Original Article

Problems associated with the apnea test in the diagnosis of brain death

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Background: Brain death is the absence of all cortical functions, including the brainstem. The apnea test (AT) is a necessary requisite to complete this diagnosis. Anecdotal reports describing hypotension and acidosis due to apnea test have been reported. However, there are few studies that evaluate complications or difficulties related to this procedure. **Objective:** To analyze medical problems associated with the apnea test. **Methods and Patients:** We analyzed clinical features, potential risk conditions, and problems in 129 brain dead patients during the apnea test. The diagnosis of brain death was made according to the American Academy of Neurology recommendations. **Results:** Clinical problems during the apnea test were detected in more than two thirds of patients, including: arterial hypotension (12%), acidosis (68%), and hypoxemia (23%). Four patients developed major complications, including: pneumothorax, cardiac arrest, bradycardia, atrial fibrillation and myocardial infarction. **Conclusion:** The apnea test is not an innocuous procedure. Complications during the AT are more common than reported and limit organ procurement for transplantation. Guidelines for performing the AT should be followed in order to avoid clinical complications.

Key Words: Apnea test, brain death, complications, hypotension, cardiac arrhythmia, pneumothorax, movements

Background

Brain Death (BD) has been subject of debate in the last decade.[1,2] This diagnosis has a broad spectrum of legal, religious, philosophical, ethical, and medical implications. BD has been defined as the irreversible cessation of cerebral functions, including the brainstem. Definition of BD challenged according to the used criteria. Since 1981 several criteria's have been proposed to determine this diagnosis varying from one country to another. The most widely accepted criteria to determine BD are the guidelines of the American Academy of Neurology (AAN), which include: unresponsiveness or coma, absence of brainstem reflexes, and apnea.[1] The apnea test (AT) is a mandatory criteria to establish the diagnosis of BD. The goal of this procedure is to document the absence of breath once pCO2 arise the appropriate level to stimulate the respiratory center. Nevertheless, this procedure is not innocuous since hypotension, hypoxia or acidosis may occur while performing this practice. As known, hemodynamic and metabolic changes limit the tissue perfusion, the condition of the potential donor, and subsequently, the organ procurement for transplantation.[3-5] The aim of this study was to analyze clinical problems related to the apnea test in the diagnosis of brain death.

Materials and Methods

From April 1998 to September 1999, we retrospectively analyzed demographic factors, hemodynamic conditions, clinical features, and etiology of brain injury in a cohort of BD patients who were considered for organ donation. We looked into the presence of changes in the arterial blood pressure, pH, and pO2, before and at the end of the AT.

Diagnosis of BD was made according to the AAN guidelines; AAN Quality standards.[1] It included a sequence of diagnostic test such as a complete neurological examination, apnea test, routine lab, and EEG. The AT was performed following the recommendations of the AAN, which includes delivering 100% O_2 (preoxygenate stage). If respiratory movements are absent and arterial pCO_2 is >60 mmHg (or 20 mmHg increase of pCO_2 over a baseline normal pCO_2), the apnea test result is positive (i.e. it supports the diagnosis of BD). If arterial hypotension (systolic blood pressure < 90 mmHg or median arterial blood pressure < 60 mmHg), severe acidosis (pH < 7.20), or hypoxemia (pO_2 <90 mmHg) were present and could not be corrected, the AT was not performed. In this scenario, the diagnosis of BD was completed with somato-sensory and auditory evoked potentials or cerebral blood flow studies.

BD diagnosis was made after two clinical evaluations, 6 hours apart, according to legal requisites in our country. All patients had a head

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CT or MRI to determine the etiology of BD.

Blood pressure was measured continuously by arterial line or by auscultation of the brachial blood pressure, manually, every 60 seconds during the apnea test. Arterial blood gas determinations were obtained every two hours, and before the apnea test and before reconnection to ventilator.

We examined arterial blood pressure, and blood gases of the potential donors before the AT and before the reconnection to the ventilator for detecting hemodynamic changes attributable to this procedure. Thus, clinical problems related to the AT were defined as follow: arterial hypotension as systolic blood pressure < 90 mmHg or median arterial blood pressure < 60 mmHg, severe acidosis was defined as pH < 7.20, and hypoxemia as pO_2 <60 mmHg.

Based on the purpose of the evaluation of the potential donors (organ procurement for transplantation), the development of cardiac arrest, myocardial infarction (MI), or bradiarrhythmia (arterial frequency <40 beats/minute) during the AT was considered as a complication related to the procedure.

