Myocardial and Endothelial Protection for Heart Transplantation in the New Millenium: Lessons Learned and Future Directions

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> For every problem there is one solution which is simple, neat and wrong.
> —H. L. Mencken

The successful development of cardiac surgery in recent decades has been based on innovations and refinements in surgical techniques, myocardial protection strategies, extracorporeal circulation and other improvements. Application of modern myocardial protection techniques is a prerequisite for successful outcome in complex cardiac operations, such as complex mitral valve repair, ROSS operations, aortic root reconstructions, etc.[1] In addition to the increased complexity of cardiac procedures in recent years, patients undergoing these operations are older and have a lower ejection fraction as well as more co-morbidities. Although a short aortic cross-clamp time is still better than a long one, application of advanced protection techniques has resulted in the fact that prolonged ischemic periods are no longer associated with an increased mortality rate.[2] Therefore, complex cardiac surgical operations are now offered even to high-risk patients (i.e., instances of reduced ejection fraction, re-operations, hypertrophied ventricles, etc.). As a result of these improvements, contraindications for almost all cardiac surgical procedures have diminished.

Many other advances have also occurred in cardiac transplantation including: (a) new immunosuppression modalities; (b) emerging therapies for chronic rejection (allograft vasculopathy); and (c) improved operative techniques (bicaval anastomosis, total cardiac transplantation). Parallel to these advances, the frequency of transplantation on high-risk patients is growing. These patients' risk factors include: high number of re-operations, greater ventricular assist device use, diabetes, numerous comorbidities, high pulmonary vascular resistance, sensitization, long ischemic times, and greater need for donor inotropic support.[3]

However, despite substantial advances in many aspects of cardiac transplantation, patients undergoing this procedure continue to face the possibility of death from 5 major causes: early graft failure; allograft rejection; infection; allograft vasculopathy; and malignancy.[3,4] During the first year after transplantation, the major causes of death were shown to be early graft failure, infection and rejection.[3] In a 10-year, multi-institutional study with 7,290 patients,[3] the percentage of patients dying from early graft failure, malignancy and infection within 3 years remained relatively stable over the last decade (1990 to 1999). This is in sharp contrast to the reduction in the likelihood of death from rejection and allograft vasculopathy during the first 3 years for patients transplanted during the latter part of the decade compared with those transplanted during earlier years,[3] indicating significant advances in immunosuppression.

These most recent data are supported by other studies of cardiac transplantation showing consistent results among reports worldwide for the immediate post-operative period[5]: Ischemic time is still a significant risk factor for 1-year mortality,[5,6] and graft failure has been a significant cause of 30-day mortality in all eras from 1982 to 2001.[5] In a multicenter clinical study between 1981 and 1991, Reichenspurner and co-workers[6] reported that acute graft failure and early mortality corelated significantly with ischemic time when no reperfusion modifications were done to the protection strategies. In another recent report operative mortality still approached 10% to 12% after heart transplantation (HTx).[7]

Although the consequences of inadequate myocardial protection, such as routine use of inotropes, significant enzyme release, wall motion abnormalities (abnormal septal wall motion, global hypokinesia) and reperfusion arrhythmias, are almost absent in most instances of non-transplant cardiac surgery, they still occur after orthotopic HTx in a large percentage of patients.

Despite significant innovations and refinements in many aspects of cardiac transplantation, along with the large number of articles on heart preservation, myocardial protection strategies have not changed much in recent decades. In the field of transplant organ protection the main area of interest is the ideal composition of

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hypothermic crystalloid storage solutions. At least 167 different types of heart preservation solutions are presently used in the USA.[8] Although advances have been made in myocardial integrity during the ischemic period with regard to composition of intra- and extracellular solutions, crystalloid cardioplegia for procurement, with no further protection strategy during the implantation or reperfusion procedure, is still the method of choice in most transplant centers. However, some investigators have had encouraging results using more advanced protection techniques.[9-14] Although some of these reports were published more than a decade ago clinical application of these techniques is not routine in all centers.

Our current protection methods allow for a safe ischemic time of 4 (maximum 6) hours. Therefore, many hearts are not accepted for HTx due to: (a) unacceptably long ischemic periods (6 hours and longer); (b) impaired donor heart function; or (c) potential myocardial damage of the donor organ after limited periods of hemodynamic instability. Furthermore, no attempts have been made in the field of HTx to use donors from "non–heart-beating-donors" (NHBDs), even though this technique is used successfully in certain countries for kidney and lung transplantation. For HTx, however, NHBDs are considered unacceptable (amid legal, practical and ethical reasons) because it is believed that the ischemic insult is so severe that early graft failure is likely to occur.

