

ORIGINAL PAPER

PERIOPERATIVE SERUM BRAIN NATRIURETIC PEPTIDE AND CARDIAC TROPONIN IN EMERGENCY INTRACRANIAL VASCULAR SURGERY

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SUMMARY

Background: intracranial bleeding is often associated with a large variety of cardiac derangements, ranging from mild regional wall motion abnormalities to frank cardiac insufficiency. There are well known associations between severe SAH and acute ischemic stroke with new occurred cardiac insufficiency. Some authors report cardiac abnormalities in major head trauma with intracranial bleeding.

Method: we conducted a prospective study during 2012 with all intracranial bleeding presented to our department and subjected to surgery, but with no prior history of cardiac disease. cTNI and NT-proBNP were measured pre- and post- operatively and we also recorded electrical changes on a 12 lead ECG, and echocardiographic changes (regional wall motion abnormalities and left ventricular ejection fraction).

Results: from 82 patients submitted to emergency surgery for intracranial bleeding, 37 had a cTNI $I > 0.3$ ng/ml (45%), 57 (69.5%) had a significant increase of > 200 pg/ml in NT-proBNP. Pover normal values as reported by hardware manufacturer and these levels were incrementally related to SAH severity (Hunt and Hess scale and Fisher scale), to GCS and midline shifts for intracranial hematoma. Numerous patients with increased cardiac troponin had also ECG abnormalities (QT prolongation, various arrhythmias) decrease under 50 % of ejection fraction and ventricular wall motion abnormalities as noted on echocardiography.

Conclusion: Cardiac injury is incrementally worse with increasing intracranial bleeding severity and associated with persistent QTc prolongation and ventricular arrhythmias. Regional wall motion abnormalities and depressed ejection fraction were recorded early in the course of disease and persist to some degree in the majority of those affected.

RÉSUMÉ

La peptide natriurétique du sérum cérébelleux intraopératoire et la troponine T cardiaque dans la chirurgie vasculaire intracrânienne d'urgence

Introduction: Les hémorragies intracrâniennes sont souvent associées aux troubles divers de la fonction cardiaque, à partir de troubles de la cinétique de la paroi cardiaque jusqu' à la insuffisance cardiaque. L'existence d'associations entre les hémorragies intracrâniennes apparues en cas d'hémorragie sous-arachnoïdienne (HAS) ou accident vasculaire cérébral (AVC) ischémique majeur et l'apparition des malfunctions cardiaques nouvellement installé est bien connue. Certains auteurs ont rapporté l'apparition de complications cardiaques en cas de traumatisme crânio-cérébral accompagné par une hémorragie intracrânienne.

Méthode: On a effectué une recherche prospective pendant toute l'année 2012, y comprenant tous les patients avec une affection vasculaire intracrânienne (des hémorragies d'étiologies variées et AVC ischémique majeur), et sans antécédents de maladie cardiovasculaire, qui se sont présentés dans notre clinique ayant subi une opération. Les valeurs du cTNI et du NT-proBNP ont été mesurées avant et après l'opération, notamment au moment de l'admission au département d'urgence et après l'opération. On a enregistré aussi les changements électriques par EKG avant et après l'opération et à l'aide de l'échographie on a enregistré les troubles cinétiques de la paroi myocardique.

Résultats: De tous les 82 patients qui ont subi a une operation en urgence pour des dommages vasculaires intracérébraux, 37 ont eu le cTNI > 0.3 ng/ml (45%) et en 57 des cas (59,5%) on a remarqué une augmentation significative de plus de 200 pg/ml du NT-pro BNP par rapport aux valeurs normales indiquées dans le manuel d'utilisation de l'analyseur. Ces niveaux ont été mis en

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Key words: cardiac arrhythmia, cardiac troponin T, echo-cardiography, electrocardiography, left ventricular ejection fraction, NT-proBNP, intracranial bleeding, wall motion abnormality

