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## Research

**Cardiac troponin and skeletal muscle oxygenation in severe post-partum haemorrhage**

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**Abstract**

**Introduction:** Cardiac troponin has been shown to be elevated in one-half of the parturients admitted for post-partum haemorrhage. The purpose of the study was to assess whether increased cardiac troponin was associated with a simultaneous alteration in haemoglobin tissue oxygen saturation in peripheral muscles in post-partum haemorrhage.

**Methods:** Tissue haemoglobin oxygen saturation of the thenar eminence muscle (StO<sub>2</sub>) was measured via near-infrared spectroscopy technology. Two sets of StO<sub>2</sub> parameters (both isolated baseline and during forearm ischaemia-reperfusion tests) were collected at two time points: upon intensive care unit admission and prior to intensive care unit discharge. Comparisons were performed using Wilcoxon paired tests, and univariate associations were assessed using logistic regression model and Wald tests.

**Results:** The 42 studied parturients, admitted for post-partum haemorrhage, had clinical and biological signs of severe blood loss. Initial cardiac troponin I was increased in 24/42 parturients (0.43 ± 0.60 µg/l). All measured parameters of muscular haemoglobin oxygen saturation, including S<sub>recovery</sub>, were also altered at admission and improved together with improved haemodynamics, when bleeding was controlled. Multivariate analysis showed that muscular S<sub>recovery</sub> <3%/second at admission was strongly associated with increased cardiac troponin.

**Conclusions:** Our study confirmed the high incidence of increased cardiac troponin, and demonstrated the simultaneous impairment in the reserve of oxygen delivery to peripheral muscles in parturients admitted for severe post-partum haemorrhage.

**Introduction**

Severe post-partum haemorrhage (PPH) remains one of the two leading causes of maternal death despite the use of

intensive care unit (ICU) facilities [1-3]. We have previously suggested that, in addition to blood loss and the occurrence of haemorrhagic shock, increased plasma cardiac troponin I with electrocardiogram tracings suggestive of myocardial ischaemia may account for the morbidity associated with PPH [4]. Increased cardiac troponin was associated with low arterial blood pressure, increased heart rate (>115 beats/minute) and the use of catecholamines, suggesting an unbalanced myocardial oxygen consumption/delivery ratio. Whether the abnormal oxygen consumption/delivery ratio is only present in the myocardium or is a global phenomenon involving other organs, in severe PPH, remains to be elucidated.

The recent application of near-infrared spectroscopy to ICU patients allows continuous and non-invasive measurement of tissue haemoglobin oxygen saturation (StO<sub>2</sub>) in the thenar eminence muscle [5,6]. StO<sub>2</sub> was obtained via the ratio of oxygenated and deoxygenated haemoglobin measured by near-infrared spectroscopy [7,8]. A low StO<sub>2</sub> value has been suggested to predict organ dysfunction [9,10]. In addition to static StO<sub>2</sub> measurements, a forearm ischaemia/reperfusion test was recently applied in patients to allow dynamic measures of StO<sub>2</sub> [11,12]. Inflation of a cuff around the patient's arm decreases StO<sub>2</sub>, which recovers when the cuff is released. The slope of StO<sub>2</sub> recovery is altered in septic shock parturients [11,13]. Similar measurements have not been performed in haemorrhagic conditions.

We accordingly postulated that increased cardiac troponin might be associated with impaired oxygen consumption/

ICU = intensive care unit; PPH = post-partum haemorrhage; S<sub>occlusion</sub> = slope of tissue haemoglobin oxygen saturation decrease; S<sub>recovery</sub> = slope of tissue haemoglobin oxygen saturation ascent; StO<sub>2</sub> = tissue haemoglobin oxygen saturation.

delivery ratio in peripheral muscles. The haemoglobin tissue oxygen saturation of thenar muscle was therefore measured, before and after rescue therapy, in parturients admitted for blood loss related to PPH.

