ORIGINAL ARTICLE

Resumption of Cardiac Activity after Withdrawal of Life-Sustaining Measures

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ABSTRACT

BACKGROUND

The minimum duration of pulselessness required before organ donation after circulatory determination of death has not been well studied.

METHODS

We conducted a prospective observational study of the incidence and timing of resumption of cardiac electrical and pulsatile activity in adults who died after planned withdrawal of life-sustaining measures in 20 intensive care units in three countries. Patients were intended to be monitored for 30 minutes after determination of death. Clinicians at the bedside reported resumption of cardiac activity prospectively. Continuous blood-pressure and electrocardiographic (ECG) waveforms were recorded and reviewed retrospectively to confirm bedside observations and to determine whether there were additional instances of resumption of cardiac activity.

RESULTS

A total of 1999 patients were screened, and 631 were included in the study. Clinically reported resumption of cardiac activity, respiratory movement, or both that was confirmed by waveform analysis occurred in 5 patients (1%). Retrospective analysis of ECG and blood-pressure waveforms from 480 patients identified 67 instances (14%) with resumption of cardiac activity after a period of pulselessness, including the 5 reported by bedside clinicians. The longest duration after pulselessness before resumption of cardiac activity was 4 minutes 20 seconds. The last QRS complex coincided with the last arterial pulse in 19% of the patients.

CONCLUSIONS

After withdrawal of life-sustaining measures, transient resumption of at least one cycle of cardiac activity after pulselessness occurred in 14% of patients according to retrospective analysis of waveforms; only 1% of such resumptions were identified at the bedside. These events occurred within 4 minutes 20 seconds after a period of pulselessness. (Funded by the Canadian Institutes for Health Research and others.)

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*The members of the site research groups are listed in the Supplementary Appendix, available at NEJM.org.

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A principle of organ donation from deceased donors is that the donor must be declared dead before initiation of organ retrieval.[1] Donation most commonly occurs after neurologic determination of death by standard criteria for brain death[2] but can also occur after circulatory determination of death. The practice of donation after circulatory determination of death after removal of life-sustaining measures has increased,[3] and the criteria used for determining death in this context have varied.[3-5] Most protocols for organ donation after circulatory determination of death recommend 5 minutes of observation of apnea and pulselessness as determined by arterial catheter monitor, although practices vary from 2 to 10 minutes.[4] After this period, without attempts to restart circulation and without spontaneous resumption of circulation, loss of circulation is considered permanent and organ recovery may begin.

Instances of organ recovery after 75 seconds of pulselessness in infants have led to debate on the minimum acceptable duration of observation to ensure that permanent loss of circulation has occurred.[6-8] Concerns about the potential for autoresuscitation, or return of spontaneous cardiac activity, are based on reports in terminated cardiopulmonary resuscitation (CPR).[9,10] The longest reported period of pulselessness between terminated CPR and observed autoresuscitation is 10 minutes.[10] Limited prospective evidence suggests that return of cardiac activity occurs less frequently after withdrawal of life-sustaining measures and circulatory determination of death than after terminated CPR.[10] Observational studies involving patients dying after withdrawal of life-sustaining measures have described transient resumption of circulation or cardiac activity occurring seconds to minutes after pulselessness, with no reports that consciousness was regained or that the patient survived to hospital discharge.[11-13] We conducted a prospective and retrospective observational study, the Death Prediction and Physiology after Removal of Therapy (DePPaRT) study, to describe the incidence and timing of resumption of cardiac electrical and pulsatile activity in critically ill adults who died after withdrawal of life-sustaining measures.

Methods

Study Design

This study was conducted at 20 adult intensive care units in Canada (16 sites), the Czech Republic (3 sites), and the Netherlands (1 site) (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The study was designed and led by a core team (whose members are listed in the Supplementary Appendix) with input from a steering committee and family partners.[14] Funding was from the Canadian Institutes for Health Research as part of the Canadian Donation and Transplantation Research Program, the CHEO Research Institute, and the Karel Pavlík Foundation. The research protocol was approved by the relevant institutional review board or ethics committee at each site, and all patients' surrogate decision makers provided written informed consent for participation in the study.