BACKGROUND

Several acute intracranial insults, in particular cerebrovascular events, are associated with cardiac abnormalities that can range from sub-clinical to life threatening. These are caused by excessive cardiac sympathetic stimulation (1) and are characterized by the well known “contraction band necrosis” (2), which is very different from the “coagulative necrosis” usually observed after cardiac ischemic injuries. Patients with aneurysmal subarachnoid hemorrhage (SAH) exhibit cardiac injury prevalence ranging from 17% to 40%. (3,4) Two serum biomarkers are frequently used to assess cardiac involvement: cardiac troponins, which are detectable after an even subtle myocardial necrosis and brain natriuretic peptide (BNP), which is released by the ventricular myocardium in response to increased wall stress or cellular hypoxia (13) and has a recognized diagnostic and prognostic value in various settings, including heart failure and acute coronary syndromes (14).

Brain natriuretic peptide (BNP) is a potent natriuretic and diuretic factor with very effective vasodilator activity (5). It is mainly produced and released by the cardiac ventricle in response to overload, and to sympathetic and humeral stimulus. (5,6) By its systemic effect, BNP reduces blood pressure (BP) and plasma volume. (5) In aneurysmal subarachnoid hemorrhage (SAH), BNP plasma concentrations were found to be elevated and responsible for the profound diuresis and natriuresis observed in many patients. (7,8) Due to its effect on BP and plasma volume, it has been suggested that elevated plasma BNP concentration might exacerbate cerebral blood flow (CBF) reduction in cerebral vasospasm. (10,11,12) In some cases, a clinically evident cardiac involvement occurs after brain damage.

This has been particularly studied after subarachnoid hemorrhage (SAH) and is most often associated with ST segment and T wave abnormalities, QT prolongation, and arrhythmias on the electrocardiogram (ECG). (15) In various critical neurological settings, especially in those involving intracranial bleeding from various origins, serum cardiac troponins and BNP elevation occurs without any evident cardiac symptom. Elevated cardiac troponin T (cTnT) has been found in nearly 30% of patients with ischemic stroke (16,17) and is correlated with infarctions of specific brain

corrélation avec la sévérité de l'hémorragie intracrânienne apparue en cas de HAS (échelle Hunt et Hess et échelle Fisher), avec un déplacement de la ligne médiane au CT en situation d'hématomes intracrâniens. De nombreux patients de ceux appartenant au groupe qui ont eu le cTNI augmenté ont présenté aussi de divers troubles électriques sur l'EKG (l'élongation de l'intervalle QT, des arythmies diverses), la diminution parfois importante du débit cardiaque inférieur à 50% et des troubles de la cinétique de la paroi myocardiaque enregistrés à l'aide de l'échographie.

Mots-clés: arythmie cardiaque, troponine T cardiaque, échographie, EKG, la fraction d'éjection ventriculaire, NT-proBNP, hémorragies intracrâniennes, anomalie du mouvement pariétal

regions. (18) Elevated BNP levels also occur immediately after stroke and predict an unfavorable clinical outcome. (19)

MATERIALS AND METHODS

The study was approved by our local Committee of Ethics and we prospectively enrolled all the patients presented to our Emergency Room with intracranial bleeding from various origin between January and December 2012. All enrolled patients or their closest relatives signed an informed consent. Intracranial bleeding was documented by CT Scan for hematoma and Stroke and digital subtraction angiography and CT Scan/AngioMRI for SAH and ruptured AVM. All were adults (age 49 ± 23 years) with a GSC of 11 or less for primary hematoma or posttraumatic hematoma, Hunt and Hess scale ≥ 3 and a Fisher scale ≥ 2 for SAH and post-traumatic SAH. Severity of stroke was assessed using the National Institutes of Health Stroke Scale (22) (NIHSS). The presence or absence of intracranial mass effect of hematoma was also recorded for each patient before surgery: this was defined as evidence of a midline shift > 5 mm.

Exclusion criteria were: American society of anesthesiologists physical status (ASA-PS) > 4 (23), revised cardiac risk index (RCRI) > 2 (24), pregnancy, age above 80 or below 18, previous history of cardiac disease, myocardial infarction, cardiac insufficiency NYHA ≥ 2 , pre-existing neurological diseases, known acute or chronic renal insufficiency and refusal to sign the informed consent form.

