Prolonged pericardial drainage using a soft drain reduces pericardial effusion and need for additional pericardial drainage following orthotopic heart transplantation

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Abstract

OBJECTIVES: Pericardial effusion can cause haemodynamic compromise after heart transplantation. We identified the effects of soft drains on the development of pericardial effusion.

METHODS: We enrolled 250 patients \( \geq 17 \) years of age who underwent heart transplantation between July 1999 and April 2012 and received two conventional tubes \( (n = 96; 32 \) French), or two tubes with a soft drain \( (n = 154; 4.8 \) mm wide). The development of significant pericardial effusion or the need for drainage procedure during 1 month after heart transplantation was compared with the use of the propensity score matching method to adjust for selection bias.

RESULTS: At 1 month after transplantation, 69 patients \((27.6\%)\) developed significant pericardial effusion. Among these, 13 patients \((5.2\%)\) underwent pericardial drainage. According to multivariate analysis, history of previous cardiac surgery \([\text{odds ratio (OR)} = 0.162; 95\% \text{ confidence interval (CI)} = 0.046–0.565; P < 0.004]\) and placement of a soft drain \([\text{OR} = 0.186; 95\% \text{ CI} = 0.100–0.346; P < 0.001]\) were significant factors that prevented pericardial effusion or the need for drainage during the early postoperative period. For the 82 propensity score matched pairs, patients receiving an additional soft drain were at a lower risk of the development of significant pericardial effusion or the need for a pericardial drainage procedure during 1 month \([\text{OR} = 0.148; 95\% \text{ CI} = 0.068–0.318; P < 0.001]\) compared with those receiving only two conventional tubes.

CONCLUSIONS: Pericardial soft drainage is a simple and safe procedure that reduces pericardial effusion and decreases the need for pericardial drainage after heart transplantation.

Keywords: Heart transplantation • Pericardial effusion • Soft drain

INTRODUCTION

Pericardial effusion is relatively commonly observed in patients who receive orthotopic heart transplantation and significant pericardial effusion \( \text{(i.e. moderate to large amount)} \) has been reported in as many as 20\% of patients \([1, 2]\). Although pericardial effusion following heart transplantation is generally benign and self-limiting, it can cause haemodynamic compromise and require additional invasive procedures in immunosuppressed patients \([1, 3]\). Some of the risk factors associated with significant pericardial effusion have been reported in previous studies, including no history of previous sternotomy for cardiac surgery \([2, 4]\), positive weight difference \( \text{(recipient weight > donor weight)} \) \([4]\), intraoperative use of aminocaproic acid during surgery \([2]\) and prolonged donor ischaemic time \([3]\). In practice, however, these risk factors are not under the surgeon’s control except avoiding the use of aminocaproic acid. In our present study, we identify the effects of a pericardial soft drain, which is very simple and completely within the surgeon’s control, on the development of pericardial effusion and the need for pericardial drainage.

METHODS

Patients

We screened our database to obtain the medical records of patients \( \geq 17 \) years of age who underwent orthotopic heart
transplantation between July 1999 and April 2012 and identified 250 patients who formed the study population. Of these, 96 patients received two conventional tubes (32 Fr curved and straight tubes) and 154 patients received two conventional tubes plus a soft drain (4.8 mm wide) (Figs 1 and 2).

Pericardial effusion was identified by transthoracic echocardiography and classified as small (<10-mm echo-free space in diastole, or ~300 ml), moderate (10–20 mm or 500 ml) or large (>20 mm or >700 ml) [5, 6]. Cardiac tamponade was confirmed based on the combination of symptoms, signs and echocardiographic criteria [7]. Patients with cardiac tamponade underwent pericardial drainage, such as pericardiocentesis (n = 1), pericardiostomy (n = 11) or a pericardial window procedure (n = 2).

This study was approved by our institutional ethics committee/review board, which waived the requirement for informed patient consent because of the retrospective nature of the analysis.

