experimental protocol

Baseline values for the variables were measured after induction of anesthesia (T0). The measurements were repeated during steady state of CPB (approximately 20 min. after start of CPB) (T1). Thereafter either quinaprilat in group A and B or saline solution (group C) were given as an intravenous bolus. The LDF measurements were performed after 5 (T2), 10 (T3), 15 (T4) minutes during CPB as well as 5 minutes after weaning off CPB (T5) and at the end of the operation (T6). The tonometric measurements were repeated at T4, T5 and T6. MAP was measured at all time points, whereas the other systemic variables were not assessed during CPB.

Statistical analysis

For statistical analysis the SPSS 7.5 for Windows NT computer package was used. Data are expressed as mean ± standard deviation (SD). Differences between the groups were analyzed by one-way ANOVA for repeated measurements followed by the post hoc Tukey's test.

$P < 0.05$ was considered significant. For a power of 80 % 10 patients in each group were required to show a 25 % change in LDF.

Results

Three patients were not enrolled because they refused the informed consent. No patient was excluded due to a concomitant therapy with vasopressors or vasodilators during the study period. Biometric data, anesthetic, and surgical procedures are comparable between the groups (Table 1). The hemodynamic and oxygenation parameters are presented in table 2. There was an increase in CI and HR immediately after weaning off bypass (T5) in all groups compared to pre-bypass values (T1). However, at the end of surgery (T6) CI returned to baseline values whereas HR remained increased in all groups. Despite the same changes in CI and MAP differences in gastric LDF were evident (Figure 1). During hypothermic CPB (T1) LDF decreased by 49 % in group A ($p < 0.05$ versus T0); 32 % in group B ($p < 0.05$ versus T0) and 44 % in group C ($p < 0.05$ versus T0). After application of quinaprilat 0.04 mg/kg (group B) LDF returned to baseline values during CPB (T3, T4) ($p < 0.05$ versus placebo). After weaning off bypass LDF in group B was increased at T5 and T6 by 55 % and 95% respectively ($p < 0.05$ versus placebo). In contrast to group B LDF remained depressed during CPB after quinaprilat 0.02 mg/kg (group A) or placebo (group C). After weaning off bypass LDF values in group A and C returned to baseline at T6. The courses of $P_{muc}CO_2$ and PCO_2 gap are shown in figure 2. No difference between the groups as well as over the time course could be seen.

Table 1: Demographic and perioperative data

	Group A	Group B	Group C
Height (cm)	172 ± 9	172 ± 8	165 ± 10
Weight (kg)	77 ± 12	83 ± 14	82 ± 13
History of Diabetes mellitus (n)	2	0	3
History of Hypertension (n)	5	8	8
Preoperative EF (%)	60 ± 7	62 ± 11	65 ± 11
Preoperative LVEDP (mm Hg)	16 ± 7	11 ± 2	11 ± 4
T_{CPB} (min)	114 ± 24	116 ± 24	114 ± 25
T_{clamp} (min)	66 ± 19	68 ± 17	68 ± 18
T_{surg} (min)	235 ± 51	240 ± 43	243 ± 24
Total doses of anesthetics and fluids:			
Sufentanil (µg)	368 ± 98	348 ± 85	345 ± 83
Midazolam (mg)	43 ± 10	44 ± 8	42 ± 4
Pancuronium (mg)	14 ± 4	14 ± 3	15 ± 3
Crystalloids (ml)	1500 ± 173	1625 ± 460	1500 ± 471
Colloids (ml)	358 ± 139	400 ± 137	317 ±157
PRC (ml)	450 ± 173	300 ± 0	317 ± 157
autologous blood (ml)	780 ± 250	830 ± 321	655 ± 158

Abbreviations: T_{CPB}, duration of cardiopulmonary bypass; T_{clamp}, duration of aortic clamping; T_{surg}, time of surgery; PRC, packed red cells; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; autologous blood, blood from extracorporeal circuit salvaged by hemofiltration.

