Dead donor rule and organ procurement

To the Editor:

Dr. Pleacher and colleagues present a report on the impact of pediatric donation after cardiac death in their hospital (1). They state that once a patient is apneic, pulseless, and unresponsive for a minimum of 2 mins, the pediatric intensive care unit attending declares death. In almost all Western countries, organ donation after death is based on the “dead donor rule” (2), which means that organ procurement is only possible after formal determination of death of the donor. The authors refer to a statement of the American Medical Association, which was amended in June 2005 (3). In this most recent recommendation of the American Medical Association, there is no mention of the duration between cardiac arrest and the declaration of death. Second, for declaring an organ donor dead, the death of the brain is paramount. In most Western countries, laws permit physicians to diagnose death based on irreversible loss of defined functions of the brain. The standard used to declare death before organ procurement is the neurologic standard. In the state of brain death, the living heart and presence of circulating blood are of no importance in declaring the patient dead. Most important is the irreversible cessation of functions of the brainstem (brainstem death). However, in most countries, additional brain function testing is needed to prove “whole brain death.” When a patient, for example, shows some electroencephalographic activity, or some residual spontaneous respiration or a single brainstem reflex, he or she is not dead. Death of the brain is a process and not a moment. Plum and Posner state: “Under clinical circumstances, total ischemic anoxia of the cerebral cortex lasting longer than about 4 mins starts to kill brain cells, with the neurons of the cerebral cortex and the cerebellum first” and “In man, severe diffuse ischemic anoxia lasting 10 mins or more begins to destroy the brain” (4). However, functional recovery of the whole brain in a normothermic patient is not reasonable beyond the 5-min boundary after cardiac and circulatory arrest. There is no therapy yet identified that consistently reverses normothermic cardiac arrest of >5 mins to complete recovery in patients (5). The 5-min boundary of normothermic ischemia is to our best of knowledge, still a valid statement in 2009. This makes that, when taking seriously the dead donor rule and the statement that brain is the essential organ in the declaration of death, declaring a patient dead after 2 mins circulatory arrest before organ procurement is not a valid argument. In other words, these children were close to (neurologic) death, but not yet dead at the time their organs were removed. There is still a scientific and philosophical rationale for declaring a human person dead at the moment his brain is in a state of total brain failure. When we take the position that the total irreversible failure of the brain is of no importance in the declaration of death, then the only acceptable ethical course is to stop procuring organs from brain dead donors.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e3181c3150d

The authors reply:

We appreciate the letter regarding our paper (1) evaluating increased donation after implementation of a donation after cardiac death (DCD) pathway at our hospital. The authors bring up the issue of what defines death, which requires careful thought, given the increasing chiasm between potential organ transplantation recipients and available donors. Efforts to increase donation in recent years in the United States has included support from the federal government of DCD (2), donation pathway that has been evaluated and supported by leading medical bodies (3–6). For many physicians, DCD is new; however, organ donation in the early 1960s was from what was then called nonheart-beating donors. This ethical tension between donation needs and the mandate to not cause harm led to the formulation of the “dead donor rule,” the concept that it is unethical to cause death by recovering organs and unethical for cadaveric organ procurement to precede death (4). French physicians developed and implemented a concept of “brain death” in 1966, which facilitated organ donation among patients with permanent loss of function of the entire brain. Expert panels developed the neurologic criteria (7, 8), and the number of nonheart-beating donors declined and virtually disappeared because organ preservation and graft function were worse compared with organs donated from “brain dead” persons.

