

## REVIEW

# Monitoring Acute Myocardial Infarction Complicated with Cardiogenic Shock — from the Emergency Room to Coronary Care Units

Andreea Barcan<sup>1</sup>, Zsuzsanna Suci<sup>2</sup>, Emese Rapolti<sup>3</sup><sup>1</sup> Medias Municipal Hospital, Romania<sup>2</sup> Gheorgheni City Hospital, Romania<sup>3</sup> Cardiovascular Rehabilitation Hospital, Covasna, Romania**ABSTRACT**

Cardiogenic shock remains the leading cause of death in patients hospitalized for acute myocardial infarction, despite many advances encountered in the last years in reperfusion, mechanical, and pharmacological therapies addressed to stabilization of the hemodynamic condition of these critical patients. Such patients require immediate initiation of the most effective therapy, as well as a continuous monitoring in the Coronary Care Unit. Novel biomarkers have been shown to improve diagnosis and risk stratification in patients with cardiogenic shock, and their proper use may be especially important for the identification of the critical condition, leading to prompt therapeutic interventions. The aim of this review was to evaluate the current literature data on complex biomarker assessment and monitoring of patients with acute myocardial infarction complicated with cardiogenic shock in the Coronary Care Unit.

**Keywords:** acute myocardial infarction, cardiogenic shock, biomarkers, coronary care unit monitoring

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**CORRESPONDENCE****Zsuzsanna Suci**Bul. Lacu Roşu nr. 16  
535500 Gheorgheni, Romania  
Tel: +40 266 364 008  
E-mail: szoke\_zsuzsanna@yahoo.com

Cardiogenic shock (CS) remains the leading cause of death in patients hospitalized for acute myocardial infarction (AMI), occurring in 7% to 10% of AMI patients.<sup>1–4</sup> In-hospital mortality rates for CS complicating AMI are reaching 50%, and short-term prognosis is linked to the severity of hemodynamic disturbances.<sup>5</sup> Several studies have suggested that short-term mortality in CS ranges between 42% and 48%, and that most patients will succumb due to multiple organ failure as a consequence of organ hypoperfusion.<sup>6–8</sup>

CS implies a systolic blood pressure lower than 90 mmHg for more than 30 minutes, caused by a severe

myocardial dysfunction, leading to systemic hypoperfusion. The clinical signs of CS can vary from decreased diuresis and indicators of peripheral vasoconstriction to altered mental status.<sup>9</sup>

Hemodynamic changes in CS trigger various biochemical pathways due to tissue ischemia, elevated systemic inflammation, cellular apoptosis, neurohormonal activation, and extracellular matrix degradation.<sup>10–13</sup> CS patients undergo rapid changes in their clinical, biochemical, and hemodynamic status, either due to the disease itself, or secondary to the multitude of therapeutic interventions. The proper determination and use of complex biomarkers

that illustrate such changes may be highly important for identifying the critical condition, leading to prompt therapeutic interventions, as well as for risk stratification.<sup>14</sup> Novel biomarkers have been under intensive research in the last years in an attempt to identify predictors for the evolution of this critical disease.

Nevertheless, AMI patients complicated with CS require immediate diagnosis and management that should include a continuous monitoring in the Coronary Care Unit (CCU) besides invasive or noninvasive therapies. A careful monitoring could be helpful for the immediate detection of changes in the clinical, hemodynamic, and biochemical status, resulting in the timely initiation of the appropriate intervention and thus reducing mortality.

The aim of this article was to review the current literature data on complex biomarker assessment and monitoring of patients with AMI complicated with CS in the CCU.

## **SERUM BIOMARKERS IN AMI COMPLICATED WITH CARDIOGENIC SHOCK**

The most used biomarkers in acute cardiovascular settings include myocardial injury enzymes, parameters that express hemodynamic stress, systemic inflammation markers, as well as other emerging biomarkers such as extracellular matrix degradation indicators or micro-RNAs. These biomarkers can be extremely important in monitoring response to treatment and for risk stratification in critical care conditions, helping to better guide the therapy of acute heart failure patients and leading to improvement in clinical management and outcomes.<sup>15,16</sup>

