Combined St. Thomas and Histidine-Tryptophan-Ketoglutarate Solutions for Myocardial Preservation in Heart Transplantation Patients


ABSTRACT

Background. To establish quicker cardiac arrest and less myocardial distension injury during heart procurement, we combined St. Thomas and histidine-tryptophan-ketoglutarate (HTK) solutions for donor heart preservation since June 2008.

Methods. From June 2008 to March 2010, we enrolled 31 heart transplantation (HT) patients in this study. During heart procurement we initially infused 1,000 mL cold St Thomas cardioplegic solution to achieve cardiac arrest. After procurement, a further 2,000 mL of cold HTK solution was infused at low perfusion pressure. Another 1,000 mL cold HTK solution was perfused before donor heart implantation. We examined donor age, recipient preoperative characteristics, ischemia time, hospital stay, postoperative graft function, major cardiac events, and transplant vasculopathy (TCAD).

Results. Twenty-two patients (71.0%) presented with dilated cardiomyopathy and 7 (23.3%) with ischemia cardiomyopathy. There were 23 (76.7%) male donors, and the mean donor age was 38.4 ± 13.8 years. Six patients underwent a redo sternotomy, 1 patient needed a third-do sternotomy, and 1 a seventh sternotomy (third HT) for repeated endocarditis and graft failure. The average ischemia time was 224.9 ± 71.0 minutes and the postoperative hospital stay was 57.7 ± 47.7 days. The surgical mortality (3.2%) was not accompanied by hospital or follow-up mortality. Patient left ventricular ejection fraction postoperative was 59.6 ± 2.3% with good functional status. Major cardiac events occurred in 8 patients (26.7%) without major complications. There were two subjects with TCAD but normal graft function. The correlation between ischemia time and hospital stay was insignificant (r = 0.21; P = .26).

Conclusions. Donor heart preservation combining St Thomas cardioplegic arrest and low-pressure perfusion with HTK solution seemed to be safe with short-term survival similar to other approaches.

Myocardial protection during ischemic arrest is the most important issue in prolonged cardiac surgery. Repeated infusion of cardioplegic solutions during long arrest time interrupts surgical procedures and increase the incidence of cellular edema and myocardial dysfunction. Many cardioplegic methods have been clinically applied for myocardial preservation. However, none of them has proved to be a satisfactory solution for all ischemia-related effects. Thus the optimal myocardial preservation and the maximum ischemia time that can be tolerated by the myocardium are unresolved issues.

Cardioplegic solutions are classified into 2 main groups. One uses extracellular components with high potassium, magnesium, and bicarbonate levels, and the other intracellular levels of electrolytes. Both types have demonstrated beneficial effects as measured by biochemical markers in bio-
logic models and in patients, but the intracellularly composed solutions appear to be more effective.\textsuperscript{5,6} We have used St Thomas extracellular solution for cardioplegia to achieve myocardial protection for the past 15 years. It is effective and appropriate for myocardial protection for patients undergoing simple surgery, especially coronary artery bypass grafting. However, it displays limited myocardial protection for patients who require longer cross-clamp times. In heart transplantation (HT), only crystalloid St Thomas cardioplegia solution can be used, but the myocardial protection may be reduced compared with a bloody solution. Therefore, we sought to prolong the tolerated ischemic time.

Histidine-tryptophan-ketoglutarate (HTK) solution was initially introduced as a cardioplegic solution for cardiac surgery by Bretschneider in the 1970s. It was also used in heart, kidney, liver, and pancreas transplantation.\textsuperscript{2–4} Its composition is based on intracellular levels of electrolytes. The basic design of the solution consists of histidine, a potent buffer, combined with two amino acids: Tryptophan serves as membrane stabilizer, and ketoglutarate improves high energy production via adenosine triphosphate during preservation.\textsuperscript{3,9–11} HTK solution has a high energy production via adenosine triphosphate during preservation.\textsuperscript{2–4} HTK solution only were excluded from this study. The choice of cardioplegic solution depended on the surgeon’s preference.

During heart procurement, an initial 1,000 mL cold (4°C–8°C) St Thomas cardioplegia solution was infused under lower perfusion pressure. After procurement and before cold storage, a further 2,000 mL of cold HTK solution was infused under lower perfusion pressure. HTK solution only were excluded from this study. The choice of cardioplegic solution depended on the surgeon’s preference.

