

Brain Death Confirmation: Comparison of Computed Tomographic Angiography With Nuclear Medicine Perfusion Scan

Christina M. Berenguer, MD, Frank E. Davis, MD, FACS, and Jay U. Howington, MD

Introduction: Brain death is a difficult diagnosis to make, relying primarily on clinical examination. Ancillary tests are used when confounders exist. Nuclear medicine perfusion test (NMPT) is currently the preferred test for confirming brain death. Computed tomographic angiography (CTA) may be an alternative test to confirm brain death. It is readily available 24 hours a day at most level I trauma centers and is easy to perform.

Methods: Patients with a clinical examination consistent with brain death were selected from the intensive care unit at a 550-bed teaching hospital. The patients underwent NMPT followed immediately by CTA. Both studies were read by radiologists blinded to the results of the alternative study. Absence of brain perfusion confirmed brain death. Multiple independent variables were collected on each patient including demographics, core body temperature, apnea challenge, mechanism of injury, timelines, renal function pre- and posttesting, organ donation, and time to procurement.

Results: There were 25 patients enrolled in the study with multiple injury patterns. No false negative exams were identified on CTA when compared with NMPT. Three patients without flow on NMPT showed minimal flow on CTA. Each of these had open skull defects. Sensitivity of CTA was 0.86 and specificity was 1. There was no induced morbidity with regards to renal failure and organ donation.

Conclusion: CTA is a quick and efficient test for brain death confirmation. CTA demonstrated no false negative studies. The resolution of CTA seems to have an increased sensitivity for cerebral blood flow. Further studies with larger sample sizes need to be performed.

Key Words: Brain death, Computed tomographic angiography, Nuclear medicine perfusion test.

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Brain death is defined as any biological event resulting in the permanent cessation of the critical cerebral functions of an organism^{1,2} and is equated to cardiopulmonary death. However, establishing the diagnosis can be challenging because the patient is many times hemodynamically stable with

normal vital signs. Each state has established guidelines for determining brain death, which rely heavily on clinical examination.³ In general, it is recognized as the absence of cerebral and brain stem functions.^{1,2} Numerous articles have been published to further define the criteria for diagnosis and help evaluate any gray areas.^{1,2,4}

Recent literature has more clearly defined the criteria for brain death. This includes a patient in a comatose state, absence of brain stem reflexes on neurologic examination, and a core body temperature >90°F.^{1,2,4} An apnea challenge test can be performed to ensure no spontaneous respirations after the PaCO₂ rises >60 mm Hg.^{1,2,4} Apnea is demonstrated when the patient fails to exhibit respiratory effort in a hypercarbic state. However, this study is often aborted secondary to hypotension, cardiac arrhythmias, and oxygen desaturation. Furthermore, when diagnosing brain death, there can be no medications or drugs, which alter the neurologic examination.^{1,2,4}

When the patient's neurologic examination is unclear due to confounding variables such as systemic medications or when an apnea challenge cannot be completed, additional tests are used to confirm the diagnosis of brain death.^{1,2,4,5} The gold standard has traditionally been four-vessel cerebral angiography.^{1,2,4,5} However, this is an invasive test requiring the expertise of a specialty trained physician to perform and interpret.⁵ The test is also time consuming and delays diagnosis of brain death. Additional tests have been developed for brain death confirmation including nuclear medicine cerebral perfusion test (NMPT), electroencephalogram, transcranial ultrasound, magnetic resonance imaging/angiography, and evoked potentials. NMPT has become the standard test at most level I trauma centers including ours.^{4–7} There are limitations to NMPT as well, including limited availability of technicians after hours, the requirement for isotope preparation, and recently, the unavailability of the isotope nationally. Combined, these factors lead to the delayed diagnosis of brain death.

More recently there have been significant advances in computed tomographic angiography (CTA) technology. CTA has started to replace more traditional tests as the preferred modality for many cerebral conditions. It is being used to diagnose carotid stenosis, cerebral aneurysms, and aortic dissections/traumas.^{8–11} CTA is readily available at level I trauma centers 24 hours a day, 7 days a week, and does not require the presence of a specialty trained physician to perform.

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From the Memorial University Medical Center (C.M.B., F.E.D.), Savannah, Georgia; Mercer University School of Medicine (F.E.D.), Savannah, Georgia; and the Neurological Institute of Savannah (J.U.H.), Savannah, Georgia.

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Address for Reprints: Christina M. Berenguer, MD, Department of Surgery, Memorial University Medical Center, 4700 Waters Avenue, Savannah, GA 31404; email: cmberen@hotmail.com, berench1@memorialhealth.com.

