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Switching to warm blood cardioplegia supplemented with magnesium sulfate: what do we gain?

The aim – to evaluate the efficacy of intermittent warm blood cardioplegia using magnesium sulfate in patients undergoing on-pump cardiac surgery.

Materials and methods. The study was performed in two groups of patients without significant differences of preoperative clinical conditions, who underwent surgery with CPB. In the 1st group (control) intermittent cold crystalloid-blood cardioplegia (8–10 °C) was delivered every 20 minutes, rectal temperature decreased to 30.0 ± 1.5 °C. In the 2nd group of patients temperature was maintained at 35.5 ± 1.1 °C applying warm blood cardioplegia according to A. Calafiore (1995) and S. Casalino et al. (2008) protocol subsequently modified by adding magnesium sulfate to all portion of cardioplegia and extending the period of ischemia up to 25 minutes. The frequency of spontaneous cardiac rhythm restoration; emergence of the ECG changes; the frequency of cardioversion after reperfusion; the requirements in inotropes during first two days after the intervention; release of CPK MB, Tn I and transaminases, length of staying in ICU were studied.

Results. Apart from convenience of cardioplegia management, several features showing superiority of warm blood cardioplegia were noted in the 2nd group. This group included fewer patients with cardioversions after reperfusion; number of patients requiring inotropic support in the early days after surgery was more in the control group; average length of stay in ICU was 2.5 ± 0.3 for the study group and 2.9 ± 0.4 days in the control group. There was less myocardial damage in the study group confirmed by significant differences of CK MB and AST release ($P < 0.05$).

Conclusions. Intermittent warm blood cardioplegia supplemented with magnesium sulfate makes possible to safely extend the period of ischemia between reperfusions to 25 minutes and has a positive impact on some clinical and biochemical parameters in the immediate post surgery period.

Key words: myocardium, protection, crystalloid-blood cardioplegia, blood cardioplegia, magnesium sulfate.

After cardioplegic solution was first described in 1955 by D. Melrose et al. [11], the technics used have become more sophisticated and the experience has been gained. A comprehensive study conducted in 1992 at the University of Nebraska, USA [14] has defined the most important areas for research related to the myocardial protection: reperfusion syndrome (cardiac lesions); development of acute myocardial infarction; metabolic supplements for improving cardioplegia solutions.

Facts about advantages or disadvantages of cardioplegia methods presented by many researchers are extremely contradictory and arise many questions [8, 3]. A particular problem is related to the temperature of the cardioplegic solution. This dilemma was first addressed by G.D. Buckberg in 1993 [5], but has not been solved until today.

Meta-analysis of randomized trials conducted by Prof. Fremes and co-authors in 2006 [9] attempted to answer the question about superiority of one or other method of cardioplegia, comparing crystalloid

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cardioplegia (CC) with blood cardioplegia (BC). It faced certain difficulties, noting, however, superiority of BC. UK study presented by S. Jakob et al. [10] showed that 56 % of surgeons use cold BC, 14 % – warm BC and 14 % – CC.

We have a positive experience of using combined blood-crystalloid cold cardioplegia in original interpretation [4] applied to more than 3000 patients. Different cardiac surgery centers show that the incidence of myocardial contracture is between 20–80 %, ventricular post ischemic dysfunction – 3–7 %, myocardial infarction – almost 20 % [12]. Therefore, there is an imperative need for new strategies in cardiac protection.

The aim – to evaluate the efficacy of intermittent warm blood cardioplegia using magnesium sulfate in patients undergoing on-pump cardiac surgery.

Table 1
Clinical characteristics of patients included in the study

Characteristics	WB CPL (n = 49)	CBC CPL (n = 45)	p
Male/Female	40/9	38/7	
Age	57.70 ± 0.97	56.30 ± 1.12	> 0.05
LVEF	59.2 ± 5.1	62,8 ± 6.4	< 0.01
Body surface	2.00 ± 0.10	1.98 ± 0.14	> 0.05
NYHA class III	38	35	
NYHA class IV	11	10	
Aortic clamping time	75 ± 21	73 ± 20	> 0.05
Hypothermia	35 ± 1	31 ± 1	< 0.01
Number of distal anastomoses	3.6 ± 0.7	3.5 ± 0.7	> 0.05

Materials and methods

The study included 94 patients undergoing CABG operation in the Republican Hospital, Republic of Moldova, during period 2010–2011.

Patients with renal failure and/or cardioversion before surgery, EF < 35 % were not included in the study. The inclusion of patients in both groups was based on computer-generated random numbers. 49 patients were included in the group with warm blood cardioplegia supplemented with magnesium sulfate (WB CPL, 1st gr.) and 45 patients in the group with cold blood-crystalloid cardioplegia (CBC CPL, 2nd group). In both cases antegrade cardioplegia was used in the aortic bulb. The clinical status of patients did not differ in both groups, besides EF which was even higher in the 2nd group *(table 1)*.

