

Applied Cardiopulmonary Pathophysiology 15: 198-206, 2011

## Donor heart preservation and perfusion

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### Abstract

Due to its technically simple and easily reproducible nature cold static preservation is still the current gold standard for myocardial protection in between donor explantation and recipient implantation. It allows "safe" overall ischemic periods of up to 4 hours with a primary graft failure rate less than 2%. Additional measures such as second rinsing or leucocyte depleted in-situ reperfusion allow to extend the ischemic tolerance in ideal donor hearts to 6 hours. Recent technological progress and research improved results of continuous warm, blood based in-vitro perfusion reducing the necessity of myocardial ischemia to the surgical procedures of ex- and implantation. First clinical experiences with this challenging but also very expensive technology indicate its safety and efficacy with at least similar results as cold static preservation even with extended transport times. Due to possible donor evaluation or even resuscitation strategies during ex-vivo perfusion, it offers furthermore promising potential to compensate the ever increasing donor risk profile and could also help to increase availability of transplantable donor hearts. As of December 2011 a German multicenter prospective registry study will start with the goal to evaluate efficacy and outcome of this method in 250 heart transplants using donor organs with extended criteria or expected transport times of >3 hours. Expected duration of this project is 2 years and final analyses of collected data will help to clarify if application of this complex and expensive technology is ultimately beneficial and justified.

Key words: myocardial ischemia, cold static heart preservation, continuous perfusion

### Historical background

The initial human heart transplants including the very first successful surgery by Christiaan Barnard in South Africa, December 1967 were performed with donor and recipient in the same hospital most often after anoxic cardiac arrest with resuscitation thereafter due to no detailed knowledge about myocardial preservation techniques. It soon became obvious that the development of safe and reproducible preservation of the heart in between explantation in the donor and reimplantation in the recipient was a prerequisite to increase

the donor pool. This would allow long distant procurement of the donor heart, i. e. harvest of the donor organ at a distant hospital from the actual transplant center. One of the earliest described methods for preservation during ischemia was the principal of hypothermia. Systematic studies from the 1950 and 1960 had revealed the relationship between hypothermia and myocardial oxygen consumption indicating that a reduction of tissue temperature to 25°C reduced oxygen demand by 75%, further reduction to 5°C brings oxygen consumption down to 5% (1-3). After this method has been applied for the

first renal transplantations it was Norman Shumway at Stanford who was able to demonstrate that successful canine orthotopic heart transplantation was possible following a 7 hour storage period in ice cold saline solution (4). The other obvious option to reduce myocardial oxygen demand was of course to suppress all mechanical myocardial activity. Even though this principle was described as early as 1934 by Hucker (5), it was the pioneering work by Bretschneider, Kirsch, Hearse and Buckberg that led to a safe application of the cardioplegic principle and to the realization that those solutions should be applied cold in order to induce fast hypothermia (6-9). Even though the resulting St. Thomas, Bretschneider and Buckberg cardioplegic solutions used different biochemical principles to achieve hypothermic myocardial arrest they all allowed more or less safe extension of ischemic time to 4 hours. It was also soon recognized that the extension of myocardial ischemic tolerance is not only determined by processes during ischemia, but even more so by reactions occurring during reperfusion. Already in 1960 Jennings et al. described excessive transmembrane calcium influx during reperfusion of previously ischemic myocardium. In order to protect the cell against resulting myofibril contraction calcium is actively shifted into mitochondria which leads to ATP depletion, ultimately uncoupling of oxidative phosphorylation and cell death histologically corresponding to myocardial contraction bands and deposits of calcium phosphate (10). According to McCord's theory formulated in 1984 elevated cytosolic calcium concentration causes conversion of Xanthine dehydrogenase into oxidase with resulting oxygen radical formation during reperfusion and reoxygenation aggravating cellular and membrane damage. Therefore the use of different calcium channel blockers as well as several oxygen radical scavengers have been proposed and tried experimentally with various and quite different success or failure.

