The Effects of Hypothermia on Human Left Ventricular Contractile Function During Cardiac Surgery

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OBJECTIVES

We investigated the interaction of heart rate (HR), temperature and contractility using a validated load independent method.

BACKGROUND

Temperature manipulation is an integral part of cardiac surgery, and postoperative hypothermia is extremely common. Myocardial contraction is a series of enzymatic and physicochemical reactions that may be differentially affected by temperature.

METHODS

Ten patients undergoing coronary artery bypass grafting were studied during moderately hypothermic cardiopulmonary bypass. After conduit procurement and heparinization but before grafting, the patient was placed on cardiopulmonary bypass and rewarmed to 37°C, and the left ventricle (LV) was instrumented with a conductance catheter allowing continuous pressure and volume measurement. The LV pressure volume relationship was examined to assess the contractility at 37, 35, 33 and 31°C, with fixed atrial pacing (100 beats/min) in five patients and at 80 and 120 beats/min, at 33 and 37°C in five patients.

RESULTS

At a HR of 100 beats/min, lower temperature resulted in a highly significant decrease in maximal elastance (100% at 37°C, 29 ± 3.5% at 31°C, p < 0.0001). At 37°C, increasing HR increased contractility (80 beats/min 100%, 120 beats/min 205.9%, p = 0.0021); however, at 33°C contractility fell with increasing HR (80 beats/min 100%, 120 beats/min, 53.7%, p = 0.0014).

CONCLUSION

At normothermia LV contractility has a direct relationship with HR. In hypothermic conditions this relationship inverses. Clinical strategies maintaining higher HRs at colder temperatures result in reduced contractility. These factors are important in the management of cardiac surgical patients.

Temperature manipulation is an integral part of cardiac surgery. Corporeal hypothermia is utilized to reduce metabolic demand and therefore increase tolerance to ischemia. Cooling has also been used as a therapeutic maneuver in hemodynamically unstable postoperative patients (1,2). Most cardiac surgical procedures are performed under conditions of moderate hypothermia (26 to 31°C) utilizing cardiopulmonary bypass (CPB). After CPB, despite prolonged rewarming using countercurrent heat exchange and restoring nasopharyngeal temperature to 37°C, a persistent temperature “afterdrop” commonly occurs (3). This afterdrop may have important effects on myocardial contractility.

Although the effects of hypothermia on myocardial contractility have been widely studied in animal models both in vitro and in vivo, studies in human subjects remain sparse. Intuitively, as myofibrillar contraction is in part an active energetic process, hypothermia might be expected to reduce the myocardial contractile state. Paradoxically, experiments with rat myofibrils (4), rabbit (5) and guinea pig (6) papillary muscle and cross-circulated canine hearts (7) have shown an increase in contractility with cooling. Furthermore, the interaction of temperature, heart rate (HR) and contractility has recently come under investigation. The increase in contractility seen with cooling of the in vitro rabbit heart is forfeited if HR is not allowed to slow as myocardial temperature falls (5).

Systolic performance can be most accurately described using the left ventricular pressure-volume relationship (LVPVR), which is largely independent of preload and afterload (7). This relationship can be assessed in humans using the conductance catheter. We have recently shown that the data from these catheters are consistent over a range of relevant temperatures (8). The aim of this study was to examine the interactive effects of temperature and HR on human left ventricular (LV) systolic function.

MATERIALS AND METHODS

Patient details. Ten patients undergoing elective coronary artery bypass grafting (CABG) were recruited. All had triple-vessel disease but good LV function (>50% ejection fraction).
fraction) and no hypertension, diabetes, atrial fibrillation, left main stenosis, unstable angina, recent infarct (<2 months) or previous cardiac surgery.

All patients received identical premedication (temazepam, 10 to 20 mg; ranitidine, 150 mg; and metoclopramide, 10 mg orally) and induction (fentanyl, 15 μg/kg; etomidate, 0.1 mg/kg; and pancuronium, 0.1 mg/kg). A central venous line, right radial arterial line and a urinary catheter were inserted. In addition, a Swan–Ganz catheter was utilized to allow measurement of cardiac output and the measurement of core blood temperature.

