Non-pharmacological heart failure therapies : evaluation by ventricular pressure-volume loops

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CHAPTER 4

Left ventricular function and chronotropic responses after normothermic cardiopulmonary bypass with intermittent antegrade warm blood cardioplegia in patients undergoing coronary artery bypass grafting

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ABSTRACT

Background. Recent studies indicate that normothermic cardiopulmonary bypass (CPB) with intermittent antegrade warm blood cardioplegia (IAWBC) may have metabolic and clinical advantages, but limited data exist on its effects on myocardial function. Therefore, we investigated the acute effects of this approach on systolic and diastolic left ventricular function and on chronotropic responses.

Methods. In 10 patients undergoing isolated CABG we obtained on-line left ventricular pressure-volume loops using the conductance catheter before and after normothermic CPB with IAWBC. Steady state and load-independent indices of left ventricular function derived from pressure-volume relations were obtained during right atrial pacing (80-100-120 beats/min) to determine baseline systolic and diastolic function and chronotropic responses.

Results. The mean time of CPB was 105±36 min (median 103, range 60-167 min) with a mean aortic cross-clamp time of 75±27 min (median 69, range 43-129 min). Baseline (80 beats/min) end-systolic elastance (E_{ES}) did not change after CPB (1.22±0.53 to 1.12±0.28 mmHg/ml, P>0.2), while the diastolic chamber stiffness constant (k_{ED}) significantly increased (0.014±0.005 to 0.040±0.007 ml^{-1}, p=0.018) and relaxation time constant (τ) significantly decreased (61±3 to 49±2 ms, p=0.004). Before CPB, incremental atrial pacing had no significant effects on E_{ES} and τ but significant negative effects on k_{ED} (0.014±0.005 to 0.045±0.012 ml^{-1}, p=0.013). After CPB, atrial pacing had significant positive effects on E_{ES}, τ and k_{ED} (E_{ES}: 1.12±0.28 to 2.60±1.54 mmHg/ml, p=0.021; τ: 49±2 to 45±2 ms, p=0.009; k_{ED}: 0.040±0.007 to 0.026±0.005 mmHg, p=0.010), indicating improved systolic and diastolic chronotropic responses.

Conclusion. On-pump normothermic CABG with IAWBC preserved systolic function, increased diastolic stiffness, and improved systolic and diastolic chronotropic responses. Normalization of the chronotropic responses post-CPB is likely due to effects of successful revascularization and subsequent relief of ischemia.

INTRODUCTION

Coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB) is a routine and safe procedure with a mortality rate of approximately 2% in elective cases. As traditional cold heart and cold cardioplegic arrest have been shown to reduce post-operative myocardial function, improvements in cardioplegic approaches are still valuable.[1] Moreover, the number of patients with heart failure who are eligible for surgical intervention is rapidly increasing and preservation of left ventricular function by cardioprotection in these patients should be optimal. Warm blood cardioplegia represents an accepted alternative method for myocardial protection. Recent studies indicate that warm blood cardioplegia results in less myocardial damage than cold crystalloid cardioplegia, whereas comparisons against cold blood cardioplegia indicated metabolic advantages, a reduced rate of low output syndrome, and improved post-operative LV function.[2,3,4,5] To facilitate construction of distal coronary anastomoses *intermittent* antegrade warm blood cardioplegia (IAWBC) is currently used by many surgeons and has shown to be a safe approach with potentially important metabolic advantages.[6,7,8,9] However, the acute effects of IAWBC on post-operative myocardial function have not been studied extensively. With on-pump CABG, postoperative myocardial function may be affected by at least three factors: the extracorporal circulation, the revascularization and the cardioplegic cardiac arrest. In addition, the interpretation of postoperative hemodynamic measurements is complicated by possible alterations in loading conditions and heart rate in comparison to preoperative values. The aim of the present study was to quantify the physiological effects of on-pump CABG using IAWBC on systolic and diastolic left ventricular function. To this end, we measured pressure-volume loops by conductance catheter and quantified systolic and diastolic left ventricular function by load-independent parameters derived from pressure-volume relations. To assess chronotropic responses the measurements pre- and post-CPB were performed during right atrial pacing at 80, 100 and 120 beats/min.

