HTK Solution Is More Effective Than UW Solution for Cardiac Preservation

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UNIVERSITY OF WISCONSIN (UW) solution is formulated as a universal preservation solution and is currently in use for kidney, pancreas, and liver transplantation.[1-5] Several investigators have compared UW solution with other solutions for heart preservation and have found it superior.[6,7] However, the generally accepted time limit for safe cold storage for clinical heart transplantation remains only 4 to 6 hours.[8] Histidine-tryptophan-ketoglutarate (HTK) organ preservation solution was initially developed by Bretschneider and coworkers as a cardioplegic solution. The protective effect of HTK solution is based on the high buffering capacity provided by histidine and its low electrolyte content, thus restricting tissue acidosis induced by ischemia. HTK solution has been reported to be effective in kidney and liver transplantation, and a clinical trial is currently underway.[9-12] The purpose of this study was to assess the efficacy of HTK solution as compared with UW solution in experimental heart preservation.

MATERIALS AND METHODS

Male Wistar rats (250 to 350 g) were used. The heart was excised and mounted on a Langendorff apparatus (IPH-W, Labo Support, Osaka, Japan) via the aorta and perfused at a constant pressure of 60 mm Hg for 3 minutes (Langendorff mode (L-mode)). Perfusion was performed with Krebs-Henseleit bicarbonate buffer, which was equilibrated with 95% O_2 and 5% CO_2 and maintained at 37°C. Following cannulation of the left atrium, the heart was switched to working mode (W-mode) with a preload of 10 mmHg and an afterload of 60 mm Hg. Baseline function was determined following 2 minutes of W-mode. Measurements were as follows: aortic flow (AF), coronary flow (CF), cardiac output (CO), heart rate (HR), systolic pressure (SP), mean pressure, and rate pressure product (RPP, HR × max SP). Then, the heart was switched back to L-mode. The hearts were divided into four groups: group 1 (n = 7), 8-hour storage in UW solution; group 2 (n = 8), 8-hour storage in HTK solution; group 3 (n = 5), 12-hour storage in UW solution; and group 4 (n = 5), 12-hour storage in HTK solution. The hearts in all groups were arrested by administration of each preservation solution (60 mL/kg at 4°C) via the aortic cannula at a pressure of 60 mmHg. Then, they were stored in each preservation solution (30 mL) at 4°C. Following cold storage, they were mounted on a Langendorff apparatus again and reperfused for 15 minutes on L-mode. Then, they were switched to W-mode. The coronary perfusate was collected following 10 minutes of W-mode reperfusion to evaluate for lactate, creatine phosphokinase, and troponin-T in each preservation group. Cardiac functional recovery of the stored heart at the end of 25 minutes of W-mode reperfusion was expressed as a percentage of the prepreservative baseline function. Following evaluation of the stored heart, LV dp/dt (mm Hg/s) was measured by puncture via the left ventricular apex. A ventricular specimen was weighed immediately, dried at 80°C to constant weight, and reweighed after 24 hours. Water content was computed using the following formula: water contents (%) = (wet weight − dry weight)/wet weight × 100.

All results are expressed as the means ± SE. A statistical analysis was performed by Student's unpaired t test. A P value of less than .05 was considered statistically significant.

RESULTS

Table 1 shows the recovery of hemodynamic data on the heart for 8 and 12 hours of preservation. Following 8 hours of preservation, the recovery of AF, CF, CO, SP, and RPP in group 2 was significantly increased compared with that in group 1 ($P < .05$). Following 12 hours of preservation, the recovery of AF and CO in group 4 was higher than that in group 3 ($P < .05$). Table 2 shows the CPK, lactate, and troponin-T leakage. There was a significant decrease in CPK leakage in group 2 compared with group 1 ($P < .05$). There were no significant differences in lactate and troponin-T leakage and myocardial water content among the four groups.

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Table 1. Cardiac Functional Recovery (%)

Group	Time (h)	CO	AF	CF	RPP
1. UW (n = 7)	8	49.7 ± 2.4	47.4 ± 4.2	57.1 ± 6.2	71.0 ± 1.8
2. HTK (n = 8)	8	78.1 ± 5.9*	71.5 ± 8.6*	87.8 ± 5.8*	83.6 ± 4.4*
3. UW (n = 5)	12	16.6 ± 3.4	10.7 ± 2.4	37.6 ± 8.4	40.9 ± 8.2
4. HTK (n = 5)	12	29.7 ± 1.4#	24.2 ± 2.5#	42.6 ± 1.5	56.7 ± 4.1

mean ± SE, *<.05 vs. Group 1, #<.05 vs. Group 3.
CO; cardiac output, AF; aortic flow, CF; coronary flow, RPP; rate pressure product.

Table 2. Enzyme Leakage

	CPK (IU/min/g)	Tn-T (ng/min/g)	Lactate (mg/min/g)
1. UW (n = 5)	0.06 ± 0.02	19.7 ± 3.4	10.3 ± 0.7
2. HTK (n = 5)	0.01 ± 0.00*	26.7 ± 9.8	6.5 ± 2.1

mean ± SE, *P < .05.
CPK; creatine phosphokinase, Tn-T; troponine-T.

DISCUSSION

In response to the need for extending the safe limit of organ preservation, numerous solutions have been proposed and evaluated. The universal preservation solution would simplify the multiorgan harvesting procedure. The introduction of UW solution has markedly extended preservation time,[1–7] but the safe time limit for cardiac preservation is only 4 to 6 hours.[8] The HTK solution has been reported to be effective in solid organ preservation,[9–11] although it has not been as extensively tested for donor hearts.[12] Hendry et al[13] reported a better recovery of human atrial myocardial function preserved with HTK solution compared with modified UW solution. In this study, we examined the cardiac functional recovery in a working mode where cardiac function could be evaluated more precisely. We found a better recovery of cardiac function and lower leakage of CPK in the hearts stored in HTK solution compared with those in UW solution following 8 hours of storage.

It is said to be important for cardiac preservation to maintain the ATP level and to limit excessive calcium influx.[14,15] The efficacy of HTK solution is attributed to the high buffering capacity provided by histidine, which suppresses ischemia-induced acidosis and sustains a cytosolic ATP level. Also in the UW solution, pH stability has been said to be maintained with phosphate buffer, and ATP synthesis is aided with adenosine. However, our findings suggest that these actions in HTK solution are more marked than those in UW solution during cold storage. A high potassium concentration is said to lead to myocardial and endothelial damage during cold storage in the presence of a low intracellular pH.[16,17] UW solution, which has a high potassium concentration, might not be suitable for cardiac preservation. The impermeability in UW solution is said to be superior to that in HTK solution in long-term preservation (beyond 24 hours).[11] However, considering graft viability, it may not be appropriate to preserve the heart for such a long term. In this study, tissue water content following 8 or 12 hours of preservation showed no statistically significant differences between each preservation solution.

In conclusion, HTK solution is much more effective than UW solution for heart preservation. HTK solution may lead to better techniques of heart preservation for transplantation.

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