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There are several sporadic reports in the literature describing CTA as an alternative test for brain death confirmation.^{12–22} However, there are no prospective studies evaluating CTA as a confirmatory test for brain death. We hypothesize that CTA is an equivalent confirmatory test for brain death when compared with NMPT. The purpose of this study is to confirm the efficacy of CTA for the determination of brain death.

PATIENTS AND METHODS

This is a prospective nonrandomized trial. Patients were selected from the trauma and neurologic intensive care units at a 530-bed academic medical center. Inclusion criteria were nonpregnant adults 18 years of age or older. All patients had a neurologic examination consistent with brain death as performed by a board-certified neurosurgeon. The family of the patient must be available to obtain informed consent.

Enrolled patients first underwent a NMPT, the control test, as per standard protocol, followed immediately by a cerebral CTA, the study test. All CTA's were performed on a Siemens Somatom Sensation 64-slice computed tomographic scanner using a three-phase scan time. The patients underwent an initial noncontrast computed tomography (CT) head and neck (to visualize any old blood or hematoma), an acute arterial phase CTA, and finally a delayed venous phase CTA. It was determined that the delayed venous phase of the CTA was not useful and should not be obtained. The study test was performed within thirty minutes of the control test to eliminate as much as possible any temporal confounders. The studies were then read by radiologists blinded to the results of the alternative study. Absence of blood flow intracerebrally confirmed the diagnosis of brain death. Examples of both NMPT and CTA with and without flow are shown in Figures 1 and 2. Independent variables were collected on each enrolled patient including demographic information such as age, race, and sex. In addition information was obtained regarding core body temperature, results of the apnea challenge (if it was able to be completed), and mechanism of injury. To ensure no added morbidity was created from the study test, pre- and post-CTA blood urea nitrogen (BUN) and creatinine levels were measured. Organ donation information was obtained from patients who progressed to procurement, including a timeline from declaration of brain death to time of donation. A timeline was measured from the time to admission to the time of suspected brain death and from suspected diagnosis to performance of the confirmatory tests.

Statistical analysis of the data were performed including Chi square test between race and injury pattern using one degree of freedom. Sensitivity, specificity, and Correl correlation coefficient were used to analyze the results of CTA. Chi square test was used to evaluate the pre- and post-CTA BUN/creatinine level. False negatives were defined as patients without flow on CTA and but flow on NMPT. This is concerning for confirming a patient brain dead when he/she may not truly be brain dead. False positives were defined as patients with cerebral blood flow on CTA but no flow on NMPT. This study was evaluated by our hospital medical research advisory committee and institutional review board.



Figure 1. Nuclear medicine perfusion study. Upper image demonstrates normal cerebral blood flow. The lower image shows the absence of flow and is consistent with brain death.

RESULTS

From March 2007 to May 2008, a total of 25 patients were enrolled in the study. There were 15 Caucasian patients (60%) and 10 African-American patients (40%). Thirty-six percent of the patients were involved in blunt trauma, 36% had strokes, and 20% suffered penetrating trauma. In addition, Table 1 shows the relationship between race and injury type. Nearly, half of Caucasians suffered motor vehicle crash, whereas half of African-Americans presented after cerebral vascular crash. Chi square test values between race and injury type show a value of 0.027 with one degree of freedom, $p = 0.87$. Thirteen patients successfully completed an apnea challenge. All 13 patients showed apnea when the ventilator was removed.

Table 2 shows the results of the NMPT and CTA acute arterial phase tests. There were 19 patients demonstrating no flow on acute arterial phase CTA, indicating brain death. All of these patients also showed absence of technetium-99 on NMPT. There were no false negative results. There were three patients who showed flow on NMPT and could not be confirmed brain dead. These same three patients showed flow on CTA. Three additional patients showed minimal uptake of contrast at the base of the skull on CTA arterial phase who

