Cardiovascular effects of simultaneous occlusion of the inferior vena cava and aorta in patients treated with hypoxic abdominal perfusion for chemotherapy†

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Background. Animal studies suggest less cardiovascular disturbance if the aorta and vena cava are occluded simultaneously. We set out to establish the effects of simultaneous clamping in humans, because oncologists suggested that perfusion for chemotherapy could be done under local anaesthesia without invasive haemodynamic monitoring.

Methods. We studied the cardiovascular effects of the onset and removal of simultaneous occlusion of the thoracic aorta and inferior vena cava, in seven ASA II patients. Two stop-flow catheters positioned in the aorta and in the inferior vena cava were inflated to allow hypoxic abdominal perfusion to treat pancreatic cancer. We measured the arterial pressure, heart rate (HR), right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP) and cardiac output (CO), and calculated systemic vascular resistance index (SVRi), pulmonary vascular resistance index (PVRi), left ventricular stroke work index (LVSWi) and right ventricular stroke work index (RVSWi). Three patients were studied with transoesophageal echocardiography.

Results. Six patients needed intravenous nitroprusside during the occlusion because mean arterial pressure (MAP) increased to more than 20% of baseline (SVRi increased by 87%). One minute after occlusion release, all patients had a 50% decrease in MAP, and mPAP increased by 50%. The procedure had severe cardiovascular effects, shown by a 100% increase in cardiac index at occlusion release with increases in left and right ventricular stroke work indices of 75% and 147%. Left ventricular wall motion abnormalities were seen on transoesophageal echocardiography.

Conclusions. Serious haemodynamic changes occur during simultaneous occlusion of the thoracic aorta and inferior vena cava, which may need invasive haemodynamic monitoring.

Br J Anaesth 2002; **88**: 193–8

Keywords: arteries, aorta occlusion; veins, vena cava inferior occlusion; heart, cardiovascular changes

Accepted for publication: September 23, 2001

Clamping the aorta has major cardiovascular effects.[1] In animal studies, clamping the inferior vena cava at the same time can prevent large haemodynamic changes.[2 3] A single clinical report suggests that haemodynamic changes are not prevented by additional inferior vena cava occlusion.[4]

A percutaneous aortic 'stop-flow' infusion technique has been used for regional cytotoxic therapy of the abdomen for a number of malignant conditions.[5] The method aims to reduce the systemic side-effects of the chemotherapeutic drugs, whilst simultaneously potentiating the cytotoxic action of the drugs by hypoxia.[5–7] In our hospital, a phase I–II chemotherapy trial based on this hypoxic abdominal perfusion procedure (HAP) is taking place. The procedure achieves a greater dose and thus a greater local concentration of melphalan and mitomycin C with a 20-min isolation and perfusion of the abdomen.

The temporary vascular isolation of the abdominal cavity for this procedure is achieved with tourniquets placed around both upper thighs to exclude the lower limbs from

†Part of this work was orally presented at the Dutch Society of Anaesthesiology 1999, Veldhoven, The Netherlands.

the circulation, and by surgical insertion of stop-flow catheters, one into the aorta and a second into the inferior vena cava, to isolate the abdominal circulation.

We wished to measure the haemodynamic effects of this simultaneous clamping in humans, because oncologists suggested that the procedure could be done using local anaesthesia and without invasive haemodynamic monitoring.

Table 1 Characteristics of the patients (mean and range)

Sex (F/M)	4/3
Age (yr)	57 (49–65)
Weight (kg)	67 (54–97)
Height (m)	1.72 (1.62–1.90)
Body surface area (m^2)	1.78 (1.61–2.03)
Additional diagnoses	Non-insulin dependent diabetes mellitus (n=1)
	Insulin-dependent diabetes mellitus (n=1)
	Sick sinus syndrome with AAI pacemaker (n=1)

Material and methods

Seven consecutive patients, all ASA II, were enrolled in the HAP phase I–II trial for locally advanced pancreatic cancer after diagnostic work-up, written informed consent, and explanation of the anaesthetic procedure. The perfusion study, using melphalan and mitomycin C, was approved by the local medical ethical committee. We excluded patients with significant cardiovascular disease (NYHA classes II, III or IV). Other patient characteristics are given in Table 1.

