

PHILADELPHIA COURT OF COMMON PLEAS
PETITION/MOTION COVER SHEET

FOR COURT USE ONLY	
ASSIGNED TO JUDGE:	ANSWER/RESPONSE DATE:
Do not send Judge courtesy copy of Petition/Motion/Answer/Response. Status may be obtained online at http://courts.phila.gov	

Rumper Banerjee, et al

VS.

Children's Hospital of Phila, et al

INDICATE NATURE OF DOCUMENT FILED:

- ☒ Petition (Attach Rule to Show Cause) ☐ Motion
☐ Answer to Petition ☐ Response to Motion

TYPE OF PETITION/MOTION (see list on reverse side)

Emergency Petition

PETITION/MOTION CODE
(see list on reverse side)

MTMNG

ANSWER/RESPONSE FILED TO (Please insert the title of the corresponding petition/motion to which you are responding):

I. CASE PROGRAM

Is this case in the (answer all questions):

A. COMMERCE PROGRAM

Name of Judicial Team Leader: _____

Applicable Petition/Motion Deadline: _____

Has deadline been previously extended by the Court?

☐ Yes ☐ No

B. DAY FORWARD/MAJOR JT

Name of Judicial Team Leader: _____

Applicable Petition/Motion Deadline

Has deadline been previously extend

☐ Yes ☐ No

C. NON JURY PROGRAM

Date Listed: _____

D. ARBITRATION PROGRAM

Arbitration Date: _____

E. ARBITRATION APPEAL PROGRAM

Date Listed: _____

F. OTHER PROGRAM: _____

Date Listed: _____

III. OTHER

By filing this document and signing below, the moving party certifies that this motion, petition, answer or response along with all documents filed, will be served upon all counsel and unrepresented parties as required by rules of Court (see PA. R.C.P. 206.6, Note to 208.2(a), and 440). Furthermore, moving party verifies that the answers made herein are true and correct and understands that sanctions may be imposed for inaccurate or incomplete answers.

CONTROL NUMBER:

045294

(RESPONDING PARTIES MUST INCLUDE THIS
NUMBER ON ALL FILINGS)

April

Month

Term, 2018

Year

No. 3761

Name of Filing Party:

Rumper Banerjee

(Check one)

☒ Plaintiff

☐ Defendant

(Check one)

☐ Movant

☐ Respondent

Has another petition/motion been decided in this case?

☐ Yes

☒ No

Is another petition/motion pending?

☐ Yes

☒ No

If the answer to either question is yes, you must identify the judge(s):

☐ Yes

☒ No

I. CASE PROGRAM

Is this case in the (answer all questions):

A. COMMERCE PROGRAM

Name of Judicial Team Leader: _____

Applicable Petition/Motion Deadline: _____

Has deadline been previously extended by the Court?

☐ Yes ☐ No

B. DAY FORWARD/MAJOR JT

Name of Judicial Team Leader: _____

Applicable Petition/Motion Deadline

Has deadline been previously extend

☐ Yes ☐ No

C. NON JURY PROGRAM

Date Listed: _____

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II. PARTIES (required for proof of service)

(Name, address and telephone number of all counsel of record and unrepresented parties. Attach a stamped addressed envelope for each attorney of record and unrepresented party.)

Rumper Banerjee

Christopher F. Baganto, Esq.

1500 Walnut Street - Suite 1420

Phila, PA 19102, (610) 484-576-0389

Children's Hospital of Phila

3615 Civic Center Blvd, Phila PA 19104

Att: Rasheen Davis Merritt

3615 Civic Center Blvd, Phila, PA

Ph: 215-582-5874

Dr. Charlotte Woods, John Doe, Jane Doe, Doe,
1-10

Chris Baganto
(Attorney Signature/Unrepresented Party)

4/26/18
(Date)

Christopher F. Baganto 308101
(Print Name) (Attorney I.D. No.)

The Petition, Motion and Answer or Response, if any, will be forwarded to the Court after the Answer/Response Date. No extension of the Answer/Response Date will be granted even if the parties so stipulate.

045294

Rumper Banerjee, individually and as
png of Areen Chakrabarti

Plaintiff

vs.

Childrens' Hospital of Philadelphia
Dr. Charlotte Woods,
John Doe, Jane Doe and Does 1-10

Defendants

COURT OF COMMON PLEAS
OF PHILADELPHIA COUNTY

April Term, 2018

No.:

045294

ORDER

AND NOW, this 26th day of April 2018, upon consideration of Plaintiff's Petition and having determined that:

1. Petitioner has shown a reasonable likelihood of prevailing on the merits of its claim;
2. Petitioner will suffer immediate and irreparable harm and loss if Respondent is permitted to proceed with or cause the termination of life support measures for Petitioner's minor son;
3. The public interest favors protecting the right of parents to decide whether to continue life support for their children;
4. Petitioner does not have an adequate remedy at law; and,
5. Greater injury will be inflicted upon Petitioner by the denial of temporary injunctive relief than would be inflicted upon Respondent by the granting of such relief.

IT IS HEREBY ORDERED THAT: Plaintiff's Petition seeking an ex parte Order for a temporary restraining order restraining Defendant CHILDREN'S HOSPITAL OF PHILADELPHIA ; and Dr. Charlotte Woods and other unidentified defendants herein designated as John Doe Jane Doe and Does 1-10, from ending Life Support for the

Petitioner's minor son Areen Chakrabarti, born July 14, 2003, and requesting for provision of life support and nutrition and other medical treatment while the Court makes its ruling. it is hereby ORDERED and DECREED that the Defendant shall place and/or leave in place proper respiratory support and nutrition so that the Petitioner's minor child can meet the conditions required for transfer to another facility.

BY THE COURT:

J.

JENSEN BAGNATO, P.C.
By: Christopher F. Bagnato, Esquire
Atty ID No. 308101
1500 Walnut Street, Suite 1920
Philadelphia, PA 19102
215-546-4700 / 215-546-7440 (Fax)

Attorneys for Defendant

Rumper Banerjee, individually and as
png of Areen Chakrabarti

Plaintiff

vs.

Childrens' Hospital of Philadelphia
Dr. Charlotte Woods,
John Doe, Jane Doe and Does 1-10

Defendants

COURT OF COMMON PLEAS
OF PHILADELPHIA COUNTY

April Term, 2018

No.: **003761**

045294

**EMERGENCY PETITION FOR TEMPORARY RESTRAINING ORDER RESTRAINING
DEFENDANTS FROM PROCEEDING WITH ENDING LIFE SUPPORT**

This application is made pursuant to Rule 1531 of the Pennsylvania Rules of Civil Procedure. The ex parte relief requested is appropriate because, absent an injunction prohibiting Defendants from proceeding with ending life support measures, Defendants are going to terminate Areen Chakrabarti's life support on April 26, 2018 (this day) thereby leading to death. If this petition is not granted then Plaintiff will suffer irreparable harm in that her son will die, whereas the only harm to Defendants if the Petition is granted will be the resulting continuation of the status quo of allowing the minor to remain on life support. Further, Plaintiff has a likelihood of succeeding on the merits of her case because, inter alia,

Defendants proposed action, i.e., removal of life support, over the objection of the parents, the health care decision makers for their minor child based upon the classification of the child as "brain dead" is against the parent's religious principals and is unconstitutional in so far as it interferes with Plaintiff's exercise of her rights to freedom of religion under the first amendment and interference with her privacy rights under the Fourth and Fourteenth Amendments, and recognized rights to privacy in health care decisions and determination over ones medical treatment. The Plaintiff is actively seeking alternate arrangements for her son and

failure to institute a TRO and Injunction will make the matter moot as Plaintiff's son would die. Also, the public interest will be served, as granting this Temporary Restraining Order will allow the public to have a clear understanding as to the rights of a parent to continue mechanical support of the life of a loved one.

