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The potential benefits of 1.5% hetastarch as a cardioplegia additive

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Abstract

Introduction: Myocardial edema is a clinically relevant problem found in post-ischemic reperfused hearts. The objective of this study was to understand the effects of hetastarch-supplemented cardioplegia on post-ischemic edema and cardiac function.
Materials and methods: Swine hearts were arrested with either St. Thomas Hospital cardioplegia with ($n = 6$) or without ($n = 7$) 1.5% hetastarch. Following hypothermic global ischemia, hearts were crystalloid reperfused in a four-chamber isolated working mode.
Results: Hetastarch decreased myocardial water content gains after three hours of reperfusion (control versus hetastarch, hour 0: 67 ± 5% versus 67 ± 3%, NS; hour 3: 82 ± 2% versus 78 ± 1%, $p = 0.1$). Post-ischemic control group left ventricular end-diastolic pressures were elevated after 1 h (in mm Hg, hour 0: 13 ± 2, hour 1: 19 ± 3, hour 2: 19 ± 3, hour 3: 20 ± 2) but remained stable (<16 mm Hg) in the hetastarch group. Post-reperfusion creatine phosphokinase perfusate levels in the hetastarch treated hearts were decreased (control: 1.6 IU/l/g versus hetastarch: 0.6 IU/l/g, $p = 0.15$).
Discussion/conclusions: Hetastarch treatment delayed myocardial edema development and attenuated myocardial creatine kinase efflux, thereby preserving diastolic function.

Keywords: Cardiac; Ischemia; Reperfusion; Hetastarch; Edema; Swine

1. Introduction

In general, ischemia causes an increase in oxygen free radical formation and altered capillary membrane permeability, both of which can ultimately lead to myocardial tissue swelling (i.e., edema) [1,2]. These factors are considered as important parts of the pathophysiology of reperfusion injury and have been previously correlated with the occurrence of myocardial edema, dysfunction, and necrosis [3]. Widespread tissue edema not only impairs the diffusion of oxygen and ATP within a given cell, but may also consequently inhibit water removal via the lymphatic drains and therefore further accelerate edema [1]. The end result is compromised coronary microcirculation and increased ischemic damage (a vicious circle). Clinically this phenomenon is represented by an increased need for inotropic support, extended ICU stays, and increased morbidity and mortality following cardiac surgery. For example, edema development in cardiac allografts during reperfusion is a clinical phenomenon that may ultimately result in allograft rejection [4].

Currently, various cardioplegia solutions are used in cardiac surgery in attempts to protect the myocardium from ischemia and reperfusion injury. Extensive research has been conducted using macromolecules as additives to commonly used crystalloid and blood cardioplegia solutions in order to prevent the deleterious effects of ischemia and reperfusion injury; however, results from these studies are varied, especially in the edema-prone porcine ischemia-reperfusion model [5]. Therefore, this study was designed to investigate the myocardial protective properties of hetastarch (a readily available synthetic hyperosmolar plasma expander) added as a 1.5% solution to a crystalloid cardioplegia in a well-defined standardized large animal preparation of cardiac arrest and reperfusion.

Using a four-chamber working isolated porcine heart model, the specific aims of this study were to investigate the effects of 1.5% (w/v) hetastarch as an additive to an extracellular-type cardioplegia to delay or prevent ischemic damage of an explanted heart by assessing: (1) increases in myocardial water content, (2) differences in

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hemodynamic performance, and (3) the extent of ischemic damage and/or myocardial necrosis over a 3-h reperfusion period.

2. Materials and methods

This experimental project was reviewed and approved by the University of Minnesota Animal Use and Care Committee. The investigation conforms with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 86-23, revised 1985).