Aneurysms were secured in the operating room with surgical clips (9) or the interventional radiology suite with endovascular embolization (14). Anterior communicating artery aneurysms (6) were addressed by orbitoperional approach. The ACoA is one of the most common locations for intracranial aneurysms as 30 to 37% occur in this location. Aneurysms of the ACoA account for the largest percentage of ruptured aneurysms (39%) and are associated with the worst surgical outcomes among all anterior circulation aneurysms. No patient required sylvian fissure dissection and one underwent gyrus rectus resection (the patient had high-riding ACoA aneurysms > 15 mm above the cranial base). Two patients underwent clipping of multiple anterior circulation aneurysms at the time of ACoA clipping. Approach-related complications recorded were 2 levator-palpebrae paralyse, which completely recovered within 6

weeks of surgery. 2 patients working before surgery returned to work within an average of 2.7 months (range, 1 to 6 months); the remaining patient returned to baseline but elected to retire. One patient who was unable to work (sequel from SAH from a middle cerebral artery aneurysm) returned to his previous condition soon after ACoA clipping. Neither patient who underwent gyrus rectus resection presented any deficits at follow-up. No frontobasal hypodensities were noted on postoperative CT scans performed within 48 hours of surgery. Posterior communicating artery (PCOM) (3) aneurysms are one of the most common aneurysms encountered by neurosurgeons and neurointerventional radiologists and are the second most common aneurysms overall (25% of all aneurysms) representing 50% of all internal carotid artery (ICA) aneurysms. Not only these aneurysms can present with a typical subarachnoid hemorrhage, but also they can present with an isolated oculomotor nerve palsy (OMNP) or a non-traumatic subdural hematoma (SDH). In addition, because of the variation in the anatomy of this aneurysm and its parent arterie(s), these aneurysms can be among the easiest and the most difficult to treat either surgically or endovascularly. The PCOM artery is one of the first branches visualized during dissection of the carotid cistern and the dome of the aneurysm is typically directed away from approach trajectory. Wide dissection of the sylvian fissure is typically not necessary for successful clipping of these aneurysms. In fact, retraction of the temporal lobe is often avoided (particularly when the fundus points laterally) until the surgeon partially exposes the neck of the aneurysm. Anterior clinoidectomy is rarely required for clipping of PCOM aneurysms. Park et al, found that only 6 out of 96 patients with PCOM aneurysms required clinoidectomy during surgical treatment. Although clipping of PCOM aneurysms may occasionally be met with complications, outcomes tend to be good for the majority of the cases. Wirth retrospectively reviewed operative morbidity amongst unruptured aneurysms. He found that PCOM aneurysms had the lowest operative morbidity (5%) compared to aneurysms in other locations (MCA 8%, ICA 12%, ACOM 16%). Although data from this study are somewhat old, and techniques and microscopes have improved surgical outcomes, PCOM aneurysm in general continues to be among the least complicated aneurysms to treat surgically. However, because of the emergence of endovascular therapy and significant technical advancements made with stent/balloon-assisted embolization, aneurysms that come to surgical management will likely be larger and more complicated. Routine care included prophylactic nimodipine (generally 60 mg every 4 hours) and magnesium. Blood pressure was managed with antihypertensives (labetalol, urapidilum) or vasopressor/inotropics (norepinephrine, dopamine, dobutamine) to maintain systolic blood pressure ≤ 140 mm Hg before aneurysm clipping and ≥ 140 mm Hg afterward. Normovolemia was maintained with crystalloids and colloids guided by central venous pressure monitoring.

Primary cerebral hematoma was evacuated using a standard craniotomy (40) maintaining the same protocol as previously described at aneurysm clipping, and using

various approaches accordingly to hematoma sites.