1. On April 26, 2018, together herewith, Petitioner filed the attached Writ of Summons seeking declaratory judgment, a true and correct copy of which is attached hereto, incorporated by reference herein and marked as Exhibit "A".

2. Unless the requested Temporary Restraining Order ("TRO") and/or Preliminary Injunction are granted, Petitioner will suffer great immediate and irreparable injury that cannot be compensated by damages because Petitioner's son would die.

3. Respondent, conversely, will not suffer any appreciable injury if the Temporary Restraining Order and/or Preliminary Injunction are granted. By granting the instant petition, Petitioner's son would remain alive and Respondent will merely be restrained from proceeding with the termination of Petitioner's son's life support, while this Honorable Court considers whether to enter an injunction and while Plaintiff continues to seek treatment for her son at another facility.

4. Unless the TRO and/or injunctive relief is granted, Respondent would be at liberty to proceed with its already-stated intention to terminate Petitioner's son's life support, which would cause the death of Petitioner's son and immediate and irreparable damage to the Petitioner.

5. Respondent's conduct is actionable and Petitioner's right is clear. See Exhibits B-1 & B-2.

6. Petitioner has a reasonable likelihood of success on the merits of her claims.

7. Petitioner has no adequate remedy at law.

WHEREFORE, Petitioner, respectfully request that this Honorable Court enter an immediate Temporary Restraining Order prohibiting Defendants from terminating life support for Petitioner's minor son Areen Chakrabarti, and enter a Rule upon Respondent to show cause why an injunction should not issue.

Respectfully submitted,

/s/ Christopher F. Bagnato, Esquire

CHRISTOPHER F. BAGNATO, ESQUIRE

DATE: April 26, 2018

COMMONWEALTH OF PENNSYLVANIA:

COUNTY OF PHILADELPHIA :

VERIFICATION

I, RUMPA BANERJEE, Plaintiff /Defendant, does hereby verify that the facts and statements made in the foregoing Pleadings are true and correct to the best of my knowledge, information, and belief, and understands that false statements are made subject to the penalties of 18 Pa C.S. Section 4904, relating to unsworn falsifications to authorities.


RUMPA BANERJEE

JENSEN BAGNATO, P.C.
By: Christopher F. Bagnato, Esquire
Atty ID No. 308101
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Philadelphia, PA 19102
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Attorneys for Defendant

Rumper Banerjee, individually and as
png of Areen Chakrabarti

Plaintiff

vs.

Childrens' Hospital of Philadelphia
Dr. Charlotte Woods,
John Doe, Jane Doe and Does 1-10

Defendants

COURT OF COMMON PLEAS
OF PHILADELPHIA COUNTY

April Term, 2018

No.: **003761**

045294

MEMORANDUM OF LAW IN SUPPORT OF
EMERGENCY PETITION TO RESTRAIN
DEFENDANTS FROM PROCEEDING WITH ENDING LIFE SUPPORT MEASURES

I. Matter before the Court and Relief Requested:

Plaintiff respectfully requests that the Court enter an immediate Temporary Restraining Order restraining Defendant from proceeding with the termination of life support measures for Petitioner's minor son Areen Chakrabarti.

II. Statement of Questions Involved:

Whether the Court should restrain the Defendant from proceeding with its stated intentions under the circumstances set forth in the attached Petition.

Suggested Response: Yes.

III. Operative Facts:

On April 14, 2018, Petitioner's home in New Jersey was destroyed by fire and her minor son was severely injured suffering from smoke inhalation. Petitioner's son was immediately admitted to Capital Health System, where life support procedures began. On April 15, 2018, Petitioner's son was transported to and admitted to Defendant Children's Hospital of Philadelphia ("CHOP").

Almost immediately upon her son being admitted to CHOP, on April 15, 2018, Petitioner's consent to terminate life support was requested. Defendant repeatedly sought Petitioner's consent to terminate life support ever since then. Despite the Defendant's contentions, Plaintiff has experienced physical responses from her son when she touches his hand. She has also seen movement in his feet, indicating that to her that he is not "brain dead." Also, although with assistance, his heart has continued to beat. But Defendant's persisted in seeking the Plaintiff's consent. Finally, on Tuesday April 24, 2018, in a meeting called and attended by Defendant's agent, servant, workman or employee ("A/S/W/E"), Dr. Charlotte Woods, also attended by a nurse named "Ben (last name unknown)" and other A/S/W/E's of Defendant, including members of an "ethics group", Plaintiff was told that a neurological test would be performed on her son on Thursday April 26, 2018, and that if the results of this test confirmed their contention that the minor child is "brain dead", that the Defendant would remove the Petitioner's son from life support without the Petitioner's consent.

Plaintiff is actively seeking alternative placement for her child and needs additional time. Despite Defendant's dire position, numerous examples can be found of persons being diagnosed as "brain dead" and then recovering and regaining consciousness after far longer period than the than the twelve day period that has elapsed since Areen's injury,

IV. Legal Argument:

Pennsylvania Rule of Civil Procedure Number 1531 sets forth the procedure for obtaining preliminary or special injunction. A petition for preliminary injunction is ordinarily made at the commencement of the action and asks the court to grant, temporarily and before trial, all or a portion of the same relief which the movant seeks in his motion as final relief after trial.

A special injunction is relief which is separate from and auxiliary or collateral to the main relief requested in the Motion and may be requested at any stage of the action Overland Enterprise, Inc. v. Gladstone Partners, L.P., 950 A.2d 1015 (Pa. Super. 2008). The purpose of preliminary or special injunctive relief is to preserve the status quo which existed before the acts complained of by restoring the last peaceable, uncontested status which preceded the controversy, and to prevent the occurrence of irreparable harm before the determination of the merits of the case at trial. Id. Preliminary or special injunctive relief usually restrains or prohibits action, but may take the form of a mandatory injunction under appropriate circumstances.

Irreparable harm means harm that is not entirely ascertainable and compensable by money damages. Obviously, losses caused to a parent by the death of a minor child constitute irreparable harm Id.

Standard-for Granting Preliminary Injunction

The standards for granting preliminary injunction were described by the Superior Court in Overland Enterprises, Inc. v. Gladstone, Partners, LP, 2008 PA Super 114, 950 A.2d 1015, 1019 (Pa. Super.2008), as follows:

- (1) a party seeking a preliminary injunction must show that an injunction is necessary to prevent immediate and irreparable harm that cannot be adequately compensated by damages.
- (2) that party must show that greater injury would result from refusing an injunction than granting it; and concomitantly, that issuance of an injunction will not substantially harm other interested parties in the proceedings.
- (3) the party must show that a preliminary injunction will properly restore the parties to their status as it existed immediately prior to the alleged wrongful conduct.
- (4) the party seeking an injunction must show that the activity it seeks through the restrain is actionable that its right to the relief is clear and that the wrong is manifest or in other words must show that it is likely to prevail on the merits.
- (5) the party must show that the injunction it seeks is reasonably suited to abate the offending activity.
- (6) the party seeking an injunction must show that a preliminary injunction would not adversely affect the public interest.

Each of these elements are present in the instant matter and compel that injunctive relief be entered in favor of the Petitioner. Without the requested temporary restraining order, Defendant will terminate life support and the Petitioner's son will die. This clearly would be irreparable harm that would be greater than any harm that could come from granting it. The Defendant would suffer no harm and would merely be restrained from terminating life support.