Procedures

Patients in intensive care at participating hospitals were eligible if surrogate decision makers had agreed on a care plan of withdrawal of life-sustaining measures without CPR and imminent death was anticipated. Patients with neurologic determination of death or a functioning cardiac pacemaker or without an arterial catheter were excluded. Clinicians provided palliation, withdrew ventilation and medications, and determined death according to their usual practices.[11]

We recorded demographic characteristics, eligibility for organ donation, palliative interventions, withdrawal of life-sustaining measures (e.g., extubation and changes in mechanical ventilation, circulatory interventions, or both), and time-of-death determination. Data on blood pressure (recorded with an arterial catheter), heart rhythm (3- or 5-lead electrocardiography [ECG]), and oxygen saturation (plethysmography) were collected continuously for at least 15 minutes before commencement of withdrawal of life-sustaining measures and up to 30 minutes after death determination according to institution-specific criteria (Fig. S1 in the Supplementary Appendix). In a subgroup of planned organ donors, monitor-

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ing devices were removed 5 minutes after pulselessness according to regional practice. Deidentified electronic data on ECG and arterial blood-pressure waveforms for all the patients were uploaded to the secure study website. This was an observational study; health care providers were asked to continue routine end-of-life practices, including monitoring and death determination, as per usual. They were asked to document their method of death determination with the use of a standardized checklist and to record and describe any observations of unassisted resumption of cardiac activity on a case-report form.[11]

Clinicians at the bedside reported resumption of circulation or cardiac activity prospectively by identifying activity on bedside ECG, arterial pressure catheter monitors, palpated arterial pulse, breaths, or physical movements. We subsequently determined the incidence of resumptions of cardiac activity independently of clinical reports using retrospective adjudicated review of ECG and arterial pressure catheter waveforms. These waveforms were used both to affirm the presence of cardiac activity as observed at the bedside and to identify additional instances that were not reported by bedside clinicians.

For the retrospective part of the study, we defined resumption of cardiac electrical and pulsatile activity as a return of arterial pulse pressure of at least 5 mm Hg corresponding to at least one QRS complex, after a period of pulse pressure of less than 5 mm Hg for at least 60 seconds, as detected by indwelling arterial pressure catheter monitor. This definition was developed by an expert clinical advisory committee with agreement from 8 intensivists and cardiac physiology experts, who were also the group retrospectively adjudicating the waveforms, and 12 members of the steering committee (see the Supplementary Appendix).

We collected, processed, and analyzed digitized data on heart rate and blood-pressure waveforms[15,16] using software that was developed to identify cessation of ECG activity, pulselessness, and resumptions of cardiac electrical and pulsatile activity (see the Supplementary Appendix, including Fig. S3). Two or more adjudicators, who were unaware of patient demographic characteristics and clinical history, reviewed waveform data with a custom-made waveform viewer. Using data on ECG and arterial pressure catheter waveforms, adjudicators located periods of absence of circulation and identified if and when activity returned. Discrepancies of more than 2 seconds in the duration of a cessation or resumption of activity were resolved at review meetings, observed by a steering committee member to ensure equity of discussion. A third adjudicator was consulted when consensus was not achieved (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Without previously published rates of autoresuscitation or resumptions of circulation or cardiac activity, we arbitrarily estimated that a sample size of 500 patients with 0 observed events would be consistent with an incidence of less than 0.7% using a binomial one-tailed 97.5% confidence interval.[17,18] MATLAB software (MathWorks) and R software, version 3.6.1 (https://www.r-project.org/),[19] were used for descriptive analyses. The incidence and timing of resumption of electrical and pulsatile cardiac activity are provided descriptively. Because of the low number of events, we calculated confidence intervals for binomial distribution for the main results using either Agresti–Coull[20] (number of events >0) or Clopper–Pearson (number of events = 0) confidence intervals.[21] We adhered to the STROBE checklist[22] for reporting of data. Interrater correlation and intrarater correlation among adjudicators were determined (see the Supplementary Appendix).