Table 2: Hemodynamic and oxygen transport data

Parameter	Group	T0	T5	T6
HR (· min^{-1})	A	68 ± 18	91 ± 18*	95 ± 7*
	B	61 ± 8	90 ± 11*	96 ± 10*
	C	56 ± 12	91 ± 15*	93 ± 14*
CI ($l \cdot min^{-1} \cdot m^{-2}$)	A	2,3 ± 0,8	3,5 ± 0,7*	2,9 ± 0,6
	B	2,0 ± 0,5	3,4 ± 1*	2,9 ± 0,6
	C	1,9 ± 0,4	3,0 ± 0,5*	2,5 ± 0,6
MAP (mm Hg)	A	76 ± 11	77 ± 11	77 ± 9
	B	76 ± 13	75 ± 8	80 ± 9
	C	83 ± 10	76 ± 13	81 ± 17
MPAP (mm Hg)	A	19 ± 5	19 ± 4	18 ± 4
	B	17 ± 6	18 ± 6	20 ± 5
	C	17 ± 6	17 ± 7	15 ± 5
CVP (mm Hg)	A	4 ± 1	6 ± 3	6 ± 3
	B	6 ± 3	6 ± 3	8 ± 4
	C	5 ± 2	5 ± 3	6 ± 3
PCWP (mm Hg)	A	10 ± 3	11 ± 3	10 ± 4
	B	10 ± 5	9 ± 3	11 ± 5
	C	8 ± 3	9 ± 6	9 ± 3
DO2I ($ml \cdot min \cdot m^{-2}$)	A	384 ± 167	434 ± 89	360 ± 67
	B	340 ± 77	434 ± 138	394 ± 106
	C	312 ± 74	377 ± 69	312 ± 98
VO2I ($ml \cdot min \cdot m^{-2}$)	A	77 ± 15	108 ± 18	104 ± 15
	B	92 ± 28	97 ± 23	106 ± 20
	C	67 ± 20	92 ± 26	91 ± 24
HB ($mg \cdot dl^{-1}$)	A	11,3 ± 1,7	8,4 ± 0,9	8,5 ± 1,2
	B	11,7 ± 1,4	8,6 ± 0,6	8,8 ± 1,0
	C	11,8 ± 1,6	8,5 ± 1,2	8,7 ± 1,5

Abbreviations: HR, Heart rate; CI, cardiac index; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; DO_2I, oxygen delivery index; VO_2I, oxygen consumption index; HB, hemoglobin.
* = $p < 0,05$ versus T0.

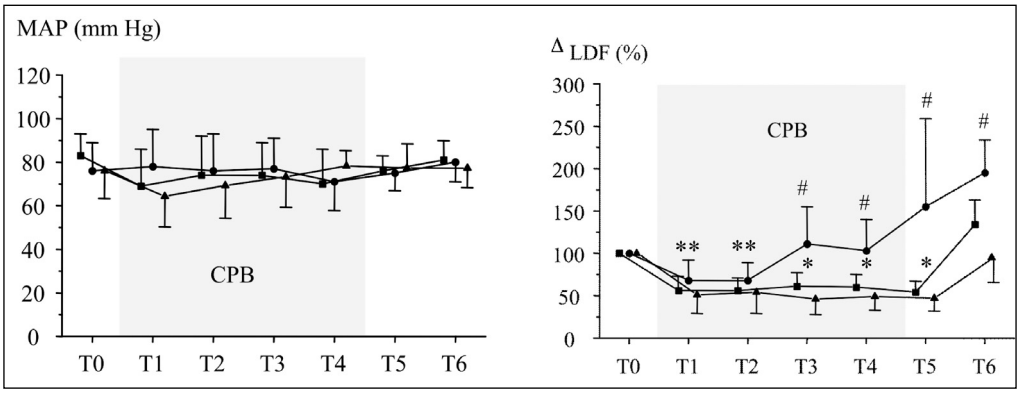

*Figure 1: Changes in mean arterial pressure (MAP, top) and laser Doppler flow (LDF, bottom) from pre-cardiopulmonary bypass baseline values (T0), during steady state CPB (T1), 5 min (T2), 10 min (T3), 15 min (T4) after administration of quinaprilat 0.02 mg/kg (triangles), 0.04 mg/kg (circles) and placebo (squares), after CPB (T5) and at the end of surgery (T6). * = p < 0.05 vs. TO, # = p < 0.05 vs. placebo.*

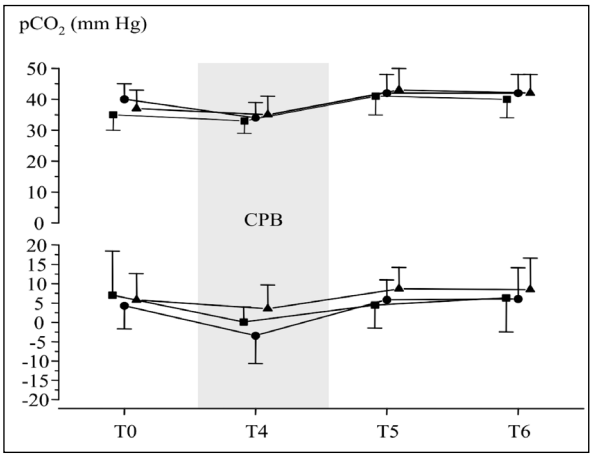

Figure 2: Time course of gastric mucosal pCO_2 (top) and pCO_2 gap (bottom) for group A (squares), group B (circles) and group C (triangles).

