Clinical question.

In adult and pediatric organ recipients (P), does the use of organs from donors brain dead after cardiac arrest (prehospital or in-hospital) (I) as opposed to the use of donors brain dead not due to cardiac arrest (C), improve outcome (O) (e.g. transplant success?)

Intervention, new

Conflicts of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

Medline
“Heart arrest” OR “Death (sudden cardiac)” OR “Cardiopulmonary resuscitation”
37163 Hits

“Heart arrest” OR “Death (sudden cardiac)” OR “Cardiopulmonary resuscitation”
AND “Brain death”
416 Hits

“Heart arrest” OR “Death (sudden cardiac)” OR “Cardiopulmonary resuscitation”
AND “Brain death” AND “Organ procurement”
98 hits

Cochrane
“Cardiac arrest” AND “organ donation”
0 hits

Other sources
Forward search was performed using ISI Web of Science and Google Scholar
The reference list of the relevant articles was scanned for additional studies and obtained:
6 additional hits

State inclusion and exclusion criteria

Inclusion criteria

P type
Adult and paediatric recipients of organs from donors brain dead after cardiac arrest.

Exclusion criteria

P type
• Recipient of organs from donors who became brain dead before having cardiac arrest.
• Recipient of organs from donors pronounced dead according to cardiac criteria (i.e., non-heart-beating donors).

Number of articles/sources meeting criteria for further review:

The literature search yielded 104 papers. Of these, 96 were excluded because they included either non-heart-beating donors or donors who had cardiac arrest after the diagnosis of brain death. One of the 8 remaining studies (Wilson, 2003, 1683-1687) was excluded because the proportion of patients who were brain dead following cardiac arrest was not specified. Two other studies (Delaunay, 1996, 2894, Kawauchi, 1993, 185-8) had insufficient quality to be included in further analysis.

Four studies (Adrie, 2008, 132-7) (Ali, 2007, 929-933, Matsumoto, 2008, 941-6, Mercatello, 1988, 749-50) fulfilled the inclusion criteria and were included in further analysis. All of them were LOE 2. The quality of evidence was good in one study (Adrie, 2008, 132-7), fair in two studies (Ali, 2007, 929-933, Matsumoto, 2008, 941-6) and poor in one study (Mercatello, 1988, 749-50).

In 2 studies (de Begona, 1993, 1196-201, Totsuka, 2000, 577-80) it was not clear whether cardiac arrest occurred before or after the diagnosis of brain death. Those studies were therefore classified as LOE 5 (i.e. studies not directly related to the specific patient/population). Their results have been described in the present worksheet but they were not directly compared with those of the previous LOE<5 studies.
## Summary of evidence

### Evidence Supporting Clinical Question

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Level of evidence:

* A = Return of spontaneous circulation
* C = Survival to hospital discharge
* E = Other endpoint
* B = Survival of event
* D = Intact neurological survival
* Italics = Animal studies

### Evidence Neutral to Clinical question

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Level of evidence:

* A = Return of spontaneous circulation
* C = Survival to hospital discharge
* E = Other endpoint
* B = Survival of event
* D = Intact neurological survival
* Italics = Animal studies

### Evidence Opposing Clinical Question

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Level of evidence:

* A = Return of spontaneous circulation
* C = Survival to hospital discharge
* E = Other endpoint
* B = Survival of event
* D = Intact neurological survival
* Italics = Animal studies
A = Return of spontaneous circulation  C = Survival to hospital discharge  E = Other endpoint
B = Survival of event  D = Intact neurological survival  Italics = Animal studies

**REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:**

**PLEASE NOTE:** in the following text, patients who were brain-dead after cardiac arrest are indicated as “CA donors”, while patients who were brain dead due to other causes are indicated as “non-CA donors”

Results of two studies (Mercatello 1988, 749-50; Adrie 2008; 132-7) were compared since they both included kidney, liver and heart as transplanted organs. The number of organs retrieved per brain dead patient was similar in the two groups. The retrospective study from Mercatello et al (Mercatello, 1988, 749-50) showed that the occurrence of acute renal failure in recipients of kidneys retrieved from CA donors was significantly lower than that observed among recipient of kidneys retrieved from non-CA donors. However, the outcome of transplanted kidneys in that study was measured only as the occurrence of acute renal failure during the first week and no information on follow-up is provided. The prospective study from Adrie (Adrie, 2008, 132-7) showed a non-significant trend towards a better outcome of kidneys and livers retrieved from CA donors, while no analysis was made on transplanted hearts for reasons of sample size. The paper from Mercatello (Mercatello, 1988, 749-50) did not report survival rates for livers and hearts.

A retrospective cohort study from Ali et al (Ali 2007, 929-33) showed that survival after transplant of hearts retrieved from 38 CA donors was not significantly different from that of transplants from 566 non-CA donors. Donor cardiac arrest was not an adverse predictor of mortality on multivariate analysis but CA donors were significantly younger than non-CA donors. The study included a 14-year follow-up with Kaplan-Meier calculation of actuarial survival. The proportion of harvested patients in the two groups was not specified.

