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False decrease of high-sensitivity cardiac troponin T assay in pneumatic tube system samples

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ABSTRACT

Background: The pneumatic tube system (PTS) is widely established in clinical laboratories. We aimed to evaluate the impacts of PTS on high-sensitivity cardiac troponin T (hs-cTnT) assays.
Methods: The hemolysis distribution of hs-cTnT PTS specimens from emergency department (ED) were determined by hemolysis index (HI). Grouped samples from 15 healthy volunteers were delivered to the laboratory via manual delivery (MD) or PTS. Interference studies were conducted to access the influence of different hemolysis degrees on hs-cTnT assays.
Results: 7.26% PTS specimens from ED were hemolyzed in clinic. Compared with MD samples, we found highly elevated free plasma hemoglobin (Hb) in PTS samples. Hs-cTnT was interfered negatively with free Hb ($R = -0.625$, $P < .001$), and it was also validated in interference studies ($R \geq -0.820$, all $P \leq .001$). Clinically significant bias occurred in each hs-cTnT concentration at 100 mg/dl free Hb (Bias $\geq -13.85\%$, all $P < .05$). Moreover, bias of hs-cTnT assays at 50 mg/dl free Hb was approaching 10%, especially at 30 ng/l hs-cTnT concentration (Bias: -11.72%, $P < .001$).
Conclusions: PTS could increase the frequency of specimen hemolysis which might cause false decrease in hs-cTnT assays. Hence, clinicians should be aware of the increased measurement bias in hs-cTnT from hemolyzed PTS samples with free Hb ≥50 mg/dl.

1. Introduction

To reduce the workload and shorten the turnaround time of clinical laboratories, pneumatic tube system (PTS) is commonly used in hospitals [1,2]. It can efficiently transport laboratory specimens, laboratory reports and medications among multi-stations [2]. However, rapid accelerations, decelerations, radial gravity forces and changes in air pressure may cause violent vibrations and damage of blood cells thus leading to hemolysis [3].

Sample hemolysis is an important source of pre-analytical errors [4]. Sample transportation is the main cause of hemolysis in vitro, which reflects a kaleidoscope of problems emerging throughout pre-analytical sample managements [5,6]. The release of laboratory report biased for the presence of hemolysis may trigger incorrect interpretation, wrong diagnosis and unfavorable outcome for the patients [7,8].

High-sensitivity cardiac troponin T (hs-cTnT) is a vital diagnostic biomarker of myocardial injury, predominantly for chest pain patients with suspected acute myocardial infraction (AMI) [9]. Hs-cTnT assays with their excellent analytical performance are designed to be superior for the early diagnosis of acute coronary syndrome (ACS) [10]. The ability of hs-cTn assays to detect measurable cardiac troponin concentration in at least 50% of healthy individuals along with their improved precision (expressed as coefficient of variation ≤10% at the 99th percentile URL) not only leads to the enhanced risk stratification of patients with suspected myocardial injury, but also enables to be used as potential prognostic tools in other conditions, including pulmonary embolus, myocarditis, and heart failure [11,12]. Numerous studies have been performed on the effect of PTS on hematology and biochemical testing [13–16]. However, its impact on hs-cTnT assay remains debatable.

2. Materials and methods

2.1. Volunteer specimens

Fifteen healthy volunteers were prospectively included in our study

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(the mean ± SD age was 24.0 ± 5.3 y; 11 males and 4 females). Grouped blood samples were drawn from a single venipuncture and performed by the same trained technologist at emergency department (ED). Blood samples were collected into lithium heparin vacuum tubes (Greiner Bio-One Vacutainer) with different volumes, and the order of sampling was alternated randomly (Supplementary Fig. S1). All specimens were both negative for lipemia or jaundice. Approval of the First Affiliated Hospital of Nanjing Medical University Local Ethics Committee was obtained as well as an informed written consent from each of the volunteers.

2.2. Description of transport

Volunteer blood samples were delivered by hand carrier or PTS. Manual delivery (MD) specimens were kept in vertical and closure-up position in a biohazard container and delivered to the laboratory within 15 min at room temperature by the laboratory staff. The PTS was supplied by Swisslog Healthcare Solutions Division in our hospital. Samples were transited by air at a constant speed of 7.0–8.0 m/s. All the carriers contain sponge-rubber to protect the samples during PTS transportation. The ED was about 800 m away from our laboratory.

