Brain Death and Pitfalls

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Prerequisites Before Determination of Brain Death

- Coma, irreversible and cause known
- Neuroimaging explains coma
- CNS depressant drug effect absent
- No evidence of residual paralysis
- No severe acid-base, electrolyte or endocrine abnormality
- Normal (or near normal) temperature ~ 36°C
- Systolic BP more than 100 mmHg
- No spontaneous respirations on ventilator
Brain Death Examination

- Motor response
- Brainstem reflexes
- Apnea test
- Document time of Death
Abnormal flexion

Extensor response

No response
Apnea (Oxygen-Diffusion) Test

PaCO$_2$ (mm Hg) vs. Duration of apnea (min)
Precautions

• Core temperature
  • ≥36°C

• Systolic BP
  • ≥90 mm Hg

• Fluid balance
  • Positive for 6 hours
Precautions

- Preoxygenate
  - FiO2=1.0 for 10 min
- ↓ ventilation freq
  - 10 breaths/min (tidal vol. 10 mL/kg)
- Arterial blood gas
  - PO2 ≥200 mm Hg
  - PCO2 ≥40 mm Hg
Precautions

• Disconnect ventilator
Procedure

- Catheter at carina
  - 100% O₂ at 6 L/min
- Observe monitor, chest wall and abdominal wall for movement
Procedure

• No respiratory movements for 8 min

• Arterial blood gas
  • If $\text{PCO}_2 \geq 60 \text{ mm Hg}$ or $\text{PCO}_2$ increases $>20 \text{ mm Hg}$

**Brain death**

• Reconnect ventilator
  • 10 breaths/min
Pitfalls
(Drugs)
Warning Signs in Brain Death

- Metabolic acidosis (salicylates, ethylene glycol)
- Hypothermia <30°C (Opioids)
- Marked miosis (heroin or organophosphates)
- Myoclonus or rigidity (lithium, SSRIs)
- Profuse sweating (organophosphates)
- Traces in drug screens
Barbiturates and Alcohol

Phenobarbital 100 hr
Pentobarbital >24 hr
Alcohol 10 mL/hr

→ Below therapeutic range
→ Below legal limit of driving
Therapeutic Hypothermia after CPR
Effects of Hypothermia on the Disposition of Morphine, Midazolam, Fentanyl, and Propofol in Intensive Care Unit Patients

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ABSTRACT

Therapeutic hypothermia (TH) may induce pharmacokinetic changes that may affect the level of sedation. We have compared the disposition of morphine, midazolam, fentanyl, and propofol in TH with normothermia in man. Fourteen patients treated with TH following cardiac arrest (33–34°C) were compared with eight matched critically ill patients (36–38°C). Continuous infusions of morphine and midazolam were stopped and replaced with infusions of fentanyl and propofol to describe elimination and start of infusion pharmacokinetics, respectively. Serial serum and urine samples were collected for 6–8 hours for validated quantification and subsequent pharmacokinetic analysis. During TH, morphine elimination half-life ($\tau_{1/2}$) was significantly higher, while total clearance ($CL_{tot}$) was significantly lower [median [interquartile range (i-q-r)]]: 1.0, 266 (43) versus 160 (11) minutes, $P < 0.01$; $CL_{tot}$, 1201 (283) versus 1867 (206) ml/min, $P < 0.01$. No significant differences were seen for midazolam. $CL_{tot}$ of fentanyl and propofol was significantly lower in hypothermic patients [median (i-q-r)]: fentanyl, 728 (239) versus 1331 (678) ml/min, $P < 0.05$; propofol, 2046 (305) versus 2665 (223) ml/min, $P < 0.05$. Compared with the matched, normothermic intensive care unit patients, $\tau_{1/2}$ of morphine was significantly higher during TH. $CL_{tot}$ was lower during TH for morphine, fentanyl, and propofol but not for midazolam. Reducing the infusion rates of morphine, fentanyl, and propofol during TH is encouraged.

Introduction

Two pivotal studies have established the efficacy of treating comatose survivors of cardiac arrest with therapeutic hypothermia (TH) (33–34°C for 12–24 hours) (Bernard et al., 2002; Hypothermia after Cardiac Arrest Study Group, 2002; Peberdy et al., 2010). Patients treated with TH are given sedatives and analgesics to tolerate mechanical ventilation and to avoid disturbing. Continuous infusions of morphine, fentanyl, midazolam, and propofol are among the most commonly used drugs for analgesia and sedation at the intensive care unit (ICU) (Payen et al., 2007).

