Pediatric Neurology 93 (2019) 17–20

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Use of Venous P_{CO_2} in Determination of Death by Neurological Criteria in Children

Alireza Fathi, MD, MBA [a, *], Jean L. Lake, MD [b]

[a] Pediatric Critical Care Unit, Miller Children's & Women's Hospital of Long Beach, Long Beach, California
[b] Pediatric Neurology, Miller Children's & Women's Hospital of Long Beach, Long Beach, California

ARTICLE INFO

Article history:
Received 18 August 2018
Accepted 2 December 2018
Available online 19 December 2018

Keywords:
Apnea challenge test
Death by neurological criteria
Brain death examination
Venous carbon dioxide
Arterial carbon dioxide

ABSTRACT

Background: Compare the increase in partial pressure of carbon dioxide (P_{CO_2}) from venous blood samples with that of arterial blood samples during apnea challenge test in determination of death by neurological criteria.
Methods: Prospective nonrandomized cohort study in tertiary care pediatric intensive care unit. Patients older than 37 week's gestation admitted to PICU with irreversible brain injury at the time when attending physician will perform apnea challenge test as part of brain death examination from October 2015 till September 2017.
Interventions: None.
Results: The primary outcome was to measure and compare the increase in P_{CO_2} from venous blood samples with that from arterial blood samples during apnea challenge test. A total of nine apnea challenge tests from seven patients (ages five months to 17 years) were included in the study. P_{CO_2} in venous blood sample increased less than that in arterial blood samples (venous, 26.1 mm Hg; S.D., 10.1; 95% confidence interval, 18 to 34 mm Hg; arterial, 33.9 mm Hg; S.D., 12.0; 95% confidence interval, 24 to 43 mm Hg) ($P = 0.02$).
Conclusion: Postapnea challenge test P_{CO_2} of 60 mm Hg along with increase of 20 mm Hg in venous blood sample correlated to P_{CO_2} greater than 60 mm Hg along with increase of greater than 20 mm Hg in arterial blood sample. Further studies are warranted to assess if current recommendations for determination of death by neurological criteria in children can be modified to allow for use of venous blood samples as an alternate to arterial blood samples.

In 1981, The President's Commission report on guidelines for brain death (death by neurological criteria) examination resulted in the Uniform Determination of Death Act.[1] This act stated "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination must be made with accepted medical standards."

Since the first published guidelines, there has been much debate about the "accepted medical standard," and as such there remain considerable practice variations both in adult[2] and pediatric practitioners.[3]

One required examination for brain death examination is the apnea challenge test. Apnea challenge test evaluates the medulla brainstem respiratory center response to a rise in carbon dioxide partial pressure (P_{CO_2}). The current guideline requires arterial sampling of P_{CO_2} and therefore either arterial puncture or arterial catheter placement for the examination.

An arterial catheter is an invasive monitoring device and its insertion is not without complications.[4] Placement of the arterial catheter in pediatric patients is also more difficult because of the smaller diameter of their radial and femoral arteries.[5]

It has been demonstrated that there is a direct correlation between peripheral venous and arterial blood gas measures and that venous P_{CO_2} measures may be used as alternatives to arterial P_{CO_2} measures.[6] The primary objective of our study was to examine if venous blood sampling during the apnea challenge test can

Conflicts of interest: None.

* Communications should be addressed to: Fathi MD, MBA; Pediatric Intensive Care Unit; Miller Children's & Women's Hospital of Long Beach; 2801 Atlantic Avenue; Long Beach, CA 90806.
E-mail address: Afathi@memorialcare.org (A. Fathi).

https://doi.org/10.1016/j.pediatrneurol.2018.12.001
0887-8994/

TABLE 1.
Patient Characteristics

Patient	Age	Gender	Underlying Condition
01	<1 year	Male	Enterovirus pneumonia, respiratory arrest
02	16 years	Male	Intracranial hemorrhage
03	<1 year	Male	Asphyxia, cardiac arrest
04	12 years	Female	Arteriovenous malformation, intracranial bleed
05	1 year	Male	Abusive head injury, cerebral edema
06	3 years	Male	Asphyxia, cardiac arrest
07	<1 year	Male	Subdural hematoma, cerebral edema

substitute arterial blood sampling. To achieve this theory, we postulated that the increase in venous blood P_{CO_2} is less than arterial blood P_{CO_2}. This would suggest that when venous P_{CO_2} is 60 mm Hg and has increased by 20 mm Hg after apnea challenge test, the arterial P_{CO_2} is greater than 60 mm Hg and has increased by more than 20 mm Hg.

