We read with interest the excellent article by Aass et al. [1] in which they demonstrate the beneficial effect of polarizing (or rather non-depolarizing) St. Thomas-based cardioplegia when compared with conventional depolarizing cardioplegic arrest in a large animal model. The positive impact on systolic left ventricular function during reperfusion is evident in this clinically relevant situation, while there was little difference in G-protein-coupled receptor kinase 2 phosphorylation or other cellular outcome parameters. The authors discuss the potential role of β-adrenergic desensitization and plasma membrane ion fluxes, but we believe that another phenomenon may also play a role: contractile protein Ca²⁺ sensitivity. Indeed, prolonged depolarization ultimately not only leads to cytosolic Ca²⁺ accumulation, which is usually considered detrimental but also induces adaptive responses, such as protein kinase C (PKC)–mediated phosphorylation of troponin I and/or T. This can impair post-ischaemic systolic function but protects the contractile apparatus from relaxation deficit and contracture [2]. Non-depolarizing arrest may prevent Ca²⁺ overload for some time, preserving contractile protein Ca²⁺ sensitivity and hence post-ischaemic systolic function. However, problems arise when ischaemia is prolonged and the net Ca²⁺ influx during reperfusion cannot rapidly be counteracted. Then, pre-served—or ‘unprotected’—Ca²⁺ sensitivity impairs relaxation, resulting in a stiff and failing heart [3]. The ischaemia-reperfusion protocol used by the authors reflects the typical clinical scenario in that is subcritical with 60 min cold cardioplegic arrest, where preserved or increased Ca²⁺ sensitivity translates in better post-ischaemic systolic function. As corrected in the comment, the St. Thomas’ polarizing cardioplegic solution (STH-POL), a mixture of esmolol, adenosine and Mg⁴⁺, is rather a non-depolarization maintaining the myocyte membrane potential at around ~70 mV compared with ~50 mV for potassium-based depolarizing cardioplegic solutions. Systolic function evaluated by left ventricular dp/ dtmax, preload recruitable stroke work (pressure-volume loops) and radial systolic strain rate (TDI echocardiography) was improved in the first 60 min of cardioplegic arrest with STH-POL compared with St. Thomas’ potassium-based (STH-2), oxygenated, cold, repeated blood cardioplegia [2]. There was no evidence for differences in ischaemia-reperfusion injury (serum TnT-levels), apoptotic activity (tissue-activated Caspase-3 levels) or β-adrenergic receptor desensitization (tissue G-protein-coupled receptor kinase 2 phosphorylation) explaining the improved left ventricular systolic function. We fully agree with the comment made by Choi and Stamm; a difference in the contractile protein Ca²⁺ sensitivity represents a possible explanation that we should have considered and discussed. In isolated myocytes, however, esmolol has no influence on myofibrillar Ca²⁺ sensitivity [3].

We are grateful for the opportunity to respond to the highly relevant comments by Choi and Stamm [1], regarding our recent study of cardiac function after polarizing and depolarizing cardiac arrest in a large animal model [2]. Cardioplegic solutions prevent triggering of the action potential and contraction in cardiac myocytes. As correctly noted in the comment, the St. Thomas’ polarizing cardioplegic solution (STH-POL), a mixture of esmolol, adenosine and Mg⁴⁺ is rather a non-depolarization maintaining the myocyte membrane potential at around ~70 mV compared with ~50 mV for potassium-based depolarizing cardioplegic solutions. Systolic function evaluated by left ventricular dp/ dtmax, preload recruitable stroke work (pressure-volume loops) and radial systolic strain rate (TDI echocardiography) was improved in the first 60 min of cardioplegic arrest with STH-POL compared with St. Thomas’ potassium-based (STH-2), oxygenated, cold, repeated blood cardioplegia [2]. There was no evidence for differences in ischaemia-reperfusion injury (serum TnT-levels), apoptotic activity (tissue-activated Caspase-3 levels) or β-adrenergic receptor desensitization (tissue G-protein-coupled receptor kinase 2 phosphorylation) explaining the improved left ventricular systolic function. We fully agree with the comment made by Choi and Stamm; a difference in the contractile protein Ca²⁺ sensitivity represents a possible explanation that we should have considered and discussed. In isolated myocytes, however, esmolol has no influence on myofibrillar Ca²⁺ sensitivity [3]. Anaesthesia, catecholamine load during cardiopulmonary bypass (CPB), hypothermia with rewarming and multiple episodes of ischaemia and reoxygenation/reperfusion of the myocardium with oxygenated blood during cardioplegic arrest and declamping influence cardiac function by causing alterations in myocardial cellular or subcellular conditions. In our standardized protocol, the difference between groups must be explained by non-depolarization with STH-POL versus depolarization with STH-2 cardioplegia. In isolated rabbit hearts with 45 min of warm hyperkalaemic cardiaca arrest followed by reperfusion, Choi et al. [4] demonstrated that contractile protein Ca²⁺ sensitizers ORG30029 and levosimendan improved post-ischaemic systolic function; ORG30029 also negatively affected diastolic relaxation. In our study, the diastolic properties of the left ventricle were not affected. Prolonged depolarization, or a critical ischaemic injury, result in intracellular calcium overload and impaired myocardial relaxation. We believe that another phenomenon may also play a role: contractile protein Ca²⁺ sensitivity. Clearly, more experiments are warranted, which is a very good thing for such an experienced group of surgical researchers and a lately somewhat neglected field.

