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L. Jacquet
P. Honore
R. Beale
D. Valadi
R. Dion
M. Goenen

Cardiac function after intermittent antegrade warm blood cardioplegia: contribution of the double-indicator dilution technique

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L. Jacquet (✉) · D. Valadi · R. Dion · M. Goenen
Cardiothoracic Intensive Care Unit,
University Hospital Saint-Luc,
10 avenue Hippocrate,
1200 Brussels, Belgium
e-mail: jacquet@rean.ucl.ac.be
Tel.: + 32-2-764 27 01
Fax: + 32-2-764 89 28

P. Honore
Intensive Care Unit,
Cliniques Saint-Pierre, Ottignies, Belgium

R. Beale
Intensive Care Unit, Guy's Hospital,
London, United Kingdom

Abstract *Objective*: To evaluate cardiac performance following coronary artery surgery using two different techniques of cardioplegia
Design: Randomized prospective study
Setting: Adult cardiothoracic intensive care unit in a university hospital
Study population: Thirty patients undergoing isolated coronary surgery
Interventions: Patients were randomized to receive either intermittent antegrade warm blood cardioplegia with normothermic bypass (group 1) or combined antegrade and retrograde cold crystalloid cardioplegia with hypothermic bypass (group 2). Hemodynamic evaluation included conventional measurements from a pulmonary artery catheter and data obtained by thermal dye dilution utilizing an arterial thermistor-tipped fiberoptic catheter
Results: The only major difference between groups was a significantly higher right atrial pressure in group 2, from 4 h to 24 h after surgery (8.8 ± 2.6 vs. 11.8 ± 3.2 mmHg at 4 h and 11 ± 3.1 vs. 8.5 ± 1.8 mmHg at 24 h, $P = 0.04$). After cold cardioplegia a significant increase in right atrial pressure was observed (7.5 ± 3.1 before surgery vs. 11.4 ± 3 mmHg at 8 h, $P = 0.003$) whereas right ventricular end diastolic volume index did not increase significantly, suggesting impaired right ventricular diastolic compliance in this group
Conclusions: Until 24 h after surgery cold cardioplegia is associated with impaired right ventricular filling, which seems better preserved by intermittent antegrade warm blood cardioplegia. End-diastolic volume measurement with the double-indicator technique allows differentiation between systolic and diastolic dysfunction.

Key words Cardioplegia · Intermittent · Right ventricle · Indocyanine green · Preload

Introduction

In vitro and in vivo studies have demonstrated the superiority of warm blood cardioplegia over conventional cold cardioplegia in myocardial metabolic and functional recovery [1, 2, 3]. Continuous administration is limited in clinical practice by blood flooding into the operating field requiring repetitive interruptions for completion of the distal anastomoses. Interruptions of up to 13 min have been shown to have no deleterious effect [4]. Deliberate use of intermittent antegrade warm blood cardioplegia (IAWBC) has therefore been proposed by Calafiore and coworkers [5] with excellent clinical results.

In a previous prospective randomized trial comparing IAWBC with a combined antegrade and retrograde cold crystalloid cardioplegia technique, we demonstrated that patients in the IAWBC group have lower post-

operative levels of cardiac-specific markers of injury (cardiac troponin I and creatinine kinase isoenzyme muscle-brain fraction) and with lower right atrial pressures (RAP) [6]. The present study was designed to investigate the reason for this difference in RAP and especially to study right ventricular (RV) behavior after cardioplegic arrest in more detail. Thirty patients scheduled for coronary surgery were randomized to receive either IAWBC or antegrade and retrograde cold crystalloid cardioplegia, and were studied using a double-indicator thermal dye dilution technique allowing determination of cardiac output (CO) and of intrathoracic and cardiac end-diastolic volumes [7, 8, 9, 10].

