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Comparison of UW versus HTK solution for myocardial protection in heart transplantation

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Abstract In order to evaluate the protective effect of University of Wisconsin (UW) solution in heart transplantation, a retrospective comparative study with histidine-tryptophane-ketoglutarate (HTK) solution was initiated. In group I, we included 160 patients with HTK preservation, while group II consisted of 50 patients who had their transplant protected with UW solution. All patients received standard quadruple drug therapy for immunosuppression. The average ischaemic time of the donor hearts in group I was 142 ± 44 min, ranging from 83 to 235 min. Acute immediate perioperative graft failure occurred in six cases (3.8%). Statistical analysis including the chi-square test, revealed a significant increase in the incidence of acute perioperative graft failure when compared with duration of ischaemic time ($P < 0.01$). Within the first 30 postoperative days, 24 patients died (15% early mortality). The same statistical correlation was evident between the incidence of early mortality and duration of graft ischaemic time. The 30-day and 6-month survival rates were 81% and 78%, respectively. The average ischemic time of the donor hearts in group II was 193 ± 50 min ranging from 100 to 360 min, which was significantly longer in comparison with the group I ($P < 0.05$). Acute perioperative graft failure occurred once (2%); the patient was retransplanted successfully. Five patients died within the first 30 postoperative days (10% early mortality). There was no correlation between length of ischaemic time and incidence of acute graft failure or early mortality. The 30-day and 6-month survival rates were 90% and 88%, respectively and, thus, better when compared with group I. In both groups similar results were achieved with regard to postoperative NYHA status of the patients and incidence of cardiac arrhythmias. Myocardial preservation with HTK solution showed satisfying results as long as the ischaemic time did not exceed 4 h. The early functional results achieved with UW graft protection were excellent, even with ischaemic times longer than 4 h and not depending on lenght of ischaemic period.

Key words Heart transplantation
Myocardial protection
Cardioplegic solution

Introduction

At present, various cardioplegic solutions are used for myocardial protection in heart transplantation with St. Thomas, Stanford and histidine-tryptophane-ketoglutarate (HTK) cardioplegic solutions being used most commonly [1, 2]. The generally accepted time limit for safe cold ischaemic preservation of the heart is 4–5 h for clinical heart transplantation [3]. Longer safe preservation times would be desirable and would greatly increase the number of potential donor hearts for patients on the waiting list and enable a better tissue matching between donor and recipient. Experimentally, a further extension of preservation time has been achieved applying various cardioplegic solutions including the University of Wisconsin (UW) solution [4, 5]. However, no clinical study exists so far that compares the protective effect of UW solution with that of HTK. Therefore, we initiated a retrospective study of UW and HTK solutions in heart transplantation.

Patients and methods

Group I included 159 recipients who had their organs preserved with HTK solution. The group consisted of 95 male and 64 female patients with a mean age of 46.2 ± 6.9 years. Group II included 50 patients with UW graft preservation and consisted of 39 male and 11 female patients, with a mean age 47.5 ± 7.8 years. In group I, preoperative diagnoses were dilative cardiomyopathy in 59%, ischaemic heart disease in 32% and other illnesses in 9%; in group II, dilative cardiomyopathy was present in 60%, ischaemic heart disease in 34% and other preoperative diagnoses in 6% of the cases. All patients received standard quadruple drug therapy consisting of cyclosporin, azathioprine and prednisone with rabbit-antithymocyte globulin induction therapy for immunosuppression.

The average ischaemic time of the transplanted hearts in group I was 142 ± 44 min, ranging from 83 to 235 min; the corresponding ischaemic time in group II was 193 ± 50 min, ranging from 100 to 360 min and, thus, was significantly longer when compared with group I ($P < 0.05$). The mean perfusion volume was 2.2 l in group I and 1.0 l in group II. Orthotopic heart transplantation was performed in all cases.

Students *t*-test and the chi-square test were used for statistical evaluation of the data and intergroup comparison including a multivariate analysis of the data.

Results

In group I, 24 patients died within the first 30 postoperative days (15% early mortality). The causes of death were acute perioperative graft failure ($n = 6$), unspecific right heart failure ($n = 5$), acute rejection ($n = 7$), infection ($n = 4$) and multiorgan failure ($n = 2$). Statistical analysis of the data revealed a significant increase in the incidence of acute graft failure when compared with duration of ischaemic time ($P < 0.01$, Fig. 1 a). The same statistical correlation was evident between the incidence of early mortality and duration of graft ischaemic time (Fig. 1 a).

