A longitudinal cohort of stress cardiomyopathy screening with speckle-tracking echocardiography after moderate to severe traumatic brain injury

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Research

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Abstract

Background. Stress cardiomyopathy is common after subarachnoid haemorrhage but has been scarcely described after traumatic brain injury.

Methods. Mono-centric longitudinal study in moderate to severe traumatic brain injury (Glasgow coma score ≤ 12). Evaluation of global longitudinal strain and 2-dimension trans-thoracic echography at day-1, day-3 and day-7. The primary outcome was the incidence of stress cardiomyopathy assessed with global longitudinal strain. Secondary outcomes were the relationship between global longitudinal strain and mortality, plasma levels of metanephrine and normetanephrine in patients with traumatic brain injury and subarachnoid haemorrhage to explore the mechanisms of stress cardiomyopathy.

Results. We included 100 patients from March 2014 to August 2017. Twenty (20%) patients died in the intensive care unit. At day 1, global longitudinal strain (-20.3(±3.6)%) and left ventricular ejection fraction (65.9 (±10.8)%) were preserved. Nine (9%) patients displayed impaired global longitudinal strain (-13.3[-14.5/-11.6]%) at baseline, with significant improvement at day-3 and day-7 ($p<0.0001$), compatible with stress cardiomyopathy. There was a slight global longitudinal strain improvement at day-3 in the overall population ((-22.2 (± 3.6)%, $p=0.004$), but was similar to baseline at day-7 (-20.7(± 3.3)%). Global longitudinal strain was not related to mortality ($p=1$). In 15 subarachnoid haemorrhage and 15 traumatic brain injury patients matched with age and severity, there were no differences in baseline normetanephrine or metanephrine plasma levels.

Conclusions. Stress cardiomyopathy could occur after traumatic brain injury, but global longitudinal strain remains preserved. The raised baseline metanephrine and normetanephrine is comparable in traumatic brain injury and subarachnoid haemorrhage patients. Thus, sympathetic hyperactivation is probably not the only mechanism involved in stress cardiomyopathy.

Background

Stress cardiomyopathy has been numerously identified after acute neurological injury such as subarachnoid haemorrhage, manifested by increased cardiac biomarkers [1] or echocardiographic anomalies [2]. In subarachnoid haemorrhage patients (SAH), stress cardiomyopathy identified with trans-thoracic echocardiography (TTE), is linked with poor outcomes in meta-analyses [3] and longitudinal multi-centric cohorts [2]. The mechanisms of stress cardiomyopathy remain controversial. It is hypothesized that a drastic increase in the blood levels of catecholamine [4] leads to systolic function impairment. Others have suggested that an increase in the intra-cranial pressure [4, 5] could lead to stress cardiomyopathy through autonomic storm with sympathetic overactivity. As a consequence, patients undergoing traumatic brain injury (TBI) might also display stress cardiomyopathy, which has been suggested by case reports [6]. However, there is little data in the literature regarding the incidence of stress cardiomyopathy in TBI patients. Speckle-tracking echocardiography (STE) can detect infra-clinical left ventricular systolic function impairment before the alteration of two dimension left ventricular

ejection fraction (LVEF) [7] and can detect stress cardiomyopathy in patients with aneurysmal subarachnoid haemorrhage [8].

We conducted a mono-centric study aiming at evaluating the incidence of stress cardiomyopathy, assessed with STE in patients undergoing moderate to severe TBI.

Methods

This was a monocentric observational study conducted in one Intensive Care Unit (ICU) of the University Hospital of Nantes, France from March 1st 2014, to August the 25th 2017. Since this study was purely observational, oral and written information were provided to the patient's next-of-kin at the early phase and to the patient when neurological recovery was deemed appropriate. This study was approved by the local ethics committee (Groupe Nantais d'Ethique dans le Domaine de la Santé – IRB N°6.02.2014). Moreover, blood samples are routinely performed in our ICU, for a biocollection in patients with brain-injury (IBIS, CPP Nantes Ouest IV, IRB approval N°46/11). For this biocollection, some patients included in the STE study provided consent. Whenever consent was not available from the patient, next-of-kin provided it.