Despite of these methods and counter measures against ischemia reperfusion injury

it is obvious that metabolic processes need to continue even at very low temperatures in order to prevent irreversible cell damage and death. It was therefore even historically recognized that preservation times longer than 6-12 hours necessitate continuous perfusion techniques in order to provide oxygen and energy substrates and clearance of metabolic end products. It was soon recognized that the key factors for success of such methods are determined by the concept of a perfusion apparatus but even more so by the composition of the perfusion fluid. The use of blood as perfusate was considered inadvisable due to cellular mechanical destruction by extracorporeal pumps and use of plasma for kidney perfusion was found to cause progressive increase of vascular resistance (11). Therefore most early works concentrated on the use of fully synthetic solutions for continuous perfusion preservation. One of the first successful experiments were performed by Proctor and Parker 1968 using a modified Krebs-Henseleit solution with added dextran 70, hydrocortison and insulin. Perfusing the heart with a physically oxygenated solution at 5°C they achieved successful orthotopic transplantation and function for 14 hours after 72 hours of extracorporeal perfusion (12). However, increasing development of severe and mostly irreversible parenchymal edema remained the main limiting factor for success not only in these early but also in subsequent concepts with cold non-blood based perfusion methods (13). Due to this combination of required sophisticated technology and no clear advantage for continuous perfusion cold hypothermic static preservation became the standard method for cardiac preservation.

In the following paragraphs we will highlight the key issues and clinical results about cardiac preservation as published in recent literature, furthermore discuss consequences resulting from recent changes in profiles of donor and heart transplant recipients.

## Cold static preservation

One of the first to develop a systematic concept for myocardial preservation was Bretschneider and his group from University of Göttingen, Germany. As early as 1975, they published extensive work about myocardial tolerance of ischemia (6). This research led to the formulation of the so called HTK solution which underlying theoretical concept will be briefly summarized in the following. Bretschneider described two basic prerequisites:

1. Limit energy consumption by reliable exclusion of electrical and mechanical activity of the myocardium and
2. achieve of a homogeneous, low myocardial temperature.

He was also one of the first to show the so called calcium paradox: a high concentration of calcium-chelate-producing substance in a cardioplegic solution induces rapid arrest, but the myocardium can not be resuscitated. Furthermore he showed that the velocity of ATP consumption is a measure of ischemic tolerance, where a drop of temperature from 35 to 5°C results in an eightfold increase of ATP-time. 80% of this effect, however, is already achieved within the first 10° of cooling. Since survival of non perfused tissue is mostly depending on ongoing anaerobic metabolism with resulting tissue acidosis, he postulated the need of a high buffering capacity within any cardioplegic solution. Histidine seemed to fulfill necessary requirements since it shows high buffering capacity which is almost temperature independent. For required energy substrate delivery to amino acids ketoglutaraldehyde and tryptophane were chosen, since they are able to produce ATP via an alternative pathway inhibiting glycolysis thereby reducing production of lactate and resulting tissue acidosis. Cardiac arrest was achieved by slightly elevated extracellular potassium concentrations in combination with low sodium and high magnesium concentration in order to reduce calcium efflux and stabilize ionic membrane status.

Mannitol was finally added to increase osmotic pressure and to counteract myocardial tissue edema.

Since this initial development a variety of clinical and experimental studies during the last three decades has proven the efficacy of this solution to preserve the myocardium during cold ischemic storage. One of the largest series was a retrospective study including 600 recipients who had orthotopic heart transplantation between 1981 and 1991 within Germany (14). The average reported ischemic time was 160 minutes ranging from 74 to 304. Immediate postoperative graft failure was observed in 4.2%, 30 day mortality was 11.8%. A statistically significant increase of acute graft failure and early mortality was observed with ischemic times beyond 210 minutes. In addition a higher incidence of graft failure was documented if perfusion volume was less than 1500 ml which is in accordance with Bretschneider's original recommendation to apply a large volume of 5 to 7 liters with perfusion pressure of less than 100 mm Hg. Apart from isolated reports about successful extension of cold ischemic time beyond 10 hours (15) most other clinical studies described HTK-solution as a safe preservation method up to 4 hours of cold ischemic time (16-18).

