REJMER, Adrian, SZALA-CZERWONKA, Karolina, WOŚ, Natalia, ROJEK, Katarzyna, BEDNARZ, Lucjan, WIJAS, Karolina, BIALIC, Kinga, BAKALARCZYK, Rafał, BIALIC, Artur & MAJEWSKI, Pawel. A breakthrough in acute coronary syndrome diagnostics – transdermal troponin assessment. Journal of Education, Health and Sport. 2023;24(1):67-74. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.24.01.006
https://apcz.umk.pl/JEHS/article/view/43525
https://zenodo.org/record/7878861

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.04.2023. Revised: 10.04.2023. Accepted: 29.04.2023. Published: 29.04.2023.

A breakthrough in acute coronary syndrome diagnostics – transdermal troponin assessment

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Abstract:

Introduction and purpose:

The measurement of cardiac troponins, besides ECG and basic patient examination, is a vital component of the diagnosis and management of patients with acute coronary syndrome (ACS), including unstable angina (UA), non-ST and ST elevation myocardial infarction (NSTEMI, STEMI). Traditionally cardiac troponins have been measured through blood samples, but a new method of transdermal wrist measurement has emerged as a promising alternative. The potential benefits of transdermal troponin measurement are numerous. First and foremost, the non-invasive nature of the method means that patients can be diagnosed "on the spot" and monitored in real time without the need for repeated blood draws, vastly reducing the time for diagnosis and patient qualification for invasive treatment, percutaneous coronary intervention - PCI, if needed. The coronary syndrome is the number 1 cause of death in developed countries which includes morbidity and mortality. With the invention of transdermal troponin assessment device, we can increase the life expectancy and the quality of life in the group of patients with acute coronary syndrome and most importantly, decrease the total turnaround time of diagnosis and significantly reduce the workload in the emergency department.

State of knowledge:

The review is based on research of available data from PubMed and other sites 2018-2023 database. It focuses on the newest breakthroughs in the field of cardiology.

Conclusion:

The introduction of transdermal troponin assessment devices may drastically improve early diagnosis and risk evaluation for patients with acute coronary syndrome. This is a very exciting opportunity because it increases our capabilities of early diagnosis of acute coronary syndromes in critical care and community settings environments. Besides very promising results there is a lot of work to be done with further research with improving the precision and overall diagnostic value of the device and potential pitfalls associated with infrared spectroscopy, but this solution could potentially address the issues with prioritization and access, for example by shortening the total turnaround time, which is the time to triage in critical care environment, or for emergency responders to plan the patient's journey to the nearest hospital where percutaneous coronary intervention can be performed if needed.

Keywords: troponin, transdermal, device, acute coronary syndrome, infrared spectroscopy

Introduction and purpose:

Definition of acute coronary syndrome, troponins and epidemiology:

Acute coronary syndrome includes heart attack (NSTEMI and STEMI) and unstable angina (UA) that occurs when blood supplied to the heart muscle by coronary arteries is suddenly blocked by a clot which usually results in STEMI or when it's flow is suddenly critically decreased which results in NSTEMI or UA [1,2]. The difference between STEMI, NSTEMI and UA is that in the first two instances necrosis of the heart muscle occurs which results in raised levels of cardiac troponin (cTnI) over 99 percentile, in the case of UA cTn are also raised but remain under 99 percentile and there is no clinically relevant necrosis of the heart [3,4,5].

Troponin is a complex of three regulatory proteins (troponin I, troponin T, and troponin C) that are integral to muscle contraction in cardiac muscle and skeletal muscle. Troponin C (TnC) binds calcium ions (Ca2+), it is the same in cardiac and skeletal muscles and therefore it's not clinically relevant for the diagnosis of myocardial infarction [6,7]. Troponin I (TnI) binds with actin filaments in muscle tissue and has an isoform with the mass of 23,5 kDa that is specific to the heart muscle. Troponin T (TnT) binds with tropomyosin and also has an

isoform with the mass of 33 kDa specific to the heart tissue. Only cTnI and cTnT are diagnostically relevant and are by far the most specific and sensitive indicators for the diagnosis of acute coronary syndrome. Clinically most important thing about cardiac troponins is the dynamic changes in cTn levels during acute coronary syndrome (Figure 1) and detection ranges provided by current technology (Figure 2).