Inclusion criteria

Patients ≥ 18 years old with a TBI, a baseline Glasgow Coma Score (GCS) ≤ 12 and with anomalies on a brain computed tomography, were eligible to this study.

Exclusion criteria

Patients were not included in case of ischemic cardiomyopathy, history of cardiac surgery, resuscitated cardiac arrest during initial management, thoracic trauma with an Acute Injury Score > 3, physical signs of brain death [9]. Pregnant women were not eligible. Patients who could not benefit from a TTE in the 24 hours after ICU admission, were not included. Patients were not upheld in the final analysis if STE quality was deemed inappropriate.

Strain echocardiography protocol

TTE was performed in the first 24 hours after the patient's ICU admission (Day 1) and on Day 3 and Day 7 after ICU admission. An electrocardiogram was systematically performed at the patient's arrival. High sensitivity troponin-T (Hs troponin-T) was routinely measured. One anaesthetist (R.C.) performed all TTEs and STE analysis. The following loops were recorded over three cardiac cycle with a high frame rate (≥ $70.s^{-1}$): left parasternal long and short axis views, apical two-, three-, four-, and five-chamber views. Doppler tissue imaging of the lateral and septal part of the mitral annulus, mitral inflow Doppler measurements (early (E) and late (A) peak diastolic velocities, E/A ratio) were measured. The velocity time integral (VTI) at the level of the left ventricular outflow tract was measured. Systolic function of the right ventricle (RV) was assessed through tricuspid annular plane systolic excursion (TAPSE) measurement.

Off-line and speckle-tracking analysis

The Left Ventricle (LV) end-diastolic diameter and wall thickness were measured with the M-mode in the left parasternal long axis view. The LV ejection fraction (LVEF) was evaluated with the Simpson method in the four and two-chamber views. The systolic S, diastolic E', and A' peak velocities, E/E' ratio were measured at the septal and lateral part of the mitral annulus.

The LV longitudinal strain was measured in the three-, four-, and two-chamber view allowing the calculation of global longitudinal strain (GLS) according to previously described technique [7]. TTE was performed with a Vivid S6® (GE Medical Systems, Milwaukee, WI, USA) equipped with a 2.5-MHz transducer. All echocardiographic acquisitions and off-line analyses were performed by a single anaesthetist expert in speckle-tracking analysis (R.C.) on an EchoPac® clinical workstation software (GE Medical Systems, Milwaukee, WI, USA). All speckle-tracking analyses were performed offline.

Data extraction

Demographic and general TBI data such as baseline GCS score, Marshall score, occurrence of intra-cranial hypertension [10], use of pentothal or decompressive craniectomy during hospital were recorded. General data such as ICU length of stay, duration of mechanical ventilation, in-ICU mortality, in-hospital length of stay and in-hospital mortality were recorded. Finally, neurological outcome was assessed in all patients at day-90 after ICU admission with a Glasgow Outcome Scale, collected by phone call [11].

Primary outcome

The primary outcome was to evaluate the incidence of stress cardiomyopathy with GLS, in TBI patients according to previously published definitions [12], combining longitudinal systolic function impairment [13] in the course of a stressful event, a moderate cardiac biomarker increase, improvement of systolic function over time and the lack of other possible diagnosis [8, 14]. A GLS >-16% was considered an a left ventricle longitudinal systolic function impairment [15].

Secondary outcomes. Echocardiographic data

The secondary outcomes of the study, were to describe the evolution of GLS as well as other echocardiographic parameters (LVEF, E/A and E/E' ratio, TAPSE) during the ICU course, and compare cardiac data between patients with moderate and severe TBI. We also described the potential link between baseline GLS and ICU mortality or 3-months neurological outcome (Glasgow Outcome Scale).

Secondary outcomes. Metanephrine and normetanephrine levels

Since the main hypothesis of stress cardiomyopathy occurrence is a major blood level catecholamine increase [4], we decided to explore the adrenergic response by dosing the blood levels of metanephrine and normetanephrine in patients with TBI and SAH, admitted in our institution [8]. Metanephrine and normetanephrine were dosed at the patient's admission, with the routine biocollection blood samples. For

these dosages, patients were randomly selected in the biocollection and were matched on age and baseline GCS. Fifteen TBI and 15 SAH patients were thus selected.