For successful short- and long-term outcome after HTx a technically perfect procedure must involve careful myocardial protection strategy that avoids damage from ischemia and reperfusion (i.e., ischemic storage period, implantation phase and reperfusion period) and brain death. HTx is the cardiac surgery procedure with the longest ischemic time and, subsequently, the most severe ischemia–reperfusion damage. The cardiac surgeon is in the unique position of "treating" the ischemic injury during the initial reperfusion phase and attempting to avoid or reduce reperfusion damage by controlling the conditions of reperfusion and the composition of the reperfusate.

One of the reasons for the slow adoption of modern methods for myocardial protection in HTx is the (false) belief that "everything is good as long as the heart is very cold." Hypothermia is a vital factor in protection for HTx, but it reflects an additional solution—rather than the only solution—to a complex problem.[15]

The benefits of applying the knowledge of current protection management techniques for non-transplant cardiac procedures are also evident in other organs. They have been used successfully to avoid the deleterious consequences of ischemia–reperfusion in skeletal muscle,[16,17] lungs[18-21] kidneys[22] and, as most recently noted, for the whole body after deep hypothermic circulatory arrest.[23]

The present review: (a) questions the efficacy of cold crystalloid cardioplegia for all phases of HTx; (b) provides data showing that the high incidence of early graft failure after longer ischemic periods is the result of sub-optimal protection; (c) endorses the application of modern forms of myocardial protection to lower the incidence of post-operative early graft failure; and (d) shows that there may be a relation between sub-optimal intra-operative myocardial and endothelial protection and late allograft vasculopathy.

IMPORTANCE OF MYOCARDIAL AND ENDOTHELIAL PROTECTION IN CARDIAC TRANSPLANTATION

Until recently, myocardial protection techniques have focused mainly on myocyte protection to avoid myocyte stunning, which could lead to the use of inotropic or even mechanical support until contractile recovery has occurred. In addition, it has been shown that the endothelium is critical not only in maintaining early graft function but may also play a role in late events (e.g., graft rejection and allograft vasculopathy).[24] It has been shown that damaged hearts exhibit loss of endothelium-dependent factors and reduced nitric oxide formation,[25] which results in peri-operative vasospasm, adherence of platelets and leukocyte attachment that causes capillary obstruction with inhomogeneous flow. A comprehensive review on endothelial damage during myocardial preservation and storage was done by Parolari and co-workers.[24] They showed that both myocardial protection and endothelial protection are needed to shift from *myocardial* to *cardiac* protection.[24]

Leukocyte filtration has been shown to be effective in treating endothelial injury after both acute coronary occlusion[26] and HTx.[12,13,27,28] In addition, prevention (rather than treatment) of endothelial stunning may be possible, because some investigators have found that delivery of the natural nitric oxide precursor, L-arginine, limits endothelial and myocyte damage, even without white blood cell depletion.[29-31]

The relation between myocyte and endothelial injury and stunning is underscored by reports that, in cardiac transplantation, myocardial protection may be important for both early graft failure and non-immunologic vascular failure of the transplanted heart, leading to allograft vascular disease.

Early Graft Failure

One of the main reasons for early graft failure after HTx is inadequate myocardial protection after prolonged ischemic periods. The spectrum of subsequent impaired graft function may range from subtle hemodynamic impairment (necessitating only moderate inotropic support) to overt graft failure (with subsequent

mechanical support). Due to the increased risk of early graft failure after prolonged ischemia, a total ischemic time of >4 hours (explantation, transport and implantation) is avoided by most transplant centers.[6] These data, however, were obtained from clinical observations and experimental settings where crystalloid cardioplegia was used for explantation and storage, and normal blood was used as the initial reperfusate without attempts to "treat" the ischemic myocardium.