METHODS

Patients

Patients undergoing elective isolated CABG were studied pre- and post-CPB. All patients had multi-vessel coronary artery disease and a relatively normal left ventricular ejection fraction (> 40%). The ejection fraction was derived from preoperative echocardiography. Patients included in the study had regular sinus rhythm and none of them had significant valvular disease. The study protocol was reviewed and approved by the medical ethics committee of our institute board and all included patients gave informed consent.

Anaesthesia

Patients received premedication (2 mg Lorazepam, sublingual) two hours before surgery. All patients received total intravenous anesthesia with target-controlled infusion of propofol, remifentanyl and sufentanyl. Pancuronium bromide 0.1 mg/kg was given to facilitate intubation. No further muscle relaxation was used. To monitor cardiac function and facilitate positioning of the conductance catheter a transesophageal multiplane echo (TEE) probe was inserted after induction of anesthesia. Subsequently, a thermal filament catheter was placed in the pulmonary artery via the right internal jugular vein for semi-continuous cardiac output "stat" measurements (Edwards Lifesciences, Uden, The Netherlands). The patients were ventilated with an oxygen/air mixture (FiO_2 = 40%) at a ventilatory rate of 12-15/min and ventilatory volume was adjusted to maintain arterial CO_2 tension between 3.5 and 4 kPa.

Cardiopulmonary bypass and cardioplegic arrest

The cardiopulmonary bypass system consisted of a centrifugal pump (Stockert SIII, Stockert instrumente GmbH, Munchen, Germany), a closed venous reservoir, a Trillium coated Affinity hollow fiber oxygenator (Medtronic Cardiac Surgery, Kerkrade, The Netherlands), a cardiotomy reservoir, and an arterial filter (Dideco, Mirandola Italy). The systems were primed with 1300 ml Ringer solution, 200 ml 20% Human albumin Cealb®solution (Sanquin, Amsterdam, The Netherlands), 100 ml 20% Mannitol and 5000 IU of heparin. CPB was performed with a nonpulsatile flow of 2.4 L/min/m^2 and the core temperature was maintained at 35 ^{0}C. Heparin (300 IU/kg) was administered before cannulation. Additional heparin was administered if the activating clotting time (ACT, Hemochron, Edison, USA) was less than 400 seconds. After cessation of CPB

protamine sulfate was administered (1 mg/ 100 IU heparin). All patients received intermittent antegrade warm blood cardioplegia as described by Calafiore et al.[6] Normothermic blood (temperature 35-37°C) was collected from the oxygenator and was infused into the aortic root using a roller pump with a mean mean flow of 280 ml/min. The tubing was connected to a syringe pump containing potassium in a concentration of 2 mmol/ml. The first dose (2 min duration, or longer if necessary to obtain a flat ECG) was given immediately after aorta cross-clamping and subsequent doses (2 min duration) after construction of each distal anastomosis or after 15 minutes. During the first dose an initial 2 ml bolus of potassium solution was given and subsequently the syringe pump was set to 150 ml/hr. During the second dose the syringe pump speed was set to 120 ml/hr, and to 60 ml/hr during all subsequent doses. Consequently, 14 mmol potassium was given during the first infusion, 8 mmol during the second, and 4 mmol in all subsequent infusions.