For the issuance of a preliminary or special injunction, it is not necessary that the Petitioner establish an absolute right to relief on the underlying claims or that the court determine the merits of the controversy at the preliminary stage. Id. Where the above factors are present, the Petitioner's right to preliminary relief is sufficiently "clear" if the Petitioner has raised substantial legal questions going to the merits which are so serious as to make them a fair ground for litigation and further investigation and consideration Id. The standard is the same for whether the injunctive relief is prohibitory or mandatory in nature, provided that the injunction does not alter the status quo as it existed before the complained of act.

The court may act on the basis of the averments of the pleadings or petition, the affidavits of the parties or third persons, and any other proof which the court may require, in deciding whether or not to grant a preliminary or special injunction. Because the purpose of a preliminary injunction is limited to preserving the relative positions of the parties until a trial on the merits can be held, and given the haste that is often necessary if those positions are to be preserved, a preliminary injunction is customarily granted on procedures that are less formal and on evidence that is less complete than in a trial on the merits. Southco, Inc. v. Kanebridge Corp., 324 F.3d 190 (3rd Cir. Pa. 2003).

In the matter at bar, the Defendant hospital has asserted its intention to take the life-ending action of removing the Petitioner's son from life-support without the consent of the Petitioner. The Defendant makes this assertion after more than a week of seeking the Petitioner's consent, but now appears to claim that it is authorized to take this action without the Petitioner's consent. In the case of *In re Estate & Pers. of Border*, 68 A.3d 946 (Pa. Super. 2013), a hospital which considered a patient brain dead, wanted to terminate life support against the wishes of the guardian. Because the guardian's consent was necessary, the hospital had to file an motion in

Orphans Court to get that guardian replaced with one who would approve the termination. The Orphans Court granted the hospital's motion, removed the non-consenting guardian, and arranged for the appointment of a guardian who would consent to terminating the patient's life support. After this occurred the patient died, but not before the non-consenting guardian filed an emergency petition attempting to enjoin the hospital from terminating life-support. It was not until after the patient died that the non-consenting guardian's emergency motion was denied as moot (because the patient was already dead). The non-consenting guardian then appealed her removal as guardian to the Superior Court. In explaining why it considered the non-consenting guardian's appeal even though the issue was moot as to this particular patient, the Superior Court said:

"Generally, an actual claim or controversy must be present at all stages of the judicial process for the case to be actionable or reviewable. *Plowman v. Plowman*, 409 Pa. Super. 143, 597 A.2d 701, 705 (Pa. Super. 1991). If events occur to eliminate the claim or controversy at any stage in the process, the case becomes moot. *Id.* Even if a claim becomes moot, we may still reach its merits if the issues raised in the case are capable of repetition, yet likely to continually evade appellate review. *Id.* See also *In re Fiori*, 543 Pa. 592, 673 A.2d 905, 909 n. 4 (Pa. 1996) *Commonwealth v. Bernhardt*, 359 Pa. Super. 413, 519 A.2d 417, 420 (Pa. Super. 1986) (holding exception to mootness doctrine exists where "(1) the question involved is capable of repetition but likely to evade review, or (2) the question involved is one of public importance"). Therefore, if the issues raised by an appeal are "substantial questions" or "questions of public importance," and are capable of repetition, yet likely to evade appellate review, then we will reach the merits of the appeal despite its technical mootness. *Id.*

In re Duran, 2001 PA Super 52, 769 A.2d 497, 502 (Pa. Super. 2001) (parallel citations omitted).

Here, [the patient's] death soon after the orphans' court issued the March 12, 2012 order renders the issues raised in this appeal technically moot. Appellant's issues on appeal, however, are of great public importance, are capable of repetition, and are likely to evade appellate review. See e.g. In re Fiori, 673 A.2d at 909 n.4 (holding death of patient did not preclude appellate review where issue was of important public interest, capable of repetition, yet apt to elude appellate review). Accordingly, we proceed with the merits of this appeal."

Ultimately, the Superior Court in *Border* ruled in favor of the non-consenting guardian, finding that the hospital's quest to terminate life support should have ended with the refusal of the non-consenting guardian to give consent. This case illustrates very clearly that the Defendant in the instant case is not at liberty to remove life support from the Petitioner's son, as they have asserted they plan to do later today.

Accordingly, Petitioner seeks, in the effort to protect her son from death, the immediate issuance of a Temporary Restraining Order.

V. Conclusion:

The Temporary Restraining Order should be granted for the reasons as set forth in the foregoing Petition and Memorandum.

WHEREFORE, the Plaintiff respectfully requests that this Honorable Court immediately enter an Order precluding and prohibiting the defendant from terminating life support for Petitioner's son.

Respectfully submitted,

BAGNATO JENSEN PC

/s/ CHRISTOPHER BAGNATO, ESQUIRE
CHRISTOPHER BAGNATO, ESQUIRE

DATE: April 26, 2018

EXHIBIT A

JENSEN BAGNATO, P.C.

By: Christopher F. Bagnato, Esquire

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Attorneys for Defendant

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png of Areen Chakrabarti

Plaintiff

vs.

Childrens' Hospital of Philadelphia

Dr. Charlotte Woods,

John Doe, Jane Doe and Does 1-10

Defendants

COURT OF COMMON PLEAS
OF PHILADELPHIA COUNTY

April Term, 2018

No.:

PRAECIPE TO ISSUE WRIT OF SUMMONS

TO THE PROTHONOTARY:

Kindly Issue Writ of Summons against Childrens Hospital of Philadelphia, Dr. Charlotte
Woods, John Doe Jane Doe and Does 1-10.

Respectfully submitted,

JENSEN BAGNATO, P.C.

/s Christopher F. Bagnato

Christopher F. Bagnato, Esquire

Commonwealth of Pennsylvania
COUNTY OF PHILADELPHIA

Rumper Banerjee, indiv. png of Areen Chakrabarti
Plaintiff

vs.

Children's Hosp of Phila, Dr. Charlotte Woods, Does
Defendant

COURT OF COMMON PLEAS

_____ Term, 20____

No. _____

To¹

Children's Hosp. of Phila

Dr. Charlotte Woods

Does 1-10

Writ of Summons

You are notified that the Plaintiff²
Usted esta avisado que el demandante

Rumper Banerjee, indiv. png of Areen Chakrabarti

Has (have) commenced an action against you.
Ha (han) iniciado una accion en contra suya.



ERIC FEDER
Director, Office of Judicial Records

By: _____

Date: _____

¹ Name(s) of Defendant(s)

² Name(s) of Plaintiff(s)

Court of Common Pleas

_____ Term, 20 _____

No. _____

Rumper Banerjee, indiv. png of Areen Chakr

Plaintiff

vs.

Children's Hosp of Phila, Dr. Charlotte Wood

Defendant

SUMMONS

EXHIBIT B-1

NEWS BIOETHICS

Thu Oct 18, 2012 - 7:08 pm EST

Film on teen who awoke from coma before having organs harvested stirs 'brain death' debate

COPENHAGEN, Denmark, October 18, 2012, (LifeSiteNews.com) - A documentary titled "Pigen der ikke ville dø" ("The girl who refused to die"), which aired last week on Danish TV, tells the story of 19-year-old Carina Melchior, a 19 year-old girl who awoke from a coma after doctors asked her family to consider donating her organs. The film has raised concern again over inexact criteria for brain death prior to organ donation.

The documentary followed Melchior's family after she was taken to Aarhus University Hospital to be treated for injuries from a car accident.

