Point-of-care high-sensitivity troponin-I analysis in capillary blood for acute coronary syndrome diagnostics point-of-care troponin-I for ACS diagnostics

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Abstract

Objectives: Patients with acute coronary syndrome (ACS) should be referred promptly to the hospital to reduce mortality and morbidity. Differentiating between low-risk and high-risk patients remains a diagnostic challenge. Point-of-care testing can contribute to earlier disposition decisions for patients excluded from ACS. This study describes the validation of the Atellica® VTLi. Patient-side Immunoassay Analyzer for high-sensitivity troponin point-of-care (POC) analysis. (The Atellica VTLi is not available for sale in the USA. The products/features (mentioned herein) are not commercially available in all countries. Their future availability cannot be guaranteed).

Methods: A total of 152 patients with acute chest pain admitted at the cardiac emergency department (ED) were included in the study. Capillary blood was compared with a whole blood and plasma sample obtained by venipuncture. All samples were analyzed using the Atellica VTLi Patient-side Immunoassay Analyzer; in addition, plasma was analyzed by a central lab immunoassay analyzer.

Results: No significant difference was observed between venous whole blood vs. plasma analyzed by the Atellica VTLi Patient-side Immunoassay Analyzer. The difference between capillary blood and venous blood showed a constant bias of 7.1%, for which a correction factor has been implemented. No clinically relevant differences were observed for the capillary POC results compared to plasma analyzed with a standard immunoassay analyzer.

Conclusions: The Atellica VTLi Patient-side Immunoassay Analyzer for high-sensitivity troponin analysis shows equivalent results for all sample types, including capillary blood. No clinically relevant discordances were observed between capillary POC and central laboratory results. With additional studies, this could pave the way towards rapid testing of high-sensitivity troponin in the ambulance or the general practitioner's office without the need for hospitalization of patients with acute chest pain.

Keywords: acute coronary syndrome (ACS); cardiac markers; immunoassay; point-of-care; troponin.

Introduction

General practitioners (GP) and ambulance paramedics are faced with a considerable number of patients presenting with acute chest pain (0.7–2.7% of all GP consultations and 60.7% of all ambulance responses) [1, 2]. Distinction between mild and life-threatening diseases is a challenge, especially in a prehospital setting, due to overlapping signs and symptoms and limited objective measurement tools. Therefore, the majority of chest pain patients are currently referred to the (cardiac) emergency department (ED) to rule out non-ST-elevation-acute coronary syndrome (NSTE-ACS) and reduce its inherent morbidity and mortality risk [3]. A previous study showed that in primary care only 3.6% of the chest pain patients are eventually diagnosed with acute coronary syndrome (ACS), 11.1% with stable ischemic heart disease, and 85% with non-cardiac chest pain (NCCP) including musculoskeletal, mental, gastrointestinal, and respiratory diseases [4]. Referring NCCP patients to the ED induces a

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great burden on the ED and has a psychological impact on patients and their families [5]. This results in high health care utilization and frequent readmissions, with high health care and societal costs [5, 6].

Cardiac troponin (cTn) assays have become essential for the diagnosis of acute myocardial infarction (AMI) [7]. Point-of-care (POC) troponin testing, defined as laboratory testing near the patient with rapid availability of results, has attracted much interest in the ED setting and seems feasible [8]. Adding POC devices that are able to measure high-sensitivity troponin might aid in earlier diagnosis, reduce stay at the ED, and improve patient flow. An elevated troponin in patients with suspected ACS aids in the fast initiation of adequate treatment. POC troponin testing might also play a substantial role in the triage and diagnosis of chest pain patients in a prehospital setting by integrating on-site POC troponin testing in validated risk stratification tools for ACS [9–11]. However, POC troponin testing typically involves venous whole blood as the measurement matrix and venous blood drawing might not be easily available in every primary care setting, especially at the GP offices [12, 13]. The Atellica® VTLi Patient-side Immunoassay Analyzer for high-sensitivity POC cardiac troponin-I (hs-cTnI) testing has been developed by Siemens Healthineers. It concerns a bedside system that requires 30 µL of capillary blood, venous whole blood, or plasma. The total test time, from sample application to result on the system's screen is <10 min. This study evaluates the analytical performance of the Atellica VTLi Patient-side Immunoassay Analyzer (method and sample comparison) using different sample types including capillary blood, in comparison with standard laboratory hs-cTnI testing. The use of capillary blood as a reliable sample type may enable on-site POC troponin testing in a prehospital setting. Equivalent analytical performance to laboratory high sensitivity troponin (hs-cTnI) testing would enable the use of POC with comparable reliability.

