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Regular Article

The effects of pneumatic tube system transport on ROTEM analysis and contact activation assessed by thrombin generation test ☆

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ABSTRACT

Thromboelastometry (ROTEM) is a popular point-of-care test. It generates results quickly and may benefit individualised guided haemostatic therapy. However, processing of specimens by non-technicians might decrease the quality and reproducibility of results. Centralised laboratory equipment receiving specimens through a pneumatic tube system (PTS) could avoid this. This study aimed to evaluate the influence of PTS transport on ROTEM results and its contribution to contact activation assessed by thrombin generation (TG).
Methods: Specimens from 44 patients were drawn immediately after arterial puncture. Two were anti-coagulated by citrate and two by citrate/corn trypsin inhibitor, a Factor XIIa pathway inhibitor. Both types of samples were transported by walking and PTS. Subsequently, analysis was performed: ROTEM on citrated blood, and TG on citrated and corn trypsin inhibitor (CTI) blood using either 0 or 1 pM tissue factor (TF).
Results: In ROTEM analysis the NATEM assay showed significant differences. The EXTEM assay revealed small significant differences for clot formation time: 65 seconds (SD ± 20) versus 67 seconds (SD ± 17), and alpha angle 79° (SD ± 3) versus 77° (SD ± 3). The results remained within reference range. TG was not significantly affected by the type of tube transport, independent of the amount of TF.
Conclusion: PTS for ROTEM analysis is feasible except for NATEM assays. The amount of contact activation via Factor XIIa in terms of TG is independent of transport type. However, due to the different characteristics of pneumatic systems, hospitals should check its impact on the results before introducing this route of transport.

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Introduction

Point-of-care (POC) laboratory monitoring is increasingly used in modern anaesthesiology. The main advantage of POC monitoring is rapid data acquisition, which enables treating patients in a more individualised way. Because anaesthesia teams who are tending to bleeding patients are occupied with stabilising vital functions, additional laboratory work (POC tests) might interfere with their regular workflow. In addition, there is concern about the quality and reproducibility of laboratory tests done by non-technicians, especially when the results are critically important in decision-making [1]. An alternative to the use of POC monitoring in the operating theatre might be to send specimens to the laboratory with minimal time delay. Pneumatic tube systems (PTS) reduce the workload and turn-around time of laboratories by accelerating the transport of blood samples, thus reducing manpower. While most haematological indices and standard coagulation indices are not influenced by transport via PTS [2–4], there have been reports of haemolysis in serum samples and in red blood cell concentrates, due to the acceleration and deceleration of PTS and due to vibration of the sample [5–7]. Haemolysis of red blood cells or platelets could lead to the generation of microparticles, which have been shown to trigger thrombin generation in a factor XII-dependent manner [13]. Most authors interpret these changes as minor and without clinical consequences. However, the transport by PTS of specific specimens such as for blood gas analysis, cerebral spinal fluid analysis, or platelet function analysis using the PFA-100® system is not recommended because results are unreliable [8–12].

On the other hand, Braun et al. showed that multiple electrode aggregrometry is possible by PTS transport of citrated samples of whole blood [14]. The influence of PTS transport on thromboelastometry (ROTEM-Tem International GmbH, Munich, Germany) has not been

Abbreviations: POC, Point of care; PTS, pneumatic tube system; CTI, corn trypsin inhibitor; TG, thrombin generation; CAT, calibrated automated thrombogram; TF, tissue factor; LI, lysis index; CFT, clot formation time; VI, velocity index; TEG, thromboelstograph.

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investigated with the type of PTS installed in our hospital and with the blood collection tubes we use (BD Vacutainer® tubes, Plymouth, UK). One of the drawbacks of PTS might be contact activation which can occur during and after collecting whole blood in test tubes [15]. Contact activation (via Factor XII) can be investigated by using citrated sample tubes with or without the addition of a Factor XII pathway inhibitor: corn trypsin inhibitor (CTI).

The aim of this study was to evaluate the influence of PTS transport on ROTEM results and to determine the contribution of contact activation caused by PTS. The latter was investigated using a thrombin generation (TG) assay and CTI as an activation inhibitor.

Methods

After approval by the local ethics board, 44 patients scheduled for elective cardiothoracic surgery at the Maastricht University Medical Centre gave written informed consent and were included in the study. Exclusion criteria were use of anticoagulants other than acetylsalicylic acid, and age younger than 18 years.

Upon arrival in the operating theatre, patients received standard monitoring for cardiac anaesthesia, including five lead electrocardiography, noninvasive blood pressure measurement and pulse oxymetry, a venous line (Vasofix® Safety, 16G or 14G, B. Braun Melsungen, Germany), which was inserted in the forearm, and an arterial line (Radial Artery Catheterization set, 20G, Arrow International, Reading, Pennsylvania, USA), which was positioned in the radial artery under subcutaneous local anaesthesia using 1 ml of lidocaine 1% solution.

