Almost 40 years of outcomes of heart transplants from uncontrolled cardiac arrest donors: Single-center experience

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INTRODUCTION

Heart transplantation (HT) remains the best treatment for patients affected by advanced heart failure. While the waiting list for HT keeps growing, the shortage of available donor organs remains a matter of concern. In recent years, the number of marginal donors has significantly grown. In certain countries, according to their legislation, donation after circulatory death (DCD) has become a source for cardiac grafts [1] despite concerns about the graft's performance due to a controlled cardiac arrest period. Uncontrolled cardiac arrest (uCA) before donation represents a frequent finding in suitable heart donors, and it is not considered a contraindication for HT nor a marginal donor criterion. However, these grafts' effect on very long-term outcomes after HT is still unknown [2, 3]. We aimed to analyze early and late outcomes of HT from donors who suffered from uCA.

MATERIAL AND METHODS

We retrospectively collected all clinical data from patients who underwent HT between November 1985 (starting year of our National HT Program) and September 2022. Patients <18 years of age were excluded. Within the overall cohort of patients, we compared and analyzed those who received a graft from a donor suffering from uCA (group 1) vs. a donor not suffering from uCA (group 2). The uCA time was defined as the time between the onset of a witnessed cardiac arrest and the recovery of blood flow pulsatility.

The primary endpoint was 30-day mortality; secondary endpoints were cardiac-related 30-day mortality, follow-up mortality, and risk of severe cardiac allograft vasculopathy (CAV). CAV was defined according to the current International Society for Heart and Lung Transplantation guidelines. Follow-up data were obtained by our HT follow-up outpatient center, in which patients have clinical visits every 4 months and coronary angiography performed every 2 years after HT. Patients' death is usually promptly referred to our Center by relatives once it occurs. The last follow-up available for each patient was included in this study.

This study was approved by the Ethical Committee of our institution, which waived informed consent from patients (n. 343n/AO/23).

Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as medians and interquartile ranges, medians and ranges, or as means and standard deviations. Comparison analysis between group 1 and group 2 was performed using both the unpaired t-test and the Mann–Whitney U test (for continuous variables) or Pearson's χ^2 test (for categorical variables). Overall follow-up survival data were analyzed with standard Kaplan–Meier curves. Hazard ratios for late survival and severe CAV were determined by univariate Cox regression analysis. All analyses were performed using SPSS version 28.0.1.0 (IBM SPSS Statistics). *P*-values <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Among 934 HT procedures performed within the study period, 120 included organs that underwent uCA (donor male 73, –60.8%, mean standard deviation [SD] donor age 36 [16] years) (group 1) vs. 814 no uCA (donor male

Table 1. Clinical characteristics of donor uncontrolled cardiac arrest (group 1) and no uncontrolled cardiac arrest (group 2)

	Uncontrolled donor cardiac arrest (group 1) (n = 120)	No uncontrolled donor cardiac arrest (group 2) (n = 814)	*P*-value
Donor sex (male)	73 (60.8%)	492 (60.4%)	0.94
Donor age, years (mean, SD)	36 (16)	39 (17)	0.09
Donor death cause, n (%)			<0.001
Brain trauma	11 (9.2)	207 (25.4)	
Multiple trauma	28 (23.3)	182 (22.4)	
Brain hemorrhage	31 (25.8)	336 (41.2)	
Suicide	16 (13.3)	19 (2.3)	
Donor h/o, n (%)			
Tobacco abuse	37 (30.8)	171 (21.0)	0.03
Substance abuse	11 (9.2)	18 (2.2)	<0.001
Alcohol abuse	8 (6.7)	20 (2.5)	0.01
CV risk factors (e.g., diabetes, hypertension)	5 (4.2)	63 (7.7)	0.16
Donor ejection fraction >55%, n (%)	114 (95.0)	794 (97.5)	0.11
Associated non obstructive coronary artery disease, n (%)	5 (4.2)	35 (4.3%)	0.95
Associated left ventricular hypertrophy (interventricular septum ≥12 mm), n (%)	2 (1.7)	42 (5.2)	0.09
Cold ischemic time, min (mean, SD)	200 (59)	187 (89)	0.01
Recipient sex (male)	100 (83.3%)	633 (77.8%)	0.12
Recipient age, years (mean, SD)	49 (19)	50 (16)	0.68
Recipient cardiac disease, n (%)			0.49
Dilative idiopathic	33 (27.5)	292 (35.9)	
Post-ischemic	49 (40.8)	295 (36.2)	
Hypertrophic	1 (0.8)	25 (3.1)	
Congenital heart disease	7 (5.8)	32 (3.9)	
Arrhythmogenic	7 (5.8)	38 (4.7)	
Valvular	4 (3.3)	47 (5.8)	
30-day mortality, n (%)	10 (8.3)	83 (10.2)	0.55
Cardiac-related 30-day mortality, n (%)	3 (2.5)	25 (3.1)	0.72

