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C. Puelacher · P. Hillinger · M. Wagener · C. Müller
Department of Cardiology and Cardiovascular Research Institute Basel, University Hospital Basel, Basel

Cardiac biomarkers for infarct diagnosis and early exclusion of acute coronary syndrome

According to the World Health Organization [1], cardiovascular diseases are the leading cause of premature death worldwide, with ischemic heart diseases, especially acute coronary syndrome (ACS), being a major cause [2]. Since a highly effective and evidence-based therapy consisting of electrocardiogram (ECG) monitoring, antiplatelet therapy, statins, and coronary revascularization is available and patients benefit from early treatment, fast diagnosis of ACS is essential. On the other hand, the importance of early exclusion of ACS is highlighted by the high costs and unnecessary anxiety of patients having to wait many hours in the emergency department (ED) until ACS is safely ruled out.

Clinical evaluation of patients with suspected ACS

In Germany 11% of all ED admissions happen because of acute chest pain or other symptoms suggestive of ACS [3]. The majority of these patients will ultimately be found not to have ACS. Therefore, the exclusion process has received increased attention. A crucial part is the first evaluation of the patient. Physical examination can show signs of hemodynamic instability (e.g., tachycardia and hypotension), but usually reveals no specific findings. Assessment of the patient history is essential and should address symptom location, onset, character, severity, radiation, alleviating and exacerbating factors, time course, history of similar episodes, and associated symptoms, including sweating or dyspnea. It should be noted that patients sometimes do not refer to their symptoms as "pain" but rather as "discomfort" [4]. The ECG is considered a vital sign in this group of patients and should always be done within the first 10 min [4, 5]. Unfortunately, it has a relatively poor sensitivity, and therefore safe exclusion requires the combined use of clinical assessment, ECG, and cardiac biomarkers, preferably cardiac troponin (cTn) [6]. Before discussing the relative importance of these three diagnostic variables, it is important to highlight that ACS consists of three different pathophysiological entities: ST-elevation myocardial infarction (STEMI), which is usually caused by a complete occlusion of an epicardial coronary artery; non-STEMI (NSTEMI), which may be caused by a complete obstruction, but more often is caused by a high-grade thrombotic coronary stenosis that has already resulted in distal embolization and thus cardiomyocyte injury; and unstable angina (UA), in which a high-grade coronary stenosis is present as well but did not cause distal embolization and/or cardiomyocyte injury. The entities STEMI and NSTEMI are summarized as acute myocardial infarction (AMI) [7]. This distinction has major clinical implications, as UA has recently been identified to be a much more benign disorder with much lower mortality rates and probably does not benefit from early and aggressive therapy [8].

Cardiac troponins I and T

In combination with symptoms and/or ECG changes, CTn is an essential component of the definition of AMI and UA [7]. The two cardiac troponins T and I are cardiomyocyte-specific proteins that play an essential role in the contraction of cardiac muscle [9]. Their function is to translate the excitation signal into contraction of the actin and myosin filaments. As they are only expressed in heart muscle cells, they are markers with a high specificity for myocardial damage [7, 10] and are released, for example, during AMI, but not in conditions representing frequent differential diagnoses, such as musculoskeletal pain, pleuritis, gastroesophageal reflux, pneumonia, or gastritis. As levels of cTn are organ- but not disease-specific, mild elevations in cTn may well be encountered in conditions that are associated with smaller amounts of cardiomyocyte injury, such as heart failure, pulmonary embolism, or aortic dissection [4]. The levels detected in peripheral blood also allow quantification of the amount of cardiomyocyte injury. A major limitation of conventional cTn assays is their low sensitivity at the time of patient presentation, which is due to a delayed increase in circulating levels, as a significant amount of cells must be damaged to reach detectable levels. Therefore, serial sampling for up to 6–12 h is necessary for safe exclusion of AMI in all patients with suspected ACS [7].

This limitation has now been largely overcome by advances in assay technology, allowing the precise measurement of very low concentrations of cTn. With these new high-sensitivity (hs-cTn) assays, cTn has become detectable in 50–90% of healthy patients [11]. This allows the definition of a range of normal cTn levels within the population and consequently the formulation of a 99th percentile of healthy individuals as the recommended upper reference limit for clinical decision making. The use of this upper limit of normal has been incorporated in-