Last October, Carina was admitted to hospital with severe injuries and slipped into a coma. Doctors advised her parents that there was little chance for her survival, that brain death would probably occur within days, and suggested withdrawing life support and making preparations for organ donation.

The parents agreed, and Carina was taken off her respirator but continued to breathe on her own.

To the astonishment of her parents and hospital staff, Carina suddenly began moving her legs and opening her eyes.

Carina's parents claim that doctors took her off life support too soon, because they were desperate for donated organs.

Kim Melchior, Carina's father, said, "Those bandits in the white coats gave up too quickly, because they wanted an organ donor."

Danish media report that Carina is making a good recovery in a rehabilitation center, where she is regaining her speech and mobility - even riding her horse Mathilde - and hopes to complete her third year of high school, as she was doing when the accident happened.

Her parents have declared they intend to sue the hospital.



The family's lawyer, Nils Fjeldberg, told the Danish newspaper *Ekstra Bladet*, "Of course this is a great trauma, both for her and her parents who were convinced that there was nothing else that could be done and agreed to donate her organs."

Aarhus University Hospital has acknowledged they made a grave error in diagnosis and admitted that the suggestion of organ donation should not have been given, as there were no clear signs that brain death would occur.

(Click "like" if you want to end abortion!)

"We are overjoyed that the young woman survived and that she is moving on after the accident," Claus Thomsen, the hospital's chief medical officer, wrote in a statement. "But we made a mistake and made the family believe that their daughter and sister would die."

Thomsen added that the hospital has since implemented new guidelines to ensure that the suggestions about organ donation would be handled more carefully.

The contentious term "brain death" was invented in 1968 to accommodate the need to acquire vital organs in their "freshest" state for transplant.

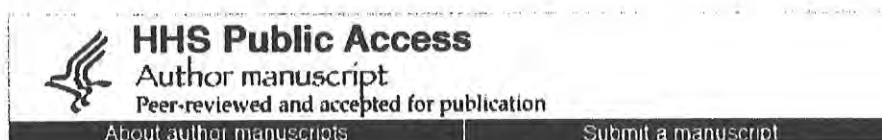
According to Dr. John Shea, the term has never been rigorously defined, and there are no standardized tests to determine if the condition exists.

Moreover, a prominent American professor of Catholic medical ethics has said that "brain death" criteria offer no "moral certitude" that a patient is really dead, a condition laid out by Popes John Paul II and Benedict XVI as necessary for removing organs.

The available evidence, said Professor E. Christian Brugger, a senior fellow of ethics at the Culture of Life Foundation, "raises a reasonable doubt that excludes 'moral certitude' that ventilator-sustained brain dead bodies are corpses."

Earlier this month, a lawsuit launched in New York stated that at least one in five patients declared "brain dead" are still alive and are being killed by the removal of vital organs.

EXHIBIT B-2



Neurol Clin. Author manuscript; available in PMC 2011 Apr 12.

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Published in final edited form as:

NIHMSID: NIHMS275346

Neurol Clin. 2008 May; 26(2): 487–ix.

PMID: 18514823

doi: [10.1016/j.ncl.2008.03.015](https://doi.org/10.1016/j.ncl.2008.03.015)

Management of Brain Injury After Resuscitation From Cardiac Arrest

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See other articles in PMC that [cite](#) the published article.

About 460,000 sudden cardiac deaths from a total of 728,743 cardiac-related deaths were reported in 1999 in the United States [1]. Thirty-six percent of the sudden deaths were in-hospital cardiac arrest and 64% were out-of-hospital arrest [1]. About 18% of patients survive to discharge following in-hospital cardiac arrest [2,3], whereas only 2% to 9% of patients who experience out-of-hospital cardiac arrest survive to discharge [4–6]. Functional outcomes of survivors are variable, but poor-quality survival is common [7], with only 3% to 7% able to return to their previous level of functioning [8]. The prevalence of coma or persistent vegetative state among survivors represents an enormous burden on patients, their families, health care personnel, and resources. The economic impact of cardiac arrest was the subject of a cost-effectiveness study that compared continuing versus withholding cardiopulmonary resuscitation (CPR) and ventilatory support after day 3. The estimated incremental cost of the more aggressive care strategy was \$140,000 (1998 dollars) per quality adjusted life year (QALY) for high-risk patients (three to five risk factors, 93% 2-month mortality) and \$87,000/QALY for low-risk patients (zero to two risk factors, 49% mortality) [9]. The economic burden of survivors of anoxic brain injury also is great, with in-patient rehabilitation lasting a mean of 41.5 days and costing \$44,181 per patient [10].

The devastating neurologic injury that is caused by cardiac arrest has been recognized since the early development of modern resuscitation techniques. The persistence of unfavorable neurologic outcomes, despite advances in CPR, led the American Heart Association to recognize brain injury after cardiac arrest as an important area for clinical research. In its 2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, the term “cardiopulmonary-cerebral resuscitation” was proposed to emphasize brain injury in relation to cardiac arrest [11]. After more than 2 decades of clinical trials failed to demonstrate benefit from a host of putative neuroprotective strategies, two clinical trials that were published in 2002 showed that induced mild hypothermia can ameliorate brain injury, improving survival and functional neurologic outcome in comatose survivors of out-of-hospital cardiac arrest. Comprehensive reviews on brain injury and cardiac arrest are available elsewhere

[12,13]. This article is an update of a previous publication [14] and provides a focused review on the advances in the care of brain injury after cardiac arrest, highlighting therapeutic hypothermia as a treatment for global ischemic brain injury.

Mechanisms of neuronal injury after cardiac arrest

[Go to:](#)

During total circulatory arrest, lack of cerebral oxygenation results in loss of ATP production and dysfunction of membrane ATP-dependent Na-K pumps. Subsequent loss of cellular integrity triggers the release of glutamate, which causes excitotoxic injury [15] that is mediated largely through N-methyl-D-aspartate (NMDA) receptors [16]. Other neurotransmitters that dampen the excitotoxicity of glutamate, such as glycine and g-aminobutyric acid (GABA), are decreased concomitantly [17]. Activation of NMDA receptors by glutamate leads to an influx of calcium into the intracellular space. Elevated intracellular calcium activates a series of second messengers, which amplifies injury by increasing calcium permeability and glutamate release [18]. Elevated intracellular calcium also increases oxygen-free radicals by interfering with the mitochondrial respiratory chain [18,19]. During re-perfusion, excitotoxicity can be enhanced by providing oxygen as a substrate for several enzymatic oxidation reactions that produce free radicals in the setting of mitochondrial dysfunction [20]. These reactive oxygen species are known to cause damage through lipid peroxidation, protein oxidation, and DNA fragmentation, all of which contribute to cell death [21]. The complexity of the injury cascade is not limited to the above processes. A more detailed description of the mechanisms of neuronal injury that are related to global ischemia is provided in several reviews [22–25]. This injury cascade begins with hypoxia and reperfusion, but it can continue for hours to days after the initial insult.

Numerous clinical studies have tested therapies that are directed at specific steps of the injury cascade, and have failed to show an outcome benefit [12,13]. Conversely, recent randomized trials demonstrate that therapeutic hypothermia is associated with improved survival and functional outcome following cardiac arrest. Although the mechanism underlying the neuroprotective effect of hypothermia is not fully understood, numerous hypotheses have been suggested [26]. The ability of hypothermia to affect multiple points of the injury cascade may contribute significantly to its success as an intervention. These effects include retarding the initial rate of ATP depletion [27,28], reducing excitotoxic neurotransmitter release [29], altering intracellular messenger activity [30], limiting breakdown of the blood–brain barrier [31], reducing inflammatory responses [32], altering gene expression and protein synthesis [33,34], reducing intracellular calcium, and changing glutamate receptor regulation [35].