2.1. The isolated heart preparation

Mongrel swine (50–70 kg) were induced with thiopental, then intubated and mechanically ventilated. Anesthesia was maintained using halothane and a 50% nitrous oxide and 50% oxygen mixture. Medial sternotomies were performed exposing the hearts and the major cardiac vessels. After cross-clamping of the aortas and the great vessels, the hearts were arrested via administration of either the standard or hetastarch-supplemented cardioplegia solutions (see cardioplegia solutions below). Each solution was pre-cooled to 4 °C and administered under pressure (60–70 mm Hg) via cannulas inserted into the ascending aortas. Details of the methods can be reviewed in Chinchoy et al. [6] and Sigg et al. [7].

Next, the hearts were excised and placed in chilled saline buffer slurries, and the major vessels of the hearts were cannulated. Cardioplegia perfusion was maintained throughout the cannulation process, approximately 60 min (total 1000 ml). The major vessels were fitted with clear Tygon® tubing cannulas and connected to the isolated heart apparatus. After 1 h of ischemic cardioplegia perfusion, the hearts were reperfused with the warmed (37 °C), oxygenated (95% O_2, 5% CO_2) modified Krebs-Henseleit buffer (in mM: 110 NaCl, 16 Mannitol, 11.5 D-Glucose, 20 $NaHCO_3$, 0.32 2Na–EDTA, 4.5 KCl, 1.46 $MgCl_2$, 1.2 NaH_2PO_4, 1.81 $CaCl_2$, and 10 IU/l insulin). Initially, the hearts were perfused using the Langendorff method of constant pressure perfusion. If normal atrioventricular electrical activity was not present upon reperfusion (e.g., ventricular fibrillation), 24–34 J defibrillation shocks were delivered via a coiled lead (Sprint™ 6932, Medtronic, Inc., Minneapolis, MN) in the apex of the right ventricle until occurrence of normal sinus rhythm. After 10 min of stable sinus rhythm, the apparatus was modified allowing the heart to eject from the right and left ventricles (four-chamber working mode) by filling the right and left atria via preload filling chambers (see Fig. 1).

2.2. Cardioplegia solutions

Control animals ($n = 7$) received a standard solution of St. Thomas Hospital cardioplegia (110 mM NaCl, 16 mM KCl, 1.2 mM $CaCl_2$, 16 mM $MgCl_2$, 10 mM $NaHCO_3$) without any pH adjustment (pH 7.45). The hetastarch (1.5% HS) group ($n = 6$) was administered modified St. Thomas Hospital cardioplegia supplemented with 1.5% (w/v) hetastarch (400 kDa fraction, hydroxyethylated amylopectin, B. Braun Medical Inc., Irvine, CA) with the pH lowered to 7.45 with NaOH. All animals were given a 25 mg bolus of adenosine for coronary vasodilation prior to cardioplegia administration.

2.3. Myocardial water content

Tissue water contents were recorded both prior to reperfusion as a baseline and again after termination of the experiment (3+ hours). These were measured by taking small (<100 mg) serial biopsies from the right atrial appendages so as not to disrupt the conduction systems.