Materials and methods

This study is a prospective, observational, cohort study executed from September 2019 until November 2020. 152 patients (55% female, 45% male) referred to the cardiac ED because of acute chest pain suspected for ACS were included in the study. The inclusion and exclusion criteria are presented in Table 1. The study was approved by the local Medical Ethical Committee (METC Maastricht) and was executed according to the World Medical Association Declaration of Helsinki.

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
– Age 18 years or older. – Referred to cardiac ED with chest pain suspected of ACS; inclusion at arrival. – Subacute STEMI or NSTEMI patients who do not need rescue PCI. – STEMI patients who already underwent rescue PCI: Inclusion post PCI.	– Out of hospital cardiac arrest. – Patients with sudden onset tachycardia and a frequency of 110 bpm or higher (supraventricular or ventricular). – Patients who are hemodynamically unstable or in which an acute non-coronary diagnosis is suspected, e.g., pulmonary embolism, thoracic aortic dissection, etc. – Patients recently already admitted for the same set of symptoms at a previous healthcare institution before being transferred to the participating clinical site. – Patients not willing or not able to provide informed consent due to their medical condition as judged by the physician.

ED, emergency department; ACS, acute coronary syndrome; STEMI, ST-segment elevation acute myocardial infarction; PCI, percutaneous coronary intervention.

Directly after inclusion (T=0), a sample of capillary blood was drawn from the study subject and analyzed by the Atellica® VTLi Patient-side Immunoassay Analyzer (Siemens Healthineers, Erlangen, Germany). Two whole blood samples were drawn by venipuncture in Barricor lithium heparin blood collection tubes (Becton Dickinson, New Jersey, USA). One sample was used for regular diagnostics and the other whole blood sample was measured by the Atellica VTLi analyzer in the central laboratory. After centrifugation (5 min, 3,000 g), the plasma sample was also measured on the Atellica VTLi analyzer. The remaining plasma was aliquoted and stored at–80 °C until hs-cTnI analysis on an ARCHITECT STAT immunoassay analyzer (Abbott Laboratories, Chicago, USA). The whole process (POC study samples included) was repeated 1 h after admission of the study subject at the cardiac ED according to the local 1 h Rule-out High Sensitive troponin-T protocol for regular diagnostics of ACS. In a previous study at our cardiac ED we evaluated the diagnostic accuracy of the modified HEART score, a validated risk stratification tool for chest pain patients at the cardiac ED, integrating the T=0 en T=1 capillary POC samples [14].

Three Atellica® VTLi analysers for study purposes only were used during this study, two analysers were located at the cardiac ED and one in the central laboratory. Before the start of this study, 27 cardiac ED nurses and 31 central laboratory analysts were informed on the study protocol by the coordinating investigators and received user training on the Atellica® VTLi Patient-side Immunoassay Analyzer (Siemens Healthineers, Erlangen, Germany) by a senior clinical research associate at Siemens Healthineers. Weekly quality controls containing low and high troponin-I levels were carried out and the three study devices were exchanged between the departments on a weekly basis.

Data analysis

The troponin-I concentration measured with the Atellica VTLi Patient-side Immunoassay Analyzer in capillary whole blood sampling from the fingertip was compared to samples collected by venipuncture. In a previous validation study, the analytical performance of the Atellica VTLi was determined [15]. In the current study, data points starting from 2.5 ng/L (20% CV of the limit of quantification) up to 5,000 ng/L were included for statistical analysis. To demonstrate the concordance between the different sample types, Passing-Bablok regression was executed on the data obtained from lithium heparin venous whole blood, lithium heparin venous plasma, and capillary blood; all collected simultaneously. Analyze-it software was used to calculate the Passing-Bablok slopes, 95% confidence intervals (CI), and correlation coefficient (Microsoft Excel plug-in, Analyse-it Software, Ltd., Leeds, United Kingdom).