Decompressive craniectomy was used in ischemic stroke (5 patients) when CT evidence for extremely raised intracranial pressure was obtained and correlated with clinical findings. The size of the craniectomy directly correlates with degree of expansion (Gaa M 1990). Small craniectomies are associated with further infarction and hemorrhage at the sites of the craniectomy margin. Mortality rates have also been reported as elevated in small diameter craniectomies (Wagner S 2001). This is due to the venous congestion that occurs in the herniated brain tissue as it is restricted and compressed by the bony boundary of the skull defect. Brain parenchyma herniates through the bony defect which in essence is the desired effect but compression of parenchyma adjacent to the bony boundary in a small craniectomy leads to venous congestion, venous infarction and further damage to brain tissue. This is more common in craniectomies smaller than 8 cm in diameter. Doubling the diameter of a craniectomy from 6 cm to 12 cm increases the decompressed brain volume from 9 ml to 86 ml. A lower margin of craniectomy relative to the floor of the middle fossa has also been described with improved outcomes. This can be related to the state of decompression of the mesencephalic cisterns. Compression of the basal cisterns is known to impair clinical outcome, a larger craniectomy to the base of the brainstem could minimize brain stem compression (Toutant S 1984; Munch E 2000). The state of the mesencephalic cisterns correlates greatly with the distance of the craniectomy to the temporal cranial floor.

Ruptured AVM were secured in the operating room with surgical clips (3) using a surgical technique very similar to aneurysmal repair.

Posttraumatic hematoma was addressed in the operating room using a multidisciplinary approach, to correct all the multiorgan dysfunction that occurred after the traumatic event (17).

Cardiac troponin cTnI and NT-proBNP was measured with a fluorescent enzyme immunoassay (Pathfast[®], Mitsubishi Chemical-DIA Instruments) in the Emergency Department at initial presentation and postoperative period (day 1). Peak cTnI was used as a continuous variable and also dichotomized as abnormal for levels ≥ 0.3 ng/mL by local clinical criteria. NT-proBNP was considered positive at levels ≥ 450 pg/ml, corrected with age. (20,21) ECG was recorded with a standard ECG machine and echocardiography was performed with GE Vivid q (GE Healthcare, USA) on a transthoracic approach. ECG was manually analyzed and RR, PR, QRS were measured, and QT intervals and averaging 3 beats excluding U-waves from QT interval measurement and rejecting bundle branch block from QT determinations.

Statistics

Comparisons between subjects with and without cTnI ≥ 0.3 ng/mL, NT-proBNP ≥ 450 pg/ml, QT ≥ 470 ms and newly installed left ventricular wall motion abnormalities were evaluated by χ^2 analyses, Student t tests, or nonparametric tests where appropriate.

RESULTS

In hematoma group we noticed a significant raise cTnI level in 32% and an above normal value of NT-proBNP in 60% of the subjects enrolled in our study and this, in conjunction with QT prolongation 21% and with regional wall motion abnormalities noted in 19% allow us to consider that the worse the bleeding the higher the plasma changes and cardiac suffering will be. (Tables 1, 2)

In the SAH group a greater proportion of patients exhibited a peak cTnI ≥ 0.3 ng/ml (42%) and we noticed that the patients with higher values of cTnI and NT-proBNP were older when compared with the others, but still relatively young (mean age 63 versus 48 years) $p=0.002$. There was no difference in gender ($p=0.83$). the same patients with raised above normal values of plasma cardiac markers exhibit also electrical disturbances (QT prolongation $p=0.001$) and RWMA ($p=0.001$) but the study group is rather small to draw statistical significant conclusions and further studies on this issue are needed. More patients with cTnI ≥ 0.3 ng/mL had aneurysm clipping (42% versus 36%) and less embolization (58% versus 63%, $P=0.016$). Significantly more patients with cTnI ≥ 0.3 ng/mL had greater aSAH severity by

clinical symptoms on admission (Hunt/Hess, $P=0.001$) and blood load on CT scan (Fisher grade, $P=0.022$). There was a stepwise rise for mean values for cTnI at each Hunt/Hess grade for increasing severity and, we consider that cTnI is a good outcome predictor in this settings. Mean QTc was longer for patients with cTnI ≥ 0.3 ng/mL (483 ± 65 ms versus 430 ± 16 ms, $P=0.0001$). At a 470-ms cut point, significantly more patients with cTnI ≥ 0.3 ng/mL had prolonged QTc (80% versus 20%, $P \leq 0.0001$). The overall RWMA prevalence was 30% on the echocardiogram (8 of 26), and patients with cTnI ≥ 0.3 ng/mL were significantly more likely to exhibit a RWMA (73% versus 7%, $P=0.0001$).