Another solution that has been originally developed for liver preservation by Dr. Belzer and colleagues at the University of Wisconsin, USA was also successfully introduced as a myocardial preservation agent in the early 80ies. This later on so called UW solution is based on a typical intra cellular principal with a very high K<sup>+</sup> and low Na<sup>+</sup> ion composition, it contains as impermeants lactobionate and raffinose to prevent cell swelling. It also includes antioxidants such as glutathione, adenine nucleotide precursors, radical scavengers, dexametasone and phosphate buffer. It also contains pentastarch, a colloidal agent with the rationale to prevent interstitial edema formation. Due to the resulting high viscosity this solution is prone to particle formation of up to 100 µm diameter causing several microcirculatory disturbances and graft

dysfunction (19). Due to this observation application rules for UW solution were changed in 1996 with the recommendation of inline filtration using a Pall filter with 50 micron pore size and addition of fresh reduced Glutathione immediately before use in order to avoid premature oxidation of this scavenger. Despite this particularities UW was found to be a save cardiac preservation solution in many clinical studies. As already suggested by early animal work (20) UW was found in some studies to allow safe extension of preservation time beyond 5 hours with improved primary graft function compared to hearts preserved with HTK-solution (21, 22). Despite these advantages with regards to short term results there were particular concerns due to the high viscosity and high potassium concentration, since in vitro studies observed myocardial and endothelial damage during cold storage, in particular if intracellular pH dropped into the acidotic range (23). Some clinical studies in which longer term increased cardiac allograft vasculopathy was observed, this was suggested as a surrogate of the observed in-vitro toxicity (24).

Another cardiac preservation solution that has been developed more recently by Dr. Menasche and colleagues in Paris, France is the so called Celsior solution. It contains impermeant inert osmotic carriers (Lactobionate and Manitol) and a strong buffer (Histidine), glutamate as energy substrate and a high magnesium content to limit calcium overload. In contrast to UW it is based on a cristalloid extracellular electrolyte concentration with only minimally elevated potassium and a high sodium concentration. Experimental work suggested reliable cardiac protection for up to 6 hours of cold ischemia and similar results to UW preservation for up to 12 hours in canine models (25, 26). Again as already described for HTK and UW there are several clinical studies documenting comparable or even improved graft function for up to 5 hours of cold ischemia when comparing Celsior to the other two solutions (27). In a recent multicenter prospective trial Celsior

solution was compared to so called conventional solutions including UW, Stanford solution and even ringers lactate and normal saline in a cohort of 131 patients (28). They noted excellent primary graft function with 3% primary failure rate in the Celsior and 9% in the control group with normal allograft function on cardiac ultrasound in both groups and a primary incidence of normal sinus rhythm of 87% in celsior and 89% in the control group. Total ischemic time, however, was just above 3 hours in both groups, donor and recipient criteria were defined to avoid any kind of high risk constellation. In another study comprising 224 patients Celsior was shown to be equivalent to UW and HTK solution for cardiac preservation quality (29). Average ischemic time reported was again 213 min. ranging from 85 to 313. Immediate and intraoperative graft function is reported into every relevant hemodynamic detail and shows absolutely no difference between solutions. Early graft dysfunction related mortality was 4.6% with no statistic significant difference between solutions. Even in grafts belonging to subgroups defined not ideal or marginal donors no significant correlation of mortality with donor classification and total ischemic time was observed. Another feature of this study is a routine protocol of endomyocardial biopsies of the donor heart immediately after explantation, at the end of ischemia and 10 min. after reperfusion. 90% of those biopsies were found histologically normal, observed pathological changes included perinuclear and interstitial edema, endothelial swelling and damage of myocardial fibers. A positive correlation of those histological changes was found with donor hearts older than 30 years and with increasing total ischemic time, however, no correlation was found with the perfusion solution used.

Until a decade ago there was no standardized preservation method and the type of solution used or reported always depended on local clinical empirical data rather than experimental evidence of superiority (30). Indeed a review from 1997 reports that as many as 167 types of different preservation

