CURRENT CONCEPTS

Persistence of Cerebral Blood Flow After Brain Death

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ABSTRACT: Persistent cerebral blood flow occasionally confounds confirmatory tests for brain death and results in the anguish of delayed diagnosis, unnecessary use of expensive resources, and loss of transplant opportunities. We reviewed the literature to examine the reasons, frequency, and meaning of this problem. We found that this phenomenon occurs: (1) before increasing intracranial pressure completely shuts down flow; (2) in infants with pliable skulls; and with (3) decompressing fractures, (4) ventricular shunts, (5) ineffective deep brain flow, (6) reperfusion, (7) brain herniation, (8) jugular reflux, (9) emissary veins, and (10) pressure injection artifacts. Isolated venous sinus visualization is common (occurring in up to 57%) but represents trivial blood flow and confirms brain death. Arterial flow is much less common (2.6% incidence in our series). Normal flow occurs but is rare. Arterial flow does not exclude brain death, but the diagnosis should be confirmed by repeated studies or other means.

WE RECENTLY REPORTED results of 229 radionuclide studies in 219 patients with suspected brain death.[1] Seven examinations showed some arterial flow in 6 patients who were clinically brain dead. Brain death was confirmed by electroencephalography (EEG) in 2 patients, repeat radionuclide angiography was done in 3, and the remaining patient had cardiac arrest within 24 hours. Six other clinically brain-dead patients had isolated superior sagittal sinus activity. One of them had no sinus activity on a repeat study. Another patient's repeat examination was unchanged. This experience led us to believe that cerebral blood flow (CBF) is not always completely shut down as soon as brain death occurs. We reviewed the literature to find other examples of this phenomenon. Our initial MEDLINE search of titles and online abstracts from 1966 through July 1999 using the key words "brain death" yielded 3,972 references. Examples cited in our review were found through examination of these titles and abstracts and from the text and bibliographies of selected articles.

Although brain death is a clinical diagnosis, confirmation by additional testing is often required by local practice standards or local law. Confirmation is also helpful if there is suspected drug or metabolic intoxication, if there is reason to shorten the observation period, or to present additional evidence to the family that the patient is dead. The diagnosis of brain death can be confirmed in two ways, either by the neurophysiologic demonstration that the brain has been destroyed or by showing that CBF is no longer present.

The authors of the Harvard criteria thought that electrocerebral silence was of great confirmatory value.[2] Thus, the EEG became the first supporting study for the determination of brain death and is still used despite important limitations.[3] Minor transient residual EEG activity can be present in the face of clinical brain death.[4] The EEG is subject to electrical artifacts in the intensive care environment.[3] It has failed to recognize reversibility of coma in patients with drug intoxication.[5,6] More recently, evoked potentials (EPs), the potentials generated by the nervous system in response to sensory stimuli, have been proposed as better tools. Visual EPs, somatosensory EPs, and brain stem auditory EPs (BAEPs) can be used.[7]

Tests for cerebral flow are important confirmatory examinations.[8-10] Current established methods include cerebral angiography, radionuclide angiography, planar cerebral perfusion scintigraphy (CPS), and computed CPS.[10,11]

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Four-vessel cerebral angiography is the standard of confirmatory tests. It can evaluate both cerebral and posterior fossa blood flow. The study can be done with flush injection of iodinated contrast media into the aortic arch or by direct injection of the cerebral vessels. Normally, the cerebral arteries are patent and are easily seen on angiography. In brain death, flow is obstructed in the internal carotid arteries and vertebral arteries due to increased intracranial pressure. Unfortunately, cerebral angiography is too expensive and too invasive for routine use. It also exposes potential donor organs to toxic contrast material. Cerebral angiography for the confirmation of brain death has had greater popularity in Europe than in the United States.

Radionuclide angiography uses an intravenous bolus of radioactive material to show the presence or absence of blood flow in the cerebral circulation. A scan is compatible with brain death when there is absence of arterial flow on the dynamic study. Venous sinuses are seen ordinarily, but they are not usually seen when there is brain death. An important advantage of radionuclide angiography is the ability to detect blood flow in patients who have coma due to drug intoxication.[12,13] There are occasional technical failures due to inadequate bolus injection of the radiopharmaceutical. The major disadvantage of the procedure is that the posterior fossa circulation is not evaluated.

