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Letter to the Editor Open Access

The Role of Biomarkers in the Emergency Cardiovascular Setting

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Letter to the Editor

Cardiovascular Diseases (CVD) are the major cause of death worldwide, accounting for an increasing prevalence of death which will reach 23.6 million of affected persons in the 2030, [1] and for an incidence varying from 3.9 per 1,000 person-years to 37.1 per 1,000 person-years according to the presence of cardiovascular risk factors [2].

Such data are not limited to the Western countries' populations: emerging countries declare increasing CVD prevalence and incidence which are able to reduce the overall quality of life and lifespan of their inhabitants [3,4].

The emergency department, in agreement with the cardiology department, is the place where all the acute aspects of CVD are gathered. Acute Coronary Syndromes (ACS) in the form of unstable angina, non-ST (NSTEMI) or ST (STEMI) segment elevation myocardial infarction, acute heart failure, pulmonary embolism, etc. are often observed in the emergency and cardiology departments. Due to the high amount of CVD, the need to early detect de-compensated conditions of individuals forced physicians to adopt tools and biochemical parameters able to detect the early sign of health instability.

Biomarkers are the most important, immediate and easy tools adopted in order to detect the early signs of CVD and their acute expression [5-9]. Furthermore, their predictive value is fundamental in order to better evaluate the patients and their future cardiovascular risk.

According to ACS conditions, troponins are the best biomarkers already established for the detection of such conditions [5,6]. Roy et al. [10] found a high predictive skill for high-sensitive troponins T (hsTnT) according to death and re-hospitalization (area under the curve [AUC] 0.81, 95% Confidential Index [CI] 0.73-0.90). A more refined analysis came from Collinson et al.'s work [11] which compared the most novel biomarkers (heart fatty acid binding protein [HFABP]-1 and copeptin and troponin) and the best troponins assays in 850 patients presenting at the emergency department for acute chest pain. According to the 68 patients who were admitted at the cardiology department with the diagnosis of myocardial infarction, the authors found an AUC ranging from 0.92 to 0.94 for troponins assays, which were data strongly higher than those coming from the AUC for HFABP-1 [0.84 (0.77 to 0.90)] or copeptin [0.62 (0.57 to 0.68)]. In particular, the novel high sensitive troponins I (hsTnI) assays demonstrate a sensibility for the detection of myocardial infarction equal to 97% (95% CI: 91-99%), specificity equal to 81% (95% CI: 76-86%), a positive predictive value equal to 63% (95% CI: 55-71%) and a negative predictive value equal to 99% (95% CI: 96-100%) [12]. Creatin kinase (CK) is another biomarker which helps physicians in the acute cardiovascular setting [5]. Chin et al. [13] recently demonstrated that both peak CK-MB and peak troponin I were independently related to the in-hospital mortality of a dataset of patients suffering from acute myocardial infarction and gathered in the National Cardiovascular Data Registry ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines). They observed that CK-MB were able to slightly increase the in-hospital mortality rate prediction of both STEMI (model C-statistic 0.881 vs 0.877, P=0.011) and NSTEMI (C-statistic 0.831 vs 0.824, P=0.001) patients, as compared to the predictive value of troponins. Nevertheless, the literature data are contrasting according to the reciprocal relationship between troponins and CK. Santos et al. [14] outlined that CK-MB mass evaluated in 1,027 NSTEMI patients failed in reaching a good reliability as predictive value for death or re-infarction within 30 days when multivariate analysis included TnI as confounding factors. Other authors tried to include different serum biomarkers in the clinical setting of ACS (consider for example osteoprotegerin [9]) but, at the best of our knowledge, further researches are needed in order to evaluate their efficacy.

More complex is the role of biomarkers in the clinical setting of acute heart failure. The most studied and important ones are the brain natriuretic peptide (BNP) and its splitted, biological inactive 76-amino acid N-terminal fragment named N-terminal pro-brain natriuretic peptide (NT-proBNP). Seronde et al. [15] pointed out a great reliability of both biomarkers in acute heart failure detection, with an AUC slightly better for NT-proBNP as compared to BNP (AUC NT-proBNP=0.953 vs AUC BNP = 0.973, p=0.003). Furthermore, the use of natriuretic peptides in patients admitted to the emergency department for dyspnea onset is able to improve the diagnostic certainty and time to appropriate treatment beginning, with an AUC for heart failure identification equal to 0.87 (95% CI: 0.81-0.93) [16]. Such results were confirmed by Kevin Rogers et al. [17] who demonstrated the skill of BNP in differentiating cardiac from non-cardiac dyspnea. In addition, NT-proBNP and BNP are good predictors of one-year mortality in patients suffering from acute decompensated heart failure, showing AUCs equal to 0.77 and 0.78 respectively at the discharge [18].