2.3. Data collection and laboratory analysis

Clinical and laboratory data of hs-cTnT samples were collected by laboratory information system. Each specimen was immediately processed as soon as its arrival to the laboratory. After 5 min centrifugation at 1600 ×*g*, we measured plasma hs-cTnT using Roche cTnT 5th Generation Method (Cobas e601, Roche) with a total CV of 8.33%. Hemolysis index (HI) was obtained from lipemia-icterus-hemolysis of plasma information index on the automated biochemical analyzer (AU5800, Beckman Coulter). The normal concentration of free plasma hemoglobin (Hb) ranges from 10 to 13 mg/dl [17,18]. We determined hemolysis degrees according to the manufacturer-recommended instructions (micro-hemolysis: 20 ≤ Hb < 50 mg/dl; mild hemolysis: 50 ≤ Hb < 100 mg/dl; moderate hemolysis: 100 ≤ Hb < 200 mg/dl; severe hemolysis: Hb ≥ 200 mg/dl).

2.4. Preparation of the hemolysate

According to the standard methods of EP7-A2 [19], the hemolysates were prepared by washing packed red cells (0.9% saline and distilled water) and then freezing. Hb concentrations of hemolysates were measured by an automated blood cell counter (2100-XE, Sysmex), with an inter-assay CV of 1.72%.

2.5. Correlation studies between HI and free plasma Hb

We measured HI in serial hemolyzed plasma specimens. Different hemolysis specimens were prepared by mixing non-hemolysis plasma and its corresponding hemolysate. Final Hb concentrations examined were: 10, 29, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500 and 600 mg/dl. The mean of duplicate measurements was used for each sample. As expected, HI was highly linear correlated with free plasma Hb ($R = 0.999$, $P < .001$, Supplementary Fig. S2). In follow-up study, the concentrations of free plasma Hb were all determined by HI measurements.

2.6. Interference studies

In order to explore the potential for the hemolysate to interfere with hs-cTnT assays, non-hemolyzed clinical samples with known hs-cTnT value were collected. Specimens with lipemia as well as jaundice were excluded. We mixed plasmas with different proportions of plasma-hemolysates pools. The different hs-cTnT concentrations were analyzed in this interference studies: 5, 14, 30, 52 and 100 ng/l. The final concentrations of Hb at each hs-cTnT concentration were 50, 100 and 200 mg/dl. Furthermore, hemolyzed specimens were measured for hs-cTnT within 2 h.

2.7. Statistical analysis

All statistical tests were performed with SPSS ver 24.0 and Graph Pad Prism Software. In all analysis, a P value < .05 was considered statistically significant.

The linear regression and spearman's correlation analysis were performed to explore the association between HI and Hb. Besides, normal distribution test of continuous variables was performed by Shapiro-Wilk test. Data from normally distributed sample populations (P value of Shapiro-Wilk test > 0.05) were expressed as mean with standard deviation (mean ± SD), and a 2-tailed paired *t*-test was used to evaluate differences between hand-delivered samples and PTS specimens. Besides, Pearson correlation analysis was used to evaluate correlations between hemoglobin and percentage of bias. Normally distributed variables were compared using one-way analysis of variance for grouped design of multiple sets of data, and the least significant differences test was employed as a post-hoc test. In addition, non-Gaussian distribution data were expressed as median with interquartile range, and Kruskal-Wallis one-way analysis of variance was used for the comparison among multiple groups. The average bias percentage > ± 10% was considered as clinical significance [20,21].

3. Results

3.1. Distribution of hemolysis from hs-cTnT specimens in clinic

In order to get a sense of the hemolysis distribution in clinical specimens, all hs-cTnT specimens from ED were collected randomly for 10 days in December 2018. HI and blood volume of each specimen were measured and noted. A total of 1640 specimens from ED were included in this study with a hemolysis ratio of 7.26%. And the percentage of specimens with inadequate blood volume reached 11.77%. Mild and micro-hemolysis accounted for 80% of hemolyzed specimens. In addition, the hs-cTnT concentrations of 69.75% hemolyzed specimens were < 100 ng/l.