References


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observed differences in cardiac function when compared with non-depolarizing cardioplegia.

Use of β-adrenergic blockers with sustained anti-adrenergic effects as part of a cardioplegic solution is questionable, due to potential problems with low systolic function during weaning from CPB and in the early postoperative phase. In our animal model with 100% of cardiopulmonary arrest, the addition of carvedilol (a non-selective β- and α1-adrenergic receptor blocker with oxygen radical scavenger properties) to potassium-based blood cardioplegia improved diastolic function judged by improved end-diastolic compliance, a reduced relaxation constant (τ) and reduced peak negative dP/dt [6]. Choi and Stamm hypothesize that a temporary reduced systolic function could easily be treated by adrenergic stimulation, whereas a stiff heart with diastolic dysfunction is more problematic. A focus on adrenergic blockers as part of cardioplegic protocols might be warranted.

REFERENCES


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Differences in cardiac surgery mortality rates

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I read with great interest the article by Kieser et al. [1] regarding comparison of logistic EuroSCORE and EuroSCORE II in predicting operative mortality of 1125 patients undergoing total arterial grafting in coronary artery bypass surgery.

Operative mortality is the most commonly used outcome measure in cardiac surgery. However, operative mortality has been defined in additive and logistic EuroSCORE settings as death during the same hospital admission (in hospitals where cardiac surgery was performed) plus death within 30 days after cardiac surgery (patients discharged from hospital) [2]. On the contrary, operative mortality definition in EuroSCORE II settings is in-hospital mortality only [3].

Although the authors [1] defined operative mortality as death occurring in the postoperative stay or at 30 days, whichever occurred last, there is a theoretical possibility that EuroSCORE II underestimation of operative risk is due to the fact that EuroSCORE II predicts only in-hospital mortality. Namely, Siregar et al. [4] reported that 20% of all deaths within 30 days occurred at home or at another care facility. Furthermore, Nashef et al. [3] have underlined that with in-hospital mortality of around 4%, addition of 30-day mortality (patients who died at home or at another care facility) would have increased operative mortality by 0.6%.

Although patients [1] were recruited in a period from July 2003 to October 2014, more than 2/3 of the patients were operated prior to implementation of the EuroSCORE II risk stratification model in everyday cardiac surgical practice. The study time span can negatively influence external validation of EuroSCORE II when applied to patients who underwent surgery prior to the time period when EuroSCORE II was introduced, back in 2012 [3]. Therefore, performing EuroSCORE II validation on a sample with patients operated before initiation of EuroSCORE II is potentially misleading [5].

REFERENCES


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Reply to Nezic

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We thank Dusko Nezic for his interest in our article [1, 2]. With regard to the first issue concerning operative mortality, we are happy to report that all patients classified as operative mortality were not discharged from the (base) hospital prior to death, prior to 30 days. Therefore these patients fulfill the criteria for operative mortality for both scores.

The second concern that performing EuroSCORE II (ESII) validation on patients operated years before initiation of ESII may be potentially misleading is challenging and complex. One would assume that any scoring system going forward in time would ‘drift’ from acceptable levels of model calibration due to dynamic changes in patient characteristics, case-mix and baseline risk. Using a scoring system to validate operative mortality of patients undergoing surgery years before the inception of a score might be inaccurate due to similar ‘drift’ but in a reverse direction. Others have expressed this concern: Hickey et al. [3] in a 2013 Letter to the Editor questioned the usefulness of retrospective performance of ESII in a study by Chalmers et al. [4], in which 5576 subjects between January 2006 and March 2010 were evaluated retrospectively.