Study protocol

Before and directly after CPB, conductance catheter measurements were performed as described previously: Briefly, temporary epicardial pacemaker wires were placed on the right atrium to enable measurement at fixed heart rates.[10] A tourniquet was placed around the inferior vena cava to enable temporary preload reductions. An 8F sheath was placed in the ascending aorta for introduction of the conductance catheter. The conductance catheter was introduced under TEE guidance and placed along the long axis of the left ventricle. Position was optimized by inspection of the segmental volume signals. Conductance catheter calibration was performed using calibration factors alpha (α) derived from thermodilution and parallel conductance correction volume (V_c) determined by hypertonic saline injections.[11,12] Continuous left ventricular pressure and volume signals derived from the conductance catheter were displayed and acquired at a 250 Hz sampling rate using a Leycom CFL (CD Leycom, Zoetermeer, The Netherlands). Data were acquired during steady state and during temporary caval vein occlusion, all with the ventilator turned off at end-expiration. Acquisition was repeated at atrial pacing rates (80, 100 and 120 beats/min). From these signals hemodynamic indices were derived as described below.

Pressure-volume analysis

Post-process data analysis was performed by custom-made software. Indices of global, systolic and diastolic left ventricular function (heart rate, cardiac output, stroke volume,

stroke work, ejection fraction, dP/dt_{MAX}, dP/dt_{MIN}, end-diastolic volume, end-systolic volume, end-diastolic pressure, end-systolic pressure, relaxation time constant τ) were calculated from steady state pressure-volume loops at 80, 100 and 120 beats/min. Systolic and diastolic pressure-volume relations were derived from pressure-volume loops acquired during caval vein occlusion at heart rates of 80, 100 and 120 beats/min. The slope of the end-systolic pressure-volume relationship (end-systolic elastance, E_{ES}) was used as relatively load-independent index of systolic left ventricular contractility.[13] Exponential regression of the end-diastolic pressure-volume relationship was used to determine the stiffness constant k_{ED} as a measure of diastolic chamber stiffness.[14]

Ischemic markers

We evaluated post-operative troponin T levels at regular intervals up to 48 hours (1, 3, 6, 12, 24 and 48 hours). Twelve-lead electrocardiographic recordings before and after CPB were routinely performed and assessed by the cardiologist for signs of myocardial infarction. Peri- and postoperative myocardial ischemia or infarction was defined as serum troponin T levels above 1 μg/l, ECG changes suspective for myocardial infarction, and new echocardiographic regional left ventricular wall motion abnormalities.

Statistical analysis

The pre- and post-CPB data were compared with paired t-tests and we used a multiple linear regression implementation of repeated measures analysis of variance to analyze the effects of chronotropic stimulation pre-CPB and post-CPB, respectively.[15] Data are presented as mean ± SEM. A p-value less than 0.05 was considered statistically significant.

RESULTS

Ten patients (9 men; age 62±10 years) were enrolled in this study. All patients had multi-vessel disease (mean number of affected vessels 2.7±0.5) and four had previous myocardial infarction. The mean pre-operative echocardiographic left ventricular ejection fraction was 58±9%. Mean CPB-time was 105±36 min (median 103, range 60-167 min) with a mean aortic cross-clamp time of 75±27 min (median 69, range 43-129 min). Note that the actual ischemic time is less because approximately 15% of cross-

clamp time is used for cardioplegic delivery. The mean number of anastomoses was 4±1; the left internal thoracic artery was anastomosed to the left anterior descending artery in all cases and used as a jump-graft to the diagonal artery in 6 cases. The right internal thoracic artery was anastomosed to the obtuse marginal artery in three cases, while it was used as a free graft off the left internal thoracic artery and anastomosed to both obtuse marginal and right descending posterior arteries in 5 cases. In two patients venous bypass grafts were used for revascularization of both these vessels.

Weaning from CPB was uneventful: four patients received low dosages of dobutamine post-CPB (≤ 5 µg/kg/min). There were no peri-operative myocardial infarctions. Troponin-T concentrations remained below the diagnostic criteria in all patients 48 hours postoperatively (Figure 1). The hospital stay was uncomplicated in all patients except in one patient who developed mediastinitis and stayed in the hospital for 35 days. The mean length of hospital stay was 11 days (range 6-35 days, median 8 days). The mean length of stay in the intensive care unit was 1.9 days (range 1-3, median 2 days).