Anaesthetic management

On the evening before the operation the patients were premedicated with lorazepam 1 mg orally. On the day of operation, ranitidine 150 mg was added to their routine medication.

In the operating room, basic anaesthetic monitoring was started (HP M1166A OmniCare Anaesthesia Component Monitoring System Release F, Hewlett® Packard GmbH, Böblingen, Germany), followed by i.v. induction of anaesthesia with sufentanil 0.30 μg kg^{-1}, thiopental 5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}. After tracheal intubation, the lungs were ventilated with a closed-circuit anaesthetic machine (Physio BV, Haarlem, The Netherlands), using IPPV with settings of $F_{I_{O_2}}$ 0.35 (oxygen–air mixture), frequency 14 min^{-1}, tidal volume 8 ml kg^{-1}, PEEP 5 cm H_2O, and I:E ratio 1:1.2. Respiratory frequency was adjusted to maintain Pa_{CO_2} between 4.5 and 5 kPa. Anaesthesia was maintained with isoflurane 0.9% end tidal and sufentanil 0.20 μg kg^{-1} i.v. was given at the start of the surgical procedure. Fluid management was standardized for all patients. Ringer's lactate was given by i.v. infusion, 20 ml kg^{-1} in the first hour of the procedure to correct the preoperative fluid restriction and venodilation caused by general anaesthesia, followed by 6 ml kg^{-1} h^{-1} for the rest of the procedure. Fluid management was not adjusted for any change in cardiovascular measurements. Sodium nitroprusside (SNP) i.v. was given as necessary to control MAP during the perfusion phase to within 20% of the preoperative value.

Additional monitoring was started. Blood pressure was measured using a radial artery cannula (Arrow radial artery catheterization set 20 Ga; Arrow Deutschland GmbH, Erding, Germany). A pulmonary artery balloon flow catheter (Arrow Thermo-Pace® Hands off® Heparin-coated Thermodilution Catheter 7.5 Fr. 5 lumen 80 cm catheter length; Arrow Deutschland GmbH) was passed through an introducer sheath (Arrow Percutaneous sheath introducer set 8.5 Fr; Arrow Deutschland GmbH) placed in the right internal jugular vein. A cardiac output measurement system (Baxter CO-set® closed injectate delivery system; Baxter Deutschland GmbH) was connected to the right atrial pressure (RAP) port of the thermodilution catheter. We used iced fluid. We studied three patients with per-operative transoesophageal echocardiography (TOE) (Sonotron Vingmed CFM 800; Vingmedsound Als, Horten, Norway) with a 5 MHz multi-plane transoesophageal echo (MPTE).

Surgical procedure

Tourniquets were placed around the upper thighs to allow isolation of the legs from the circulation. Then a small incision in the right groin was made to insert two catheters (arterial stop-flow catheter F12–600 mm and venous stop-flow catheter F12–600 mm; PFM Produkte für die Medizin GmbH, Köln, Germany) into the femoral artery and vein. They were advanced to above the coeliac trunk in the aorta and the level of the diaphragm in the inferior vena cava, using radiological control (Fig. 1). Heparin 5000 IU was given i.v.

The abdomen was then isolated. First, the tourniquets on both upper thighs were inflated to a pressure of 350 mm Hg. Then the balloon of the aortic catheter was inflated with a mixture of 25 ml NaCl 0.9% with contrast fluid and immediately afterwards the balloon of the caval catheter was also inflated. The maximum diameter of the balloons was 30 mm.