Surgical procedures

Donor hearts were prepared using histidine–tryptophan–keto glutarate solution (Custodiol® HTK; Essential Pharmaceuticals, Newtown, PA, USA), which was injected through the aortic root cannula, with venting through the right superior pulmonary vein and inferior vena cava. All donor hearts were routinely flushed with 2 l of Custodiol® HTK solution and preserved using the same solution. When the cold ischaemic time was >120 min, 1 l of Custodiol® HTK solution was infused again before anastomosis in some cases. All recipients were routinely prepared for open heart surgery. Aortic and bicaval cannulations were performed for cardiopulmonary bypass following median sternotomy. The bicaval technique was performed in all patients. Before declamping the aorta, 500 mg methylprednisolone was intravenously administered. During anastomosis, carbon dioxide was insufflated into the surgical field to prevent air embolism. After the recipient was weaned off bypass, two conventional tubes were placed through sub-xiphoid incisions. One curved tube was placed in the pericardial space inferiorly, and the other straight tube was placed anteriorly overlying the heart. These tubes were connected to a three-bottle drainage system (negative pressure of 20 cmH2O). An additional soft drain was placed in the oblique sinus (Fig. 2) and connected to a closed drainage system (negative pressure of 90 mmHg). Pericardial soft drainage placement was decided by the surgeon or the first assistant. Before closing the sternum, a pair of epicardial ventricular pacing wires was inserted [8]. When pericardial drainage was needed postoperatively, pericardiostomy was performed via the sub-xiphoid approach and the pericardial window procedure was performed via the left mini-thoracotomy approach.

Imunosuppressive protocol

The preoperative immunosuppressive protocol consisted of anti-IL2 receptor monoclonal antibody (anti-IL2 R mAb), 1.5–2.0 g mycophenolate mofetil PO and 3–4 mg/kg cyclosporine PO (not used since January 2007). Cyclosporine was withheld if serum creatinine (Cr) was >1.5 mg/dl. Intravenous methylprednisolone (500 mg) was intraoperatively administered. Patients were treated with 1–2 g/day mycophenolate mofetil and anti-IL2 R mAb postoperatively to maintain the white blood cell count in the range 4000–6000/μl. Cyclosporine trough levels were maintained at 300–400 ng/ml for the first year and 150–200 ng/ml thereafter using the enzyme-multiplied immunoassay method. FK 506 has been used since January 2007 and the trough levels of this drug were maintained at 10–15 ng/ml during the first year and 6–8 ng/ml thereafter. Three injections of 125 mg methylprednisolone were injected over 24 h (one injection every 8 h). The initial postoperative dose of prednisone was 1 mg/kg/day, which was decreased to 0.25 mg/kg/day at 1 month and 0.1 mg/kg/day at 1 year. If possible, prednisone was discontinued at 1 year after transplantation.

Statistical analysis

Categorical variables are presented as numbers and percentages and were compared using the χ2 and Fisher’s exact tests. Continuous variables are expressed as the mean ± standard deviation (SD) and were compared using Student’s unpaired t-test or the Mann–Whitney U-test. For multivariate analyses, logistic regression models were used to determine the risk factors for the development of significant pericardial effusion and the need for pericardial drainage. Preoperative and operative variables were evaluated using these models, and variables with P ≤ 0.20 according to univariate analyses were considered candidates for multivariate logistic regression modelling. Multivariate analyses involved backward elimination. Matched propensity score analyses were used to ascertain the results of primary analysis due to the possibility of selection bias and confounding in observational studies [9]. Propensity scores

[Figure 1: Drainage system consisting of a 32-Fr curved tube (upper), 32-Fr straight tube (middle) and 4.8 mm flat soft drain (lower).

Figure 2: A soft drain in the oblique sinus.]

