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Yuji Maruyama and David J. Chambers

*Interact CardioVasc Thorac Surg* 2008;7:745-749; originally published online Jun 11,  
2008;

DOI: 10.1510/icvts.2008.181057

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1569-9293.

Work in progress report - Experimental

# Myocardial protection: efficacy of a novel magnesium-based cardioplegia (RS-C) compared to St Thomas' Hospital cardioplegic solution

Yuji Maruyama, David J. Chambers\*

Cardiac Surgical Research/Cardiothoracic Surgery, The Rayne Institute (King's College London), Guy's and St Thomas' Hospital, London SE1 7EH, UK

Received 2 April 2008; received in revised form 20 May 2008; accepted 22 May 2008

## Abstract

Cardiac surgery patients now tend to be sicker with more severe disease; consequently, improved protection is important. We compared St Thomas' Hospital solution (STH2: hyperkalaemia and hypermagnesaemia) to a hypermagnesaemia-alone cardioplegia (RS-C) based on a novel non-phosphate buffered crystalloid solution (Aqix® RS-I). Isolated Langendorff-perfused rat hearts were used (function measured). Initial studies established optimal magnesium concentration as 25 mmol/l (LVDP recovery after 50 min at 37 °C global ischaemia (GI) for 16, 25, 35, 50 mmol/l magnesium vs. STH2 was  $48 \pm 3$ ,  $50 \pm 2$ ,  $50 \pm 3$ ,  $30 \pm 3$  and  $51 \pm 2\%$ , respectively). Contracture-related measurements (onset time, peak) for 25 mmol/l RS-C ( $32 \pm 1$  min,  $35 \pm 1$  mmHg) compared favourable ( $P < 0.05$ ) to STH2 ( $26 \pm 1$  min,  $43 \pm 2$  mmHg). LVDP recovery after a single 2-min cardioplegic infusion (with RS-C-25 or STH2) and 20, 30, 40 or 50 min GI was higher for RS-C-25 than STH2 after 20 min GI ( $81 \pm 1\%$  vs.  $74 \pm 1\%$ ; [ $P < 0.05$ ]) but similar at other GI durations. Subsequent multi-infusion studies (60 min GI,  $3 \times 2$  min infusions every 20 min) demonstrated significantly improved recovery with RS-C-25 vs. STH2 (LVDP:  $73 \pm 2\%$ ,  $44 \pm 1\%$  [ $P < 0.001$ ]; LVDP:  $9 \pm 2$  mmHg,  $45 \pm 2$  mmHg [ $P < 0.001$ ]). We conclude that single RS-C infusion with optimal 25 mmol/l magnesium improved protection after short (20 min) GI durations, or after multi-infusions during prolonged (60 min) GI durations. Magnesium-based cardioplegia may be a useful alternative to hyperkalaemic cardioplegia under certain specific conditions.

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**Keywords:** Myocardial protection; Cardioplegia; Magnesium

## 1. Introduction

The demographic shift in cardiac surgery towards elderly patients with more impaired ventricular function has increased the operative risks [1]. However, myocardial protection with hyperkalaemic cardioplegia has been used with little change for more than 30 years, despite its known limitations [2]. There is a need to explore improved methods of myocardial protection to delay the damaging effects of global myocardial ischaemia, especially for high-risk patients.

Increased extracellular magnesium in hyperkalaemic cardioplegic solutions has been shown to protect against calcium overload during myocardial ischaemia and reperfusion [3, 4], with efficacy observed in the aging myocardium [5]. Magnesium can also act as a cardioplegic agent per se, but is less effective at inducing arrest than potassium unless used at high concentration [2]. However, in the absence of hyperkalaemia, the optimal concentration of magnesium required to induce arrest is unknown.

Recently, a novel non-phosphate buffered solution (Aqix® RS-I; [Table 1]) has been reported to provide improved

characteristics for isolated organ perfusion [6] by preventing metabolic inhibition attributed to phosphate-buffered solutions.