We enrolled 5 patients with severe ischemic stroke (as documented on initial MRI scan) 3 men and 2 women, median age 69 ± 5 years, with history of mild cardiac disease or none. Stroke severity, as assessed by NIHSS, was 19 ± 5 . Raised cTnI value above cut-off limit was recorded in 3 of 5 patients and above normal NT-proBNP was found in all of our patients and there were strong correlations between raised plasma values of cardiac markers and electrocardiographic and echographic findings. Due to small sample we were unable to obtain statistically significant conclusions in this case.

Table 1 - Demographics and clinical characteristics of the Hematoma Group

	No. of patients (57)	cTnI ≥ 0.3 ng/m	NT-proBNP ≥ 450 pg/ml	QT ≥ 470 ms	RWMA
Age 43 ± 20 years (SD)					
Male/female	35/22				
Traumatic/Spontaneous	17/40				
Type of injury					
Subdural hematoma	36	11	21	8	6
Epidural hematoma	15	4	9	3	3
Intracerebral hematoma	6	3	4	2	2
Midline shift	9 mm \pm 3 mm (SD)				
GCS on admission	7 \pm 3				

Table 2 - Demographics and clinical characteristics of the SAH Group

	No. of patients (26)	cTnI ≥ 0.3 ng/ml	NT-proBNP ≥ 450 pg/ml	QT ≥ 470 ms	RWMA
Age 49 ± 18 years (SD)					
Male/female	15/11				
Type of injury					
Ruptured Aneurysm (SAH)	23				
Surgically repaired	9				
Endovascular embolization	14				
Ruptured AVM	3				
Hunt and Hess Score					
3	13	6	6	4	2
4	9	3	5	4	3
5	4	2	4	2	4
Fisher Score					
2	11	3	4	4	2
3	12	7	8	4	4
4	3	2	3	2	3
GCS on admission	9 \pm 3 (SD)				

DISCUSSION

The results of our work suggest that NT-proBNP plasma concentrations are elevated shortly after head injury, intracranial bleeding or aneurysmal rupture with SAH. The high circulatory levels of NT-proBNP, which were found after TBI, might suggest that the initial injury induced markedly increased production of BNP from the heart ventricles as a result of increased sympathetic flow, the same mechanism as suggested for ruptured aneurysmal SAH. According to Tsubokawa (23) a higher increase of BNP is observed in patients suffering from severe neurological deficit findings, which are similar to our findings showing significant correlation between trends in BNP plasma concentration and outcome. Our findings in non-traumatic hematoma are consistent with other authors, the bigger the hematoma, with important midline shift and newly occurred neurological deficit the greater the increase in plasma NT-proBNP and cTNI, although, the latter is inconsistent across study group. Cardiac injury is common after aneurysmal SAH and was observed in 42% (11 out of 26) of our patient population with minimal cardiac disease history. Our findings confirm that elevated cTnI prevalence is almost equal to values reported by some others [Naidech et al, 42% (2); Rampappa et al, 37% (22)], our data demonstrate cardiac injury prevalence across our entire prospectively evaluated ruptured aneurysmal SAH population. In aneurysmal SAH, Tomida et al. and Wijidicks et al. have suggested that increased BNP plasma concentrations can be of cardiac origin. According to Tomida, augmented cardiac release of BNP may be triggered by stress and noradrenaline release. Consistent with our findings, the neuroscience literature indicates that neuro-cardiac injury contributes to poorer outcomes independent from subarachnoid hemorrhage severity alone (25,26,27), but mechanisms remain unclear. Our result suggests that elevated cTnI prevalence increases as SAH severity increases. Consistent with literature findings (25), our study demonstrates that the cTnI rises in proportion to the degree of aSAH severity in a stepwise fashion (ie, the higher the Hunt/Hess grade, the higher the mean cTnI value). For the time being, it is unclear what prognostic significance have alterations in plasma concentrations of cTNI and NT-proBNP and how can these cardiac markers be used for scoring and predicting outcome of brain trauma with SAH. It is well known that even modest and transient cardiac functional abnormalities may decrease the perfusion to the area of injured brain and the relationship may be inverse. Another explanation may reside in inflammatory response which may contribute to raise plasma values of cardiac markers [ex. Septic shock (28), acute massive stroke (29), ARDS (30)]. But inflammation alone cannot provide an explanation for decreased cardiac stroke volume and RWMA distribution in study group population. In Hrahanak study (25), late echocardiography noted that although 68% of patients with RWMA showed some improvement, only 26% had normalized. Kovethal (45) reported that 70% of patients with RWMA had improved by 5 days post SAH but did not report if return was to normal, Khush (46) indicated that 75% to 90% of patients with