### **MARKERS FOR MYOCARDIAL INJURY IN THE EMERGENCY ROOM**

Creatine kinase (CK) is an enzyme that was described in 1965 as a biomarker for myocardial injury, having a sensitivity of 90%, but a low specificity for the detection of myocardial infarction.<sup>17</sup> CK is detected in the serum at 12 hours from the onset of myocardial damage, peaks in 24 to 35 hours and normalizes in 48 to 72 hours, this dynamic making it inappropriate for early diagnosis of AMI. Despite its low specificity (increasing as well in other conditions such as hemolysis, muscle damage, rhabdomyolysis, burns, trauma, sepsis, or pregnancy), the creatine kinase assay is still used for the diagnosis of AMI due to its relatively low costs and wide availability.<sup>18,19</sup>

CK-MB (creatine kinase - myocardium brain) is one of the three major isoenzymes of CK, found in high concentrations in the cardiac muscle, as well as in lower levels in

the brain and skeletal muscles.<sup>20</sup> CK-MB presents similar releasing patterns to that of CK, and shows high specificity and sensitivity in detecting AMI, being more reliable in the 12–24-hour time window from the onset of AMI. Nevertheless, CK-MB has been shown effective in identifying AMI patients presenting in the emergency department with acute chest pain with a nonspecific ECG, thus allowing timely reperfusion therapies.<sup>21,22</sup>

The current gold standard biomarker for myocardial infarction is considered to be cardiac troponin, which is highly specific for the cardiac muscle.<sup>23</sup> Troponin assays have become widely available and are used in cardiovascular emergency settings, as they allow the identification of acute myocardial infarction at 6 hours from the onset of symptoms, having a sensitivity of 80.75% and a specificity of 63.8%.<sup>24,25</sup> The newer high-sensitivity assays can detect lower levels of troponin (3 pg/mL) within a shorter time from MI onset (3 to 4 hours from the onset of symptoms).<sup>24</sup> Despite its high diagnostic accuracy, false positive results may be encountered, caused by troponin elevation in conditions with increased oxygen demand, reduced cardiac output, or ventricular strain, such as heart failure, pulmonary embolism, or septic shock.<sup>26</sup> Other non-cardiac causes for elevated troponin levels are anemia, renal failure, pulmonary disorders, ischemic and hemorrhagic cerebrovascular events, or intense exercise.<sup>27,28</sup> Also, an increased level of troponin in heart failure patients has been linked to poorer outcomes, regardless of the presence of AMI, and elevated high-sensitive troponin expresses a considerably higher amount of myocardial injury in patients with heart failure, thus being a useful risk stratification biomarker.<sup>29–31</sup> Moreover, a sub-study of the Global Registry of Acute Coronary Events (GRACE) on 16,318 non-ST elevation myocardial infarction patients revealed that increased levels of troponin were associated with higher rates of cardiac arrest, new heart failure, cardiogenic shock, and death.<sup>32</sup>

Myoglobin is a myocardial necrosis marker that can be detected in the blood stream within the first 3 hours from the onset of MI symptoms, but it lacks myocardial specificity, as it is raised in skeletal muscle damage, trauma, electrical cardioversion, renal disease, and patients with genetic muscular disorders.<sup>19</sup> The kinetics of plasmatic myoglobin levels have been shown to be a reliable way for assessing the coronary artery patency following thrombolytic therapy in MI patients; increased baseline levels of this enzyme were observed in patients who did not respond to streptokinase, while there was a significantly higher myoglobin release among responders to thrombolysis as compared to non-responders.<sup>33</sup>

The Heart-Type Fatty Acid Binding Protein (H-FABP) is one of the most abundant proteins in the cardiac muscle, absent from the plasma or interstitial fluid, that is released during an episode of myocardial necrosis.<sup>34</sup> H-FABP is released into the blood stream within 2 hours from symptom onset, with a peak at 4 to 6 hours, having an over 80% sensitivity in diagnosing AMI. Serial determinations of H-FABP are useful for the diagnosis of AMI, for identifying patients in need of reperfusion therapies, for detecting re-infarctions, as well as for estimating the infarct size.<sup>35</sup> As in case of myoglobin, the levels of H-FABP can be elevated in other non-cardiac conditions such as renal failure, muscular trauma, traumatic cardiopulmonary resuscitation, or intramuscular injections, causing interference with the results of the assays. Some studies have questioned the role of myoglobin and H-FABP in the early detection of AMI, stating that cardiac troponins are more specific and possess higher diagnostic accuracy.<sup>36,37</sup>

#### **BIOMARKERS FOR RISK ASSESSMENT IN THE CORONARY CARE UNIT**

No reliable indicators have been established for the early risk assessment of developing heart failure or CS in AMI patients; however, various biomarkers that reflect the evolution towards ventricular dysfunction have been shown to associate with poorer outcomes after an acute coronary event.