Methods

This study was reviewed and approved by the Institutional Review Board of Memorial Health System. Informed consent was obtained before enrollment in the study.

Children admitted to pediatric intensive care unit (PICU) from October 2015 till September 2017 with irreversible brain injury and with the intent of the attending physician to perform brain death examination were screened for eligibility. Inclusion criteria included age greater than 37 weeks' gestation, irreversible brain injury with the intent of the attending intensivist to perform apnea challenge test, presence of arterial catheter or arterial blood sampling during apnea challenge test, and presence of central venous catheter. Our exclusion criteria included age less than or equal to 37 weeks' gestation at the time of examination, inability to perform apnea challenge test as determined by attending physicians, and family request for organ donation after cardiac death.

Study design

This was a prospective nonrandomized cohort study. Before brain death examination, the family was approached for obtaining consent. If the attending physician believed that the family was having an extremely difficult time coping with their child's death, they were not approached for the study.

The attending physician performed apnea challenge test in accordance with our hospital policy. All the blood gases were measured using the Abbott i-STAT blood gas analyzer. Patients were preoxygenated for 10 minutes with 100% fraction of inspired oxygen. Baseline arterial and venous blood gas were obtained simultaneously. Active mechanical ventilation was stopped while a catheter inserted in the oral cavity provided 100% fraction of inspired oxygen. During the apnea challenge period, patients were monitored for any spontaneous respiratory effort. Vital signs and oxygen saturations were monitored continuously. After eight to 10 minutes if no spontaneous respiratory effort was seen, arterial and venous blood gas samples were drawn simultaneously and patient was placed back on mechanical ventilation.

A positive apnea challenge test required no respiratory effort during the apnea challenge test and an arterial P_{CO_2} of greater than or equal to 60 mm Hg with a minimal increase of 20 mm Hg from the preapnea level. If the required value for arterial PCO_2 was not reached after eight to 10 minutes, the attending physician could do another apnea period for additional five minutes or perform further testing, such as electroencephalography.

Statistical analyses

Our alternative hypothesis stated that P_{CO_2} in venous blood samples increased more than arterial blood samples. To reject the null hypothesis of similar rise in average P_{CO_2} using the two methods a paired *t* test was performed, which required a two-sided *P* value of <0.05. Consistency of results using the two methods in measuring P_{CO_2} on a continuous scale was assessed by calculation of the intra-class correlation coefficient (ICC). As the two methods currently represent the only methods (raters) of interest, the ICC was computed by fitting a two-way mixed model wherein measure effects were fixed and patient effects were random (i.e., considered from a larger population). Furthermore, agreement between the two methods in terms of threshold value rise in $P_{CO_2} \geq 20$ versus < 20 mm Hg was also assessed by evaluation of the percent agreement and kappa statistic. IBM SPSS V18.0 was used to calculate mean values and the ICC statistic, whereas percent agreement and the kappa statistic were produced using Microsoft Excel AgreeStat2015.6.

Results

A total of 15 patients were eligible and screened for the study. Informed consent was obtained for seven patients (Table 1).

Blood gas values are shown in Table 2. Patient 2 did not have the required 20 mm Hg rise in arterial P_{CO_2} after eight minutes of apnea challenge (2a). Apnea challenge was repeated for 15 minutes, and arterial P_{CO_2} increased above the required 20 mm Hg (2b). Patient 3

TABLE 2.
Changes in Arterial and Venous From Baseline

Patient	Pre-$Paco_2$	Post-$Paco_2$	Rise in $Paco_2$	Pre-$Pvco_2$	Post-$Pvco_2$	Rise in $Pvco_2$	Apnea Time (min)
1	38	69	31	33	63	30	7
2a	44	61	17	47	61	14	8
2b	49	98	49	54	85	31	15
3a	36	71	37	36	69	33	8
3b	46	86	40	54	85	31	5
4	43	85	42	36	64	28	8
5	49	73	24	48	64	16	8
6	50	68	18	51	62	11	4
7	38	85	47	39	80	41	8
Mean (S.D.)	43.7 (5.3)	77.6 (11.6)	33.9 (12.0)	44.2 (8.3)	70.3 (10.1)	26.1 (10.1)	7.9 (3.1)
% Rise > 20			77.8%		66.7%		

Pre-$Paco_2$: partial pressure of arterial co_2 prior to apnea challenge test. Post-$Paco_2$: partial pressure of arterial co_2 at the end of apnea challenge test. Pre-$Pvco_2$: partial pressure of venous co_2 prior to apnea challenge test. Post-$Pvco_2$: partial pressure of venous co_2 at the end of apnea challenge test.