solutions were clinically used with the majority of those methods claiming a safe preservation time of 4 hours with acceptable failure rates of less than 3 to 5%. Another review on two decades 1980-2000 calculated that up to 83% of the literature on cardiac preservation is generated in the laboratory. Most clinical reports are based on single center experience and almost all of them are of retrospective character. Less than 2% were represented by prospective clinical trials (31). During the last decade, however, increasing regulation requirements for standardized approval procedures even for medicinal products including solid organ preservation solutions forced most transplant centers within Europe and North America to use only officially approved solutions with CE mark, federal European or FDA approval respectively. This trend enforced by legal regulatory issues is also supported by the virtual lack of clinical data for superiority of any available cold static preservation solution as long as total ischemic time does not exceed 4 hours. Analyses from the ISHLT registry data 2010 disclose that any ischemic time beyond 210 min. imposes a statistically significant increased mortality risk at 1 year (300 min. odds ratio 1.7) and even at 5 years (300 min. odds ratio 1.4) (32). These data, however, simply reflect the natural limit of any cold static preservation method since survival of tissue will always be dependant on sufficient presence of energetic substrates at cellular level. In a recent publication Lee and colleagues could elegantly show that tissue ATP level was best preserved by HTK solution but even in the HTK group myocardial ATP concentration dropped to 75% of normal after 6 hours and less than 15% after 12 hours of cold ischemia corresponding with significant histological and micro cellular damage after 3 hours of graft reperfusion (33). To overcome this natural limitation only concepts of second or extended perfusion of the allograft prior to reperfusion might achieve to increase ischemic tolerance. Beyersdorf and colleagues proposed a method of repetitive retrograde blood cardioplegia during graft implantation

given via a white blood cell filter plus an additional hot shot immediately before opening the aortic clamp (34). They found this method allowed save extension of ischemic time of beyond 6 hours in a large animal model. In our own institution at the University Heart Center Hamburg such method was introduced clinically 2006 and applied in a total cohort of 114 orthotopic heart transplantations. Primary preservation was based on UW preservation followed by repetitive antegrade Buckberg blood cardioplegia including hot shot prior to reperfusion. Mean donor age was  $43 \pm 17$  year with a mean ischemic time of 255 min. ranging from 182 to 365. Despite this increased donor risk profile we observed excellent primary graft function with only 1.8% failure rate (unpublished data).

This natural limitation of cold static preservation time in combination with donor risk factors such as age, left ventricular hypertrophy (LVH) and high dose vasopressor use limit transport radius and thereby the available donor pool. Extension of heart transplantation to a growing subset of high risk recipients with complex surgery such as in patients depending on VAD support and the restricted availability of donor hearts lead on one hand to prolonged ischemic times, on the other hand to an increased acceptance rate of marginal and high risk donors. The latter have been defined clinically on the basis of age, previous cardiac arrest, use of high catecholamine support, significant wall motion abnormalities at echocardiogram, significant (>20%) donor-recipient size match disparity, presence of coronary artery disease and total ischemic time (35). Analyses of the ISHLT registry data 2010 still indicate that the use of a donor older than 50 implies a rate of 1.38 and 1.44 respectively for 1 and 5 year mortality. The same source indicates that the mean donor age has increased to over 41 years with 10% of hearts from donors aged 50 and older. Each of these mentioned factors have been challenged clinically, however, most published data deriving from very small single center based experiences. An-

other well exploited risk factors for cardiac allograft dysfunction is the unavoidable event of previous brain and brain stem death (BoD). Its role in donor organ function has been studied numerous clearly proving that BoD induces a massive catecholamine release in combination with a systemic inflammatory response syndrome causing capillary leak, myocardial necrosis and variable degree of acute organ injury (36). Most data related to the impact of BoD stem from experimental work. In a large multicenter trial including 475 heart transplantations it could be shown, however, that donor heart explantation more than 72 hours after BoD translated into significantly reduced long-term survival of up to 15 years post transplant (37). Most BoD related injury such as edema formation and myocardial dysfunction are potentially reversible requesting different preservation strategies with potential of quality assessment and graft reconditioning or treatment during storage.

### Continuous perfusion for cardiac preservation

Above mentioned limitations of cold static preservation in combination with an ever increasing mean age of the donor population enforced the search for more sophisticated preservation methods. One option to achieve this is of course to loosen donor heart exception criteria termed marginal or extended donors associated with an obvious risk for post transplant failure due to decreased ischemic tolerance as discussed in the previous paragraphs. Cold preservation only minimizes oxygen and energy consumption for maintenance of cellular function, but does not offer any option to resuscitate organs or correct existing injury during storage (38). Particularly reports about successful warm blood perfusion in experimental models based on new pump and modern oxygenator technologies triggered the rebirth for such concepts (39). Theoretically blood offers several optimal preservation properties

