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Distant heart procurement

Impacts of storage solution composition on cardiac performance following transplantation

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Abstract. In distant heart procurement, optimal storage conditions remain to be defined, especially with respect to the electrolytic concentrations of storage solutions. Between December 1986 and April 1987, heart transplants were carried out in 18 patients. After cardioplegic arrest (St. Thomas), the hearts were randomly stored in either Euro-Collins' solution (ECS; $n=9$) or Ringer's solution (RS; $n=9$) at 4°C. For the first 24 h postsurgery, atrial pressures (LAP, RAP), systemic (MAP) and pulmonary pressures (PAP), and cardiac output (CO) were monitored. In addition, catecholamine and nitroglycerine requirements as well as the type of cardiac rhythm were documented. There was no significant difference between the groups in terms of the period of graft ischemia (ECS, 162 ± 28 min; RS, 141 ± 47 min); the MAP, RAP, LAP, and CO were also similar in both groups. The total amount of epinephrine needed to maintain the MAP between 60 and 80 mm Hg was 10.5 mg/24 h ± 4.1 mg in ECS compared with 19.9 mg/24 h ± 12 mg in RS ($P<0.05$). Despite less inotropic support, the left cardiac work index was considerably higher in the ECS group ($P<0.05$). In the first few postoperative hours, 8/9 RS patients needed either atrial ($n=4$) or ventricular pacing ($n=4$) for a heart rate of 90-100 beats/min (bpm), whereas only three ECS patients required atrial pacing ($P<0.05$). All other ECS hearts showed a spontaneous sinus rhythm. At the 24th postoperative h eight RS patients remained pacemaker-dependent, as opposed to two ECS patients with atrial and one with ventricular pacing. We conclude that storage of the donor heart in a medium with intracellular ionic composition, such as ECS, is superior to RS (extracellular composition). ECS appears to result in better preservation of cardiac performance and electrical stability of the transplanted heart.

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In recent years there has been a growing debate concerning the type of preservation solution to be used for storage of the explanted heart in the experimental setting. Extracellular solutions, the media primarily used for storage in clinical cardiac transplantation, have been compared in various experimental trials to intracellular as well as cardioplegic (e.g., St. Thomas Hospital solution; see Table 1) solutions [5, 10, 12]. In 1969, the scientific research by Collins and co-workers [3] resulted in a modification of the preservation media for kidney transplantation from the originally extracellular to the now universally used intracellular solutions (e.g., Euro-Collins' solution, ECS; Table 1). These authors emphasized the importance of reducing the transmembrane cation gradients and minimizing the ion exchange across the cell membrane during hypothermic preservation [4].

Research in this area has also shown that preservation in solutions resembling fluids containing

Table 1. Ionic concentrations of preservation solutions

	Euro-Collins (intracellular)	Ringer's solution (extracellular)	St. Thomas Hospital (cardioplegic)
Na	10	137	116
K	115	4	16
Ca	-	-	1
Mg	-	2	17
Cl	15	111	117
HCO_3	10	14	25
HPO_4	43	-	1
H_2PO_4	15	-	-
Glucose	198	-	-
Osmolarity	406	298	298
pH	7.3	7.3	7.4

Table 2. CPB, Cardiopulmonary bypass; RS, Ringer's solution; ECS, Euro-Collins' solution

Preoperative patient data				
Group	Age (years)	Body weight (kg)	Pulmonary arteriolar resistance (mm Hg per min/ml)	Cardiac index (l per m^2/min)
RS				
Mean	39.11	66.11	320.50	2.04
±SD	13.80	8.99	247.62	1.23
ECS				
Mean	44.56	75.44	356.29	2.01
±SD	10.05	7.62	374.48	0.36
Ischemic times				
	Duration of CPB (min)	Aortic cross-clamp time (min)	Total graft ischemia (min)	
RS				
Mean	66.22	28.56	141.2	
±SD	6.96	6.57	47.4	
ECS				
Mean	64.56	30.33	162.1	
±SD	12.95	4.50	28.3	