In a retrospective cohort study from Matsumoto et al (Matsumoto 2008, 941-46), the outcome of the intestinal transplants from 12 CA donors was compared with that of intestinal transplants from 55 non-CA donors. The outcome variables analysed were ventilation days, hospital length of stay, time to enteral independence, rejection, enteric bacteraemia, and one-year patient survival. All but one CPR donors were below 18 years of age. There were no significant differences of outcome between the two groups, however there was a non-significant trend towards a worse outcome in recipients from CA donors (longer postoperative ventilation, time to TPN independence and hospital length of stay; higher incidence of enteric bacteraemia, shorter freedom from early rejection).

**LOE5 Studies**

Results of LOE5 studies are reported apart and must be considered as only marginally relevant to the worksheet question.

A study from De Begona et al (de Begona, 1993, 1196-201) included 140 paediatric patients who underwent heart transplant. Of them, 72 received heart from CA donors and 68 from non-CA donors. Mean ischemic times were almost identical in the two groups: 4.43 +/- 2.0 hours in CA group vs. 4.5 +/- 2.1 hours in non-CA group. Functional evaluation of transplanted hearts was based on the number of ventilator days and the use of inotropes (early), and on echocardiography (early and late). Duration of follow-up was 2 years. There were no differences between the two groups, both in terms of early and late cardiac function.

In a study from Totsuka et al (Totsuka, 2000, 577-80) the outcome of livers retrieved from 37 CA donors (Group A) was compared with that of livers retrieved from 144 non-CA donors. Group A donors had lower age (34.6 vs. 40.8 years: p = NS) than group B donors, a higher percentage of anoxia and a lower percentage of intracranial haemorrhage and head trauma as a cause of death than group B donors. Recipients’ characteristics were not significantly different between the two groups. Livers from group A donors had higher pre-transplant levels but lower post-transplant levels of aspartate transaminase and alanine transaminase. The transplant outcome, measured as the percentage of graft failure and complications within 90 days, and the length of ICU and hospital stay, were not significantly different between the two groups.

**Confounders/heterogeneity**

**Donor age**

In the papers from Adrie et al (Adrie, 2008, 132-7) and Ali et al (Ali, 2007, 929-933) the age of CA donors was significantly lower than that of non-CA donors. In the papers from Matsumoto et al (Matsumoto, 2008, 941-6) and Mercatello et al (Mercatello, 1988, 749-50) there was a trend towards lower donor age in CA donors. Cox proportional hazards regression in the study from Ali et al showed that donor age was an independent predictor of outcome.
**Other confounders**

In the paper from Adrie et al (Adrie, 2008, 132-7) the major investigated confounders were: use of vasopressors, cold ischemia time, recipient age and serum levels of urea, creatinine, AST and ALT. Those confounders were not significantly different in the two groups of donors, except for the serum levels of AST and ALT, which were higher in CA patients. In the study from Mercatello et al (Mercatello, 1988, 749-50), potential confounders as cold ischemia time, number of patients with prolonged hypotension and serum creatinine were described but no statistical analysis between the two groups is reported.

In the paper from Ali et al (Ali, 2007, 929-933) the major investigated confounders were: brain death duration, total ischemic time, intubation time, use of inotropes, recipient age. There was a trend towards a longer time of intubation and a more frequent use of inotropes in the CA group. On Cox proportional hazards regression, intubation time was not an independent predictor of outcome. Use of inotropes does not appear in the list of regression variables. There is no definitive evidence that results could have been influenced by a patient selection in the cardiac arrest group. However, in Mercatello (Mercatello, 1988, 749-50) the proportion of harvested patients was significantly lower among cardiac arrest patients than in patients brain dead from other causes (22/56 [39.3%] vs. 86/148 [58.1%]; p<0.02) (see Table 1). In the other three studies the comparison could not be done, since the proportion of harvested patients in the non-CA group is not reported.

**Characteristics of the population of cardiac arrest donors**

Cardiac arrest patients who develop brain death after resuscitation may not be representative of the general cardiac arrest population. Three elements support this observation:

1. First, in both the studies from Mercatello et al (Mercatello, 1988, 749-50) and Ali et al (Ali, 2007, 929-933) the commonest causes of arrest were primary cerebral events (22/56 [39%] and 26/38 [67%] cases, respectively), e.g. traumatic brain injury or intracranial hemorrhage, which are rarely reported causes of out-of-hospital cardiac arrest (OHCA). In the study from Matsumoto et al (Matsumoto, 2008, 941-6) cerebral pathologies represented 50% of the causes of death in cardiac arrest patients.

2. Second, in all studies adult cardiac arrest patients with brain death were younger than the general out-of-hospital cardiac arrest (OHCA) population described in larger observational studies. In fact, patients brain dead after cardiac arrest had a median age of 50 years (IQR 38-65) in the paper from Adrie (Adrie, 2008, 132-7), a mean age of 36 ± 16 years in the paper from Mercatello et al (Mercatello, 1988, 749-50), and a mean age of 29 ± 12 years in the paper from Ali et al (Ali, 2007, 929-933); in comparison, the modal age range in an European observational study (Herlitz, 2007, 1025-1031) on OHCA enrolling 40,503 patients was 65-79 years, while the median age of a population of 11,898 EMS-treated OHCA patients reported in a recent American study (Nichol, 2008, 1423-1431) was 67 years (IQR 53-79).