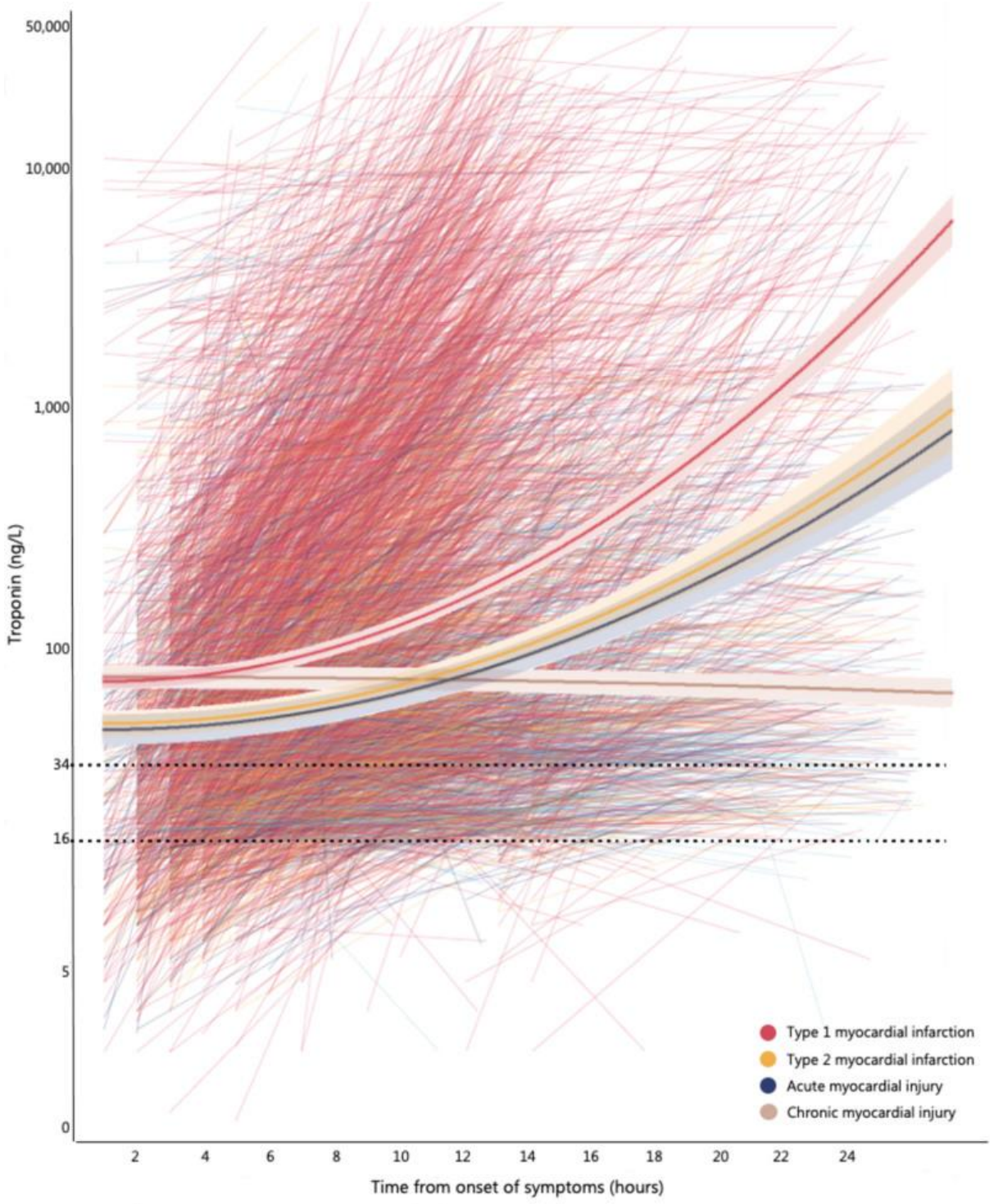

Figure 1. Kinetics of high sensitivity cardiac troponin I concentration form first symptoms of myocardial injury and infarction [8].