extracellular electrolytic concentrations not only decreases the maximally possible ischemic times but also damages the lipoprotein complexes in the endothelium [11]. According to studies by Jennings and Ganote [8], the main injury to the myocardium is characterized by extensive cellular swelling and contracture, which lead to a "no-flow phenomenon" in some instances and to myocytic and vascular disruption and hemorrhage in others. The term "stunned myocardium" has been used to describe reperfused muscle that temporarily cannot spontaneously contract but histologically shows no sign of necrosis or tissue damage [2]. Certain types of preservation media might prevent or lessen this effect. Kohno et al. [10] have recently published an article describing an experimental setting of long-term storage at very low temperatures (0°C), resembling the clinical situation of distant organ procurement and thereby suggesting the superior preservation capabilities of intracellular solutions such as ECS. Due to successful experimental animal studies [5, 10], especially in the field of kidney preservation [3, 13], we decided to compare a medium resembling intracellular fluids with ionic concentrations (ECS) with a solution containing extracellular concentrations (Ringer's solution, RS) in a prospective, randomized clinical study of heart transplants (Table 1). Our goal was to investigate the immediate and short-term hemodynamic or rhythmic implications of storage in either solution rather than a possible prolongation of ischemic intervals.

Materials and methods

Patients

Two groups of patients were studied in the immediate postoperative period following heart transplantation. Entrance requirements for both groups were in accordance with the Stanford criteria of 1979 [1]. Every patient underwent preoperative right-heart catheterization. The salient clinical features are summarized in Table 2. For this prospective, randomized study, all hearts suitable for cardiac transplantation were arrested with St. Thomas cardioplegic solution (20 ml/kg) and then stored in either ECS or RS for the time of transport; both solutions were kept at 4°C. A comparison of the period of graft ischemia, aortic cross-clamp times, and durations of bypass surgery can be seen in Table 2. There were no differences between the groups in any of the parameters thus far mentioned.

Hemodynamic measurements

In the immediate preoperative period, every patient had a 20-gauge plastic catheter inserted into a radial artery for arterial pressure measurement (MAP) and a central venous line installed for central venous pressure measurement (CVP). Prior to the completion of the operation, a pressure line was installed in the left atrium by direct puncture for left atrial pressure measurement (LAP). On the patient's arrival at the intensive care unit (ICU), the pulmonary artery was catheterized with a balloon-tipped, flow-directed pulmonary arterial catheter (American Edwards Laboratories, Santa Ana, Calif.) by previously described techniques [15]. Mean pulmonary arterial pressures (PAP), heart rates (HR), CVP, LAP, and MAP were measured with conventional monitoring devices (Hellige MP 4100). Cardiac output (CO) values were measured in triplicate by thermodilution (Hemodynamic Profile Computer, Gould, Cardiovascular Products Division, Oxnard, Calif.). Derived hemodynamic parameters were

calculated by standard formulas.[1] All flow and volume variables were indexed according to the patient's body surface area by standard normograms. The following parameters were calculated: cardiac index (CI), left cardiac work index (LCWI), right cardiac work index (RCWI), right ventricular systolic work index (RVSWI), left ventricular systolic work index (LVSWI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI). All patients had both atrial and ventricular pacemaking wires placed intraoperatively. In cases with a HR below 80 bpm, an AV-block, an irregular or a primary ventricular rhythm-appropriate external pacemaker was initiated. At every hourly measurement, the pacemaker was temporarily disconnected and the type of rhythm was diagnosed by monitor and paper strip.

Protocol

Initial measurements were started in both groups 1 h after the beginning of reperfusion in the operating room. At this time, pulmonary pressures were not available; therefore, CI and derived parameters were not obtained. The next measurements were taken on the patient's arrival at the ICU (60–90 min following termination of the cardiopulmonary bypass) and then every 60 min for the first 6 h, followed by every 3 h for an additional 18 h. The ICU measurements included all hemodynamic values mentioned above, as well as blood-gas analysis, temperature measurements, urinary output with a fluid input-output calculation, and serum potassium levels. Serum creatine phosphokinase (total and MB fraction) and serum lactate levels were collected every 6 h. In addition, the cardiac rhythm and type of pacemaker, as well as dosages of catecholamine and nitroglycerine infusions, were carefully recorded. For fluid-balance calculations, all furosemide regimens and fluid infusions were also noted.

Statistical evaluation

A repeated measures analysis of covariance, as provided by the program MANOVA of the SPSS statistical software package [14], was used to investigate the differences between the two groups in hemodynamic values dependent on catecholamine or nitroglycerine infusions over time. With other parameters, unpaired significance tests or Fischer's exact tests were used on discrete values such as the type of cardiac rhythm; P values of <0.05 were considered statistically significant.

