Implications of ischemic penumbra for the diagnosis of brain death

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Abstract

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The data reviewed here suggest the possibility that a global reduction of blood supply to the whole brain or solely to the infratentorial structures down to the range of ischemic penumbra for several hours or a few days may lead to misdiagnosis of irreversible brain or brain stem damage in a subset of deeply comatose patients with cephalic areflexia. The following proposals are advanced: 1) the lack of any set of clinically detectable brain functions does not provide a safe diagnosis of brain or brain stem death; 2) apnea testing may induce irreversible brain damage and should be abandoned; 3) moderate hypothermia, antipyresis, prevention of arterial hypotension, and occasionally intra-arterial thrombolysis may contribute to good recovery of a possibly large subset of cases of brain injury currently regarded as irreversible; 4) confirmatory tests for brain death should not replace or delay the administration of potentially effective therapeutic measures; 5) in order to validate confirmatory tests, further research is needed to relate their results to specific levels of blood supply to the brain. The current criteria for the diagnosis of brain death should be revised.

Criticism

Irreversible damage to the brain stem or whole brain is assumed when consciousness and cephalic reflexes remain absent usually for six hours in a patient with known intracranial pathology, provided that reversible conditions such as drug intoxication, hypothermia, and metabolic or endocrine disturbance are reliably excluded (1,2). A 10-min apnea testing is advised to evaluate the respiratory reflex (2). Among several alternatives, a flat electroencephalogram (EEG) or an angiogram showing no images of intracranial vessels may ultimately confirm death for procurement of transplantable organs, but the reliability of neurological examination

followed by apnea testing has been mostly considered, up to the point of regarding brain death as a clinical diagnosis (2).

In most cases progressing to brain death, the damage to the brain is of an ischemic nature. Hemorrhage, edema, and/or swelling progressively increase intracranial pressure (ICP), thereby reducing the perfusion pressure and brain blood flow (BBF). Irreversible damage to the nervous tissue results from maximally increased ICP which reduces BBF beyond recovery. However, that may not be the actual pathophysiological condition of a possibly large number of cases fulfilling the current diagnostic criteria for brain death.
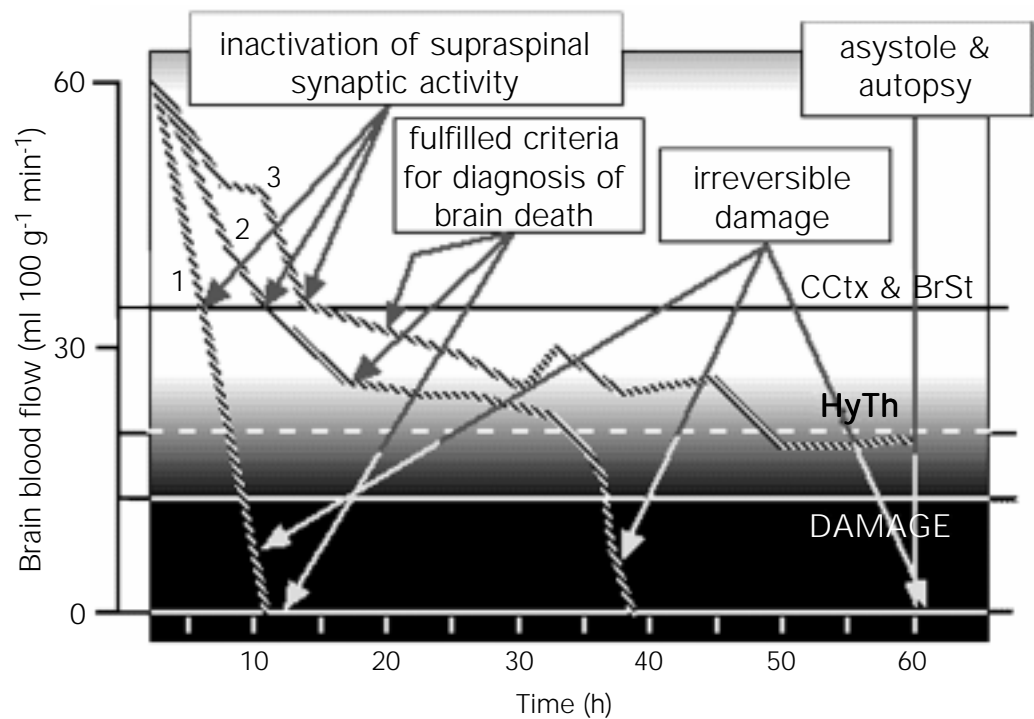
Accumulated knowledge on the patho-

