Cardioplegic Solutions in pigs

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Contributor: Maja-Theresa Dieterlen , Susann Oßmann

Cardioplegic solutions are essential in cardiac surgery since they create a silent operating field and protect the myocardium against extensive ischemic damage and ischemia-reperfusion injury (IRI). Cardioplegia is defined as controlled-induced cardiac arrest. A cardioplegic solution induces cardioplegia leading to reversible cardiac arrest.

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1. Introduction

Cardioplegic solutions are essential in cardiac surgery since they create a silent operating field and protect the myocardium against extensive ischemic damage and ischemia-reperfusion injury (IRI). Cardioplegia is defined as controlled-induced cardiac arrest [1][2]. A cardioplegic solution induces cardioplegia leading to reversible cardiac arrest. To create a bloodless surgical field, the heart should be excluded from circulation by aortic clamping. This induces whole-organ ischemia of the heart, which can be tolerated for only a few minutes without additional protection [1][2]. The application of a cardioplegic solution increases the time of ischemic tolerance in the heart for up to several hours. Furthermore, cardiopulmonary bypass (CPB) compensates for the pump function of the heart, provides oxygen and nutrients to organs and tissues, and removes metabolites.

The basic principle of any cardioplegic solution is electromechanical decoupling, which influences the extracellular and intracellular ion concentrations. With this, the energy consumption of the myocardium is significantly reduced and ischemia tolerance is increased [2]. In recent years, several different cardioplegic solutions have been developed [3][4], which are based on either a crystalloid electrolyte solution or patients‘ blood with added electrolytes. However, there are no national or international guidelines or recommendations for choosing cardioplegic solutions for different cardiac surgery procedures [5]. Hence, the selection is largely based on the personal preferences of the surgeon. Furthermore, this must be constantly adapted to new conditions.

Due to demographic changes, patients undergoing cardiac surgery are becoming older and sicker, which necessitates complex cardiac procedures, such as combined heart valve/coronary bypass surgery [6]. Cardioplegic solutions must be adapted to this patient population to provide sufficient myocardial protection and to minimize cardiac damage.

2. Clinical Relevance of Data Analyzing Cardioplegic Solutions in Pig Models

Due to the changing characteristics of the patient cohort and more complex surgical interventions in cardiac patients, it is essential to investigate the effects of cardioplegic solutions. Furthermore, it is necessary to perform structured comparisons and to identify the advantages of different cardioplegic solutions. Especially for new compositions of cardioplegic solutions, adequate tests for their safety and efficiency are necessary. Also, translational research requires testing new drugs in two independent species to fulfill the criteria of the application for ethical and regulatory approval [7].

The pathophysiological processes that are induced by cardioplegic arrest of the heart and CPB are very complex and also affect the kidneys, brain, gut, and lungs. If the effects of cardiac cardioplegia and CPB need to be further investigated, invasive procedures, such as biopsy withdrawal, are necessary. For ethical reasons, it is not possible to conduct studies, including extensive biopsy withdrawal, directly in humans. Hence, animal models are used. Alternative methods to investigate the effects of cardioplegic solutions, such as cell cultures or isolated organs, are not able to fully display the effects of surgical intervention and CPB, such as surgical trauma, blood loss, blood contact with foreign surfaces and shear stress during CPB, inflammatory response to CPB, and changes in the coagulation system [8][9][10]. The animal model is therefore of particular clinical relevance. However, the ethical consideration of the risk-benefit balance in animal experiments is significant. The benefit of information from a study should always be greater than the expected risks and suffering of the animals. Throughout the entire study, the focus must be on animal welfare along with the achieved results. Therefore, good experimental planning is necessary, and the requirements of the study must be precisely defined to achieve satisfactory validity of the results. Owing to the reproducibility of the study, it is important to investigate meaningful parameters in a targeted manner [11][12]. The first step is the selection of a suitable animal model that produces transferable results for future human clinical applications. In many cardiac surgery studies, pig models have been established due to their special anatomical and physiological similarities to the human heart [13]. Thus, not only heart valves and coronary care are comparable, but also the hemodynamics of the circulatory system. Furthermore, the responses to certain events, such as the lack of volume, are very similar in pigs and humans [14][15]. Thus, the results obtained from pig models can be transferred to humans [14].