Neurologic injury and clinical manifestations

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Global cerebral ischemia during cardiac arrest results in heterogeneous injury to the brain. Large projection neurons of the cerebral cortex, cerebellar Purkinje cells, and the CA-1 area of the hippocampus are the most vulnerable areas [36]. The subcortical areas, such as the brainstem, thalamus, and hypothalamus, are more resistant to injury than the cortex [37,38]. If the thalamocortical complex or extensive bilateral cortical regions are injured, dysfunction in arousal and consciousness may result [39]. The impairment in arousal remains the most predominant neurologic problem during the early post-resuscitative period. A review on neuroanatomic and physiologic considerations of coma related to brain injury after cardiac arrest was recently published by Hoesch and colleagues in 2008 [40]. Other areas that are prone to ischemic injury include the basal ganglia and cerebellum, which account for movement disorders and dyscoordination that are seen often after cardiac arrest. The brainstem can tolerate a greater degree of global ischemia. This is manifested as preservation of cranial nerve and sensory motor reflexes. Significant impairment of the cortex and thalamus with relative preservation of the brainstem results in vegetative and comatose states.

Neurologic evaluation

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The clinical evaluation of survivors of cardiac arrest in this article focuses on patients who remain unresponsive or unable to follow verbal commands after return of spontaneous circulation (ROSC). With the exception of a few recent studies, all of these observations were made on patients who were not subjected to treatment with mild therapeutic hypothermia [41–45]. Because most cardiac arrest survivors do not receive therapeutic hypothermia, it is important to review the evaluation of the survivor who is not treated with hypothermia. A complete neurologic evaluation must be undertaken following ROSC. It is important to exclude factors that may obscure the neurologic examination, such as paralytic and sedative medications, illicit drugs used before arrest, ongoing cerebral hypoperfusion, seizures or postictal encephalopathy, electrolyte abnormalities, and metabolic derangements. The evaluation should assess mental status by documenting the patient's ability to arouse and interact meaningfully with the examiner. Evaluation of the brainstem includes the testing of cranial nerve function and reflexes, most importantly the pupillary light reflex, corneal reflex, grimacing to noxious stimulation, cough and gag reflexes, and the presence of spontaneous respirations. In a comatose patient, the motor and sensory examination relies on the evaluation of the patient's response to a noxious stimulus, which may be purposeful (warding off the stimulus), reflexive (extensor or flexor posturing), or absent. It is also helpful to note the autonomic responses such as respiratory pattern, temperature lability, and heart rate and blood pressure variability. Diagnostic tests may be performed to enhance the neurologic assessment of these patients. The diagnostic tests that have been studied best include electroencephalography (EEG), median nerve somatosensory evoked potentials (SSEPs), serum testing for elevated neuron-specific enolase, and neuroimaging [43]. Recently, the American Academy of Neurology published an evidence-based review and generated practice parameters on the prediction of poor outcome in comatose survivors of cardiac arrest [43]. The practice parameters defined specific indicators of poor outcome on bedside examination: absent pupillary light response and corneal reflexes and extensor or no motor response to pain after 3 days of observation (level A), and myoclonic status epilepticus (level B). Based on neuroelectrophysiologic testing, the bilateral absence of cortical responses (N20 potentials) on somatosensory evoked potential recordings 3 days after CPR also predicted poor outcome (level B). Serum neuron-specific enolase greater than 33 mg/L also was specific for poor outcome (level B). Neurologic prognosis cannot be determined by the circumstances of CPR alone. Although neuroimaging may be helpful in characterizing structural brain injury, its role in outcome prediction in cardiac arrest survivors remains uncertain [43]. Outcome prediction data have been shown to influence physicians and families' decision regarding withdrawal of life support in patients with poor outcome after resuscitation from cardiac arrest [46].

Neuroprotective trials after cardiac arrest

Go to:

The landmark controlled clinical trials that primarily targeted brain injury after cardiac arrest span from the Brain Resuscitation Clinical Trial (BRCT) of barbiturates in 1986 [47] to the more recent trials of therapeutic hypothermia [48,49]. The barbiturate thiopental was the first agent used in a controlled clinical trial. Thiopental reduced metabolism, edema formation, intracranial pressure (ICP), seizure activity, and damage by focal and incomplete ischemia [47]. Although successful in a primate model of global ischemia [50] and successful pilot studies in humans [51], it failed to show a therapeutic benefit over placebo in the BRCT 1 trial [47]. The BRCT 1 trials also allowed for the addition of glucocorticoid treatment to the study agent (thiopental or placebo) at the discretion of the treating physician. The glucocorticoid treatment doses did not show additional benefit [52]. A follow-up study (BRCT 2) found no benefit in the treatment with the calcium channel blocker lidoflazine [53]. Based on the observation that the nimodipine reduced death or severe ischemic deficits in subarachnoid hemorrhage, a clinical trial using nimodipine was conducted [54,55]. This study found no difference in mortality or other outcomes between nimodipine and placebo treatment at 1 year [54]. Following the observation by Longstreth and colleagues [56] that hyperglycemia was associated with poor recovery after cardiac arrest, a randomized controlled trial performed by the same group did not find an outcome

difference between patients who were resuscitated with solutions that did (5% glucose) or did not (0.45% NaCl) contain glucose [56]. Another controlled clinical trial found no outcome benefit with intravenous magnesium, despite its antiarrhythmic effects and ability to block excitatory neurotransmitters [57]. A subsequent study that combined magnesium with diazepam, an inhibitor of neuroexcitotoxic injury, also reported outcomes that were not different from treatment with placebo [58]. Most of these agents showed preclinical benefit in animal models of focal and global ischemia or clinical benefit in human studies of other neurologic diseases. With the notable exception of induced hypothermia, none of these trials demonstrated significant neurologic or functional outcome benefit.

The failed clinical trials did provide critical insight into the epidemiology, pathophysiology, preclinical modeling, and clinical trial design that may have contributed to the success of recent trials in hypothermia.

Clinical trials in hypothermia and cardiac arrest

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Induced hypothermia as a therapy for acute brain injury was described in the 1940s by Fay [59]. In 1950, Bigelow and colleagues [60] reported the usefulness of hypothermia during cardiac surgery. Over the following decade, Rosomoff [61] designed the landmark experimental models of therapeutic hypothermia in brain injury. In the 1980s, researchers in Pittsburgh [24,25] and Miami [26,62] approached induced hypothermia for brain injury after cardiac arrest in a more systematic manner. This led to extensive pre-clinical studies that showed functional and survival benefit in rodent [63,64] and canine models [65,66]. The first human clinical study on induced hypothermia for survivors of out-of-hospital cardiac arrest was performed by Bernard and colleagues [67] in 1997. In this pilot safety and feasibility study, hypothermia was induced in 22 patients using surface cooling with ice packs and maintained for 12 hours in the ICU. In 1998, Yanagawa and colleagues [68] reported a study of 13 cardiac arrest survivors who were cooled to a target temperature of 33°C for 48 hours using cooling blankets and convective heat loss through alcohol evaporation. Both studies suggested a potential therapeutic benefit to hypothermia after cardiac arrest and paved the way for definitive trials.