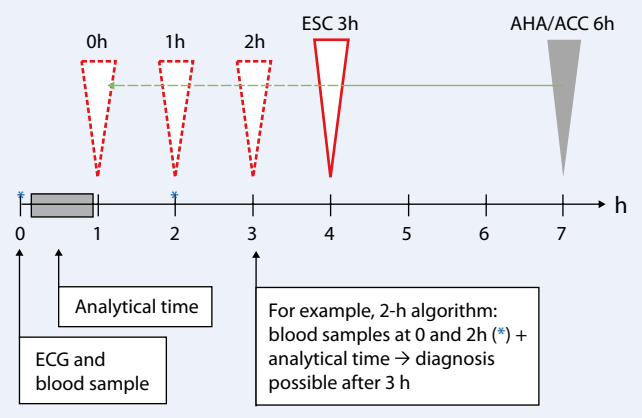

Fig. 1 ▲ The use of hs-cTn assays allows more rapid exclusion and inclusion. Inclusion of acute myocardial infarction (AMI) can be made at presentation (0 h) in patients with unequivocal ST elevations, at 1 h in patients with elevations in cTn in the measurement performed at presentation (analytical time is around 1 h in most hospitals), but only at 7 h if the first cTn is normal and the elevation in cTn becomes apparent only at the second measurement performed after 6 h. Exclusion requires a normal second cTn level and therefore 7 h. According to the 2011 European Society of Cardiology (*ESC*) guidelines, AMI can be reliably ruled out at 4 h if the hs-cTn assay is used. Recent research has indicated that hs-cTn assays may allow even earlier exclusion and inclusion if assay-specific algorithms are used or if applied in combination with copeptin. *AHA/ACC* American Heart Association/American College of Cardiology

to the Universal Definition of Myocardial Infarction [7]. As a consequence, differentiation between especially NSTEMI and UA is more easily possible, as UA usually presents with no or only small changes of cTn levels not exceeding the 99th percentile [7]. Again, this distinction has major implications.

Use of the 99th percentile as the upper limit of normal results in the detection of a considerable number of patients with mild elevation in cTn from causes other than ACS. These include chronic disorders, such as heart failure, valvular heart disease, and stable coronary artery disease, as well as cardiac and noncardiac acute disorders with cardiac involvement, such as myocarditis, arrhythmias, or severe sepsis with cardiomyocyte injury [4, 12, 13]. Overall, a strategy including hs-cTn seems to be the most practical and cost-efficient method currently available for diagnosis and treatment of ACS [14]. When dealing with hs-cTn assays, there is one caveat: Experts have started advocating the reporting of cTn levels in nanograms per liter (ng/l) instead of micrograms per liter (µg/l), as was common in the last two decades. The new concept should limit errors due to the use of the decimal point with µg/l. Furthermore, the 99th percentile is inherently an assay-specific cut-off, complicating interpretation and transfer of findings from one assay to another.

Exclusion

Evaluation of patients with suspected ACS is time-consuming, resource-intense, and contributes to overcrowding of EDs. This leads to duplication of effort during shift changes, waste of resources, and unfavorable outcomes for patients [15, 16]. While the use of hs-cTn assays for inclusion of AMI is not without challenges, particularly in patients with mild elevation, hs-cTn might just be the perfect tool for rapid and reliable early exclusion of AMI. With conventional cTn assays, two consecutive measurements within 6–12 h are necessary to safely rule out AMI. Recently, several protocols using hs-cTn with or without a clinical risk score and ECG findings were derived and validated for more rapid exclusion (◘ **Fig. 1**). The current European Society of Cardiology (ESC) guidelines from 2011 [17] propose an algorithm allowing safe exclusion after only 3 h, when using hs-cTn assays. The new ESC algorithm also suggests that depending on the onset or maximum of acute chest pain, if known with certainty, an even earlier exclusion is feasible. An accelerated diagnostic protocol incorporating the thrombolysis in myocardial infarction (TIMI) score, the ECG and cTn levels at 0 h and 2 h have been found to allow fast and safe exclusion in up to 40% of consecutive patients [18]. To further accelerate the protocol, we derived and tested an exclusion within 1 h, based solely on hs-cTnT values and absolute change, and were able to rule out patients with a very high sensitivity and a negative predictive value (NPV) [19]. This hs-cTnT 1-h algorithm has prospectively been validated in a large international study (TRAPID-AMI), with the main results expected to become available in the second half of 2014. Another strategy to reduce the time to discharge is the use of point-of-care cTn assays. While clearly reducing the turnaround time, the current generation of point-of-care cTn assays do not reach the sensitivity offered by the hs-cTn assays run on large laboratory platforms. This may at least to some extent explain the mixed results obtained in initial clinical trials [20].

It is important to highlight that we still do not have a biomarker accurately indicating myocardial ischemia without cardiomyocyte injury; therefore, clinical assessment and the ECG remain the key elements for a positive diagnosis of UA. As cTn is an integral part of the AMI diagnosis, methodologically it is very difficult for any other biomarker to provide an incremental value. Only two biomarkers were able, at least to some extent, to show a diagnostic benefit for the early exclusion of AMI: copeptin and heart-type fatty acid binding protein (h-FABP).

Copeptin

Arginine vasopressin (AVP) plays an important role in fluid balance and vascular tone [21, 22]. It is secreted as a prohormone from the pituitary gland and then cleaved from its precursor. The C-terminal part of the provasopressin is called copeptin and, from an analytical viewpoint, offers a distinct advantage as it is much more stable while being secreted in equimolar amounts with AVP. Rapid increas-

es of copeptin reflect acute endogenous stress [23], as caused by stroke, sepsis, or AMI [24]. Used in conjunction with conventional cTn assays, measurement of copeptin was associated with a substantial increase in early diagnostic accuracy, particularly the NPV for AMI at presentation. The high sensitivity of a dual-marker strategy (negative hs-cTn and negative copeptin) for early exclusion of AMI at presentation has been confirmed by several prospective observational studies including more than 8,000 patients [25]. In addition, the safety of this approach has recently been confirmed in a multicenter randomized controlled study [26].