Statistics were performed using the EPI Info 6.0 database. In univariate analyses the Wilcoxon (Mann-Whitney) test was used for continuous data and Fisher exact test was used for non-continuous data. For all variables, a p value <0.05 was considered as statistically significant.

Results

Among 129 consecutive patients evaluated, 70 (54%) were men. Mean age was 41± 18 years. Mean temperature was 35.8 ± 1.8 C.

The most common causes of the BD were: hemorrhagic stroke in 51 (40%) patients, subarachnoid hemorrhage in 37 (29%), traumatic brain injury in 36 (28%), anoxic encephalopathy in 9 (7%), and other causes in 6 (5%) (3 had bleeding in the surgical lodge, 2 intratumoral hemorrhage, and one subdural hematoma).

Fifty patients had a prior history of arterial hypertension. Sixteen were current smokers (more than 20 cigarettes per day), 10 had chronic obstructive pulmonary disease, 10 patients had more than 4 daily drinks of alcohol intake, and 6 had diabetes mellitus.

The apnea test was completely performed in 65 (50%) patients. Data were incomplete in two patients. In the rest of the patients the AT could not be performed because of refractive hypotension, pO2 below 90 mmHg or did not fulfill the AAN recommendations for performing the AT. The diagnosis of BD was made using electrophysiological studies (EEG, evoked potentials). Ninety five (74%) patients were receiving catecholamines before the apnea test.

Clinical problems due to AT were observed in more than two thirds of patients (Table 1). Mean pH reduction due to apnea test was 0.17 (range 0.02-0.32) units. When baseline pH was < 7.3, twelve patients developed pH reduction < 7.10, or 0.2 units. When baseline pH was > 7.3, no patient developed pH reduction < 7.10 (p< 0.001).

We looked for previous conditions or demographic data that could predispose to difficulties during the AT. There were no differences in sex, age, temperature, neurological examination, catecholamine use, or etiology of BD between patients with or without problems during to AT.

A comparative analysis was performed to determine whether the hemodynamic condition could predispose to problems during the TA by examine arterial blood pressure, pH, and pO2 before performing the AT and before the reconnection to the ventilator (Table 1). The more common previous conditions were as follows: acidosis (pH< 7.3) in 27 patients, hypotension in 13, and hypoxemia in 4 patients. Among 36 patients with one or more previous conditions, 15 (42%) had a reduction in the baseline pH greater than 0.2 points after to the AT. Individuals with previous conditions had higher frequency of problems during the AT than those patients without (80% vs 55%; p=0.03) (Table 1).

Complications during the AT were detected in four patients. All four had cerebral bleeding as the etiology of BD. They also had had previous risk conditions (Table 2). Patient#4 developed acute changes in the cardiac rhythm (atrial fibrillation) during the apnea test, and subsequently, myocardial infarction.

Discussion

BD patients may be suitable organ donors, and the apnea test is an essential procedure to establish this diagnosis. However, AT has not been validated in a large series of patients, and there are few studies on the predisposing conditions, nature, and frequency of complications during performing this procedure.[6-11] Pitfalls in performing the apnea test can be encountered in clinical practice.[1,12] Any complication during this procedure may limit organ perfusion, the diagnosis of BD, and subsequently the organ procurement for transplantation.

Table 1: Demographic features, etiology of brain death and problems during apnea test.

Patients	Total	Risk Conditions (+)	Risk Conditions (-)	P Value
N	63	36	27	ns
Mean age, years	41±18	41±19	41±17	ns
Sex (M/F)	39/24	22/14	17/10	ns
Temperature, °C	35.8± 1.8	35.7± 1.8	35.9 ± 1.7	ns
Cause of BD				
Intracerebral hemorrhage	21 (33)	11 (31)	10 (37)	ns
Brainstem hemorrhage	6 (10)	3 (8)	3 (11)	ns
SAH	17 (27)	12 (33)	5 (18)	ns
Head trauma	11 (17)	4 (11)	7 (26)	ns
Anoxic Encephalopathy	5 (8)	4 (11)	1 (4)	ns
Miscellaneous	3 (5)	2 (6)	1 (4)	ns
Clinical Problem	44 (68)	29 (80)	15 (55)	0.03
Hypoxemia	8 (12)	4 (11)	4 (15)	ns
Hypotension	15 (23)	13 (36)	2 (7)	0.005
Acidosis	41 (63)	27 (75)	14 (52)	0.05

SAH= subarachnoid hemorrhage, ns= not significant (p < 0.05). Numbers between parentheses indicate percentages. Risk conditions (+) indicate presence of acidosis (pH < 7.3), hypoxemia (pO2 < 90), or arterial blood pressure < 100 mmHg before the AT.