In this study, we used RS-I as the base solution for magnesium cardioplegia (RS-C) to investigate the optimal protective concentration of magnesium for RS-C and evaluate its efficacy compared to the St Thomas' Hospital cardioplegic solution using single-dose or multidose infusions.

## 2. Material and methods

### 2.1. Animals

Adult male Wistar rats (240–300 g body weight) were used (Bantin and Kingman, Hull, UK). All animals received humane care in accordance with the Guidance on the Operation of the Animals (Scientific procedure) Act of 1986 published by Her Majesty's Stationery Office, London, UK. Rats were anaesthetised with sodium pentobarbitone (60 mg/kg i.p.) and anticoagulated with heparin (1000 IU/kg i.v.).

### 2.2. Heart isolation, perfusion and solutions

Hearts were excised, immersed in cold (4 °C) Krebs Henseleit buffer (KHB; Table 1) and the aorta cannulated

\*Corresponding author. Tel.: +44 207 1880958; fax: +44 207 1880970.

E-mail address: david.chambers@kcl.ac.uk (D.J. Chambers).

Table 1  
Comparative composition of Aqix®RS-I, Krebs Henseleit Buffer (KHB) and St Thomas' Hospital cardioplegic solution No 2 (STH2)

Component	Aqix®RS-I	KHB	STH2
NaCl	110.0	118.5	110.0
KCl	5.0	4.8	16.0
CaCl <sub>2</sub>	1.25	1.4	1.2
MgCl <sub>2</sub>	0.45	–	16.0
MgSO <sub>4</sub>	–	1.2	–
NaHCO <sub>3</sub>	25.0	25.0	10.0
KH <sub>2</sub> PO <sub>4</sub>	–	1.2	–
BES	5.0	–	–
D-Glucose	10.0	11.0	–
Glycerol	0.11	–	–
L-Glutamate	0.30	–	–
L-Glutamine	0.40	–	–
L-Aspartate	0.02	–	–
L-Carnitine	0.05	–	–
Choline chloride	0.01	–	–
TPP (cocarboxylase)	40.0 nmol/l	–	–
Human (recomb.) insulin	28.0 mIU	–	–

All units in mmol/l unless specified.

within 30 s for perfusion in the Langendorff mode with KHB, oxygenated with 95% O<sub>2</sub>: 5% CO<sub>2</sub>, at constant pressure (75 mmHg) and temperature (37 °C). The pulmonary artery was incised allowing free drainage of coronary effluent.

An ultrathin intraventricular balloon, attached to a pressure transducer, was inserted into the left ventricle and pressure recorded on a computer (Apple Computer Inc., Cupertino, CA) using the PowerLab system (ADInstruments Ltd, Chalgrove, Oxfordshire, UK).

Hearts were equilibrated for 20 min aerobic perfusion (37 °C) at a left ventricular end-diastolic pressure (LVEDP) of 4.5–5.5 mmHg; baseline function (left ventricular systolic pressure (LVSP, mmHg), LVEDP (mmHg), heart rate (beats/min), and coronary flow rate (ml/min)) was measured and left ventricular developed pressure (LVDP) calculated (LVSP minus LVEDP).

Table 1 shows St Thomas' Hospital cardioplegia No. 2 (STH2) and Aqix®RS-I (prepared by dilution of 100 ml concentrate (Aqix Ltd, London, UK) to 1000 ml for RS-C (MgSO<sub>4</sub> added to 16, 25, 35, and 50 mmol/l). Cardioplegic infusions were delivered for 2 min at 37 °C and 45 mmHg.

At the time of baseline readings (20 min of aerobic perfusion), hearts were excluded if acceptable levels of LVDP (>100 mmHg), heart rate (>220 beats/min), and coronary flow rate (8–16 ml/min) were not met.

### 2.3. Experimental protocols

All hearts were subjected to a 20-min equilibration period of aerobic KHB perfusion at 37 °C.