RESULTS

PATIENTS

We screened 1999 adult patients between May 1, 2014, and May 1, 2018, and determined that 695 were eligible for the study; 48 families of eligible patients declined participation and 16 patients were ineligible after enrollment, which resulted in the inclusion of 631 patients (Fig. 1 and Table S1). The characteristics of enrolled and nonenrolled patients are shown in Table S2. Of enrolled patients, 205 (32%) were eligible for organ donation after circulatory determination of death, of whom 67 (33%) became donors and had at least one organ retrieved. The median time from the

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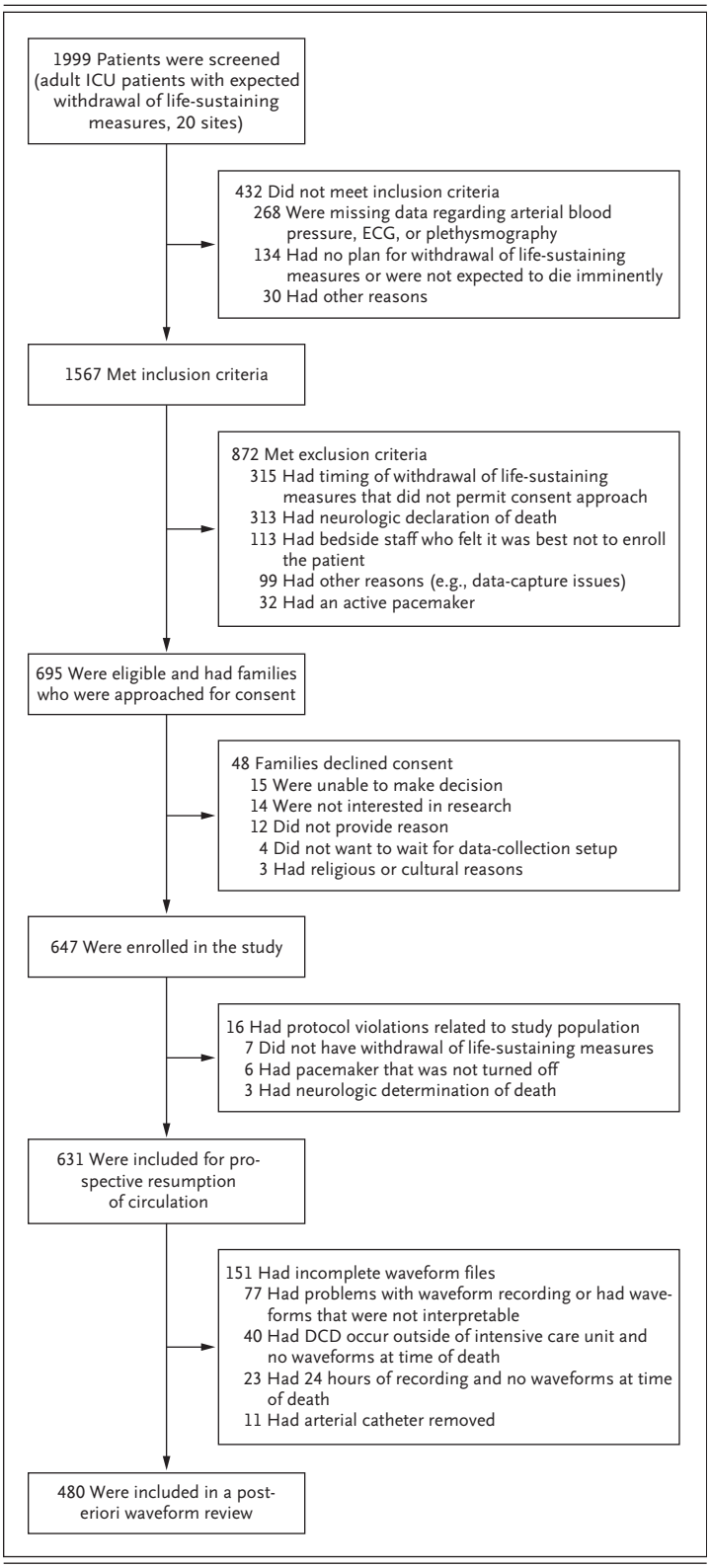

Figure 1. Study Enrollment.

DCD denotes donation after circulatory determination of death, ECG electrocardiographic, and ICU intensive care unit.

start of withdrawal of life-sustaining measures to determination of death by cardiac criteria was 60 minutes (interquartile range, 21 to 283; range, 1 minute to 11 days 5 hours 54 minutes).