Soluble ST 2 (sST2) is a novel marker expressing inflammation and interstitial fibrosis associated with heart failure that is up-regulated during myocardial strain as well as post-AMI. Soluble ST 2 has been shown to illustrate progressive decongestion in acute heart failure, and it has been demonstrated that circulating levels of sST2 decreased after 1 month in cases where mechanical circulatory assisting devices were used.<sup>38-40</sup>

Natriuretic peptides (NP) with the 3 isoenzymes: atrial NP, brain NP (BNP), and NT-proBNP, act as protective hormones that counteract the physiologic abnormalities of myocardial dysfunction and injury.<sup>41</sup> BNP has also diagnostic and prognostic value in myocardial infarction, as a serum level higher than 30 pmol/L was shown to be highly sensitive for diagnosing AMI, with a negative predictive value of 96%.<sup>42</sup> Furthermore, BNP is an efficient risk stratification tool for short- and long-term major adverse cardiac events following an AMI. In combination with echocardiographic assessment of left ventricular ejection fraction, BNP leads to an increased predictive capacity for death, heart failure, and repeated ischemic episodes.<sup>42,43</sup>

Co-peptin is a plasmatic peptide that increases in critical conditions such as shock, sepsis, stroke, or cardiovascular diseases, carrying diagnostic and prognostic value for myocardial injury. Persistently elevated levels of co-peptin after 3 to 5 days post-AMI are associated with higher rates of mortality and re-admissions for heart failure, and if associated with NT-proBNP assessment, it provides a more accurate risk prediction tool in AMI patients.<sup>44,45</sup>

#### **INFLAMMATORY BIOMARKERS IN ACUTE CORONARY SYNDROMES AND CRITICAL CONDITIONS**

The systemic inflammatory response occurring in cardiogenic shock due to AMI is caused by myocardial necrosis, generalized tissue hypoperfusion, and hypoxia.<sup>46</sup> Several inflammatory cytokines, including interleukins (IL-6, IL8), tumor necrosis factor alpha (TNF- $\alpha$ ), C-reactive protein (CRP), and soluble adhesion molecules, show increased levels in AMI complicated with CS.<sup>47-49</sup> The elevated baseline levels of inflammatory biomarkers have high predictive power for the development of CS and mortality in this patient population. A sub-study of the COMMA trial showed that increased values in the serum levels of IL-6, TNF- $\alpha$ , and CRP predicted the combined mortality and CS in AMI patients.<sup>50</sup>

C-reactive protein is an acute inflammatory response protein that can be elevated in subjects with atherosclerosis. This biomarker expresses an enhanced inflammation, and is especially increased in acute coronary syndromes. Furthermore, an increased level of CRP has been linked to worse outcomes following an acute coronary event.<sup>51-56</sup> Elevated plasmatic CRP concentrations are associated with the worsening of the hemodynamic and neurohormonal state of heart failure patients, being a valuable predictor for ischemic and non-ischemic complications.<sup>57</sup> Also, elevated levels of high-sensitive CRP (hs-CRP) have been associated with increased short-term death rates in AMI patients who underwent primary coronary angioplasty.<sup>58-60</sup>

Interleukin-6 is the main promoter of CRP production at the level of the liver, being involved in acute inflammation, macrophage activity, hemato- and thrombopoiesis, and stem cell function. Also, the plasma concentration of IL-6 was shown to independently predict 30-day mortality in AMI patients with CS.<sup>49</sup> A study on 75 AMI patients who underwent primary angioplasty found significant correlations between increased levels of IL-6 and CRP and impairment of left ventricular systolic and diastolic function, as well as a good predictive power of these biomarkers for the development of systolic and diastolic dysfunction at 6 months.<sup>61</sup>

Pentatraxin-3 (PTX-3) is a novel biomarker linked with the inflammatory response in heart failure patients, being shown to correlate with poor evolution of heart failure and with major adverse cardiac events in patients with known diastolic heart failure.<sup>62,63</sup> Also, PTX-3 levels have been proposed as prognostic markers for adverse events in patients with unstable angina and myocardial infarction.<sup>64</sup>