#### 2.3.1. Study 1: optimal Mg concentration in RS-C

To determine the efficacy of increasing magnesium concentrations in RS-C in comparison to STH2, hearts were randomised to five groups: Group 1: STH2 ( $n=6$ ); Group 2: 16-Mg, RS-I+16 mmol/l magnesium ( $n=7$ ); Group 3: 25-Mg, RS-I+25 mmol/l magnesium ( $n=6$ ); Group 4: 35-Mg, RS-I+35 mmol/l magnesium ( $n=6$ ); Group 5: 50-Mg, RS-I+50 mmol/l magnesium ( $n=8$ ); 50 min global 37 °C

ischaemia and 60 min reperfusion (recovery of function measured).

#### 2.3.2. Study 2: comparison of protective efficacy of STH2 or RS-C-25 (single infusion)

The efficacy of single-dose (2 min) infusion of either RS-C with 25 mmol/l magnesium (RS-C-25) or STH2 was compared for global 37 °C ischaemic durations of 20, 30, 40, or 50 min followed by 60 min reperfusion (recovery of function measured). Hearts were randomised to one of eight groups ( $n=6$  per group): Group 1 (20-S): STH2 before 20 min ischaemia; Group 2 (20-R): RS-C-25 before 20 min ischaemia; Group 3 (30-S): STH2 before 30 min ischaemia; Group 4 (30-R): RS-C-25 before 30 min ischaemia; Group 5 (40-S): STH2 before 40 min ischaemia; Group 6 (40-R): RS-C-25 before 40 min ischaemia; Group 7 (50-S): STH2 before 50 min ischaemia; Group 8 (50-R): RS-C-25 before 50 min ischaemia.

#### 2.3.3. Study 3: comparison of protective efficacy of STH2 or RS-C-25 (multidose infusion)

The efficacy of multidose cardioplegia (RS-C-25 vs. STH2) infused before and at 20 and 40 min during 60 min of global 37 °C ischaemia was examined. Hearts were randomised to one of two groups ( $n=6$  per group): Group 1 (multi-S): multidose STH2 infusion; Group 2 (multi-R): multidose RS-C-25 infusion, and 60 min reperfusion (recovery of function measured).

### 2.4. Expression of results

Post-ischaemic recovery of LVDP, heart rate, and coronary flow were expressed as a percentage of baseline values; LVEDP was expressed in mmHg. Where applicable, ischaemic contracture development was also measured (study 1 and 3). Measurements were: (1) contracture onset time (minutes from when LVEDP increased by 4 mmHg from the 2 min ischaemia value); (2) 50% contracture time (minutes to achieve half of peak); (3) peak contracture (mmHg). Additionally, mechanical arrest time (s) and cardioplegic infusion volume (ml) were measured in study 1 and 3, respectively.

### 2.5. Statistics

Statistical analysis was performed with SPSS. Data are mean  $\pm$  standard error of the mean. Comparisons between groups were assessed for significance by analysis of variance (ANOVA) or repeated measures ANOVA, as appropriate; if significance was established, post-hoc analysis was assessed by the Bonferroni test, which allowed for multiple comparisons. Within group comparisons were assessed by unpaired *t*-tests, as appropriate. A value of  $P<0.05$  was considered statistically significant.

## 3. Results

There were no significant differences in any between group values for LVDP, LVEDP, coronary flow rate, and heart rate at 20 min of equilibration perfusion for each study.

3.1. Study 1: optimal Mg concentration in RS-C

3.1.1. Recovery of function

Postischaemic recovery of LVDP (Fig. 1a) for STH2 and 25-Mg groups was almost identical, and slightly faster than other groups. Final (60 min) recovery was similar for STH2, 16-Mg, 25-Mg, and 35-Mg groups, whereas 50-Mg group hearts had worse ( $P < 0.05$ ) recovery than other groups.

Elevated postischaemic LVEDP (Fig. 1b) increased further to peak values at 5 min, then declined throughout reperfusion whilst remaining higher than baseline, indicating increased myocardial stiffness. LVEDP in the 50-Mg group was significantly ( $P < 0.01$ ) higher than other groups throughout reperfusion; no differences were seen between other groups. Heart rate and coronary flow recovery were similar (~100% and ~70%, respectively) in all groups.