The cytotoxic drugs were perfused according to a set regimen using an extra-corporeal circuit connected to both catheters (Hypoxic perfusion set; PFM Produkte für die Medizin GmbH), flow rate, 250 ml min^{-1}. No oxygen was added to this extra-corporeal circuit. The perfusion of the chemotherapy was maintained for 10 min, followed by a 10-min period without drugs. After a total of 20 min hypoxic abdominal perfusion, the circulation to the abdomen was restored by deflation of the balloon in the aorta, followed immediately by deflation of the inferior caval vein balloon. After a stabilization period of 10 min the tourniquets were released from the thighs.

Data collection

ECG, MAP, heart rate (HR), RAP, mean pulmonary artery pressure (mPAP), blood temperature (measured by the

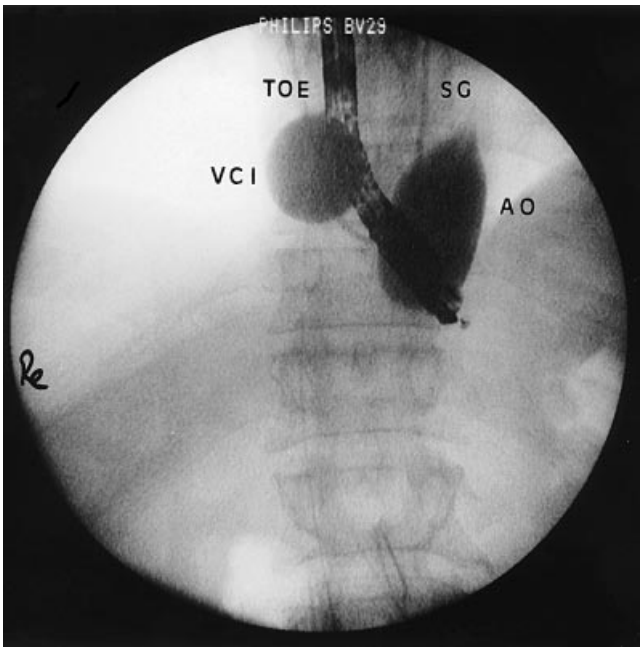

Fig 1 Radiograph taken during HAP phase; AO=aortic catheter; VCI= inferior caval vein catheter; TOE=transoesophageal echo probe; SG=Swan–Ganz catheter (see text for details).

thermodilution catheter) and peripheral oxygen saturation (Sp_{O_2}) were measured continuously, and a record made of the values for each minute of the procedure.

Measurements were noted at previously defined times; these were 'steady state' (SS), during stable anaesthesia before tourniquet inflation; 'legs separated' (LS), when the tourniquets around the thighs were inflated; early in the 'HAP phase' (HAPa), just after complete abdominal isolation; late in the 'HAP phase' (HAPb), within 5 min before removal of occlusion; 'abdominal recirculation' (AR), when only the balloons of the catheters were deflated; 'complete recirculation' (CR), the tourniquets were also deflated; and 'end operation' (EO), just before reversal of anaesthesia was started. Cardiac output (CO) (measured in triplicate) and pulmonary artery wedge pressure (PAWP), measured just before CO, were measured at these times. If i.v. SNP was given during the perfusion phase, the infusion of SNP was turned off after determination of HAPb, but at least 4 min before abdominal reperfusion started. The time needed for the surgical preparation varied so that the time between SS and LS was a mean 47 min (range 30–65 min); thereafter, a rigid time schedule was maintained starting with the separation of the legs. Thus, LS was defined as t=0 min; HAP, t=4 min; AR, t=24 min; CR, t=34 min; EO, t=54 min. Cardiac index (CI), stroke index (SI), systemic vascular resistance index (SVRi), pulmonary vascular resistance index (PVRi), left ventricular stroke work index (LVSWi) and right ventricular stroke work index (RVSWi) were calculated with standard formulae. For each patient, these calculations were done using continuously measured variables that had been collected at the same time-points that CO was measured. Because CO and PAWP were measured 'early in the HAP phase' and not for instance always at 'the third minute of the HAP-phase', it was not possible to construct an exactly time-related set of the values of these intermittently measured variables for the entire group. The function of the left ventricle was monitored by TOE, with a transgastric short axis mid-papillary view, continually recorded on VHS videotape. Left ventricle end diastolic area (LVEDA) and left ventricle end systolic area (LVESA) were traced by the contouring program of the TOE device. Fractional area change was calculated [(LVEDA – LVESA) / LVEDA×100] and left ventricular wall motion was classified with a semi-quantitative scoring system:[8] a normally contracting wall segment is scored as 1, mild hypokinesis as 2, severe hypokinesis as 3, akinesis as 4, and dyskinesis as 5. The left ventricular wall motion score index (LVWMSi) was calculated from the sum of all scores, divided by the number of segments observed.