Dosages of metanephrine and normetanephrine blood level

Plasma from blood samples (containing K_2EDTA*) was collected and stored at − 80 °C until analysis. Plasma free metanephrine levels were measured using liquid chromatography–tandem mass detection (Waters Xevo® TQ-D mass spectrometer, Waters Corporation, Milford, MA, USA), after extraction from 50 microL of samples with a mixed-mode weak cation exchange solid-phase extraction (SPE) plate (Oasis® WCX 96-well µElution Plate, Waters Corporation), followed by rapid separation with hydrophilic interaction chromatography (ACQUITY UPLC® BEH Amide Column, Waters Corporation).

Statistical analysis

Continuous data are expressed as mean (± Standard deviation) or median (25–75 percentile) and categorical data as N(%) and are analysed with the Student or Mann-Whitney test, and χ^2 tests, respectively. The evolution of GLS over time was analysed with a one-way ANOVA. Pearson test was used to assess correlation between variables. According to previously published data [15], 22% of patients after moderate to severe TBI could display LVEF impairment. Owing to the sensitivity of STE in neuro-ICU patients we chose to include 100 patients with moderate to severe TBI, in order to detect at least 30 patients with STE impairment along with preserved LVEF [8]. Statistical significance was set at $p = 0.05$. All analyses were performed with Prism® v5, Graphpad®, California, USA.

Results

During the study period, 241 patients were screened and 100 were kept in the final analysis (Fig. 1). The mean age was 42.6 (± 19.6) and GCS upon admission was 7 [4–10]. We included 75 (75%) male and 25 (25%) female patients. Fifteen (15%) patients suffered from chronic hypertension. Decompressive craniectomy was performed in 8 (8%) patients, and 27 (27%) patients received pentothal in the ICU. The median duration of mechanical ventilation was 9 [5–14] days and the mean ICU length of stay was 16 [9–25] days. Demographic data and outcome are displayed in Table 1.

Table 1

Baseline characteristics.

	Overall population N = 100	**Severe TBI GCS 3–8 N = 66**	**Moderate TBI GCS 9–12 N = 34**	**p value**
Age	43 (± 20)	38.7 (± 19)	50.9 (± 19)	0.004
Gender Male/Female	75(75)/25(25)	49(74)/17(26)	26(76)/8(24)	1
BMI	24 (± 4)	24 (± 4)	25 (± 5)	0.09
GCS	7 [4–10]	5 [3–7]	11 [10–11]	
SOFA score	8 [7–10]	9 [8–10]	7 [6–8]	
SAPS II	44 (± 7)	44 (± 5)	44 (± 10)	0.3
Marshall score				0.9
I	4 (4)	3 (4)	1 (3)	
II	23 (23)	14 (21)	9 (26)	
III	8 (8)	6 (9)	2 (6)	
IV	6 (6)	4 (6)	2 (6)	
V	33 (33)	21 (32)	12 (35)	
VI	26 (26)	18 (28)	8 (24)	
Hb ($g.dL^{-1}$)	10.8 (± 2.3)	10.6 (± 1.9)	11.1 (± 2.2)	0.3
Lactates ($mmol.L^{-1}$)	2.1 (± 1.3)	2.2 (± 1.2)	1.6 (± 0.9)	0.03
pH	7.3 (± 1.6)	7.3 (± 0.08)	7.36 (± 0.06)	0.001
Troponin hs ($ng.L^{-1}$)	54 (± 153)	56 (± 185)	51 (± 94)	0.9
Hypertension	15 (15)	8 (12)	7 (20)	0.3
Diabetes mellitus	9 (9)	5 (7)	4 (12)	0.4
Active smoking	17 (17)	10 (15)	7 (20)	0.5
Alcohol abuse	17 (17)	8 (12)	9 (26)	0.09

Legend: Analysis of baseline data between moderate and severe TBI. Student t test or Mann-Whitney£, χ^2 test or with Fisher exact. BMI: Body Mass Index. GCS: Glasgow Coma Score. SOFA: Score Organ Failure Assessment. SAPS: Simplified Acute Physiologic Score. Hb: Haemoglobin. Troponin hs: hyper-sensitive.