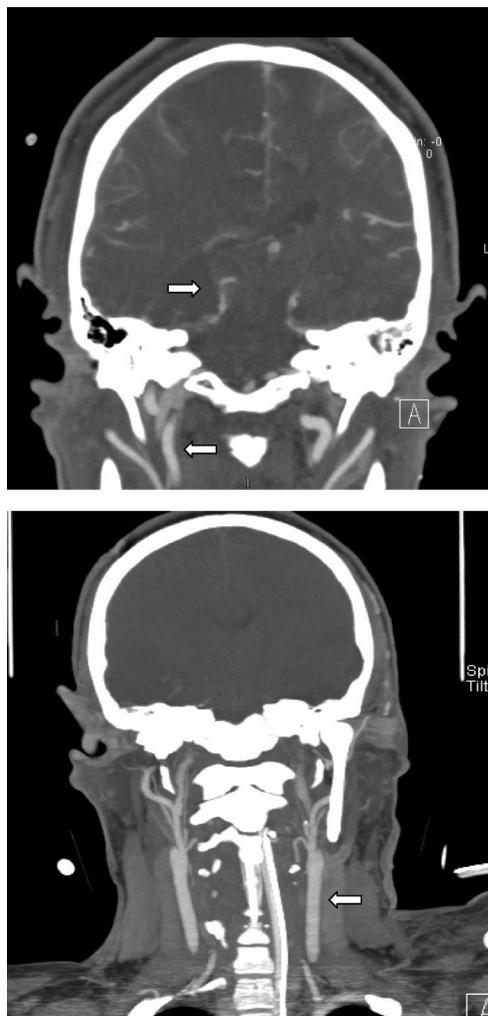


Figure 2. Cerebral CTA. CTA of a normal patient is shown in the upper image. The lower image show the absence of intracerebral blood flow. The arrows delineate flow extracerebrally (both images) and intracerebrally (upper image only).

did not show uptake on NMPT. These three patients represented our false positive results. Of note, all patients did progress to brain death regardless of the results of the control or study test.

Several tests were performed to determine whether the CTA results were equivalent to the standard NMPT test, including a Correl correlation, an odds ratio, sensitivity, and specificity. The odds ratio could not be calculated because of the value of zero for the denominator. The remaining tests showed a positive preliminary result, but none were statistically significant because of the small sample size. When comparing the acute arterial phase of CTA with NMPT, the sensitivity is 0.86 and specificity is 1. A Correl correlation coefficient was then performed to determine whether there was a relationship between positive and negative results from NMPT and CTA. There is a positive correlation $r = 0.66$ indicating a fairly strong positive correlation that CTA give similar results to the NMPT.

Pre- and post-CTA creatinine levels were measured. The precontrast BUN/creatinine levels were obtained within 2 hours before the dye load. The postcontrast BUN/creatinine were measured between half an hour after dye load if organ donation was not chosen and up to 48 hours after dye load if the patient was an organ donor. There were five patients who experienced no change in creatinine. Ten patients showed an increase in creatinine by a mean of 0.19 and 10 patients showed a decrease in creatinine by a mean of 0.18. No patient showed a change in creatinine by 0.5, indicating renal failure. A single-tailed t test was performed comparing pre- and postcontrast creatinine. This revealed a value of $t = 0.23$, indicating little variance between pre- and postcontrast renal function. A Chi square test was performed showing a value of $X = 1.085$. Finally, a covariance reconfirmed the minimal difference with a value of 0.25.

Fourteen patients, or 56%, progressed on to organ donation. This is consistent with historical controls at our institution. There was a slightly negative relationship between race and organ donation with $r = -0.26$. This again was very similar to historical controls for our institution. The mean procurement time was 27.4 hours. Table 3 shows the percentage of organ donors as divided by race.

After suspected diagnosis of brain death, the mean time to performance of the NMPT followed immediately by CTA was 5.75 hours. Once the patients arrived to the radiology suite, the time for execution of each test was 10 minutes.

DISCUSSION

Almost all of our severe closed head injury patients undergo a repeated CT of the head without contrast after any significant neurologic deterioration. In our institution, it takes ~30 minutes for the noncontrasted CT to be ordered and subsequently performed. We noted that our neurosurgical colleagues use CT evidence of herniation in addition to a clinical examination consistent with brain death to establish this diagnosis. On a number of occasions in which confounding variables are present, NMPT is obtained to confirm the suspected diagnosis. This test is often difficult to obtain after hours, often delaying the diagnosis of brain death. From request to test execution, it takes an average of 5.75 hours. This prolongs family anxiety and potential organ procurement. Several patients continue to deteriorate during this time delay and became ineligible for organ donation. Because the patients are having a noncontrasted CT scan anyway, a CTA at the time of neurologic deterioration would allow more timely confirmation of brain death.