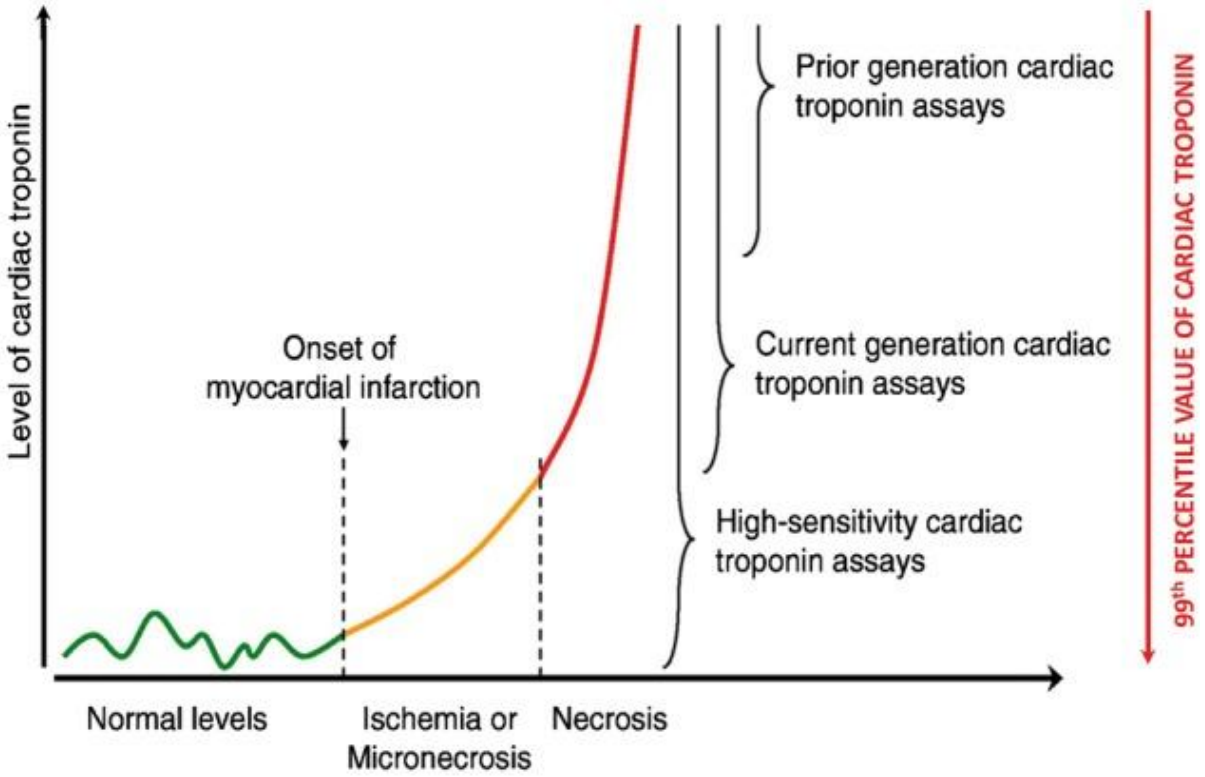

Figure 2. Detection ranges of different cardiac troponin (cTn) assays. After 2-6 hours there is a significant rise in cTn levels which may reflect in myocardial ischemia or necrosis [9].

Measurement of cardiac troponins is recommended in patients with ACS within 60 minutes of total turnaround time (TAT) [10]. The introduction of high sensitivity troponin assessment (hs-cTn) over the last 11 years has significantly reduced the time to diagnosis to 1-3 hours [11,12]. A decrease in the diagnosis time reduces the infarction area which leads to a faster patient recovery, better ejection fraction and ventricle performance overall and lower frequency of adverse events such as arrhythmias [13,14,15,16]. The 2020 European Society of Cardiology (ESC) guidelines recommend the 0/1 – hour algorithm as the first option because it provides the best balance between safety and efficiency by decreasing the length of stays in the Emergency Department only if patients present very high or very low levels of cardiac troponin. Despite the usefulness of 1 hour algorithms there is still a debate whether these compared to 0-3 hour algorithms in patients with acute coronary syndrome are better. Some guidelines suggest that the rapid algorithms do not seem to be applicable in some clinical laboratories in Europe or USA and should be restricted to ones that have fully automated platforms for hs-cTn assessment where it's possible to reduce the total turnaround time to less than 1 hour. These turnover times are in practice hard to implement in critical care settings because of limited hospital resources and staff shotages [17] which then can be associated with delays in blood sampling [18]. A promising solution to this problem is to implement a point of care test for estimating cardiac troponin levels [19]. Point of care tests for estimating cardiac troponin are available but there are no FDA approved hand-held devices for clinical use. Therefore, we have recently reported a novelty of a wrist worn transdermal infrared spectrophotometric sensor (T-ISS) for the assessment of cTnI levels [20].