	Overall population N = 100	Severe TBI GCS 3–8 N = 66	Moderate TBI GCS 9–12 N = 34	p value
Beta-blockers	7 (7)	4 (6)	3 (9)	0.6
Calcic inhibitor	6 (6)	4 (6)	2 (6)	1
MV duration (days)	9 [5–14]	9 [5–15]	7 [4–10]	0.04£
Norepinephrine (days)	3 [2–6]	4 [2–7]	3 [1–5]	0.03£
In-ICU mortality	20 (20)	15 (23)	5 (15)	0.5

Legend: Analysis of baseline data between moderate and severe TBI. Student t test or Mann-Whitney£, χ^2 test or with Fisher exact. BMI: Body Mass Index. GCS: Glasgow Coma Score. SOFA: Score Organ Failure Assessment. SAPS: Simplified Acute Physiologic Score. Hb: Haemoglobin. Troponin hs: hyper-sensitive.

Primary outcome

At day 1, LVEF was preserved (66 (± 11) % as well as GLS (-20.3(± 3.6) %). Nine (9%) patients displayed a significant GLS impairment (-13.3[-14.5/-11.6]%) at day 1 (Fig. 2). In these 9 patients, there was a significant improvement at day-3 (-22.2 [-25.1/-18.7]%) and day-7 (-21.1 [-23.2/-18.1]%) ($p < 0.0001$), compatible with stress cardiomyopathy. At baseline, the mean Hs-Troponin was 54.5 (± 161.2) $pg.mL^{-1}$. There was no correlation between day-1 Hs-Troponin and GLS ($r^2 = 0.04$, $p = 0.06$).

Secondary outcomes

The mean GLS at day 3 was − 22.2 (± 3.6) % and − 20.7(± 3.3) % at day 7. There was a slight significant improvement at day 3 ($p = 0.004$), but GLS remained preserved during the overall ICU course (Table 2). On day-1 right ventricular TAPSE was preserved (21.6 (± 7.6) mm) and significantly improved at day-3 (24.8 (± 5.3) mm, $p = 0.003$). There was no significant modification of the E/A and E/E' ratios or lateral S wave during the ICU course. Full echocardiographic data are available in Table 2. There were no statistically significant differences regarding baseline circulatory and echocardiographic parameters between patients with moderate (N = 34) and severe (N = 66) TBI (Table 3). Twenty (20%) patients died in the ICU. In the sub-group of patients with altered GLS (>-16%), 2 patients died. Altered GLS was not linked to either in-ICU mortality ($p = 1$) or day-90 Glasgow outcome score ($p = 0.07$).

Table 2

Evolution of circulatory and echocardiographic parameters from day 1 to day 7.

	Overall population N = 100			**p value**
	Day 1	Day 3	Day 7	
Heart rate	77 (± 21)	73 (± 20)	82 (± 18)	0.06
MAP (mmHg)	83 (± 12)	89 (± 13)	92 (± 14)	0.0002
LVEF, %	66 (± 11)	64 (± 13)	68 (± 9)	0.3
GLS, %	-20.3 (± 3.6)	-22.2 (± 3.6)	-20.7 (± 3.3)	0.004
E/A	1.5 (± 0.7)	1.6 (± 0.7)	1.4 (± 0.5)	0.2
Lateral E/E’	6.7 (± 2.4)	6.4 (± 2.3)	6.7 (± 2.7)	0.7
Lateral S, cm/s	9 (± 4)	9 (± 3)	9 (± 3)	0.9
TAPSE, mm	21.6 (± 6.5)	24.8 (± 5.3)	23.7 (± 5.6)	0.003

Legend: MAP: Mean Arterial Pressure. GLS: Global Longitudinal Strain. LVEF: Left Ventricular Ejection Fraction. TAPSE: Tricuspid Annular Plane Systolic Excursion. One-way ANOVA analysis.

Table 3
Baseline hemodynamic, cardio-vascular and echocardiographic parameters in the overall population and patients with moderate and severe TBI.