Blood was drawn out of the arterial line immediately after insertion. The first 10 mL were discarded before filling one ethylenediaminetetraacetic acid tube (K_2-EDTA 7.2 mg, BD Vacutainer® tubes, Plymouth, UK), two tubes containing citrate (sodium citrate 1.005 M, BD Vacutainer® tubes, Plymouth, UK) and two tubes with citrate and corn trypsin inhibitor (CTI 40 μg/mL, Haematologic Technologies, Inc, Vermont, USA), a Factor XIIa inhibitor. Two sets of labelled tubes – both sets containing one citrate and one CTI tube – were sent to the central laboratory: one by PTS and one by walking transport. Platelet poor plasma (PPP) was prepared according to the standard protocol at our laboratory, consisting of an initial centrifugation step at 2.000 × g for 5 minutes (min) and a second centrifugation step at 10.000 ×*g* for 10 min. All aliquots were snap frozen in liquid nitrogen and stored at -80 °C until analysis.

The PTS (Swisslog-ErgoTrans BV, Apeldoorn, the Netherlands) connects the central surgical complex on the third floor with the haematological laboratory on the fifth floor. This circuit includes two switching stations for change of direction. There are no heat or cold sources along this route. The system generates a maximum speed of 8 m/s. Transport time from the operating theatres to the laboratory is between 83 and 110 seconds.

Sample analysis for the haematological parameters, haemoglobin, haematocrit and platelet count, was performed on a Beckman Coulter® LH-750 analyser (Beckman Coulter, Woerden, the Netherlands). ROTEM analysis was performed using the following standard assays according to the manufacturer's recommendations at 37 °C: NATEM (recalcification, no trigger), INTEM (partial thromboplastin and ellagic acid), EXTEM (tissue factor) and FIBTEM (tissue factor and cytochalasin D) [16]. To investigate contact activation via Factor XIIa pathway as a possible cause of differences induced by PTS the remaining blood was centrifuged and TG was assessed using the Calibrated Automated Thrombogram® (CAT, Thrombinoscope BV, Maastricht, the Netherlands) with phospholipids (4 μM) using either 0 or 1 pM tissue factor (TF). Previously, our group showed that normalization, with normal pooled plasma as a reference, of the time-independent parameters ETP and peak height is necessary to obtain acceptable inter-assay variations [17].

Considering 20% difference from reference values (ROTEM) as clinically relevant 44 samples are necessary to reach a statistical power of 90% with an α-error of 0.05. Statistical analyses were performed using GraphPad Prism software (GraphPad Software, San Diego, California, USA). After testing for distribution the paired Student's *t*-test analysis for normally distributed variables and the Wilcoxon signed-rank test for nonparametric variables were used to compute the differences where applicable. A p-value of < 0.05 was considered statistically significant.

Results

A total of 44 patients were included in this study. Thirty patients (68.2%) were male and 14 (31.8%) were female. The mean age was 69.7 years (SD ± 11.5). Haematological parameters revealed a mean haemoglobin of 7.7 mmol/L (SD ± 0.8), a mean haematocrit of 0.38% (SD ± 0.04), and a mean platelet count of 210×10^9/L (SD ± 60.1×10^9/L).

ROTEM analysis was done on all pairs of 44 citrated samples (transported by walking or with PTS) using the four ROTEM assays per run. The NATEM assay showed statistically significant differences ($p<0.05$) for the transport method. Only the lysis index at 60 minutes (LI60) did not differ significantly. In the EXTEM assay, the clot formation time (CFT) 65 seconds (SD ± 20) versus 67 seconds (SD ± 17), and the alpha angle 79° (SD ± 3) versus 77° (SD ± 3) revealed small significant differences (Table 1). However, all results were still within their specific reference range.

CAT analysis was performed on the blood samples of 31 of the 44 patients (citrate transported by walking or with PTS, and citrate/CTI transported by walking or with PTS). Blood from thirteen patients could not be sampled for CAT analysis because CTI tubes were not available.

Independent of the transport method, there is a significant inhibition of contact activation in all CTI tubes compared to citrate tubes. This difference is more pronounced when CAT analysis is triggered without tissue factor. There is no endogenous thrombin potential (ETP) without tissue factor triggering, and also no velocity index (VI) detectable in the CTI tubes. Whereas nearly an equal amount of contact activation is detectable within the group of citrate tubes (Table 2).

After triggering with 1 pM tissue factor, the contact activation still was suppressed in the CTI tubes independent of transport method. Again the citrate tubes show an equal amount of contact activation in both groups (Walking versus PTS, Table 3).