PROSPECTIVE BEDSIDE OBSERVATIONS

Table 1 shows the characteristics of enrolled patients. A total of 13 of 631 patients had bedside observation of return of cardiac activity, but only 5 of these instances (1%; 95% confidence interval [CI], 0 to 2) were corroborated by retrospective waveform analysis. Three of these 5 instances were described as a return of heart rhythm and blood pressure, the fourth was described as a return of heart rate (without comment on blood pressure), and the fifth was described as a return of respiration (without comment on heart rate or blood pressure). The 5 reports that were confirmed by waveform showed resumptions of cardiac electrical and pulsatile activity at 64 seconds, 66 seconds, 2 minutes 30 seconds, 2 minutes 31 seconds, and 2 minutes 56 seconds after a period of pulselessness. There were 2 clinical reports of resumption of activity for which waveform vital-signs data were not available for review; 1 was described as transient resumption of heart rate after a 3-minute cessation, and 1 was reported as transient resumption of heart rate and blood pressure after a cessation of 1 minute 42 seconds.

RETROSPECTIVE WAVEFORM ANALYSIS

Of the 631 patients enrolled, 151 did not have complete waveform data, resulting in a subgroup of 480 with both bedside clinical observations and complete data on ECG and arterial pressure catheter waveforms that were available for retrospective analysis. Review of the data from the 480 patients with complete ECG and arterial pressure catheter waveforms and at least 5 minutes of continuous waveform monitoring after pulselessness showed 67 of 480 patients (14%; 95% CI, 11 to 17) with resumption of cardiac activity, including the 5 who had a resumption identified by bedside observation and 7 (1%) who had more

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Table 1. Characteristics of Enrolled Patients at Baseline.*

Variable	Clinical Observations		Retrospective Waveform Adjudication	
	All Patients (N=631)	Confirmed Bedside Report of Resumption of Cardiac Activity (N=5)	All Patients (N=480)	Resumption of Cardiac Activity Identified in Waveforms (N=67)
Demographic characteristics				
Age — yr				
Mean	63±16	66±6	65±15	66±13
Range	18–95	58–74	18–95	22–94
Female sex — no. (%)	241 (38)	3 (60)	184 (38)	26 (39)
Chronic condition — no./total no. (%)	518/630 (82)	3/5 (60)	411/479 (86)	56/67 (84)
Primary reason for ICU admission — no. (%)				
Neurologic	307 (49)	2 (40)	226 (47)	27 (40)
Cardiac	23 (4)	0	18 (4)	2 (3)
Respiratory	96 (15)	2 (40)	74 (15)	15 (22)
Sepsis or infection	95 (15)	1 (20)	78 (16)	12 (18)
Trauma	28 (4)	0	18 (4)	1 (1)
Other†	82 (13)	0	66 (14)	10 (15)
CPR in previous 24 hr — no. (%)	84 (13)	0	71 (15)	7 (10)
Glasgow Coma Scale score at ICU admission‡				
Patients evaluated	626	5	476	66
Median score (range)	4 (3–15)	9 (3–15)	4 (3–15)	4 (3–15)
APACHE II score§				
Patients evaluated	627	5	477	66
Mean	28±9	23±6	28±8	28±8
Range	5–55	17–31	5–55	9–43
Traumatic brain injury — no./total no. (%)	86/630 (14)	0/5	65/479 (14)	4/67 (6)
Length of stay in ICU				
Patients evaluated	630	5	479	67
Median stay (range) — days	4 (0–61)	5 (2–23)	3 (0–61)	5 (0–30)
DCD donor — no. (%)	67 (11)	2 (40)	32 (7)	2 (3)
Bedside report of resumption of cardiac activity — no. (%)	13 (2)	5 (100)	12 (2)¶	7 (10)‖
Determination-of-death form completed — no. (%)	596 (94)	5 (100)	463 (96)	63 (94)
Life-sustaining measures				
Receiving invasive mechanical ventilation — no. (%)	552 (87)	5 (100)	416 (87)	63 (94)
Extubated during withdrawal of life-sustaining measures — no./total no. (%)	389 (62)	4 (80)	277 (58)	43 (64)
No. of vasopressors or inotropes — no. of patients (%)				
0	270 (43)	3 (60)	189 (39)	26 (39)
1	232 (37)	1 (20)	192 (40)	29 (43)
2	78 (12)	0	62 (13)	7 (10)
≥3	51 (8)	1 (20)	37 (8)	5 (7)
Receiving sedation — no. (%)	463 (73)	4 (80)	346 (72)	58 (87)
Receiving analgesia — no. (%)	588 (93)	5 (100)	445 (93)	65 (97)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CPR denote cardiopulmonary resuscitation, DCD donation after circulatory determination of death, and ICU intensive care unit.
† Other reasons include gastrointestinal bleeding, abdominal aortic aneurysm, multiple causes, hypovolemic shock, and multiorgan failure.
‡ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating a reduced level of consciousness.
§ Score on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease.
¶ One clinical report of resumption of circulation did not have waveform data available because it occurred more than 24 hours after withdrawal of life-sustaining measures. A second report had waveform data but a loss of signal in the data coincided with the clinical report of resumption of circulation.
‖ Two patients had clinical reports of resumption of circulation that did not correspond to our definition of a resumption of circulation but later had a resumption of circulation verified by waveform adjudication that was not reported clinically.