### Parturients and methods

Forty-two parturients with severe PPH, defined as blood loss >1,000 ml associated with haemorrhagic shock [14-16], were included in the present study. All parturients had attended primary-care centres located within or around Paris (Ile-de-France region) and were transferred to our centre when locally available treatment options became inefficient in controlling the bleeding. Our tertiary-care centre is specialized in severe PPH with standardized management procedures including two major therapeutic options: when bleeding still persists, haemostatic surgery and/or an angiography with uterine embolization is performed; or, if the bleeding has stopped, the patient is monitored under intermediate care. Eight parturients with no PPH were also studied as a control group.

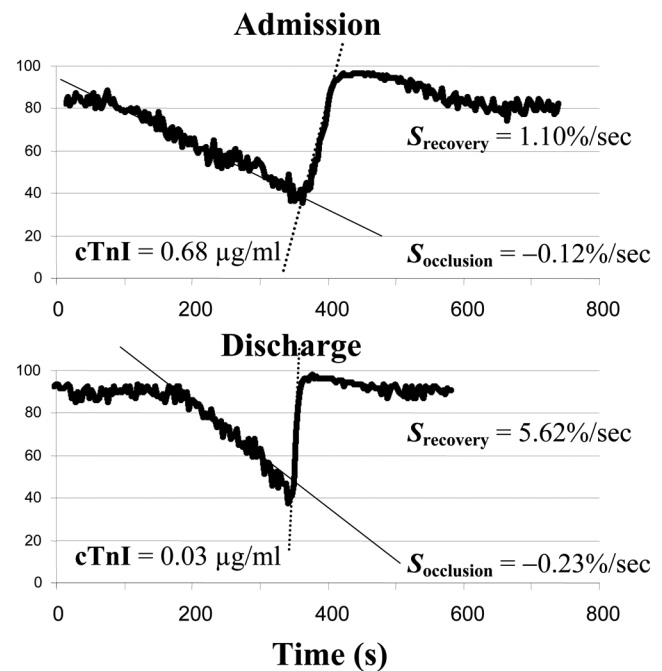
The following items were collected: medical history, obstetrical characteristics as obstetric procedure, details on the medical treatment, the type of surgical intervention performed, and the rate of blood transfusion. The following variables, previously described as indicators of bleeding intensity [4], were recorded during the first hour of ICU admission and at ICU discharge: the lowest systolic blood pressure and diastolic blood pressure, the highest heart rate, the lowest pH (IU), haemoglobin, prothrombin time (%) and fibrinogen (normal range = 2 to 4 g/l), and the highest lactate (normal range = 0.7 to 2.1 mmol/l) and troponin I level (normal range <0.04 µg/l).

### Quantification of haemoglobin saturation in the thenar eminence muscle

Near-infrared spectroscopy technology uses the principles of light transmission and absorption to non-invasively measure the ratio of oxygenated and deoxygenated haemoglobin within arterioles, capillaries, and venules of thenar skeletal muscle [17]. The location of thenar eminence was chosen because of little interference with skin or fat tissue on the obtained signal and because interstitial oedema is limited [7,18,19]. StO<sub>2</sub> was measured via a tissue spectrometer (InSpectra™ Model 325; Hutchinson Technology, Hutchinson, MN, USA) linked to a probe placed on the thenar eminence. This probe contains two fibre-optic endings with a spacing of 25 mm, allowing a 23 mm in-depth measurement [7,20,21]. StO<sub>2</sub> was continuously monitored and recorded using InSpectra™ software.

In addition to baseline measurements, StO<sub>2</sub> was also measured during ischaemia-reperfusion tests performed in all our parturients. Measurement consisted of a cessation of forearm blood flow induced by a rapid pneumatic cuff inflation above the elbow to a pressure 50 mmHg above the systolic arterial pressure. During this no-flow phase, thenar StO<sub>2</sub>

Figure 1



Thenar muscle tissue haemoglobin oxygen saturation in a patient hospitalized for severe post-partum haemorrhage. Representative example of thenar muscle tissue haemoglobin oxygen saturation (StO<sub>2</sub>) at admission and at intensive care unit discharge in the same patient. Set of measurements: StO<sub>2</sub> at baseline, during cuff inflation ( $S_{occlusion}$ ) and after cuff release (reperfusion phase,  $S_{recovery}$ ). cTnI, cardiac troponin I (normal range <0.04 µg/l).