Statistical analysis

Results are expressed as mean and standard deviation (SD) unless otherwise indicated. Statistical analysis was with SPSS for Windows, version 10.0. Data were analysed with a Wilcoxon signed ranks test to compare the observed mean difference between a value of a defined time point with the value at SS as recommended by Myles and Gin.[9] A P-value <0.05 was considered significant.

Results

Figures 2 and 3 show the time course of changes in the continuously measured values MAP, HR, RAP, mPAP and temperature.

With simultaneous clamping, MAP quickly increased to greater than 120% of the preoperative value in six patients. To control MAP within 20% of this value, i.v. infusion of SNP was started. This infusion was continued until the end of the HAP phase to control MAP. Although the SNP infusion was stopped at least 4 min before balloon deflation, a 50% reduction in MAP occurred in all patients in the first minute after balloon deflation. One minute later, however, MAP recovered spontaneously (Fig. 2).

The pacemaker of the patient with the sick sinus syndrome was set at a fixed rate of 70 beats min^{-1}. Except for HR, the haemodynamic changes in this patient were comparable with the changes measured in the other six patients. HR increased by 42% during the second part of the HAP phase (Fig. 2).

RAP changed little despite the other cardiovascular changes, except at the fourth and fifth minute after the abdominal clamping, when it increased by 15% (Fig. 3).

Three minutes after balloon deflation, all the patients developed pulmonary hypertension; mPAP increased by 50% (Fig. 3).

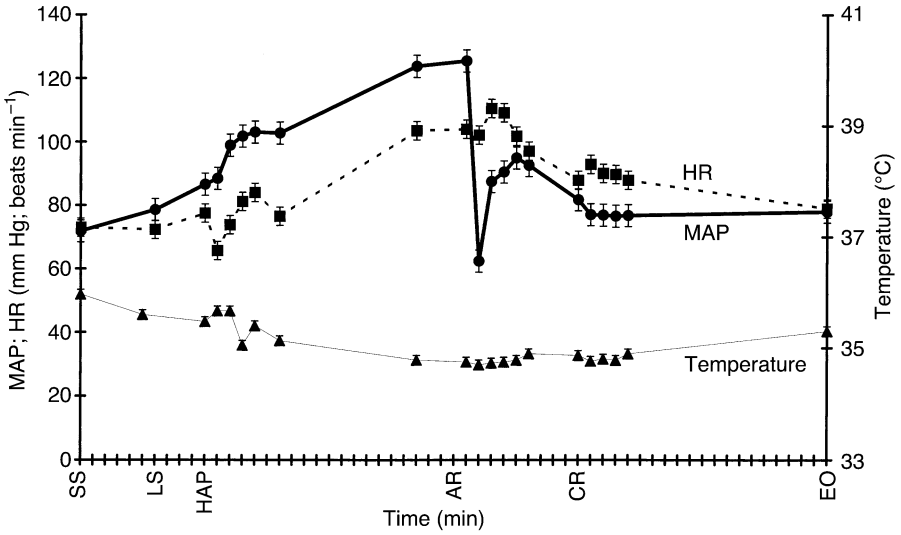

Fig 2 HR, MAP and temperature during the HAP procedure. Each bar on the abscissa represents one minute. Data are mean (SE).