The most careful analysis and review of what defines death was done by the US President’s Commission in 1981 and was entitled Defining Death: Medical, Legal and Ethical Issues in the Determination of Death (9). A primary goal of Defining Death was to incorporate the emerging practice of neurologic criteria for death into the common practice of declaring death based on cessation of cardiorespiratory function. To this end, the President’s Commission focused on criteria and tests to confirm brain death (10). To enhance the uniformity of death statutes in the United States, the Uniform Determination of Death Act was also proposed. Although the letter writers treat the neurologic criteria for death as unproblematic, the President’s Council on Bioethics recently released a white paper arguing that new empirical findings require a re-characterization of those criteria (11).
It is desirable and logical for physicians to apply the circulatory-respiratory tests for death in a consistent way, regardless of organ donor considerations. The permanent cessation of circulation and respiration is sufficient for physicians to determine death because, in the absence of autoresuscitation or cardiopulmonary resuscitation, those brain functions will rapidly and inevitably cease irreversibly and brain destruction will ensue (12). Alternatively, one can characterize the definition of death as the loss of integrated functioning and the neurologic and cardiorespiratory criteria as independent of one another. Such reasoning is the ethical foundation that DCD occurs within the boundaries of the dead donor rule.

However, the duration of asystole required to prove permanent cessation of heartbeat remains controversial. Studies of autoresuscitation which are, by nature, observational and have not included infants; however, current reports are that 65 secs is the longest observed period of monitored asystole followed by autoresuscitation (13). Reflecting this medical uncertainty, medical bodies have disagreed on the duration of asystole observation recommended to declare death based on cardiorespiratory cessation. The U.S. Institute of Medicine recommended a minimum of 5 mins (14). The Ethics Committee of the Society of Critical Care Medicine endorsed waiting a minimum of 2 mins and a maximum of 5 mins based on analysis of autoresuscitation data (4), and more recently, the National Conference on Organ Donation after Cardiac Death recommended a minimum of 2 mins of observation and recommended against >5 mins (15). Our selection of 2 mins is consistent with these recommendations. Conversely, the letter writer’s proposed 5-min waiting period is not sufficient to establish irreversible loss of function of the entire brain, including the brain stem (16).

Careful consideration of what defines death is important, as the boundaries for DCD are being tested by use of extracorporeal membrane oxygenation (17, 18) after declaration of death and by protocols used to procure cardiac donation after shortened periods of asystole observation (19). Clearly, this is an evolving practice which further information and studies may alter clinical practice and societal acceptance. An upcoming status report on cardiorespiratory criteria for death and DCD will be published soon and will reflect the current practice and ethical debate (20).

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e3181cbde10

Study of hypothermia therapy after pediatric cardiac arrest

To the Editor:

We would like to congratulate Meert et al on their recent article reporting the outcomes of a multicenter cohort study of in-hospital pediatric cardiac arrest (1). The objectives of this study were to describe patient characteristics and factors that would help inform the design of a randomized trial of therapeutic hypothermia after in-hospital cardiac arrest. This study was also appraised in an accompanying editorial (2). We recently published a report of outcomes associated with the use of therapeutic hypothermia after pediatric cardiac arrest (3). Our outcomes were remarkably similar to those of Meert et al, despite differences in inclusion criteria. In our study, a 2-yr, retrospective, five-center study of 79 patients with cardiac arrest, almost all (95%) of the patients had in-hospital cardiac arrests. We included pediatric patients with cardiac arrest. We

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arrest of at least 3-min duration and with return of circulation for at least 12 hrs, whereas Meert et al included patients with a cardiac arrest of at least 1 min and return of circulation for at least 20 mins. In our study, the 30-day and 6-month survival were 55.7% and 50.6%, respectively, whereas the hospital survival was 48.7% in the Meert et al study.

We also reported that therapeutic hypothermia was associated with higher mortality, but was used in resuscitation scenarios that are associated with greater risk of poor outcome. When adjustment was made for these risks, no statistically significant differences in mortality were found between patients treated with hypothermia therapy and those treated without. We concluded that the effectiveness of hypothermia therapy was neither supported nor refuted (3).