TABLE 3.
Consistency of Results Using Arterial Compared With Venous Measurement

Dichotomous Scale Rise in P_{CO_2} > 20 vs ≥ 20 mm Hg		Continuous Scale P_{CO_2}
% Agreement (95% CI), *P* value	Kappa (95% CI), *P* value	ICC* (95% CI), *P* value
0.89 (0.65, 1.00), *P* < .001	0.73 (0.16, 1.00) *P* = .019	0.88 (0.57, 0.97) *P* < .001

Abbreviations:
CI = Confidence interval
ICC = Intraclass correlation coefficient
* The ICC determined consistency between the two methods of measuring P_{CO_2} on continuous scale.

became hypoxic after five minutes (3b); after patient was preoxygenated for additional 30 minutes the test was repeated (3a). Patient 6 became significantly hypoxic and hypotensive after four minutes of apnea challenge and did not meet the required 20 mm Hg increase in arterial P_{CO_2}.

On average, venous P_{CO_2} increased by 26.1 mm Hg (S.D. = 10.1, 95% confidence interval [CI], 18.4 to 33.9 mm Hg), whereas arterial P_{CO_2} increased by 33.9 mm Hg (S.D. = 12.0; 95% CI, 24.6 to 43.1 mm Hg). The average increase of P_{CO_2} in venous blood sample was significantly less than that of the arterial blood samples ($t_{(df = 8)} = 4.34$, $P = .002$). However, postapnea venous P_{CO_2} of 60 mm Hg and an increase of 20 mm Hg corresponded with an arterial P_{CO_2} of greater than 60 mm Hg and an increase of greater than 20 mm Hg (percent agreement = 0.89 [0.65, 1.00], $P < .001$). Furthermore, the increase in venous P_{CO_2} during apnea challenge test correlated with the increase in arterial P_{CO_2}, showing consistency of results between the two methods (ICC = 0.88; 95% CI, 0.57, 0.97; $P < .001$) (Table 3). Removal of repeat measurement within two patients did not significantly alter the aforementioned findings (Tables 4 and 5).

Discussion

Since the first efforts to define a new diagnosis for death by the Ad Hoc Committee of Harvard Medical School in 1968,[7] there have been multiple modifications by the American Academy of Neurology and the American Academy of Pediatrics, including efforts to enable the diagnosis of brain death (death by neurological criteria) in children.[8-10] Today, over 20% of all pediatric deaths are diagnosed by neurological criteria.[10]

In the current guidelines, apnea challenge test is an integral part of brain death examination.[8-10,11] It is recommended that patients be pre-oxygenated before examination. The rise of arterial P_{CO_2} during the apnea challenge test is used to diagnose irreversible medullary respiratory centers' loss of function. Although this theory has not been validated, in the United States the threshold for respiratory center stimulation has been arbitrarily set at P_{CO_2} of 60 mm Hg and a value that is 20 mm Hg higher than the normal baseline.[12,13] In the United Kingdom, this arbitrary value is set at arterial P_{CO_2} of 50 mm Hg.[14]

Based on these guidelines, only an increase in P_{CO_2} from arterial blood samples can be used for an apnea challenge test. Not all children who have had brain hypoxia have hemodynamic instability and require arterial catheters. In fact, with the advances in pulse oximeter and its use as the fifth vital sign, there has been a decreased need for arterial catheter placements in the PICU.[15] Even pediatric acute lung injury and acute respiratory distress syndrome can be diagnosed with pulse oxygen saturation index and without the use of arterial blood samples.[16] Yet, once the decision is made to proceed with brain death examination, patients will require either arterial catheter placement or timely arterial puncture for apnea challenge test. Placement of arterial line catheter can be challenging in critically ill children. It is not uncommon to have more than one attempt at more than one site before successfully cannulating the artery. In children, use of ultrasound has not demonstrated any benefit for radial artery cannulation.[17]

This is the first study to evaluate the use of venous P_{CO_2} for apnea challenge test. In our study, we were able to show that the increase in venous P_{CO_2} was always less than the increase in arterial P_{CO_2} (26.1 mm Hg versus 33.9 mm Hg; $P < 0.03$). In addition, the postapnea arterial P_{CO_2} was always greater than the venous P_{CO_2} ($P < 0.03$) (Fig). These findings suggest when venous P_{CO_2} increases by 20 mm Hg and is above 60 mm Hg, the arterial P_{CO_2} during the same time interval will increase by greater than 20 mm Hg and be greater than 60 mm Hg.