Hypothermia can induce significant physiologic changes that affect drug disposition and action through changes in both metabolism and distribution (Kadar et al., 1982; Koren et al., 1987; Bansinath et al., 1988; Alcoraz et al., 1989; Beaumont et al., 1995; Leslie et al., 1995; Aouikamar et al., 1998; Caldwell et al., 2006; Fatusitska et al., 2004; Trottier et al., 2007; Arpino and Greer, 2008; Polderman, 2009). Reduced metabolism due to changes in enzyme activity during hypothermia may increase drug serum levels, and thus drug effects and duration of action (Polderman, 2004; Arpino and Greer, 2008). However, the effects of hypothermia on the activity of different enzymes vary; whereas 10°C lower temperature reduced cytochrome P450 (P450) activity to diuron by 22%, conjugation of oxazepam was reduced by only 14% (Mortensen and Dale, 1995). In addition, whereas CYP2A and CYP2E activity as measured by clearance of midazolam and chlorzoxazone was approximately 50 and 66% lower in rats given cardiac arrest and TH compared with the control group, no differences were demonstrated for CYP2C/D (Zhou et al., 2011). This substrate specificity implies that the effects of hypothermia on pharmacokinetics (PK) may vary between drugs (Mortensen and Dale, 1995; Zhou et al., 2011; Zhou and Polsebac, 2011).

Morphine is metabolized by uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), but to our knowledge, no studies on the effect of hypothermia on isolated UGT2B7 exist. In animals, reduced glucuronidation and increased serum concentrations are consistent with results from monkeys, who had approximately 40% higher serum concentrations and 23% reduced clearance at 33–34°C compared with

Abbreviations: CaL, calibration standard; $CL_{tot}$, total clearance; $CL_{e}$, renal elimination clearance; $CL_{st}$, steady-state concentration; GCS, Glasgow Coma Scale; ICU, intensive care unit; IS, internal standard; $\lambda_\lambda$, elimination rate constant; LOQ, limit of quantitation; MGD, morphine-3-glucuronide; MG6, morphine-6-glucuronide; MA4S, Motor Activity Assessment Scale; MAP, mean arterial pressure; MP, mobile phase; OH-midazolam, $\alpha$-hydroxy-midazolam; P450, cytochrome P450; PK, pharmacokinetics; QC, quality control; SAPS II, Simplified Acute Physiology Score II; i-q-r, semi-interquartile range; $\tau_{1/2}$, start of the pharmacokinetic study period; TH, therapeutic hypothermia; UGT2B7, uridine diphosphate glucuronosyltransferase 2B7.
## Estimates in Clearance Change in Drugs Used in Hypothermia for Cardiac Arrest

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent per 1°C decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>11</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>6.3</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>11.3</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>6</td>
</tr>
<tr>
<td>Propofol</td>
<td>8</td>
</tr>
</tbody>
</table>
SYSTEMATIC REVIEW

The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis

Claudio Sandroni, Sonia D’Arrigo, Clifton W. Callaway, Alain Cariou, Irina Dragancea, Fabio Silvio Taccone and Massimo Antonelli

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Meta-Analysis 2002-2016 of CPR

• 274 studies
  • 217 studies brain death not mentioned or excluded

• 26 studies
  • Duration cardiac arrest mean 42 minutes
  • 5% in conventional CPR and 9% in ECMO CPR
Pitfalls
(Spinal reflexes)
Spinal Reflexes
Brain Death and Spinal Reflex (Triple Flexion Response)
Pitfalls
(Apnea test)
Apnea Test

Disconnection ventilator

6 L O₂ transtracheal

Breathing Tv 400 mL/f10

PCO₂

Minutes

0 5 10 15
Our Experience With Apnea Testing  
n=228

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically unstable</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Apnea test aborted</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Mild hypoxemia</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Factors Associated with Aborting the Apnea Test

- T piece oxygen administration
- High flow oxygen (>10 L/min)
- High A-a gradient (>300)
- Hypotension (≤90 systolic blood pressure)
- Chest tubes for pneumothorax
Try or not?
A Last Resort Method?

- Gradual recruitment to PEEP of 25 cm H₂O
- FiO2 of 1
- Every 3 minutes

- Oxygen flow 6L/min
- 20 cm H₂O CPAP valve connected to a self inflating bag
Pneumothorax as a Complication of Apnea Testing for Brain Death

Lauren Elizabeth Gorton1 · Rajat Dhar2 · Lindsey Woodworth3 · Nitin J. Anand2 · Benjamin Hayes2 · Joanna Isabelle Ramirez2 · Abhay Kumar3

Abstract

Background Pneumothorax is an under-recognized complication of apnea testing performed as part of the neurological determination of death. It may result in hemodynamic instability or even cardiac arrest, compromising ability to declare brain death (BD) and viability of organs for transplantation. We report three cases of pneumothorax with apnea testing (PAT) and review the available literature of this phenomenon.