declines; when it reached a value of 40%, the pneumatic cuff was immediately released. Figure 1 shows a representative example of an StO<sub>2</sub> tracing during forearm ischaemia-reperfusion tests in one parturient. This test allowed one to measure: during the forearm no-flow phase, the slope of StO<sub>2</sub> decrease ( $S_{occlusion}$ ) that was previously described as an index of forearm muscular oxygen consumption [22,23]; and, after the cuff release, the slope of StO<sub>2</sub> ascent ( $S_{recovery}$ ), an index of re-oxygenation capabilities of thenar skeletal muscle. Both slopes were calculated from numerical values using the least-square linear regression method. Of note, we choose 40% as a target to release the pneumatic cuff – instead of 3 minutes – because this level is safe, and because altered oxygen consumption in diseased patients might markedly alter StO<sub>2</sub> at 3 minutes, which may influence the recovery slope of StO<sub>2</sub>. The stability of the thenar skin temperature and the absence of muscular contraction were checked during measurements.

The baseline thenar StO<sub>2</sub> and changes following the forearm ischaemia-reperfusion test were recorded twice: at ICU admission, at the time of haemorrhagic shock; and immediately before ICU discharge, 12 to 24 hours after the control of genital bleeding.

The protocol was approved by the Ethics Committee of the French Society of Intensive Care (CE-SRLF 07-185).

### Statistical analysis

Data are summarized as frequencies and percentages for categorical variables. Quantitative variables are presented as the median (25th to 75th percentiles) or as the mean  $\pm$  standard deviation – except for  $S_{\text{recovery}}$ , for which a histogram is given.

Comparisons between measurements at admission and at the time bleeding was stopped were performed using Wilcoxon paired tests.

Univariate associations between plasma troponin I level  $>0.04 \mu\text{g/l}$  and variables at admission were assessed using the logistic regression model and Wald tests. All factors with  $P < 0.05$  in the univariate analysis were included in a multiple logistic regression model. Variable selection was performed using a backward procedure. Odds ratios with their 95% confidence intervals are presented as a measure of association. Furthermore, the receiver operating characteristic curve of  $S_{\text{release}}$  was used to detect association with troponin I level  $>0.04 \mu\text{g/l}$ ; the area under the curve is presented.

All tests were two-sided at the 0.05 significance level. Analyses were performed using the R statistical package [24].

## Results

### Demographic data and management of post-partum haemorrhage

Data from 42 consecutive parturients admitted for PPH are presented in Table 1. Twenty-three parturients were successfully managed medically and 19 parturients needed emergency invasive procedures: two had an immediate hysterectomy and 17 underwent angiography with a subsequent arterial embolization (predominantly in uterine arteries), which was successful for 15 of them and the last two parturients needed a combined hysterectomy and arterial embolization. Parturients required a median of 3 (0 to 7) units red blood cells. All parturients survived with a length of stay in our centre (intermediate care/ICU) of 2.1 (1.3 to 4.1) days.

### Haemodynamics, biology and haemoglobin tissue oxygen saturation

Table 2 shows the impact of blood loss on the haemodynamic and biological parameters measured at admission. This includes low blood pressure, elevated heart rate, low haemoglobin (7.1 (6.3 to 8.7) g/dl), increased serum lactate at  $2.8 \pm 1.3 \text{ mmol/l}$  (normal range = 0.7 to 2.1 mmol/l) and increased serum cardiac troponin I in 24/42 parturients ( $0.43 \pm 0.60 \mu\text{g/l}$ , while  $<0.04 \mu\text{g/l}$  in the other 18 parturients). The three parturients requiring catecholamines all had an increased troponin I level. Control parturients ( $n = 8$ ) had stable haemodynamics and haemoglobin at 10.8 (10.5 to 11.0) g/dl.