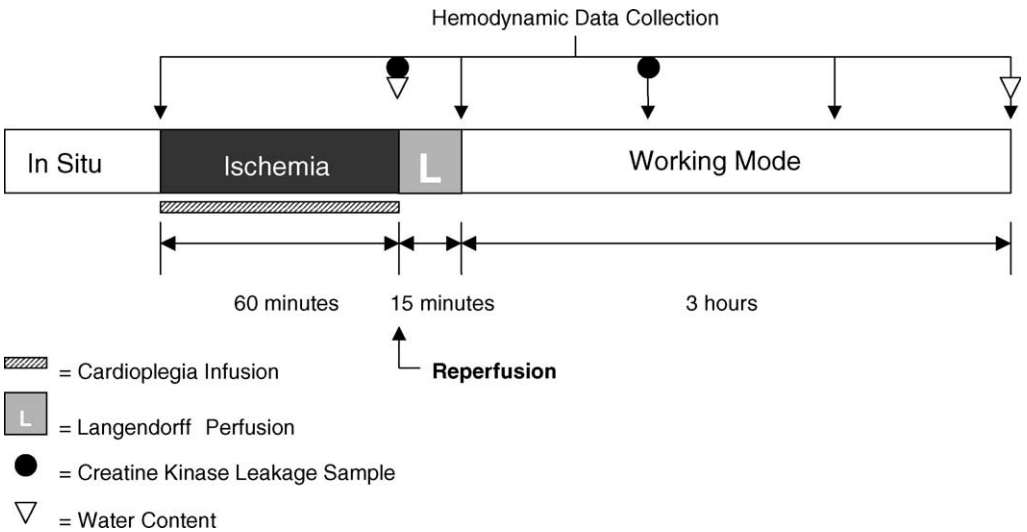

Fig. 1. A schematic representation of the experimental protocol used to evaluate the potential benefits of hetastarch cardioplegia.

Samples were lightly blotted to remove excess water and the wet weights were recorded. The samples were then lyophilized for 24 h and reweighed when dry. Water content was calculated as $\%H_20$:

$$\%H_2O = \frac{(\text{wet weight} - \text{dry weight})}{\text{wet weight}} 100$$

2.4. Pressures and flows

Hemodynamic data were collected at the initiation of working mode (hour 0, ex vivo) and for the subsequent three hours (hours 1, 2, and 3; see Fig. 1). Right and left ventricular pressures were measured by Mikro-Tip catheter transducers (5 French Model MPC-500, Millar Instruments, Inc., Houston, TX), and right atrial, left atrial, and aortic pressures were measured via fluid column pressure transducers placed at the inlet of the right atria (inferior vena cava), at the inlet of the left atria (pulmonary vein), and at the proximal end of the descending aortas distal to the occluded left brachiocephalic and subclavian arteries, respectively. The left ventricular outputs (i.e., cardiac outputs) were measured via transonic flow probes (Transonic Systems Inc., Ithaca, NY) placed at the entrance to the left atria (pulmonary vein). An ATCODAS^{TM} (Dataq Acquisition Systems, Akron, OH) data acquisition program was used to capture the measured values. Post-processing of data included determinations of maximal positive and negative pressure changes ($\pm dP/dt_{max}$). Additionally, coronary blood flows (CBF) were calculated as the mean difference between the cardiac outputs (CO) and aortic blood flows (ABF): CBF = CO − ABF.

2.5. Creatine phosphokinase leakage

Serial aliquots of perfusate (3 ml) were taken from a catheter (6 French Venaport Coronary Sinus Guiding Catheter, Cardima, Inc., Fremont, CA) placed in the coronary sinuses to analyze creatine phosphokinase (CK) activity prior to reperfusion (baseline, $t < 0$ h) and at hour 1. Colorimetric determination (CK Kit, No. 520, Sigma Chemical, St. Louis, MO) and spectrophometric analysis of the samples were performed to determine CK activity, normalized to pre-perfusion (wet) heart weight (IU/l/g wet heart weight).

2.6. Statistical analysis

All data were presented as mean values ± standard errors of the mean (SEM). Repeated measures ANOVA was used for time-based intra-group comparisons, and ANOVA with a Bonferroni post-test was used for inter-group comparisons. Simple linear regression analysis with ANOVA were used to model the interaction between parameters. A p value less than or equal to 0.05 was considered to be statistically important.

3. Results

The hetastarch (1.5% HS) cardioplegia solution had a relatively higher osmolarity than the non-modified St. Thomas Hospital cardioplegia (309 ± 2 versus 296 ± 2 mOsM/l, $p = 0.001$).

3.1. Myocardial water content

An increase in myocardial water content ($\%H_2O$) was observed in both the control ($67 \pm 5\%$ to $82 \pm 2\%$) and 1.5% HS groups ($67 \pm 2\%$ to $78 \pm 1\%$) from baseline to the end of the experimental period (Fig. 2); however, this increase was significant only in the control group ($p < 0.05$). The myocardial water content of the 1.5% HS treatment group was less edematous when compared to the control group at experiment termination (control = $82 \pm 2\%$ versus 1.5% HS = $78 \pm 1\%$), though not significant.