In contrast, reperfusion with substrate-enriched, leukocyte-depleted blood cardioplegic solution for the first 3 minutes of reperfusion and leukocyte-depleted blood for additional 7 minutes after prolonged hypothermic ischemia resulted in shorter duration of inotropic support, decreased leakage of myocardial enzymes and prevention of ultrastructural damage.[9,10]

Our group has successfully applied advanced techniques of myocardial protection during explantation, storage and initial, reperfusion to the most severe form of ischemia–reperfusion damage in the transplant setting—specifically, orthotopic transplantation of pig hearts from non–heart-beating donors after 30 minutes of normothermic ischemia without donor pre-treatment.[12,14] In this experimental model, unmodified reperfusion after crystalloid cardioplegia for myocardial protection resulted in ischemic contracture ("stone heart") within a few minutes after the start of reperfusion. In contrast, controlled reperfusion with leukocyte-depleted, substrate- and HOE-642-enriched blood cardioplegia in the same model resulted in markedly improved contractility, and the animals were weaned successfully from extracorporeal circulation.[12,13] Hemodynamic measurements 24 hours after HTx revealed no significant difference between the non–heart-beating donors and a control group transplanted from heart-beating donors. Post-mortem examination showed only minimal histologic damage to the myocardium.[14]

The clinical applicability of these approaches is severely restricted[32] and can be made only in "controlled" non–heart-beating donors," as noted by the Pittsburgh group.[32] However, the data show that significant improvements in post-HTx can be achieved by applying modern protection techniques in the transplant setting. Currently, we are applying these experimentally developed principles in our transplant program, with improved hemodynamic allograft performance, less inotropic support and better immediate contractility (unpublished data).

Non-Immunologic Allograft Vascular Disease

In the setting of HTx, the presence of endothelial injury as a result of the initial insult during organ procurement, preservation, reperfusion and ongoing injury/repair during the lifespan of the cardiac allograft results in endothelial activation.[33]

Ischemic injury has been related to both the development of rejection[34] and accelerated allograft vasculopathy.[35] Damage to endothelial cells increases the production of platelet-derived growth factor and basic fibroblast growth factor, which stimulates smooth muscle cell proliferation in the media.[36] This proliferation contributes to the development of allograft vasculopathy,[36] which modulates late survival after HTx.[37]

Therefore, if protection strategies can successfully reduce ischemia–reperfusion damage, they may also provide a beneficial effect on long-term results of HTx by their protective effects on endothelial cells. However, this approach does not suggest that tissue damage is the only cause of rejection and allograft vasculopathy—it may simply be one of many well known immunoreactions leading to late post-transplant complications.

Until recently, rejection of a transplanted organ was always thought to be mediated by the incompatibility of the recipient immune cells to the cells within donor allografts.[38] In addition, short- or long-term failure of a transplanted organ was thought to be due to acute or chronic rejection (cellular and/or humoral).[38] However, organs may fail or may be rejected without cellular infiltration.[39]

On the basis of these observations Labarrere and co-workers[40] postulated that failure of a transplanted organ is caused by failure of the microvessels within the allograft to remain open, not due to an immunologic process mediated by the presence of cellular infiltrates that compromise the allograft. These investigators[40] reported that failure of the microvasculature of the donor allograft occurs because the vessels become prothrombogenic.

Prothrombogenicity of allograft vessels has been reported to be associated with 3 risk factors:

1. Loss of vascular anti-thrombin.[41]
2. Loss of vascular tissue plasminogen activator.[42]
3. Microvascular endothelial activation.[43]

Labarrere et al[40] showed that allografts with prothrombogenic microvessels during the first weeks after heart transplantation subsequently develop coronary artery disease, show significantly disease progression, and ultimately fail.[41–43] Once transplant-associated coronary artery disease develops, regimens of new and varied immunosuppressive agents fail to improve allograft survival.[44]

There is increasing evidence (see Labarrere et al[40]) that it is also the status of the microvasculature—and not only the presence of cellular rejection—that is associated with coronary artery disease and subsequent graft failure.

The natural thromboresistant character of endothelial cells is due to the presence of cell-surface proteoglycans that form the surface coat, and also due to the expression of prostacyclin (PGI_2), nitric oxide (NO) and various plasminogen activators.[45] Injury to the endothelium leads to underexpression of these factors and promotes vasoconstriction, abnormal flow characteristics, platelet interactions and thrombus development.[45] However, there is also convincing evidence that (in early periods after HTx) enhanced fibrinolytic activity may also promote intimal proliferation after vascular injury.[45–47]

On the other hand, it is possible that the microvascular alterations observed may also be the result of either endothelium-specific T lymphocytes initially damaging the endothelium[48] or a consequence of recipient antibodies initially damaging the donor endothelium.[49,50]

All these changes occur during the peri-transplant period. Labarrere et al[40–43] postulated that these changes might very well be the result of ischemia and reperfusion. Ischemia and reperfusion promote the generation of microthrombi within the allografts and, therefore, early endothelial injury could play an important role in the development of allograft vascular disease (AVD).