Results

The primary cardiac medication consisted of epinephrine, dopamine, and nitroglycerine. Of these, dopamine was chiefly given in renal doses, whereas the epinephrine requirements as an inotropic agent differed significantly between the ECS and RS groups. Hearts stored in RS required about twice the dose of epinephrine needed for those stored in ECS (Fig. 1) for the MAP to reach the desired range between 60 and 80 mm Hg (Fig. 2). An initial peak occurred during the first ICU measurements, followed by an almost linear decrease in catecholamine requirements. This difference was statistically significant ($P<0.05$, MANOVA). Nitroglycerine dosages were varied to maintain the CVP between 5 and 12 mm Hg. Figure 3 shows the CVP range of both groups over time. In the first few postoperative hours, both groups required peak dosages of 3–4.5 μg/kg per min, after which a fairly steep decline occurred. By hour 6 in ICU, the ECS group had reached a significantly lower level, with

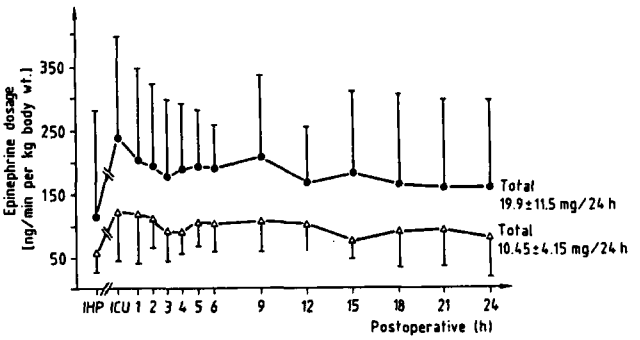

Fig. 1. Dosage of epinephrine (ng/kg × min) with time (mean ± SD). The difference between the two curves (multivariate analysis for repeated measures) was significant ($P<0.05$; $n=9$) for both groups. Δ ECS group, ● RS group, *IHP* measurement 1 h after beginning reperfusion, *ICU* initial measurement upon arrival in intensive care unit. Total epinephrine dosage over 24 h for the RS group was 19.9 mg/24 h compared to 10.5 for the ECS group ($P<0.05$)

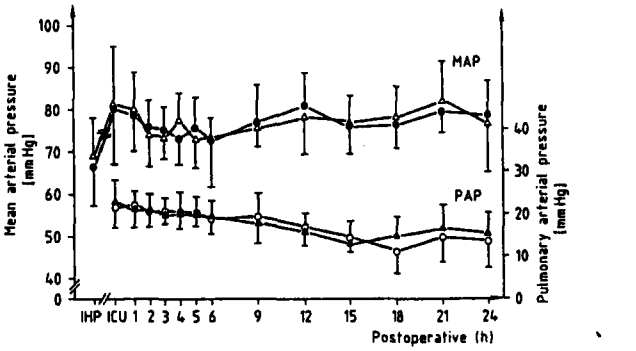

Fig. 2. Mean arterial *(MAP)* and pulmonary arterial pressure *(PAP)* over time (mean ± SD). MAP was maintained in the range of 60 to 80 mm Hg by catecholamine infusion. PAP showed a significant drop over the 24-h time period. There was no statistical difference between groups in either parameter. Δ MAP in ESC group, ● MAP in RS group, ▲ PAP in ESC group, O PAP in RL group, *IHP* measurement 1 h after beginning of reperfusion, *ICU* initial measurement upon arrival in intensive care unit

[1] Cardiac index: $CI = CO/BSA$ (l/min × m²)
Left cardiac work index: $LCWI = CI \times MAP \times 0.0136$ (kg × m/min × m²)
Right cardiac work index: $RCWI = CI \times PAP \times 0.0136$ (kg × m/min × m²)
Right ventricular systolic work index: $RVSWI = CI \times PAP \times 13.6/HR$ (g × m/m²)
Left ventricular systolic work index: $LVSWI = CI \times MAP \times 13.6/HR$ (g × m/m²)
Systemic vascular resistance index: $SVRI = MAP - CVP/BSA \times CO$ (mm Hg × min/ml × m²)
Pulmonary arteriolar resistance index: $PARI = PAP - LAP/BSA \times CO$ (mm Hg × min/ml × m²)

requirements of 1.3 compared with 2.5 µg/kg per min for the RS group. However, due to fairly high SDs, these differences were not significant. Both groups had an LAP of 9-11 mm Hg at the beginning of the measurements, which fell to 6-8 mm Hg by 24 h in ICU (Table 3). The same type of curve can be seen with the PAP, demonstrated in Fig. 2. Starting with pressures in the range of 20-22 mm Hg, both groups showed a drop to 13-15 mm Hg. The statistical analysis of both parameters showed no significant differences.