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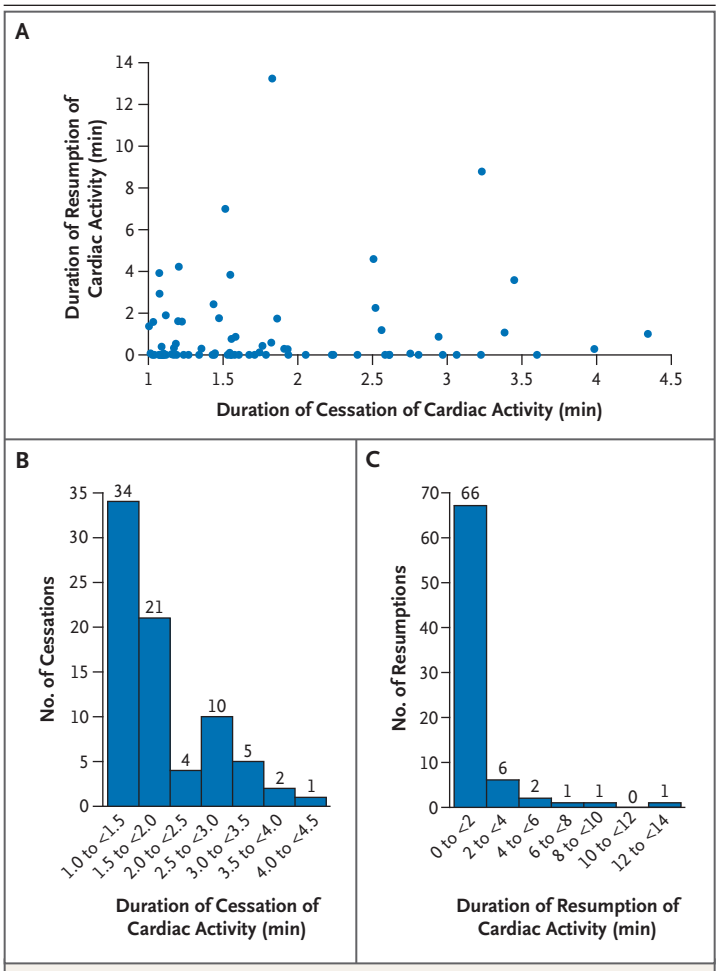

Figure 2. Duration of Cessation of Cardiac Activity as Compared with the Duration of Resumption of Cardiac Activity.