3.2. Comparison of PTS with manual transport on hs-cTnT assay

A total of 45 blood samples from 15 healthy volunteers were delivered to the laboratory by hand or via PTS. The free plasma Hb of volunteer samples were estimated by HI upon delivery. We found 56.67% PTS samples were hemolyzed, while no hemolysis occurred in MD samples. Compared with MD samples, free plasma Hb in PTS samples was significantly higher (MD: 4.46 ± 3.59 mg/dl, PTS: 59.68 ± 46.89 mg/dl, $P < .001$) (Fig. 1A). When free Hb concentration was up to 50 mg/dl, hemolysis could be recognized with naked eyes definitely [23]. The negative bias observed in visually hemolyzed PTS specimens was obviously greater than that of apparent non-hemolysis specimens ($P = .001$, Fig. 1B).

Moreover, the Pearson correlation test results indicated a negative correlation between free plasma Hb and the percentage bias ($R = -0.652$, $P < .001$, Fig. 1C). We speculated that the negative interference in hs-cTnT assays could be dependent upon hemolysis degrees in PTS specimens. As shown in Table 1, with the comparison of MD samples, there was a − 10.19% bias in PTS samples (MD: 4.69 ± 1.04 ng/l, PTS: 4.20 ± 0.89 ng/l, $P < .001$). Additionally, specimens with halved blood volume produced a greater bias (Bias: -12.58%, PTS: 4.06 ± 0.81 ng/l, $P < .001$).

Owing to the hs-cTnT values from 4 female volunteers were lower than the limit of blank, we excluded these data while calculating bias. MD indicates manually delivery, PTS indicates pneumatic tube system, full tube indicates specimens with qualified blood volume, half tube