Acute coronary syndromes (ACS) including unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) are the leading cause of morbidity and mortality in developed countries [21]. Around 10 million patients annually present with chest pain in critical care emergency departments in the USA [22]. Vast majority of these are caused by non-cardiac diseases which results in an unnecessary ED overload, revealing the need for a fast non-invasive screening. Moreover, around 20% of patients with ACS don't show any symptoms whatsoever [23], this is especially true with diabetic patients, leading to almost 200 000 silent myocardial infarctions a year in the USA alone and this is why the development of new technology which allows early non-invasive assessment of cardiac troponins is essential because the delays in initiating effective treatment can impact the death rate and quality of life [24,25,26].

Description on current state of knowledge:

Infrared spectroscopy implemented in wrist-worn device:

Infrared spectroscopy can find chemicals and biological materials to a depth determined by the wavelength and the refractive indices of the chemicals that the infrared light passes through [27]. The infrared light interacts with many proteins, body fluids, aminoacids and even the sweat on the surface of the skin so there are many possible ways of interference. The transdermal device is designed to operate within wavelengths that can show the levels of cardiac troponin to reduce a potential chance of interference with other enzymes.

Even though high sensitivity point of care testing methods provide a short TAT because we can get the results by the patients bed, they still require blood draws. A possible and very promising solution is the development of wearable devices able to estimate circulating cTn levels transdermally [28]. Developing wearable devices with similar reliability and performance to POCT hs-cTn assay is a very hard task. A recent report of the assessment of cTnI levels through skin, an infrared spectroscopy device (Figure 3) seems to be an inherently sensitive detection mode due to its ability to interact with the cardiac troponins at the fundamental level and doesn't require any blood sampling or blood processing [29].

Figure 3. Evolution of the infrared spectroscopy device from the prototype to the current production-ready form [30].

Authors tested the device on 52 adult patients with chest pain under suspicion of acute coronary syndrome enrolled from two different clinical institutions. Troponin was measured using two cTnI assays: Sinbe Maglumi – 1000 high sensitivity cTnI method and Siemens ADVIA Centaur hs-cTnI method using two different 99th percentiles. Authors report a very significant correlation (n=52, r=0.777, p<0.001) with AOC = 0.895 (sensitivity=96%, specificity=60%) comparing two results obtained with the attenuated total reflectance (ATR) – based infrared spectrometer, which means that we can get clinically relevant information of elevated cTnI levels in patients with acute coronary syndrome. This device and provide results in 5 minutes or less without the need of a blood draw. Moreover, we can measure the cTnI levels in series or continuously. Furthermore, there is a possibility for the device to measure not only cardiac troponins but also other useful biomarkers such as BNP which means that capabilities of the device can be extended to provide a more complete information on cardiac function in instances such as heart failure [31].

In yet another study [32], the authors show similar results in which a transdermal-ISS derived deep-learning model predicted the elevated cTnI levels in 238 patients with the area under the curve of 0.90 (95% confidence interval CI, 0,84-0,94; sensitivity=0.86; specificity=0.82) and 0.92 (95% CI, 0.80-0.98; sensitivity=0.94; specificity=0.64) for internal and external validation cohorts. A wrist-worn transdermal infrared device can give clinically relevant information of elevated cTnI levels in patients with acute coronary syndrome and therefore reduce time to diagnose, triage and therapy in emergency settings.

Summary:

The new infrared wrist-worn spectroscopy devices seem very promising in evaluating cardiac troponin levels in patients with acute coronary syndrome, it may become applicable to many areas such as emergency departments, critical care units, cardiology or internal medicine departments and reduce significantly TAT but they are nevertheless preliminary steps in the long run towards a reliable transdermal device and further research needs to be performed including safety, reliability and cost/effectiveness ratio in comparison to commercially available traditional blood draw POCT troponin tests.

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