Patients and methods

Protocol

With approval of the institutional ethics committee and after giving their informed consent, 30 patients scheduled for isolated coronary artery bypass surgery were randomized to receive either IAWBC (group 1) or combined antegrade and retrograde cold crystalloid cardioplegia (group 2). Patients with abnormal liver function tests were excluded from the study to avoid any possible interference with indocyanine green metabolism. Anesthesia was induced with sufentanyl (3 μg/kg) and midazolam (0.05 mg/kg) and maintained by a continuous administration of sufentanyl (1–1.5 μg/kg per hour) and propofol (1–2.5 mg/kg per hour). Muscle paralysis was obtained with pancuronium (0.1 mg/kg). Cardiopulmonary bypass (CPB) was instituted with a heparin-coated circuit (Duraflo II, Baxter, Irvine, California) and a heparin-coated hollow fiber membrane oxygenator (Spiragold, Baxter). The circuit was primed with 1.5 l crystalloid solution (Plasmalyte, Baxter) and 2 ml/kg mannitol 15 %. Systemic heparin was given to achieve an activated clotting time of longer than 450 s. In group 1, cardiac arrest was achieved by intermittent infusion of normothermic potassium-enriched blood in the aortic root. The potassium solution (2 mEq/ml) was administered by a syringe pump into a side-arm of the CPB return cannula at the rate and duration described by Calafiore et al. [5]. The time between two infusions never exceeded 15 min. Blood temperature was maintained around 37 °C. In group 2, cardiac arrest was obtained by infusion of 500 ml cold crystalloid solution (St. Thomas solution) into the aortic root and 500 ml of the same solution into the coronary sinus at a pressure lower than 40 mmHg after retrograde cannulation. An additional 500 ml was administered every 60 min or whenever necessary. Body temperature was allowed to decrease to 30 °C.

In the intensive care unit, sedation was systematically maintained until the sixth postoperative hour with a continuous infusion of sufentanyl (0.5 μg/kg per hour) and propofol (0.5–2 mg/kg per hour). Ventilation was achieved in intermittent mandatory ventilation with a volume set at 8 ml/kg and a rate adapted for a pCO_2 between 35 and 40 mmHg. Extubation was performed as soon as patients were able to maintain adequate gas exchange with a pressure support at 5 cmH_2O above end-expiratory pressure and a respiratory rate less than 20/min.

Hemodynamic monitoring

As part of our routine monitoring a 7.5-F pulmonary artery catheter (Baxter, Irvine, Calif., USA) was inserted after induction of anesthesia. A 4-F thermistor-tipped fiberoptic catheter (Pulsion, Munich, Germany) was inserted in the descending aorta through a 5-F introducer sheath placed in the femoral artery. Four patients initially enrolled in the study were withdrawn because the catheter could not be correctly located in the descending aorta. Both pulmonary artery and fiberoptic catheters were connected to a dedicated bedside computer (Cold Z-201 System, Pulsion, Munich, Germany). After injection of indocyanine green diluted in 10 ml ice-cold 5 % glucose at a concentration of 1 mg/ml, a pulmonary artery and an aortic thermodilution curve were recorded together with an aortic dye dilution curve. To avoid volume variations related to respiratory phases, injections were always performed at end-expiration.

CO was calculated using the standard Stewart-Hamilton formula. The volume of distribution of an indicator between the point of injection and detection can be calculated from the product of total flow and the mean transit time (MTT) of the indicator. Accordingly, the volume of distribution of the thermal indicator between right atrium and detection in the aorta is the intrathoracic thermal volume (ITTV) calculated as:

$$ITTV = CO \times MTT_{TA} \quad (1)$$

where MTT_{TA} is the MTT of the thermal indicator between right atrium and aorta. The dye indicator binds to plasma proteins immediately after injection and stays strictly intravascularly so giving the intrathoracic blood volume (ITBV) calculated as:

$$ITBV = CO \times MTT_{D} \quad (2)$$

where MTT_D is the MTT of the dye between right atrium and aorta. The volume of distribution of the thermal indicator between right atrium and pulmonary artery corresponds to the right heart end diastolic volume (RHEDV) and can be calculated by:

$$RHEDV = CO \times MTT_{TPA} \quad (3)$$

where MTT_{TPA} is the MTT of the thermal indicator between right atrium and pulmonary artery.