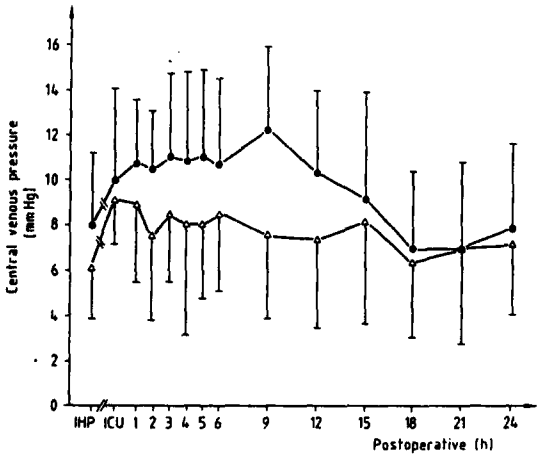

Fig. 3. Central venous pressure *(CVP)* over time (mean ± SD). CVP was maintained in the range of 5 to 12 mm Hg with nitroglycerine infusions. Although the total nitroglycerine dosage in the RS group was 319 mg/24 h compared to 222 mg/24 h in the ECS group, the CVP in the RS group was higher over the entire length of the study. However, the statistical differences for the parameters CVP and nitroglycerine were not significant. Δ ECS group, ● RS group, *IHP* measurement 1 h after beginning reperfusion, *ICU* initial measurement upon arrival in intensive care unit

A comparison of the CI reveals that it was higher in the ECS group, with a maximal difference at 18 h postsurgery. The CI of the ECS group averaged 3.5 l/min per m^2 compared with an average of 2.8 for the RS group (Fig. 4; $P < 0.05$, Student's *t*-test). Table 3 summarizes patient data for the SVRI and PARI. The systemic resistance was higher in the RS group for the entire 24-h period of measurement. This difference even increased to values of > 600 mm Hg per min/ml per m^2 in the RS group by the end of the study. The differences in the PARI were not as pronounced ($P < 0.08$, MANOVA). The RCWI and LCWI curves are shown in Fig. 5. Both parameters showed little change over time. Although the RCWI of both groups differed insignificantly, this was not true for the LCWI. In the ECS group, the latter was significantly higher, with an average value of 3.8 kg/m^2 per min compared with 3.2 in the RS group ($P < 0.05$, MANOVA). Whereas the LCWI in the RS group had a tendency to drop, it remained stable in the ECS group.

A total of eight patients in the RS group could not produce a sinus rhythm of > 80 bpm in the immediate postoperative period (Table 4). Of these patients, three were temporarily asystolic, requiring a ventricular pacemaker. In addition, three patients showed a higher-degree AV block or a sinus rhythm of < 80 bpm. In comparison, only three patients in the ECS group required atrial pacemakers ($P < 0.05$, Fischer test). At 24 h, the situation in the RS group remained unchanged, with eight patients being pacemaker-dependent, whereas one of three pacemaker-dependent patients in the ECS group now required ventricular pacemaking ($P < 0.05$). The enzyme analysis revealed lower CKMB/CK fractions in the ECS group for the duration of the

Table 3. Patient data for the SVRI, PARI, and LAP. IHP, Initial measurement 1 h after the start of reperfusion; ICU, initial measurement on the patient's arrival at the ICU; RS, Ringer's solution; ECS, Euro-Collins' solution