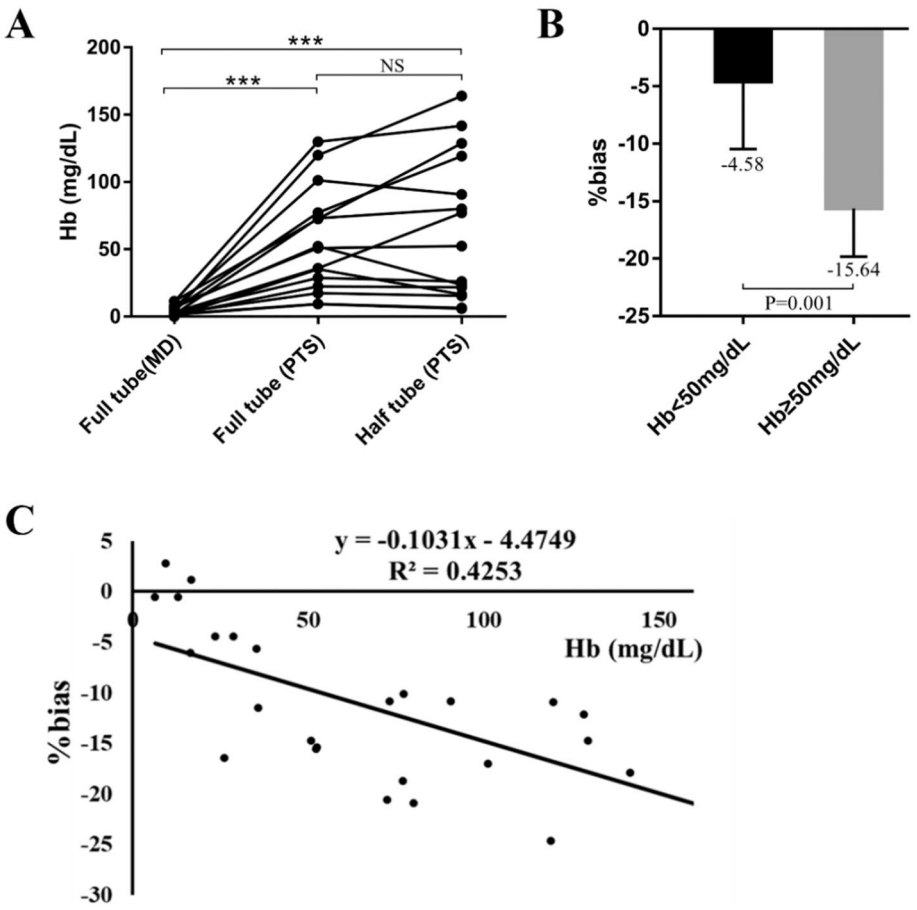

Fig. 1. Distribution of free plasma Hb and detection bias from volunteer specimens. The concentrations of free plasma Hb in different transport samples were shown in(A). The detection percentage bias between visual hemolyzed and apparent non-hemolyzed PTS samples was presented in (B). And, the relationship of free plasma Hb and the percentage bias of PTS specimens was shown in (C). All the percentage bias was calculated by comparing to the concentrations of hs-cTnT in MD specimens. Hb indicates hemoglobin, PTS indicates pneumatic tube system, full tube indicates specimens with qualified blood volume, half tube indicates specimens with halved blood volume, %bias indicates the percentage of bias, "***" indicates $P < .001$, "NS" indicates no significance.

Table 1
Comparison of hs-cTnT results from volunteer samples transported by PTS and manual carrier.

Sample	results	Avg. bias	% Avg. bias	*P* value
Full tube (MD)	4.69 ± 1.04	–	–	–
Full tube (PTS)	4.20 ± 0.89	−0.50	−10.19	< 0.001
Half tube (PTS)	4.06 ± 0.81	−0.62	−12.58	< 0.001

indicates specimens with halved blood volume, Avg. bias, the average of bias (PTS - MD); % Avg. bias, the average of percentage bias [((PTS - MD) / MD) *100%].

3.3. The negative interference of free plasma Hb in hs-cTnT assays

To validate the negative interference of free plasma Hb on hs-cTnT assays, we measured hs-cTnT concentrations in sets of different hemolyzed samples. The spearman correlation analysis indicated that the hemolysis degree was highly negatively correlated with the hs-cTnT results in each group (5 ng/l: R = -0.820, $P = .001$; 14 ng/l: R = -0.958, $P < .001$; 30 ng/l: R = -0.923, $P < .001$; 52 ng/l: R = -0.885, $P < .001$; 100n g/l: R = -0.954, $P < .001$). As shown in Fig. 2, the hs-cTnT measurement values of hemolyzed specimens were decreased with the increasing concentration of free Hb. Except at hs-cTnT concentration of 52n g/l, biases were approaching 10% in the case of mild hemolysis (to free Hb 50 mg/dl). It was worth noting that the bias even reached −11.72% at hs-cTnT concentration of 30 ng/l, which exceeded the assay imprecision according to the manufacturer's claim (total coefficient of variation ≤10%) [22]. Meanwhile, consistent with the Roche reagent instruction, free Hb concentrations above 100 mg/dl caused significant negative interference on hs-cTnT measurement and loss of assay precision at each concentration (all $P < .05$, Table 2). Besides, all of them were over twice the allowable error at severe hemolysis (free Hb up to 200 mg/dl) (all $P \leq .001$, Table 2).

4. Discussion

Although the effects of PTS on hematology and biochemical testing have been well studied [13–16], research on that of myocardial biomarkers is still deficient. The present study aimed to assess the influence of PTS on the Roche hs-cTnT assay.

The PTS is a cost-effective method of transport in hospitals. However, the decrease in turnaround time might appear at the cost of sample quality [4]. Hemolysis is a leading cause of preanalytical errors in PTS. Ellis et al. found that PTS samples had a higher frequency of hemolysis than MD samples (PTS: 10.9%, MD: 3.3%) [24,25]. Similarly, we found that the hemolysis incidence of PTS samples from ED was 7.26%. Meanwhile, when we choose a longer PTS pathway in volunteer study, it increased dramatically to 56.7%. It suggested that the hemolysis degree of PTS samples was associated with the distance and path of the transmission.

Sample hemolysis often occurs during sample transportation, which may cause preanalytical errors in hs-cTnT assays. According to the volunteer study, the negative bias from visually hemolyzed PTS samples was statistically greater than that from apparent non-hemolysis PTS samples ($P = .001$). Much more interesting, the measurement value of hs-cTnT were interfered negatively with the increasement of free plasma Hb in PTS volunteer samples (R = -0.625, all $P < .001$). Our data indicated that hs-cTnT was falsely decreased in total PTS samples, and free plasma Hb released from PTS samples was responsible for the negative interference. It might be explained that proteases and Hb