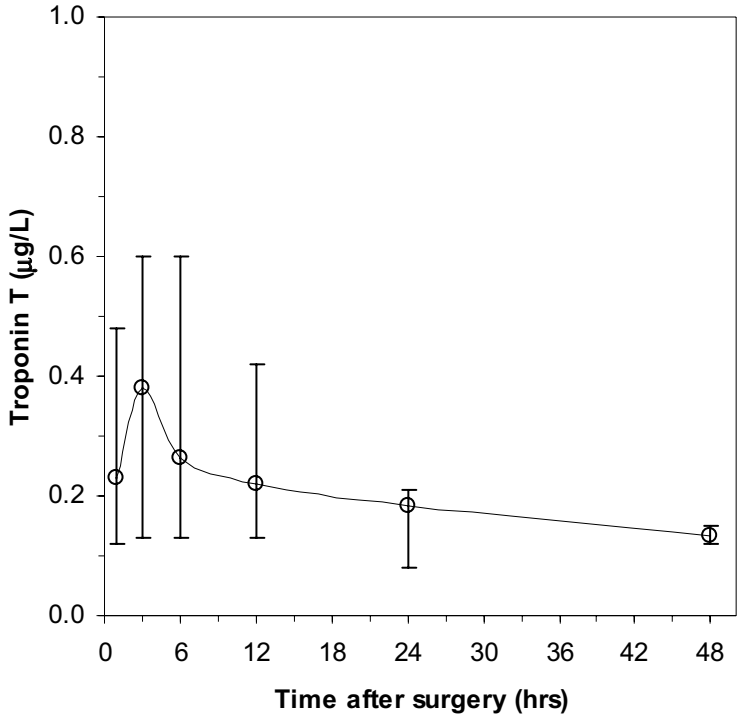

Figure 1. Postoperative troponin T plasma levels. The concentration of troponin T (TnT) remained below the diagnostic criteria for myocardial infarction in all patients in the post-operative period up to 48 hrs. Symbols show median values, error bars indicate ranges

Pressure-volume data

Hemodynamic data from pre- and post-CPB at paced heart rates of 80 (baseline), 100 and 120 beats/min are summarized in Table 1. Figure 2 shows pressure and volume

signals and corresponding pressure-volume loops during preload reduction at paced heart rate of 80 beats/min before and after CPB in a typical patient. The effects of pacing pre- and post-CPB on the main systolic and diastolic function indices are presented in Figure 3.

Table 1. Hemodynamic data obtained at incremental paced heart rate, pre- and post CPB

	Pre-CPB			Post-CPB		
	pre-80	pre-100	pre-120	post-80	post-100	post-120
HR (beats/min)	81.5±1.6	101.1±0.6 *	120.0±1.4 *	86.2±3.9 $^{\&}$	102.5±1.3 $^{\#}$	121.2±0.3 $^{\#}$
CO (l/min)	6.0±0.6	5.9±0.7	6.0±0.7	5.6±0.3	5.9±0.3	6.2±0.3 $^{\#}$
SV (ml)	73±7	58±6 *	50±5 *	66±3	58±3 $^{\#}$	51±2 $^{\#}$
EF (%)	45±7	41±6 *	38±6 *	50±8 $^{\&}$	47±8	47±9
ESV (ml)	123±38	118±37 *	112±36 *	93±27	93±27	87±27
EDV (ml)	191±41	171±41 *	159±40 *	152±26	149±28	137±28 $^{\#}$
ESP (mmHg)	80±5	77±6	72±5 *	78±6	76±3	70±5 $^{\#}$
EDP (mmHg)	10.1±1.2	7.2±0.7 *	9.0±1.1	16.3±2.8 $^{\&}$	14.9±2.7	11.5±1.9 $^{\#}$
SW (mmHg.ml)	5,584±729	4,630±645 *	3,567±455 *	4,471±383	4,007±367 $^{\#}$	3,312±260 $^{\#}$
dP/dt_{MAX}(mmHg/s)	981±90	1,004±102	1,014±123	991±84	985±64	997±64
dP/dt_{MIN} (mmHg/s)	-937±94	-956±110	-896±88	-923±67	-936±59	-903±70
τ (ms)	61±3	58±3	57±3	49±2 $^{\&}$	49±3	45±2 $^{\#}$
E_{ES} (mmHg/ml)	1.22±0.53	1.21±0.43	1.43±0.61	1.12±0.28	1.76±0.92	2.60±1.54 $^{\#}$
k_{ED} (ml^{-1})	0.014±0.005	0.015±0.008	0.045±0.012*	0.040±0.007$^{\&}$	0.023±0.005$^{\#}$	0.026±0.005$^{\#}$

