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Analytical evaluation of a new point of care system for measuring cardiac Troponin I

Danielle WM Kemper [a,*], Veronique Semjonow [a], Femke de Theije [a], Diederick Keizer [a], Lian van Lippen [a], Johannes Mair [b], Bernadette Wille [b], Michael Christ [c], Felicitas Geier [c], Pierre Hausfater [d], David Pariente [d], Volkher Scharnhorst [e], Joyce Curvers [e], Jeroen Nieuwenhuis [a]

[a] Philips Handheld Diagnostics, Eindhoven, The Netherlands
[b] Department of Internal Medicine III — Cardiology and Angiology, Medical University of Innsbruck, Innsbruck, Austria
[c] Department of Emergency and Critical Care Medicine, Paracelsus Medical University, Nuernberg General Hospital, Nuernberg, Germany
[d] Emergency Department, Hôpital Pitié-Salpêtrière, AP-HP et Sorbonne Universités UPMC Univ-Paris 06, France
[e] Clinical laboratory, Catharina Ziekenhuis Eindhoven and Technical University Eindhoven, Eindhoven, The Netherlands

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ABSTRACT

Objectives: Point-of-care cardiac troponin testing with adequate analytical performances has the potential to improve chest pain patients flow in the emergency department. We present the analytical evaluation of the newly developed Philips Minicare cTnI point-of-care immunoassay.

Design & methods: Li-heparin whole blood and plasma were used to perform analytical studies. The sample type comparison study was performed at 4 different hospitals. The 99th percentile upper reference limit (URL) study was performed using Li-heparin plasma, Li-heparin whole blood and capillary blood samples from 750 healthy adults, aging from 18 to 86 years.

Results: Limit of the blank, limit of detection and limit of quantitation at 20% coefficient of variation (CV) were determined to be 8.5 ng/L, 18 ng/L and 38 ng/L respectively without significant differences between whole blood and plasma for LoQ. Cross-reactivity and interferences were minimal and no high-dose hook was observed. Total CV was found to be from 7.3% to 12% for cTnI concentrations between 109.6 and 6135.4 ng/L. CV at the 99th percentile URL was 18.6%. The sample type comparison study between capillary blood, Li-heparin whole blood and Li-heparin plasma samples demonstrated correlation coefficients between 0.99 and 1.00 with slopes between 1.03 and 1.08. The method comparison between Minicare cTnI and Beckman Coulter Access, AccuTnI + 3 demonstrated a correlation coefficient of 0.973 with a slope of 1.09. The 99th percentile URL of a healthy population was calculated to be 43 ng/L with no significant difference between genders or sample types.

Conclusions: The Minicare cTnI assay is a sensitive and precise, clinical usable test for determination of cTnI concentration that can be used in a near-patient setting as an aid in the diagnosis of acute myocardial infarction.

1. Introduction

Measurement of cardiac Troponin-I or Troponin-T (cTnI, cTnT) concentration in blood is required for assessment of patients suspected of Non ST-segment elevation acute myocardial infarction (NSTE-AMI) to support or exclude a diagnosis of acute myocardial infarction (AMI) [1,2,3]. Measuring cTnI at the point of care (next to the patient) with a short turnaround time (TAT) has the potential to improve patients flow in the emergency department (ED), enabling rapid clinical decision making. A patient blood sample can be withdrawn and directly tested by a doctor, a nurse or a paramedic to provide cTnI concentration during clinical examination, rather than having to wait at least 1 h for laboratory results [4,5]. A point-of-care (POC) cTn assay may allow the institution to meet the 1-h TAT criteria for the measurement of cTn from the

Abbreviations: AA, amino acid; AMI, acute myocardial infarction; CI, confidence interval; CLSI, clinical laboratory standards institute; COPD, chronic obstructive pulmonary disease; cTn, cardiac Troponin; cTnC, cardiac troponin C; cTnI, cardiac Troponin I; CV, coefficient of variation; ED, emergency department; eGFR, estimated glomerular filtration rate; HAMA, human anti-mouse antibody; Li-heparin, lithium heparin; LoB, limit of the blank; LoD, limit of detection; LoQ, limit of quantitation; NSTE-AMI, non ST-segment elevation acute myocardial infarction; NT pro BNP, N-terminal pro brain natriuretic peptide; POC, point-of-care; RF, rheumatoid factor; RFID, radio-frequency identification; TAT, turnaround time; URL, upper reference limit.

* Corresponding author at: Philips Handheld Diagnostics, High Tech Campus 29, 5656AE Eindhoven, The Netherlands.
E-mail address: Danielle.Kemper@philips.com (D.W.M. Kemper).

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guidelines [2,6]. Ideally, the analytical performance of a POC device for cTn testing should not differ from that provided by the central laboratory system [6]. We here present the results of the analytical evaluation of the novel Minicare cTnI POC assay from Philips Electronics.

2. Materials and methods

2.1. Instrumentation

The Philips Minicare cTnI consists of a handheld instrument and plastic disposable cartridge. The system makes use of the Philips Magnotech technology, which is based on the precisely controlled motion of magnetic particles (beads) in a small sample volume (typically 30 μL). The same magnetic particles also serve as labels that are detected using frustrated total internal reflection (FTIR) imaging [7,8].

2.2. Design of the minicare cTnI assay

The Minicare cTnI assay is a homogeneous sandwich immunoassay. The traditional liquid manipulation steps of an immunoassay have been replaced by magnetically controlled movements of magnetic nanoparticles within a stationary liquid (see Fig. 1). The magnetic beads carry antibodies directed against cTnI whereas the other side of the sandwich is formed by antibodies printed on the bottom of the cartridge (the sensor surface).