Planar CPS involves localization of radioactive material in the brain tissue itself and has the advantage of direct visualization of perfusion of the cerebral cortex and brain stem. Since a cohesive bolus of radioactive material is not necessary, a simple intravenous injection is given. This is easier and more reliable than a bolus injection. Normally, static planar imaging with a scintillation camera shows the radioactive agent localized within and throughout the brain. Usually, there is no significant activity within the cranium in a patient with brain death. Cerebral perfusion scintigraphy is advocated by many as a replacement for radionuclide angiography. The most important advantage of this procedure is its ability to directly show the posterior fossa. The major disadvantage is the considerably higher cost when compared with radionuclide angiography.

Tomographic CPS involves the same principles and diagnostic agents as planar CPS. A single photon emission computed tomographic scintillation camera is used to make the images. In brain death, image slices do not show concentration of radioactivity within the brain substance. This procedure is the most expensive of the three radionuclide tests and costs three or four times as much as radionuclide angiography. Although considerable improvement in diagnostic detail is possible with this test, no investigations have been reported to show that tomography offers significant advantages over planar images in the confirmation of brain death.

In 1998, a consensus opinion regarding the use of Doppler sonography was published,[14] stating that Doppler sonography is sufficient to reliably confirm brain death. It is completely noninvasive. Like all blood flow tests, the procedure is of special value when the therapeutic use of sedative drugs renders EEG unreliable. The development of cerebral circulatory arrest is identified by characteristic changes of the velocity wave form of the basal cerebral arteries.

Tests less frequently used, but able to quantify flow, include positron emission tomography (PET) and stable xenon computed tomography (XeCT). These examinations are expensive, complex, and not readily available. In addition to their clinical utility, they are excellent research tools.

The destruction of the lower brain stem causes the loss of capacity to breathe spontaneously, and brain death is observed only in patients supported by respirators. Confirmatory tests measuring or showing CBF are based on the assumption that there is cessation of blood flow with brain death. Although this is usually eventually true, it is not absolute. Persistence of CBF after brain death can result in the anguish of delayed diagnosis, unnecessary use of expensive resources, and loss of transplant opportunities.

CAUSES OF PERSISTENT INTRACRANIAL BLOOD FLOW

As a result of our review, we propose 10 reasons why persistent CBF occurs in brain death. These reasons are not mutually exclusive, and more than one of them can occur in any given patient.

Insufficient Intracranial Pressure

The most common cause of persistent CBF is that intracranial pressure has not reached sufficient levels to completely shut down blood flow. If the CBF is tested after brain death, but before intracranial pressure equals or exceeds

systolic blood pressure, arterial blood flow may be present. Our experience[1] with three patients who were clinically brain dead but had blood flow on the first study and no blood flow on the repeat examination suggests that some patients meet the criteria for brain death before intracranial pressure exceeds arterial perfusion pressure. In some of these, the intracranial pressure will continue to rise until blood flow to the brain is no longer possible.

Of the many examples of this in the literature, Shah et al[15] reported the case of a 58-year-old woman who collapsed in her office. She was brought to the emergency department unconscious, intubated, and nonresponsive with a Glasgow coma score of 3, the lowest possible value. Computed tomography (CT) showed a subarachnoid hemorrhage and a 2.5 cm giant aneurysm at the bifurcation of the right internal carotid artery. A CPS scan showed activity in the region of the aneurysm but no cerebral or cerebellar activity. On repeat CPS scan 24 hours later, this activity was no longer present. Wieler et al[16] reported that 2 of 16 adult patients with clinical brain death had CBF. No analgesics, barbiturates, or muscle relaxants had been given for 24 hours. There was electrocerebral silence on EEG. A CPS scan showed normal cerebellar blood flow in 1 of the 2 patients. In the other, CPS and cerebral angiography showed normal flow, except in the left hemisphere. Repeat CPS and cerebral angiography showed absent CBF throughout the brain.

Usually in brain death, cerebral edema progresses until the intracranial pressure prevails. Bergquist and Bergstrom[17] documented progressive circulatory arrest with serial angiography. The cerebral circulation deteriorated progressively and was finally arrested completely over a period of about 45 minutes. Clinical experience indicates that the length of this phase may vary considerably.

At times, circulatory arrest occurs before cessation of CBF or before it has been shown. Before the era of brain death as a clinical diagnosis, Heiskanen[18] reported 25 cases of extremely high intracranial pressure studied by cerebral angiography. In case 12, the patient was a deeply comatose 71-year-old woman with widely dilated pupils and apnea who had been a pedestrian involved in a motor vehicle collision. Filling of the intracranial vessels was good on both right carotid and vertebral arterial injections. Cerebral circulation was extremely slow. In case 21, a 23-year-old man who had been in a motor vehicle collision was in deep coma, with dilated, fixed pupils and apnea. Very slow filling of the internal carotid, anterior cerebral, and middle cerebral vessels was seen. Neither patient recovered.