Australian hypothermia study

The Australian study that was undertaken by Bernard and colleagues [49] enrolled comatose patients after successful resuscitation with an initial cardiac rhythm of ventricular fibrillation. This study randomly assigned 77 patients to receive hypothermia or normothermia using an alternating-day methodology. The hypothermia treatment arm included 43 patients and the normothermia arm had 34 patients. Paramedics in the field initiated early hypothermia by applying cold packs to the patients' head and torso. Upon arrival at the hospital, vigorous cooling was performed by application of ice packs around the head, neck, torso, and limbs to reduce the core temperature to 33°C, as monitored by a tympanic or bladder thermometer. The target temperature was maintained for 12 hours, and patients were sedated and paralyzed with repeated boluses of midazolam and vecuronium as needed to prevent shivering. The patients were actively rewarmed with a heated-air blanket beginning at 18 hours after arrival, with continued sedation and neuromuscular blockade to suppress shivering. Similar sedation and paralysis protocols were provided to patients assigned to the normothermic group, but the target core temperature was maintained at 37°C. Passive rewarming was used in these patients if there was mild spontaneous hypothermia on arrival. The primary outcome measure was place of discharge: home, rehabilitation facility, or long-term nursing facility. Discharge to home or to a rehabilitation facility was regarded as a good outcome, whereas in-hospital mortality or discharge to a long-term nursing facility was regarded as a poor outcome. Neurologic outcome batteries were not analyzed as outcome measures. The study found that 21 (49%) of 43 patients who were treated with hypothermia had good outcomes compared with 9 (26%) of 34 patients in the normothermia group (relative risk [RR] of good outcome, 1.85; 95% confidence interval [CI], 0.97–3.49). Mortality at discharge was 51% (22 of 43) in the hypothermia group and 68% (23 of 34) in the normothermia group (RR, 0.76; 95% CI, 0.52–1.10).

European study: hypothermia after cardiac arrest

A larger, multicenter European study was conducted by the Hypothermia After Cardiac Arrest (HACA) group [48]. The study screened 3551 potential subjects and included 273. The study randomized patients to induced hypothermia beginning after arrival at the hospital versus standard normothermia after resuscitation. There were 137 patients in the hypothermia arm and 138 patients in the normothermia arm. Patients in the hypothermia group were cooled to a target temperature of 32°C to 34°C. Hypothermia was achieved using external cooling by a mattress and blanket that delivers cold air over the body. The goal was to reach the target temperature within 4 hours of resuscitation. Core temperature was monitored with a bladder thermometer and maintained within the target range for 24 hours. Patients were rewarmed passively over a period of 8 hours. Sedation with midazolam and paralysis with vecuronium were used to prevent temperature increases due to shivering. Seventy-five (55%) of the 136 patients in the hypothermia group had a favorable neurologic outcome at 6 months compared with 54 (39%) of 137 in the normothermia group (RR, 1.40; 95% CI, 1.08–1.81). At 6 months, there were 56 deaths among the 137 participants (41%) in the hypothermia group and 76 death among the 138 patients (55%) in the normothermia group (RR, 0.74; 95% CI, 0.58–0.95).

Following these two studies, the International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association published an interim scientific statement with recommendations on the use of therapeutic hypothermia in comatose survivors of cardiac arrest [69]. This was followed, in 2005, by the American Heart Association Guidelines for CPR and Emergency Cardiovascular Care, which included the following treatment recommendations [70,71]: Unconscious adult patients resuscitated after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F–93.2°F) for 12 to 24 hours when the initial rhythm was ventricular fibrillation (Class IIa) Similar therapy may be beneficial for patients with in-hospital cardiac arrest or out-of-hospital arrest associated with an initial rhythm other than ventricular fibrillation (Class IIb).

Clinical impact of therapeutic hypothermia

To further assess the impact of hypothermia on neurologic outcomes, a systematic review of hypothermia for neuroprotection after cardiac arrest was undertaken by Holzer and colleagues [72]. This review evaluated three controlled clinical trials of adult cardiac arrest survivors who were treated with hypothermia within 6 hours of arrival at the emergency department. In addition to the study by Bernard and colleagues [49] and the HACA trial [48], a feasibility study by Hachimi-Idrissi and colleagues [73] was included. This study included 30 comatose cardiac arrest survivors with initial rhythms of asystole and pulseless electrical activity who were randomized to a target bladder temperature of 34°C for a maximum of 4 hours using a helmet device containing an aqueous glycerol solution. The meta-analysis of the three studies, using an intention-to-treat methodology, determined that favorable neurologic recovery occurred more often in the hypothermia groups (RR, 1.68; 95% CI, 1.29–2.07) [72]. This observation translates into a number needed to treat of 6 patients, even after controlling for several variables, such as age, gender, arrest duration, CPR time, and CPR technique. In 2006, a meta-analysis by Cheung and colleagues [74] added another study to the three studies above for a total of 436 patients, with 232 cooled to a core temperature of 32°C to 34°C. Their analysis showed that mild hypothermia decreased in-hospital mortality (relative risk [RR] 0.75; 95% CI, 0.62–0.92) and reduced the incidence of unfavorable neurologic outcome (RR 0.74; 95% CI, 0.62–0.84). This shows that the numbers needed to treat were 7 patients to save 1 life, and 5 patients to improve neurologic outcome. They did not find evidence of treatment-limiting side effects.

Post-clinical trial experience

After the completion of the therapeutic hypothermia trial in Europe, the European Resuscitation Council Hypothermia After Cardiac Arrest Registry (ERC HACA-R) was formed to monitor

developments in medical practice after the ILCOR recommendations on hypothermia in cardiac arrest were published [75]. Data on 650 cardiac arrest patients with successful restoration of spontaneous circulation from 19 sites within Europe were entered between March 2003 and June 2005. The decision to cool patients was made by the treating physicians in 462 (79%) of patients. The method of cooling in 347 (59%) was by an endovascular device, and in 114 (19%) was by other methods such as ice packs, cooling blankets, and cold fluids. The beneficial effects of hypothermia in the clinical trials were reflected in this registry result. Of those that had unfavorable outcome, 55% were in the hypothermia-treated group compared with 68% of the non-hypothermia-treated group ($P = .02$). Of those who died during the hospital stay, 43% were in the hypothermia-treated group compared with 68% of the non-hypothermia-treated group ($P < .001$). The adverse events reported were minimal with 15 (3%) episodes of hemorrhage and 28 patients (6%) with 1 episode of arrhythmia within 7 days after cooling. No fatalities as a result of cooling were reported [75]. This registry data show that therapeutic hypothermia is feasible and can be used safely and effectively outside a randomized clinical trial.

Timing of cooling and rewarming

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The best time to initiate hypothermia after resuscitation and the optimal duration of hypothermia have not been defined. It is reasonable to believe that the benefits may be maximized if hypothermia is initiated as soon as possible after resuscitation. In the European study, the interval between resuscitation and attainment of target temperature had an interquartile range of 4 to 16 hours, with a mean of approximately 8 hours [48,69,76]. Despite some delay, hypothermia still provided benefit. Rewarming should be undertaken slowly to avoid worsening neurologic injury, sudden vasodilatation, and shock [77,78]. The European study rewarmed patients passively over 8 hours after 24 hours of hypothermia, whereas the Australian study reported active rewarming for 6 hours using a heated-air blanket, beginning 18 hours after ROSC [48,49]. Preclinical studies have shown that delayed cooling negates the beneficial effect of hypothermia [79], and its beneficial effects may be enhanced even if it is initiated during the intra-arrest or resuscitation period [80,81] or immediately after return of spontaneous circulation [82]. There is a need to translate this preclinical research into human studies to help determine the optimal onset and duration of therapeutic hypothermia, and rates of cooling and rewarming.