Our data demonstrated three false positive results on CTA when using NMPT as the control. All three patients demonstrated minimal amounts of blood flow at the Circle of Willis. Our neurosurgeon noted that all of these patients had open skull defects, however, not all patients with open skull defects showed blood flow on CTA. Furthermore, our neurosurgeon and neuroradiologist believe that the small amount of flow seen at the base of the brain was clinically insignificant but can confuse the diagnosis. It may indicate that CTA is a more sensitive test than NMPT for identifying minimal cerebral blood flow. Combes et al.¹⁷ suggest this small

TABLE 1. Race and Injury Pattern Type

	Motor Vehicle Accident, n (%)	Motor Cycle Collision, n (%)	Penetrating Trauma, n (%)	Cerebral Vascular Accident, n (%)
Caucasian	7 (46.6)	3 (20)	1 (8)	4 (26.6)
African-American	2 (20)	2 (20)	1 (10)	5 (50)

The type of injury sustained is compared between the two different racial groups. Nearly, half of Caucasians suffered motor vehicle crash, whereas half of African-Americans suffered cerebral vascular crash. The n indicates the actual number of patients with the injury type.

TABLE 2. Results of NMPT and CTA Acute Arterial Phase

	NMPT	CTA Acute Arterial Phase
Cerebral blood flow	3	6
No cerebral blood flow	22	19

The results of the NMPT and CTA for cerebral blood flow.

TABLE 3. Race in Relationship to Organ Donation

	Organ Donation, n (%)	No Organ Donation, n (%)
African-American	4 (40)	6 (60)
Caucasian	10 (66.6)	5 (33)

This table shows the patients who proceeded to organ donation by race. The n represents the actual number in each category. Two thirds of Caucasians donated organs compared with just over one third of African-Americans. This is similar to historical controls at the study institution.

amount of flow originates from meningeal perfusion which could explain our findings. Further investigation is warranted to definitively determine the significance of such blood flow.

Figures 3 and 4 show two of the three false positive patients. Inherent in the technology and technique, NMPT is a lower resolution study. The NMPT of both these patients was read as no intracerebral blood flow consistent with brain death. The lower images are that of the patients' CTA scan. These showed a minimal amount of blood flow at the base of the skull. The thin arrow delineates flow. The thick arrow indicates old intracerebral blood flow. Finally, the star demonstrates a bullet fragment. Brain death was confirmed in these three patients based on clinical examination and confirmatory testing with repeat NMPT. Currently, these patients with minimal amounts of blood flow at the base of the skull are not confirmed as brain dead. Further investigation of these patients needs to be performed to determine what threshold of blood flow is consistent with brain death.

In addition to the three false positive patients, there were seven patients who showed blood flow on the delayed venous phase of the CTA. Quesnel et al.¹⁹ shows a similar finding in their study comparing CTA to electroencephalogram with delayed venous blood flow in 70% of their study participants. This is a similar finding to what is seen on delayed imaging on four-vessel cerebral angiography. This delayed blood flow is from collaterals and is not significant. Therefore, this phase of the scan can be omitted.

After measuring pre- and post-CTA BUN and creatinine levels, there was no evidence for renal failure as defined

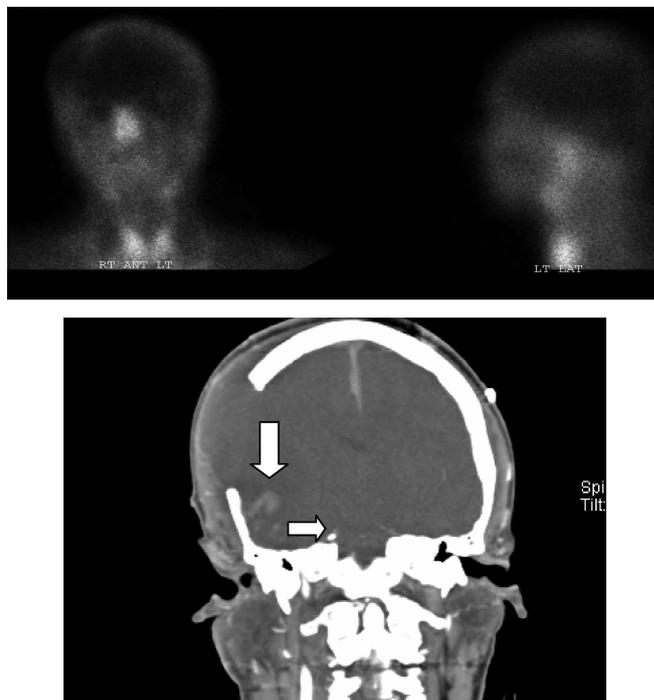


Figure 3. False positive patient. Small amount of blood flow detected at the base of the skull delineated by the thin arrow on CTA (lower image). The thick arrow represents old intracerebral blood. There was no blood flow detected on the NMPT (upper image).

by an increase in creatinine by 0.5. As these patients are a source of kidneys for transplantation, it was imperative to ensure no morbidity of renal failure was induced after giving these patients the contrast dye load for the CTA. This increases support for the use of CTA.