For a number of different serial mixing chambers constituting different mixing volumes but identical chamber flow, the decay of the dilution curve is determined predominantly by the largest chamber [11]. Using this dilution decay approach, the volume of the largest mixing chamber of an indicator can be derived from the total flow and the exponential downslope time (τ) of the indicator. The largest mixing chamber for the thermal indicator between right atrium and pulmonary artery is the right ventricle at end diastole, the volume of which (RVEDV) can be calculated as:

$$RVEDV = CO \times \tau_{TPA} \quad (4)$$

where τ_{TPA} is the decay time of the thermal indicator in the pulmonary artery. The largest mixing chamber for the thermal indicator between right atrium and aorta is the pulmonary thermal volume (PTV), which can calculated as:

$$PTV = CO \times \tau_{TA} \quad (5)$$

where τ_{TA} is the decay time of the thermal indicator in the aorta.

Left heart end diastolic volume (LHEDV) can then be calculated by substracting from the intrathoracic thermal volume, the right heart end-diastolic volume and the pulmonary thermal volume:

Table 1 Preoperative and perioperative data of the two groups

	Cold cardioplegia ($n = 15$)	Warm cardioplegia ($n = 15$)	P-value
Male/female	9/6	12/3	0.42
Weight (kg)	73.7 ± 9.2	73.0 ± 10.5	0.8
B. S. A. (m^2)	1.80 ± 0.15	1.82 ± 0.15	0.65
LV ejection fraction (%)	54.9 ± 11.8	49.2 ± 11.9	0.2
Three-vessels disease (%)	86	93	0.8
Distal anastomoses (n)	2.8 ± 0.8	3.2 ± 0.8	0.1
CPB duration (min)	106.4 ± 42.8	112.7 ± 43.4	0.69
Aortic cross-clamp (min)	73.9 ± 26.5	75.4 ± 27.7	0.88
Dobutamine (n) (mean dose)	3 (2 μg/kg/min)	3 (3.5 μg/kg/min)	1
Adrenaline (n) (mean dose)	4 (0.03 μg/kg/min)	3 (0.02 μg/kg/min)	0.85
Milrinone (n) (mean dose)	1 (0.25 μg/kg/min)	–	0.96
Duration of intubation (hours)	Median = 17 [12–33.5]	Median = 20 [13–23.5]	0.1
Patients extubated at 24 hours (%)	40	73	0.1