3.2. Pressures and flows

As seen in Table 1, there were no differences between the two groups in heart rates (HR), mean right atrial pressures (RAP), mean left atrial pressures (LAP, left side preload), and mean aortic pressures (MAP, left side afterload). All hearts demonstrated similar ventricular developed pressures (systolic minus end-diastolic pressure) with the exception of the control right ventricular developed pressure, which was decreased at hour 3 when compared to hour 0 ($p < 0.05$, Table 2). Additionally, contractilities ($+dP/dt_{max}$) and cardiac outputs followed a similar trend, with the cardiac outputs remaining relatively stable in both groups. There was a trend of higher myocardial oxygen consumption in the 1.5% HS group compared to controls; however, this difference was not statistically significant and data were not available from all 1.5% HS hearts due to difficulties cannulating the coronary sinus.

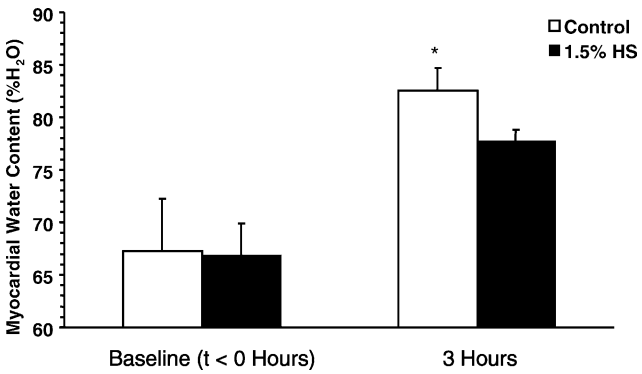

Fig. 2. Right atrial appendage myocardial water content taken before reperfusion (baseline, $t < 0$ h) and at the conclusion of the experiment (3+ hours). Myocardial water content was not different between groups prior to reperfusion; however, after 3 h of working mode perfusion (3.25 h after reperfusion) the control group exhibited increased myocardial water content. *Significantly different from baseline, $p < 0.05$.

Table 1
Working heart right and left side experimentally controlled variables

Time (h)	Group	Heart rate (bpm)	RAP (mm Hg)	LAP (mm Hg)	MAP (mm Hg)
0	Control	80 ± 6	12 ± 4	11 ± 2	56 ± 2
	1.5% HS	71 ± 1	10 ± 1	11 ± 3	59 ± 3
1	Control	82 ± 4	9 ± 1	9 ± 1	57 ± 1
	1.5% HS	79 ± 4	11 ± 1	12 ± 3	53 ± 7
2	Control	90 ± 4	9 ± 1	10 ± 1	55 ± 2
	1.5% HS	93 ± 6	10 ± 1	12 ± 3	51 ± 8
3	Control	89 ± 4	8 ± 2	11 ± 1	56 ± 1
	1.5% HS	92 ± 6	10 ± 1	12 ± 3	57 ± 4

All values are expressed as mean ± S.E.M.; RAP = mean right atrial pressure; LAP = mean left atrial pressure; MAP = mean aortic pressure.

Table 3
Left ventricular diastolic profile after reperfusion

Time (h)	Group	LVEDP (mm Hg)	LV $-dP/dt_{max}$ (−mm Hg/s)
0	Control	12.7 ± 2.4	472 ± 34
	1.5% HS	14.6 ± 3.1	499 ± 74
1	Control	19.4 ± 3.0[a]	707 ± 45
	1.5% HS	16.0 ± 3.6	686 ± 53
2	Control	19.0 ± 3.3	711 ± 31
	1.5% HS	11.9 ± 1.9	653 ± 67
3	Control	19.7 ± 2.4[a]	701 ± 63
	1.5% HS	13.4 ± 1.6	636 ± 59

LVEDP = left ventricular end-diastolic pressure; LV $-dP/dt_{max}$ = left ventricular maximal negative pressure change.
[a] significantly different from control (hour 0, $p < 0.05$).