Procalcitonin is an inflammatory response biomarker produced by the parathyroid gland, which has been correlated with the severity of organ injury in AMI and CS, being used as a guiding tool for treatment and risk stratification in severe heart failure patients.<sup>65-68</sup>

#### **EMERGING BIOMARKERS IN MYOCARDIAL INFARCTION – EXTRACELLULAR MATRIX REMODELING AND MIRNAS**

The extracellular matrix (ECM) is the complex network within the intercellular space that has critical signaling functions. ECM provides the mechanical support for the myocardial fibers to perform their mechanical and biochemical function, and regulates cell proliferation, adhesion, and migration.<sup>69</sup> Following myocardial infarction, cardiac cells undergo necrosis and are replaced by a scar that is mainly composed by ECM components. Several components of the ECM have been linked to cardiac fibrosis and remodeling after an acute cardiac event. Galectin-3 is a complex biomarker that is elevated in patients with important ventricular remodeling following AMI complicated with acute heart failure. The PRIDE trial demonstrated that elevated levels of Galectin-3 are highly predictive for 60-day mortality rates and re-admissions in the hospital for acute heart failure.<sup>70-74</sup>

Matrix metalloproteinases (MMPs), with their various isoenzymes, are biomarkers involved in the degradation of ECM components, together with serine proteases.<sup>75</sup> MMP-2 is activated during cardiac injury due to increased oxidative stress, resulting in the cleavage of intracellular contractility substrates in the cardiac myocytes such as troponin I and myosin light chain.<sup>76</sup> Concentrations of MMP-1 were shown to be significantly higher in patients with reduced systolic function. At the same time, MMP-2, MMP-9, and MMP-7, which express an enhanced collagen turnover, were more increased in subjects with diastolic dysfunction.<sup>77</sup> According to the I-PRESERVE trial results, elevated levels of MMPs were associated with a higher incidence of the composite end-point of death due to heart failure, repeated hospitalizations, and all-cause mortality in patients with diastolic heart failure.<sup>78</sup>

Non-coding micro-ribonucleic acids (miRNAs) have recently emerged as useful risk stratification tools for the

development of heart failure following an AMI. The identification of this new class of biomarkers could contribute to triggering prompt therapeutic intervention for preventing this potentially fatal complication.<sup>79</sup> Many gene alterations have been examined for myocardial infarction response and the integration of mRNA and messenger RNAs in a genetic profile, which could help in elucidating the mechanisms of MI development, providing novel biomarkers for risk stratification following an acute coronary event.<sup>80-82</sup> However, these promising tools are yet to be applied in clinical practice and require further research.

#### **HEMODYNAMIC MONITORING IN THE CORONARY CARE UNIT**

Various devices can be used in the CCUs, in order to provide essential information regarding the clinical and hemodynamic status of complicated AMI cases.

#### **NONINVASIVE MONITORING IN THE CCU**

One of the most useful devices in the CCUs are represented by continuous surface electrocardiogram (ECG) monitoring systems, which offer continuous monitoring for 2-3 days following an AMI, or throughout the entire period of hemodynamic instability. These systems allow the early identification of arrhythmias and conduction disturbances as well as ST-segment and T-wave changes.<sup>83</sup> ST-segment and T-wave changes can reveal repeated episodes of ischemia in the early post-AMI period, or can indicate an inefficient reperfusion therapy, which can serve as predictors for negative outcomes.<sup>84-88</sup> Furthermore, it has been demonstrated that more than three ischemic events, or more than one hour repeated ischemic event on the continuous ECG tracing records indicate a three-vessel coronary artery disease or severe coronary atherosclerosis.<sup>84,87,88</sup>

The evaluation of arterial oxygen saturation with the use of pulse oximetry is used for noninvasively detecting the ventilatory status of the patients in the CCU. The technique is based on the photometric analysis of the pulse wave in the fingernail, requiring a systolic blood pressure of more than 85 mmHg. Therefore, clinical situations in which the patients present hypovolemia, low blood pressure, CS, or other types of shock associated with decreased tissular perfusion, can impair the evaluation of ventilatory status using this method.<sup>89</sup> Tissular hypoperfusion is the most common event that proceeds multiple organ dysfunction during shock.<sup>90</sup> Another method for the non-invasive assessment of tissue oxygenation includes near-

infrared spectroscopy (NIRS), a technique that monitors muscular tissue oxygenation (StO<sub>2</sub>) using infrared light absorption, through placement of a noninvasive sensor at the level of the thenar eminence. It has been shown that the normalization of StO<sub>2</sub> levels is associated with improved outcomes in patients with hemorrhagic shock, and that low levels of the same parameter were correlated with the development of multiple organ dysfunction of trauma patients.<sup>90-93</sup>