Maintenance anesthesia (fentanyl and propofol) and bypass techniques were standardized in all patients. A maximum heat exchanger temperature gradient of 10°C was used for cooling/warming while on cardiopulmonary bypass. After sternotomy and conduit procurement, pericardiotomy was performed and the patient was prepared for CPB.

The conductance catheter. The conductance method of determining LV volume is based on the measurement of blood conductivity within the LV. The technique has been described in detail elsewhere (9,10). Briefly the Millar conductance catheter (Millar Instruments, Houston, Texas) has 12 electrodes arranged with an interelectrode distance of 1.0 cm. The catheter is inserted into the LV along its long axis. A conditioner/processor applies a current between the most distal and proximal electrodes and quantifies the conductances (reciprocal of resistances) between the electrode pairs. The sum of these signals is used to obtain an expression for the total volume of the LV. The catheter also contains a solid-state pressure transducer. Hence, the Millar conductance catheter allows online assessment of pressure and volume. A Leycom Sigma-5 signal conditioner processor (Cardio-dynamics; Rynsburg, Netherlands) was used to process volume signals. Analysis of data was performed using a customized software package. End-systolic elastance (Ees) was evaluated from the end-systolic pressure-volume relation (ESPVR) using an iterative method as described by Sagawa et al. (11). The stroke-work end-diastolic volume relationship (12) is the ratio of stroke work to end-diastolic volume (EDV) at a fixed EDV, where stroke work is calculated from the area bounded by the pressure-volume (P-V) loop. Time to reach peak ejection rate (tPER) is defined as the time between the instant when the aortic valve opens (i.e., at dP/dt_max) and the instant when ejection reaches its peak rate (i.e., dV/dt_min). It is related to the time to peak elastance (T_max).

Study protocol. The conductance catheter was inserted via the aortic root, and its position was verified by observing the volume signals from each segment. End-expiratory thermodilution cardiac output was measured at this point to calibrate the catheter for stroke volume. The resistivity of the blood was measured, and a series of steady-state P-V loops were obtained at end expiration. Parallel conductance effect was measured by injection of 10 ml of 5% saline into the pulmonary artery port of the Swan–Ganz catheter. Patients were then assigned to one of two groups of five patients. All measurements were made following the temporary discontinuation of CPB.

In the first group (HR100), right atrial pacing was established at a fixed rate of 100, to minimize variation in HR with temperature and to simulate the postoperative period. A series of loops at differing preloads were then generated by brief occlusion of the inferior vena cava at end-expiration. Following this, CPB was instituted and the patient re-warmed to 37°C. The blood resistivity measurement was then repeated, and a further series of pressure-volume loops were generated. The patient was then core-cooled on CPB. At 35, 33 and 31°C (by Swan–Ganz thermistor and myocardial temperature probe), the data collection was repeated including repeat resistivity estimation at each temperature. Heart rate was maintained at 100 beats/min throughout. In the second group (HR80/120), the relationship between HR and temperature was investigated further. Right atrial pacing was established. Following this, CPB was instituted and the patient re-warmed to 37°C. After warming, the patient was weaned from CPB, the blood resistivity was measured, and runs of pressure-volume loops were generated at this temperature at atrially paced HRs of 80 and 120 beats/min. The patient was then core-cooled on CPB to 33°C. The sequence of measurements was then repeated at the two different HRs.

Following the final measurement in each group, CPB was re-instituted, cooling was continued to 28°C, and CABG was performed. Each patient received three bypass grafts. Mean CPB time was 88 ± 11 mins. All patients survived the study and suffered no complications attributable to the conductance catheter. One patient died after an acute myocardial ischemic event postoperatively.

Ethical committee approval. Approval was granted for this study by the South Birmingham Local Research Ethics Committee. All patients gave informed, written consent.

Statistical analysis. Statistical analysis was performed using one-way analysis of variance (ANOVA) with multiple comparison (Tukey-Kramer) with the ARCUS software (Cambridge Software Publishing, Cambridge, UK) package, on a standard personal computer. Statistical signifi-
cance was assumed when \( p < 0.05 \). In group 1 (HR100), \( p \) values were calculated by standard ANOVA to compare all results for each index of contractility and by ANOVA with multiple comparison to compare consecutive temperatures (i.e., 37 vs. 35, 35 vs. 33). In group 2 (HR80-120), \( p \) values were calculated by using the paired \( t \) test.