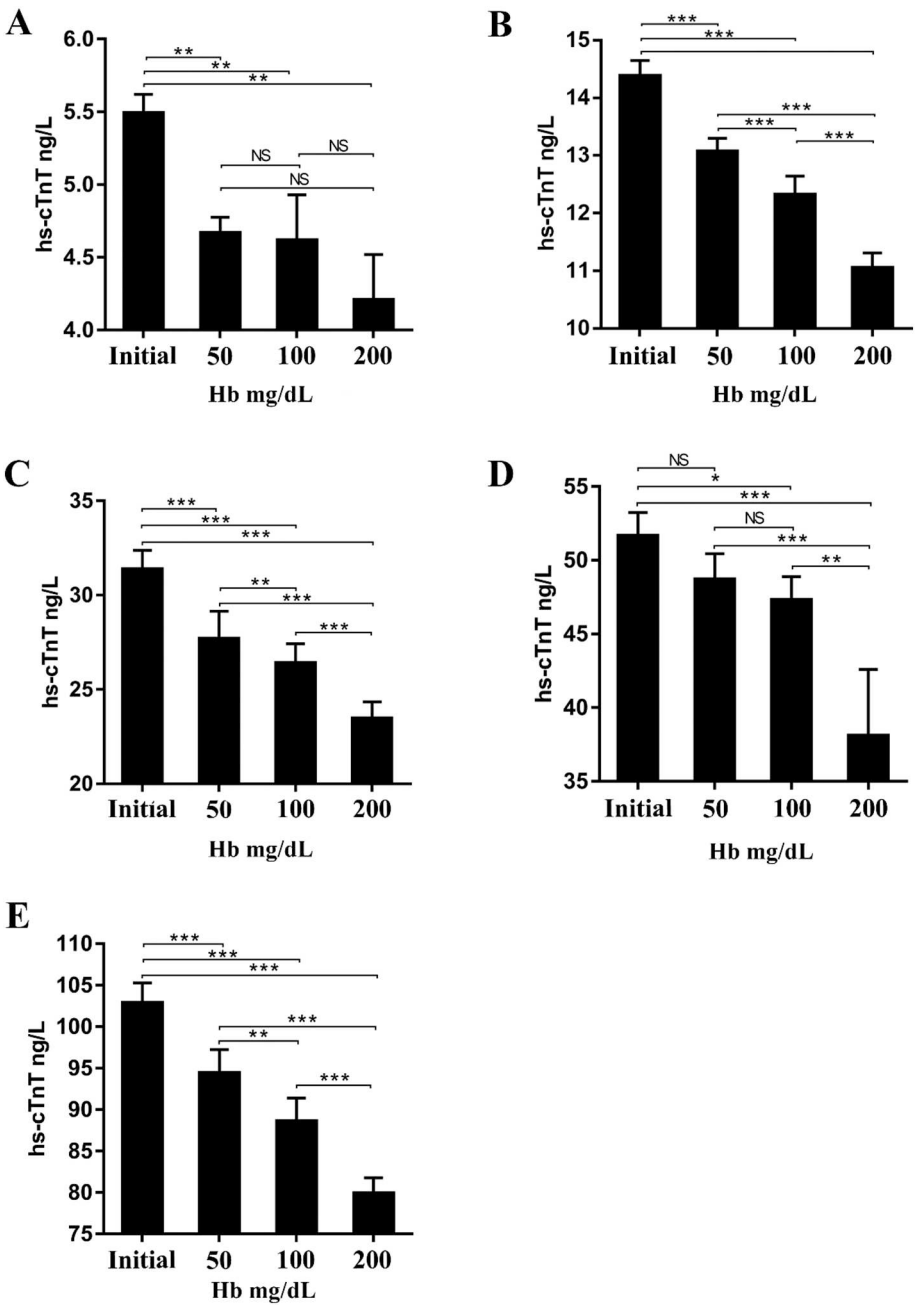

Fig. 2. The impact of hemolysis on the hs-cTnT measurement at different concentrations. Series of hemolytic gradient model samples were prepared at hs-cTnT concentration of 5 ng/l (A), 14 ng/l (B), 30 ng/l (C), 52 ng/l (D) and 100 ng/l (E). The X-axis indicates different free plasma Hb concentrations of hemolyzed samples. Initial indicates the original specimens, with no hemolysis (all free Hb ≤5 mg/dl), lipemia as well as icterus. Hs-cTnT indicates high-sensitivity cardiac troponin T.

released from the mechanically injured blood cells could degrade plasma troponin [26,27]. In addition, the bias from half tube PTS samples was larger than that from full tube PTS samples. It is probably due to the increased friction power in half-filled PTS samples, which could aggravate hemolysis. Therefore, we recommend that laboratories should standardize the blood collection and specimen transport requirements to avoid hemolysis, including appropriate blood collection volume and wrapping samples in the bubble wrap before placing them into the pod.