All patients gave the informed consent for enrollment. We used the same type of anesthesia: induction with midazolam (0.05 mg/kg), propofol (1 mg/kg), and fentanyl (2.5 to 5 mg/kg), maintaining with fentanyl (3 mg/kg) and propofol (2.5 to 5 mg/kg).

CPB was performed by cannulation of ascending aorta and right atrium. For blood oxygenation oxygenator Terumo Capiox CXSX 25 was used. The prime solution included Ringer Acetate solution 1.2 l with added sol. Mannitol 20 % 100 ml and sodium bicarbonate, if applicable. The priming was added by 1 ml of heparin. The prime solution received heparin at rate 300 U/kg to achieve activated clotting time > 480 s.

Surgical techniques. The same surgical techniques were used in both groups. As material for grafts, LIMA and saphenous vein were used. Distal anastomoses were applied during cross-clamping period. The proximal anastomoses were performed after partial clamping and restarting of heart contractions.

Cardioplegia. Cardioplegia was administered in the aortic root immediately after clamping aorta. Patients operated under normothermia (WB CPL) received whole blood based cardioplegia solution derivated from oxygenator through a separate line. Assembled circuit is shown in the *figure*. A mixture of 22 % potassium chloride solution 35 ml and 25 % magnesium sulfate solution 15 ml were loaded into a pump-syringe of 50 ml. The volume of cardioplegia is determined by diastolic left ventricular mass, which should be multiplied by 2. The composition is shown in *table 2*.

In the 2nd group cardioplegia solution was achieved by mixing crystalloids under temperature 2–4 °C with blood in a 3:1 ratio. It was administered every 20 minutes at temperature 8–10 °C. Crystalloid solutions were containing K^+ (24 mmol), Na^+ (110 mmol), Ca^{2+} (1.8 mmol) and Cl^- (160 mmol). Additional doses of 500 ml were administrated every 20–25 min. Body temperature dropped to a minimum of 30 °C. Re-warming was initiated after finishing last anastomose.

Laboratory tests. Troponin I was measured in blood samples taken after surgery. We used CTn I Rapid Test Device (MK Bio GmbH, Germany) – visual immunoassay for the qualitative detection of cardiac troponin I. It helps to determine the presence of troponin I.

In blood creatine phosphokinase MB (Liquik Cor-K test, Poland) and NAC immunoassay (EliTech, France) and aspartate transaminase activity were measured.

Table 2
Modality to administrate warm blood cardioplegia

Where	Aortic root
Line pressure	Not to exacerbate 130 mmHg
CPL pump speed (presumption of aortic valve competence)	300 ml/min (±50 ml)
I dose (immediately after Xclamp)	KCl – 200 ml/h (+ bolus 1–2 ml KCl, if needed)
II dose (after 25 min)	KCl 90 ml/h
III dose (after 25 min)	KCl 60 ml/h
IV (and further) each 25 min	KCl 60 (or 40) ml/h

Post surgery clinical data evaluation was based on the amount of catecholamines administered within 24 hours, duration of intubation, length of stay in ICU.

A special aspect is heart rate restoration after aortic declamping. Number of cardioversions was recorded in each group. Extubation was carried out as soon as patients were able to maintain adequate gas exchange and hemodynamics.

Statistical methods. Two sample T-tests were used to compare continuous variables and the Pearson's chi-square were used to compare categorical variables. Differences were considered statistically significant when $p < 0.05$.

Results and discussion

Since the qualitative determination of Troponin I was made, positive results were considered at 12 hours after surgery. I. Bird et al. [2] from Bristol Heart Institute have observed troponin I peak between 8 and 12 hours after aorta declamping during bypass operations. In our case detection of troponin I revealed no difference between groups (χ^2=0.887). A series of investigators [15] observed lower blood troponins in WB CPL compared to any other form of cardioplegia. The advantage of using quantitative methods for determination of these markers is obvious.

Most patients after cardiac operations show increased release of creatine kinase MB fraction (CK-MB) from 6 to 8 hours, returning to normal in 2–3 days, which corresponds to literature data [7]. Total CK activity tends to increase more slowly after surgery reaching peak in about 21 hours. The term of 12 hours allowed us to record differences in patients of the study groups.