This review provides an overview of the in vivo application of cardioplegic solutions in adult and pediatric pig models over the past 25 years. This review focuses on the induction of cardioplegic arrest in CPB procedures, except for the preservation strategies necessary for heart transplantation. Investigations in isolated pig hearts and in vitro studies were excluded from the analysis. The advantages, disadvantages, limitations, and refinement strategies of the pig models are discussed.

3. Investigations in Pediatric Models

Cardioplegic solutions have been used in pediatric surgery. Thus, pediatric pig models were used to investigate the effects of the cardioplegic solutions. Sixteen studies reported the effects of different cardioplegic solutions,

including St. Thomas cardioplegia (n = 9), HTK (n = 4), Del Nido (n = 2), and Calafiore/blood cardioplegia (n = 4).

Direct comparisons between different cardioplegic solutions revealed that the modified Calafiore cardioplegia had a superior contractility after CBP surgery when compared to HTK [16]. For adult pig models, additives such as ebselene [17], olprinone [18], diazoxide [19], and sivelestat [20] have been investigated. A reduction in myocardial IRI with the antioxidants ebselene and olprinone has been proven [17][18]. Diazoxide protected the integrity of the mitochondrial structure when applied to a cardioplegic solution [19]. The neutrophil elastase inhibitor sivelestat reduced neutrophilic activation in the lungs and improved oxygenation after CPB in 7 to 14-week-old pigs [20]. The pediatric pig models investigated short-lasting ischemic periods of 10–45 min [21][22] as well as longer ischemic periods of 60–120 min. The on-pump and off-pump reperfusion periods ranged from 10 to 120 min and 30 min to 48 h, respectively.

4. Refinement Strategies

Several aspects could be considered to refine preclinical investigations of cardioplegic solutions in pig models. Due to a special susceptibility to distress, it is necessary to avoid each conscious perceived stressful moment, such as a noise or any painful handling. Transportation to the operating room should be kept as short as possible. Intramuscular premedication consisting of midazolam, atropine, and ketamine is recommended.

To avoid the perception of any procedure-related pain, premedication of the sedated pigs (e.g., metamizole, fentanyl, or sufentanil) and anesthesia maintained by propofol and fentanyl, respectively, sufentanil is indicated.

Excessive hemodilution can have a significant impact on the outcome. Therefore, the total volume of the cardioplegic solution should be completely filtered. If blood donor pigs are included in the study, experiments should be planned such that the blood of one donor pig could be provided to several surgically-treated pigs. Furthermore, arterial and venous cannulas should be removed at the end of the CPB period, and the remaining blood in the tubes of the perfusion system should be re-transferred to the pig.

Sample withdrawal should comprise all organ systems that could be affected by IRI or supplements added to cardioplegic solutions. This allows for further investigation of this research field.

References

1. Seyboldt-Epting, W. Kardioplegie: Myokardschutz Während Extrakorporaler Zirkulation; Springer: Berlin/Heidelberg, Germany, 2013.
2. Gravlee, G.P. Cardiopulmonary Bypass: Principles and Practice; Wolters Kluwer Health/Lippincott Williams and Wilkins: Philadelphia, PA, USA, 2008.