A comparison was made of the costs for CTA and NMPT. The cost of a NMPT scan is \$186.52. CTA costs \$250 per scan to perform. These are costs incurred by the hospital for the scans and not charges to the patient. Although NMPT is slightly cheaper than CTA, the cost does not include the cost of ICU care during the delay to perform the NMPT, which further increases the cost of care for NMPT as a confirmatory test. On average, the delay for a NMPT is 6 hours, whereas CTA can be performed within half an hour.

One of the limitations of this study is the small sample size. Although multiple modalities for analysis were used, statistical significance was not achieved secondary to the small sample size. In addition, the statistical design was initially intended to be more quantitative but was more

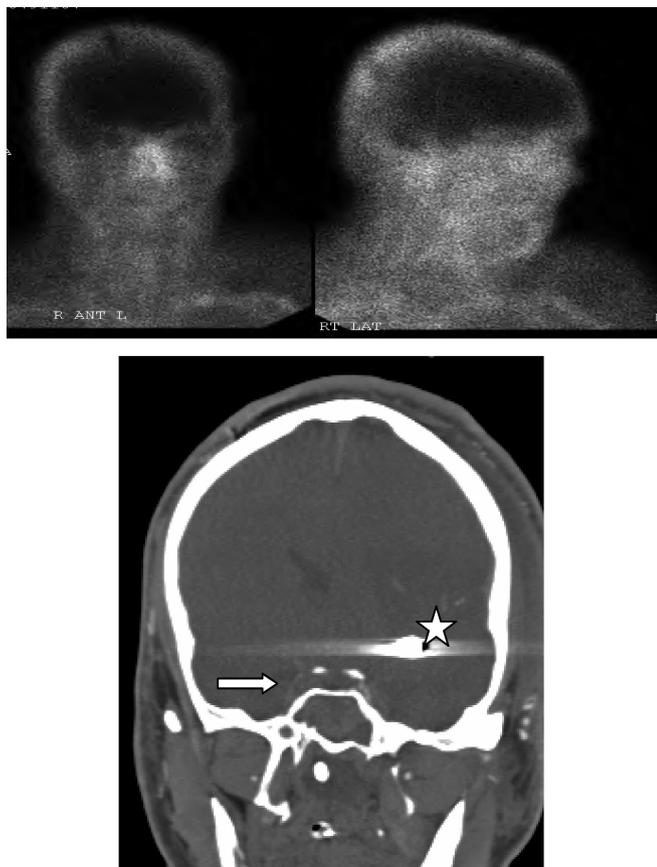


Figure 4. False positive patient. Note the small amount of blood flow detected at the base of the skull on CTA (lower image) indicated by the thin arrow. The star marks a bullet fragment. There was no blood flow detected on NMPT (upper image).

descriptive again secondary to the small sample size. The study is currently ongoing to gather a larger sample size and further evaluate those patients with minimal flow on CTA.

Another limitation of the study was the inadequate follow-up time for the postcontrast dye infusion renal testing. The last measured BUN/creatinine was used for analysis. This was up to 48 hours after the CTA dye load for those patients who proceeded to organ donation. However, this was merely 30 minutes after dye load for some patients whose families opted to forgo organ donation. A follow-up of those posttransplant kidneys procured from study patients would shed further light but is hampered by patient confidentiality.

CONCLUSIONS

In patients with severe closed head injuries, a noncontrasted CT scan of the head is frequently performed with any significant neurologic deterioration or suspected brain death. CTA can be performed at the same time with minimal additional resources or risks. If there is no blood flow on the acute arterial phase of the CTA, brain death can be confirmed and no further testing is necessary. Further evaluation is needed in patients with open skull defects who demonstrate

minimal cerebral blood flow. In addition, a larger study sample would enhance statistical analysis.

All patients undergoing a CTA for suspected brain death need to have a two-phase scan. The initial scan is a noncontrasted CT head that extends caudad to the base of the skull. This allows evaluation of old intracerebral blood. This is followed by an acute arterial phase. There is no utility in obtaining a delayed venous phase CTA.

CTA can often be executed within 30 minutes after being ordered, unlike NMPT, which usually is delayed by nearly 6 hours. CTA demonstrated no added morbidity. There were no measured instances of renal failure secondary to contrast dye exposure. Also, the number of organ donation was similar to historical controls at our institution. Using this new modality to confirm brain death, this could decrease the time to brain death declaration and potentially increase the number of organs procured. For the families of brain dead patients, expedited brain death confirmation by using CTA could bring more timely closure.