Discussion

Quinaprilat has vascular effects beyond the inhibition of angiotensin II formation. In contrast to enalaprilat it causes vasodilation by increasing vascular nitric oxide production (10). Therefore lower dosages than the dosage of enalaprilat (0.06 mg/kg) used by Boldt et al. to reduce blood pressure during cardiac surgery were used (11). The present study has demonstrated a 32 - 49 % decrease in gastric LDF during hypothermic non pulsatile CPB. A similar decrease in gastric LDF during non pulsatile hypothermic CPB has also been reported by other groups (12, 13). Hypothermia is recognized to reduce intestinal microcirculation (14), whereas isovolamic hemodilution was not found to decrease LDF in an animal model, when a constant systemic oxygen delivery was maintained (12). However during normothermic CPB Ohri et al. reported as well a reduction in gastric mucosal LDF, suggesting that factors other than hypothermia contribute to gastric mucosal hypoperfusion (13). In the present study LDF has returned to baseline values during constant pump flow after administration of quinaprilat 0.04 mg/kg without changes in

MAP whereas LDF remained lower after quinaprilat 0.02 mg/kg and placebo. Because LDF has been found, in animal studies, to correlate well with mucosal blood flow as measured by standard techniques (15) this finding suggests a selective increase in gastric mucosal blood flow after quinaprilat 0.04 mg/kg persisting in the immediate post-CPB period. An activation of the RAS with increased levels of angiotensin II during CPB has been described by Tayler et al. (16). This increase in circulating angiotensin II may directly influence splanchnic blood flow during CPB because angiotensin II is a potent vasoconstrictor with a mesenteric selectivity due to an increased affinity of the angiotensin II receptors on splanchnic vascular smooth muscle (17). We have previously shown that circulation of angiotensin II decreases significantly after intravenous administration of Quinaprilat (18). This may explain the observed increase in gastric mucosal blood flow during CPB.

Impaired gastrointestinal blood flow during cardiac surgery has also been suggested on the basis of gastric tonometry (19) (20). Our data have shown no difference in $P_{muc}CO_2$ and PCO_2 gap between the groups as well as over the time course. An explanation for this finding may be that we stopped the observation at the end of surgery (approximately 60 min after termination of CPB). In a study by Ohri et al. the first significantly lower gastric pHi was observed 2 hours post CPB and the nadir was reached 3 to 5 hours after the end of CPB despite a significant decrease in gastric LDF during CPB (13). Furthermore it must be considered that the interpretation of data derived from saline tonometry has been limited by technical problems (21). Air tonometry, as used in the present study, has resolved many of the technical difficulties associated with saline tonometry. In vitro as well as in vivo studies have shown a good correlation between saline- and air tonometry (22, 23).

The present study has some limitations. The observation period was stopped at the end of surgery therefore late effects of the ACE inhibition were out of the scope of this study. However, changes in tonometric variables have been described as effects occurring 2 to 4 hours after weaning off CPB (13). Although an increased requirement of vasoconstrictors has been reported after CPB in patients with chronic preoperative ACE inhibitor use (24), no patient in the present study required vasoconstrictive or inotropic support. However this study has not enough power to analyze safety issues. In conclusion our data suggest that quinaprilat 0.04 mg/kg improves gastric mucosal blood flow during cardiac surgery with non pulsatile hypothermic CPB. The effects of this intervention on the occurrence of gastrointestinal complications after CPB and on patients outcome needs further elucidation.

References

1. Papa M, Halperin Z, Rubinstein E, Orenstein A, Gafin S, Adar R. The effect of ischemia of the dog's colon on transmural migration of bacteria and endotoxin. J Surg Res 1983; 35 (3): 264-9
2. Roumen RM, van der Vliet JA, Wevers RA, Goris RJ. Intestinal permeability is increased after major vascular surgery. J Vasc Surg 1993; 17 (4): 734-7
3. Andersen LW, Landow L, Baek L, Jansen E, Baker S. Association between gastric intramucosal ph and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor-alpha concentrations in patients undergoing cardiopulmonary bypass. Crit Care Med 1993; 21 (2): 210-7
4. Reilly PM, Bulkley GB. Vasoactive mediators and splanchnic perfusion. Crit Care Med 1993; 21 (2 Suppl): S55-68
5. Taylor KM, Bain WH, Russell M, Brannan JJ, Morton IJ. Peripheral vascular resistance and angiotensin II levels during pulsatile and no-pulsatile cardiopulmonary bypass. Thorax 1979; 34 (5): 594-8
6. Freeman JG, Hock CE, Edmonds JS, Lefer AM. Anti-Shock actions of a new converting enzyme inhibitor, enalaprilic acid, in hemorrhagic shock in cats. J Pharmacol Exp Ther 1984; 231 (3): 610-5