B. S. A. = Body Surface Area
LV = Left ventricle

Table 2 Conventional hemodynamic data

		T-1	T0	T4	T8	T24
Heart rate (bpm)	Warm	72.4 ± 16.6*	84.0 ± 12.4	86.0 ± 11.4	87.6 ± 7.6	85.6 ± 11.2
	Cold	65.5 ± 16.5*	83.0 ± 11.2	83.0 ± 12.4	85.6 ± 10.2	83.2 ± 13.5
Blood pressure mean (mm Hg)	Warm	79.2 ± 14.2	84.1 ± 13.0	71.0 ± 6.5**	70.9 ± 6.3**	83.1 ± 9.0
	Cold	76.1 ± 13.2	82.2 ± 14.7	71.6 ± 9.1	76.2 ± 9.6	78.0 ± 9.5
Right atrial pressure (mm Hg)	Warm	7.8 ± 2.6	7.9 ± 2.7§	8.8 ± 2.7§	8.8 ± 2.6§	8.5 ± 1.8§
	Cold	7.5 ± 3.1*	9.8 ± 2.1	11.8 ± 3.2	11.4 ± 3.0	11.0 ± 3.2
Pulmonary artery pressure (mm Hg)	Warm	17.6 ± 4.4	19.3 ± 3.6	20.1 ± 5.7	20.2 ± 4.4	22.5 ± 5.1
	Cold	18.8 ± 4.0	21.5 ± 3.7	23.2 ± 5.1	22.8 ± 5.1	22.0 ± 5.7
Pulmonary artery occlusion pressure (mm Hg)	Warm	9.6 ± 2.7	10.2 ± 4.4	10.1 ± 3.7	10.4 ± 3.1	10.2 ± 2.3
	Cold	11.8 ± 4.5	11.9 ± 3.8	13.8 ± 3.0	12.7 ± 4.0	12.8 ± 3.8
Cardiac index ($l/min/m^2$)	Warm	2.2 ± 6*	2.8 ± 8	3.3 ± 1	3.4 ± 9	3.8 ± 8
	Cold	2.8 ± 6*	3.5 ± 7	3.4 ± 7	3.8 ± 9	3.5 ± 6
Stroke index (ml/m^2)	Warm	30.2 ± 14.9	34.6 ± 9.8	39.7 ± 11.0	39.2 ± 10.1	45.5 ± 11.1***
	Cold	38.0 ± 10	43.2 ± 8.8	42 ± 7.5	45.0 ± 11.6	43.6 ± 7.7
LVSWI ($g.m/m^2$)	Warm	33.9 ± 13.5	36.7 ± 13.1	32.7 ± 9.8	38.1 ± 10.8	39.0 ± 10.6
	Cold	31.0 ± 10.3	40.8 ± 13.7	33.6 ± 8.5	34.1 ± 11.5	42.6 ± 12.4
RVSWI ($g.m/m^2$)	Warm	4.7 ± 2.3	5.5 ± 2.8	6.1 ± 3.4	7.0 ± 3.0	7.4 ± 3.5
	Cold	5.9 ± 2.2	6.3 ± 2.2	6.8 ± 3.3	6.7 ± 3.8	6.4 ± 2.3

LVSWI = Left Ventricular Stroke Work Index
RVSWI = Right Ventricular Stroke Work Index
* $p < 0.05$ T-1 vs all other time points
** $p < 0.05$ T4 and T8 vs T-1, T0, T24
*** $p < 0.05$ T24 vs T-1
§ $p < 0.05$ warm vs cold

LHEDV = ITTV-PTV-RHEDV = Eq. 1–Eq. 5–Eq. 3 (6)

A baseline hemodynamic evaluation was performed after induction of anesthesia but before sternal opening (t_{-1}), at arrival in ICU (t_0), and at 4 h (t_4), 8 h (t_8) and 24 h (t_{24}) after surgery.

Statistical analysis

Data are presented as mean ± standard deviation for normally distributed variables and as median (interquatile range) if distribution was not normal. For between groups comparisons, the unpaired t test was used for continuous variables and the χ^2 test for proportions. For comparison of serially recorded variables, an analysis of variance for repeated measures was used. If a difference was found, the t test with the Bonferroni correction was used to compare groups at each time point or different time points within a single group. Correlations between variables were calculated by Pearson's correlation coefficient. A P value less than 0.05 was considered significant. Statistical analyses were computed by Crunch statistical package (Oakland, Calif., USA).

Table 3 Hemodynamic data derived from the double indicator technique

		T-1	T0	T4	T8	T24
ITBVI	Warm	801 ± 295	807 ± 203	881 ± 197	879 ± 141	957 ± 383
(ml/m^2)	Cold	813 ± 291	962 ± 273	938 ± 225	952 ± 263	1042 ± 198
RVEDVI	Warm	130 ± 39	127 ± 43	129 ± 28	132 ± 19	154 ± 21
(ml/m^2)	Cold	134 ± 34	137 ± 27	149 ± 35	146 ± 38	146 ± 26
RHEDVI	Warm	254 ± 58	289 ± 84	294 ± 67	288 ± 44	341 ± 45*
(ml/m^2)	Cold	309 ± 160	314 ± 54	321 ± 57	320 ± 70	322 ± 48
LHEDVI	Warm	359 ± 147	409 ± 113	410 ± 145	427 ± 99	513 ± 135
(ml/m^2)	Cold	337 ± 211	461 ± 213	429 ± 178	432 ± 169	429 ± 138
RVSWI/RVEDVI	Warm	0.039 ± 0.014	0.046 ± 0.012	0.049 ± 0.027	0.048 ± 0.020	0.045 ± 0.019
	Cold	0.038 ± 0.019	0.046 ± 0.020	0.048 ± 0.020	0.053 ± 0.020	0.051 ± 0.020