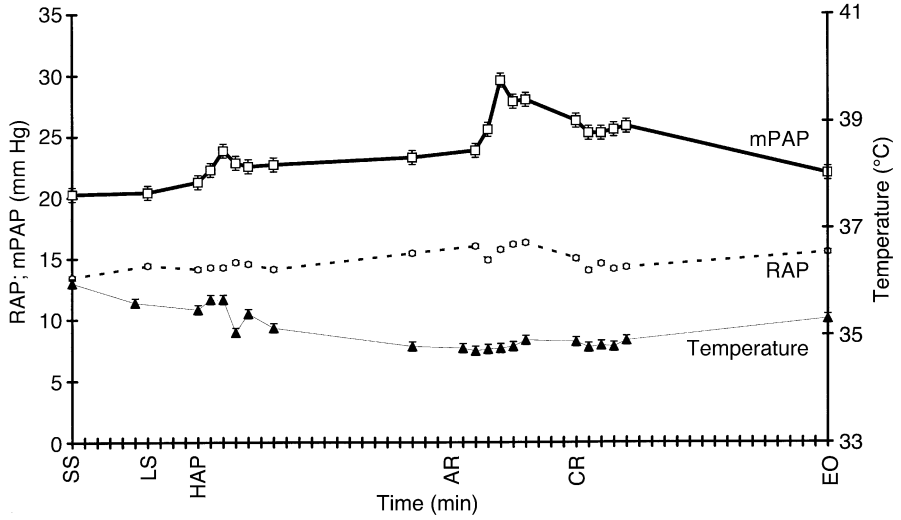

Fig 3 RAP, mPAP and temperature during the HAP procedure. Each bar on the abscissa represents 1 min. Data are mean (SE).

Table 2 shows the time course of changes in PAWP, CI, SI, SVRi, PVRi, LVSWi and RVSWi.

TOE was done in three patients. Because of recording problems in two procedures, we could only analyse and calculate the LVEDA, LVESA and FAC in detail in one patient. Global intra-operative analysis of changes in the left ventricular wall motion was possible in all three procedures and revealed the same trend in LVWMSi. Table 3 presents the time course of changes in LVEDA, LVESA and FAC in one patient and of the changes in LVWMSi in all three patients.

SVRi increased by 87% with simultaneous occlusion of the aorta and vena cava. At the end of the HAP phase, although SNP was given, a further increase by 98% was measured (Table 2, HAPb) and this immediately affected left ventricular filling. LVESA increased by 68% after 2 min, and LVEDA increased by 49% after 5 min (Table 3). PAWP increased by 73% at the end of the perfusion phase (Table 2, HAPb). Although the CI initially decreased in the patient who did not need an i.v. SNP infusion (by 50% at the start of the HAP phase) the overall CI of all the patients did not decrease significantly during the HAP phase (Table 2).

Immediately after opening both vessels, SVRi decreased by 35% compared with the baseline value, and by 67% compared with the value measured at the end of the HAP phase (Table 2, SS, HAPb, AR). Although left ventricular filling and left ventricular wall motion returned immediately to their steady state value in response to this decrease (Table 3), PAWP did not return to its baseline value until the end of the procedure (Table 2). CI increased by 100%, stroke

Table 2 Cardiovascular measurements during the procedure. Values are mean (SD). *$P<0.05$ compared with the value at SS

Parameter	SS	LS	HAPa	HAPb	AR	CR	EO
CI (litre min^{-1} m^2)	2.7 (0.9)	2.4 (0.6)	2.3 (1.1)	2.5 (0.5)	5.5 (2.2)*	4.3 (1.4)*	2.9 (0.7)
PAWP (mm Hg)	11 (3)	14 (4)*	16 (7)	19 (5)*	18 (8)*	15 (6)*	14 (3)
SI (ml m^{-2})	40 (21)	34 (6.7)	31 (13)	28 (11)	57 (22)*	50 (18)*	38 (6.4)
SVRi (dyne s cm^{-5} m^2)	1849 (656)	2244 (811)	3450 (1152)*	3662 (959)*	1196 (384)*	1257 (414)*	1745 (675)
PVRi (dyne s cm^{-5} m^2)	279 (111)	230 (67.8)	256 (131)	200 (152)	148 (110)*	223 (67.9)*	222 (40.8)
LVSWi (g m m^{-2} $beat^{-1}$)	32 (13)	30 (10)	38 (24)	39 (12)	56 (23)*	42 (19)*	34(15)
RVSWi (g m m^{-2} $beat^{-1}$)	3.8 (3.5)	2.9 (2.6)	4.2 (3.8)	3.1 (2.5)	9.1 (5.6)*	8.3 (5.2)*	3.6 (2.6)