These tests have found better preservation of energy phosphate transfer reaction (high energy phosphates) to produce creatine phosphate for muscle contraction in the 1st group with myocardial protection by warm blood cardioplegia. Attempt

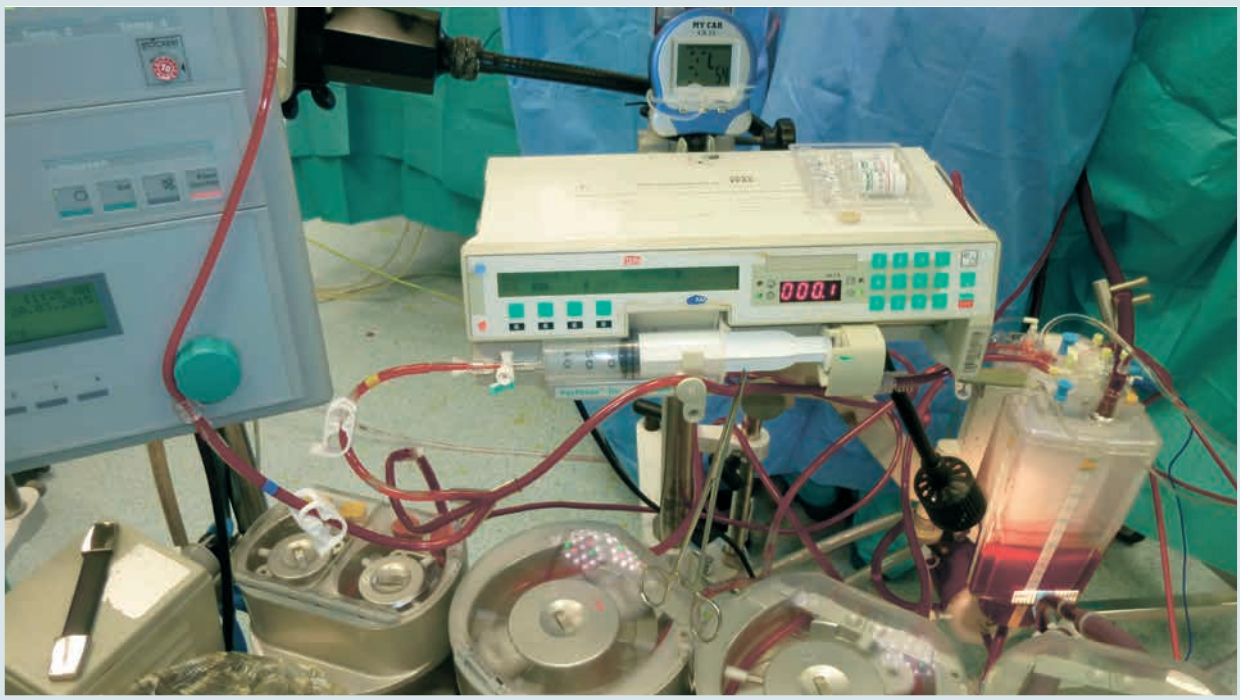

Figure. **Warm blood cardioplegia circuit**

Table 3
Enzymatic markers of ischemia in patients with CABG

Enzyme	WB CPL	CBC CPL	p
CK-MB	76.9 ± 11.4	139.4 ± 25.7	< 0.05
CK-NAC	656.4 ± 60.7	1391.6 ± 122.8	< 0.001

to use aspartate transaminase as a marker did not reveal any differences between study groups (*table 3*).

The restoration of cardiac contractions in WB CPL group showed greater capacity to restore the rhythm. Among 49 patients, heart rhythm was spontaneously restored in 43 persons. Six patients required cardioversion, defibrillations' total number being 8. In the CBC CPL group 17 of 45 patients (38 %) required cardioversion with a total of 24 defibrillations. AV block occurred equally often in the study groups.

No differences were revealed regarding the need in inotropes. Yet, among 37 patients of the 1st group there were 6 (16 %) who required high dose inotropic support; in the 2nd group among 36 patients 5 (13 %) required high dosages of catecholamines. Intraoperative positive fluid balance was more pronounced in the group with CBC CPL, caused largely by repeated administration of cardioplegic solutions.

Duration of stay in intensive care unit was higher in blood-crystalloid cardioplegia group (2.9 ± 0.4) compared to warm blood cardioplegia group (2.5 ± 0.3). Many authors have found the duration of stay in ICU almost the same in both groups. Perhaps it is very difficult to evaluate the influence of type of cardioplegia because it could be dispersed by other external factors that may influence the early postoperative status of patients.

Thus, in parallel with cardioplegia protocol proposed by S. Casalino et al. [6], permanent supplementation of warm blood cardioplegia with magnesium sulfate may be considered a safe method of myocardial protection, adding new features to already existing protocols used in other cardiac surgery centers [13].

Conclusions

Intermittent warm blood cardioplegia supplemented with magnesium sulfate allows to extend the period of ischemia between reperfusions to 25 minutes and has a positive impact on some clinical and biochemical parameters of patients in the immediate postoperative period.

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Перехід до теплої кров'яної кардіоплегії: в чому перевага?