Group			IHP	ICU	1 h	2 h	3 h	4 h	5 h	6 h	9 h	12 h	15 h	18 h	21 h	24 h
RS	LAP	Mean	7.6	9.4	9.1	10.2	10.4	9.1	9.1	9.2	8.9	9.0	8.0	6.7	6.9	5.8
		±SD	2.8	1.8	2.1	3.2	3.0	2.6	3.3	4.0	3.9	3.9	5.6	3.4	3.8	2.4
ECS		Mean	6.2	10.4	11.4	8.7	9.4	9.7	9.3	8.9	8.0	7.0	7.5	6.6	7.9	8.8
		±SD	2.0	2.2	3.3	2.4	1.7	4.6	3.1	3.0	3.7	4.5	3.1	3.2	3.9	4.8
Multivariate test, not significant																
RS	PARI	Mean		131	135	126	131	121	123	112	131	100	86	71	98	85
		±SD		47	35	37	25	40	34	37	54	31	46	26	22	32
ECS		Mean		123	114	114	103	111	95	95	82	83	67	64	76	73
		±SD		47	57	46	45	54	33	41	35	45	32	32	38	36
Multivariate test, $P < 0.06$																
RS	SVRI	Mean		539	532	524	535	489	516	507	595	630	645	647	600	602
		±SD		124	146	139	131	136	146	174	207	187	168	118	105	156
ECS		Mean		486	470	475	437	460	395	399	445	518	483	472	480	485
		±SD		150	163	181	166	150	130	95	162	169	165	106	117	101
Multivariate test, $P < 0.08$																

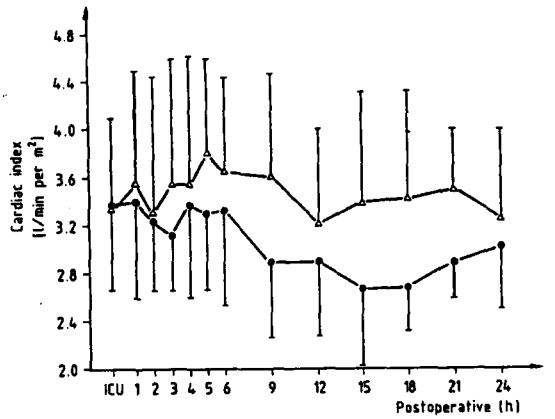

Fig. 4. Cardiac index *(CI)* over time (mean ± SD). Over the entire 24-h study period, the mean CI in the ECS group was higher (3.49 ± 0.17 l/min m^2) than in the RS group (3.11 ± 0.26 l/min m^2). At 18 h postoperatively, the statistical difference between groups was significant ($P < 0.05$). Δ ECS group, ● RS group, *ICU* initial measurement upon arrival in intensive care unit

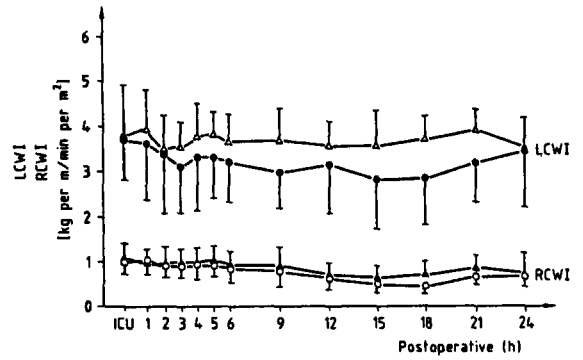

Fig. 5. Left *(LCWI)* and right cardiac work index *(RCWI)* over time (mean ± SD). Both parameters remained fairly constant over the 24-h period. There was a borderline statistical difference between groups for the two parameters ($P < 0.08$; MANOVA). Δ LCWI in ESC group, ● LCWI in RS group, ▲ RCWI in ESC group, O RCWI in RS group, *ICU* initial measurement upon arrival in intensive care unit

study; however, these differences were not statistically significant. Maximal CK fractions of 13.5% in the RS group and 11.5% in the ECS group were determined in the initial ICU analysis; these fell to 5.9% and 4.5%, respectively, by the end of the study. At 24 h postsurgery, the fluid balance of the ECS group was approximately 1000 ml (−2171 ± 1465 ml) more negative than that of the RS group (−1047 ± 940 ml). However, the ECS group required an average of 100 mg more furosemide to maintain adequate urinary flow; this difference was again not statistically significant. A comparison of blood-gas analysis, temperature curves, serum bicarbonate levels, and ventilatory settings also proved to be not significant.