Rosenklint and Jorgensen[19] reported on 10 comatose patients studied by aortocervical arteriography who had no cranial nerve reflexes and flat EEG recordings. Filling of intracerebral arteries was seen in 1 of the patients who had a posterior fossa tumor. Contrast material moved very slowly. Internal cerebral and basilar veins were observed by the subtraction technique.

Nau et al[20] reported the results of four technical investigations in 50 clinically brain-dead patients. In 2 of the 50 patients, arterial digital subtraction angiography showed residual cerebral perfusion. No signs of cortical or brain stem function were noted. Results of formal apnea tests were positive, with a measured P_{CO_2} >50 mm Hg. Electroencephalograms were isoelectric, and brain stem BAEPs were absent.

Larer and Nagel[21] reported the case of a 48-year-old female teacher who collapsed at school from intracranial bleeding. She had an arteriovenous malformation of the cerebellar hemispheres and a basilar artery aneurysm. A new bleed occurred on day 14 with subsequent clinical brain death. No brain stem or cortical function was present, and an apnea test yielded a positive result (P_{CO_2} 66 mm Hg). Dynamic images showed activity along the anterior and middle cerebral arteries. Planar CPS images showed moderate diffuse intracranial uptake.

Fackler and Rogers[22] described the case of an 8-year-old boy with intracranial abscesses. The Glasgow coma scale was 3, and no brain stem reflexes were present. There was no respiratory effort during a formal apnea test. The P_{CO_2} was >70. The radionuclide angiogram showed no flow. On EEG, two recordings were nearly flat, one probably flat, and one flat. A four-vessel cerebral arteriogram showed filling of the anterior and middle cerebral arteries and some sylvian vessels.

Blend et al[23] reported normal radionuclide angiography results in a child with electrocerebral silence. A 3-year-old boy with trisomy 18, psychomotor retardation, seizure disorder, and ventriculomegaly had a cardiopulmonary arrest. He was deeply comatose for 26 days, and no barbiturates or sedatives were given. Electrocerebral silence was seen on two consecutive EEG recordings. Preservation of cerebral circulation was confirmed by CT and by

radionuclide angiography. The patient died from circulatory collapse on day 27.

Expansible Skulls in Infants

In infants, the skull is relatively elastic, and this elasticity resists the rise in intracranial pressure that usually results in cerebral circulatory arrest. Ashwal and Schneider[24] recorded brain death in 17 preterm and term infants. Six had flow on radionuclide angiography. In another article describing brain death determination in the newborn, Volpe[25] found 2 infants with pathologic evidence of diffuse necrosis at autopsy. Measurements by PET were approximately 20 and 84 mL/100 g/min for cerebral flow and 132 and 164 mL/100 g/min for brain stem flow. Altman et al[26] described preservation of cerebral hemispheric blood flow (mean, 19.7 mL/100 g/min; peak, 30 mL/100 g/min) and exuberant brain stem blood flow (132 mL/100 g/min) in an asphyxiated newborn infant with no clinical evidence of brain function, electrocerebral silence, and autopsy evidence of multifocal neuronal necrosis in all brain sections studied, including cerebrum, pons, and cerebellum. Glasier et al[27] studied 9 clinically brain-dead infants. One had preserved intracranial systolic and diastolic flow until cardiac arrest. This was a full-term baby with birth asphyxia; fixed, dilated pupils; absent brain stem reflexes; and apnea. The EEG recording was flat, and cerebral edema was seen on CT. Radionuclide angiography showed preserved intracranial flow and normal activity in the sagittal sinus.

Extensive Decompressing Fractures

Decompressing fractures also reduce intracranial pressure. Alvarez et al[28] wrote about brain death determination by angiography in the setting of a skull defect. A 29-year-old man had a two-story fall onto his head. He was clinically brain dead, with a positive result on a formal apnea test and two isoelectric EEGs. Slow flow was present in the cerebral arteries on the left. These vessels showed diffuse extravasation of contrast material. Large amounts of brain parenchyma protruded through a left occipitoparietal skull defect.

Ventricular Shunts or Drains

Shunts and drains relieve intracranial pressure. Pribram[29] described the case of a 22-year-old woman with an angiomatous malformation and intracranial circulatory arrest. Cerebral circulation was restored by draining the ventricles. This did not improve the patient's clinical status. In another report, Hansen et al[30] described radionuclide flow in brain death caused by a ventricular drain. A 25-year-old man with congenital hydrocephalus, a hairline fracture, and subarachnoid hemorrhage was clinically brain dead. A ventricular drain was placed. Radionuclide angiography appeared normal; cerebral circulation persisted until the drain was removed. Kosteljanetz et al[31] detailed the case of a 44-year-old man with severe subarachnoid hemorrhage due to a ruptured basilar artery aneurysm. Extraventricular drainage was established. Examinations on 3 consecutive days fulfilled criteria of brain death. Cerebral angiography showed intracranial filling until day 3. Hartshorne et al[32] reported that two radionuclide angiographies showed normal flow in a 2-month-old brain-dead infant with cerebrospinal fluid–shunted Arnold Chiari malformation.