RWMA improved at 5 days, again not specifying if improvement indicated normalization. Sugimoto (47) reported on 11 patients with RWMA, all normalizing by Day 10. Hrahanak study (25) data demonstrated that at late echocardiogram (mean, 7 days; range, 5 to 12 days), most RWMA had improved but failed to normalize. This finding is consistent with myocardial stunning behavior where in the time needed for full recovery ranges from 14 to 90 days, perhaps making it prudent to follow patients with RWMA with a repeat echocardiogram at 6 to 12 weeks to determine if dysfunction has normalized as expected with stunning.

According to Tsubokawa (23), a higher increase of BNP is observed in patients suffering from severe neurological deficit findings, which are similar to our findings showing significant correlation between trends in BNP plasma concentration and outcome.

Massive acute ischemic stroke is a leading cause of cardiac abnormalities and the fatality rate is rather high in this settings. Authors reports variable increase in cTnT [from 4.6% (32) to 17% (33)], cTNI [elevate in 7.8% (32)], NT-proBNP and other electrical and echographic abnormalities in massive stroke. Heart failure is an independent predictive factor for death after first cerebral infarction. (34,35) In patients with chronic heart failure, cTnT is increased and the level parallels the severity of the disease. (36) Elevated levels of cTnT also identify patients with latent and progressive myocardial damage and with an increased risk of cardiac events. (37) Measurement of NT-proBNP has recently become valuable in the rapid diagnosis of heart failure (38) has been used for risk stratification (39,40), and is even predictive of short-term mortality. (41) Because heart failure is associated with dependency after stroke (42), early recognition using NT-proBNP could help rapid initiation of an adequate therapy and might consecutively improve clinical outcome. According to one study (32), which is the first providing data about the role of NT-proBNP in acute stroke, nearly two thirds of acute stroke patients show raised NT-proBNP levels. This may indicate the presence of at least slight ventricular dysfunction or heart failure in a major proportion of ischemic stroke patients. Another reason for a generally higher level of NT-proBNP in stroke patients could be the sympathetic activation after stroke. (43,44) Our findings are consistent with Thoraleif. We consider cardiac dysfunction is very common as documented by increase in cTNI over cut-off in 60% of patients and significant increase plasma level of NT-proBNP. Newly installed electrocardiographic abnormalities and RWMA are common (4 out of 5 patients). This can be explained also by sympathetic activation in stroke which precipitate a known cardiac insufficiency or produce a newly installed one.

CONCLUSION

In conclusion, our study confirms frequent cardiac implications in intracranial bleeding as shown by increase in plasma levels of cTNI and NT-proBNP and documented by QT prolongation and newly installed and persistent

RWMA. However, due to small size of our study group we cannot provide reliable and statistically significant results to sustain our hypothesis. Further research is needed on this issues in order to evaluate how this parameters, in conjunction with neurologic and neurosurgical classifications of intracranial bleeding, can be used to assess the outcome of individual patients.

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