*pre-80, pre-100, pre-120: paced heart rate 80 beats/min (respectively 100, 120 beats/min) pre-CPB; post-80, post-100, post-120: paced heart rate 80 beats/min (respectively 100, 120 beats/min) post-CPB. HR = heart rate, CO = cardiac output, SV = stroke volume, EF = ejection fraction, ESV = end-systolic volume, EDV = end-diastolic volume, ESP = end-systolic pressure, EDP = end-diastolic pressure, SW = stroke work, dP/dt_{MAX} maximal rate of pressure change during contraction; dP/dt_{MIN} maximal rate of pressure change during relaxation; τ = relaxation time constant, E_{ES} = end-systolic elastance, k_{ED} = diastolic chamber stiffness constant. Significances: * : $p<0.05$ vs pre-80; $^{\#}$ $p<0.05$ vs post-80; $^{\&}$ $p<0.05$ post-80 vs pre-80*

Baseline data. Hemodynamic data at baseline (i.e. at 80 beats/min) pre- and post-CPB are included in Table 1 and Figure 3. Cardiac output and stroke volume remained unchanged after CPB, while left ventricular ejection fraction improved significantly.

End-diastolic volume (EDV) and end-systolic volume (ESV) had a clear tendency to decrease post-CPB (EDV: -39 ml; ESV: -30 ml), but these changes did not reach statistical significance. Both end-diastolic pressure and diastolic chamber stiffness increased significantly after CPB, while the relaxation time constant τ decreased significantly. End-systolic elastance (E_{ES}) remained unchanged after CPB.