ITBVI: intra-thoracic blood volume index
RVEDVI: right ventricular end diastolic volume index
RHEDVI: right heart end diastolic volume index
RVSWI: right ventricular stroke work index
LHEDVI: left heart end diastolic volume index
* $p < 0.01$ T24 vs T-1

Results

Preoperative and perioperative values did not differ significantly between the two groups (Table 1). Conventional hemodynamic data are presented in Table 2. When comparing the two types of cardioplegia, right atrial pressures (RAP) were higher in the cold cardioplegia group from arrival in ICU until 24 h after surgery. Cardiac index and stroke volume index also tended to be higher in the cold group at t_0, but this difference was not significant and had disappeared 4 h later. When considering the course over time, heart rate and cardiac index were significantly higher at all time points after surgery than preoperative values in both groups. In the cold group we also observed a significant increase in RAP especially at t_4 (11.8 ± 3.2 vs. 7.5 ± 3.1 mmHg before surgery, $P = 0.003$) and t_8 (11.4 ± 3 vs. 7.5 ± 3.1 mmHg before surgery, $P = 0.006$). Hemodynamic data derived from the double-indicator technique are presented in Table 3. None of these parameters were significantly different between the groups at any time. Ventricular diastolic and systolic function curves can be constructed from the pressure and volume data. No significant difference in pressure or volume was noted for the left ventricle, and therefore only RV curves are presented in Figs. 1 and 2.

Discussion

Methodological aspects

The technique used for measuring fluid volumes is based on MTT for thermal and dye indicators and of the decay time volumes calculated from the indicator dilution curves. The MTT technique has been used extensively, especially for measuring lung water [12, 13]. Several studies in animals and in organ donors have reported a good correlation between gravimetric extravascular lung water and extravascular thermal volume, defined as the difference between ITTV and ITBV [14, 15]. Therefore ITBV and ITTV must be accurately calculated from the MTT of the dye and thermal indicators. An ITBV of 800 ml/m^2 at baseline is indeed in accordance with the cardiopulmonary blood volume of 741 ml/m^2 reported by London et al. [16] who measured the MTT of the indicators with a catheter placed at the level of the aortic valve.

The exponential decay time technique has been less extensively studied, and a direct comparison of volumes as determined by the present technique and in situ measurement has not been published [11]. However, Thorvaldson et al. [17], using a different technique, measured a mean pulmonary blood volume of 3.8–4.2 ml/kg in open-chest dog studies, which is well in accordance with our baseline values around 4 ml/kg. Moreover, the exponential decay approach has been validated using a fast-response thermistor equipped pulmonary artery catheter to calculate the residual fraction, the ejection fraction, and RV volumes [18, 19]. The present technique must apply an adaptative algorithm to correct for the slow response time of the thermistor, which has been validated in an animal study [20]. Right ventricular volumes have been measured by several investigators in coronary artery bypass graft patients using a fast-response thermistor equipped pulmonary artery catheter [21, 22]. Baseline values of ± 90–120 ml/m^2 have been reported by this method, which are only slightly lower than our preoperative level of ± 130 ml/m^2.