**Table 1**

Patient characteristics	
Characteristic	Value
Age <sup>a</sup>	34 (30 to 36)
Gravidity	2 (1 to 3)
Parity	2 (1 to 3)
Mode of delivery	
Vaginal	28 (67%)
Caesarean section	14 (33%)
Forceps	10 (24%)
Mode of treatment in our centre <sup>b</sup>	
Medical management alone	23 (55%)
Embolization	17 (40%)
Hysterectomy	4 (10%)
Sulprostone	40 (95%)
Catecholamines	3 (7%)
Red blood cells (units) <sup>c</sup>	3 (0 to 7)
Mechanical ventilation	8 (19%)

Data are presented as the median (interquartile range) or  $n$  (% of total);  $n = 42$ . <sup>a</sup>Seven patients had both general and regional anaesthesia. <sup>b</sup>Two parturients had both embolization and hysterectomy. <sup>c</sup>Total including before admission and the care unit stay in our centre.

At admission, haemoglobin tissue oxygen saturation showed an initial  $\text{StO}_2$  at 82% (78 to 86%),  $S_{\text{occlusion}}$  at  $-0.25\%/ \text{second}$  ( $-0.33$  to  $-0.19\%/ \text{second}$ ) and  $S_{\text{recovery}}$  at 4.5%/second (2.4 to 6.0%/second). Control parturients had  $\text{StO}_2$  at 88% (80 to 90%),  $S_{\text{occlusion}}$  at  $-0.44\%/ \text{second}$  ( $-0.66$  to  $-0.44\%/ \text{second}$ ) and  $S_{\text{recovery}}$  at 7.6%/second (5.9 to 9.5%/second) (all  $P < 0.0001$  versus admission for severe PPH). Figure 2 shows that  $S_{\text{recovery}}$  at admission exerted a bimodal distribution in our 42 severe PPH parturients, with the threshold at 3%/second. Figure 2 also shows that  $S_{\text{recovery}} < 3\%/ \text{second}$  was associated with 87% of troponin-positive patients while  $S_{\text{recovery}} > 3\%/ \text{second}$  was associated with only 37% of troponin-positive patients ( $P < 0.002$ ). The receiver operating characteristic curve confirms that the  $S_{\text{recovery}}$  threshold of 3%/second had the optimal sensitivity and specificity for the association with increased cardiac troponin (Figure 3). Of note, neither baseline  $\text{StO}_2$  nor  $S_{\text{occlusion}}$  showed a similar bimodal distribution or was associated with levels of cardiac troponin (data not shown).

Table 2 shows that the actions taken to control genital tract bleeding restored haemodynamic and biological parameters and improved all measured parameters of  $\text{StO}_2$  ( $S_{\text{occlusion}}$  and  $S_{\text{recovery}}$ ). Figure 1 shows a representative example of improvement of both  $S_{\text{occlusion}}$  and  $S_{\text{recovery}}$  after bleeding was controlled by uterine embolization.

**Table 2****Haemodynamic, biological and NIRS measurements during first hour of admission and when bleeding was stopped**

Variable	At admission	Intensive care unit discharge	P-value
<b>Hemodynamic</b>			
Systolic blood pressure (mmHg)	106 (100 to 120)	122 (110 to 130)	0.005
Diastolic blood pressure (mmHg)	53 (45 to 66)	60 (50 to 69)	0.28
Heart rate (beats/minute)	105 (90 to 134)	90 (70 to 100)	0.0002
<b>Biology</b>			
pH (IU)	7.37 (7.34 to 7.42)	7.42 (7.40 to 7.43)	0.0004
Lactate (mmol/l)	2.4 (1.9 to 3.5)	1.4 (0.9 to 2.0)	<0.0001
Haemoglobin (g/dl)	7.1 (6.3 to 8.7)	8.2 (7.4 to 9.6)	<0.0001
Prothrombin time (%)	63 (48 to 73)	83 (74 to 94)	<0.0001
Fibrinogen (g/l)	2.1 (1.3 to 2.9)	3.6 (3.1 to 4.5)	<0.0001
Cardiac troponin I ( $\mu\text{g/l}$ )	0.07 (0.02 to 0.18)	0.02 (0.02 to 0.08)	0.0008
<b>NIRS measurements</b>			
StO <sub>2</sub> (%)	82 (78 to 86)	87 (80 to 91)	<0.0001
S <sub>occlusion</sub> (%/second)	-0.25 (-0.33 to -0.19)	-0.32 (-0.4 to -0.23)	0.001
S <sub>recovery</sub> (%/second)	4.5 (2.4 to 6.0)	5.8 (4.6 to 7.0)	0.0003