Death of a child is one of the most devastating and challenging times for parents and is associated with an intense emotional stress and grief.[18,19] The intensity and chronicity of parental bereavement can be influenced by events surrounding their experience in the PICU.[20] During these difficult times, to perform the apnea challenge

TABLE 4.
Changes in Arterial and Venous From Baseline (Seven Apnea Samples)

Patient	Pre-P_{aCO_2}	Post-P_{aCO_2}	Rise in P_{aCO_2}	Pre-P_{vCO_2}	Post-P_{vCO_2}	Rise in P_{vCO_2}	Apnea Time (min)
1	38	69	31	33	63	30	7
2b	49	98	49	54	85	31	15
3b	46	86	40	54	85	31	5
4	43	85	42	36	64	28	8
5	49	73	24	48	64	16	8
6	50	68	18	51	62	11	4
7	38	85	47	39	80	41	8
Mean (S.D.)	44.7 (5.2)	80.6 (11.0)	35.9 (11.8)	45.0 (8.8)	71.9 (10.9)	26.9 (10.1)	7.9 (3.5)
% Rise ≥ 20			85.7%		71.4%		

Restricted to one observation per patient (selected measurement "b" for two patients where relevant—checked for undue weighting/bias of repeat measurement within patient). Consistency measurements were similar after removal of repeat measurements within two patients.
Pre-P_{aCO_2}: partial pressure of arterial CO_2 prior to apnea challenge test. Post-P_{aCO_2}: partial pressure of arterial CO_2 at the end of apnea challenge test. Pre-P_{vCO_2}: partial pressure of venous CO_2 prior to apnea challenge test. Post-P_{vCO_2}: partial pressure of venous CO_2 at the end of apnea challenge test.

TABLE 5.
Consistency of Results Using Arterial Compared With Venous Measurement (Seven Apnea Samples)

Dichotomous Scale Rise in P_{CO_2} ≥20 vs <20		Continuous Scale P_{CO_2}
% Agreement (95% CI), *P* value	Kappa (95% CI), *P* value	ICC* (95% CI), *P* value
0.86 (0.53, 1.00), $P < .001$	0.59 (0, 1.00) $P = .141$ Kappa may be unstable due to small numbers and 0 cell value *Gwet's AC_1 alternative measure of agreement:* 0.78 (0.24, 1.00), $P = .012$	0.87 (0.43, 0.98) $P = .002$

Abbreviations:
CI = Confidence interval
ICC = Intraclass correlation coefficient
* ICC determined consistency between the two methods of measuring P_{CO_2} on continuous scale.

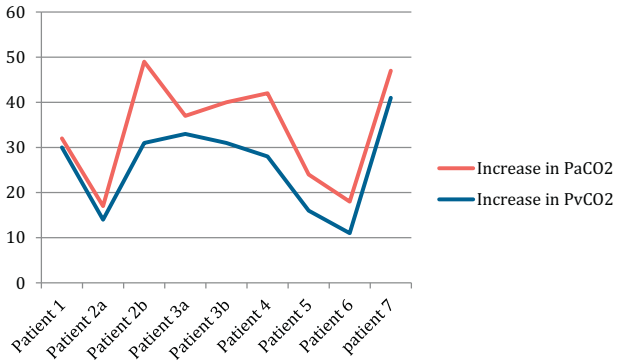

FIGURE. At the completion of apnea challenge test, the increase in venous P_{CO_2} was always less than the increase in arterial P_{CO_2}. The color version of this figure is available in the online edition.

test, if an arterial catheter is not yet in place, parents are asked to leave their dying child while at times multiple attempts are made for placing the arterial catheter. Our study shows that venous blood samples can potentially be used for apnea challenge test in determination of death by neurological criteria in children.