REFERENCES

1. Wijdicks EF. The diagnosis of brain death. *N Engl J Med.* 2001;344:1215–1221.
2. Young GB. Diagnosis of brain death. Available at: www.uptodate.com. Accessed June 2009.
3. Memorial Health University Medical Center. *Patient Care Policy: End-of-Life Care Policy.* Savannah, GA: Memorial Health University Medical Center; August 1–16, 2006.
4. Donatelli LA, Geocadin RG, Williams MA. Ethical issues in critical care and cardiac arrest: clinical research, brain death, and organ donation. *Semin Neurol.* 2006;26:452–459.
5. Young GB, Shemie SD, Doig CH, Teitelbaum J. Brief review: the role of ancillary tests in the neurological determination of death. *Can J Anaesth.* 2006;53:620–627.
6. Munari M, Zucchetta P, Carollo C, et al. Confirmatory tests in the diagnosis of brain death: comparison between SPECT and contrast angiography. *Crit Care Med.* 2005;33:2068–2073.
7. Karantanas AH, Hadjigeorgiou GM, Paterakis K, Sfriso D, Komnos A. Contribution of MRI and MR angiography in early diagnosis of brain death. *Eur Radiol.* 2002;12:2710–2716.
8. Benvenuti L, Chibbaro S, Carneseccchi S, Pulerà F, Gagliardi R. Automated three-dimensional volume rendering of helical computed tomographic angiography for aneurysms: an advanced application of neuronavigation technology. *Neurosurgery.* 2005; 57 (1 suppl):69–77; discussion 69–77.
9. Hoh BL, Cheung AC, Rabinov JD, Pryor JC, Carter BS, Ogilvy CS. Results of a prospective protocol of computed tomographic angiography in place of catheter angiography as the only diagnostic and pretreatment planning study for cerebral aneurysms by a combined neurovascular team. *Neurosurgery.* 2004;54:1329–1340; discussion 1340–1342.
10. Sakuma I, Tomura N, Kinouchi H, et al. Postoperative three-dimensional CT angiography after cerebral aneurysm clipping with titanium clips: detection with single detector CT. Comparison with intra-arterial digital subtraction angiography. *Clin Radiol.* 2006;61:505–512.
11. Alvarez-Linera J, Benito-Leon J, Escibano J, Campollo J, Gesto R. Prospective evaluation of carotid artery stenosis: elliptic centric contrast-enhanced MR angiography and spiral CT angiography compared with digital subtraction angiography. *AJNR.* 2003;24:1012–1019.
12. Dupas B, Gayet-Delacroix M, Villers D, Antonioli D, Veccherini MF, Soullou JP. Diagnosis of brain death using two-phase spiral CT. *AJNR.* 1998;19:641–647.
13. Qureshi AI, Kirmani JF, Xavier AR, Siddiqui AM. Computed tomographic angiography for diagnosis of brain death. *Neurology.* 2004;62:652–653.
14. Yu SL, Lo YK, Lin SL, Lai PH, Huang WC. Computed tomographic angiography for determination of brain death. *J Comput Assist Tomogr.* 2005;29:528–531.

15. Leclerc X, Taschner CA, Vidal A, et al. The role of spiral CT for the assessment of the intracranial circulation in suspected brain death. *J Neuroradiol.* 2006;33:90–95.
16. Arnold H, Kuhne D, Rohr W, Heller M. Contrast bolus technique with rapid CT scanning. A reliable diagnostic tool for the determination of brain death. *Neuroradiology.* 1981;22:129–132.
17. Combes JC, Chomel A, Ricolfi F, d'Athis P, Freysz M. Reliability of computed tomographic angiography in the diagnosis of brain death. *Transplant Proc.* 2007;39:16–20.
18. Yoshikai T, Tahara T, Kuroiwa T, et al. Plain CT findings of brain death confirmed by hollow skull sign in brain perfusion SPECT. *Radiat Med.* 1997;15:419–424.
19. Quesnel C, Fulgencio JP, Adrie C, et al. Limitations of computed tomographic angiography in the diagnosis of brain death. *Intensive Care Med.* 2007;33:2129–2135.
20. Yoo H, Kim IO, Wang KC, Cho BK. Preenhanced computed tomographic findings in brain death. *J Korean Med Sci.* 1993;6:305–307.
21. Tatlisumak T, Forss N. Brain death confirmed with CT angiography (Letter to the Editor). *Eur J Neurol.* 2007;14:e42–e43.
22. Joffe AR. Limitations of brain death in the interpretation of computed tomographic angiography: correspondence. *Intensive Care Med.* 2007;33:2218.