Discussion

The present study demonstrates that PTS transport does not inflict clinically relevant consequences on ROTEM analysis results. Even though collection of blood samples is associated with a measurable degree of contact activation, in the CAT assay, this is not further enhanced by PTS transport as compared to manual (walking) transport to the laboratory.

Management of acute haemorrhage demands swift reaction and clinical decision-making. Some current literature recommends transfusing haemorrhagic patients as quickly as possible, even without knowledge of haemostatic properties, in order to prevent haemodilution and aggravation of bleeding [18]. Other authors state that ROTEM analysis provides important information on coagulation parameters in acute bleeding patients [19–21]. An actual debate at this moment is whether to perform ROTEM analysis at the bedside (i.e. operating theatre or emergency department) or at a central laboratory. The main argument supporting bedside testing is fast availability of results for tailored haemotherapy. On the other hand, concerns arise on the quality of POC results and some authors recommend performing laboratory analysis by trained technicians in the hospitals central laboratory [22–25].

Table 1
ROTEM analysis in citrated whole blood of 44 patients. One sample was sent to the laboratory by pneumatic tube transport (PTS) and one was transported by walking. ROTEM analysis was performed using INTEM (partial thromboplastin and ellagic acid, ref range: CT-130-195 s, CFT-32-127 s, **α**-angle-66-83°, MCF-46-70 mm, LI60-84-98%), EXTEM (tissue factor, ref. range: CT-36-60s, CFT-39-150 s, **α**-angle-60-83°, MCF-48-72 mm, LI60-85-91%) and FIBTEM (tissue factor and cytochalasin D, ref. range: CT-36-57 s, MCF-6-23 mm, CFT, **α**-angle, LI60-n/a), NATEM (recalcification, no trigger, ref. range: CT-300-1000 s, CFT-150-700s, **α**-angle-30-70°, MCF-40-65 mm, LI60-94-100%). Values are shown as mean and min-max values. CT: clotting time, CFT: clot formation time, MCF: mean clot firmness, LI60: lysis index *significant pneumatic system vs. walking, n/a not applicable.

	INTEM			EXTEM			FIBTEM			NATEM		
	PTS	Walking	P-value	PTS	Walking	P-value	PTS	Walking	P-value	PTS	Walking	P-value
CT (s)	135 (97-172)	137 (83-189)	0.47	35 (24-49)	35 (18-57)	0.93	33 (10-53)	33 (22-57)	0.73	508 (213-846)	571 (187-990)	0.01*
CFT(s)	64 (36-103)	63 (40-99)	0.54	65 (36-119)	67 (33-107)	0.02*	n/a	n/a	n/a	127 (46-263)	136 (54-305)	0.03*
Alpha angle (°)	78 (73-83)	78 (71-82)	0.17	79 (68-84)	77 (68-84)	0.01*	n/a	n/a	n/a	67 (47-80)	65 (44-79)	0.04*
MCF (mm)	62 (51-76)	62 (52-75)	0.56	63 (51-77)	62 (53-77)	0.08	18 (10-25)	18 (9-26)	0.57	61 (51-72)	60 (46-79)	0.01*
LI60 (%)	91 (86-97)	91 (86-97)	0.50	90 (79-98)	91 (84-97)	0.16	n/a	n/a	n/a	93 (85-98)	92 (86-97)	0.82

The main argument against determination of ROTEM in a central laboratory is the time consuming walking transport of blood samples. PTS transport may reduce this transportation time. However, rapid transport in pneumatic systems may influence reliability of results by platelet activation and/or contact activation. Several authors reported significant effects on laboratory parameters when transport by PTS was used [6,8,12]. For this reason PTS transport was not recommended for several POC tests [10,12]. Wallin and colleagues described significant differences in r time on the thromboelastograph (TEG) when they compared walking transport with PTS [26]. Unfortunately, the authors do not describe which trigger substances (kaoline/tissue factor) were used. This might be of interest because tissue factor activation reveals significantly different results comparing citrated with native fresh blood samples [27]. However these results are in accordance with our findings, because the NATEM assay reveals also a shortening of the CT which reflects the initiation of clot forming as the r-time in the TEG does. Assuming that Wallin and co-workers used the most common trigger substance (kaolin) one might interpret this activation not as strong as the activation by ellagic acid which is the activator in the INTEM assay. The stronger activation in this assay might explain why we do not see a prolongation of the CT here. This might be also an explanation for the EXTEM and FIBTEM assays where the activator might be stronger. At the same time, all results of Wallin were within reference ranges and would also not impact treatment strategy [28]. Another recent study revealed no significant differences in ROTEM analysis when PTS transport was performed. However, these results cannot be automatically generalised to other hospitals since tube transport has different features in terms of switching points, speed and acceleration/deceleration [24]. Furthermore, we used different collection tubes, namely BD tubes instead of Sarsted tubes. Generally, there are two differences between these collecting systems. First, our system is a glass tube system which may activate the Factor XIIa pathway of coagulation [29]. Due to this, the amount of contact activation may differ significantly between ours and the plastic system of Sarsted, which Colucci and colleagues used. Further, the Sarsted system does not collect blood by vacuum suction, but with a plunger. This may lead to inconsistent filling of the tubes which may translate into different mixtures with the anticoagulants. Vacuum suction might induce stronger contact activation due to higher shear stress than a plunger system as suggested by Lippi and co-workers who compared different blood drawing techniques [30].