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were estimated without regard to outcome variables, using multiple logistic regression analysis. The propensity score matched pairs were created by matching patients receiving an additional soft drain and patients receiving only two conventional tubes on the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score [10]. After propensity score matching, matching balance was assessed with standardized differences for each covariate (Table 1). All of the standardized differences for each of the baseline variables were less than 0.1 (10%). All reported $P$ values were two-sided, and a value of $P < 0.05$ was considered statistically significant. SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA), was used for statistical analyses.

### RESULTS

#### Baseline patient characteristics

Patients who received an additional pericardial soft drain with two conventional tubes were older than patients who received only two conventional tubes. After adjustment of the baseline profiles with the use of propensity scores, the cohort was well balanced for all baseline covariates (Table 1).

#### Outcomes and pericardial effusion

The mean follow-up duration was $65.3 \pm 42.8$ months (0.2–173.6) and 4 cases of in-hospital mortality were documented. One patient, a 41-year old female, did not receive a soft drain and underwent pericardiostomy for pericardial tamponade at 13 days after transplantation. She died from pneumonia following septic shock at 64 days post-transplantation. The other 3 patients received soft drains and did not develop significant pericardial effusion. The first patient, a 56-year old female, was supported by extracorporeal membrane oxygenation because right ventricular failure developed on the first postoperative day. One week later, she died from intracranial haemorrhage. The second patient, a 60-year old male, died from pneumonia following septic shock at 21 days after transplantation. The last patient, a 66-year old female, developed postoperative thrombocytopenia and died due to intracranial haemorrhage at 16 days post-transplantation.

The length of time the tubes were maintained and the amount of drainage 24 h prior to removal were similar between groups. Pericardial soft drains were maintained for $15.6 \pm 6.2$ postoperative days, and the amount of drainage through the pericardial soft drain for 24 h prior to removal was $26.6 \pm 23.5$ ml. Prophylactic antibiotics were stopped 48 h after transplantation and were not used because of the existence of drains. Patients who received an additional pericardial soft drain with two conventional tubes were less likely to develop moderate to large amounts of pericardial effusion and require pericardial drainage during the early postoperative period. At 1 month after transplantation, 69 patients (27.6%) developed significant pericardial effusion (moderate to large amounts). Among these, 13 patients (5.2%) developed haemodynamic compromise and underwent pericardial drainage such as pericardiocentesis ($n = 1$), pericardiostomy ($n = 11$) or a pericardial window procedure ($n = 1$). Only 1 patient who received a pericardial soft drain with two conventional tubes and did not show pericardial effusion on transthoracic echocardiography at 1 month post-transplantation underwent a pericardial window procedure at 77 days after transplantation due to newly developed cardiac tamponade. Recurrent effusion did not develop, nor were additional procedures performed (Table 2).

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort</th>
<th>Propensity score matched</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two tubes ($n = 96$)</td>
<td>Two tubes with a soft drain ($n = 154$)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.0 ± 12.5</td>
<td>47.8 ± 12.2</td>
</tr>
<tr>
<td>Male sex, $n$ (%)</td>
<td>76 (79.2)</td>
<td>106 (54.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>21.8 ± 6.9</td>
<td>22.5 ± 3.65</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.674 ± 0.160</td>
<td>1.684 ± 0.200</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>31.1 ± 9.6</td>
<td>33.3 ± 10.9</td>
</tr>
<tr>
<td>Donor sex, $n$ (%)</td>
<td>78 (81.3)</td>
<td>122 (79.2)</td>
</tr>
<tr>
<td>Aetiology of HTPL, $n$ (%)</td>
<td>71 (74.0)</td>
<td>115 (74.7)</td>
</tr>
<tr>
<td>DMCP</td>
<td>12 (12.5)</td>
<td>25 (16.2)</td>
</tr>
<tr>
<td>ICMP</td>
<td>6 (6.3)</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>HCMP</td>
<td>6 (6.3)</td>
<td>7 (4.6)</td>
</tr>
<tr>
<td>Others</td>
<td>7 (7.3)</td>
<td>23 (14.9)</td>
</tr>
<tr>
<td>Previous sternotomy, $n$ (%)</td>
<td>13 (13.5)</td>
<td>30 (19.5)</td>
</tr>
<tr>
<td>HTN, $n$ (%)</td>
<td>13 (13.5)</td>
<td>21 (13.6)</td>
</tr>
<tr>
<td>DM, $n$ (%)</td>
<td>7 (7.3)</td>
<td>23 (14.9)</td>
</tr>
<tr>
<td>CRF, $n$ (%)</td>
<td>1 (1.0)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>CVA, $n$ (%)</td>
<td>5 (5.2)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Preoperative status, $n$ (%)</td>
<td>44 (45.8)</td>
<td>66 (42.9)</td>
</tr>
<tr>
<td>Admission</td>
<td>2 (2.1)</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Ventilator support</td>
<td>1 (1.0)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Ischaemic time (min)</td>
<td>153.6 ± 56.7</td>
<td>163.9 ± 59.6</td>
</tr>
</tbody>
</table>