Methods Series of three cases supplemented with a systematic review of literature (including discussion of apnea testing in major brain death guidelines).

Results Two patients were diagnosed with PAT due to immediate hemodynamic compromise, while the third was diagnosed many hours after BD. An additional nine cases of PAT were found in the literature. Information regarding oxygen cannula diameter was available for nine patients (range 2.3–5.3 mm), and flow rate was available for ten patients (mean 11 L/min). Pneumothorax was treated in the majority of patients (n = 8), although only six completed apnea testing following diagnosis/treatment of pneumothorax and only three patients became organ donors afterward. Review of major BD guidelines showed that although use of low oxygen flow rate (usually ≤ 6 L/min) during apnea testing is suggested, the risk of PAT was explicitly mentioned in just one. Conclusion Development of PAT may adversely affect the process of BD determination and could limit the opportunity for organ donation. Each institution should have preventive measures in place.

Keywords Pneumothorax · Apnea testing · Brain death examination · Organ donation

Introduction

An apnea test is a critical component of the neurological determination of death. This requires disconnecting the patient from the ventilator while allowing hypoxemia to develop in the absence of spontaneous respirations. Hypoxemia and hypotension are well-recognized complications of apnea testing [1, 2]. Preventive strategies such as preoxygenation and inflation of oxygen into the endotracheal tube (ETT) during testing have been suggested to decrease the incidence of hypoxemia [3]. If the administered gas inadequately diffuses out of the lungs, either due to exclusion of the ETT or from high rates of administration, then it can result in increased tension in the lungs causing pneumothorax. The development of pneumothorax during apnea testing (PAT) is felt to be relatively rare, and many practitioners who perform apnea testing may not be aware of the possibility of this complication. However, its occurrence can be dramatic; it can result in acute hemodynamic or pulmonary instability and even cardiac arrest. This may lead to prematurely aborting the apnea test or critical hypoperfusion of viable organs that may be otherwise utilized for transplantation after death. Only prompt recognition that worsening cardiopulmonary dysfunction is
PNEUMOTHORAX

• High oxygen flows (>6 L/min) or catheters pushed too far into the bronchial tree and wedged into a branch may trap gas

• Insertion of a catheter with sharp endings (when cut) may damage the bronchial wall.

• High flows can cause dangerous wiggle in a catheter that has no side ports.
OXYGEN CATHETER FLOW AND WHIPPING
I Declared A Patient Brain Death

Phone call at night  6 hours later

“Patient triggers the ventilator”
DAWN OF THE DEAD
WHEN THERE'S NO MORE ROOM IN HELL
THE DEAD WILL WALK THE EARTH.
Ventilator self-cycling may falsely suggest patient effort during brain death determination

Eelco F.M. Wijdicks, MD; Edward M. Manno, MD; and Steven R. Holets, RTT

Brain death is suspected when a patient with a destructive neurologic brain injury on a ventilator fails to generate respirations and other brainstem reflexes are absent. An apnea test is mandated in brain-death evaluation. Apnea is concluded when no breathing effort is observed at PaCO₂ of 60 mm Hg or with a 20 mm Hg increase from normal baseline.¹ There are no reported cases of adult patients who were declared brain dead and later initiated respirations. Two cases from the U.K. (brain death and cardiac death) have been described where the ventilator readings were erroneous but remotely suggested patient effort.²,³ We have recently come across several instances during brain-death determination when it appeared that patients falsely triggered the ventilator. We would like to call attention to this phenomenon of ventilator self-cycling.
“Over-breathing ventilator”

Disconnection apnea test

Decrease flow sensitivity

Switch to pressure sensitivity

Find cause/ troubleshoot

Cardiac oscillations

Water in circuit

Leaks
Mistakes and Brain Death
Potential donor was wrongly declared brain-dead, data show

The apparent close call is the second in recent months to raise questions about whether, amid a national organ shortage, doctors might be compromising the care of prospective donors. Law enforcement authorities in San Luis Obispo County are investigating whether a transplant surgeon tried to hasten the death of a 36-year-old patient last year by ordering high volumes of pain medication.

