Editorial

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Transdermal measurement of cardiac troponins: the future is now

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A very common aphorism among experts in laboratory medicine is that "good, fast and cheap" laboratory testing is a mission impossible [1]. However, this aphorism is certainly catchy, but it may be also misleading, because a cheap test may not be cost-effective (or vice versa). Anyway, accurate, rapid and cost-effective laboratory methods are exactly what is needed to detect an acute ischemic myocardial injury in patients admitted to the Emergency Department (ED) with chest pain.

Over the last 10 years, the introduction of high-sensitivity cardiac troponin (hs-cTn) assays with increasingly better analytical performance has made it possible to reduce the time to diagnosis of acute myocardial infarction (AMI) from 6-12 h vs. to 1–3 h [1, 2]. From a pathophysiological point of view, a decrease in the ischemic time reduces the area of necrosis, leading to a more rapid patient recovery, a better functional performance of the myocardium, and even a lower frequency of adverse events such as cardiac arrhythmias [3–6]. In particular, the 2020 European Society of Cardiology (ESC) guidelines recommend the rapid 0/1-h algorithm (blood draw at admission at baseline and 1 h later) as the first option because it provides the best balance between safety and efficacy by allowing the decrease of the length of stays in ED of patients with suspected acute coronary syndromes without persistent ST-segment elevation [NSTE-ACS] [3]. In some specific cases, it is even possible to accurately rule-in or rule-out the NSTE-ACS with just a sample collected at admission to ED, if patients present very high (i.e., more than about five folds the cut-value) or very low (i.e., below the limit of detection of the method) hs-cTn values [3]. However, there are still some doubts regarding the routinary use of the most rapid (0–1 h or 0–2 h) compared to 0–3 h algorithms in the NSTE-ACS patients [4, 5]. In particular, some guidelines or expert opinion documents [4–6] have observed that the rapid algorithms (particularly the 0 h/1 h algorithm) do not seem to be applicable in several clinical laboratories of European and North America countries. In particular, these documents suggest that the clinical implementation of these rapid algorithms should be currently restricted to hospital laboratories which adopt pre-analytical facilities (i.e., pneumatic tube transportation) and fully-automated platforms for hs-cTn assays where it is possible to reduce the total turnaround time (TAT) to significantly less than 60 min [4–6].

The use of reliable point-of-care-testing (POCT) methods may represent a formidable progress because they should ensure a more rapid TAT, thus facilitating the management of patients admitted to ED with chest pain [1]. Furthermore, POCT assays create the opportunity for a "decentralized" diagnosis of myocardial injury and infarction, even in primary care and other remote clinical settings [1, 7]. Unfortunately, until a few years ago, the shorter TAT of commercially available POCT methods was counterbalanced by their lower sensitivity, lower diagnostic accuracy, and lower negative predictive value [1]. The results of some very recent studies indicate that POCT methods for cTn have a comparable analytical performance to hs-cTn assays used in central laboratories [1]. In 2019, Sorensen et al. reported that the PATHFAST POCT cTnI assay using the PATHFAST immune-analyzer system has an analytical performance compatible with a hs assay [8]. The results were firstly obtained in 669 patients presenting to the ED with suspected AMI and validated in an additional 610 patients and compared with those obtained with the Architect hs-cTnI method [8].

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In 2020 Boeddinghaus et al. reported that the POC hs-cTnI-TriageTrue assay provided high diagnostic accuracy in patients with suspected AMI with a clinical performance comparable to that of the best-validated central laboratory assays using specific 0/1-h algorithms in 1,261 patients (178 with AMI, 14%) [9]. More recently, Apple et al. [10] reported the sex-specific 99th percentile upper reference level (URL) values using the Siemens POC Atellica VTLi hs-cTnI immunoassay in heparinized plasma from a reference population (age range 18–91 years, 693 males and 363 females). The percentages of male and female subjects with measurable concentrations above the level of detection were much higher than 50% (men 87.3%, women 79.7%) [10]. Notably, the Authors excluded possible outliers using some surrogate biomarkers, also including NT-proBNP, as recommended by expert documents [11, 12].