Several limitations for our study are noteworthy. First, our sample size was small. Not all parents were approached for the study; specifically if the attending physician believed that the parents had a very difficult time coping with their dying child. Second, as the increase in arterial carbon dioxide partial pressure is set arbitrary, we only looked at comparing these arbitrary increase values with that of venous carbon dioxide partial pressure. It is possible that a much less increase in venous carbon dioxide partial pressure is in fact needed for the apnea challenge test. Third, as venous carbon dioxide partial pressure increased less than arterial carbon dioxide partial pressure, some of the apnea challenge tests might require longer time to achieve the required increase in value if venous blood samples are used.

Conclusions

Our pilot study shows that during apnea challenge test for determination of death by neurological criteria in children, P_{CO_2} of 60 mm Hg along with increase of 20 mm Hg in venous blood sample correlated with P_{CO_2} of greater than 60 mm Hg along with increase of greater than 20 mm Hg in arterial blood sample. Further studies with larger sample size are warranted to assess if current recommendations for determination of death by neurological criteria in children can be modified to allow for use of venous blood samples as alternate to arterial blood samples.

Funding: Funding for this study was provided by Memorial Health System (MHS).

References

1. Barclary WR. Guidelines for the determination of death: report of the medical consultants on the diagnosis of death to the President's commission for the study of ethical problems in medicine and biochemical and behavioral research. JAMA. 1981;246:2184–2186.
2. Wijdicks EFM, Varelas NP, Gronseth SG, et al. Evidence-based guideline update: Determining brain death in adults. Neurology. 2010;74:1911–1918.
3. Mathur M, Ejike JC, Petersen F, et al. Variations in brain death determination practices in children in southern California. CritCare Med. 2005.
4. Bernd VS, Azriel P, Ulrich JP. Clinical review: Complications and risk factors of peripheral arterial catheters used for hemodynamic monitoring in anesthesia and intensive care medicine. CritCare. 2002;6:199–204.
5. King MA, Garrison MM, Vavilala MS, et al. Complications associated with arterial catherization in children. PediatrCritCare Med. 2008;9:367–371.
6. Kim BR, Park SJ, Shin HS, et al. Correlation between peripheral venous and arterial blood gas measurements in patients admitted to the intensive care unit: A single-center study. Kidney ResClinPract. 2013;32:32–38.
7. Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, AD. "A Definition of Irreversible Coma.". JAMA. 1968;205:337–340.
8. Annas GJ, Bray PF, Bennett DR, et al. Task Force for the Determination of Brain Death in Children. Guidelines for the determination of brain death in children. ArchNeurol. 1987;44:587–588.
9. Nakagawa TA, Ashwal S, Mathur M, et al. Clinical report-Guidelines for the determination of brain death in infants and children: An update of the 1987 Task Force recommendations. Pediatrics. 2011;128:e720–e740.
10. Burns PJ, Sellers ED, Meyer CE, et al. Epidemiology of death in the pediatric intensive care unit at five U.S. teaching hospitals. CritCare Med. 2014;42:2101–2108.
11. Lang CJG, Heckmann JG. Apnea testing for the diagnosis of brain death. Lancet Neurol. 2005;112:358–369.
12. Joffe AR, Anton NR, Duff JP. The Apnea Test: Rationale, Confounders, and Criticism. JChild Neurol. 2010;25:1435–1443.
13. Wijdicks EF. The diagnosis of brain death. N Engl J Med. 2001;344:1215–1221.
14. Harman MJ. Academy of Medical Royal Colleges.A code of practice for the diagnosis and confirmation of death. London: PPG Desgin and Print Ltd; 2008.
15. Mower WR, Sachs C, Nicklin EL, et al. Pulse oximetry as a fifth pediatric vital sign. Pediatrics. 1997;99:681–686.
16. Thomas NJ, Shaffer ML, Wilson DF, et al. Defining acute lung disease in children with the oxygen saturation index. PediatrCritCare Med. 2010;11:12–17.
17. Ganesh A, Kaye R, Cahill AM, et al. Evaluation of ultrasound-guided radial artery cannulation in children. PediatrCritCare Med. 2009;10:45–48.
18. Middleton W, Raphael B, Burnett P, et al. A longitudinal study comparing bereavement phenomena in recently bereaved spouses, adult children and parents. AustNewZealand J Psychiatry. 1998;32:234–241.
19. Meert KL, Thurston CS, Sarnaik AP. End of life decision-making and satisfaction with care: Parental perspectives. PediatrCritCare Med. 2000;1:179–185.
20. Meert KL, Thurston CS, Thomas R. Parental coping and bereavement outcome after the death of a child in the pediatric intensive care unit. PediatrCritCare Med. 2001;2:324–328.