Contacted Wednesday, Community Medical Center's spokesman John Zellem characterized Foster's case as "unusual" and said it "wouldn't surprise me" if the medical staff launched an internal review.

"This hasn't fully played out yet," he said. National experts said they believe that it is uncommon for a patient to be declared brain-dead incorrectly. But the ramifications are great, they said, both for the potential donors and for the integrity of the organ donation process.

"It's one of those things that is pretty spooky when it happens," said Dr. Michael A. Williams, chairman of the ethics committee of the American Academy of Neurology. "It's a rare, but high-stakes, error." Williams, a professor of neurosurgery and internal medicine at the University of Texas Health Science Center at Houston. "It only takes one or two of those situations to really sour the public and sour people upon whom we depend so much for donation."

Brain death means that a person has suffered a total and irreversible loss of brain function. The patient is comatose, cannot breathe without support and lacks自主性. It is often determined by a mixture of physical examination and clinical tests, and meets the legal standard for death.

There are no national criteria for declaring brain death, but California law requires that two physicians independently verify the condition and that those physicians not have any role in procuring the patient's organs. Organs cannot be retrieved until a patient is declared legally dead.

Foster, an auto mechanic, collapsed Feb. 18 and was diagnosed with an inoperable Penfield bleed, a catastrophic hemorrhage in his brain stem with almost no hope of recovery. Hours later, hospital personnel alerted the California Transplant Donor Network — the organ procurement group for much of Central and Northern California — that he was a potential candidate for organ donation. Such notification is routine.

After Sanchez agreed to donate, she said, she got calls "at least twice a day" from the organ group, saying: "We have to get the body parts in a certain time. Your dad can be a life-saver to someone else. How is he doing today? Did he go up or down?"

In the afternoon of Feb. 21, it seemed the end had arrived for Foster. First, one doctor declared him brain-dead, according to confidential internal records kept by the organ group and reviewed by The Times. Then, a couple hours later, a second doctor, an emergency physician, shined a light on his pupils and agreed. With two such declarations, Foster was legally dead under California law.

Sanchez said she was concerned because the second doc
tor seemed in a rush.

3rd opinion sought

After the exam, Sanchez re
called, "he just came in and threw the paper on my dad's legs and said, 'We got two signatures. We're pulling the plug.' He said, 'That's hospital policy.'"

She said she demanded a third opinion.

About the same time, a nursing supervisor asked the family to leave the room and did her own examination, the organ group's records show. Foster displayed a strong gag and cough reflex and slightly moved his head, all inconsistent with brain death. She shared her concerns with physicians.

The third doctor, neurosurgeon Makoto Mura, determined that Foster was not brain-dead and supported Sanchez's decision not to remove her father from life support, records show.

Mura declined to comment on his colleagues' actions, but said, "I know what I did was right."

Dr. Robert Grazer, the sec
dond physician who declared Fos
ter brain-dead, acknowledged that he performed a brief examina
tion. "I examined the patient and I confirmed the first doctor's findings that were made. That was about it," Grazer said.

"My involvement in it was pretty minimal," he said.

The Fresno hospital's policy does not specify how long a physi
cian must spend examining a patient nor what tests the doctor should order. It only says that the doctor must write his find
ings in the patient's chart.

Williams, the ethics expert, said he sets aside 30 to 45 min
tutes to perform a brain-death examination or confirmation exam. Told of notes in Foster's record, he said, "If the documenta
tion is correct, they should never ever have considered the possibility of brain death for that patient. That's not even close."

Phyllis Weber, executive di
ger of the California Transplant Donor Network, said the donation would not have pro
ced anyway because her organ procurement staff also had concerns about whether the pa
tient was brain-dead.

"They do a careful examination, and if there's any questions, the process gets halted until all their questions are resolved," Weber said. "The public should be really grateful that that happen
e.

If her staff had concerns, howev
er, they were not reflected in the confidential case notes kept by the donor network.

She said she was sorry to hear that Sanchez felt pressured. Other family members told The Times that they did not feel co
erced, although the ultimate de
cision was Sanchez's.

"It's certainly not our position to pressure families to make this decision," Weber said. "We have people who are very trained, have a great deal of ex
erience, and we give families a lot of time."

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THE PERFECT STORM

Inexperienced physicians
Misjudgement confounders
Incomplete evaluations
Misinterpretation confirmatory tests
Pitfalls (Don’ts)

- Do not proceed if there could be a lingering effect of a sedative drug
- Do not proceed in the emergency department
- Do not use ancillary tests to solve your uncertainties
- Do not perform an examination if you have to look it up and just ask somebody else