	Overall population N = 100	**Severe TBI GCS 3–8 N = 66**	**Moderate TBI GCS 9–12 N = 34**	**p value**
EKG				0.5
Sinus rhythm	99 (99)	65 (98)	34 (100)	
Negative T waves	4 (4)	3 (4)	1 (3)	
Positive-ST	2 (2)	2 (3)	0	
Hemodynamic				
Heart rate	77 (± 30)	77 (± 19)	77 (± 24)	0.9
MAP (mmHg)	83 (± 24)	80 (± 11)	87 (± 14)	0.008
Norepinephrine ($\mu g.kg^{-1}.mn^{-1}$)	0.26 (± 0.27)	0.28 (± 0.26)	0.21 (± 0.26)	0.2
Pentothal	11 (11)	8 (12)	3 (9)	1
ICP (mmHg)	12.6 (± 8.8)	12 (± 8)	15 (± 8)	0.08
TTE				
LVEF	66 (± 14)	66 (± 9)	66 (± 14)	0.7
Global Longitudinal Strain	-20.3 (± 3.6)	-20.5 (± 3.3)	-19.8 (± 4.1)	0.3
Cardiac output ($L.mn^{-1}$)	4.4 (± 2)	4.4 (± 1.4)	4.4 (± 1.7)	0.9
E/A	1.5 (± 0.7)	1.6 (± 0.7)	1.3 (± 0.4)	0.03
Lateral E/E'	6.7 (± 2.4)	6.7 (± 2.4)	6.7 (± 2.2)	0.9
Septal E/E'	8.7 (± 4.4)	8.7 (± 5.2)	8.9 (± 3.1)	0.8
TAPSE (mm)	21.6 (± 6.5)	21.7 (± 5.6)	21.2 (± 7.8)	0.7

Legend: Analysis of baseline data between moderate and severe TBI. Student-t test, χ^2 or Fisher exact test. TAPSE: Tricuspid Annular Plane Systolic Excursion.

Metanephrine and normetanephrine blood levels

In order to assess the adrenergic response, which could lead to stress cardiomyopathy in patients with brain injury, we measured baseline metanephrine and normetanephrine blood levels in 15 SAH and 15 TBI patients admitted in our institution. In patients with SAH, the median normetanephrine plasma level was

2.5 [0.7–4.2] nmol.L^{-1} and the median metanephrine level was 0.2 [0.17–0.23] nmol.L^{-1}. In patients with TBI, the median plasma level of normetanephrine was 2.9 [1-4.4] nmol.L^{-1} and the median metanephrine level was 0.17 [0.1–0.21] nmol.L^{-1}. There was no significant difference in the plasma levels of normetanephrine and metanephrine between TBI and SAH patients (Fig. 3).

Discussion

In our prospective large cohort of patients with moderate to severe TBI, STE can detect stress cardiomyopathy. However, this phenomenon seems less common than in SAH, and the catecholamine increase may not be the only factor to trigger stress cardiomyopathy.

Studies regarding left ventricular systolic function after TBI are scarce, unlike in SAH [2, 8]. In a monocentric cohort of moderate to severe TBI patients [15], the authors described that 22% of patients displayed abnormal LV function assessed with 2D echocardiography. However, the authors did not perform a systematic LV function assessment, but extracted data from TBI patients who underwent echography. This selection bias could artificially increase the incidence of cardiac anomalies. Moreover, the authors studied regional wall motion abnormality index, which bears substantial inter and intra-observer variability [16]. Recently, another monocentric study, evaluated fractional shortening in moderate to severe TBI patients [17]. The authors found a 22% incidence of decreased fractional shortening, exclusively in the group of severe TBI patients. The choice of fractional shortening as the primary outcome for LV systolic function evaluation is questionable. First, in case of cardiac segmental impairment which could occur during stress cardiomyopathy [12], fractional shortening is inadequate to study global systolic function. Second, this echographic parameter has not been extensively studied in the ICU to assess LV systolic function. In their article, Krishnamoorthy et al. [17] do not provide LVEF, rendering questionable the accuracy of LV dysfunction evaluated with fractional shortening. We used STE, which provides robust and sensitive evaluation of LV function [7, 18] and was already studied in SAH patients [8]. Another monocentric pilot study performed in TBI patients also suggested a preserved GLS at baseline [19]. Our data, suggest that stress cardiomyopathy may occur but is not frequent.