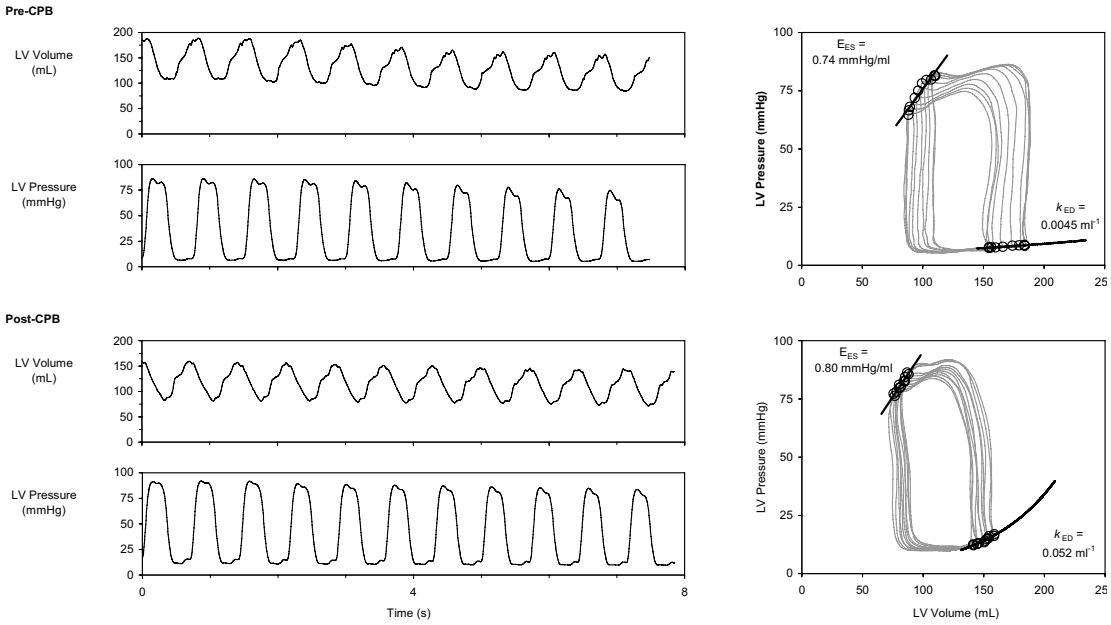

Figure 2. Typical LV pressure and volume signals and pressure-volume loops during preload reduction by transient vena cava occlusion, pre- and post-CPB, at paced heart rate of 80 beats/min

Effects of pacing. Hemodynamic data pre- and post-CPB at 80, 100, and 120 beats/min are given in Table 1 and Figure 3. Note that post-CPB the mean baseline heart rate was 86±4 beats/min because in some patients sinus rhythm exceeded the target pacing rate of 80 beats/min. Cardiac output increased with incremental pacing post-CPB, while pre-CPB pacing did not affect cardiac output. Stroke volume decreased both before and after CPB with pacing, but this decrease was less pronounced after CPB (-24 ml pre-CPB vs -14 ml post-CPB). The smaller reduction in stroke volume with pacing post-CPB was the result of a less pronounced reduction in end-diastolic volume (pre-CPB: -33 ml; post-CPB: -15 ml), since end-systolic volume decreased by 11 ml pre-CPB and by 6 ml post-CPB. Apparently, the capability of the ventricle to fill despite a high heart rate is relatively improved post-CPB. This is supported by the results for the diastolic indices. Active relaxation, τ, improved during pacing post-CPB, while it remained unchanged during pacing pre-CPB. Furthermore, the end-diastolic chamber stiffness constant increased significantly during pacing pre-CPB, whereas it decreased during pacing post-CPB. It should be mentioned that baseline diastolic stiffness (i.e. at 80

beats/min) was higher post-CPB as compared to pre-CPB, but with pacing at 120 beat/min the post-CPB values dropped below the pre-CPB values.