3. Finally, in Adrie et al (Adrie, 2008, 132-7), among all patients resuscitated from cardiac arrest those who developed brain death were the youngest (median age 50 years vs. 57 years in those who had good outcome and 55 years in those who had bad outcome other than brain death), had the lowest incidence of myocardial ischemia (15% vs. 39 and 25%) and VF/VT rhythms (17% vs. 44% and 23%), had the longest median CPR duration (30 minutes vs. 10 and 26 minutes) and the lowest percentage of therapeutic hypothermia (17% vs. 25% and 32%). None of those differences were statistically significant for the brain death group, but this result could have been due to an insufficient sample size. The CPR duration reported in the paper from Ali et al (Ali, 2007, 929-933) and Matsumoto et al (Matsumoto, 2008, 941-6) was 15 ± 8 and 19.3 ± 12.7 minutes, respectively.

In summary, patients who develop brain death after resuscitation from cardiac arrest tend to be younger, had causes of cardiac arrest other than myocardial ischemia or hypoxia, had more commonly non-VF/VT rhythms and long duration of resuscitation attempts.

**Limitations**

The major limitation of the studies included in the present review is their small sample size. The total number of patients brain dead after cardiac arrest in those studies was 91. Moreover, for organs as heart and intestine there is only one study reporting a sufficiently large sample to perform statistical analysis. Another limitation is the retrospective nature of all but one studies included in this review. High-quality prospective studies specifically aimed to assess the suitability of patients brain dead after resuscitation to become organ donors are needed.

**Acknowledgements:**
The Author is indebted with Dr. Cristina Marano for her precious bibliographic work.
Citation List

   Study type: prospective
   Patient type: adult
   Organ: kidney, liver, heart, lung
   Inclusion: included.
   No information on industry funding. However, C. Adrie received a grant from the publicly funded organization Agence de Biomédecine which manages organ donor data in France.

   Study type: retrospective
   Patient type: Adult
   Organ: heart
   Inclusion: included after contact with authors (it was not clear from the text whether cardiac arrest was the cause of brain death or it occurred after the diagnosis of brain death).
   No mention of industry funding.

   Patient type: paediatric
   Study type: retrospective
   Organ: heart
   Inclusion: excluded since it is not clear whether cardiac arrest occurred before or after brain death.

   Study type: retrospective
   Patient type: unknown
   Organ: heart (?)
   Excluded, since it is not clear whether cardiac arrest occurred before or after brain death.
   Delaunay, L
   Denis, V
   Darmon, P L
   Catoire, P
   Bonnet, F
   United states
   Transplantation proceedings

   No comments on industry funding

Study type: unknown
Organ: heart
Patient type: paediatric
Inclusion: excluded. CA presumably occurring after brain death. Poor group definition (no or "minimal" CPR).


Study type: retrospective
Patient type: paediatric and adult
Organ: intestine
Inclusion: included. The text specifies "We sought to analyze our experience in using intestinal grafts from donors who suffered cardiopulmonary arrest before death".

No information on industry funding.


Patient type: adults
Study type: retrospective
Organ: kidney
No information on industry funding.


Financial Disclosures: Dr Nichol reported that he is a member of the American Heart Association ACLS Subcommittee and the Medic One Foundation board of directors; has received research grants from the National Institutes of Health (NIH); has received equipment donations to support overseas medical missions from Laerdal Inc and Medtronic Physio-Control Inc; has received travel expenses payments from INNERcool Inc and Radiant Medical Inc; and has served as a consultant to Northfield Laboratories Inc and Paracor Medical Inc. Dr Callaway reported that he is a member of the American Heart Association ACLS Subcommittee; has received research grants from the NIH and the American Heart Association; has received equipment donations to support laboratory research from Medivance Inc; and is named as a coinventor on patents related to ventricular fibrillation waveform analysis. Dr Aufderheide reported that he is a member of the American Heart Association BLS Subcommittee; has received research grants from the NIH; and has served as a consultant to Take Heart America, JoLife, and Medtronic. Dr Brown reported that he has received research grants from the NIH, the Alabama Department of Public Health, and the Centers for Disease Control and Prevention; has received salary from the South Central Center for Public Health Preparedness to teach the "Blast Injuries" course throughout Alabama; and has received an equipment loan from Medtronic Physio-Control Inc for ROC. Dr Rea reports that he is a member of the American Heart Association BLS Subcommittee and has received research grants from the NIH. Dr Davis reports that he has received research grants from the NIH, ZOLL, and Cardinal Health. No other disclosures were reported.

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Study type: prospective (?)
Organ: liver
Patient type: unknown
Inclusion: excluded. CA occurred after brain death.

11. Wilson, D.J., Donors with cardiac arrest: improved organ recovery but no preconditioning benefit in liver allografts

Inclusion: excluded since cardiac arrest occurred before brain death in an unspecified proportion of patients.