The evaluation of body temperature can offer important information on the overall status of the critically ill patient, as fever is a negative prognostic factor that can indicate elevated systemic inflammation or infection, while a decreased peripheral temperature is a sign of decreased tissue perfusion.<sup>94-98</sup> Body temperature is assessed through peripheral (tympanic membrane, temporal artery, axillary, or oral), or central (pulmonary artery catheter, urinary bladder, esophageal, or rectal) methods. However, a meta-analysis on 75 studies that assessed the accuracy of peripheral thermometry for the estimation of core body temperature stated that peripheral thermometers should not be used if the body temperature will influence the therapeutic management, as they do not present an acceptable clinical accuracy.<sup>99,100</sup> Fever can be an appropriate response to infection, and one study showed a lower in-hospital mortality rate in patients with peak temperatures of 39-39.4 °C compared to peak temperatures of 36.5-36.9 °C (OR, 0.56; 95% CI 0.48-0.66).<sup>101</sup>

Diuresis monitoring (urine output on a given time frame) is of essence in the CCU, as it can provide relevant information on the renal function and hydration status of the patient, helping to guide fluid and diuretic therapy.<sup>94</sup> A normal urine output ranges between 0.5-1 mL/kg/h, while the presence of oliguria, a diuresis of less than 500 mL over a 24-hour period, might indicate a decreased renal perfusion that could be related to the onset of acute heart failure.<sup>102,103</sup> The presence of oliguria in critically ill subjects with AMI is a sensitive marker of acute kidney injury, and it has been shown to be linked to higher mortality rates in these patients.<sup>104,105</sup> Patients with CS secondary to AMI present decreased arterial pressure and an overall organ hypoperfusion, which leads to hypotension-induced renal injury. The main cause of acute kidney insufficiency in critically ill AMI patients is acute circulatory failure, through a pre-renal mechanism.<sup>106</sup> A mean arterial pressure (MAP) of over 65 mmHg is required to avoid organ failures, including renal dysfunction.<sup>107</sup> An additional cause of renal dysfunction in patients with AMI is contrast-induced nephropathy, a complication of contrast media administration during coronary angiography and

the third most common cause of hospital-acquired acute renal injury.<sup>108</sup>

#### MONITORING HEMODYNAMIC STATUS IN THE CCU

Usually, continuous recording of blood pressure and cardiac output (CO) is essential for the optimization of diuretic, inotropic, and vasodilator therapies in critical patients admitted in the CCU.<sup>109</sup> The finger-cuff technology can provide continuous noninvasive monitoring of BP and cardiac output, using a cuff placed around the finger for continuous BP measurement and beat-to-beat cardiac output calculation through pulse contouring.<sup>110</sup> Several studies have shown that this method is comparable to invasive monitoring systems.<sup>111,112</sup>

The noninvasive evaluation of stroke volume and cardiac output can be achieved using thoracic electrical impedance, ultrasound, and pulse contour analysis.<sup>113,114</sup> The parameters assessed with cardio-impedance methods are the fluid content of the thoracic cavity, which has a negative correlation with thoracic impedance, ventricular preload, and left ventricular contractility, thus allowing the estimation of cardiac output, systemic vascular resistance, and the overall mechanical function of the left ventricle. However, systems that use electrical impedance to estimate CO cannot be used in certain situations that include septic shock, aortic valve replacement, uncontrolled hypertension, arrhythmias, the presence of an intra-aortic balloon pump, body weight of more than 155 kg or less than 30 kg, as well as a heart rate above 200 beats per minute.<sup>115-117</sup> Pulse contour analysis systems are based on the fact that the area under the systolic segment of the arterial pulse wave is correlated with the stroke volume.<sup>118</sup> The first and most used device that uses pulse wave contour and thermo-dilution for CO evaluation is the minimally invasive PiCCO system (PULSION medical system, Munich, Germany), which requires a central venous line for cold saline injection and an arterial cannulation for placement of the temperature sensor that records the thermodilution curve.<sup>119</sup> In addition, the PiCCO system can assess intrathoracic blood volume, global end-diastolic volume, and extravascular lung water, allowing the measurement of cardiac preload and pulmonary edema quantification.<sup>120</sup> The Non-Invasive Cardiac Output (NICO) monitoring device is based on partial re-inhalation of CO<sub>2</sub>, using Fick's equation applied to carbon dioxide, and its accuracy is comparable to that of the gold standard thermodilution technique.<sup>121</sup>