**RESULTS**

**Group 1 (HR100).** In one patient the study was terminated at 33°C due to atrial fibrillation. At a paced HR of 100 beats/min, there was a progressive fall in Ees (Figs. 1 and 2) and stroke work at constant volume (Fig. 3) with
cooling. The tPER (Fig. 4) increased progressively as the temperature was reduced.

**Group 2 (HR80/120).** Since Ees appeared the most sensitive indicator of change in contractility in group 1, only this index was assessed in group 2. At 37°C, Ees increased with increasing HR (Fig. 5). Mean contractility at 120 beats/min was 205.9 ± 13.2% of baseline (p = 0.0021). However, at 33°C, this effect was reversed with a significant fall in Ees at an HR of 120 beats/min (mean 53.7 ± 13.2%) compared to an HR of 80 beats/min (100%, p = 0.0014) (Fig. 6). No consistent changes in the volume intercept, V₀, were demonstrated in either group.

**DISCUSSION**

This study shows that human LV contractility is profoundly depressed by hypothermia when the HR is maintained at a rate of 100 beats/min. Furthermore, the positive inotropic response to increasing HR seen at normothermia is reversed at 33°C. These facts are highly relevant in the postoperative management of cardiac surgical patients, where optimization of HR, stroke volume and contractility are essential in the maintenance of cardiac output.

This is a new finding in humans, but there are consistent animal data. In pigs, a depression of systolic function
occurred during cooling at a constant atrial paced HR of 150 beats/min (13). However, when the HR is allowed to vary, contradictory results have been obtained. In anesthetized, unpaced dogs, subjected to veno-venous cooling, Goldberg (14) showed that systolic function, as measured by a strain gauge to assess contractile force, was augmented as temperature decreased. These results have been confirmed using load independent techniques (15,16). These apparently contradictory results may be reconciled by considering the effects of alterations in HR on the changes in cellular activity induced by hypothermia.

Mechanism. Myocardial contractility is dependent on myosin and actin crossbridge formation and is sensitive to the concentration of calcium ([Ca$^{2+}$/H$^{1+}$]) prevailing within the cell. The Ca$^{2+}$ is dependent on both the duration of the action potential and the activity of adenosine triphosphate-dependent ion exchange pumps within the cell wall and the sarcoplasmic reticulum. Since enzymatic activity is directly related to temperature, the effect of cooling is therefore dependent on the relative thermal sensitivity of each enzymatic reaction step. Consequently the effects of hypothermia on systolic function cannot easily be predicted. If the negative effects of decreasing temperature are relatively greater on myosin/actin crossbridge formation, then contractility will fall. If hypothermia exerts a greater relative inhibitory effect on Ca$^{2+}$/H$^{1+}$ ion exchange activity and causes a rise in intracellular Ca$^{2+}$, this may lead to increased contractility. Although Ruf et al. (17) demonstrated that the reduction in actin/myosin crossbridge cycling rate in a human muscle preparation was directly proportional to temperature, Henderson et al. (4) showed that the force of contraction was increased with decreasing temperature down to 29°C in rat myofibrils, suggesting that Ca$^{2+}$ handling is the more temperature sensitive of the two processes. Variations in Ca$^{2+}$/Na$^{+}$ exchange with temperature, causing an increase in the intracellular level of Ca$^{2+}$, have been demonstrated in vitro at the level of the Ca$^{2+}$ channel, in guinea pigs (6) and dogs (18), the Ca$^{2+}$/Na$^{+}$ exchange

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**Figure 4.** Change in normalized time to peak ejection rate from baseline at constant paced heart rate (100 beats/min) with cooling. Group 1. **p < 0.05.