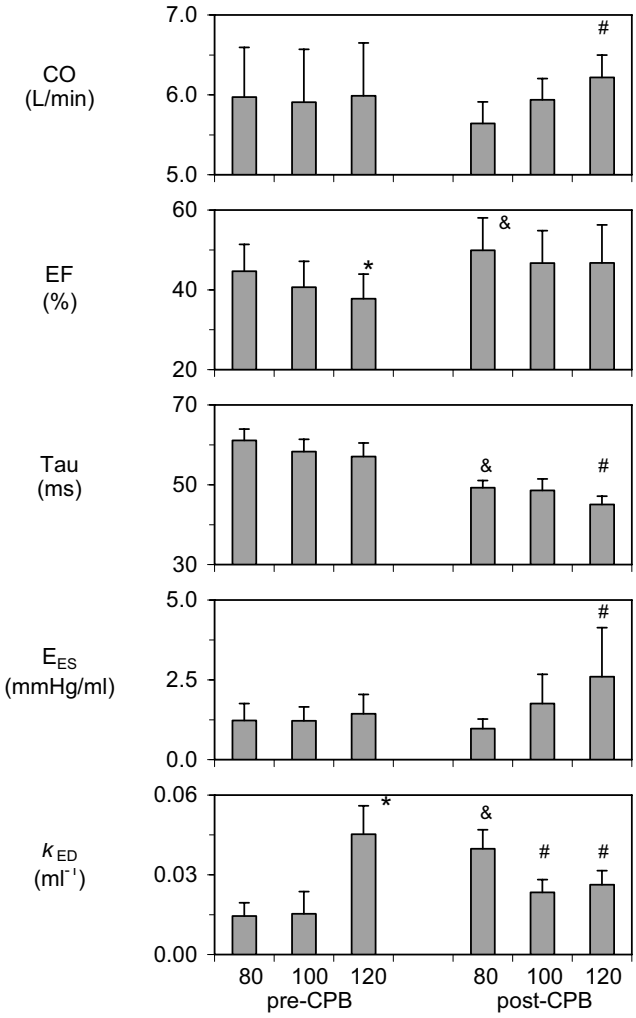

*Figure 3. Main systolic and diastolic hemodynamic indices pre-and post-CPB at paced heart rates of 80, 100 and 120 beats/min. Significances: * : p<0.05 vs pre-80; # : p<0.05 vs post-80; & : p<0.05 post-80 vs pre-80*

During pacing end-diastolic pressure remained constant pre-CPB, which is the result of a reduced end-diastolic volume (which should lower end-diastolic pressure) combined with an increased diastolic stiffness (which increases end-diastolic pressure). However, post-CPB end-diastolic pressure gradually dropped with incremental pacing, since both end-diastolic volume and stiffness decreased. With regard to systolic function, pre-CPB EF decreased significantly at 120 beats/min, whereas it was unchanged post-CPB. dP/dt_{MAX} was unchanged both before and after CPB. Furthermore, no systematic effects were seen on E_{ES} during pacing pre-CPB, but post-CPB E_{ES} increased significantly at 120 beats/min indicating an improvement in systolic function (Figure 3).

DISCUSSION

CABG is increasingly performed in heart failure patients with concomitant surgical valvular repair and/or left ventricular restoration. Optimal preservation of myocardial function is important to facilitate these surgical procedures. Traditional cold heart and cold cardioplegic arrest may have negative effects on post-operative myocardial function and currently normothermic procedures are increasingly used as an alternative.[1] Previous studies indicate that normothermic arrest with warm blood cardioplegia provides metabolic benefits and less cell damage, possibly mediated by a better protection from from ischemia-reperfusion injury.[2,3,9] However, few data are available on the acute effects on ventricular function. The aim of our study was therefore to quantify the effects of normothermic on-pump CABG and IAWBC on systolic and diastolic left ventricular function. In brief, our results show that this approach has no negative effects on baseline systolic function, whereas it tended to improve the response of systolic function during incremental pacing. With regard to diastolic function we found an improved early relaxation, but the end-diastolic stiffness was increased at baseline. However, incremental pacing revealed improved relaxation and filling characteristics post-CPB, whereas pre-CPB the diastolic indices remained constant or worsened during pacing.

Baseline hemodynamic changes

The baseline hemodynamic results (i.e. comparing pre- vs. post-CPB at 80 beats/min) show a slight but significant increase of ejection fraction after CPB, which is due to a marked decrease in end-diastolic volume (-39 ml) with a relatively unchanged stroke volume. Stroke volume remained largely unchanged due to a similar decrease of end-systolic volume (-30 ml) after CPB. Note that, except for EF, none of these volumetric changes reached statistical significance. The effect on EDV is the result of impairment of late passive diastolic function (k_{ED} and EDP increased significantly after CPB), despite the fact that active relaxation (τ) significantly improved after CPB. The improved ejection fraction and the finding of a reduced end-systolic volume with maintained end-systolic pressure both point towards an improved systolic function. However, the load-independent contractility index E_{ES} did not change significantly. Therefore, we would conclude that normothermic CPB with IAWBC at least preserves systolic function in this patient group. This is in contrast with studies using cold blood

cardioplegia during hypothermia in which a reduced systolic left ventricular function after CPB was reported.[1]