Ineffective Deep Brain Flow

Thompson et al[33] measured CBF in clinically brain-dead children with XeCT and radionuclide angiography. Two of five had radioactivity in the superior sagittal sinus. One had spotty CBF with a maximum of 10 to 15 mL/100 g/min. The other had peripheral flow of 1 to 5 mL/100 g/min and periventricular flow of 15 to 20 mL/100 g/min. They concluded that persistent flow determination by radionuclide angiography may only reflect deep brain flow and ignore a virtual absence of flow in the peripheral gray and white matter.

Reperfusion

After intracranial circulatory arrest, if the blood pressure is raised to levels above the intracranial pressure or if the intracranial pressure is lowered below systolic pressure, reperfusion of the brain may occur. This reperfusion is not effective in restoring neurologic function after brain death. Ashwal and Schneider[34] described brain death in eight full-term infants. Two had flow on repeat radionuclide angiography after an absence of flow on the initial study. In another investigation, Schroder[35] concluded that the regular onset of inflammatory alterations after long brain death intervals can only be explained by partial recirculation due to a decline of the high intracranial pressure.

Extracranial Herniation of Intracranial Vessels

If there is herniation of the brain outside the cranium, the reduced pressure outside the skull can account for blood flow within the herniated brain. Pribram[29] described the case of a 2½-year-old girl with coma, areflexia, greatly increased intracranial pressure, and tonsilar

herniation with good filling of both vertebral arteries and the left posterior inferior cerebellar artery. The proximal part of this artery was well below the foramen magnum. Thus, this usually intracranial vessel was outside the cranium.

Jugular Reflux

It has been shown that jugular reflux can enable visualization of the dural sinuses. Brill et al[36] reported brain death in a 54-year-old woman who had marked reflux into the left jugular venous system and retrograde filling of the venous sinuses. Shore et al[37] described massive jugular and dural sinus reflux associated with cerebral death. Two children with the clinical diagnosis of brain death had massive reflux of technetium Tc 99m into the jugular vein during radionuclide angiography. The tracer followed the course of the sigmoid and transverse dural sinuses, then down the opposite jugular vein. Jugular reflux is one of the documented causes of persistent venous sinus activity.

Emissary Veins

It has been proposed that emissary veins from the external circulation can supply blood to the venous sinuses and enable isolated venous sinus visualization. This has not been proven. It is much more likely that sagittal sinus activity results from severely reduced and slowed intracranial circulation, which is ineffective in preserving brain viability. Kricheff et al[38] described stasis filling of the transverse sinus in 1 of 10 patients with no intracranial flow. This was attributed to an emissary vein from the external carotid circulation.

Artifact from Pressure Injection

Artifactual visualization of cerebral vessels can be produced by raising injection pressure above intracranial pressure. In an investigative study, Mitchell et al[39] showed that increased intracranial pressure could be overcome by increasing the injection pressure of the contrast media. Unperfused vessels could be shown artifactually by simply increasing the force of the injection. Heiskanen[18] also documented this phenomenon by showing that the level reached by contrast material was greater in cerebral arteries that were directly injected than it was from aortic arch injection.

DISCUSSION

Brain death can occur before the cerebral circulation completely ceases. It is obvious from the many examples cited that cessation of intracranial blood flow is not invariable. As early as 1963, Heiskanen[18] concluded that the point of irreversible damage to brain cells is reached well before the final arrest of the cerebral circulation. The mere filling of the intracranial vessels is no indication of the adequacy of the perfusion.