Additional evidence supporting the afore mentioned concept was recently published by the group from Harefield.[51] They reported a decreased incidence and severity of transplant-associated coronary artery disease in recipients of domino hearts compared with that reported in recipients of cadaveric hearts.[51] They concluded that these data support the hypothesis that brain death may contribute to the development of transplant coronary artery disease in recipients of cadaveric organ donors.[51] In addition, these data may also support the aforementioned hypothesis that reduced ischemia reperfusion injury (i.e., shorter ischemic times and therefore reduced reperfusion injury in heart transplantation from live donors) results in less endothelial injury with subsequently reduced AVD. The same group earlier reported the absence of AVD on the basis of early coronary angiograms from 12 of their first domino heart recipients.[52]

These findings emphasize the importance of: (a) applying currently strategies for endothelial and myocardial protection, and are the basis for further innovative developments in reducing peri-transplant endothelial injury; and (b) performing long-term prospective studies to evaluate the effects of peri-operative myocardial protection on the incidence of AVD.

Later Injuries to Vascular Endothelium

The endothelium is injured continuously after transplantation, and this injury contributes to the development of AVD.[45] The treatment and prevention of this damage include a variety of strategies, among them combinations of anti-coagulants (particularly low-molecular-weight heparins), anti-platelet drugs (i.e., clopidogrel), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and HMG–coenzyme A reduction inhibitors.[45] The level of contribution of both forms of endothelial injury (late endothelial injury and immediate peri-operative endothelial damage from ischemia–reperfusion) to the development of AVD is not known.

IMPROVEMENTS OF MYOCARDIAL PROTECTION FOR HTx

Current organ protection allows interventions to be made during 5 different phases of the transplant procedure:

1. Donor cardiovascular management.
2. Protection during explantation.
3. Protection during transportation.
4. Protection during implantation.
5. Protection during the immediate reperfusion period.

Donor Cardiovascular Management

Many potential donors undergo hemodynamic deterioration caused by brain death, leading to inotropic support and often massive fluid administration with resultant derangements in hemoglobin concentrations, electrolytes, etc. This cardiovascular instability leads to sub-optimal utilization of donor hearts and has compounded the problem of donor shortage in the USA and Europe, because a significant number of donor hearts are not transplanted. To increase the donor yield, recommendations have been published to improve the evaluation and successful utilization of potential cardiac donors.[53]

Functional assessment and management of donor hearts has been described by Potter et al,[54] and advantages of the pulmonary artery catheter as an instrument in guiding the steps necessary to prevent the functional decline frequently seen in the donor circulation have been described by Stoica et al.[55] However, these investigators also noted that even well-managed organs from marginal donors should be used with caution when combined with other risk factors, particularly long ischemic time.[55]

Another approach to this vulnerable pre-harvesting phase is the possibility of pre-treating these hearts with substances that limit ischemia–reperfusion damage[11] (e.g., free radical scavengers, HOE-642) and to provide them with intravenous metabolic substances for resolution of some of these hemodynamic problems (e.g., amino acids, GIK).[56,57]

Protection During Explantation

Myocardial damage due to brain death, hemodynamic instability in the pre-harvesting period and subsequently prolonged ischemia would ideally call for a strategy to "resuscitate" these damaged hearts. However, most current cardioprotective strategies are designed to "prevent further damage" rather than to improve the myocardial and endothelial integrity of the donor heart.

Myocardial protection during explanation is essential because this step should prevent further damage to the donor organ and prepare it for a long ischemic period, especially when the hearts are harvested from distant sites. The key element of this phase is the introduction of deep hypothermia because it reduces the metabolic rate and avoids the cumbersome need for continuous organ perfusion. However, data have shown that a gradual reduction in perfusion temperature is preferable as the heart is perpared for cold storage.[58] Our data,[12-14] as well as those of others,[58] support these assumptions, and also indicate that re-warming should be done gradually.

Many studies have compared the efficacy of both extra- and intracellular crystalloid solutions for graft preservation without unequivocal results.[59] Although studies have suggested improved protection in using blood cardioplegic techniques with the possibility of warm induction,[60] the use of these techniques is very cumbersome (if not impossible) in most donor hospitals. Therefore, almost uniformly, crystalloid cardioplegic solutions are used during this phase in the clinical setting.

