Understanding the role of echocardiography in remodeling after acute myocardial infarction and development of heart failure with preserved ejection fraction

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Abstract

Despite the use of reperfusion therapies in the last decades, acute myocardial infarction further remains one of the most frequent causes of mortality. This is mainly caused by changes in the ventricular architecture leading to ventricular remodeling, followed by progressive development of heart failure. Transthoracic echocardiography is a non-invasive instrument which can provide information about the extent of the ischemic process and its consequences but can also predict the outcomes after myocardial infarction. Although standard echocardiographic parameters are currently used for risk stratification of these patients, they might not truly reflect left ventricular systolic dysfunction in acute myocardial infarction patients, since the detection of subtle changes in the myocardial function is beyond their limits. The aim of this review is to underline the use of advanced echocardiographic parameters in identifying patients at risk for developing post-acute myocardial infarction heart failure and subsequent adverse events. Advanced echocardiographic parameters derived from speckle tracking echocardiography provide a detailed assessment on the global and regional left ventricular deformation. Therefore, speckle tracking echocardiography has a major role in predicting the prognosis of acute myocardial infarction patients and particularly in the development of subsequent heart failure, which might be prevented with early initiation of adequate therapy.

Keywords: myocardial infarction; heart failure; speckle tracking; echocardiography

Introduction

Ischemic heart disease is at the present the most frequent cause of death worldwide. The incidence of mortality caused by acute myocardial infarction (AMI) has decreased in the last 30 years due to the use of reperfusion therapies [primary percutaneous coronary intervention (PCI) or thrombolysis], associated with antithrom-

botic treatment and secondary prevention. Nevertheless, mortality still remains high (one-years mortality in patients with ST-elevation acute myocardial infarction is approximately 10%), because of other factors that influence the prognostic of this pathology [1]. These factors can lead to post-AMI remodeling of the ventricular fibers. Ventricular remodeling refers to the alteration of ventricular structure, due to the progressive changes in its geometry (modifications in wall thickness, cavity diameter and progression from elliptical to spherical configuration). Potential factors involved in this process are myocytic death, imbalance between oxygen supply and consumption, oxidative stress, inflammation, fibrosis and neuro-hormonal activation [2]. All of these mechanisms lead to a deterioration of the ventricular function, with progressive development of heart failure (HF).

Although the incidence HF has decreased over the last few years due to the reperfusion therapies, mortality

Received 22.10.2018 Accepted 04.12.2018

Med Ultrason

2019, Vol. 21, No 1, 69-76

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seems to be associated with initial left ventricular (LV) systolic dysfunction [3]. Furthermore, the number of patients developing diastolic dysfunction still remains high (20-30%) [4]. Progression of diastolic dysfunction to HF with preserved ejection fraction (HFpEF) is associated with a poor prognosis and increase in the incidence of adverse effects due to the therapeutic limitations [5].

Post-AMI systolic LV dysfunction in relation to the development of HF has been intensively studied, but data relating to the prevalence and prognosis of patients with post-AMI HFpEF are still lacking [6,7]. A few studies specifically evaluated post-AMI HFpEF, but generally without simultaneous assessment of both ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI). Moreover, heterogeneous LVEF cut-off points were used in the establishment of the diagnosis of HFpEF [8-10].

Studies using various imaging techniques (cardiac magnetic resonance, echocardiography, radionuclide ventriculography) in the evaluation of post-AMI ventricular remodeling have demonstrated that initial LV volumes and their modification on follow-up have prognostic implications. Transthoracic echocardiography (TTE) is a noninvasive investigation, which can be safely and routinely used. Among systolic function parameters, LV ejection fraction (LVEF), LV end diastolic volume index (LVEDDVi), LV end systolic volume index (LVESVi), LV mass index (LMVi), end-diastolic wall thickness (EDWT), end systolic wall thickness (ESWT) and the wall motion index (WMI) have proven to be of prognostic value [11]. Although LVEF is easy to calculate, it is preload dependent and does not correlate with the symptoms. Moreover, its specificity in detecting incipient changes in the myocardium is low. Kostam et al showed that routinely used techniques are observer dependent and have low sensitivity and specificity [12]. Speckle tracking echocardiography (STE) has overcome these limits, by allowing both global and regional analysis of myocardial deformation, in different directions and angle independent [13,14].

In this context, the aim of this review is to underline the use of advanced echocardiographic parameters in identifying patients at risk for developing post-acute myocardial infarction heart failure and subsequent adverse events.