In addition, a qualitative method comparison was performed on the data of 152 patients, to show the analytical concordance between the capillary hs-cTnI as measured by the Atellica VTLi Patient-side Immunoassay Analyzer and the hs-cTnI plasma results as measured on the ARCHITECT immunoassay analyzer, which is considered a standardized method. The agreement was calculated using EP Evaluator software (Data Innovations LLC, Colchester, USA). For both tests, the 99th percentile was used as a cut-off value; >26.2 ng/L is considered 'positive' for the ARCHITECT method, >22.9 ng/L is considered 'positive' for the Atellica VTLi method [15, 16]. Discordant samples were compared to the troponin-T concentration (Elecsys hs-TnT immune assay, Cobas 801e, Roche, Basel, Switzerland), measured as part of the regular diagnostics at the cardiac ED for patients with acute chest pain.

Results

Sample matrix comparison

Lithium heparin plasma vs. lithium heparin whole blood

Table 2 shows the results of Passing-Bablok regression analysis comparing the Atellica VTLi hs-cTnI measurements in lithium heparin plasma and whole blood matrices. A correlation coefficient of 0.996 was found, and the 95% confidence interval of includes 1.00, meaning no statistical difference was observed between venous whole blood vs. venous plasma.

Venous samples vs. capillary blood

The correlation analysis between raw data of capillary blood and lithium heparin plasma or lithium heparin whole blood matrices shows an over-recovery of 6–9% for capillary values vs. the other two matrices. A compensation factor was determined for the measuring range of 2.5 ng/L–1,250 ng/L by combining all capillary blood data for both lithium heparin plasma and whole blood comparisons (n=303). The resulting intercept of the regression plot was found to be 0.3 ng/L, the Passing-Bablok slope 1.071. Accordingly, a compensation factor of 7.1% was implemented in the Atellica VTLi analyser software.

Table 2: Sample comparison by Passing-Bablok regression of hs troponin-I analyzed with the Atellica VTLi Patient-side Immunoassay Analyzer.

	Passing-Bablok slope	95% CI	r^2	n
Venous whole blood vs. venous plasma	1.02	0.983 to 1.07	0.996	152
Capillary vs. venous plasma	1.01	0.963 to 1.05	0.997	147
Capillary vs. venous blood	0.98	0.951 to 1.02	0.995	142

95%CI, 95% confidence interval; r^2, correlation coefficient; n, number of samples.

As shown in Table 2, for both plasma and whole blood results there is a good correlation to the capillary results with slopes of 1.01 and 0.98. No statistical difference was observed as both correlation coefficients were ≥0.995. Passing-Bablok fits for the different sample types are shown in Figure 1.

Qualitative method comparison

A qualitative method comparison was performed to show the clinical agreement between the analysis of hs-cTnI by the Atellica VTLi Patient-side Immunoassay Analyzer and the ARCHITECT immunoassay analyzer, which is considered a standardized laboratory method. To determine the agreement, the 99th percentile for each test was used as a cut-off value; >26.2 ng/L is considered 'positive' for the ARCHITECT method, >22.9 ng/L is considered 'positive' for the Atellica VTLi method [15, 16]. This resulted in the agreement table presented as Table 3, showing an overall agreement of 97.4%. The positive agreement is 95.5% and the negative agreement is 98.1%. Table 3 shows discordance between the ARCHITECT and Atellica VTLi assay for 4 out of 152 patients. Two patients were found to have an elevated troponin-I concentration by the Atellica VTLi assay, but not elevated by the ARCHITECT assay. In 2 other patients, an elevated troponin-I concentration was found by the ARCHITECT assay, but not by the Atellica VTLi assay. Table 4 summarizes the results of these patients, including the troponin-T concentration, determined for regular diagnostics (Cobas, Roche, Switzerland).