Hs-cTnT assay is commonly used in ED patients with symptoms compatible with AMI [28]. Accurate hs-cTnT result is vital for early identification of myocardial injury and effective therapy [29,30]. In this study, we observed that hemolysis was highly associated with a false reduction of hs-cTnT in ED patients. The false decrease of hs-cTnT overstepped the allowable detection error at obvious hemolysis concentration (free Hb ≥100 mg/dl), which is consistent with the manufacturer's instructions [22]. Moreover, we also found that even if free Hb was only 50 mg/dl, the measurement bias was approaching 10%. Especially at 30 ng/l hs-cTnT concentration, the bias was 11.72%, and the total error (TE) reached 28.38%. Dynamic change of hs-cTnT is crucial for AMI diagnosis. According to the European Society of Cardiology (ESC) diagnostic algorithm, chest pain patients with hs-cTnT change exceeding 20% within 1–3 h should be considered as AMI [30,31]. However, the measurement error induced by hemolysis might conceal the actual change of hs-cTnT, which might mislead clinical judgement. For this reason, even the impact of mild hemolysis (free Hb up to 50 mg/dl) on hs-cTnT results could not be ignored. Clinicians should be vigilant to the possibility that PTS could induce hemolysis

Table 2
Biases in hs-cTnT assay from different degrees of hemolysis samples.

Hs-cTnT (ng/L)		Free plasma Hb					
		50 mg/dL		100 mg/dL		200 mg/dL	
		Bias	*P* value	Bias	*P* value	Bias	*P* value
5.0	Avg. bias	−0.825	0.008	−0.875	0.006	−1.285	0.001
	% Avg. bias	−14.93		−15.75		−23.23	
14.0	Avg. bias	−1.31	< 0.001	−2.06	< 0.001	−3.34	< 0.001
	% Avg. bias	−9.08		−14.31		−23.18	
30.0	Avg. bias	−3.67	< 0.001	−4.96	< 0.001	−7.91	< 0.001
	% Avg. bias	−11.72		−15.79		−25.19	
52.0	Avg. bias	−2.96	NS	−4.36	0.040	−13.57	< 0.001
	% Avg. bias	−5.68		−8.41		−26.17	
100.0	Avg. bias	−8.47	< 0.001	−14.30	< 0.001	−22.98	< 0.001
	% Avg. bias	−8.20		−13.85		−22.31	

Avg. bias indicates the average of bias (hemolysis - initial), % Avg. bias indicates the average of percentage bias [((hemolysis - initial) / initial) *100%].

and exaggerate the total error in hs-cTnT assay. Hemolysis could be identified by naked eyes, when free Hb concentrations reach 50 mg/dl. If hemolysis is visible, laboratory technicians should remark it on hs-cTnT test reports to remind clinicians. Moreover, HI assessment is suggested in fully equipped laboratories.

There are several strengths and weaknesses of this study that should be noted. First, we used HI to assess sample hemolysis, and it can be easily incorporated into the automatic preanalytical quality management [32]. Second, the impact of inadequate sample volumes on the detection of hs-cTnT was investigated in this study. Nevertheless, some limitations must also be considered. Due to different PTS and sample transfer paths, the impacts of PTS on hs-cTnT assays in other hospitals may be not exactly the same as ours. What's more, the sample size in this study was small. We would need to include more patients in a future study.

5. Conclusions

We showed a higher hemolysis ratio in PTS samples and false reductions of hs-cTnT might occur in hemolyzed PTS specimens. Clinicians should realize the risk of increased measurement bias in hs-cTnT assays from hemolyzed PTS samples with free Hb ≥ 50 mg/dl. In order to reduce hemolysis caused by PTS, we also recommend that phlebotomists should strictly implement standard procedures to avoid samples with inadequate volume.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.05.027.

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