The advantages of blood cardioplegic techniques as compared with crystalloid solutions have been reconfirmed recently,[33] showing that, in human recipients, donor hearts arrested with crystalloid cardioplegia had significantly higher transforming growth factor-β (TGF-β) expression as compared with those arrested in blood/insulin cardioplegia. Increased expression of TGF-β has been correlated with accelerated coronary artery vasculopathy. Therefore, the investigators concluded that the use of blood/insulin cardioplegia may help to decrease the extent of endothelial damage and attenuate the progression of AVD.[33]

Depletion of cardiac substrates in hemodynamically compromised brain-dead donors may be counteracted by pre-treating them with an intravenous infusion before harvesting because our previous studies have shown that such metabolic support improves post-ischemic ventricular performance in depressed hearts.[56,57]

The advantage of inhibiting Na^+/H^+ exchange during cooling and re-warming has been described by several investigators.[12,61,62] Stowe et al demonstrated that Na^+/H^+ isoform-1 exchanger inhibition, particularly when given intravenously before storage and as an intracoronary dose during cooling and re-warming, adds to the protection of cardioplegic solutions.[61]

It has also been shown that the supplementation of L-aspartate and L-glutamate of either crystalloid or blood cardioplegic solutions results in enhanced improvements of both functional and metabolic recovery after the ischemic period.[63-66]

Protection During Transport

The storage interval for the organ during transport is the longest portion of the ischemia period in heart transplantation. Many studies have been published about the ideal storage conditions with regard to the solution (e.g., Bretschneider, University of Wisconsin, St. Thomas, Stanford, etc.) and the temperature (0°, 4°, 8°C).[67] There are data showing that the solution used is more important than the temperature.[67] However, frostbite must be avoided by careful wrapping of the organ in 3 different isolation bags, and temperature measurement using a probe has also proven to be important.

Protection During Implantation

Immediately after starting to anastomose the left atrium, the storage phase, and thus the ischemic period, can be ended by given retrograde cold blood cardioplegia. We have noted immediate and continuous effluent of dark, desaturated blood from the coronary ostia during the first infusion of cardioplegia, indicating oxygen uptake of an organ stored in 2° to 4°C cold crystalloid solution. Due to the relatively high vascular resistance in the coronary vasculature during this phase, initial flows were restricted to approximately 150 ml/min.

After this initial blood cardioplegic dose, additional re-infusions can be given after 20 minutes by applying the same strategies as those used in non-transplant surgery.[68]

Standard blood cardioplegic solutions may be further improved by white blood cell filtration, free radical scavengers, magnesium supplementation, lowered Po_2 to limit re-oxygenation damage, reduction of calcium to prevent calcium-related injury, and use of sodium hydrogen ion-exchange inhibitors.[12-15,69] It has also been shown that adding L-arginine to a preservation solution can limit myocardial stunning during the early reperfusion period by better preservation of the NO pathway.[69] Others[70] have shown that chimeric superoxide dismutase can bind to cell surfaces and may aid in preventing superoxide-mediated endothelial damage and may function as a useful therapeutic agent for treating free radical–mediated diseases.

Table 1. Implantation Protocol, Freiburg

I. *After removal of the donor heart from the preservation solution*
- Insertion of a coronary sinus catheter and infusion of 10°C cold blood cardioplegia (solution for cold induction)
- Duration: 3 minutes
- Perfusion pressure: 40 to 60 mm Hg
- Blood cardioplegia given via a leukocyte filter (BC1B)

II. *After right atrial anastomosis (approximately 20 minutes)*
- Re-infusion of cold blood cardioplegia
- Duration: 3 minutes
- Perfusion pressure: 40 to 60 mm Hg
- Blood cardioplegia given via a leukocyte filter (BC1B)

III. *Before opening the aortic clamp*

Step A
- Warm terminal reperfusate with blood cardioplegia
- Duration: 1 minute
- Perfusion pressure: 40 to 60 mm Hg
- Blood cardioplegia given via a leukocyte filter (BC1B)

Step B
- Warm, leukocyte-depleted blood until heart resumes sinus rhythm
- Removal of the aortic clamp at a systemic pressure of 60 mm Hg

Another approach for ending the ischemic period and "resuscitating" the ischemic heart involves application of integrated myocardial management.[68,71] This approach uses antegrade/retrograde delivery of cardioplegic and non-cardioplegic blood; has reduced the ischemia periods significantly; and has shown excellent results in complex, non-transplant cardiac procedures.[68,71] Results of integrated myocardial management during the transplantation procedure have not been published, but these may represent another promising approach for improving the metabolic and functional status of myocardial and endothelial cells after implantation.