The pathogenesis of stress cardiomyopathy after acute brain injury is still a matter of debate. Increased intra-cranial pressure has been advocated [5], while another hypothesis is a drastic catecholamine blood level increase [4], which could be secondary to brain injury. This rapid increase of plasma catecholamine levels induces a modification of β-adrenergic cardiac receptors, from β_1 to β_2 type [4]; β_2 receptors have a negative inotropic effect and lead to systolic function impairment and thus stress cardiomyopathy after acute brain injury or other stressful events [12]. In the follow-up of SAH the blood level of catecholamine remains elevated [20]. However, other authors have also described a high level of catecholamine in TBI patients compatible with an adrenergic sympathetic autonomous system activation [21]. To the best of our knowledge, no studies have compared catecholamine levels in TBI and SAH patients. In our sample of 30 patients adjusted on age and baseline severity, the levels of metanephrine and normetanephrine were not statistically different. This raises the question of pathogenesis in stress cardiomyopathy after brain injury. Although it is very likely that stress cardiomyopathy is induced by a drastic increase of

circulating epinephrine and norepinephrine, hormones like estrogens could bear a protective role in this setting. In an experimental model of epinephrine-induced stress cardiomyopathy in ovariectomized female rats, the administration of estrogens significantly improved myocardial contraction and decreased the level of epinephrine [22]. Since SAH is more likely to occur in female patients around 50 years old, it is possible that modifications in the hormonal status due to menopause, could explain the higher prevalence of stress cardiomyopathy [23]. It is also possible, that SAH bears a higher cardio-vascular tropism than TBI, since SAH survivors display a major long-term cardio-vascular morbidity and mortality [24].

Our study has several limitations. Despite the size of our cohort, this is a mono-centric study and we cannot ascertain that this result would be retrieved by others. To this day, it remains difficult to perform multi-centre studies with STE, because of the high inter-vendor variability in strain data, although SLG seems the most reproducible strain parameter [25]. Also, our centre performs continuous osmotherapy in the management of TBI patients [10], which has been identified in an experimental model of haemorrhagic shock, as a potent enhancer of cardiac contractility [26]. Thus, the consequences of TBI on LV function could have been blunted by continuous osmotherapy resuscitation. Regarding the results on metanephrine and normetanephrine, this subset of patients is rather small. However, owing to the major differences in the stress cardiomyopathy rate that we detected in SAH patients in the same institution with the same methodology [8], we believed that such sample would have been enough to detect differences in metanephrine and normetanephrine levels. Also, we did not measure the blood level of catecholamine which is technically challenging. We measured normetanephrine and metanephrine which are both strong surrogate markers of the catecholamine level. Finally, dosages were performed several hours after the onset of TBI/SAH, and the very initial peak of plasma catecholamine is difficult to retrieve. We therefore cannot ascertain that TBI and SAH patients have the same plasma level of catecholamine.

Conclusions

Stress cardiomyopathy exists after TBI but remains rather uncommon. Thus, the systematic screening with biomarkers or echocardiography is questionable. The differences in stress cardiomyopathy rates between SAH and TBI patients may not be only related to plasma increase of metanephrine and normetanephrine.

Abbreviations

TBI
Traumatic Brain Injury
GLS
Global Longitudinal Strain
TTE
Trans-Thoracic Echocardiography
SAH

Aneurysmal Subarachnoid Haemorrhage
LVEF
Left Ventricular Ejection Fraction
LV
Left Ventricle
ICU
Intensive Care Unit
GCS
Glasgow Coma Score
TAPSE
Tricuspid Annular Plane Systolic Excursion

Declarations

-Ethics approval and consent to participate. Study approved by the local ethics committee (Groupe Nantais d'Ethique dans le Domaine de la Santé – IRB N°6.02.2014). Biocollection IBIS, CPP Nantes Ouest IV, IRB approval N°46/11.