Nevertheless, new molecules are emerging in the context of emergency setting as optimal biomarkers in the evaluation of patients suffering from acute heart failure. Soluble suppression of tumorigenicity 2 (sST2) is one of the most recent biomarkers introduced in clinical practice [8]. ST2 is a gene discovered in 1989 and placed on chromosome 2q12, whose transcription product is a membrane receptor member of the interleukin-1 receptor family. An alternative splicing of the promoter of the mRNA of such a gene give birth to the soluble receptor (i.e., sST2), easily detectable in the serum [8]. The comparison with NT-proBNP in predicting 90-day mortality

in patients admitted to emergency department for acute de-compensated heart failure reveals similar skills between the two biomarkers, outlining an AUC of 0.78 for both sST2 and NT-proBNP (95% CI: 0.69 to 0.88 and 95% CI: 0.67 to 0.90, respectively) [19]. The predictive value of sST2 is high even according to the mortality rates at 1-year [20], while studies pointed out that the combination of sST2, NT-proBNP and BNP was able to improve the overall definition of cardiovascular risk of heart failure patients [21]. A further biomarker able to ameliorate the evaluation of patients suffering from acute heart failure is galectin-3 which is a member of the β-galactoside-binding animal lectin family, able to interacts with several extracellular matrix receptors and structure and to be produced by activated cardiac macrophages, influencing heart and ventricular remodeling [22]. When compared with NT-proBNP, galectin-3 showed an AUC at receiver operating characteristic (ROC) analysis higher than NT-proBNP in mortality prediction (0.74, p=0.0001 vs 0.67, p=0.009) [23]. Multivariate analysis confirmed such results pointing out that galectin-3 was a strong and independent predictor of 60-day mortality and death/recurrent heart failure (odds ratio=10.3, p<0.01 and=14.3, p<0.001, respectively) [23].

Within the field of cardiovascular biomarkers in the acute setting, microRNAs (miRNAs) deserve a last consideration. These are short oligonucleotides expressed in a cell- and tissue-specific manner that regulate gene expression and organ function. Heart and other organs are all able to create miRNA and to excrete them in the bloodstream. Therefore, they can be used as biomarkers. Devaux et al. found that low blood concentrations of miRNA-150 in patients suffering from ST-segment-elevation acute myocardial infarction were related to the remodeling of the left ventricle, i.e. to an increase in left ventricle end-diastolic volume during the period between the hospital discharge and the further 4 months-follow up [24]. Furthermore, miRNA-133a seemed to regulate the myocardial fibrosis process in the setting of acute myocardial ischemia-reperfusion [25]. Nevertheless, further analysis and researches are needed in order to better validate miRNA in acute cardiovascular settings.

Thus, despite the predictive value of all the above-mentioned biomarkers, there still persist many limitations in their clinical and daily use. Thus, further studies are needed in order to definitely outline their importance in the management of patients admitted to the emergency department.

Furthermore, physicians must always consider the clinical evaluation of the patients before trusting all the instrumental supports for the diagnosis, by considering biomarkers and technical instrument as pure appendix of the rational mind.