During heart procurement, an initial 1,000 mL cold (4°C–8°C) St Thomas cardioplegia solution was infused to achieve cardiac arrest. After procurement and before cold storage, a further 2,000 mL of cold HTK solution was infused under lower perfusion pressure. The heart was stored in cold HTK solution. Another 1,000 mL cold HTK solution was perfused before donor heart implantation.

During the operation, rabbit antithymocyte globulin (ATG); 1.25 mg/kg/d was used for induction therapy. The dose was adjusted according to infection status, daily flow cytometry, T-lymphocyte, and platelet counts. Solumedrol (500 mg) was infused before the release of the aortic cross-clamp, and another 500 mg in the intensive care unit. Oral mycophenolate mofetil (MMF; Cellcept); 1–2 g/d was dose-adjusted to maintain a white blood cell count of 4,000–9,000/μL. Prednisolone (0.3–0.4 mg/kg/d) started on the second day was tapered to 5–10 mg/d at 1 month. Oral cyclosporine (CsA) or tacrolimus (FK506) was also started on the second day; it was adjusted based upon the patient’s renal function and drug blood concentrations. During the first 3 months, the CsA trough level was kept at 300–400 ng/mL and shifted to 100–250 ng/mL 6 months later. The initial trough level of tacrolimus was at 10–20 ng/mL with a maintenance level of 5–10 ng/mL. Prophylactic anticytomegalovirus (CMV) therapy with intravenous ganciclovir was indicated for 14 days; the dose was adjusted based on renal function. Generally, the patient underwent an endomyocardial biopsy (EMB) twice in the first month after surgery, monthly for 3 months, trimonthly for 1 year, and yearly thereafter. If the pathologic results of the EMB showed grade II or above (ISHLT, 1990) rejection or there was positive C4d staining, the dosage of immunosuppressants was increased or we delivered pulse therapy with steroids. Strict diet control and appropriate medications were used to treat hyperlipidemia, diabetes, and hypertension. To survey transplant vasculopathy (TCAD), we routinely performed a coronary angiogram (CAG) annually or when the patient developed a cardiac event, such as heart failure, arrhythmia, or electrocardiogram changes. TCAD was defined when the CAG showed coronary artery irregularities, decreased luminal diameter, or >60% stenosis.

We obtained donor age, recipient preoperative characteristics, ischemia time, hospital stay, postoperative cardiac function, major cardiac events (MACE), hospital mortality, short-term survival, TCAD, and functional status.

Statistical Analysis
For the univariate analysis, student’s t test was calculated for continuous variables. Pearson correlation coefficient was used to evaluate the relationship between days of hospitalization, donor age, and ischemia time. Statistical analysis was performed using SAS 8.1 (SAS Institute, Cary, NC). The P value <.05 was considered to be statistically significant.

RESULTS
Among 31 HT patients enrolled in this study, 22 (71.0%) presented with dilated cardiomyopathy and 7 (23.3%) with ischemia cardiomyopathy. There were 26 (83.9%) male recipients with a overall mean age of 46 years (range, 18–69) and a donor age of 38.4 ± 13.8 years. Six patients underwent redo 1 third-do and 1 a seventh sternotomy (third-do HT) owing to repeated endocarditis with ventricular dysfunction. Clinical and postoperative recipient characteristics are presented in Table 1. Sixteen patients (51.6%) needed preoperative intra-aortic balloon pump (IABP)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age of recipients (y) (n = 31)</td>
<td>45.6 ± 13.2</td>
<td>18–69</td>
</tr>
<tr>
<td>Age of donors (y) (n = 31)</td>
<td>38.4 ± 13.8</td>
<td>11–68</td>
</tr>
<tr>
<td>Ischemia time (min) (n = 31)</td>
<td>224.9 ± 71.0</td>
<td>101–323</td>
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<tr>
<td>Postoperative hospital stay (d)</td>
<td>57.7 ± 47.7</td>
<td>24–214*</td>
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<tr>
<td>Postoperative LVEF (%)</td>
<td>59.6 ± 2.2</td>
<td>48–60*</td>
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<tr>
<td>Postoperative LVEDD (mm)</td>
<td>43.4 ± 5.4</td>
<td>32–53*</td>
</tr>
<tr>
<td>MACE</td>
<td>0.5 ± 0.88</td>
<td>0–3*</td>
</tr>
<tr>
<td>Postoperative NYHA functional class</td>
<td>1.0 ± 0.0</td>
<td>1–1*</td>
</tr>
</tbody>
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Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; MACE, major cardiac events; NYHA, New York Heart Association