3.1.2. Mechanical arrest and ischaemic contracture characteristics

Mechanical arrest time (Table 2) was shorter with STH2 than all magnesium groups (with 16-Mg and 25-Mg being significantly ( $P < 0.05$ ) longer).

Ischaemic contracture development (Fig. 1c and Table 2) was earlier, more rapid and higher in the STH2 group, but least in the 25-Mg group.

3.2. Study 2: comparison of protective efficacy of STH2 or RS-C-25 (single infusion)

3.2.1. Recovery of function

Increasing durations of global ischaemia (20, 30, 40 or 50 min) decreased LVDP recovery similarly for STH2 ( $74 \pm 1$ ,  $73 \pm 2$ ,  $58 \pm 2$ ,  $51 \pm 2\%$ ) and RS-C-25 ( $81 \pm 1$ ,  $72 \pm 1$ ,  $59 \pm 2$ ,  $50 \pm 2$ ) although RS-C-25 (20 min) was significantly ( $P < 0.01$ ) higher than STH2. LVEDP increased similarly with increasing ischaemic durations in STH2 and RS-C-25 groups, except ischaemia where RS-C-25 (30 min) was significantly ( $P < 0.01$ ) lower. Heart rate and coronary flow recovery were similar in all groups.

3.3. Study 3: comparison of protective efficacy of STH2 or RS-C-25 (multidose infusion)

3.3.1. Recovery of function

Multidose infusions of RS-C-25 (multi-R) significantly ( $P < 0.001$ ) improved LVDP recovery (Fig. 2a) compared to

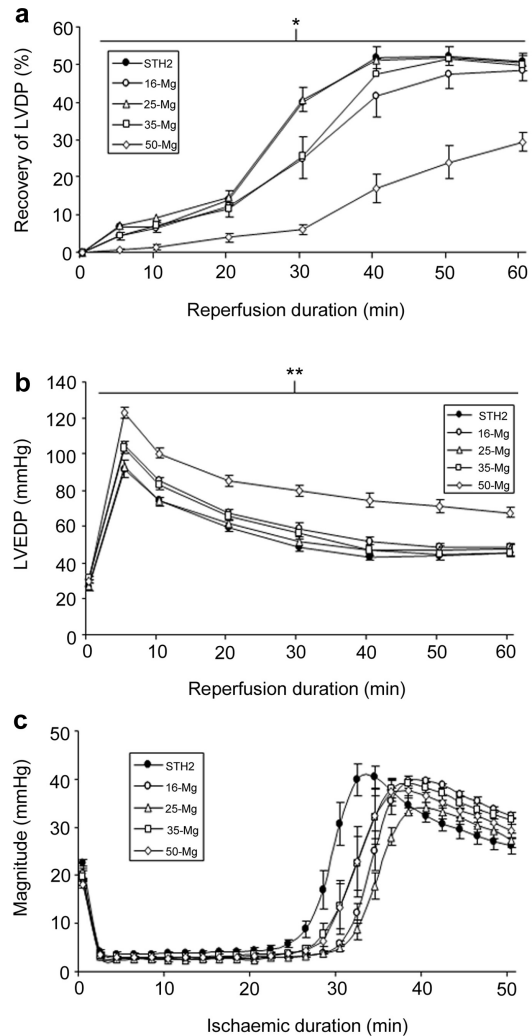


Fig. 1. Recovery of function and contracture in hearts subjected to study 1. (a) Recovery of LVDP, expressed as a percentage of pre-ischaemic control value at baseline. (b) Recovery of LVEDP, in mmHg, throughout the 60 min reperfusion duration. (c) Temporal profiles for ischaemic contracture development during 50 min ischaemia. Values are mean  $\pm$  standard error of the mean. \* $P < 0.05$  for 50-Mg compared with all other groups; \*\* $P < 0.01$  for 50-Mg compared with all other groups.