Abbreviations: CV, cardiovascular; SD standard deviation

492, –60.4%, mean [SD] donor age 39 [17] years) (group 2). The median time of uCA was 10 minutes (range 0.5–90 minutes). Table 1 summarizes the main clinical differences between the two groups: in particular, group 1 was more frequently associated with donor suicide as the cause of death, substance abuse, and tobacco and alcohol abuse.

We found that there was no statistically significant difference between the 2 groups in terms of 30-day mortality (group 1 = 10, –8.3% vs. group 2, 83, –10.2%; $P = 0.55$) and cardiac-related 30-day mortality (group 1 = 3, –2.5% vs. group 2 = 25, –3.1%; $P = 0.72$).

At long-term follow-up (median time 7.5 years, interquartile range 2–14, max 36 years), the 2 groups had no statistically significant difference in terms of the overall survival rate (HR, 1.12; 95% CI, 0.84–1.50; $P = 0.45$) and the severe CAV rate (HR, 0.91; 95% CI, 0.28–3.00; $P = 0.88$). The univariate analysis of long-term mortality risk factors found that younger donor age (HR, 0.70; 95% CI, 0.58–0.84; $P < 0.001$) and younger recipient age (HR, 0.64; 95% CI, 0.54–0.77; $P < 0.001$) were a protective factor, while recipient male sex was a risk factor for long-term mortality (HR, 1.34; 95% CI, 1.08–1.65; $P = 0.01$). All these follow-up data are summarized in the Supplementary material, *Figure S1*.

This study shows that within a large study period, 12.9% of patients received a heart from a donor who suffered uCA. The results of our study show that uCA does not affect 30-day survival, long-term survival, and long-term severe CAV incidence.

As already shown by Galeone et al. [4, 5], cardiac arrest is not a risk factor for early or late death in cardiac recipients and should not be considered an exclusion criterion for organ selection. Galeone et al. underline that donor younger age (as in our experience, even if not statistically significant) associated with the ischemic preconditioning effect of cardiac arrest might be a favorable factor in predicting good outcomes after HT [6]. Additionally, our long-term experience is similar to the US [7]. However, in both Western countries, it is important to ascertain that uCA donors might be preferentially used when ejection fraction is preserved and troponin levels are low. Regarding the ischemic preconditioning effect, Murray et al. [6] hypothesized that uCA might help protect the myocardium from the subsequent ischemia/reperfusion injury occurring at the time of transplantation. He found that a short period of ischemia and subsequent reperfusion might improve myocardial resistance to a prolonged time of ischemia. In particular, intermittent occlusion of a coronary artery in an animal model, rather than continuous occlusion, showed less myocardial damage. This was caused by a lower depletion of ATP, less catabolite accumulation, and improved synthesis of antioxidant enzymes. According to our univariate analysis, the recipient's male sex was found

to be an adverse predictor of long-term survival, a result which is in contrast with current evidence [8]. We did not find a real explanation for this result, but almost 80% of recipients from this analysis were male; consequently, this might be a bias of the study.

In our study, we also showed that >20 minutes of uncontrolled cardiac arrest was not associated with worse outcomes in the long term. Even if we had a lower number of donors with much longer times, this is of paramount importance because it would be a model to analyze the effect of longer cardiac arrest, such as those who are nowadays encountered in specific countries with longer no-touch periods for DCD [9, 10]. In particular, even if, in this specific case, we still do not have enough long-term data to support DCD-HT, we can hypothesize that longer warm ischemic times might not affect overall survival of patients.

Despite this long-term follow-up, we enrolled only 120 patients in the uCA group, and a larger cohort group might help. Moreover, another limitation of this study is its retrospective nature. Indeed, we were not able to retrieve additional clinical data on recipients other than the ones already presented in this analysis.

In conclusion, according to our study, grafts with uncontrolled cardiac arrest have similar early and long-term outcomes (in terms of survival and chronic vascular rejection) as grafts without cardiac arrest history. These favorable long-term outcomes might predict similar results from DCD-HT outcomes with longer warm controlled ischemia times.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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