Overall, these studies [8–10] confirm that some hs-cTnI POCT methods meet the quality specifications recommended for hs-cTnI assay according to international guidelines [13, 14]. From a clinical perspective, hs-cTnI POCT method should be considered the best solution when timely access to laboratory facilities for decision-making is not possible. This is particularly the case in settings where sample transportation strongly affects the TAT and/or patient transfer to another hospital is complex for logistical issues [14]. Another important use of the hs-cTnI POCT methods may be to rule-out myocardial infarction without persistent segment elevation (NSTEMI) in the doctor's office by monitoring the patients for short time periods (i.e.,≤2 h). However, recent guidelines stated that further evidence on to the cost-effectiveness of hs-cTnI POCT methods for the diagnosis and management of NSTEMI patients is needed [5, 14].

Although hs-cTnI POCT methods significantly reduce the TAT because test results can be obtained at patient bed, they still require a blood draw. A possible new perspective is the development of wearable devices able to estimate circulating cTn levels through the skin (so-called "on vivo" testing) [15]. The development of reliable wearable devices with analytical performance similar to hs-cTn assay is a very complex task. A recent article reported the results of the assessment of devices based on infrared spectroscopic detection of cTn through the skin [16]. Infrared spectroscopy is an inherently sensitive mode of detection due to its ability to interact with the material at the molecular level [16], and has the advantage of requiring minimal or no sample preparation.

A very recent article describes the analytical performance and the preliminary results obtained with a benchtop attenuated total reflectance (ATR)-based spectrometer in a cardiac care setting [16]. The Authors preliminary tested this device on the thumb of four normal adult subjects and five cardiac patients with ACS in order to specifically detect the wavelength range including some of the unique absorbance features relating to cTnI. Later, in an independent study the Authors tested an improved device on 52 adult patients with chest pain under suspicion of ACS enrolled from two different clinical institutions (23 from Sengupta Hospital and Research Institute, Nagpur, India; 29 from Zuckerberg San Francisco General, San Francisco, USA). The plasma cTnI was measured in the two different clinical institutions using two cTnI assays: Snibe Maglumi-1000 high sensitivity cTnI method (in Nagpur, India) and hs-cTnI Siemens ADVIA Centaur method (San Francisco, US) using two different 99th percentiles. Comparing the results obtained with the ATR-based spectrometer with those of the two hs-cTnI assays, Authors reported a significant correlation ($n=52$, $r=0.777$, $p<0.001$) with an area under the curve of 0.895 (sensitivity 96%, specificity 60%) to predict a clinically meaningful elevation of cTnI in the 52 patients with chest pain and suspicion of ACS [16].

This study introduces the clinical advantages of a transdermal measurement of cTnI by molecular spectroscopy. This sensor can produce results within 5 min without the need of collecting and processing blood [16]. Furthermore, serial measurements of cTnI are possible (i.e., at 5-min intervals) if the device is left on the patient. This system even allows for the combined measurement of both cardiac-specific biomarkers (i.e., cTnI and BNP) [16]. Therefore, the device can provide a more complete pathophysiological information on both cardiac function and presence of myocardial injury [17], which may be useful for monitoring patients in ED, critical care units, and during cardiac or extra-cardiac surgery, possibly including the neonatal and pediatric age.

Of course, this study is a very preliminary step in the long process towards a reliable optical device. Most notably, we must evaluate if this system present adequate analytical performances and comparable cost/effectiveness ratio in comparison to commercially available fully automated hs-cTnI assays [18]. Nonetheless, if this device lives up to expectations, it might become applicable to many facilities such as urgent and critical care units, not requiring the need for blood sampling and drastically reducing the TAT.

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