References

1. Laslett LJ1, Alagona P Jr, Clark BA 3rd, Drozda JP Jr, Saldivar F, et al. (2012) The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. J Am Coll Cardiol 60: S1-49.
2. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, et al. (2011) Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol 57: 1690-1696.
3. He L1, Tang X, Song Y, Li N, Li J, et al. (2012) Prevalence of cardiovascular disease and risk factors in a rural district of Beijing, China: a population-based survey of 58,308 residents. BMC Public Health 12: 34.
4. Yang ZJ1, Liu J, Ge JP, Chen L, Zhao ZG, et al. (2012) Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007-2008 China National Diabetes and Metabolic Disorders Study. Eur Heart J 33: 213-220.
5. Thygesen K1, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, et al. (2012) Third universal definition of myocardial infarction. Eur Heart J 33: 2551-2567.
6. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, et al. (2012) How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J 33: 2252-2257.
7. Thygesen K, Mair J, Mueller C, Huber K, Weber M, et al. (2012) Recommendations for the use of natriuretic peptides in acute cardiac care: a position statement from the Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Eur Heart J 33: 2001-2006.
8. Ciccone MM1, Cortese F, Gesualdo M, Riccardi R, Di Nunzio D, et al. (2013) A novel cardiac bio-marker: ST2: a review. Molecules 18: 15314-15328.
9. Ciccone MM1, Scicchitano P, Gesualdo M, Zito A, Carbonara R, et al. (2013) Serum osteoprotegerin and carotid intima-media thickness in acute/chronic coronary artery diseases. J Cardiovasc Med (Hagerstown) 14: 43-48.
10. Roy AK1, McCullagh BN2, Segurado R3, McGorrian C2, Keane E4, et al. (2014) Detection of high-sensitivity troponin in outpatients with stable pulmonary hypertension identifies a subgroup at higher risk of adverse outcomes. J Card Fail 20: 31-37.
11. Collinson P1, Gaze D, Goodacre S (2014) Comparison of contemporary troponin assays with the novel biomarkers, heart fatty acid binding protein and copeptin, for the early confirmation or exclusion of myocardial infarction in patients presenting to the emergency department with chest pain. Heart 100: 140-145.
12. Bonaca MP1, Ruff CT, Kosowsky J, Conrad MJ, Murphy SA, et al. (2013) Evaluation of the diagnostic performance of current and next-generation assays for cardiac troponin I in the BWH-TIMI ED Chest Pain Study. Eur Heart J Acute Cardiovasc Care 2: 195-202.
13. Chin CT, Wang TY, Li S, Wiviott SD, deLemos JA, et al. (2012) Comparison of the prognostic value of peak creatine kinase-MB and troponin levels among patients with acute myocardial infarction: a report from the Acute Coronary Treatment and Intervention Outcomes Network Registry-get with the guidelines. Clin Cardiol 35: 424-429.
14. Santos ES1, Baltar VT, Pereira MP, Minuzzo L, Timerman A, et al. (2011) Comparison between cardiac troponin I and CK-MB mass in acute coronary syndrome without st elevation. Arq Bras Cardiol 96: 179-187.
15. Seronde MF1, Gayat E, Logeart D, Lassus J, Laribi S, et al. (2013) Comparison of the diagnostic and prognostic values of B-type and atrial-type natriuretic peptides in acute heart failure. Int J Cardiol 168: 3404-3411.
16. Burri E1, Hochholzer K, Arenja N, Martin-Braschler H, Kaestner L, et al. (2012) B-type natriuretic peptide in the evaluation and management of dyspnoea in primary care. J Intern Med 272: 504-513.
17. Kevin Rogers R1, Stehlik J, Stoddard GJ, Greene T, Collins SP, et al. (2009) Adjusting for clinical covariates improves the ability of B-type natriuretic peptide to distinguish cardiac from non-cardiac dyspnoea: a sub-study of HEARD-IT. Eur J Heart Fail 11: 1043-1049.
18. Noveanu M1, Breidthardt T, Potocki M, Reichlin T, Twerenbold R, et al. (2011) Direct comparison of serial B-type natriuretic peptide and NT-proBNP levels for prediction of short- and long-term outcome in acute decompensated heart failure. Crit Care 15: R1.
19. Boisot S1, Beede J, Isakson S, Chiu A, Clopton P, et al. (2008) Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure. J Card Fail 14: 732-738.
20. Mueller T1, Dieplinger B, Gegenhuber A, Poelz W, Pacher R, et al. (2008) Increased plasma concentrations of soluble ST2 are predictive for 1-year mortality in patients with acute destabilized heart failure. Clin Chem 54: 752-756.
21. Rehman SU1, Mueller T, Januzzi JL Jr (2008) Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. J Am Coll Cardiol 52: 1458-1465.

22. Lin YH1, Lin LY, Wu YW, Chien KL, Lee CM, et al. (2009) The relationship between serum galectin-3 and serum markers of cardiac extracellular matrix turnover in heart failure patients. Clin Chim Acta 409: 96-99.

23. van Kimmenade RR1, Januzzi JL Jr, Ellinor PT, Sharma UC, Bakker JA, et al. (2006) Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. J Am Coll Cardiol 48: 1217-1224.

24. Devaux Y1, Vausort M, McCann GP, Zangrando J, Kelly D, et al. (2013) MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. Circ Cardiovasc Genet 6: 290-298.

25. Eckhouse SR1, Akerman AW, Logdon CB, Oelsen JM, O'Quinn EC, et al. (2013) Differential membrane type 1 matrix metalloproteinase substrate processing with ischemia-reperfusion: relationship to interstitial microRNA dynamics and myocardial function. J Thorac Cardiovasc Surg 145: 267-275, 277.