BSA: body surface area; CRF: chronic renal failure; CVA: cerebrovascular accident; DMCP: dilated cardiomyopathy; DM: diabetes mellitus; ECMO: extracorporeal oxygenation; HCMP: hypertrophic cardiomyopathy; HTN: hypertension; HTPL: heart transplantation; ICMP: ischaemic cardiomyopathy; $n$: numbers.
Through the first 12 months after the procedure, pericardial effusion was spontaneously absorbed in most patients, and 9 patients retained moderate to large amounts of pericardial effusion. In all 9 of these patients, pericardial effusion was spontaneously absorbed within 2 years and did not cause additional pericardial pathological changes.

Constrictive pericarditis was diagnosed in 4 patients without a pericardial soft drain within 32 months after transplant (at 12.3, 22.6, 27.1 and 31.1 months, respectively). These patients developed a large amount of pericardial effusion by 1 month after orthotopic heart transplantation, but the clinical course is usually benign due to pericardial tamponade. Neither did recurrent effusion occur, nor did patients develop symptoms and receive follow-up examinations at the outpatient clinic. The other patient was admitted with rhodococcal pneumonia, and constrictive pericarditis was subsequently diagnosed. Despite antibiotic therapy, rhodococcal sepsis occurred and the patient died.

**Risk factor analysis**

Multivariate logistic regression analysis identified placement of a pericardial soft drain [odds ratio (OR) = 0.186; 95% confidence interval (CI) = 0.100–0.346; P < 0.001] and previous sternotomy for cardiac surgery (OR = 0.162; 95% CI = 0.046–0.565; P = 0.004) as protective factors against the development of significant pericardial effusion and the need for drainage during the early postoperative period. On the other hand, dilated cardiomyopathy (OR = 2.324; 95% CI = 1.065–5.070; P = 0.034) was identified as a predictive factor for significant pericardial effusion and the need for drainage during the early postoperative period. After adjustment of the baseline profiles with the use of propensity scores, placement of a pericardial soft drain (OR = 0.148; 95% CI = 0.068–0.318; P < 0.001) was identified as a protective factor against the development of significant pericardial effusion and the need for drainage during the early postoperative period (Table 3).