Patient 1 concerns an 88 year-old female with chest pain and a slight rise of troponin-T. Pulmonary emboli and

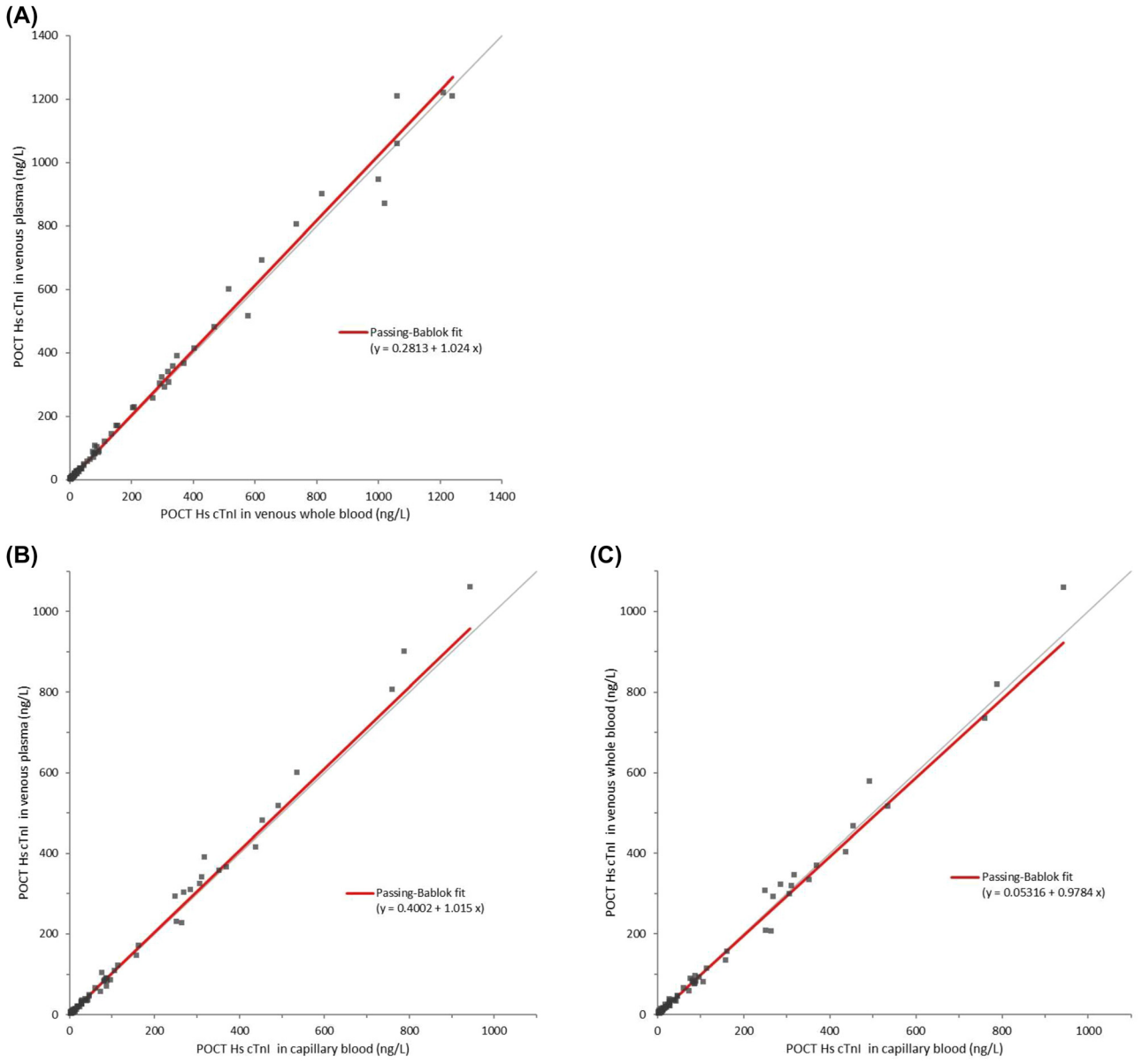

Figure 1: Passing-Bablok regression plots for sample matrix comparison of high-sensitivity troponin-I measured with the Atellica VTLi Patient-side Immunoassay Analyzer.
(A) lithium heparin whole blood vs. lithium heparin venous plasma (B) capillary whole blood vs. lithium heparin venous plasma, and (C) capillary whole blood vs. lithium heparin venous whole blood.