Increases in left ventricular end-diastolic pressures (LVEDP) in the control group were noticeable after the first hour of reperfusion (Table 3). All control LVEDPs after hour 1 were greater than hour 0 in the control group, with significant increases from hour 0 at hours 1 and 3. While this increase in LVEDP was seen in the controls, the 1.5% HS group maintained stable end-diastolic pressures over the duration of the experiment and, after the second hour of reperfusion, there was a notable difference between the groups. Additionally, there was a positive linear relationship between edema development and LVEDP in the control group ($r = 0.62$, $p < 0.05$) indicating a possible causal relationship (Fig. 3). Conversely, no significant correlation was found between these parameters in the hetastarch group. Finally, left ventricular relaxation ($-dP/dt_{max}$) was impaired upon reperfusion (hour 0); however, it did not decline with time in either group.

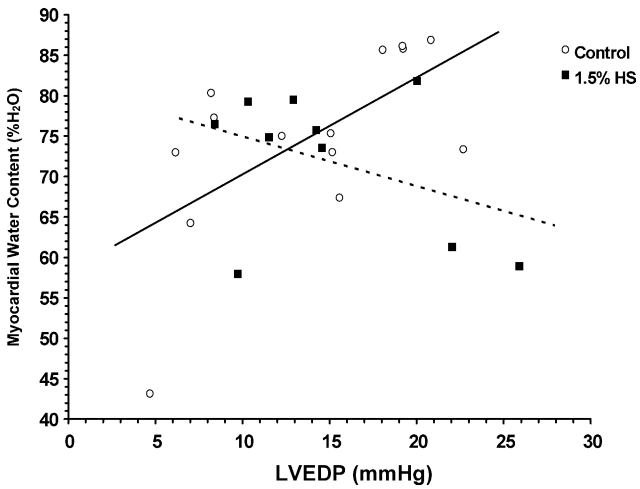

Fig. 3. The relationship between left ventricular end-diastolic pressure (LVEDP) and myocardial water content at hours 0 and 3. There was a positive linear correlation between LVEDP and myocardial water content in the control (solid line, $r = 0.62$, $p < 0.05$); however, no statistically significant correlation between LVEDP and myocardial water content was found in the 1.5% HS group (dotted line, $p > 0.20$).

3.3. Creatine phosphokinase efflux

Fig. 4 illustrates the amount of creatine phosphokinase (CK) activity in the perfusate taken from each group at the beginning of the study (baseline, $t < 0$ h) and 1 h following working mode initiation. CK efflux into the perfusate during the first hour of perfusion was not statistically different in the 1.5% HS group (hour 0 = 0.1 ± 0.2 IU/l/g versus hour 1 = 0.6 ± 0.3 IU/l/g); however, it was sig-

Table 2
Left ventricular systolic hemodynamic profile after reperfusion

Time (h)	Group	LVDP (mm Hg)	RVDP[a] (mm Hg)	LV $+dP/dt_{max}$ (mm Hg/s)	CO (l/min)	MVO_2 (ml/min)
0	Control	88 ± 4	26 ± 3	1020 ± 81	1.6 ± 0.2	616 ± 58
	1.5% HS	90 ± 7	25 ± 2	1003 ± 102	1.8 ± 0.1	707 ± 57[b]
1	Control	81 ± 5	20 ± 2	990 ± 85	1.7 ± 0.2	645 ± 48
	1.5% HS	84 ± 6	21 ± 2	964 ± 99	1.5 ± 0.1	762 ± 76[b]
2	Control	78 ± 5	18 ± 2	904 ± 87	1.7 ± 0.2	717 ± 59
	1.5% HS	74 ± 6	21 ± 3	813 ± 120	1.7 ± 0.1	870 ± 103[b]
3	Control	74 ± 6	14 ± 3[c]	841 ± 67	1.6 ± 0.2	720 ± 85
	1.5% HS	72 ± 5	16 ± 2	769 ± 110	1.7 ± 0.1	753 ± 75[b]