A droplet of sample (30 μL) of whole blood or plasma is applied to the cartridge and the reaction chamber fills by capillary action. Red blood cells are retained by an integrated separation membrane to prevent impact on the assay. About 2 μL of plasma will be extracted and the microfluidic design ensures that precisely 0.25 μL is metered into the reaction chamber. In the first phase of the assay, beads coated with antibody capture cTnI molecules in the sample. Subsequently, magnetic fields gradients are engaged to transport the particles rapidly to the sensor surface towards immobilized antibodies able to capture the troponin-bearing nanobeads. Thereafter, a sequence of finely tuned magnetic pulses is applied to facilitate optimal binding and mixing of the beads containing cTnI molecules at the antibody-functionalized surface. After the beads reacted with the sensor surface, un-bound and non-specifically bound beads are rapidly removed with a magnetic wash by applying a magnetic field gradient oriented away from the detection surface [7,8].

2.3. Selection of antibodies

Antibodies are applied to the magnetic beads and onto the plastic surface of the cartridge to form both parts of the sandwich, as described above. The choice of antibodies is crucial for assay performance. Mouse-monoclonal antibodies were selected for the Philips Minicare cTnI assay. The primary anti-cTnI mouse-monoclonal antibody is directed against the stable region of the cTnI molecule (amino acid (AA) 41–49) and has been covalently bound to the magnetic beads. A mixture of three secondary antibodies have been attached to the sensor surface by physisorption, which consists of two anti-cTnI antibodies with epitopes in the range AA 20–100 and a single anti-cTnC antibody, to optimize measurement of total cTnI including cTnI-TnC complexes.

2.4. Standardization

Due to the lack of a suitable commutable primary calibrator for cTnI immunoassay standardization, new cTnI standards have been developed from pooled native human samples. These standards are dose-assigned on the Beckman Coulter Access 2, AccuTnI + 3 as a reference method. Primary calibrators are prepared, based on the standard reference material of the National Institute of Standards and Technology (NIST SRM) 2921 Human Cardiac Troponin Complex, and are dose-assigned on the native standards. Additionally, secondary calibrators are prepared from NIST SRM 2921 and dose assigned using the primary calibrators. Calibration parameters were obtained from dose-response curves and programmed in the radio-frequency identification (RFID) of each cartridge.

2.5. Study samples

For the precision, detection capability, linearity, high-dose hook effect, cross-reactivity and interferences studies, left-over Li-Heparin blood samples from patients from the Canisius-Wilhelmina hospital (CWZ) in Nijmegen, The Netherlands, and Li-Heparin blood samples from healthy volunteers (informed consent obtained) from Sanquin Blood bank in Nijmegen, the Netherlands were obtained. From these samples negative and high cTnI Li-heparin plasma pools were selected to be able to prepare sample pools with different levels of cTnI as specified for each study.

For the method comparison and sample type comparison studies, three sample types (capillary whole blood from finger stick, Li-heparin whole blood and Li-heparin plasma) were collected for each patient at four European hospitals (Medizinische Universitaet Innsbruck, Austria, Klinikum Nurnberg Germany, Catharina Ziekenhuis Eindhoven, The Netherlands and Hôpital de la Pitié-Salpêtrière Paris, France) participating to the Lab2Go project. Lab2Go is a European Union funded multicenter Research and Development project involving several hospitals in the European Union. Patients were selected to represent the range of cTnI concentrations likely to be encountered in clinical practice, covering the measurement range of the Minicare cTnI. Samples were analysed on Minicare cTnI by Minicare-trained users (nurses, research assistants) within 2 h after blood drawn. Li-heparin plasma samples were centrifuged a second time and transferred to a new container before freezing at <− 55 °C. Frozen samples were sent to the core lab at Philips on dry ice for parallel testing on the Beckman Coulter AccuTnI + 3 assay and

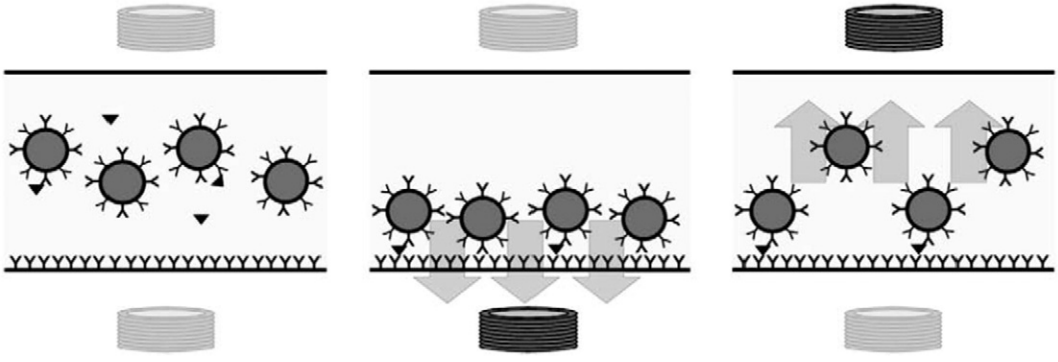

Fig. 1. Depiction of the reaction chamber and actuation magnets showing the assay processes: analyte binding by beads bearing anti-cTnI antibodies (top and bottom magnets off), bead binding to the sensor surface (bottom magnet on) and magnetic removal of free and weakly bound beads (top magnet on).