STH2 (multi-S). Similarly, LVEDP recovery (Fig. 2b) in multi-R hearts was significantly ( $P < 0.001$ ) lower than multi-S hearts. Heart rate and coronary flow recovery were also

Table 2

Characteristics of mechanical arrest time (s) and ischaemic contracture: time to onset (min), time to 50% peak (min), and peak contracture (mmHg) in study 2 hearts

	STH2 (n=6)	16-Mg (n=5)	25-Mg (n=6)	35-Mg (n=6)	50-Mg (n=6)
Mechanical arrest					
Time to arrest (s)	22.0 $\pm$ 2.1	88.6 $\pm$ 6.5*	57.5 $\pm$ 8.6*	40.5 $\pm$ 3.4	31.2 $\pm$ 4.4
Contracture					
Time to onset (min)	26.1 $\pm$ 0.7	30.7 $\pm$ 0.3*	31.9 $\pm$ 0.6*	29.1 $\pm$ 0.9	29.8 $\pm$ 1.3*
Time to 50% peak (min)	28.9 $\pm$ 0.6	33.5 $\pm$ 0.5*	34.0 $\pm$ 0.6*	31.7 $\pm$ 0.9	31.8 $\pm$ 0.9
Peak (mmHg)	43.4 $\pm$ 2.2	40.9 $\pm$ 0.7	35.0 $\pm$ 0.9*	41.3 $\pm$ 0.9	39.4 $\pm$ 2.4

\* $P < 0.05$  compared with the STH2 group.

In the 16-Mg group, two hearts were excluded due to failure to achieve arrest within the 2 min infusion period. In the 50-Mg group, two hearts were excluded due to prolonged ventricular fibrillation.

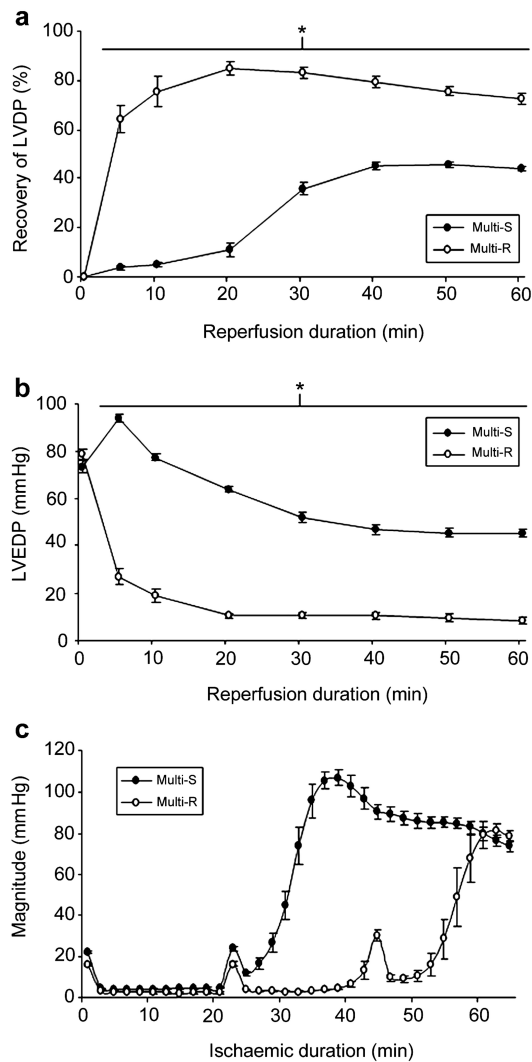


Fig. 2. Recovery of function and contracture in hearts subjected to study 3. (a) Recovery of LVDP, expressed as a percentage of pre-ischaemic control value at baseline. (b) Recovery of LVEDP, in mmHg, throughout the 60 min reperfusion duration. (c) Temporal profiles for ischaemic contracture development during 60 min ischaemia (multi-S: 3 cycles of multidose STH2 infusion; multi-R: 3 cycles of multidose RS-C-25 infusion). Values are mean  $\pm$  standard error of the mean, 6 hearts per group. \* $P < 0.001$ .

significantly ( $P < 0.01$ ) higher for multi-R compared to multi-S hearts (data not shown).