DISCUSSION

Dr. Amy Wyrzykowski (Atlanta, Georgia): Good morning. I would like to congratulate the authors on their excellent presentation and their timely submission of a very well written manuscript. I looked at the UNOS website yesterday and I noted that greater than 100,000 people were on the waiting list for organ donation. Clearly, the importance of timely and accurate diagnosis of brain death to facilitate organ donation cannot be overstated.

I enjoyed reading your manuscript. Although the number of patients was rather small, at twenty-five, you presented a good argument for the use of computed tomographic angiography in a diagnosis of brain death. While you were unable to reach statistical significance in your comparison of CTA to nuclear medicine perfusion scan, due to the small sample size, the results are intriguing. That being said, I have several questions.

Your manuscript states that there was no evidence of renal failure in patients undergoing CTA. A very common definition of renal contrast nephropathy is an increase in serum creatinine of greater than 25 percent from baseline at forty-eight to seventy-two hours after contrast load. The post-contrast BUN and creatinine values in your study were obtained at anywhere from thirty minutes to thirty-six hours after the administration of dye.

Is that really far enough out from the contrast load to draw definitive conclusions about the safety of CTA? It would be very interesting to know if any of the transplanted kidneys had delayed graft function, which may have been related to contrast nephropathy. Various authors have noted that delayed graft function is an independent predictor of both short and long-term graft survival. Don't you think this would be important information to have before deeming it safe? Are there any plans to obtain information on the function of the renal allografts?

In the manuscript, you noted that the delayed venous phase was not useful and should not be obtained. Other authors who have written on this topic have felt otherwise.

For example, Dupas and colleagues found that the absence of venous blood return and the enhanced visibility at the superior ophthalmic veins were actually confirmatory in the findings of brain death.

Quesnel et al. suggested that the absence of venous return in three vessels, specifically the bilateral internal cerebral veins and the great cerebral vein, may actually be more accurate in diagnosing brain death in the arterial phase. What led you to conclude that the venous phase was not useful and discard it?

In your study, you noted three false positives, three patients with absence of cerebral perfusion on nuclear medicine perfusion scan who were subsequently found to have flow on CTA. Quesnel and colleagues noted a similar phenomenon in their comparison of EEG documentation of brain death and CTA. In their study, several patients that had findings consistent with brain death on EEG were found to have flow on CTA. They concluded that the use of CTA may actually delay the diagnosis of brain death, by being oversensitive for cerebral flow. Do you agree or disagree with this?

Finally, are you still obtaining nuclear medicine perfusion scans at your institution or have your results convinced you that CTA is definitive? I would like to thank you for the privilege of the floor.

Citations:

1. Quesnel C, Fulgencio J, Adrie C et al. Limitations of computed tomographic angiography in the diagnosis of brain death. *Intensive Care Med* 2007;33:2129–2135
2. Dupas B, Gayet-Delacroix M, Villers D. et al. Diagnosis of brain death using two-phase spiral CT. *Am J Neuroradiol* 1998;19:641–647.

Dr. Christina Berenguer (Savannah, Georgia): Thank you for the well thought out questions. The first question was in regard to renal failure and the safety of CTA. This is one of the problems with our study. There was not a great timeline for follow-up of obtaining creatinine levels. Our study design was such that we obtained the furthest BUN and creatinine level from the time of testing that we could.

For those patients who were not organ donation candidates, the post contrast dye infusion BUN and creatinine levels were measured at times within a half hour of the testing, which is not adequate for contrast nephropathy. For those patients who did go on to organ donation, we got the last available level. I agree that further follow-up of these patients post-transplantation would be of efficacy in our study. However, we were not able to do it on our initial study, due to HIPAA and patient confidentiality issues. It's definitely something we're looking into.

For the second question, in regards to the venous phase of the CTA, most of the literature describes using a venous phase. However, upon closer examination of cerebral angiography, our gold standard, the study is performed using an acute arterial phase scanning. Contrast is injected until an arterial image is obtained. If contrast is continued to be injected beyond the arterial phase, you will see venous oozing and filling from collaterals. Therefore, because of this finding on cerebral angiography, we concluded that the same finding should be true with CTA.

The third question was in regards to EEG and CTA and delaying diagnosis due to minimal amounts of blood flow.

We definitely saw three patients with a minimal amount of blood flow. We are currently expanding our study to include an additional seventy-five patients, for a total of hundred patients, which would give us better statistical analysis, with hopefully some significance of our numbers. In addition to those numbers, we also want to look at those patients with minimal amounts of blood flow and see if we can make a determination on what amount of blood flow would exclude a diagnosis of brain death. I think this is an area that has not been answered. Perhaps we are pronouncing patients too soon based on EEG criteria who may not truly be brain dead.