Table 4. Rhythm and pacemaker requirements

	Patients with sinus rhythm	Patients needing pacemaker	Patients with ventricular pacemaker
Time period: 1-4 h postoperatively			
Group			
RS	3/9	8/9	4/9
ECS	8/9	3/9	0/9
	$P < 0.05$	$P < 0.05$	$P < 0.05$
Time period: 21-24 h postoperatively			
Group			
RS	3/9	8/9	4/9
ECS	8/9	3/9	1/9
	$P < 0.05$	$P < 0.05$	not significant

Discussion

Distant organ procurement with graft ischemic times of up to 4 h have generally been regarded as safe in clinical heart transplantation. For this purpose, crystalloid cryocardioplegia is usually applied for the initial arrest of the donor heart. Cold storage is provided by iced crystalloid solutions and reperfusion is then initiated with extracorporeally circulating blood from the organ recipient. According to the most recent information in the registry of the International Society for Heart Transplantation [9], a critical analysis of this approach appears mandatory. These data disclose a strong correlation between graft ischemic time (in h) and early mortality. Ischemic times of < 1 h are associated with an early (30-day) mortality of 4.6%, followed by a 3-h mortality of 15.7%, which increases to 28.6% after > 4 h. With these figures in mind, the present myocardial preservation for transplantation, including distant procurement and prolonged graft ischemia, cannot be considered optimal. Renewed efforts must be made to improve either the method of initial cardioplegic arrest or the method of reperfusion and storage during transportation. Our interest centered on the latter aspect. Recent data in the literature on animal research suggest that the fluid composition of the storage media has an important impact on the postoperative function of the myocardium, favoring solutions resembling intracellular fluids with ionic compositions [5, 10]. The purpose of this clinical study was to compare preservation media resembling fluids containing intra- and extracellular electrolytic concentrations for cardiac allografts in terms of their impact on hemodynamics, rhythmicity, and medicinal requirements. Nitroglycerine was used in both groups to titrate similar ranges of CVP. The MAP was kept between 60 and 80 mm Hg with an epinephrine drip.

This study disclosed three major differences in myocardial performance between the two methods of preservation: rhythmicity, contractility, and the need for catecholamine support. Of these, the most striking difference was the immediate recovery of sinus-node function in donor hearts stored in ECS vs the delayed and impaired sinus-node function in the RS group. All patients of both groups who initially required an atrial or ventricular pacemaker eventually regained their sinus rhythm, with the exception of one recipient in the RS group, who required the installation of a permanent pacemaker system for sustained sinus arrest. According to our data, the group of hearts stored in ECS demonstrated better contractility (LCWI) with lower catecholamine requirements and preload reduction. This may partly have been due to lower systemic and pulmonary vascular resistance in the ECS group, which is also partly influenced by low-dose catecholamine administration. The difference in the catecholamine doses given to both groups clearly delineates the higher catecholamine dependency of the control group (Fig. 1). Within the first 24 h, the total dose of epinephrine needed in the control group was approximately twice that required in the ECS group. Simultaneous estimations of right and left ventricular contractility as well as the CI reveal that, despite lower catecholamine support, myocardial function was better preserved in ECS hearts (Figs. 4, 5). Preload reduction by nitroglycerine, necessary to reduce atrial filling pressures, was also achieved at lower doses in the ECS group. Improved myocardial function in the ECS group could be considered a result of the higher rate of spontaneous sinus rhythm in these hearts. However, the effective heart rate was identical in both groups, and the majority of hearts could be stimulated by atrial pacemakers. In patients with an AV block, sequential pacemakers ensured AV synchrony. Thus, hemodynamic measurements were taken under comparable conditions.

Controversy exists regarding the mechanism of protection of intracellular solutions. In a study on kidney transplantation, Collins et al. [3] explained the beneficial effect of decreasing ion exchange across the membrane, a process requiring energy. On the other hand, Green and Pegg [7] have suggested that the inclusion of impermeable solutes with a consecutive increase in osmolarity would prevent cellular swelling. In addition, ECS is essentially calcium-free, and certain calcium concentrations are known to be harmful to myocardial performance. It is difficult to estimate the relative importance of any of these factors by comparison.

In conclusion, ECS seems to be advantageous over RS for preservation of the donor heart during storage. In this clinical investigation, the catecholamine requirements were lower and the left myocardial performance improved. Conduction system abnormalities were markedly more common in hearts stored in RS. Our study suggests that, in addition to the method of primary cardiac arrest and the modulation of reperfusion conditions, the mode of storage during ischemia is critically important to the postoperative performance of cardiac allografts. Due to the results of this study, all donor hearts transplanted in our clinic since then have been stored in ECS with equal success. Further experimental studies seem warranted to elucidate further the optimal composition of the storage media, with its possible impact on prolonging the critical time limits for graft ischemia.

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