### 3.3.2. Ischaemic contracture characteristics and cardioplegic infusion volume

Ischaemic contracture (Fig. 2c) occurred earlier in multi-S hearts (50% contracture time was  $31.1 \pm 0.6$  min vs.  $55.6 \pm 1.0$  min for multi-R,  $P < 0.001$ ), with increased peak contracture ( $112.0 \pm 3.1$  mmHg vs.  $85.0 \pm 3.3$  mmHg for multi-R,  $P < 0.001$ ). Contracture onset time was not measured (see Fig. 2c for obvious differences).

First and second cardioplegic infusion volumes were similar for multi-S ( $18.1 \pm 0.5$  and  $15.1 \pm 0.5$  ml) and multi-R ( $17.7 \pm 0.6$  and  $14.5 \pm 0.6$  ml), but third infusion was significantly ( $P < 0.001$ ) lower ( $4.3 \pm 0.4$  ml) in multi-S than multi-R ( $12.8 \pm 0.6$  ml).

## 4. Discussion

This study demonstrated that (i) a novel non-phosphate buffered perfusion solution (Aqix<sup>®</sup>RS-I) is effective as the basis for magnesium cardioplegic solutions (RS-C), with an optimal magnesium concentration of 25 mmol/l in the absence of hyperkalaemia, (ii) single RS-C infusion provides equivalent cardioprotection to STH2 during various periods of 37 °C global ischaemia, (iii) multiple RS-C infusions improved cardioprotection compared to STH2 over prolonged (60 min) global 37 °C ischaemia.

Aqix<sup>®</sup>RS-I, a novel non-inorganic phosphate perfusion solution designed for use with any organ at all physiological temperatures [6], utilises the physiological buffering of sodium bicarbonate/carbon dioxide and the zwitterionic Good's buffer, BES, giving an ideal  $pK_a$  over 10–37 °C to provide stable pH. It has similar osmolality to serum (286 mOsmol/l) with an ionic composition that maintains isosmotic characteristics (Table 1). RS-I also contains a number of essential substrates to retain metabolic homeostasis of isolated tissues and organs and provide additional protection [6].

Although hyperkalaemia is the most consistently used cardioplegic agent during cardiac surgery, many alternatives have been examined and even used clinically. Magnesium is one such agent, used at very high concentrations (160 mmol/l) with considerable success [2]. However, we are unaware of previous systematic characterisation studies into the optimal magnesium concentration used alone as a cardioplegic agent. In these studies, an optimal magnesium concentration of 25 mmol/l was observed; higher concentrations were detrimental. Elevated magnesium is thought to be associated with improved ATP availability and reduced ATP utilisation [4, 7, 8]. This should influence ischaemic contracture development [7], confirmed in these studies with delayed contracture development compared to hyperkalaemia when used either as single- or multi-dose infusions. This is likely to be associated with direct reduction in intracellular calcium accumulation [8], possibly via its calcium antagonist effects [9]. Magnesium inhibits L-type calcium channels, sodium/calcium exchange, sarcoplasmic reticulum calcium release and calcium binding to troponin C [10]. All these effects may have influenced the benefit seen with RS-C compared to STH2.

The formulation of cardioplegic solutions has been controversial since their development, especially the relative ratio of cations. In hyperkalaemic solutions and normothermic ischaemia, optimal protection required reciprocal magnesium and calcium concentrations [11]; however, hypothermia influenced this relationship, with optimal protection requiring a lower calcium concentration for any given magnesium concentration [12]. Thus, using RS-C (1.25 mmol/l calcium) at hypothermia may require magnesium to be higher than the optimal 25 mmol/l obtained; hence, further hypothermic studies would be important.