Another possible reason for the differences between PTS and walking transport might be an activation of platelets. However this might be of minor influence because platelet activity is poorly reflected in ROTEM analysis [31]. On the other hand is the amount of platelet activation in PTS still a matter of debate. As showed by our group and by others is platelet function not always altered by PTS [10,14,32].

In the present study, some statistically significant differences were seen with the NATEM parameters and the alpha angle of the EXTEM assay. Still, all the results were within normal range, as determined by Lang et al., and as such, would not affect patient management [33].

The thrombin generation assay is a powerful tool to reflect small changes in the coagulation system [34,35]. Therefore, it was used to investigate the potential effect of contact activation induced by PTS. The use of CTI, a specific Factor XIIa inhibitor, eliminates the possible effect of contact activation. CAT analysis was performed in paired tubes (with or without CTI and/or PTS) in order to investigate whether the small differences in the ROTEM results might reflect contact activation via Factor XIIa pathway due to transport. However, no influences of transport PTS could be detected, and it seems there is no additive stimulation of this pathway.

From clinical practice, it is known that an acutely bleeding patient requires intense manpower support on the scene, limiting the time available to perform additional tests by team members themselves. In addition, working under pressure might result in less reliable laboratory results [36], and might lead to a large variability and lack of reproducibility [25,37]. In the UK, Kitchen et al. demonstrated a precision in ROTEM results that vary between 7 and 84 per cent in POC settings in hospitals [25]. Moreover, to maintain a high assay quality, a quality control programme needs to be established and performed by dedicated people [37–39]. Because of this, it remains preferable to maintain carrying out POC tests in the laboratory.

Table 2
Calibrated Automated Thrombogram (CAT) analysis in citrated whole blood with or without Corn Trypsin Inhibitor (CTI) of 31 patients. One citrate and citrate/CTI sample was sent to the laboratory by pneumatic tube transport (PTS) and one was transported by walking. CAT was performed with phospholipids (4 μM) triggered by 0 pM tissue factor (TF). Values are shown as medians (Q1-Q3). No significant differences were seen (Wilcoxon signed-rank test: $p > 0.05$). LT: lag time, PH: peak height, ETP: endogenous thrombin potential, VI: velocity index.

	Citrate 0 pM TF		Citrate and CTI 0 pM TF	
	PTS	Walking	PTS	Walking
LT (min)	12 (10-15)	13 (10-17)	99 (38-99)	62 (28-99)
PH (nM)	292 (179-331)	296 (218-333)	1 (0-1)	1 (0-1)
ETP (nM/min)	1278 (791-1450)	1287 (957-1386)	0 (0-0)	0 (0-0)
VI (nM/min)	137 (78-172)	144 (91-167)	0 (0-0)	0 (0-0)

Table 3
Calibrated Automated Thrombogram (CAT) analysis in citrated whole blood with or without Corn Trypsin Inhibitor (CTI) of 31 patients. One citrate and citrate/CTI sample was sent to the laboratory by pneumatic tube transport (PTS) and one was transported by walking. CAT was performed with phospholipids (4 μM) triggered by 1 pM tissue factor (TF). The results are normalised with standard plasma for the sake of interpretation. Values are shown as medians (Q1-Q3). No significant differences were seen (Wilcoxon signed-rank test: $p > 0.05$). LT: lag time, nPH: normalised peak height, nETP: normalised endogenous thrombin potential, VI: velocity index.

	Citrate 1 pM TF		Citrate and CTI 1 pM TF	
	PTS	Walking	PTS	Walking
LT (min)	3 (3-4)	3 (3-4)	4 (4-5)	4 (4-5)
nPH (% of normal)	183 (116-206)	183 (134-208)	74 (53-103)	74 (55-111)
nETP (% of normal)	120 (89-134)	118 (95-134)	82 (72-101)	84 (74-101)
VI (nM/min)	86 (60-120)	88 (56-121)	21 (14-34)	20 (14-36)

In conclusion, our study demonstrated the feasibility of PTS transport for ROTEM analysis. The amount of contact activation via the Factor XIIa pathway in terms of thrombin generation is independent of transport method. Because of the differences between the PTS – in terms of distance length of time and maximum speed – and the type of collection tubes used, each hospital should check the impact of transport in its own system before implementation this route of transport.

Conflict of Interest Statement

None of the authors has a conflict of interest.

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