Data presented as median (interquartile range);  $n = 42$ . *P*-values were calculated using the Wilcoxon test. NIRS, near-infrared spectroscopy; S<sub>occlusion</sub>, slope of tissue haemoglobin oxygen saturation decrease; S<sub>recovery</sub>, slope of tissue haemoglobin oxygen saturation ascent; StO<sub>2</sub>, tissue haemoglobin oxygen saturation.

### Factors associated with increased cardiac troponin in post-partum haemorrhage parturients

Univariate analysis showed that, among all measured parameters, heart rate >115/minute and muscular S<sub>recovery</sub> <3%/second, both measured at admission, were independently associated with increased cardiac troponin. The adjusted odds ratios were 5.0 (95% confidence interval = 1.1 to 21.9,  $P = 0.03$ ) for heart rate >115/minute and 11.2 (95% confidence interval = 2.1 to 60.0,  $P = 0.005$ ) for muscular S<sub>recovery</sub> <3%/second. Furthermore, multivariate analysis showed that S<sub>recovery</sub> <3%/second at admission was strongly associated with increased cardiac troponin, with an odds ratio of 8.8 (95% confidence interval = 1.6 to 49.0,  $P = 0.01$ ).

### Discussion

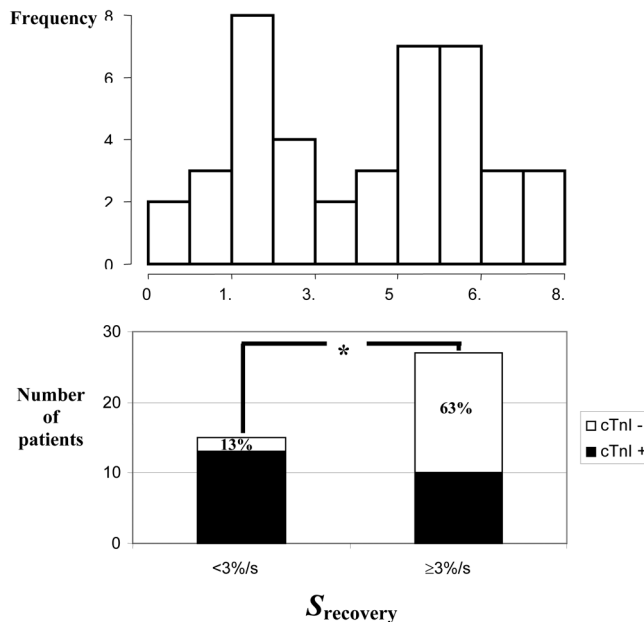
The present study confirms the high incidence of increased cardiac troponin and, more importantly, showed for the first time a simultaneous deterioration in all measured parameters of StO<sub>2</sub>, at admission, in our PPH parturients.

StO<sub>2</sub> was assessed using the near-infrared spectroscopy device that measures the ratio of oxygenated and deoxygenated haemoglobin within arterioles, capillaries, and venules of skeletal muscle with little influence from skin or other tissues [7,20]. The thenar StO<sub>2</sub> was previously described to be  $87 \pm 6\%$  in healthy volunteers and  $80 \pm 12\%$  in patients with blood loss [10]. Our study results are in line with those published results as we found a median StO<sub>2</sub> of 88% (80 to 90%) in control parturients, and of 82% (78 to 86%) at admission and 87% (80 to 91%) before ICU discharge in our PPH parturients.

During the forearm ischaemia–reperfusion test [22,25], the slope of StO<sub>2</sub> decrease during the no-flow phase (S<sub>occlusion</sub>; Figure 1) was previously described as an index of thenar oxygen consumption [23,26]. In our study, S<sub>occlusion</sub> was impaired at admission when parturients were haemodynamically unstable (-0.25%/second) compared with -0.32 %/second at discharge. This suggests that thenar oxygen consumption was low at admission and increased over time when bleeding was controlled and haemodynamics improved.