All values expressed as mean ± S.E.M; LVDP = left ventricular developed pressure; RVDP = right ventricular developed pressure; LV $+dP/dt_{max}$ = left ventricular maximal positive pressure change; CO = cardiac output; MVO_2 = myocardial oxygen consumption.
[a] control: $n = 6$, 1.5% HS: $n = 5$.
[b] $n = 4$.
[c] Significantly different from control (hour 0, $p < 0.05$).

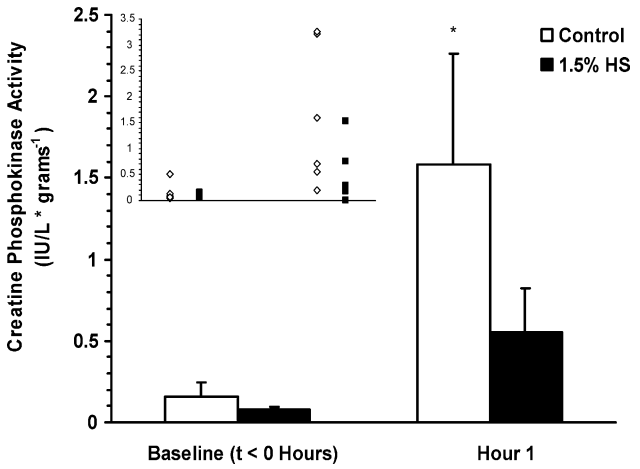

Fig. 4. Perfusate creatine phosphokinase (CK) levels measured before reperfusion (baseline, $t < 0$ h) and 1 h post-working mode initiation. Control hearts ($n = 6$) showed a significant increase in CK levels after 1 h. While CK levels also increased in the 1.5% HS group ($n = 5$), this trend was not significant. Inset graph: scatter plot of actual values. *Significantly different from baseline, $p = 0.05$.

nificant in the control group (hour $0 = 0.2 \pm 0.1$ IU/l/g versus hour $1 = 1.6 \pm 0.6$ IU/l/g, $p < 0.05$).

4. Discussion

It has been shown previously that while cardioplegic arrest alone significantly decreases myocardial oxygen consumption (MVO_2) during ischemia, hypothermic cardioplegic administration may provide superior cardioprotection by further reducing MVO_2 [8]. High molecular weight cardioplegia additives have been used extensively in cardioplegia solutions to prevent edema development. However, the use of high concentrations of macromolecules in the cardioplegia during hypothermic administration may be limited due to the increased viscosity of these solutions at low temperatures. In this study we have shown that a coronary perfusion of a low viscosity hetastarch-supplemented cardioplegia during ischemia stabilized diastolic pressure, limited edema development, and prevented significant creatine phosphokinase efflux 1 h following reperfusion when compared to controls (a solution without hetastarch).

4.1. Myocardial water content

Attenuation of edema formation was evident at study termination in the hetastarch group when compared to the controls (Fig. 2). Similar to results from a study comparing University of Wisconsin cardioplegia (6% hetastarch additive) to Stanford solution (mannitol additive) in a blood reperfused transplant model, the hetastarch-supplemented cardioplegia reduced myocardial edema following reperfusion compared to the crystalloid cardioplegia [9]. However, in this blood reperfused model, as in our crystalloid reperfused isolated heart model, the development of edema was only attenuated and not completely prevented with the colloid additive [9].