Panel A shows a scatterplot of retrospective waveform analysis indicating the duration of cessation of cardiac activity (arterial blood pressure, <5 mm Hg) as compared with the duration of resumption of cardiac activity (arterial blood pressure, ≥5 mm Hg concurrent with ECG activity). There were a total of 77 cessations and resumptions in 67 patients (of 480), with 7 patients having more than 1 cessation and resumption. Panel B shows a histogram of the number of cessations of cardiac activity, with the x axis of the scatterplot used for binning intervals. Panel C shows a histogram of the number of resumptions of cardiac activity, with the y axis of the scatterplot used for binning intervals. (Note that the scales on the y axes in Panel B and Panel C are not the same.)

than one cessation followed by resumption of cardiac activity. The durations of cessation of cardiac activity and subsequent resumptions are shown in Figure 2. The majority of resumptions of cardiac activity (55 resumptions in 45 patients) followed pulselessness of 1 to 2 minutes. The longest duration of pulselessness before a resumption of cardiac electrical and pulsatile activity was 4 minutes 20 seconds (Fig. S5 and Video 1). Among 32 potential organ donors with waveform data that could be interpreted, there were two resumptions of cardiac activity, one after 1 minute 4 seconds and one at 2 minutes 31 seconds after pulselessness, both reported by bedside clinicians.

Videos showing blood-pressure and ECG waveforms are available at NEJM.org

The median duration of resumed cardiac activity was 3.9 seconds (range, 1 second to 13 minutes 14 seconds) (Fig. S5 and Video 2). Of the 67 patients who had a resumption of cardiac activity, 33 (49%) had a resumption lasting only one cardiac cycle (Fig. 2).

In patients with waveform recordings of 30 minutes (432 of 480) after determination of death, all instances of resumption of cardiac activity occurred within 5 minutes after pulselessness. We estimated the probability of observing resumptions after more than 5 minutes to be less than 1% (3.7 of 432, with the use of a binomial one-tailed 97.5% confidence interval).[20,21]

Cessation of cardiac electrical activity coincided within 2 seconds with the last arterial pulse of at least 5 mm Hg in 93 patients (19%). The median time between final arterial pulse and final QRS complex was 3 minutes 37 seconds (range, 0 seconds to 83 minutes 28 seconds). Cardiac electrical activity after the last arterial pulse was observed for more than 30 minutes in 33 of 480 patients (7%) and until the end of recording in 23 of 480 patients (5%) (Fig. S6 and Video 3).

DISCUSSION

After a period of loss of cardiac activity that followed the planned withdrawal of life-sustaining measures, 1% of the patients in our study had transient resumption of cardiac activity observable by bedside reports that were corroborated by retrospectively identified ECG and arterial pulse catheter waveform activity. Retrospective waveform review showed resumption of cardiac activity in 14% of the patients, including resumptions identified at the bedside. The longest period of pulselessness that was followed by resumption of cardiac activity was 4 minutes 20 seconds. Activity on ECG after pulselessness often continued past cessation of arterial catheter pressure.

A systematic review,[10] which included one prospective study involving 30 patients,[11] showed a return of cardiac activity in 0 to 3% of patients

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after withdrawal of life-sustaining measures; the longest duration of pulselessness was 1 minute 42 seconds before observed resumption of cardiac activity. Concerns about this type of autoresuscitation can potentially limit the implementation of the practice of donation after circulatory determination of death. The term "autoresuscitation" used in this context may be a misnomer if it is interpreted as a return to viable life. In the current study, no patients who had a resumption of cardiac activity regained consciousness or survived. However, transient resumption of cardiac activity did occur, which suggests that the physiologic processes of somatic death after removal of life-sustaining measures occasionally include periods of cessation and resumption of cardiac electrical and pulsatile arterial activity. These transient resumptions of cardiac activity after withdrawal of life-sustaining measures are not equivalent to autoresuscitation as observed after terminated CPR, in which returns of circulation have rarely resulted in return of consciousness and survival.

Our analysis of clinical reports by bedside clinicians and vital-sign waveform recordings from a large international sample supports the current 5-minute observation period required by most protocols and guidelines for proceeding with organ donation after circulatory determination of death. Our results also confirm the known phenomenon of electrical cardiac activity continuing in the absence of pulsatile cardiac activity. Waiting for cessation of ECG activity to determine circulatory death is a recommendation in some protocols.[4]

This study has limitations. Of 13 clinically reported resumptions of circulation, 2 did not have waveform data available for confirmation of cardiac activity and were not included in our estimates. The generalizability of our results may be limited because we excluded patients without arterial pressure catheters and 24% of enrolled patients could not be included in the retrospective waveform analysis owing to incomplete data. The group of patients that we studied included 67 who proceeded to organ recovery, 32 of whom had waveform data. These patients were monitored for only 5 minutes of pulselessness, consistent with organ-donation protocols; this limited the observation period for return of circulatory activity. There were 2 clinical reports of return of cardiac activity within the 5-minute observation period in organ donors, both confirmed by waveform analysis.