We strongly agree that randomized controlled trials are needed to evaluate rigorously the benefits and harms of hypothermia therapy after pediatric cardiac arrest. Based on our data, we calculated that, given a mortality rate of approximately 40% in the normothermia group, to detect an odds ratio of 2.0 with 80% power and a two-sided alpha = 0.05, 165 patients in both arms would be required (3). This is a significant undertaking, given the heterogeneity of the pediatric cardiac arrest population, and poses challenges in the timely recruitment and randomization of patients for a prospective study. Nonetheless, this is an extremely important research question, that can only be answered through rigorous trial design, and as such, we thank the authors of this paper for advancing knowledge on this topic.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e3181cbddb0

The authors reply:

We appreciate the comments of Drs. Doherty and Hutchison regarding our article (1). As our data were collected to help plan a prospective trial of therapeutic hypothermia after pediatric cardiac arrest, we find their recently published retrospective report on the use of hypothermia after cardiac arrest in children of great interest (2). In their report, the use of hypothermia therapy was associated with greater duration of cardiac arrest, more resuscitation interventions, higher postresuscitation lactate levels, more frequent use of extracorporeal membrane oxygenation, and higher mortality. However, after adjusting for cardiac arrest duration, extracorporeal membrane oxygenation use, and propensity scores, no differences in mortality or adverse events between hypothermia and normothermia groups were observed. We strongly agree with Drs. Doherty and Hutchison that a randomized controlled trial to evaluate the benefits and harms of therapeutic hypothermia after pediatric cardiac arrest is urgently needed.

The Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trials will evaluate the effect of hypothermia on survival and neurobehavioral outcomes post cardiac arrest in children. Because in-hospital and out-of-hospital pediatric cardiac arrest differ substantially in terms of prearrest characteristics, resuscitation and postresuscitation interventions, and hospital outcomes (3), two separate yet simultaneous trials will be conducted for children experiencing cardiac arrest in these settings. The THAPCA trials are funded by the National Heart, Lung and Blood Institute of the National Institutes of Health. Two established pediatric research networks have joined forces to conduct the THAPCA trials. These include the Pediatric Emergency Care Applied Research Network funded by the Emergency Medical Services for Children program and the Collaborative Pediatric Critical Care Research Network funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The THAPCA trials opened to patient enrollment September 1, 2009. We anticipate that approximately 900 children will eventually be enrolled in the THAPCA trials, which will include 30 clinical sites.

Important features of the THAPCA trials include their explicit protocols for both the hypothermia and normothermia arms of the research, careful documentation of adverse events, and detailed longitudinal outcome measures to assess neurobehavioral functioning. Parents provide permission and children are randomized to a treatment arm within 6 hrs of return of circulation. Participants randomized to hypothermia are cooled to 33°C (32°C–34°C) for 48 hrs duration using Servo-controlled external thermoregulation blankets, then warmed to 36.8°C (36°C–37.5°C) over 16 hrs and maintained in this range through completion of day 5. Participants randomized to normothermia are kept at 36.8°C (36°C–37.5°C) for 5 days, using the same type blankets. Use of two core body temperature monitoring probes and Servo-controlled blankets help to avoid overcooling and fever—both of which may be harmful in the postarrest state. The primary outcome is survival with good neurobehavioral status at 12 months post arrest. The Vineland Adaptive Behavioral Scales are used to provide a standardized, quantifiable measure of neurobehavioral outcome. Secondary outcomes include change in the Vineland Adaptive Behavioral Scales from baseline retrospective assessment, neuropsychological evaluations, and neurologic examination. Safety end points include frequencies of infection and arrhythmias, need for blood products within 7 days of arrest, and all-cause 28-day mortality.

The THAPCA investigative team is grateful for the many intensivists and consultants who have contributed to the design of these trials, and the site investigators and research coordinators who are now actively recruiting patients. We look forward to reporting our findings on this important topic to the pediatric critical care community. For further information about the THAPCA trials, please see our website at www.THAPCA.org.

Drs. Meert, Moler, and Dean have received grant support from the National Institutes of Health.

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DOI: 10.1097/PCC.0b013e3181cbde6f

The authors reply:

We would like to thank Catherine Preissig and Mark Rigby for their additional remarks in the January issue of PCCM about our recent publication on management of hyperglycemia in the pediatric intensive care by implementation of our glucose control protocol (1).