due to excellent capability for oxygen delivery, high content of numerous antioxidant free radical scavengers, abundant buffer systems to protect against acidosis and toxic metabolites. It should be less harmful to the endothelium compared to non physiological colloids helping to decrease ex-vivo perfusion injury through all these effects. The physiological high osmotic composition of any blood based perfusion should also allow to prevent progressive parenchymal edema formation. Fedalen and colleagues proved the efficacy of a blood based warm perfusion concept in a pig model where hearts were successfully resuscitated after they arrested due to hypoxia after animal disconnection from the ventilator. The ex vivo reperfusion system consisted of the heart ejecting blood in a compliance chamber from where it was directed back to the heart after reoxygenation and recirculation through a heater. All hearts could be recovered and restarted normal function after 4 hours of the perfusion (40). Despite limited interest in the development of complex devices for such a small market a transportable and commercially viable system for warm blood perfusion has recently been developed. The organ care system (OCS) manufactured by Transmedics (Endover, MA, USA), consists of a miniature pulsatile pump with an inline heater. The system is equipped with modern monitoring technology of ex-vivo heart performance in form of cardiac output, temperature, coronary flow and blood pressure via a wireless remote flat-panel screen and online management of the metabolic performance of the heart. The other key element is the specifically developed and designed perfusion solution which consists of a crystalloid part containing glucose and amino acids as energetic substrate, physiological extra cellular electrolyte concentrations, pharmacological components such as radical scavengers and antibiotics as well as a calculated level of catecholamines and insuline. This is combined with oxygenated warm blood to achieve a hematocrit of 20 to 25% within the system. Another feature of this system is that it allows

direct continuous visual and echocardiographic surveillance of the ex-vivo beating heart as well as the option to perform a direct coronary angiogram. This perfusion apparatus was introduced in 2007 in a first clinical European trial (41). In this "Protect I" trial 25 organs were perfused and evaluated with the OCS system. Out of these, 20 organs were orthotopically transplanted and showed good 95% 30 day survival with 1/20 failure. However, 5 organs were perfused but ultimately not transplanted, 2 due to technical problems within the perfusion system, 3 more due to observed increases in lactate production or changes in relation of coronary to systemic flow values. This first experience clearly proved feasibility of this new warm perfusion preservation technology, however, it also demonstrated its complexity especially compared to simple cold preservation and a significant learning curve how to deal with vital parameters during ex vivo perfusion. Key issues are the correct interpretation of coronary flow values in relation to systemic aortic flow as well as interpretation of lactate values measured in coronary sinus blood. This initial experience led to some technical modifications inside the system rendering it ultimately safer and more effective. Another important issue relates to excessive cost per case for this fairly complex technology in comparison to low cost cold static preservation. In the following 2<sup>nd</sup> part of this European trial (PROTECT-II) further 34 transplants were performed with hearts preserved using the OSC system. Again excellent survival rates were documented with only 2% primary graft failure and warm perfusion times within the system of up to 6 hours. A similar experience is reported from a still ongoing US American multicenter trial ("PROCEED") with similar failure and patients survival rates at 30 days. An interesting observation from this trial are data indicating a very low rate of early incidence of acute rejection within 30 days of transplant with 5% in the protect and 7% in the proceed trial (42). It has been speculated that this low incidence might be due to the overall very short is-

chemic time of in average 80 min., since previous experimental work showed that particularly cold ischemia induces upregulation of inflammatory signals due to activation of the innate immunity with ultimate upregulation of adhesion molecules and increased inflammatory cytokine expression during reperfusion (43).

Therefore one can summarize that this technology obviously has the potential for significant advantages allowing to expand transport time without significant increase of cold ischemic injury and resuscitation or reconditioning of marginal donor hearts that might have been otherwise lost to transplantation. Due to extension of transport radius it might also increase the overall availability of transplantable donor organs. This is contrasted however by the risk that malfunction of this obviously complex technology causes prompt organ injury due to its warm and perfused status. Of course further and larger clinical trials are mandatory to prove the absolute safety of this warm perfusion technique with regards to its technical aspects, but ultimately also to prove that continuous warm blood perfusion does not inflict by itself any injury within a closed system and without elimination of cumulative toxic metabolites on the perfused beating donor heart.

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