Complications of hypothermia

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Potential complications of mild induced hypothermia include renal insufficiency, bleeding, sepsis, and pancreatitis; however, these complications have been seen in control groups. The study by Bernard and colleagues [49] and the HACA group [48] reported no statistically significant difference in complications between groups. In the HACA study, there was a trend toward increased bleeding and sepsis in the hypothermia group, but this was not statistically significant. In the study by Bernard and colleagues [49], the hypothermia group had a trend toward lower cardiac index, higher systemic vascular resistance, and more hyperglycemia. The proportion of patients with any complication was high in both groups: 70% in the normothermia group and 73% in the hypothermia group. Relative hypokalemia and metabolic acidosis are other potential metabolic derangements that are associated with hypothermia [83]. Close monitoring and appropriate correction of these conditions is important, with the understanding that potassium increases the rewarming phase as it shifts to the extracellular space. From a neurologic perspective, seizures have been noted in normothermia and hypothermia-treated patients, and likely are secondary to the global ischemic injury that was sustained during the cardiac arrest and reperfusion [84,85]. It is advisable to have a low threshold for performing an electroencephalogram (EEG) on patients who are suspected to be seizing, especially those who are paralyzed or heavily sedated, because this can mask the clinical manifestation.

The effect of therapeutic hypothermia on cognitive functioning and neurophysiological outcome was also recently studied in a subset of patient in the HACA study [48,86]. In this cohort,

neuropsychological examination was performed in 45 of the 47 conscious survivors of CA (27 in hypothermia and 18 in normothermia group) 3 months after the injury. The investigators found no differences in demographic variables, depression, or delays related to the resuscitation. They also found no differences in any of the cognitive functions tested; with 67% of patients in hypothermia and 44% patients in normothermia group were cognitively intact or had only very mild impairment. Severe cognitive deficits were found in 15% with hypothermia and 28% with normothermia [86]. This study shows that that use of therapeutic hypothermia was not associated with cognitive decline or neurophysiological deficits in this subset of patients studied.

Management of shivering

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Shivering in response to hypothermia may cause significant disruption of therapy by heat generation leading to an increase in core temperature and increased oxygen consumption [69,76]. Shivering is most prominent during induction; therefore, more attention needs to be provided on the use of sedatives and paralytics during this period. The European and Australian studies used vecuronium as a paralytic agent and intravenous midazolam for sedation [48,49]. The use of sedation and paralysis requires full mechanical ventilatory support; however, these patients are comatose and likely require this level of ventilatory assistance anyway. A detailed neurologic evaluation is essential before initiation of paralysis and sedation, and it should be repeated once the drugs have been discontinued, remembering that patients will clear these agents in variable timeframes. Although no comparison studies exist that formally compared the degree of shivering with the different methods of inducing hypothermia, more patients have been noted to shiver with rapid surface cooling systems [87]. Other agents that have been effective in controlling shivering are meperidine [88–90] and buspirone, which has synergistic properties with meperidine; however, the side-effect profile of the latter drug makes it a poor candidate for use in neurologically impaired patients [91]. In another study the combination of dexmedetomidine and meperidine was also shown to reduce the shivering threshold [92].

Methods of achieving hypothermia

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Cooling can be achieved externally or internally, and methods vary from simple techniques using ice bags and iced lavage, to devices that are designed specifically to induce, maintain, and reverse hypothermia. The technologies used to induce therapeutic hypothermia were recently reviewed [93]. The technologies include various surface cooling devices and intravascular cooling catheters. The surface cooling devices can be divided into selective regional brain cooling and generalized cooling that involves most of the body with a systemic temperature response. Some studies have been undertaken comparing the effectiveness of newer technologies to standard surface cooling. One prospective study comparing a specialized pad for surface cooling [94] and another retrospective study using endovascular cooling catheter [95] found significant stability at maintaining temperature within therapeutic range. Both studies, however, did not provide definite faster cooling rate compared with standard surface cooling. In the absence of definitive studies showing the best method of inducing hypothermia, the decision on the means of cooling is dependent on the treating team. Factors to consider in relation to the technology are the following: the place where hypothermia is initiated (in the field, emergency department, or intensive care unit [ICU]), the capacity of first responders to initiate hypothermia, the rapidity of induction and stability of temperature during treatment, the ability to control rewarming, the portability of the device, specific adverse effects, whether the device hampers provision of care in the critical care environment, and cost.

The ability of infused cold intravenous solutions to decrease core temperature provides another opportunity to induce hypothermia. Several studies have shown the feasibility and safety of cold fluid infusions to reduce core temperature after resuscitation from cardiac arrest. Bernard and colleagues [96] infused 30 mL/kg of ice-cold (4°C) Ringer's lactate solution to cardiac arrest survivors, with a reduction in median core temperature from 35.5°C to 33.8°C. The investigators reported no

hemodynamic, renal, or acid-base complications. No patient developed pulmonary edema. Kim and colleagues [97] showed that an infusion of 2 L of normal saline at 4°C to 17 survivors of out-of-hospital cardiac arrest was safe and effective in decreasing body temperature rapidly by 1.4°C within 30 minutes after the initiation of infusion. This rapid infusion did not affect ejection fraction or increase central venous pressure, pulmonary pressures, or left atrial filling pressures. Intravenous infusion of cold saline is effective in decreasing core temperature, but is not as effective in maintaining it over time; thus, a secondary method to maintain hypothermia is needed. A study of 134 patients by Polderman and colleagues [98] examined the combined effect of a water-circulating cooling blanket and intravenous infusion of 2.3 L (mean) of 4°C saline over 50 minutes. They noted a mean reduction of core temperature from 36.9°C at baseline to 32.9°C at 1 hour. This study showed that induction and maintenance of hypothermia by means of combined cold-fluid infusion and ice-water cooling blankets is quick, safe, and efficacious.

Therapeutic hypothermia and neurologic prognostication

Go to:

The recent practice parameters that were issued by the American Academy of Neurology focused on predictors of poor outcome in patients who were not treated with hypothermia [43]. Although this publication is an important synthesis clarification, critical aspects in the care of these patients remain unresolved. What is the best way to assess brain injury during the early period when it may still be amenable to treatment with hypothermia? Are there neurologic parameters that can identify which patients are most likely to benefit from therapy? Do the prognostic indicators discussed in the practice parameter apply to patients who are treated with hypothermia? For patients who were treated with hypothermia, the existing studies of prognostic indicators have focused on biochemical markers and evoked potentials. A substudy of the HACA trial compared two serum markers, neuron-specific enolase (NSE) and S-100b, in 34 hypothermic and 32 normothermic patients after cardiac arrest [99]. NSE is an enzyme specific to neurons and neuroectodermal cells that is not ordinarily found in serum; it has a half-life of approximately 24 hours. The S-100b protein is a calcium-binding protein that is found predominantly in astroglia and Schwann cells; it has a serum half-life of approximately 0.5 hours. The investigators reported that the NSE concentration was lower in hypothermia-treated patients, but there was no difference in S-100b levels. Survival, recovery of consciousness, and good outcome correlated significantly with decreasing levels of NSE between 24 and 48 hours. Although the investigators identified cut-off values for NSE concentrations that were predictive of poor outcomes, these values differed significantly between the hypothermia and normothermia groups [99].

The effects of hypothermia on SSEPs were studied previously in patients who did not experience cardiac arrest, because SSEP is used often for intra-operative monitoring of patients who are treated with hypothermia during neurosurgical procedures [72]. The median nerve cortical (N20) potential amplitude is unaffected, but the latency is prolonged, in hypothermic patients compared with normothermic patients. A substudy of the European HACA trial examined the prognostic accuracy of SSEPs in 57 patients 24 to 28 hours after cardiac arrest [100]. Thirty patients were treated with hypothermia, and the N20 latency was prolonged in all of these patients. Eleven patients had absent N20 responses (3 hypothermic and 8 normothermic patients), none of which regained consciousness. Despite the small number of patients, this study suggests that SSEP performed 24 to 28 hours after cardiac arrest retains specificity for poor outcomes, even in hypothermic patients [100]. The ability to predict poor outcome after therapeutic hypothermia using SSEPs needs to be confirmed in a larger, prospectively designed study.