Comparison of cardioplegia techniques

In a previous randomized trial of 200 patients undergoing coronary surgery we compared IAWBC with a combined antegrade and retrograde crystalloid cardiople-

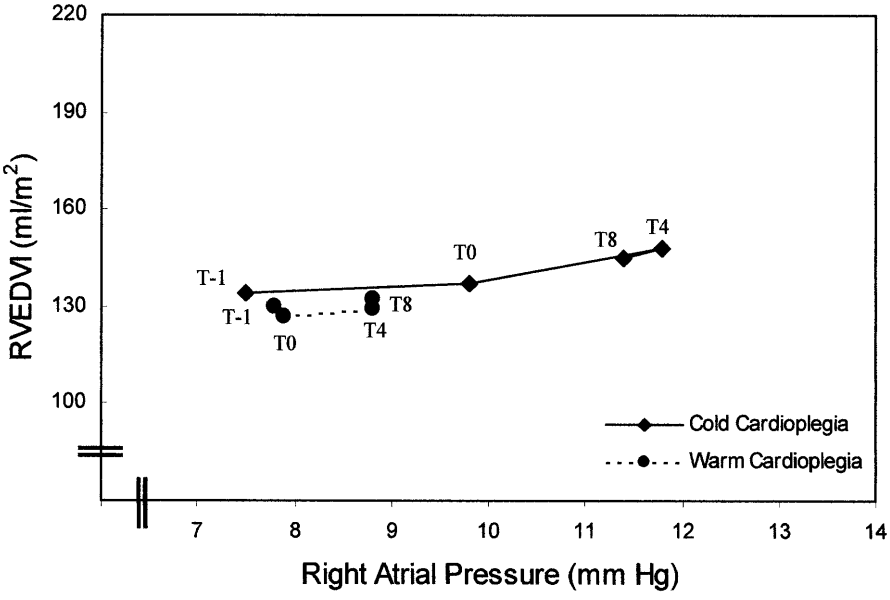

Fig. 1 RV diastolic function curve until the eighth postoperative hour, when sedation and ventilation were unchanged

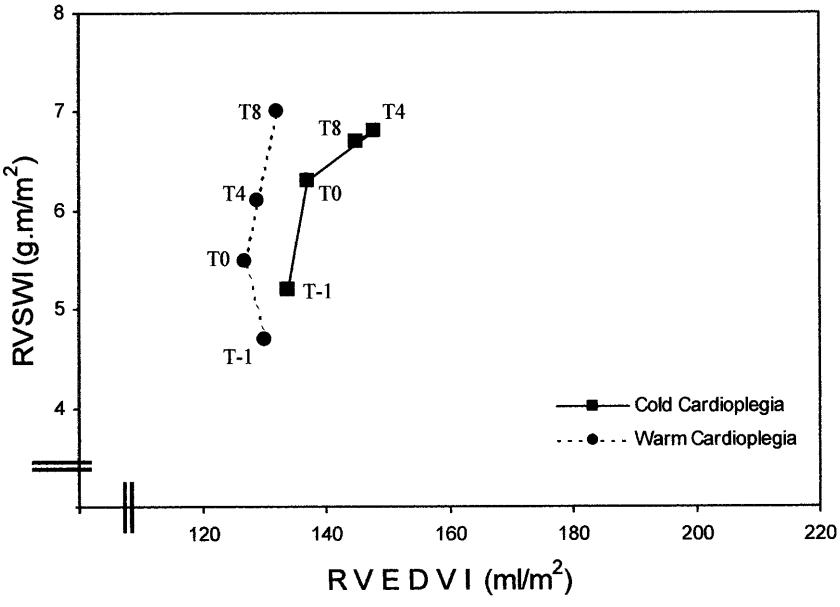

Fig. 2 RV systolic function curve until the eighth postoperative hour, when sedation and ventilation were unchanged

gia. The only hemodynamic difference that we noted was a higher RAP in the cold cardioplegia group [6]. This difference may have been related to a more positive fluid balance in the cold group (larger volume of the cardioplegic solution) or to impaired systolic or diastolic RV function. In the present study following the same protocol we reached the same results as far as conventional hemodynamic parameters are concerned.