Our study definition of cardiac activity used an arbitrary threshold of pulse pressure (≥5 mm Hg) that does not imply meaningful circulation. This conservative consensus definition may have been partially responsible for the ostensibly high incidence (14%) of transient resumptions of cardiac activity identified through waveform adjudication.

After a period of pulselessness that followed planned withdrawal of life-sustaining measures, clinically reported resumption of cardiac activity that was confirmed by waveform analysis occurred in 1% of the patients. Retrospective analysis of continuous ECG and arterial pressure monitoring identified resumption of cardiac activity in 14% of the patients, all occurring within 5 minutes after pulselessness.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

1. Youngner SJ, Arnold RM. Ethical, psychosocial, and public policy implications of procuring organs from non-heart-beating cadaver donors. JAMA 1993;269:2769-74.
2. Greer DM, Shemie SD, Lewis A, et al. Determination of brain death/death by neurologic criteria: the World Brain Death Project. JAMA 2020 August 3 (Epub ahead of print).
3. Smith M, Dominguez-Gil B, Greer DM, Manara AR, Souter MJ. Organ donation after circulatory death: current status and future potential. Intensive Care Med 2019;45:310-21.
4. Dhanani S, Hornby L, Ward R, Shemie S. Variability in the determination of death after cardiac arrest: a review of guidelines and statements. J Intensive Care Med 2012; 27:238-52.
5. Weiss MJ, Hornby L, Witteman W, Shemie SD. Pediatric donation after circulatory determination of death: a scoping review. Pediatr Crit Care Med 2016;17(3): e87-e108.
6. Boucek MM, Mashburn C, Dunn SM, et al. Pediatric heart transplantation after declaration of cardiocirculatory death. N Engl J Med 2008;359:709-14.
7. Bernat JL. The boundaries of organ donation after circulatory death. N Engl J Med 2008;359:669-71.
8. Curfman GD, Morrissey S, Drazen JM. Cardiac transplantation in infants. N Engl J Med 2008;359:749-50.
9. Hornby K, Hornby L, Shemie SD. A systematic review of autoresuscitation after cardiac arrest. Crit Care Med 2010;38: 1246-53.
10. Hornby L, Dhanani S, Shemie SD. Update of a systematic review of autoresuscitation after cardiac arrest. Crit Care Med 2018;46(3):e268-e272.
11. Dhanani S, Hornby L, Ward R, et al. Vital signs after cardiac arrest following withdrawal of life-sustaining therapy: a multicenter prospective observational study. Crit Care Med 2014;42:2358-69.
12. Cook DA, Widdicombe N. Audit of ten years of donation after circulatory death experience in Queensland: observations of agonal physiology following withdrawal of cardiorespiratory support. Anaesth Intensive Care 2018;46:400-3.
13. Sheth KN, Nutter T, Stein DM, Scalea TM, Bernat JL. Autoresuscitation after asystole in patients being considered for organ donation. Crit Care Med 2012;40: 158-61.
14. van Beinum A, Talbot H, Hornby L, Fortin MC, Dhanani S. Engaging family partners in deceased organ donation research — a reflection on one team's experience. Can J Anaesth 2019;66:406-13.
15. Bravi A, Longtin A, Seely AJ. Review and classification of variability analysis techniques with clinical applications. Biomed Eng Online 2011;10:90.
16. Seely AJE, Bravi A, Herry C, et al. Do heart and respiratory rate variability improve prediction of extubation outcomes in critically ill patients? Crit Care 2014;18: R65.
17. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions, version 5.1.0. London: Cochrane Collaboration, 2011.
18. Newcombe R, Altman D. Proportions and their differences. In: Altman D, Machin D, Bryant T, Gardner M, eds. Statistics with confidence. 2nd ed. London: BMJ Books, 2000:45-56.
19. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2019 (https://www.r-project.org/).
20. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998; 52:119-26.
21. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007;4(10):e296.

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