4.2. Pressures and flows

Post-ischemic contracture was observed in the control group as the average left ventricular end-diastolic pressure increased nearly 50% at 1 h post-reperfusion (Table 3). Importantly, the addition of 1.5% hetastarch to the cardioplegia attenuated the development of post-ischemic contracture relative to controls, which can impair left ventricular filling, reduce cardiac output, and decrease coronary perfusion. As with previous studies, a significant positive correlation was found between LVEDP and myocardial water content in the control hearts (Fig. 3) [10]. However, this causal relationship was not found in the hetastarch treated group, where there was a slight increase in myocardial water content and no relative change in LVEDP. Differences in LVEDP increases and edema development did not have an effect on the systolic performance of the heart as left ventricular developed pressures and contractility indices were similar between groups, and myocardial hemodynamic performance showed comparable declining trends with time (Table 2). Nonetheless, previous studies with crystalloid perfused isolated rat hearts have found a similar dissociation between systolic function and degree of cellular edema [11,12].

4.3. Creatine phosphokinase efflux

It has been suggested that hetastarch limits myocardial edema by plugging ischemia-induced cellular membrane perforations [5,13,14]. The proposed mechanism by which hetastarch acts is via aggregation of the molecules at the gaps in the endothelial and cellular membranes which prevents the flux of other macromolecules into the interstitium and retrograde into the vascular cavity [15]. Hetastarch cardioplegia potentially delayed the progression of cellular damage, as a significant increase in CK levels after 1 h of reperfusion was found only in the control group. However, while these data suggest that hetastarch may slow the flux of CK from the cytoplasm or interstitial space into the perfusate, the difference between the 1.5% HS group and the controls at hour 1 was not significant, and it is not known whether hetastarch prevents necrosis following 1 h of reperfusion. Furthermore, it is conceivable that the benefits of 1.5% HS on necrosis may only be acute, as the long-term effects were not investigated.

4.4. Limitations

While this working heart model mimics reperfusion following hypothermic ischemia and is a useful tool for examining reperfusion injury, it represents an extreme of post-ischemic dysfunction. Due to the severity of reperfu-

sion injury in this model, a relatively short ischemic time (60 min) was chosen to obtain functional control hearts. The absence of oxygen carrying molecules and decreased perfusate viscosity (higher coronary flows) are two factors that may accelerate the deterioration of the heart preparation more so than that found in a blood perfused model. Furthermore, recirculation of approximately 5 liters of buffer was required to maintain working-mode perfusion on this isolated heart apparatus. Thus, to replenish glucose and electrolytes, a buffer change was completed following every hour of reperfusion and serial measurements of CPK in the buffer after the first hour of reperfusion were not attempted. However, in this study a recognized deterioration, as in the controls, was considered helpful in identifying the benefits of 1.5% hetastarch cardioplegia. In future studies, it would be important to examine the effects of this cardioplegia solution following a prolonged ischemic period (>4 h) and investigate the effects of hetastarch cardioplegia on delayed necrosis during reperfusion.

Right atrial appendage (RAA) biopsies were used as a means of examining myocardial water content so as to allow serial sampling without disruption of the conduction system, a phenomenon which has repeatedly occurred in our laboratory when attempting to acquire serial left ventricular biopsies from the porcine heart. Left ventricular (LV) samples taken at the end of three experiments revealed that RAA biopsies might have underestimated LV water content (LV: 86% versus RAA: 78%). However, since all myocardial water content samples were taken from the RAA, we do not believe this method influenced the results presented. Further studies are needed to examine the correlation between LV and RAA water content to determine the impact of this difference on similar studies.

5. Conclusions

The results of this study provide evidence to support the hypothesis that the administration of a low viscosity extracellular-like cardioplegia solution to arrest the heart has the potential to decrease reperfusion injury and delay contracture development in edema-prone four-chamber isolated porcine hearts. Specifically, the preservation of left ventricular diastolic function by use of a 1.5% hetastarch cardioplegia could ultimately lead to enhanced post-ischemic recovery of edema-prone hearts.

Acknowledgements

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