Table 3: Qualitative method comparison of hsTnI analyzed by the Atellica VTLi Patient-side Immunoassay Analyzer and ARCHITECT immunoassay analyzer.

Atellica VTLi	ARCHITECT		Total
	Negative	Positive	
Negative	106	2	108
Positive	2	42	44
Total	108	44	152

The discrepancies between the two methods are marked in grey.

aorta dissection were ruled out and she was admitted to the cardiology ward for clinical observation. The troponin-T concentration rose to 34 ng/L the next day, but the patient did not have any complaints. Oral antianginal drugs were prescribed, she was discharged and a SPECT scan at the outpatient clinic showed non-significant perfusion defects and no signs of left ventricle dysfunction.

Patient 2 is 65 year-old female admitted to the cardiac ED with typical chest pain suspected for stable angina pectoris. Acute coronary syndrome was ruled out based on

Table 4: Discordance between ARCHITECT and Atellica VTLi hs-cTnI results.

	ARCHITECT hs-cTnI (99th percentile cut-off 26.2 ng/L)	Atellica VTLi hs-cTnI (99th percentile cut-off 22.9 ng/L)	Cobas, Roche hs-cTnT (99th percentile cut-off 14 ng/L)
Patient 1	22.6 ng/L	24.3 ng/L	23 ng/L
Patient 2	<2.0 ng/L	110.9 ng/L	6 ng/L
Patient 3	40.4 ng/L	10.5 ng/L	23 ng/L
Patient 4	27.6 ng/L	16.1 ng/L	11 ng/L

The troponin-T results after admission at the cardiac ED are shown as a comparison. The discrepancies between the methods are marked in grey.

troponin-T results. Due to recurring chest pain coronary microvascular disease is considered. The patient is currently awaiting functional coronary artery testing.

Patient 3 is an 83 year-old female with slightly elevated troponin-T, admitted to the cardiology department with suspected unstable angina pectoris. A coronary angiogram showed non-obstructive coronary artery disease and an echocardiogram showed no abnormalities. Eventually the slight troponin-T rise could be explained by a pre-existent renal failure.

Patient 4 is a 57 year-old female who was diagnosed with a subacute myocardial infarction in 2015 and currently admitted to the cardiac ED with atypical chest pain which could be induced by palpation. Troponin-T levels were low. She was diagnosed with musculoskeletal chest pain and discharged. During follow-up no abnormalities were observed.

Discussion

The Atellica VTLi hs-cTnI measurements described in this study show no statistical difference between the different sample types (capillary blood, venous whole blood and venous plasma). To compensate for a slight over-recovery of capillary samples vs. venous samples, a correction factor of 7.1% has been implemented in the analyzer software.

To test clinical agreement, a quantitative study was performed to compare the Atellica VTLi measurements with a standardized high-sensitivity troponin-I assay. Both positive and negative agreements were found to be high (95.5 and 98.1%, respectively). In respect to diagnostics of acute coronary syndrome, the negative agreement is the most important parameter to consider, as high-risk patients could be missed. However, the 2 patients showing a negative result by the Atellica VTLi Patient-side Immunoassay Analyzer but a positive result by the ARCHITECT assay were both clinically ruled out from acute coronary syndrome. It can be concluded that the clinical performance of the POC device is comparable to standardized laboratory testing.

This study proves that POC hs-cTnI testing in capillary blood at the (cardiac) emergency department is feasible and reliable. An extensive follow-up study is needed to test the use of this method in a prehospital setting to facilitate triage and risk-stratify in chest pain patients suspected of ACS. The next step will be implementing POC hs-cTnI analysis by the Atellica VTLi Patient-side Immunoassay Analyzer in the modified HEART score in a prospective prehospital setting (emergency medical transport (EMT)). A future multicenter randomized controlled clinical trial in EMT chest pain patients will be conducted. Subjects will be 1:1 randomized into the intervention group (modified HEART score screening including POC hs-cTnI testing) or control group (regular triage and care). This study should provide more clinical evidence on the use of POC hscTnI testing by the Atellica VTLi Patient-side Immunoassay Analyzer in a prehospital setting.

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