physiology of ischemic damage to diverse body tissues has invalidated the assumption that a sustained absence of the specialized cellular functions is invariably irreversible or reflects cell necrosis. For instance, a region of the myocardium rendered akinetic as a consequence of a partial reduction in blood supply may actually resume contraction upon restoration of normal circulation (the phenomenon of the hibernating myocardium) (3). Similarly, under incomplete ischemic conditions (BBF between 10.0 and 35.0 ml 100 g^{-1} min^{-1}; 4), suppressed neurological functions remain recoverable by recirculation for up to 48 h, provided that the oxygen extraction fraction continues to be elevated (5). The phenomenon is known as ischemic penumbra and was originally described by Astrup and colleagues (6). Disruption of ionic homeostasis occurs only at BBF levels lower than 10.0 ml 100 g^{-1} min^{-1}, and launches

the cascade of detrimental biochemical reactions that determines irreversible damage to the brain tissue within approximately one hour under such severe ischemic conditions (4). Rather than an exclusive attribute of the outer zone of focal ischemia, the phenomenon of ischemic penumbra is clearly a consistent response of general brain structures to partially reduced circulatory levels.

In contrast to the postulates related to the diagnosis of brain death and brain stem death, it is conceivable that partial occlusions of the vertebro-basilar artery, or progressive hypertension affecting either the whole intracranial space or solely the infratentorial compartment may keep the blood supply to the whole brain or to the brain stem within the range of ischemic penumbra for many hours. This pathophysiological concept advanced here is referred to as global ischemic penumbra or GIP. Its importance for under-

Figure 1 - Evolution of brain blood flow (BBF) in three hypothetical cases of increased intracranial pressure (ICP) with absent supraspinal synaptic activity (coma and absent cephalic reflexes) for at least 48 h prior to cardiac arrest at 60 h-survival. While in case 1 brain damage becomes irreversible within 6 h from the onset of the "brain death" syndrome, in case 2 irreversibility is only achieved within 24 h, and in case 3 the brain tissue is still recoverable by the time of cardiac arrest which may result from metabolic disorders related to hypothalamic failure. If case 1 was representative of all (or at least most) cases of increased ICP at risk of brain death, full maturation of pathological features would develop during the next 48 h of continuous heart beating, and nearly 100% of autopsies (if not all of them) should demonstrate the respirator brain. In contrast, since respirator brain is only seen in 40% of these cases (21), global ischemic penumbra of variable duration is to be alternatively considered. CCtx & BrSt = BBF threshold below which cerebral cortex and brain stem functions become inactive (35 ml 100 g^{-1} min^{-1}); DAMAGE = BBF threshold below which cells depolarize (10-15 ml 100 g^{-1} min^{-1}). HyTh = BBF threshold below which hypothalamic secretory functions become inactive (CCtx & BrSt > HyTh > DAMAGE).

standing the relationship between the BBF levels and clinical findings in patients with progressively increased ICP is illustrated by the 3 hypothetical case examples presented in Figures 1 to 3.

At least two unique features may enhance the survival of brain tissue under GIP as compared with the penumbra zone of focal ischemia. Firstly, the absence of a source of neurotoxins contiguous to the whole tissue under reduced perfusion in GIP contrasts with the situation of focal ischemia. The infarcted core of the latter continuously releases diverse neurotoxins (including excitotoxins, nitric oxide and other inflammatory mediators) into the vicinity, and triggers repeated episodes of spreading depression that exhaust the already marginal energy supplies of the adjacent penumbra zone, leading to transformation of hitherto non-lethal injury into an irreversible one (5). Secondly, the decreased perfusion pressure that causes GIP may conversely attenuate the accumulation of vasogenic edema and taper off further increases in ICP, thereby sustaining the BBF

within the upper range of ischemic penumbra for many hours or a few days.

As illustrated in Figure 1, the secretory functions of the hypothalamus may be sustained by BBF levels lower than those required for synapse-dependent brain functions such as those evaluated for the diagnosis of brain death. The existence of different thresholds of BBF for the maintenance of different specialized activities of the brain is supported by studies demonstrating regional glucose consumption. Under normal conditions the metabolic rate of the hypothalamus is about one-third of that observed in cerebral cortex (7).

