**Title: Almost 40-year outcomes of heart transplant~~s~~ from uncontrolled cardiac arrest donors: single-center experience**

**Short title: uncontrolled cardiac arrest donors for heart transplantation**

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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 raising, the shortage of available donor organs is still a matter of concern. In the last years, the number of marginal donors has significantly grown and in certain countries, according to their Legislation, donation after circulatory death (DCD) has become a source for cardiac grafts [1], despite concerns about graft’s performance due to 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, grafts its effect on very long-term outcomes after HT is still unknown [2-3]. We aimed to analyze the early and late outcomes of HT from donors who suffered uCA.

**Materials and Methods**

We retrospectively collected all clinical data of 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 uCA (Group 1) vs donor not suffering 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 and follow-up mortality, and risk of severe cardiac allograft vasculopathy (CAV). CAV was defined according to current ISHLT Guidelines. Follow-up data were obtained by our HT follow-up outpatient clinic, in which patients undergo a clinical visit every 4 months, and a coronary angiography every 2 years after HT. Patients’ death is usually promptly referred to our Center by relatives once it occurs. Last follow-up available for each patient was included for this study.

This study was approved by the Ethical Committee (EC) of our Institution and informed consent was waived by our local EC (n. 343n/AO/23).

Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as medians and interquartile range (IQR), medians and range, or as mean and standard deviations. A 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 chi-square 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 performed within the study period, 120 were performed with an organ which suffered uCA (donor male 73 -60.8%-, mean (SD) donor age 36 (16) years) (Group 1) vs 814 no uCA (donor male 492 -60.4%-, mean (SD) donor age 39 (17) years) (Group 2). Median time of uCA was 10 minutes (range 0.5-90 minutes). Table 1 summarizes the main clinical differences among the two groups: in particular, Group 1 was more frequently associated to donor suicide as cause of death, substance abuse, tobacco and alcohol abuse.

We found that there was no statistically significant difference among the two 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, IQR 2-14, max 36 years), the two groups had no statistically significant difference in terms of overall survival rate (HR 1.12, CI 95% 0.84-1.50, P=0.45) and severe CAV rate (HR 0.91, CI 95% 0.28-3.00, P=0.88). The univariate analysis on long-term mortality risk factors, found that younger donor age (HR 0.70, CI 95% 0.58-0.84, P<0.001) and younger recipient age (HR 0.64, CI 95% 0.54-0.77, P<0.001) were protective factor, while recipient male gender was a risk factor for long-term mortality (HR 1.34, CI 95%1.08-1.65, P=0.01). All these follow-up data are summarized in the Supplementary file.

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 showed 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 from organ selection. Galeone et al., underline that donor younger age (as in our experience, even if not statistically significant) associated to the ischemic preconditioning effect of cardiac arrest might be a favorable factor to predict good outcomes after HT [6]. Additionally, our long-term European experience is similar to the one of U.S. [7]. However, in both western countries, it is important to consider that uCA donors might be preferentially used when ejection fraction is preserved and troponin levels are low. Regarding the ischemic preconditioning effect, Murray hypothesized that uCA might help in myocardium protection from the subsequent ischemia/reperfusion injury occurring at the time of transplantation [6]. In fact, he found that a short period of ischemia and subsequent reperfusion might improve myocardium resistance to prolonged time of ischemia. In particular, intermittent occlusion of a coronary artery in an animal model rather that continuous occlusion, showed less myocardial damage. This was caused by a lower depletion of ATP, less catabolite accumulation and an improved synthesis of anti-oxidant enzymes. According to our univariate analysis, recipient male gender was found as adverse factor for 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 to long-term worse outcome. Even if we had a lower number of donors with such 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 rather than the ones already presented in this analysis.

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

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**Table legends**

**Table 1**.Clinical characteristics between donor uncontrolled cardiac arrest (Group 1) and no uncontrolled cardiac arrest (Group 2).

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| --- | --- | --- | --- |
|  | **Uncontrolled donor cardiac arrest (Group 1)**  **(n=120)** | **No uncontrolled donor cardiac arrest (Group 2)**  **(n=814)** | **P-value** |
| Donor gender (male) | 73 (60.8%) | 492 (60.4%) | 0.94 |
| Donor age (years) (mean, SD) | 36 (16) | 39 (17) | 0.09 |
| Donor death cause (n, %)   * Brain trauma * Multiple trauma * Brain hemorrage * Suicide | 11 (9.2%)  28 (23.3%)  31 (25.8%)  16 (13.3%) | 207 (25.4%)  182 (22.4%)  336 (41.2%)  19 (2.3%) | <0.001 |
| Donor h/o (n, %)   * Tobacco abuse * Substance abuse * Alcohol abuse * CV risk factors (e.g. diabetes, hypertension) | 37 (30.8%)  11 (9.2%)  8 (6.7%)  5 (4.2%) | 171 (21.0%)  18 (2.2%)  20 (2.5%)  63 (7.7%) | 0.03  <0.001  0.01  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 ventricle hypertrophy (interventricular septum≥12mm) (n, %) | 2 (1.7%) | 42 (5.2%) | 0.09 |
| Cold ischemic time (min) (mean, SD) | 200 (59) | 187 (89) | 0.01 |
| Recipient gender (male) | 100 (83.3%) | 633 (77.8%) | 0.12 |
| Recipient age (years) (mean, SD) | 49 (19) | 50 (16) | 0.68 |
| Recipient cardiac disease (n, %)   * Dilative idiopathic * Post-ischemic * Hypertrophic * Congenital heart disease * Arrhythmogenic * valvular | 33 (27.5%)  49 (40.8%)  1 (0.8%)  7 (5.8%)  7 (5.8%)  4 (3.3%) | 292 (35.9%)  295 (36.2%)  25 (3.1%)  32 (3.9%)  38 (4.7%)  47 (5.8%) | 0.49 |
| 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 |

**Supplementary file legend**

Panel A. Kaplan Meier analysis on follow-up overall survival; Panel B. Kaplan Meier analysis on follow-up freedom from severe cardiac allograft vasculopathy (CAV); Panel C. Univariate Cox regression analysis on long-term mortality risk factors.