Enhancing neuromonitoring in cardiac arrest survivors

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Therapeutic hypothermia demonstrates that brain injury after cardiac arrest can be ameliorated. The implementation of hypothermia as a brain-directed therapy might be slowed by the unavailability of a readily interpretable bedside real-time brain function monitor. The temperature reduction provided

empirically is monitored from the bladder or the heart; the actual effect on the brain as the target organ is not monitored directly. This is a stark contrast to the availability and ease of interpretation of cardiac function using ECG, or pulmonary function using the pulse oximetry in the ICU. While available, bedside neurologic tests, such as the EEG and SSEP, are limited to centers with specialized neuroelectrophysiologic expertise. The importance of brain injury and the need to interpret these tests properly necessitates a closed collaboration with a neurointensivist or neurologists. To truly advance the care of these patients, technologies need to be developed to allow the non-neurologists and other health workers to evaluate the evolution of brain injury. Therefore, SSEP and EEG technologies need to be simplified, automated, and quantified in a manner that is easily interpretable. Recently, the ability of quantitative EEG to track the brain recovery with hypothermia therapy has been investigated in animal studies [101,102] and in humans [103–105]. Continued research is required to determine whether other prognostic indicators retain accuracy in patients who are treated with hypothermia. Recently, much interest has centered on SSEPs to prognosticate in normothermia- and hypothermia-treated patients after cardiac arrest, and suggest the need to adapt and simplify this technology for wider application.

Other neuroprotective measures in the ICU

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Cerebral perfusion

Hypotension after ROSC can worsen cerebral ischemia, and it should be avoided [70]. Microvascular dysfunction and autoregulatory failure are the two main factors that impair cerebral perfusion after cardiac arrest. The identification of cerebral microvascular thrombi following cardiac arrest has suggested the possibility of benefit from thrombolytic therapy, and this has been tested in clinical trials [106,107]. Cerebral perfusion can be compromised further by altered autoregulation of the cerebral vasculature, which has been described as absent or right-shifted in the acute phase in many survivors of cardiac arrest [108]. The clinical implication of this finding is that a patient's mean arterial blood pressure (MAP) may need to be maintained at higher levels to ensure adequate cerebral blood flow [108]. Notwithstanding, there are little data to suggest an optimal blood pressure goal to maintain cerebral perfusion following cardiac arrest. One study indicated that a MAP of greater than 65 mm Hg, which may support adequate coronary perfusion, probably is not sufficient to provide adequate blood supply to the brain, unless other therapies that are designed to decrease cerebral metabolic demand are implemented (eg, sedation, hypothermia) [108]. A MAP of 80 to 100 mm Hg has been suggested to be beneficial, at least for the first 24 hours after arrest [109].

Cerebral edema and increased intracranial pressure

Usually, ICP is not elevated after cardiac arrest [110], but high ICP can compromise cerebral blood flow, and cerebral herniation can cause structural brain damage and death. In comatose patients with evidence of increased ICP, such as clinical signs of herniation or cerebral edema on CT scan, ICP monitoring may be helpful to guide therapies for optimization of ICP and cerebral perfusion pressure [111]. Hypoxia, hypotension, and hypercapnia can worsen brain damage and should be avoided [70]. In the absence of ongoing ICP elevation, prophylactic and long-standing hyperventilation aggravated a wide range of brain injury [70,112]. Therefore, it is suggested that comatose patients be mechanically ventilated to achieve normocapnia [70].

Fever management

Fever may worsen secondary brain damage after cardiac arrest. Each degree over 37°C was correlated with an increased risk for severe disability, coma, or persistent vegetative state [113]. Evidence that temperature elevation worsens outcome makes the need to provide therapeutic hypothermia after cardiac arrest even more significant. In patients who are not deemed candidates for therapeutic

hypothermia as a cerebral protective mechanism, antipyretics and surface or invasive cooling measures should be used aggressively to ensure that the body temperature is less than 38°C.

Hyperglycemia management

Hyperglycemia after ischemic brain injury has been associated with worse outcome [56,114]. Recent studies have shown that tight glucose control in critically ill patients can lead to better outcome [115]. A recent study found a strong association between blood glucose levels at 12 hours after restoration of spontaneous circulation and neurologic recovery over 6 months (Losert and colleagues, 2008 [116]). The favorable neurologic outcome was noted not only in the glucose range of 67 to 115 mg/dL, but also in those with blood glucose levels from 116 to 143 mg/dL [116]. As more clinical trials are needed to clarify the impact of glucose control, it is important to recognize the detrimental effect of hypoglycemia as we control blood glucose levels in cardiac arrest survivors.

Seizure control

Seizures and myoclonus are common after cardiac arrest [117] and the occurrence of status epilepticus is a strong predictor of death [118]. Seizures can be detrimental to recovering brain because of the increased cerebral metabolic demand and elevated ICP. Seizures also can slow recovery of consciousness after resuscitation. Prophylactic antiepileptic drugs are not used commonly; however, if a patient develops seizure activity, it should be treated with standard antiepileptic medications [117]. An EEG should be performed on any patient who is suspected of having seizures, and it should be considered if the patient fails to regain consciousness after resuscitation to rule out nonconvulsive status epilepticus.

Summary

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Brain injury continues to be the leading cause of disability after cardiac arrest, despite seminal advances in intensive care and cardiovascular therapy over the past several decades. Care of these patients can be challenging, and it requires a great deal of medical resources and expense. In addition, dozens of clinical trials of neuroprotective strategies that showed promise in preclinical studies have yielded disappointing results in clinical trials. The emergence of therapeutic hypothermia as a successful neuroprotective measure in comatose survivors of ventricular fibrillation arrest demonstrating benefit in survival and functional outcome measures has created renewed enthusiasm for the amelioration of brain injury in these patients. Several challenges and uncertainties persist about therapeutic hypothermia, including basic understanding of mechanisms of benefit, the optimal depth of hypothermia, timing of initiation of therapy, treatment duration, the best mechanism for achieving hypothermia (internal or external cooling), and the availability of a bedside indicator of brain response to hypothermia. These questions need to be answered by larger series of clinical trials and registry-reported data. Implementation of the American Heart Association and ILCOR recommendations to initiate hypothermia as soon as possible after resuscitation from out-of-hospital ventricular fibrillation arrest has been slow, even in academic medical centers. With a number needed to treat of around six to achieve survival and functional benefits, hypothermia is proving to be an extremely robust and important therapy for cardiac arrest survivors. Hospitals must prioritize establishing hypothermia protocols and systems to improve compliance with treatment recommendations.

Acknowledgments

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Plaintiff

vs.

Childrens' Hospital of Philadelphia
Dr. Charlotte Woods,
John Doe, Jane Doe and Does 1-10

Defendants

COURT OF COMMON PLEAS
OF PHILADELPHIA COUNTY

April Term, 2018

No.:

CERTIFICATE OF SERVICE

The undersigned Petitioner hereby certifies that the foregoing Petition was served upon all necessary persons in the manner, at the address, and on the date stated below:

Service by the court's ECF filing system and/or hand delivery addressed as follows:

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Respectfully submitted,

/s/ CHRISTOPHER F. BAGNATO, ESQUIRE
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