The relationship between magnesium and potassium in cardioplegia, however, has not been assessed. Magnesium causes effects similar to hyperkalaemia, including decreased atrioventricular conduction, decreased intraventricular conductance and sinus node suppression [13]. Supplemental magnesium facilitates asystole at lower

potassium concentrations; therefore, the optimal cardioplegic magnesium concentration with normokalaemia should be high. This explains our findings of 25 mmol/l optimal magnesium concentration in Aqix<sup>®</sup>RS-I (at 5.0 mmol/l potassium).

Surprisingly, multidose infusions (study 3) of RS-C-25 (multi-R) improved protection compared to STH2 (multi-S), especially as no differences between RS-C-25 and STH2 occurred with single infusions prior to relatively long (40 or 50 min) ischaemic durations (study 2). Magnesium reduces sodium accumulation during ischaemia [14], and multidose STH2 infusions abolished intracellular sodium increases whereas single infusions could only delay (by ~20 min) this increase [15]; thus, the higher magnesium may influence the observed difference after 20 min ischaemia between RS-C and STH2, but not at the longer ischaemic durations (study 2). The development of contracture in the multi-S group (study 3) was also probably involved in the reduced recovery (possibly influenced by the significantly lower 3rd STH2 infusion volume), possibly indicating calcium overload from reverse sodium/calcium exchange activity to correct sodium accumulation [14, 15]. This may be particularly relevant in senescent myocardium (with increasingly elderly cardiac surgery patients [1]) which is more sensitive to ischaemia and has a 30% more rapid rise in intracellular calcium than mature myocardium [5].

#### 4.1. Limitations of the study

The present study used healthy rat hearts; thus, any effects on injured myocardium or solution maldistribution would not be determined. It is also known that rat myocardium is more responsive to magnesium than human [14] or rabbit [7] myocardium, suggesting higher magnesium concentrations may be required for any clinical use of magnesium cardioplegia. We have already alluded to the potential differences between normothermia and hypothermia; crystalloid cardioplegia is invariably used at hypothermia and additional studies would be required. Caution should, therefore, be exercised against extrapolating these results to other species, especially humans.

These studies have demonstrated some interesting beneficial effects for a magnesium-based cardioplegic solution in the context of a novel non-phosphate buffered perfusion solution (Aqix<sup>®</sup>RS-I). In particular, the striking improvement in protection with multidose infusions of RS-C compared to STH2 during prolonged ischaemia warrant further studies to determine the efficacy of this potentially beneficial alternative to hyperkalaemic arrest.

#### Acknowledgments

We are grateful to Dr Douglas Rees, Founder and CSO, Aqix Ltd (UK), for advice regarding the use of Aqix<sup>®</sup>RS-I and RS-C. We also thank Aqix Ltd for provision of Aqix<sup>®</sup>RS-I used in this study.

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**eComment: Myocardial protection: efficacy of a novel magnesium-based cardioplegia (RS-C) compared to St Thomas' Hospital cardioplegic solution**

**Authors:** Leo A. Bockeria, Bakoulev Center for Cardiovascular Surgery, 121552 Moscow, Russia; Ruben R. Movsesyan, Dmitriy V. Ryabtsev, Tigran R. Grigoryants

doi:10.1510/icvts.2008.181057A

In spite of the fact that St. Thomas' Hospital solution is commonly used, there are some well known disadvantages. First of all, the slight buffer base makes difficulties during a prolonged ischaemia. But the new buffered solution might improve cardiac protection [1]. In relation to the electrolytic part we need to be more exact. Potassium is absent in the described solution so histiocytes that accumulate calcium, can be damaged [2]. Calcium can not leave a cell because magnesium blocks the cells penetrability. At present a low-calcium solution (Custodiol HTK solution) is used for calcium elimination, but the described solution is maladapted for it. We conclude that the new non-potassium solution still requires long-term experimental and clinical research.

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*Interact CardioVasc Thorac Surg* 2008;7:745-749; originally published online Jun 11, 2008;

DOI: 10.1510/icvts.2008.181057

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