The hypothalamus is supplied with blood from the circle of Willis, and is expected to undergo the same level of circulatory shortage as any other intradural structure as a consequence of increased ICP. As the hypothalamic nuclei provide both the releasing hormones for the anterior hypophysis and the hormones to be liberated from the posterior hypophysis, preserved hypothalamic-hypophyseal function in some patients pre-
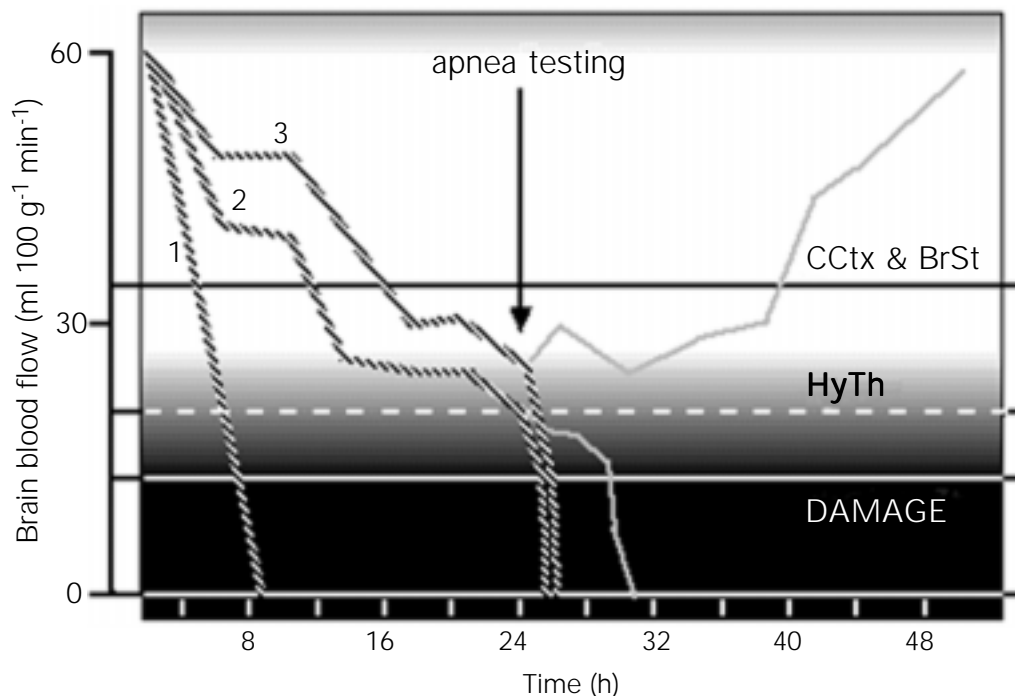

Figure 2 - Evolution of brain blood flow (BBF) in three hypothetical cases of intracranial hypertension: influence of hypotension induced by apnea testing at 24-h survival. Whilst BBF is unaffected in case 1, apnea testing hastens and sets the clinical outcome to irreversible brain damage in cases 2 and 3 by inducing collapse of intracranial vessels. For abbreviations see legend to Figure 1.

sumed to be brain dead cannot be explained by a hypothetical collateral blood flow to the anterior hypophysis through the inferior hypophyseal arteries arising extradurally from the internal carotid arteries. A reduced BBF down to 10.0 ml 100 g^{-1} min^{-1} or less would also disrupt the ionic homeostasis at all hypothalamic nuclei and result in failure of both anterior and posterior hypophyseal lobes.

Sustained hypophyseal function is therefore indirect evidence for active function, circulation and structural integrity of hypothalamic nuclei. Gramm and co-workers (8) followed 32 potential organ donors over a period of up to 80 h after the diagnosis of brain death established according to current criteria, determining the serum and plasma concentrations of hypothalamic-pituitary hormones, thyroid hormones, and cortisol. While 78% of the subjects eventually developed diabetes insipidus during the period of observation, no hormone concentration (except for arginine vasopressin) was found to be subnormal. In addition, none of the circulating hormones of the anterior hypophysis

declined progressively according to their plasma half-lives from the onset of the "brain-death syndrome". These results are in agreement with earlier and less extensive studies (9,10).