-Consent for publication. Not applicable

-Availability of data and material. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

-Competing interests. Pr Karim Asehnoune received fees from Baxter, Edwards, LFB, Fisher and Payckel. Pr Roquilly received fees from MSD and Biomérieux. Pr Bertrand Rozec received fees from Baxter, Ethypharm, LFB, NordicPharma, Haemonetics, Fisher and Payckel, AstraZeneca. Pr Thierry Le Tourneau received speaker fees from Philips, Bayer and Shire. The other authors do not have other conflicts of interest to declare.

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-Authors contribution. RC, TLT designed the study. RC included patients, performed the TTEs and GLS analysis, statistical analysis, analysed results and wrote the article. KA, TLT analysed results and wrote the article. KNB, DM performed metanephrine and normetanephrine dosages, analysed results and edited the manuscript. MB, PJM, MLM included patients on site and edited the manuscript. AR, BR analysed the results and edited the manuscript.

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Figures

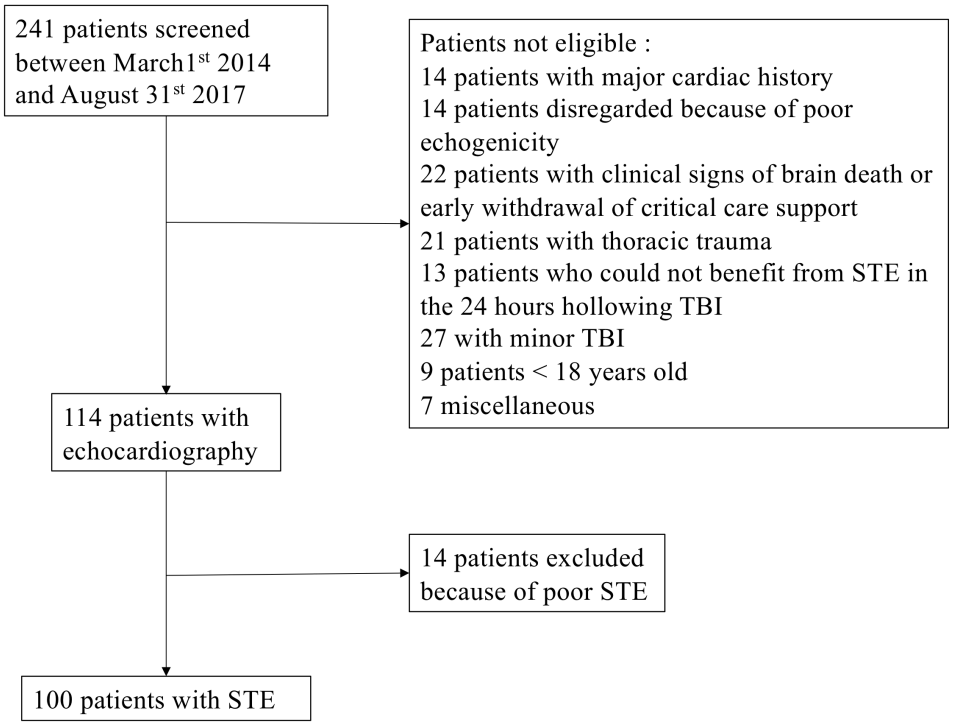

Figure 1

Flowchart.