In the cold cardioplegia group, indeed, we observed a highly significant increase in RAP after surgery compared to preoperative values whereas no significant change was noted in the warm cardioplegia group. As a consequence RAP was significantly higher in the cold than in the warm group from arrival in ICU until 24 h later. According to the study protocol, patients were sedated and ventilated with the same tidal volume and end-expiratory pressure from induction of anesthesia until the eighth postoperative hour to keep intrathoracic pressure as stable as possible. It is therefore most likely that transmural atrial pressure increased in parallel to the measured intracavitary RAP.

Data derived from the double-indicator dilution technique, whether using the exponential decay approach to calculate RVEDVI or the MTT to measure

RHEDVI, indicated that higher right filling pressures in the cold cardioplegia group do not translate into higher right filling volumes. This strongly suggests that impaired RV diastolic filling after cold cardioplegia was responsible for the observed higher RAP.

In the warm cardioplegia group both filling pressures and volumes were unchanged after surgery. RVEDVI did not differ from volumes of the cold group, but RAP was significantly lower, suggesting that RV filling is better preserved after warm cardioplegia.

Depression of systolic function could theoretically explain an increase in RAP in the cold group, but the RVSWI/RVEDVI relationship is well preserved and even slightly improved after surgery. This relationship is probably not the best index of contractility and must be cautiously interpreted, keeping in mind that 30 % of the patients in both groups received inotropic medications that could blunt some systolic dysfunction. Nevertheless, stroke work was maintained without ventricular dilatation, excluding systolic dysfunction as the reason for the higher RAP.

Further studies, using transesophageal echocardiography, for instance, would be necessary to explain the different behavior between cold and warm cardioplegia. Cold cardioplegia delivery by a combined antegrade and retrograde route would allow better distribution of the solution than an antegrade route alone, especially if the right coronary artery is severely stenosed [23]. In our patients, right coronary artery disease was evenly distributed in the two groups, but the difficulty of maintaining hypothermia in the thin walled RV could decrease the quality of myocardial protection.

Increased RV stiffness in the cold group could also be related to more pronounced myocardial edema when crystalloids with low colloid osmotic pressure are used as opposed to blood cardioplegia. In this hypothesis, retrograde infusion into the coronary sinus would contribute even more to the development of RV parietal edema and decreased compliance [24].

The use of inotropes, especially phosphodiesterase inhibitors, could have influenced the results through their effect on myocardial relaxation. However, the medications used and their mean doses were not different between groups, with only one patient in the warm group having received milrinone at 0.25 μg/kg per hour. Thus the difference in vasoactive or inotropic support cannot explain the significantly different RAP between groups.

Data on the left ventricle are more hazardous to interpret since we were unable to measure left ventricular end-diastolic volumes, but rather global left heart volumes. Moreover, left heart volumes are calculated by mathematical manipulation of various intrathoracic volumes, decreasing the precision of the results. Nevertheless, no statistical difference in left-sided pressures or volumes was noted neither between groups, nor over time.

Assessment of preload

As already pointed out by several investigators, relying on measured intracardiac pressure to estimate preload can be misleading, especially in the context of mechanical ventilation [7, 10, 25]. In our study, if RAP had reflected RV preload, the observed significant increase in RAP without significant change in RVSWI in the cold cardioplegia group would indicate decreased RV systolic function. In fact, volume measurements clearly demonstrate that the increased RAP after cold cardioplegia is related to impairment of diastolic filling rather than to depressed systolic function or to volume overload. To be completely conclusive, transmural RAP should have been measured to confirm that intrathoracic pressure remained stable during the study period as intended by our protocol.

In conclusion, the only hemodynamic difference observed between IAWBC and cold crystalloid cardioplegia was a higher RAP during the first postoperative day when cold cardioplegia was used. Measurement of cardiac end diastolic volumes with the double-indicator technique demonstrates that this higher right atrial filling pressure is related to decreased RV compliance in the cold cardioplegia group whereas RV systolic function was well preserved in both groups.

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