The implantation protocol (which will undergo a comparison with historic controls) currently used at the University of Freiburg is shown in Table 1.

The entire implantation procedure is done with constant flooding of the surgical field with CO_2 (1.5 liters/min), thus reducing the possibility of air embolism. Immediately after starting left atrial anastomosis, the coronary sinus is cannulated through the open right atrium and the first dose of retrograde cold BCP (induction) is given (10°C, perfusion pressure <50 mm Hg, 150 ml/min for 3 minutes). After 20 minutes, another 3-minute dose of cold BCP (re-infusion) is given. After another 20-minute period, all anastomoses are constructed and myocardial management is continued as described in the next subsection.

All these steps can prolong the aortic cross-clamp time during implantation by 5 to 8 minutes, which results in improved post-operative outcome. It is important to note that prolonged intensive care unit and hospital stay, as well as increased mortality, may be due to the nature of the disease but may also be a consequence of not using the currently available protection techniques. The value in terms of reduced morbidity and reduced costs of consecutive hospital cases was elegantly demonstrated in a study by Loop and colleagues several years ago at the Cleveland Clinic.[72]

Protection During the Immediate Reperfusion Period

After all anastomosis are constructed, warm, leukocyte-depleted, substrate-enriched BCP is given for 3 minutes at 150-ml/min flow and a temperature of 37°C. Thereafter, leukocyte-depleted non-cardioplegic blood is given until normal sinus rhythm has been resumed and vigorous contractions become present. Then the aortic clamp is removed at a systemic pressure of 50 mm Hg. The empty beating state is continued until bypass can be stopped without significant inotropic support. Routinely, intra-operative transoesophageal echocardiography is used to control global and regional contractility, residual intracavital air, function of the valves and anatomy of the anastomosis sites.

The availability of retrograde cardioplegic techniques may allow the reperfusion process to begin during implantation and thereby limit ischemia.[11]

The advantages of leukocyte depletion are based on the interaction between leukocytes and coronary endothelium. Yamamoto et al[27] showed that a leukocyte-depleting filter placed in the cardiopulmonary bypass circuit prevents leukocyte-mediated endothelial cell injury, improves microcirculation of the myocardium, and leads to improved graft function. In addition Fukushima et al[28] reported that leukocyte-depleted terminal blood cardioplegia in 24-hours-preserved hearts replenished the energy-depleted myocardium and reduced reperfusion injury with subsequent adequate cardiac function.

FUTURE DIRECTIONS

The aim of myocardial protection for heart transplantation has been to reduce the ischemic damage of the donor organ imposed by explantation, storage and implantation. Up to a certain limit of ischemic time (4 hours) this goal was achieved by cold, crystalloid solutions, provided there was no pre-existing injury to the heart.

Over the last decade, new data have broadened our knowledge of the implications of myocardial protection strategies for early graft function. Myocardial management can now be used to: (a) shorten the ischemic period; (b) limit ischemic–reperfusion injury after release of the aortic clamp; and (c) "resuscitate" hearts previously damaged either before brain death occurred, or by the consequences of brain death and/or during phases of hemodynamic instability before organ pro-

curement. In addition, several reports have suggested that long-term graft failure (transplant-associated coronary artery disease) may be due, at least in part, to ischemia–reperfusion injury during the transplant procedure. Therefore, an increased focus on protection of donor myocardial and endothelial cells may reduce peri-operative graft failure as well as the incidence of cellular rejection.

In the future, myocardial management techniques may not be used only for protecting the organ from ischemia–reperfusion injury (thus ensuring sufficient early graft function and lowering the incidence of allograft vasculopathy). This time period may also be used to consider other potential treatment options. It may be possible to inject adult stem cells suspended in an intracoronary solution to replace the donor heart with recipient cells to avoid long-term immunosuppression. Bone marrow cells of the recipient can be harvested at the time of transplant listing and also be isolated and grown during the waiting period on the transplant list. Thus, the start of generation of an organ immunologically similar to that of the recipient can be induced as part of the myocardial management strategy.

CONCLUSIONS

HTx is a cardiac procedure in which long ischemic periods for a pre-injured organ can be expected, with potentially severe sequelae of ischemia–reperfusion injury. With the currently available myocardial management techniques, powerful tools are available not only to reduce ischemic reperfusion damage but also to induce injury repair, which can occur before organ retrieval. In addition improved peri-operative myocardial protection may result in a decreased incidence of allograft coronary disease.

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