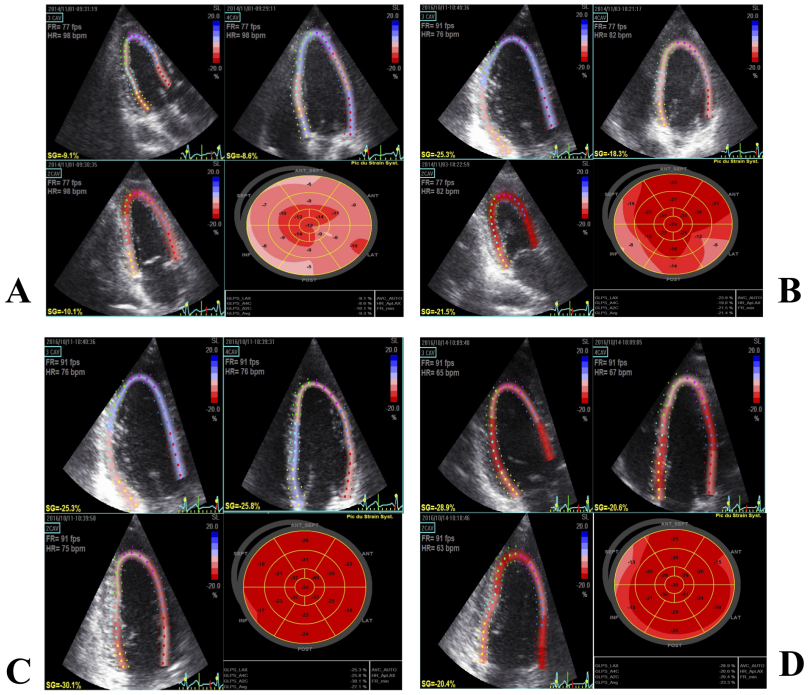

Figure 2

Example of Strain data in TBI patients with and without baseline impaired Global Longitudinal Strain. Panel A. The figure displays the Longitudinal strain in the 3 (upper left), 4 (upper right) and 2 chamber view (lower left), the overall Global Longitudinal Strain as well as the segmental regional longitudinal Strain data with the Bull's eye (lower right). This patient showed a marked impairment of the Global Longitudinal Strain at baseline. Panel B. Strain data in the same patient at day-3, showing a significant improvement. Panel C. Strain data in a TBI patient with preserved GLS at baseline. Panel D. Strain data in the same patient at day-3.

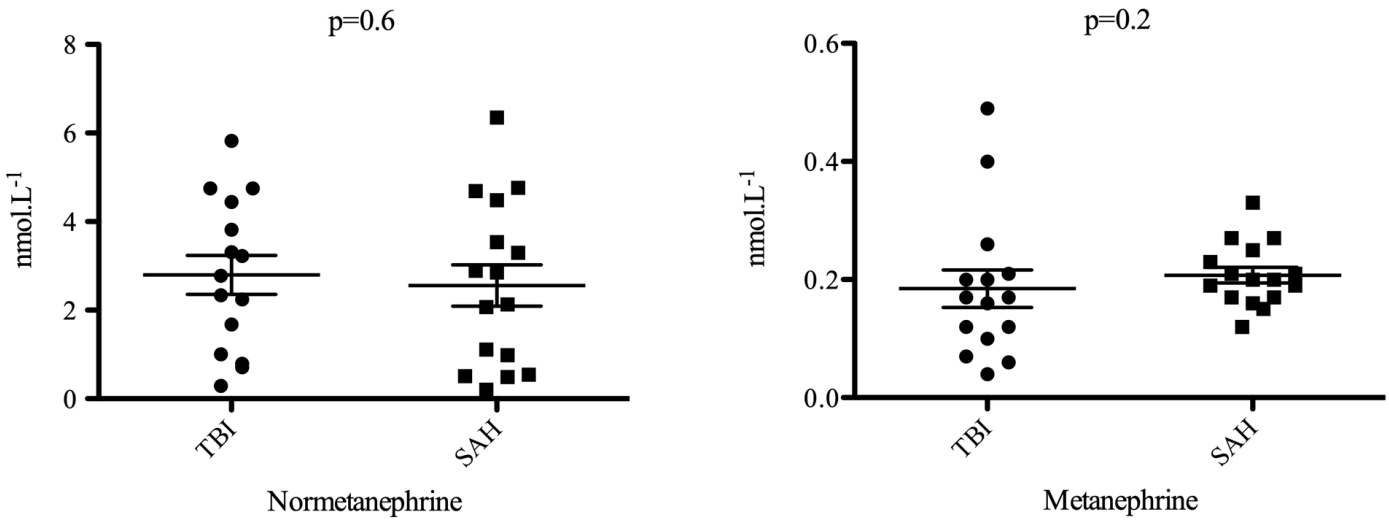

Figure 3

Baseline blood levels of metanephrine and normetanephrine in 30 patients with TBI or SAH admitted in a single institution. . There was no statistically significant difference in metanephrine and normetanephrine blood levels, in 30 randomly selected patients with TBI (15 patients) and SAH (15 patients), matched on age and baseline Glasgow Coma Score. Mann-Whitney test.