* n = 30; 1 surgical mortality patient was excluded.
support, and 6 (19.3%) extracorporeal membrane oxygenator (ECMO) support. Fifteen patients (48.4%) showed ischemia times of > 240 minutes. The average ischemia time was 224.9 ± 71.0 minutes, and postoperative hospital stay was 57.7 ± 47.7 days. In the operating room 12 patients had their IABP and 2 patients ECMO weaned. Two patients needed postoperative IABP support; their ischemia times were 231 and 272 minutes. All mechanical support except in one patient were weaned off thereafter. Our surgical mortality was 3.2%; there was no hospital or follow-up mortality.

The deceased patient was a 22-year-old man who was a victim of dilated cardiomyopathy. Pre-HT IABP and ECMO support were mandatory owing to cardiogenic shock with renal failure, liver dysfunction, pneumonia, and complicated pulmonary hemorrhage. Concomitant HT and right-lung lobectomy were performed owing to severe pulmonary hemorrhage. Sustained IABP and ECMO support were needed for the poor oxygenation and right ventricular failure. The patient's ischemia time was 323 minutes; his postoperative creatine kinase MB/creatine kinase was 1.0%. The patient died at 10 days after HT owing to sepsis and multiple organ failure.

The other TCAD patient's postoperative left ventricular ejection fraction was 59.6 ± 2.3%. MACE occurred in 8 patients (26.7%) without major complications. One patient had grade II rejection; the others presented with temporary arrhythmias. The 2 patients were TCAD showed normal graft function, one of whom underwent coronary balloon angioplasty and stenting. The lack of correlations between postoperative hospital stay, donor age, and ischemia time is presented in Table 2 Patients with ischemia times of ≥240 minutes, showed no statistical difference compared with other patients in postoperative levels of cardiac enzymes, hospital stay, cardiac function, or MACE incidence (Table 3).

DISCUSSION

The optimal composition of donor heart preservation solutions remains uncertain as reflected by the variety of techniques currently used for heart protection.13 The main purpose of using a cardioplegic is to establish cardiac arrest in the diastolic phase; potassium is the primary agent used for this purpose.14 Cardioplegic solutions based on an high potassium level are the most widely used because this produces rapid arrest of the myocardium. However, it also increases cellular edema and damages endothelial function owing to the need for repeated perfusion during ischemia.10,13,15 St Thomas crystalloid cardioplegia has a higher potassium level than HTK solution, and has been used for myocardial protection. Because it must be administered every 20–40 minutes however, it interrupts an ongoing surgical procedure that requires a prolonged ischemia time.

HTK solution has low viscosity. According to Brettschneider, high volumes at a low flow rate should be applied to guarantee “equilibration.”12 The advantages of HTK solutions are based on the buffer effect of histidine, which may enhance the efficiency of anaerobic glycolysis. Ketoglutarate acts as an intermediary in the Krebs cycle and is a precursor of nicotinamide adenine dinucleotide. The addition of mannitol decreases cellular edema.2–10,12–15 Another advantage is that only a single dose is required which can simplify the surgical procedure. Its effectiveness for myocardial protection has been demonstrated by measurements of energy demand of the myocardium, of creatine kinase, and of lactate dehydrogenase levels in several studies.1,10,16,17 The low level of potassium and freedom from calcium in the HTK solution have been suggested to be advantageous for organ preservation, but it can be disadvantageous for cardioplegic purposes because of the long time to initiate arrest.11 Ischemic and reperfusion damage is expected to be greater using HTK because of the longer electrophysiologic arrest time after aortic clamping, which is crucial for myocardial protection using a marginal donor with left ventricular hypertrophy.

Based on the advantages and disadvantages between St Thomas and HTK solutions, we adapted the protocol to use St Thomas cardioplegia to achieve an initial quick cardiac arrest and HTK cardioplegia for prolonged myocardial storage. From our clinical results, the lower surgical mortality and similar short-term survival and graft function support this technique of donor heart preservation. Even in the patients with longer ischemia times, the postoperative recovery was not inferior to those with shorter ischemia times.

The main limitation of our study was the low number of patients. Long-term follow-up is mandatory for a further survey.

In conclusion our early experience showed donor heart preservation using combined St Thomas cardioplegic arrest and low-pressure perfused HTK solution to be safe.
REFERENCES