**Figure 5.** Change in normalized end systolic elastance with changing heart rate at 37°C. Group 2.

**Figure 6.** Change in normalized end systolic elastance with changing heart rate at 33°C. Group 2.
pump in humans (19) and in the sarcoplasmic reticulum $\text{Ca}^{2+}$ pump, $\text{Ca}^{2+}/\text{Na}^+$ exchanger, sarcolemmal $\text{Ca}^{2+}$ pump and the mitochondrial $\text{Ca}^{2+}$ uniporter in small mammals (20).

In addition, changes in $\text{Ca}^{2+}$ handling are likely to have an effect on the timings of the contractile cycle. This is because the rate of release and sequestration of $\text{Ca}^{2+}$ directly determine the rate of interaction of myosin and actin (21). As a result of this, hypothermia has been shown to cause a prolongation of the time to peak tension (TPT) (4,22).

**Implications.** An explanation that unites the effects of hypothermia on myosin/actin and $\text{Ca}^{2+}$ handling and explains the aforementioned apparently contradictory findings is that even if the rate of tension development ($\text{dP}/\text{dT}$) is decreased by hypothermia because of myosin/actin effects, then because the duration of contraction is increased (TPT or $T_{\text{max}}$), maximum inotropy may well be increased (22,23).

Hence, the increased inotropy seen with hypothermia in these earlier experiments may be due to an alteration in the duration of contraction. This positive inotropic effect is likely to be sensitive to changes in HR. In both load independent experiments (15,16) in which cooling increased contractility, HR was either allowed to vary (15) or the dog was paced at a normal resting HR (16). However, in a study performed in hypothermic (30°C) isolated rabbit hearts, Mattheussen et al. (5) showed that the increased contractility noted at low HR (30 beats/min) was reversed, and reduced contractility was noted when HR was increased to 90 beats/min by pacing.

Our results confirm the findings of these animal studies. The interaction may occur because of an increase in maximal elastance ($E_{\text{max}}$) and $T_{\text{max}}$ with cooling. Hence although there may be an increase in $E_{\text{max}}$, this is at the expense of an increase in the time taken to reach maximal contraction. In the circumstances of a high HR, $E_{\text{max}}$ may not be reached, resulting in a decrease in the amount of available work (13).

**Clinical implications.** The postoperative management of hypothermic cardiac surgery patients would appear to represent a compromise between HR and contractility. Care should be taken when increasing a hypothermic patient’s HR either through pacing or the use of chronotropic agents.

**Experimental limitations.** Pressure-volume analysis with the conductance catheter does not give a perfect measure of LV kinetics. This is due to, for example, problems with the nonlinearity of P-V relations at the extreme ends of the physiologic range (24,25) and the difficulty in measuring absolute volumes (9,26). However, it does represent the best technique currently available for human in vivo studies, particularly in the situation where patients act as their own controls. A potential limitation of this study was the fact that the patients were cooled on bypass. Although Wood et al. (27) have shown that cooling on bypass does not affect catecholamine levels in children, the period of time on bypass itself may have a detrimental effect on myocardial function. Knowledge of changes in cardiac function in the early stages of bypass is rather limited (28,29). However, data from Pavlides et al. (30) imply that little change occurs in cardiac function during CPB used to support coronary angioplasty. A further potential limitation relates to possible changes in parallel conductance with changing temperature. Although resistivity was checked prior to each contractility assessment, pre-set time constraints to ensure patient safety precluded repeated measurement of parallel conductance, which was assessed only at normothermia. It is therefore possible that the corrected calculation of absolute volume at lower temperature was inaccurate (Fig. 1). Nevertheless, we believe that the conclusions drawn remain valid, as Ees, the main measure of contractility used in this study, is determined by relative changes in volume rather than the absolute volume. The conductance catheter is thought to provide a more accurate determination of relative rather than absolute volume, even at normothermia (31).

In summary, our results confirm that contractility falls with temperature if HR is artificially maintained. Increasing HR at low temperature causes a fall in contractility. These findings are consistent with differential thermal sensitivities of the two prime elements of contractility: actin-myosin crossbridge formation and intracellular $\text{Ca}^{2+}$ handling. These effects may be clinically important in unstable postsurgical patients. Optimization of postoperative cardiac function in hypothermic patients would appear to represent a compromise between contractile status and HR.

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**REFERENCES**