There is a lower limit of CBF and cerebral oxygen consumption ($CMRO_2$) required by the human brain. These values are about 10 to 15 mL/100 g/min for regional cerebral blood flow and 1.3 mL/100 g/min for regional cerebral metabolic rate of oxygen ($rCMRO_2$).[40]

Shalit et al[41] studied the relationship between clinical signs, CBF, and $CMRO_2$ in the dying brain. They showed that when brain oxygen consumption reaches levels lower than one third of the normal value (<1 mL/100 g/min), a total breakdown of brain vital mechanisms occurs. At this critical level, spontaneous respiration stops, blood pressure drops, pupils begin to dilate, and muscle tone is lost. These severe signs do not appear simultaneously but rather gradually within the narrow margins of $CMRO_2$ between 1 and 1.3 mL/100 g/min. One of the last brain functions to disappear is electrical activity. Shalit et al[41] reported on three of their patients who were deeply comatose and had wide pupils, no response to stimuli, and apnea. These patients had CBF values of 7.4, 10, and 10 mL/100 g/min, respectively, and $CMRO_2$ values of 0.17, 0.3, and 0.38 mL/100 g/min. Cardiac arrest occurred 1, 4, and 2 hours, respectively, after the study.

Altman et al[26] have shown that CBF required for premature infants is lower than in adults. Premature newborns without the clinical findings of brain death have survived with blood flow as low as 5 mL/100 g/min measured by PET. They recommend that confirmation by CBF not be used in the determination of brain death in the newborn period. Even so, the presence of CBF need not rule out the diagnosis of brain death in the newborn.

All 10 reasons given for persistent blood flow after brain death have one thing in common: the intracranial pressure or pressure outside the visualized vessels does not exceed systolic pressure or the pressure inside the vessels. This cause for filling or nonfilling of intracranial arteries in brain death was not always obvious. Initially, vascular occlusion and spasm were proposed as major factors. In 1961, Pribram[29] reported 11 well-documented cases of acute in-

tracranial hypertension. He surmised that an acute rise in intracranial pressure was responsible for nonfilling of the cerebral vessels by angiography and suggested that in similar cases, lowering of the intracranial pressure would permit visualization of the cerebral vessels. In 1962, Mitchell et al[39] studied this phenomenon experimentally in monkeys and dogs. When the intracranial pressure was equal to or exceeded the systolic blood pressure, cerebral arteries did not fill. The complete circle of Willis, including the basilar artery, was shown by forceful injection, suggesting total interruption of intracranial flow, since this angiographic pattern does not occur with normal intracranial pressure. If the intracranial pressure was lowered below the systolic blood pressure, cerebral vessels filled well. Arteriograms made at an intracranial pressure below the recorded systolic blood pressure appeared no different from the control (normal) arteriograms.

Our experience and this review of the literature suggest that persistence of intracranial blood flow after brain death is much more common than is generally realized. The actual numbers depend on the diligence of the search, the method of blood flow evaluation, and the timing of the examination. Blood flow determinations by PET and XeCT can show flow not seen by radionuclide angiography, and sagittal sinus activity from trivial flow can be seen on radionuclide angiograms when there is stasis on cerebral arteriography. Using radionuclide angiography, Goodman et al[12] described an original protocol that required complete nonvisualization of all intracranial vascular structures. They encountered a delay in more than half of their patients while waiting for sequential scans to show disappearance of uptake in dural sinuses. There was initially 57% residual blood flow in the venous sinuses. They concluded that absence of the arterial phase in the presence of some visualization of a lateral or sagittal sinus was sufficient evidence for brain death.

In our series,[1] there was isolated sinus visualization in only 6 of 229 studies. We believed from the start that isolated sinus activity was not clinically significant and did not actively seek to show it with multiple delayed views. Analysis of these suggests that in 4 the intracranial pressure had not reached sufficient levels to completely shut down blood flow. The other 2 involved infants, and the patients' skulls were expansible. In another 7 of our studies in 6 patients who were clinically brain dead and whose subsequent course confirmed brain death, some arterial flow was present. In all cases, this was obviously abnormal. The incidence of demonstrated residual arterial flow was 2.6%. Analysis of these cases suggests that in 5 of them the intracranial pressure had not reached sufficient levels to completely shut down blood flow. The sixth patient was an infant whose skull could expand.

The series by Goodman et al[12] and our series[1] are the two largest studies to evaluate CBF confirmatory tests. Normal blood flow was not seen in any of these 407 brain-dead patients who had interpretable studies. However, 4 patients included in this review were clinically brain dead and had normal or virtually normal CBF confirmatory tests.[23,27,30,32]

SUMMARY

Cerebral blood flow after brain death occurs in those conditions where the intracranial pressure is less than the intravascular pressure. The observed incidence depends on the diligence of the search, the method of blood flow evaluation, and the timing of the examination. Isolated venous sinus visualization is common (occurring in up to 57%) but represents trivial ineffective blood flow and confirms brain death. Residual arterial flow is much less common (occurring in 2.6% in our series), and normal confirmatory tests for blood flow occur but are rare. Visualization of arterial flow does not exclude brain death, but the diagnosis should be confirmed by repeat studies or by other means.

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