Although transthoracic echocardiography cannot provide continuous hemodynamic measurements, it is the

best bedside method to repeatedly evaluate the cardiac function, regional wall motion abnormalities, left ventricular ejection fraction, pulmonary artery pressure, aortic flows, and stroke volume, as well as acute complications occurring during the acute ischemic events, such as valve regurgitation, cardiac tamponade, left ventricular wall or papillary muscle rupture.<sup>122-124</sup> Transesophageal echocardiography is a useful tool in hemodynamically unstable patients under mechanical ventilation; despite of the associated inter and intraprocedural variability, the method has been validated in agreement to the thermodilution method in measuring the cardiac output.<sup>125,126</sup> Moreover, the esophageal Doppler flexible probe can measure the aortic flow by multiplying the cross-sectional area with the velocity, which will allow the estimation of the left ventricular stroke volume. The major limitation of this method is that it provides measurements from the descending aorta (only 70% of the total flow), and that discrepancies appear in case of aortic coarctation, aneurysms, or in the presence of an intra-aortic balloon pump.<sup>127</sup> Nevertheless, the evaluation of stroke volume with esophageal Doppler has been shown to be in concordance with well-established invasive methods.<sup>128,129</sup>

#### INVASIVE MONITORING OF HEMODYNAMIC PARAMETERS IN THE CORONARY CARE UNIT

Invasive monitoring in the CCU is performed when the hemodynamic status of the patients is not stabilized and requires additional invasive measures.<sup>130</sup>

The invasive evaluation of blood pressure is achieved by placing a catheter in a superficial artery (radial, femoral, or pedis artery), which is connected to a transducer that transforms the mechanical pulse wave into a pressure curve. Analysis of the invasive arterial pressure waveform allows the estimation of CO and ventricular ejection fraction, and the invasive measurements are performed simultaneously with the noninvasive evaluation of blood pressure.<sup>131,132</sup>

Central venous pressure (CVP) is a marker that illustrates intravascular volume and right ventricular function, being measured by inserting a catheter in the superior caval system (subclavian or internal jugular vein), with continuous ECG recording, under local anesthesia. An increased CVP is suggestive of decreased ventricular function, increased venous return, increased systemic vascular resistance or elevated intrathoracic pressures. The assessment of CVP is of utmost importance in hemodynamically unstable AMI patients, as it guides fluid administration in this critical condition.<sup>133</sup>

The invasive assessment of CO and stroke volume is performed by Swan Ganz catheterization using the thermodilution method, which also allows the evaluation of right cardiac pressures and the pulmonary capillary wedge pressure, being largely used in CCUs for invasive hemodynamic monitoring.<sup>134-137</sup> Other invasively assessed parameters used in the CCU for critical AMI patients are those reflecting ventricular contractility such as the left ventricular stroke volume and the mechanical work, which can indicate whether inotropes or vasodilator therapies are required.<sup>138,139</sup>

The pressures in the right ventricular and pulmonary artery illustrate the pulmonary circulation, while the capillary wedge pressure reflects the end-diastolic pressure in the left ventricle, indicating the preload alteration and estimating the systolic and diastolic function of the left heart chambers.<sup>140,141</sup> Furthermore, the pulmonary capillary wedge pressure evaluation provides information on the hemodynamic impact of various acute complication of MI such as ischemic mitral regurgitation, interventricular septum defect, or newly developed intracardiac shunts of papillary muscle rupture with acute mitral regurgitation.<sup>142</sup>

#### CONCLUSION

CS is a life-threatening complication of AMI that requires intensive monitoring of the hemodynamic, biochemical, and inflammatory status, being essential in providing a proper and complex diagnostic and therapeutic management, as well as for accurate risk stratification. Complex serum biomarker panels able to identify early changes in the clinical status, to detect high risk patients, and to evaluate response to treatment should be introduced in current clinical practice for a proper and prompt therapeutic intervention. Also, various invasive and noninvasive monitoring techniques should be used as complementary tools for guiding diagnosis and treatment in acute coronary care units.

#### CONFLICT OF INTEREST

Nothing to declare.

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