Table 3 TOE values measured during the procedure. HAPI=within 8 min after starting the hypoxic abdominal perfusion phase; HAPII=within 8 min before the end of the hypoxic abdominal perfusion phase

	SS	LS	HAP1	HAP2	HAP3	HAP4	HAP5	HAPI	HAPII	AR	CR
Patient 1											
LVEDA (cm^2)	8.2	8.4	9.0	10.5	10.7	11.4	12.2		13.4	9.1	7.5
LVESA (cm^2)	3.7	4.6	4.8	6.2	6.1	6.7	7.0		8.1	3.6	3.7
FAC (%)	54	45	47	41	43	41	43		39	60	51
LVWMSi	1	1.9	1.6	1.3	1.8	1.8	1.8		1.5	1	1
Patient 2											
LVWMSi	1.1	1.6						1.8	1.4	1.1	1
Patient 3											
LVWMSi	1	1.4						2.5	2	1.1	1

index, and left and right ventricular stroke work indices also increased at this stage (Table 2). Simultaneously, pulmonary vascular resistance index decreased by 50%.

Discussion

We found that the additional occlusion of the vena cava had only a small stabilizing effect on haemodynamics when the thoracic aorta was occluded. Although RAP, mPAP, CI, SI, LVSWi and RVSWi were stable during simultaneous occlusion of the aorta and vena cava (HAP phase), large changes in important variables such as MAP, FAC and LVWMSi, followed by an increased PAWP, required infusion of SNP in six patients to control these changes. Although SNP infusion was stopped at least 4 min before abdominal reperfusion, opening of both vessels caused profound cardiovascular changes. MAP decreased by 50%, while CI increased by 100%, pulmonary hypertension developed, LVSWi increased by 75% and RVSWi increased by 147%.

Our data contrast with those of animal studies, which reported the additional vena cava inferior occlusion had a stabilizing effect.[2,3] In mongrel dogs anaesthetized with sodium pentobarbital, systolic left ventricular pressure and superior caval vein flow did not change during simultaneous clamping; and left ventricular end diastolic volume decreased.[2] The decrease in stroke volume was assumed to be caused by reduced preload; no activation of the Frank–Starling mechanism was found.[2] Gelman and colleagues[3] studied simultaneous clamping and declamping in pigs anaesthetized with sodium methohexital followed by enflurane. Their report confirmed the data on clamping measured by Stokland and colleagues,[2] i.e. no significant change in MAP or superior caval vein flow, and reduced CO.

Our data confirm the results of the only published clinical report, which found haemodynamic changes similar to those described during thoracic aortic occlusion alone.[4] However, our methods were different. In the previous study, haemodynamic stability after inflation of the aortic balloon was sought by increasing isoflurane concentration, and by starting i.v. SNP, before the inferior caval vein balloon was inflated.[4] The authors speculated that the stepwise clamping, in which a few minutes elapsed between aortic balloon inflation and inferior caval vein balloon inflation, allows the typical, single thoracic aortic cross-clamping redistribution of blood volume, to occur.[4] In our study, less than 1 min elapsed between thoracic aorta and vena cava inferior occlusion. Nevertheless, we also observed changes comparable with those during single thoracic aortic cross-clamping. This is in contrast to the animal experiments, when occlusion of the cava during aortic cross-clamping resulted in the same flows and pressures whether the aorta and inferior caval vein were occluded simultaneously or at different timepoints.[2] Nevertheless, the authors stated that end diastolic volume, superior vena cava flow and systolic left ventricular pressure were very sensitive to changes in blood volume.[2]

The effects of blood volume expansion on haemodynamic changes, studied by infusing blood in 50-ml volumes into the jugular vein during the simultaneous clamping, was found to depend very much on shunting between the upper and lower part of the body.[2] Anatomical shunts exist via the spinal arteries and veins and via azygos and hemi-azygos veins.