3. Donnelly, A.J.; Djuric, M. Cardioplegia solutions. Am. J. Hosp. Pharm. 1991, 48, 2444–2460.
4. Hoyer, A.; Kiefer, P.; Borger, M. Cardioplegia and myocardial protection: Time for a reassessment? J. Thorac. Dis. 2019, 11, e76–e78.
5. Ferguson, Z.G.; Yarborough, D.E.; Jarvis, B.L.; Sistino, J.J. Evidence-based medicine and myocardial protection-where is the evidence? Perfusion 2015, 30, 415–422.
6. Wegscheider, K. Deutscher Herzbericht 2016; Deutsche Herzstiftung: Frankfurt am Main, Germany, 2016; ISBN 978-3-9817032-5-2.
7. Holers, V.M.; Thurman, J.M. The alternative pathway of complement in disease: Opportunities for therapeutic targeting. Mol. Immunol. 2004, 41, 147–152.
8. Cavarocchi, N.C.; England, M.D.; Schaff, H.; Russo, P.; Orszulak, T.A.; Schnell, W.A.; O'Brien, J.F.; Pluth, J.R. Oxygen free radical generation during cardiopulmonary bypass: Correlation with complement activation. Circulation 1986, 74, 130–133.
9. Janeway, C.A.; Travers, P.; Walport, M.; Shlomchik, M. Immunologie; Spektrum Akademischer Verlag: Heidelberg, Germany, 2002.
10. Cheluvappa, R.; Scowen, P.; Eri, R. Ethics of animal research in human disease remediation, its institutional teaching; and alternatives to animal experimentation. Pharmacol. Res. Perspect. 2017, 5, e00332.
11. Hooijmans, C.R.; De Vries, R.; Leenaars, M.; Curfs, J.; Ritskes-Hoitinga, M. Improving planning, design, reporting and scientific quality of animal experiments by using the Gold Standard Publication Checklist, in addition to the ARRIVE guidelines. Br. J. Pharmacol. 2011, 162, 1259–1260.
12. Crick, S.J.; Sheppard, M.N.; Ho, S.Y.; Gebstein, L.; Anderson, R.H. Anatomy of the pig heart: Comparisons with normal human cardiac structure. J. Anat. 1998, 193, 105–119.
13. Nguyen, P.K.; Wu, J.C. Large Animal Models of Ischemic Cardiomyopathy: Are They Enough to Bridge the Translational Gap? J. Nucl. Cardiol. 2015, 22, 666–672.
14. Leonhardt, H. Anatomie des Menschen. Band II: Innere Organe; Georg Thieme Verlag: Stuttgart, Germany, 1987.
15. Sim, E.K.; Muskawad, S.; Lim, C.-S.; Yeo, J.H.; Lim, K.H.; Grignani, R.T.; Durrani, A.; Lau, G.; Duran, C. Comparison of human and porcine aortic valves. Clin. Anat. 2003, 16, 193–196.
16. Münch, F.; Purbojo, A.; Kellermann, S.; Janssen, C.; Cesnjevar, R.A.; Rüffer, A.; Czerny, M.; Reser, D.; Eggebrecht, H.; Janata, K.; et al. Improved contractility with tepid modified full blood cardioplegia compared with cold crystalloid cardioplegia in a piglet model. Eur. J. Cardio-Thorac. Surg. 2014, 48, 236–243.

17. Chen, Y.; Liu, J.; Li, S.; Yan, F.; Xue, Q.; Wang, H.; Sun, P.; Long, C. Histidine-Tryptophan-Ketoglutarate Solution with Added Ebselen Augments Myocardial Protection in Neonatal Porcine Hearts Undergoing Ischemia/Reperfusion. Artif. Organs 2015, 39, 126–133.
18. Kinouchi, K.; Morita, K.; Ko, Y.; Nagahori, R.; Shinohara, G.; Abe, T.; Hashimoto, K. Reversal of oxidant-mediated biochemical injury and prompt functional recovery after prolonged single-dose crystalloid cardioplegic arrest in the infantile piglet heart by terminal warm-blood cardioplegia supplemented with phosphodiesterase III inhibitor. Gen. Thorac. Cardiovasc. Surg. 2012, 60, 73–81.
19. Wang, L.; Kinnear, C.; Hammel, J.M.; Zhu, W.; Hua, Z.; Mi, W.; Caldarone, C.A. Preservation of mitochondrial structure and function after cardioplegic arrest in the neonate using a selective mitochondrial KATP channel opener. Ann. Thorac. Surg. 2006, 81, 1817–1823.
20. Ando, M.; Murai, T.; Takahashi, Y. The effect of sivelestat sodium on post-cardiopulmonary bypass acute lung injury in a neonatal piglet model. Interact. Cardiovasc. Thorac. Surg. 2008, 7, 785–788.
21. Liuba, P.; Johansson, S.; Pesonen, E.; Odermarsky, M.; Kornerup-Hansen, A.; Forslid, A.; Aburawi, E.H.; Higgins, T.; Birck, M.; Perez-de-Sa, V. Coronary flow and reactivity, but not arrhythmia vulnerability, are affected by cardioplegia during cardiopulmonary bypass in piglets. J. Cardiothorac. Surg. 2013, 8, 157.
22. Jones, J.; Wilson, K.; Koch, W.; Milano, C. Adenoviral gene transfer to the heart during cardiopulmonary bypass: Effect of myocardial protection technique on transgene expression. Eur. J. Cardio-Thorac. Surg. 2002, 21, 847–852.