Table 2: Complications during apnea test

Patient #	Sex, Age	BD etiology	Risk condition	Complication
1	M, 54 y	SAH	Acidosis (pH 7.22) Hypoxemia (pO_2 60mmHg)	PT/PP Cardiac arrest
2	F, 61 y	ICH	Acidosis (pH 7.24) Hypotension (MAP 58 mmHg)	Bradycardia (pulse <35/min) Cardiac arrest
3	F, 56 y	SAH	Acidosis (pH 7.21)	Bradycardia (Pulse = 32/min)
4	M, 58 y	ICH	Acidosis (pH 7.25)	Atrial fibrillation MI

SAH= subarachnoid hemorrhage; ICH= intracerebral hemorrhage;

MI= myocardium infarction; PT/PP= pneumothorax and pneumoperitoneum. MAP: Median arterial blood pressure.

There are anecdotal reports of clinical problems or complications during or after the apnea test.[4-6,12] However, prospective studies are lacking in the literature. Gad Bar and other authors reported patients that developed tension pneumothorax during the apnea test.[3,4] All patients presented arterial hypotension and bradycardia, and finally had a cardiac arrest. Marks and Zisfein mentioned a patient with subcutaneous emphysema and thoracic insuflation during the apnea test.[5]

Wijdicks cautioned against the hypercarbia, acidosis, hypoxemia, and pulmonary edema during the AT.[6] He questioned the safety of this procedure, and suggested the AAN recommendations for performing this procedure be followed in order to avoid clinical complications.

Cardiovascular effects related to the apnea test have been reported in small series, including: a 30% decrease in systemic vascular resistance, an increased cardiac index, hypoxemia, arterial hypotension, and pulmonary hypertension.[9,11,12]

Effective tissue perfusion is the cardinal condition to preserve organ function. Prophylactic treatment with vasoreactive drugs has been suggested to prevent hemodynamic complications. However, there is no evidence favoring this intervention.

Several conditions may predispose to these complications, such as: a) Time between the BD diagnosis and performance of the apnea test, and b) Patient´s condition (e.g.: age, COPD, hypotension, hypothermia, acidosis, etc.). However, very few studies have specifically investigated the contribution of these conditions as risk factors when performing the AT.

Goudreau reviewed 145 apnea procedures in 121 patients to determine the frequency of complications and their predisposing factors.[13] Complications occurred in 26% of the procedures. Arterial hypotension was the most common complication (24%). Cardiac arrhythmia occurred in 4/145 (<3%) procedures. The most common predisposing conditions were inadequate preoxygenation, and acidosis. Complications were more common in individuals with inadequate precautions to perform the AT (39% vs 15%, p=0.01). The authors concluded that the AT is performed without adequate precautions or adherence to the AAN guidelines.[13]

We found relevant clinical problems during the AT in two third of the patients. The most frequent complications were acidosis, hypoxemia and arterial hypotension. Patients with pH < 7.3, pO2 < 90, or arterial blood pressure < 100 mmHg had a higher frequency of hemodynamic changes limiting the organ perfusion. Four patients had complications related to the procedure, which implied a myocardium damage or cardiac arrest. In view of their clinico-physiological conditions may be these patients should not have undergone the apnea test.

Our findings are coincident with Goudreau results.[13] However, we found higher frequency of complications (68% vs. 26%) related to the AT. Differences in the predisposing conditions, following the AAN guidelines, and data analysis may explain this results.

In our country, as well as in others, the EEG is a legal requirement to determine the diagnosis of BD. The apnea test is usually performed at the end of the clinical exam and before the EEG. Thus, a cardiac arrest due to a complication during this procedure has legal implications because the BD diagnosis has not been established yet. In other words, the patient has to afford the risk of this test before the brain death is declared.

Because of the aforementioned complications during the apnea test, we believe that this practice is necessary, although not innocuous.

In summary, clinical problems and complications due to the apnea test are more frequent in patients with previous risk conditions (i.e.: arterial hypotension, acidosis) and when the AAN guidelines are not systematically followed. Prospective studies are necessary to establish risk factors and to define the entire spectrum and frequency of complications during this necessary practice.

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