The slope of thenar StO<sub>2</sub> ascent after the ischaemic no-flow challenge (S<sub>recovery</sub>) was used to quantify the post-ischaemic reoxygenation capabilities in the thenar muscle [27,28]. Our study shows that S<sub>recovery</sub> was low in our PPH parturients at admission and improved towards levels measured in parturients with no PPH. As described above, the low S<sub>recovery</sub> at admission cannot be explained by a high oxygen consumption in the thenar muscle of our parturients. Accordingly, the low S<sub>recovery</sub> measured at admission is probably explained by an impaired post-ischaemic reserve of oxygen delivery in the thenar muscle at the time of admission for PPH.

We have previously described a high incidence of increased cardiac troponin that was associated with low blood pressure, high heart rate, low haemoglobin level, T-wave inversions and echocardiography changes in severe PPH [4]. Several hypotheses, including subendocardial ischaemia due to a mismatch between myocardial oxygen supply and demand [29,30], have been proposed – but the mechanisms by which these features cause increases in cardiac troponin in the absence of acute coronary syndrome in PPH par-

**Figure 2**

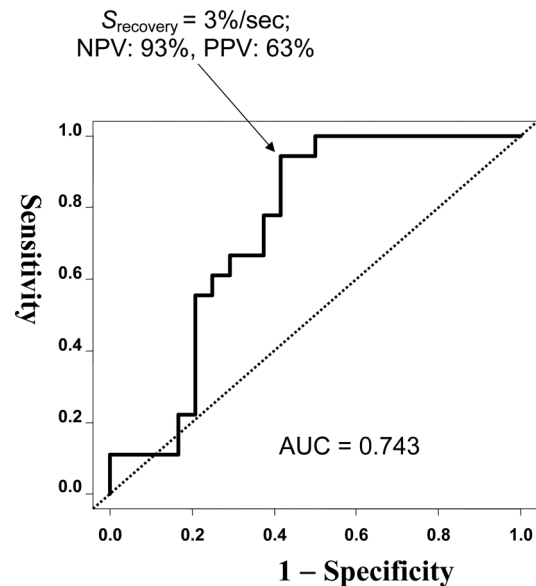
Tissue haemoglobin oxygen saturation ascent at admission. Upper panel: bimodal distribution of the baseline ascent slope ( $S_{\text{recovery}}$ ). Lower panel: most parturients (16/18) with negative cardiac troponin I (cTnI) showed  $S_{\text{recovery}} > 3\%/second$ , only 13% had negative cTnI. \* $P < 0.002$ .

parturients remain uncertain. Our study revealed that increased cardiac troponin was strongly associated with muscular  $S_{\text{recovery}} < 3\%/second$  and not with baseline  $StO_2$  or with  $S_{\text{occlusion}}$ . Muscular  $S_{\text{recovery}} < 3\%/second$  was even more strongly associated (odds ratio  $> 10$ ) with increased cardiac troponin than a high heart rate in our PPH parturients. This might suggest – if the increased cardiac troponin was related to a mismatch between myocardial oxygen supply and demand, and if simultaneous impairments observed in the myocardium and in peripheral muscle were related to similar mechanisms – that increased cardiac troponin was rather due to an impaired myocardial oxygen supply than to an increased oxygen demand. This hypothesis needs further evaluation.

In summary, our study confirmed the high incidence of increased cardiac troponin and demonstrated a simultaneous impairment in the reserve of oxygen delivery to the peripheral muscles in our severe PPH parturients when admitted with unstable haemodynamics. These data confirm that haemodynamic management in this patient subpopulation should focus on the early simultaneous restoration of both blood pressure and haemoglobin levels and, if possible, the reduction of tachycardia.

### Competing interests

DP received honoraria from Hutchinson Company for lectures. The other authors declare that they have no competing interests.

**Figure 3**

Association of tissue haemoglobin oxygen saturation ascent with plasma troponin I. Receiver operating characteristic curve of tissue haemoglobin oxygen saturation ascent ( $S_{\text{recovery}}$ ) to association with plasma troponin I. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

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