The fourth question asks which test we are obtaining at our hospital to confirm brain death, NMPT or CTA. Because we are still enrolling patients in our study, we are obtaining both NMPT and CTA. However, there have been a few patients who have been unstable and could not withstand undergoing both tests and therefore, only CTA was obtained. Our neurosurgeons feel very confident that this is a good and accurate test for brain death diagnosis and confirmation.

Dr. Samir Fakhry (Charleston, South Carolina): I enjoyed your presentation and I commend you on taking on what is undeniably one of the most complex subjects in medicine, but I also caution you. This field, if you look back over the last twenty-five to fifty years, is one of the most controversial and most inflammatory fields in medicine.

When I looked at your paper, I came up with a slightly different conclusion than you did. You concluded that CTA is a quick and efficient test for brain death confirmation and my conclusion was that CTA was almost as confusing as NMPT in the diagnosis of brain death. The reason I say that has to do with the methodology of your study.

You've heard about the small sample size issue and apparently you are preparing to remedy that. Before you can confirm or deny this, I think you should look at a power analysis that determines for you how many patients you would need to enroll to reach your desired differential between the two tests. I would also recommend one other thing. For many of us, the gold standard continues to be four vessel angiography and for many of the organ donation groups in this country, it continues to be that as well. I think you may want to reconsider the conclusions of your study when your reference test has a high false positive.

Finally, I have found that talking about organ donation in the same breath as confirming brain death confuses people and creates issues of conflict of interests. We may want to shy away from getting into the transplant issues, because we've found them to be a huge distraction in talking about brain death. I commend you on the work and I hope you'll continue it, but I would really reconsider the above points. Thank you very much.

Dr. Christina Berenguer (Savannah, Georgia): Thank you for your questions. To answer the first question, in regard to power analysis, we have done a power analysis and the number that we need for our study achieve adequate power is ninety-six and so we've expanded our study to a hundred patients, which would go slightly above power.

The second question was in regards to four vessel angiography, which is the gold standard. I agree with you in that this would be the best comparison test for CTA. How-

ever, there are issues with performing cerebral angiography, particularly because it is invasive and it's a little bit more difficult to get consent from family members to perform this invasive test. Also, it would expose the patients to two dye loads, whereas they would only be given one if we just did the CTA with NMPT.

I agree with your point about organ donation. We looked at it just as one of the factors, because we didn't want our study to decrease the amount of organ donation that we were already undergoing at the hospital. Thank you very much.

EDITORIAL COMMENT

The authors present data acquired prospectively to evaluate computed tomography angiography (CTA), when compared with nuclear medicine perfusion testing (NMPT), as a confirmatory tool to establish brain death. They evaluated 25 patients undergoing NMPT with subsequent CTA and evaluated results using blinded radiologists. The results that they report do corroborate their contention that CTA is as good or superior to NMPT for evaluation of blood flow to the cerebrum and brain stem. They had, most importantly, no false negatives and a few false positives, with a specificity of 0.86 and a sensitivity of 1.

These data correlate well with previous such comparisons made with electroencephalography¹ and with digital subtraction angiography.² There appears to be an increased sensitivity of CTA with persistent evidence of some perfusion, which is not evident by other modalities such as digital subtraction angiography. The precise significance of such perfusion is not entirely clear; however, the authors do well to mention these references and similarities in their discussion. The two examples listed in their study (Figs. 3 and 4) may reflect perfusion of meningeal structures such as tentorium, clivus, and cavernous sinus through meningeal branches of the internal carotid or external carotid branches.

Overall, this is a worthwhile, preliminary study that continues to advance our work up of this terminal cohort of patients with important implications in terms of evaluation for organ donation and timely harvesting. It is also prudent to note that although CTA is now almost universally available and, particularly, at level I trauma centers is available 24/7, NMPT use is more restricted. Although the differences between the two modalities did not reach statistical significance likely due to a small sample size, this is an important data set that needs to be further investigated and confirmed in larger cohorts before CTA can surpass NMPT as a reliable test for brain death confirmation.

Adnan H. Siddiqui, MD, PhD

Departments of Neurosurgery and Radiology and Toshiba Stroke Research Center
University at Buffalo, State University of New York
Buffalo, NY

REFERENCES

1. Quesnel C, Fulgencio JP, Adrie C, et al. Limitations of computed tomographic angiography in the diagnosis of brain death. *Intensive Care Med.* 2007;33:2129–2135.
2. Combes JC, Chomel A, Ricolfi F, d'Athys P, Freysz M. Reliability of computed tomographic angiography in the diagnosis of brain death. *Transplant Proc.* 2007;39:16–20.