To explain the different results between animal and clinical studies, three differences in the conditions may be considered. First, anatomical and physiological differences between species must be taken into account. A second difference is the method of clamping. The clamps in the animal studies were 'extravascular', while both clinical studies used endovascular occlusion. Because MAP increased during the endovascular occlusion, the outside pressure put on the partly compliant balloons (which are only available with a maximum diameter of 30 mm), will be increased, which might have allowed leakage past these balloons during the HAP phase, and increased shunt between the upper and lower compartment. Extravascular cross-clamping with instruments will prevent leakage past the clamps. A third difference between the animal and the clinical studies is the use of atropine. Both animal studies used atropine in order to avoid reflex bradycardia before simultaneous clamping was started,[2 3] whereas the clinical studies did not.[4] Therapeutic doses of atropine can occasionally dilate cutaneous blood vessels, although the mechanism of this anomalous vascular response is unknown.[10] This dilation of cutaneous vessels could affect shunting.

Our data on occlusion release only partly confirm the results of the previously published clinical report.[4] We obtained more detailed data than the study of Berkenstadt and colleagues, who presented values 1 min and 30 min after declamping.[4] We found significant changes in filling pressures. PAWP remained increased to the end of the procedure in all our patients (Table 2), whereas Berkenstadt and colleagues reported no significant changes in filling pressures during these phases.[4] Another difference was their use of ephedrine and phenylephrine to treat hypotension. We did not treat this response, although we found a significant decrease in MAP and increase in CI and HR.[4]

Two patients in our study developed ventricular ectopic beats, PVC (premature ventricular complex) in bigeminy, after occlusion release. These changes in haemodynamic values and the observed arrhythmia are compatible with a post reperfusion syndrome (PRS). The existence of a PRS is known from studies describing liver transplantation.[11 12] It is characterized by brady-arrhythmia, a decreased MAP, SVR and increased mPAP, PAWP and RAP. From studies on single aortic cross-clamping it is also assumed that splanchnic hypoperfusion releases myocardial-depressant factor(s) from the hypoxic tissues, causing myocardial dysfunction after declamping.[1] A rapid decrease in temperature may contribute to PRS.[11 12] As a result of perfusion of the abdomen with fluid below room temperature, hypothermia develops during the HAP phase. There was, however, no immediate change in blood temperature in the AR phase or the CR phase (Figs 2 and 3).

This less invasive perfusion procedure has been said to avoid significant pain or bleeding and be possible even in frail and debilitated patients.[4 5] These studies reported cardiovascular changes, but neither mentioned changes in cardiac performance.[4 5] We disagree that the procedure is trivial. Six patients in our study needed i.v. SNP to control cardiovascular changes. Cardiac wall motion abnormalities were observed in all the TOE monitored patients, probably as a result of myocardial ischaemia, and these abnormalities did not disappear until occlusion release. The increase in the left and right ventricular stroke work indices remained, accompanied by elevated PAWP. Carrying out perfusion under local anaesthesia, without invasive haemodynamic monitoring, in frail or debilitated patients, seems unwise because of the possible additional cardiac stress caused by awareness. The suggested stabilizing effect of additional vena cava occlusion was small. We therefore conclude that the large circulatory changes during simultaneous occlusion of the thoracic aorta and inferior cava make invasive haemodynamic monitoring necessary.

Acknowledgement

We thank Laraine Visser-Isles for English-language editing.

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