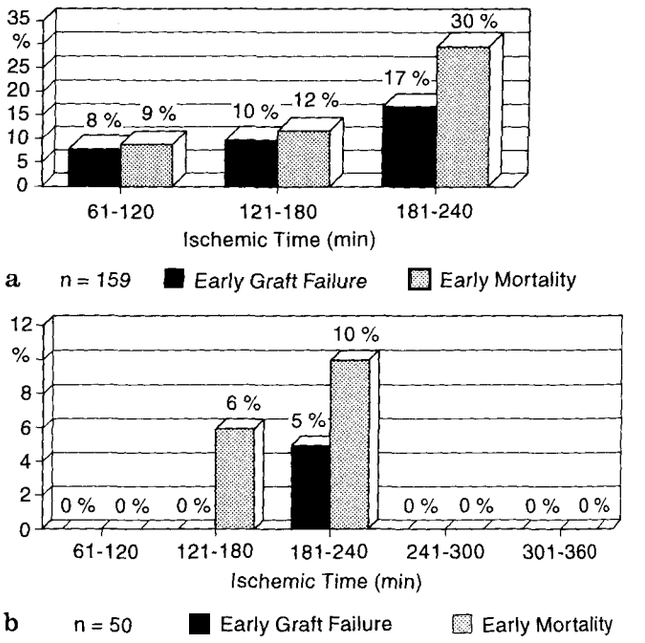

Fig. 1 **a** Length of ischaemic time and its significant influence on incidence of early graft failure and early mortality after transplantation in group I ($P < 0.01$). **b** Length of ischaemic time versus incidence of early graft failure and early mortality after transplantation in group II, demonstrating no correlation

Analysis of cardiac rhythm immediately after reperfusion showed the presence of sinus rhythm in 73%, AV-block in 8% and pacemaker-dependent arrhythmias in 19%; at the time of discharge, sinus rhythm was present in 87%, AV-block in 3% and only 13 patients (10%) had a permanent pacemaker implanted (Fig. 2 a). At the same time, 34% of the patients were in NYHA-class I, 63% in NYHA-class II and 3% in class III (Fig. 3 a). The 30-day and 6-month survival rates were 81% and 78%, respectively.

In group II, five patients died within the first 30 postoperative days (10% early mortality). The causes of death were acute rejection ($n = 3$), infection ($n = 1$) and multiorgan failure ($n = 1$). Only one case with acute perioperative graft failure occurred (2.0%, ischaemic time = 193 min). The patient was successfully retransplanted 24 h later. There was no correlation between length of ischaemic time and incidence of acute graft failure or early mortality (Fig. 1 b).

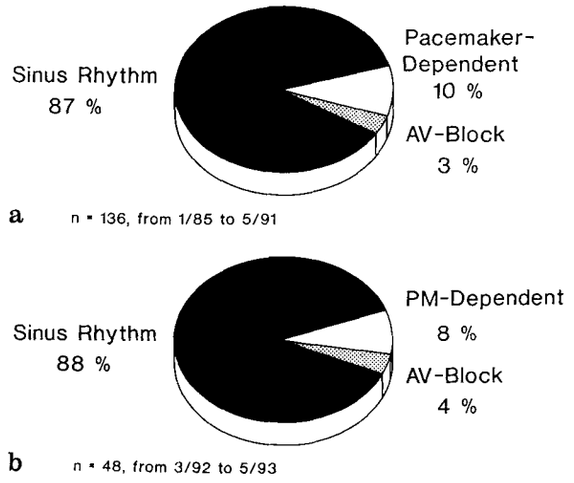

Fig. 2a, b Incidence of cardiac arrhythmias after transplantation in **a** group I and **b** group II

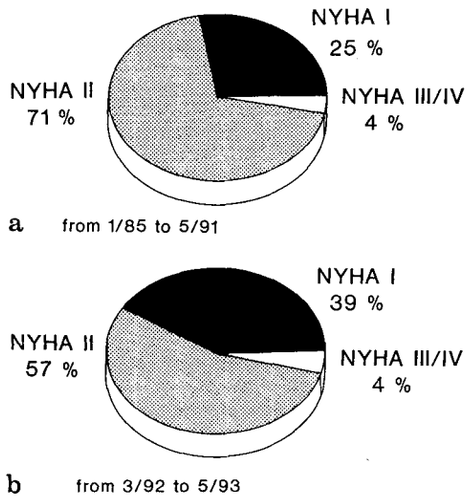

Fig. 3a, b Distribution of NYHA status of heart recipients at time of discharge in **a** group I and **b** group II