**DISCUSSION**

The incidence of significant pericardial effusion is reportedly 21–35% during the early postoperative period following orthotopic heart transplantation, but the clinical course is usually benign and resolves within 3 months; however, some cases persist and may cause cardiac tamponade [1–3, 11]. In our current study, moderate to large pericardial effusion was identified in 63 patients (25.2%) at 1 month after orthotopic heart transplantation and, among these cases, 13 patients (5.2%) needed pericardial drainage due to pericardial tamponade. Neither did recurrent effusion develop, nor were additional procedures required. Through 1 year of follow-up examinations, it was observed that pericardial effusion was spontaneously absorbed in most patients, and only 9 patients retained moderate to large amount of pericardial effusion. In all 9 of these patients, pericardial effusion was...
Some risk factors associated with moderate to large amounts of pericardial effusion have been reported in previous studies, including no history of previous cardiac surgery [2, 4], positive weight difference (recipient weight > donor weight) [4], intraoperative use of aminocaproic acid during surgery [4] and prolonged donor ischaemic time [3]. In our present series, no history of previous cardiac surgery was identified as a risk factor for moderate to large pericardial effusion. Positive weight difference and the intraoperative use of aminocaproic acid, however, were not evaluated in our present analyses because of the lack of medical records describing these variables. In contrast to a previous study [3], prolonged ischaemic time was not associated with moderate to large amounts of pericardial effusion in our current study. Surgeons can predict the incidence of significant postoperative pericardial effusion by considering these factors. In practice, however, these factors cannot be controlled by the surgeon other than avoiding aminocaproic acid. Here, we sought to identify the effects of a pericardial soft drain, which is a very simple procedure that is completely under the surgeon's control, on the development of pericardial effusion and the need for pericardial drainage. Perhaps this method has been routinely used by several centres, but well-designed studies are sparse.

Some authors have suggested that patients who receive a transplant for dilated cardiomyopathy are significantly younger and less likely to have undergone previous cardiac surgeries [2]. In our present series, patients who received a transplantation for dilated cardiomyopathy were indeed significantly younger (44.9 ± 12.2 vs 49.1 ± 13.0 years; P = 0.022), but we found no correlation between age and a history of previous cardiac surgery (P = 0.41). Other reports have suggested that pericardial effusion following heart transplantation is associated with a higher incidence and more severe histological grading of acute rejection episodes [12, 13]. However, the relationship between pericardial effusion and acute rejection was not a focus of our current study because both of these are postoperative results. Instead, we focused on the pre- and intraoperative factors that may affect postoperative pericardial effusion or the need for pericardial drainage.

Pericardial drainage was performed 22.1 ± 17.0 (4–77) days after heart transplantation. This suggests that maintaining tubes or soft drainage for a sufficient period of time could prevent the development of significant pericardial effusion and decrease the need for drainage procedures. The mean duration of maintaining the soft drain (15.6 ± 6.2 days) in the patients with two tubes and a soft drain was significantly longer than the mean duration of maintaining tubes (4.4 ± 1.6 days) in patients with two tubes. Maintaining soft drainage for a long period of time, however, is controversial due to the risk of wound infection. However, the incidence of sternal wound infection and mediastinitis demonstrated no differences between the patients with two tubes and patients with two tubes and a soft drain (P = 0.65; after adjustment with the use of propensity scores, P > 0.99) even though prophylactic antibiotics were not given to the patients for the prolonged use of the drain. We always stop prophylactic antibiotics 48 h after transplantation. The additional prolonged use of a drain (mean duration, 15.6 ± 6.2 days) may increase hospital stay but, in our institute, the patients routinely undergo myocardial biopsy a month after transplantation and are discharged after it. Therefore, the length of postoperative hospital stay demonstrated no difference between the two groups. To minimize the risk of wound infection and prolonged hospital stay caused by the long-term installation of soft drains, further studies are needed to determine the adequate duration of maintaining soft drains and thereby prevent significant pericardial effusion and the need for pericardial drainage.

**Study limitations**

This study is subject to the inherent limitations of retrospective analyses of observational data. Some of the donor records regarding baseline characteristics, weight, height etc. were lost and unavailable for analysis. The decision to place an additional soft drain was affected by the preferences of the surgeon and first assistant, which was taken without definite indications. Furthermore, there are no guidelines regarding the removal of soft drainage. Despite the positive results of this study, further investigation including a randomized clinical trial would be necessary.

**CONCLUSION**

Placing a pericardial soft drain is a simple, effective and safe procedure that reduces pericardial effusion and decreases the need for a subsequent drainage procedure following orthotopic heart transplantation when performed using the bivacaval technique. Further studies are needed to determine the adequate duration of maintaining soft drains in order to prevent significant pericardial effusion and the need for pericardial drainage.

**Conflict of interest:** none declared.