Heart-type fatty acid binding protein

h-FABP is a cytoplasmic carrier protein that facilitates transport of long fatty acids from the cell membrane to mitochondria [27]. As it is small, soluble, and not structurally bound like cTn, it appears in the peripheral blood shortly after myocardial damage and therefore might contribute to early diagnosis of AMI. Nonetheless, recent studies investigating the added value of h-FABP on top of hs-cTn failed to show a clinically relevant benefit [28, 29]. A remaining niche might be patients presenting very early after symptom onset. This small subset of patients warrants studies with both copeptin and h-FABP.

Further and future biomarkers

Additional biomarkers have been tested for the evaluation of patients with symptoms suggestive of ACS, but a clinically relevant diagnostic advantage was not seen. Some proved to have prognostic value and will be listed here. The best known is B-type natriuretic peptide (BNP) [30, 31], which is expressed in the cardiomyocytes in response to ventricular wall sheer stress or ischemia [32, 33]. Its functions are cardioprotective and include mechanisms such as a shift of intravascular volume and inhibition of sympathetic drive. As an analytical alternative, N-terminal pro-BNP (NT-proBNP) or mid-regional pro-ANP (MR-proANP) provide similar prognostic, but not meaningful diagnostic, information for AMI and/or ACS [34].

An even stronger prognostic value than BNP seems to be associated with mid-regional pro-adrenomedullin (MR-proADM) [35, 36], a stable cleavage product of the prohormone of ADM. ADM has effects similar to BNP, being a potent vasodilator, increasing cardiac output, and inducing diuresis and natriuresis [36]. Another new biomarker is growth differentiation factor 15 (GDF-15), which is produced in response to tissue injury, oxidative stress, or inflammation. Its prognostic value was shown for STEMI [37] as well as NSTEMI [38].

Furthermore, there is a group of biomarkers associated with plaque rupture, such as high-sensitive C-reactive protein (hs-CRP), myeloperoxidase (MPO), myeloid-related protein 8/14 (MRP), and pregnancy-associated plasma protein-A (PAPP-A). Although AMI is mostly associated with plaque rupture, this group of markers could not show an additional diagnostic value for the diagnosis of AMI [39].

As a future perspective, advances of proteomics might soon allow the identification of other potential cardiac biomarkers that might provide help in addressing the remaining unmet needs in the hs-cTn era [40].

Conclusion

hs-cTn is an essential component of the evaluation of patients with suspected ACS. Used either alone with serial measurements at 1 h, 2 h, or 3 h, or in combination with a clinical score or copeptin, hs-cTn allows the early and safe exclusion of ACS in a substantial number of these patients. This will contribute to better and faster patient management.

Corresponding address

Prof. C. Müller
Department of Cardiology and Cardiovascular Research Institute Basel, University Hospital Basel
Petersgraben 4, 4031 Basel
Switzerland
christian.mueller@usb.ch

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Cardiac biomarkers for infarct diagnosis and early exclusion of acute coronary syndrome

Abstract

The acute coronary syndrome (ACS) represents a diagnostic challenge: on the one hand patients need to be quickly identified to initiate treatment and on the other hand early exclusion of patients without ACS is important to relieve patient stress as well as overcrowded emergency departments. A growing number of biomarkers are becoming available to aid physicians with this task. This review gives an overview of the current research concerning early exclusion with an emphasis on the clinically most important biomarker: cardiac troponin.

Keywords

Biomarkers · Troponin · Acute myocardial infarction · Acute coronary syndrome · Exclusion

Kardiale Biomarker für die Infarktdiagnose und den frühzeitigen Ausschluss eines akuten Koronarsyndroms

Zusammenfassung

Das akute Koronarsyndrom (ACS) stellt eine diagnostische Herausforderung dar: einerseits müssen kranke Pateinten schnell identifiziert werden, um die entsprechende Therapie zu beginnen. Andererseits ist der sichere Ausschluss von Patienten ohne ACS ebenfalls essenziell, um weder Patienten noch überfüllte Notfallstationen zu belasten. Eine wachsende Zahl von Biomarkern steht Ärzten als Hilfsmittel dazu zur Verfügung. Dieser Übersichtsartikel gibt eine Zusammenfassung der aktuellen Forschungsarbeiten zum frühzeitigen Ausschluss des ACS mit einem besonderen Fokus auf den klinisch wichtigsten Biomarker: kardiales Troponin.

Schlüsselwörter

Biomarker · Troponin · Akuter Herzinfarkt · Akutes Koronarsyndrom · Ausschluss

Compliance with ethical guidelines

Conflict of interest. C. Müller has received research support and consulting/speaking honoraria from several diagnostic companies. C. Puelacher, P. Hillinger, M. Wagener, and C. Müller state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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