Analysis of cardiac rhythm immediately after reperfusion of the transplanted heart showed the presence of sinus rhythm in 78%, AV-block in 8% and pacemaker-dependent bradyarrhythmias in 14%; after hospitalization 42 patients (84%) were in sinus rhythm, 2 patients (5%) had AV-block and 4 patients (8%) needed a permanent pacemaker implanted (Fig. 2b). At time of discharge, 54% of the patients were in NYHA-class I, 43% in class II and 3% in class III (Fig. 3b).

In group II, the 30-day and 6-month survival rates were 90% and 88%, respectively and, thus, significantly better when compared to the results achieved in group I (81% and 78%, $P < 0.05$). With regard to the incidence of postoperative arrhythmias and postoperative NYHA status there was no significant difference in between groups I and II. In both groups there was no statistical correlation between donor age, donor catecholamine support and number of hypotensive periods of the donor heart, on the one hand, and incidence of acute graft failure or early mortality on the other.

Discussion

Many recent publications have concentrated on experimental and clinical prolongation of graft ischaemic time for cardiac transplantation [4, 5, 6]. In animal experiments, possible graft ischaemic times up to 16 h have been reported [5]. With regard to possible extension of the preservation period, the different cardioplegic solutions seem to demonstrate major differences.

In this study, a retrospective comparison was undertaken between two cardioplegic solutions used for myocardial preservation. The HTK cardioplegic solution is an extracellular solution that works by reducing the extracellular sodium concentration to a cytoplasmatic level; at the same time the free extracellular calcium concentration is minimized in order to effect not only electrical, but also complete mechanical inactivation of the cardiac muscle cells [7]. Due to its specific composition and histidine-based buffer system, HTK has a higher buffering capacity over a wider pH range [7]. In contrast, the UW formulation makes it an intracellular solution with high potassium concentration for immediate cardiac arrest, potent buffer system, effective membrane stabilizers, osmotic agents to minimize hypothermic cellular swelling, free radical scavengers to reduce reperfusion injury and precursers for repletion of high energy phosphate stores during reperfusion [8]. One possible disadvantage of UW solution is its high potassium concentration, which may lead to contraction band necrosis [9]. However, in canine and primate animal experiments, the extent of these necroses is limited and is not worse when compared to other cardioplegic solutions and does not obviously influence the myocardial protective effect [5, 10].

A recent experimental study comparing HTK cardioplegia with UW solution in the primate model has demonstrated that excellent results (e.g. haemodynamic performance after transplantation, myocardial water content, pathological ultrastructure) can be achieved with both solutions up to a graft ischaemic time of 8 h [5]. With longer heart preservation times, the use of UW solution gives significantly better results with regard to survival rates, haemodynamic recovery, myocardial water content

and graft histology [5]. The superiority of UW solution when compared to HTK solution and Stanford cardioplegia has also been demonstrated in other experimental studies [8, 10].

The significant correlation between length of ischaemic time and incidence of early mortality, which was evident in our clinical study after HTK preservation, has also been published by the registry of the International Society for Heart and Lung Transplantation, although various different cardioplegic solutions were used among the patients included in the registry [11]. Another clinical multicentre study has also confirmed the length of ischaemic time as a significant risk factor in outcome after heart transplantation [12].

This retrospective analysis of 50 heart transplantations in which UW solution was used for myocardial protection confirmed the experimentally described superiority of this solution in graft protection [4, 5]. A recent clinical comparison of UW solution with crystalloid cardioplegia has also reported better myocardial protection with UW as demonstrated by enzymatic analysis [13]. Although the number of patients in the UW group was small, the early functional results were significantly better, although the average ischaemic time was longer in this group. There was just one case with acute graft failure and no correlation was evident between length of ischaemic time and incidence of acute graft failure or early mortality. The 30-day and 6-month survival rates were also excellent in the UW-group. No difference, however, was noted with regard to postoperative clinical condition, NYHA status and incidence of cardiac arrhythmias in both groups.

Thus, according to the clinical results, myocardial protection with UW solution decreased the incidence of early, ischaemic time dependent graft failure and, thus, allowed longer ischaemic times up to at least 6 h. This protective effect of UW solution in cardiac transplantation corresponds well with the excellent data also achieved with this protective agent after kidney and liver transplantation [14].

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