Direct evidence of sustained hypothalamic secretory activity was provided by Arita and co-workers (11) who measured the serum concentrations of 3 different releasing hormones (growth hormone-releasing hormone - GH-RH, adrenocorticotrophic hormone-releasing hormone - ACTH-RH, luteinizing hormone-releasing hormone - LH-RH) in 24 cases within 24 h after the diagnosis of brain death. Serum concentrations were above the sensitivity of the radio-immunoassay (higher than 5 pg/ml for GH-RH, 2 pg/ml for ACTH-RH, 0.2 pg/ml for LH-RH) in 13 out of 23 cases for GH-RH, in 12 out of 19 cases for ACTH-RH, and in 21 out of 22 cases for LH-RH. In general, one or more hypothalamic hormones were detectable in every case. Sustained thermoregulation, paradoxically considered a prerequisite for the diagnosis of brain death (2), is clear evidence for preserved hypothalamic function

Figure 3 - Evolution of brain blood flow in three hypothetical cases of increased intracranial pressure (ICP): influence of moderate hypothermia (33°C) induced at 24-h survival. Simultaneous normalization of intracranial pressure observed during cooling to 33°C (27) leads to recirculation of cases 2 and 3 whilst case 1 is unaffected. Remarkable absorption of brain edema during the next few hours of hypothermic treatment should prevent recurrence of ICP (27). For abbreviations see legend to Figure 1.
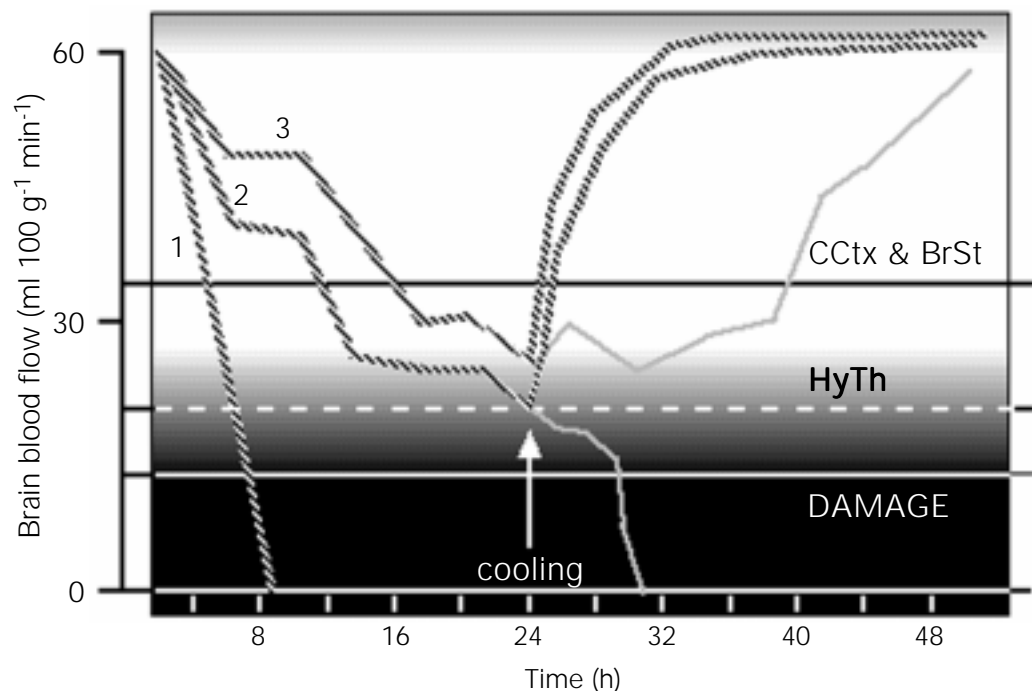
and rather suggests GIP in patients with increased ICP and suppressed cephalic reflexes. Therefore, although eventually depressed (as suggested by signs of diabetes insipidus), the blood supply to the hypothalamus seems to be high enough to sustain most of its secretory functions in most patients for the first 2-3 days after the current criteria for the diagnosis of brain death are fulfilled.

Sustained hypothalamic circulation (implying circulation above 10.0 ml 100 g^{-1} min^{-1}), when concomitant with deep coma and cephalic areflexia, also suggests that the neural structures with higher metabolic demands (as those functionally evaluated for the diagnosis of brain death) may be under GIP. That situation is illustrated in Figure 1 with hypothetical case examples No. 2 (from 11- to 33-h survival) and 3 (from 14- to 48-h survival).

On the other hand, the concept of GIP contradicts the assumption that hypercarbia induced by apnea testing would help to differentiate recoverable from irreversible cases of brain stem injury. Rather, hypercarbia may further impair the blood supply to the brain stem in these patients. Although vascular responses to changes in CO_2 are diminished, for instance, in victims of severe head trauma, some reactivity persists even in deeply comatose patients. As intracranial compliance is remarkably reduced following severe head trauma, even a minor hypercarbia-induced aggravation of brain swelling may largely worsen the intracranial hypertension and the resulting global ischemic insult (12).