With respect to diastolic function we found a somewhat prolonged τ at baseline pre-CPB, which has already been shown to be representative for patients with coronary artery disease.[16,17] In our study τ decreased significantly after CPB with warm blood cardioplegia indicating an improved early, active relaxation. This normalization of τ after revascularization is consistent with previous studies regardless of the use of cold or warm blood cardioplegia and is most likely related to enhancement of the, highly oxygen-dependent, calcium re-uptake process by the sarcoplasmic reticulum after revascularization, and not due to effects of CPB.[18] After CPB increased circulating catecholamines resulting from CPB and ischemia may influence active relaxation. However, the unchanged systolic pressure and heart rate after CPB indicate that this effect is unlikely to be very prominent in our study. In contrast to the improvement in τ, the diastolic chamber stiffness constant, which represents passive late diastolic function was significantly increased post-CPB. This increased stiffness (thus reduced diastolic compliance) is likely due to temporary myocardial edema and increased water content after CPB.[19,20] This finding is important when interpreting changes in diastolic function after surgical interventions such as ventricular restoration and other procedures.[21] Apparently, part of the changes in diastolic function, at least in the acute phase, are related to the cardioplegic arrest and CPB, and should not be attributed to the surgical procedure per se.

Chronotropic responses

We found a significant improvement of cardiac output during incremental atrial pacing post-CPB, whereas cardiac output remained constant pre-CPB. This effect reflected a more pronounced decrease in stroke volume with pacing pre-CPB, compared to post-CPB. In normal physiology maintained stroke volume (or a limited reduction) during increased heart rate is obtained by a combination of increased systolic function (Bowditch effect), which reduces or maintains end-systolic volume, and an improved relaxation, which limits the reduction in end-diastolic volume resulting from the reduced diastolic filling time. Our results indicate that neither of these mechanisms is operative in patients with coronary artery disease (CAD) pre-CPB and consequently cardiac output did not increase during incremental pacing. Moreover, diastolic stiffness substantially increased during pacing which further limited filling. The finding that systolic function does not improve or even decreases with increased heart rate in CAD

patients is consistent with previous studies.[22] A recent echocardiographic study in patients undergoing CABG indicates an increased diastolic stiffness during pacing very similar to our findings.[23] Numerous studies have documented increased diastolic pressure, increased stiffness and upward shifts of the diastolic pressure-volume relation with pacing angina, however our study shows that more subtle increases in diastolic stiffness are obtained with a relatively small increase in heart rate in CAD patients with relatively preserved EF.[24]

After CPB, diastolic chamber stiffness, end-diastolic pressure and τ all significantly decreased during pacing which may explain the improvement of cardiac output at higher heart rates. In addition, E_{ES} gradually increased with incremental pacing post-CPB, whereas it remained constant pre-CPB, indicating that improvement in systolic function contributed to the increase in cardiac output.

The effects of pacing pre- vs. post-CPB in our study largely mimic the effects of exercise before and after revascularization surgery as described in a study by Caroll et al.[25] After surgery, but not before, both pacing and exercise induced improvements in systolic and diastolic function, which enable the required increase in cardiac output. However, during exercise end-diastolic pressure and volume increased whereas during pacing in our study these indices decreased. These differences are presumably due to recruitment of blood volume during exercise leading to increased preload, which does not occur during pacing.

The impaired chronotropic responses pre-CPB as found in our study are presumably due to coronary artery disease and the normalization of these responses post-CPB due to effects of successful revascularization and subsequent relief of ischemia.

Limitations

We did not include a control group with a cold cardioplegic approach. However, this approach is well documented in the literature and we compared our results against those reports. Furthermore, our study was performed in patients with relatively normal LV function, whereas the advantages of IAWBC are presumably most important for patients with poor LV function. However, in heart failure patients the effects of IAWBC would be difficult to assess separately because the surgical interventions (CABG and additional procedures like mitral annuloplasty and/or surgical restoration) may importantly affect post-operative LV function.

In conclusion, this study shows that intermittent antegrade warm blood cardioplegia during normothermic cardiopulmonary bypass provides excellent myocardial protection

of systolic properties, whereas improved diastolic and systolic left ventricular chronotropic responses were found acutely after surgery. This cardioprotective stategy may be particularly advantageous in patients with heart failure who undergo complex surgical procedures with long procedure times.

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