Today, our protocol is indeed the third peer-reviewed description of an active approach to glycemic control in the pediatric intensive care. Preissig et al (2) and Vlasselaers et al (3) have recently published their protocolized approach to control hyperglycemia in critically ill children. In addition, at this moment, there is a large multicenter study in England investigating if strict blood glucose control in pediatric intensive care units is beneficial when compared to current standard practices (Control of Hyperglycemia in Pediatric intensive care, CHIP trial) (4).

There are some notable differences between the protocolized approaches to control hyperglycemia that need to be discussed. First, although our glucose control protocol is designed for all ages (same as the work of Vlasselaers et al and CHIP trial), Preissig et al only use their protocol for pediatric intensive care patients aged >6 months and weighing >5 kg. Second, different target ranges for plasma glucose levels are being used: 4.4–7.7 mmol/L (80–140 mg/dL) by Preissig et al, 2.8–4.4 mmol/L (51–80 mg/dL) for infants aged 0–1 yr and 3.9–5.5 mmol/L (71–100 mg/dL) for children aged 1–16 yrs by Vlasselaers et al, 4–7 mmol/L (72–128 mg/dL) in the CHIP trial and 4–8 mmol/L (72–145 mg/dL) in our study. Third, in the study by Preissig et al and CHIP trial, no glucose intake ranges are recommended, whereas we advocate to start with a standard glucose regimen, in children <30 kg: 4–6 mg/kg/min and in children >30 kg: 2–4 mg/kg/min. In the study of Vlasselaers et al, median glucose intake on day 1 after admission was only 3.5 mg/kg/min for infants <1 yr of age and 2.8 mg/kg/min for children 1–16 yrs of age. Fourth, we start with an insulin infusion rate depending on the exact glucose level varying between 0.02 IU/kg/hr and 0.05 IU/kg/hr, whereas the other protocols use one or two starting doses, which are considerably higher than our insulin starting doses: 0.05 IU/kg/hr by Preissig et al, 0.1 IU/kg/hr to 0.2 IU/kg/hr depending on initial blood glucose level by Vlasselaers et al and CHIP trial.

It should be further investigated whether one or more of the above issues are associated with early achievement of normoglycemia, the prevalence of hypoglycemia (especially in infants), and most importantly beneficial outcome. We agree with Preissig and Rigby that hypoglycemic rates of 25%, as described in the randomized control trial by Vlasselaers et al, with the majority of hypoglycemia in infants <1 yr (70 infants and 17 children), raises concerns. With our approach, no hypoglycemia <2.2 mmol/L (<40 mg/dL) occurred, and Preissig et al also showed that, with their approach, the occurrence rate of hypoglycemia was very low (4%). At this moment, we have treated 323 children with our glucose control protocol, and an ad hoc analysis of 7195 blood glucose samples showed hypoglycemia of <2.2 mmol/L (<40 mg/dL) in only 0.3% of the samples, corresponding with 4% of the patients.

Furthermore, mean time until target blood glucose level was 5 hrs with both our and Preissig’s approach. Concerning the issue on how successful our approach was to maintain the target glucose ranges of 4–8 mmol/L (72–145 mg/dL), we found in 50% of the patients a rebound hyperglycemia with median blood glucose levels of 8.9 mmol/L (162 mg/dL). However, duration of this rebound was relatively short with a median of 1 hr. Interestingly, there is a marked discrepancy between the duration of insulin treatment in our group in comparison with other studies. Although we only treated patients for a mean of 2.1 days, Preissig et al treated patients for 6.3 days and Vlasselaers et al treated patients with intensive insulin therapy throughout intensive care stay for 5.5 days. This might be due to the strict stopping criteria for insulin administration in our protocol.

In conclusion, we agree with Drs. Preissig and Rigby that it is important to describe efficient protocols for glycemic control in pediatric critically ill patients, which do not increase the occurrence of hypoglycemic events. Vlasselaers et al reported a beneficial short-term outcome in pediatric patients treated with intensive insulin therapy. However, the majority (75%) of their patients was admitted after cardiac surgery, which means that further research is necessary to establish the beneficial effects of insulin therapy in all disease categories affecting critically ill children.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/PCC.0b013e3181d2e61a