Furthermore, in about 40% of cases, apnea testing induces severe hypotension (13), which is the most important secondary insult related to poor outcome (death or persistent vegetative state) in human victims of severe head trauma (14). Preservation of brain blood flow in these patients requires significantly higher levels of perfusion pressure than in other individuals (12). Accordingly, tran-

sient arterial hypotension leads to irreversible collapse of intracranial circulation in cats subjected to severe head trauma, so that even supranormal levels of perfusion pressure cannot restore the brain blood flow in these animals (15). The sudden association of hypercarbia-induced increase in ICP with severe hypotension (presumably related to the detrimental effects of acidemia on the myocardium) possibly enables the establishment of tension forces between the intraluminal surfaces of brain vessels, and thereby causes irreversible collapse of intracranial circulation. Therefore, apnea testing may induce rather than diagnose irreversible damage to brain tissue, and the results of all confirmatory tests carried out thereafter may reflect the deleterious effects of induced apnea with or without hypoxia.

Direct measurements of BBF following the diagnosis of brain death support the detrimental effects of apnea testing. Due to such a sudden and permanent efflux of blood volume from intracranial space (vascular collapse) determined by apnea testing, normal levels of intracranial and perfusion pressures may be subsequently found in paradoxical association with absent or extremely reduced intracranial blood flow (less than 10.0 ml 100 g^{-1} min^{-1}). Accordingly, Obrist and colleagues (16) found this combination of features in all of 9 patients fulfilling the current diagnostic criteria for brain death. Their results were in complete disagreement with those of the study by Baslev-Jørgensen and colleagues (17) carried out several years earlier, when the apnea test was not part of the routine for the diagnosis of brain or brain stem death. During progression to brain death - solely defined as "loss of cranial nerve reflexes and flat EEG" in deeply comatose patients - these authors found that "ICP increased to and remained at or above the level of mean arterial pressure" in all of 10 patients up to spontaneous cardiac arrest.

The consistent low levels of BBF found by Obrist and colleagues (16) are also in

disagreement with earlier data obtained by other investigators who (like Baslev-Jørgensen and colleagues, 17) did not induce the apnea test. In three studies (18-20) comprising altogether 12 cases of deep coma and wide pupils, dependent on mechanical ventilation, 6 patients (50%) presented circulatory values ranging from 11.0 to 32.0 ml 100 g^{-1} min^{-1} - therefore characteristic of ischemic penumbra. The electroencephalogram was not flat only in those cases whose levels of BBF were in the upper range of ischemic penumbra ($\geq$25.0 ml 100 g^{-1} min^{-1}; 20), suggesting that the values encountered did reflect actual levels of BBF. The possible detrimental effects of the apnea test on a subset of potentially recoverable hypothetical case examples (No. 2 and 3) are illustrated in Figure 2.

This percent value (50% of patients in deep coma and cephalic areflexia presenting BBF levels within the range of ischemic penumbra) is in close agreement with histopathological data obtained from the largest collaborative work so far carried out (see Figure 1) - The NINCDS Collaborative Study of Brain Death -, which included 226 autopsies (21). As in most early studies that followed the emergence of brain death in medical practice, apnea testing was avoided, and the "lack of any observed effort of the patient to override the respirator or by a ventilatory effort or movement other than that induced by the respirator" was chosen to characterize the loss of respiratory reflex (22). The signs of necrosis that characterize the so-called "respirator brain" (21) were found in only about 40% of cases of deep coma and absent brain stem reflexes for at least 6 h (21). Forty-eight hours of cephalic areflexia did not significantly change that percent value (21). In contrast with the quite consistent structural damage following a 4-min apnea test (23), the brain stem was morphologically intact in 15% of all cases (21).

Yet, moderate hypothermia (33°C) sus-tained for a few hours enables resumption of normal daily life in 70 and 50% of the patients following severe head trauma (24,25) and normothermic cardiac arrest lasting for 30-47 min (24) respectively, including individuals with nonreactive and wide pupils and a Glasgow coma scale of 3 on admission or following successful cardiac reanimation. Those surprisingly good results were obtained despite the fact that the neurological conditions of the head trauma victims probably further deteriorated from admission up to an average survival of 16 h, when a 24-h treatment with moderate hypothermia was initiated (25).