7. Bailey RW, Bulkley GB, Hamilton SR, Morris JB, Haglund UH. Protection of the small intestine from nonocclusive mesenteric ischemic injury due to cardiogenic shock. Am J Surg 1987; 153 (1): 108-16
8. Breslin E, Posvar E, Neub M, Trenk D, Jahnchen E. A pharmacodynamic and pharmacokinetic comparison of intravenous quinaprilat and oral quinapril. J Clin Pharmacol 1996; 36 (5): 414-21
9. Hornig B, Arakawa N, Haussmann D, Drexler H. Differential effects of quinaprilat and enalaprilat on endothelial function of conduit arteries in patients with chronic heart failure. Circulation 1998; 98 (25): 2842-8
10. Haefeli WE, Linder L, Lüscher TF. Quinaprilat induces arterial vasodilation mediated by nitric oxide in humans. Hypertension 1997; 30 (4): 912-7
11. Boldt J, Schindler E, Wollbrück M, Görlach G, Hempelmann G. Cardiorespiratory response of intravenous angiotensin-converting enzyme inhibitor enalaprilat in hypertensive cardiac surgery patients. J Cardiothorac Vasc Anesth 1995; 9 (1): 44-9
12. Sicsic JC, Duranteau J, Corbineau H, Antoun S, Menestret P, Sitbon P et al. Gastric mucosal oxygen delivery decreases during cardiopulmonary bypass despite constant systemic oxygen delivery. Anesth Analg 1998; 86 (3): 455-60
13. Ohri SK, Bowles CW, Mathie RT, Lawrence DR, Keogh BE, Taylor KM. Effect of cardiopulmonary bypass perfusion protocols on gut tissue oxygenation and blood flow. Ann Thorac Surg 1997; 64 (1): 163-70
14. Sinard JM, Vyas D, Hultquist K, Harb J, Bartlett RH. Effects of moderate hypothermia on O2 consumption at various O2 deliveries in a sheep model. J Appl Physiol 1992; 72 (6): 2428-34
15. Shepherd AP, Riedel GL. Continuous measurement of intestinal mucosal blood flow by laser-doppler velocimetry. Am J Physiol 1982; 242 (6): G668-72
16. Taylor KM, Bain WH, Morton JJ. The role of angiotensin II in the development of peripheral vasoconstriction during open-heart surgery. Am Heart J 1980; 100 (6 Pt 1): 935-7
17. Gunther S, Gimbrone MA, Alexander RW. Identification and characterization of the high affinity vascular angiotensin II receptor in rat mesenteric artery. Circ Res 1980; 47 (2): 278-86
18. Kwapisz MM, Müller M, Schindler E, Demir S, Veit M, Roth P, Hempelmann G. The effect of intravenous quinaprilat on plasma cytokines and hemodynamic variables during cardiac surgery. J Cardiothorac Vasc Anesth 2004; 18 (1): 53-8
19. Ohri SK, Becket J, Brannan J, Keogh BE, Taylor KM. Effects of cardiopulmonary bypass on gut blood flow, oxygen utilization, and intramucosal ph. Ann Thorac Surg 1994; 57 (5): 1193-9
20. Croughwell ND, Newman MF, Lowry E, Davis RD, Landolfo KP, White WD et al. Effect of temperature during cardiopulmonary bypass on gastric mucosal perfusion. Br J Anaesth 1997; 78 (1): 34-8
21. Takala J, Parviainen I, Siloaho M, Ruokonen E, Hämäläinen E. Saline PCO2 is an important source of error in the assessment of gastric intramucosal ph. Crit Care Med 1994; 22 (11): 1877-9
22. Creteur J, De Backer D, Vincent JL. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: In vitro and in vivo validation studies. Anesthesiology 1997; 87 (3): 504-10
23. Janssens U, Graf J, Koch KC, Hanrath P. Gastric tonometry: In vivo comparison of saline and air tonometry in patients with cardiogenic shock. Br J Anaesth 1998; 81 (5): 676-80
24. Tuman KJ, McCarthy RJ, O'Connor CJ, Holm WE, Ivankovich AD. Angiotensin-Converting enzyme inhibitors increase vasoconstrictor requirements after cardiopulmonary bypass. Anesth Analg 1995; 80 (3): 473-9

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