Мета роботи – оцінити ефективність інтермітентної теплої кров'яної кардіоплегії з додаванням Mg^{2+} у пацієнтів, які перенесли операцію із застосуванням штучного кровообігу.

Матеріали і методи. Дослідження проводили у двох групах пацієнтів, які не мали значущих відмінностей в передопераційних клінічних умовах. У 1-й групі (контрольній) інтермітентну холодову кристалоїдно-кров'яну кардіоплегію (8–10 °С) проводили кожні 20 хв, ректальна температура знижувалася до (30,0 ± 1,5) °С. У 2-й групі (група дослідження) температуру підтримували на рівні (35,5 ± 1,1) °С із застосуванням теплої кров'яної кардіоплегії відповідно до протоколу A. Calafiore (1995) та S. Casalino і співавт. (2008), зміненим нами шляхом додавання сульфату магнію у всіх дозах кардіоплегії і продовження терміну ішемії до 25 хв. Досліджували частоту спонтанного відновлення серцевого ритму, появу змін на ЕКГ, частоту застосування кардіоверсії після реперфузії, потребу в інотропних препаратах протягом перших двох днів після втручання, рівні МВ-КФК, тропоніну І і трансаміназ, тривалість перебування у відділенні інтенсивної терапії.

Результати. Крім зручності у проведенні, виявлено такі переваги теплої кров'яної кардіоплегії: у 2-й групі відзначено меншу кількість хворих, у яких застосовували кардіоверсію після реперфузії (атріовентрикулярну блокаду реєстрували однаковою частотою); кількість пацієнтів, які потребують інотропної підтримки в перші дні, була значною в контрольній групі; середня тривалість перебування у відділенні інтенсивної терапії становила (2,5 ± 0,3) доби для групи дослідження і до (2,9 ± 0,4) доби – для контрольної групи. Пошкодження міокарда були меншими в основній групі, що підтверджується істотними відмінностями щодо рівнів МВ-КФК і АСТ ($p < 0,05$).

Висновки. Інтермітентна тепла кров'яна кардіоплегія з додаванням Mg^{2+} забезпечує безпечне продовження терміну ішемії між реперфузіями до 25 хв і позитивно впливає на деякі клінічні та біохімічні показники хворих у ранній післяопераційний період.

Ключові слова: міокард, захист, кристалоїдно-кров'яна кардіоплегія, кров'яна кардіоплегія, магній.

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Переход к теплой кровяной кардиоплегии: в чем преимущество?

Цель работы – оценить эффективность интермитентной теплой кровяной кардиоплегии с добавлением Mg^{2+} у пациентов, которые подверглись операции с применением искусственного кровообращения.

Материал и методы. Исследование проводили в двух группах пациентов, не имевших значимых различий в предоперационных клинических условиях. В 1-й группе (контрольной) интермитентную холодовую кристаллоидно-кровяную кардиоплегию (8–10 °С) проводили каждые 20 мин, ректальная температура снижалась до (30,0 ± 1,5) °С. Во 2-й группе (группа исследования) температуру поддерживали на уровне (35,5 ± 1,1) °С с применением теплой кровяной кардиоплегии в соответствии с протоколом A. Calafiore (1995) и S. Casalino и соавт. (2008), впоследствии измененным нами путем добавления сульфата магния во всех дозах кардиоплегии и продления срока ишемии до 25 мин. Исследованы: частота спонтанного восстановления сердечного ритма; появление изменений на ЭКГ; частота применения кардиоверсии после реперфузии; потребность в инотропных препаратах в течение первых двух дней после вмешательства; уровни МВ-КФК, тропонина I и трансаминаз; длительность пребывания в отделении интенсивной терапии.

Результаты. Кроме удобства в проведении кардиоплегии, выявлены следующие преимущества теплой кровяной кардиоплегии: во 2-й группе отмечено меньшее количество больных, у которых применяли кардиоверсию после реперфузии (атриовентрикулярную блокаду регистрировали с одинаковой частотой); количество пациентов, нуждающихся в инотропной поддержке в первые дни, было большим в контрольной группе; средняя продолжительность пребывания в отделении интенсивной терапии составила (2,5 ± 0,3) сут для группы исследования и до (2,9 ± 0,4) сут – для контрольной группы. Повреждения миокарда были меньше в основной группе, что подтверждается существенными различиями в выбросе МВ-КФК и АСТ ($p < 0,05$).

Выводы. Интермитентная теплая кровяная кардиоплегия с добавлением Mg^{2+} обеспечивает безопасное продление срока ишемии между реперфузиями до 25 мин и оказывает положительное влияние на некоторые клинические и биохимические показатели больных в ранний послеоперационный период.

Ключевые слова: миокард, защита, кристаллоидно-кровяная кардиоплегия, кровяная кардиоплегия, магний.