The mechanisms that account for recovery from such a pre-mortal state may include a) avoidance of detrimental effects related to apnea testing (26), b) normalization of ICP (recirculation from GIP - see Figure 3) during cooling to 33°C (27), c) regression of brain edema (27), d) inhibition of the detrimental cascade of neurochemical events triggered by a transient ischemic insult (28), and e) prevention of intracranial thermal pooling that increases brain temperature to levels capable of damaging vascular and neuronal proteins (29).

Brain temperature may reach more than 2°C above rectal temperature, and antipyresis effectively reduces this difference (30). In addition to reducing acute neuronal damage (31), postischemic administration of an antipyretic drug prevented the development of chronic neurodegeneration when associated with the hypothermic treatment in rats (32). Accordingly, Jones and co-workers (33) found hyperthermia to be one of the most important determinants of poor outcome following head trauma. Prevention of arterial hypotension also impedes intracranial thermal pooling (29), and may act synergistically with antipyresis to protect the injured brain tissue.

Cases of basilar artery occlusion presenting apneic coma seem to evolve invariably to death when recirculation is not induced (34).

In contrast, intra-arterial thrombolysis has been reported to induce remarkable functional recovery from basilar artery occlusion in a case of apneic coma and cephalic areflexia for 4-6 h (35). A subset of these cases may therefore sustain ischemic penumbra of the brain stem for a few hours from the onset of symptoms, and respond to timely intra-arterial thrombolysis, provided that apnea is not allowed for the diagnosis of brain death.

Absence of clinically detectable cephalic reflexes may occur in association with other signs of preserved brain stem function. Cortical somatosensory-evoked potentials were abolished 46 h but not 2.5 and 22 h after the onset of brain stem death syndrome in a case of cerebellar hemorrhage (36). Similarly, the existence of spinal cord cardiovascular centers does not exclude the brain stem as the anatomical site responsible for maintenance of normal blood pressure, or for the hemodynamic responses to surgical incisions for removal of transplantable organs in patients currently diagnosed as brain or brain stem dead (37). Rather, the absence of a recordable period of profound hypotension that follows acute inactivation of vasomotor centers by ischemia due to rising intracranial pressure is not consistent with that diagnosis (37).

The diverse cephalic reflexes evaluated for the clinical diagnosis of brain death do not disappear simultaneously as the blood supply to the brain stem decreases (38), suggesting that some synaptic circuits expend higher amounts of energy than others. Similarly, both the neuronal control of hemodynamic conditions and the verification of somatosensory-evoked potentials may require lower levels of blood supply than the demonstration of cephalic reflexes upon neurological examination. Accordingly, even the evidence for one single and depressed sign of brain stem activity may imply levels of infratentorial blood flow above the threshold associated with disruption of ionic ho-

meostasis of neuronal cells. Therefore, these signs may identify patients with a higher likelihood for recovery following resuscitative hypothermia (39).

As compared to tests for those synapse-dependent functions, which are expected to be cumulatively suppressed as BBF falls from around 35.0 ml 100 g^{-1} min^{-1}, the validation of direct tests for intracranial circulatory arrest is even less clear, and may provide paradoxical results. Even after fulfillment of clinical diagnostic criteria, the vertebro-basilar artery remained visible on 2 consecutive daily angiograms in a case of infratentorial hemorrhage (40). Other cases of delayed or partial opacification of the intracranial arteries following the diagnosis of brain death have been reported (41-46). Conversely, angiography may fail to detect intracranial blood flow despite indirect evidence for continuous endocrine activity of hypothalamic nuclei (8,9). These data contradict the long-held assumption that the absence of angiographic images of brain arteries should be considered an indisputable evidence for intracranial circulatory arrest. Actually, for optimal visualization of vascular images, the contrast media must be infused intra-arterially at specific rates considering a normal range of intracranial blood flow (47). A reduced perfusion pressure may therefore decrease the brain blood flow and affect vascular opacification (48). Angiographic findings as well as the results of other less reliable confirmatory tests therefore are to be correlated with specific levels of intracranial blood flow.

The hypothesis of GIP is supported by both direct and indirect data, and is in agreement with previous criticisms against a) the definition of brain death by statute as "irreversibility of cessation of brain function" (49), and b) current misconceptions regarding diagnosis and prognosis of death (50). More effective therapeutic resources based on new pathophysiological concepts may improve the prognosis of patients in critical

conditions. Likewise, the confirmation of the GIP hypothesis may indicate the value of hypothermia and other resources for the treatment of a subset of patients in a coma with cephalic areflexia nowadays conceivably misdiagnosed as neurologically unrecoverable.

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