Global strain of the LV

After STEMI and PCI, the injured myocardium may recover or may become irreversibly remodeled. Remodeling occurs in 30-35% of the patients despite PCI, since the changes in the myocardial geometry begin in the

acute phase of ischemia, increasing post-AMI mortality [15,16]. STE provides detailed assessment of global and regional myocardial LV deformation, which may not be detectable with LVEF. Longitudinal, circumferential and radial strains are the three directions of myocardial deformation that can be evaluated by STE [17]. Nevertheless, global longitudinal strain (GLS) was mostly evaluated in studies and was proven to have both diagnostic and prognostic implications [18].

GLS versus LVEF in the prediction of remodeling and HF of AMI patients

Studies have shown that GLS was superior to LVEF in detection of systolic dysfunction, by demonstrating a significant reduction in GLS in the absence of a correspondent reduction of the LVEF in patients with coronary artery disease and HFpEF [19,20]. This can be explained by geometrical factors, as LVEF can be constant for a large variation in shortening if other geometric factors compensate (increased wall thickness and reduced EDV can maintain normal LVEF despite reduced shortening) [21].

Myocardial deformation is linked to the longitudinally oriented fibers, located in the sub-endocardium, which are the most susceptible to ischemic changes. It was demonstrated in many studies that GLS detects longitudinal abnormalities in the absence of reduction in LVEF [22-25]. This is due to the fact that fibers located in the mid-wall, which are circumferentially oriented, may compensate in the case of reduction of the longitudinal mechanics in order to maintain LVEF normal. Studies showed that circumferential shortening contributes twice as much in maintaining LVEF as longitudinal shortening [21].

However, some studies demonstrated a reduction in both GLS and global circumferential strain (GCS) while LVEF was still normal. This was shown to appear in ventricles with thicker walls or smaller volume, where both longitudinal and circumferential shortening are less required to maintain a normal LVEF [19].

Recent studies have explored the prognostic value of GLS in post-AMI and PCI patients. Park et al demonstrated that GLS was an independent predictor of HF and cardiac death in 50 anterior AMI patients treated with primary PCI [26]. Antoni et al demonstrated in a study performed on 659 patients with AMI treated with primary PCI, GLS ($>-15.1\%$) and longitudinal strain rate ($>-1.06 \text{ sec}^{-1}$) were independently correlated with mortality [27]. Ersbøl et al showed that a reduced GLS could predict HF in AMI patients even in the presence of a normal LVEF [28]. Furthermore, it was demonstrated that reduced GLS ($>-14\%$) was an independent predictor of mortality, HF and cardiac death in the absence of reduced LVEF [29]. In a study performed on 576 AMI patients treated with

PCI, GLS was also independently associated with mortality, HF and stroke, in spite of normal LVEF and LV volumes. The most severe adverse events were experienced by patients with a $GLS \geq -10\%$ [30]. Lacalzada et al demonstrated that $GLS (>-12.46\%)$ was a predictor of adverse remodeling and cardiac events in patients with AMI [31]. Moreover, Bastawy et al demonstrated that $GLS (>-12.5\%)$ and LV torsion ($< 9.5^\circ$) early after anterior STEMI treated with primary PCI are independent predictors of six months LV remodeling [24].

Therefore, GLS was able to predict post-AMI remodeling and HF not only for anterior location, but also in any other location (fig 1).

Several studies evaluated the role of STE in the prediction of LV remodeling after STEMI or NSTEMI [25-36], but there was one report exclusively investigating the role of strain in patients with post AMI HFpEF. Hsiao et al showed that remodeling occurred in 28.9% of patients with AMI and preserved LVEF after PCI. The study also reported a new index, the injury longitudinal strain (InjLS) as the average strain of which segmental longitudinal strains $>-15\%$, which was an independent predictor for remodeling in patients with HFpEF even after PCI [37].

Considering these results, GLS is able to identify patients at risk, who might benefit from antiremodeling therapies (angiotensin-converting enzyme inhibitors, aldosterone antagonists, beta blockers) independently of reduced LVEF and it might represent a selection criteria for future studies.

GCS and radial strain in the prediction of remodeling and HF of AMI patients

On the other hand, the role of GCS and global radial strain were only evaluated in small studies. Peak circumferential strain (PCS) was also a predictor of adverse remodeling [34,37-39]. Bonioset al [38] showed the value of PCS as a predictor of adverse remodeling in apical segments of the myocardium. The VALIANT study, performed on 603 patients with post AMI LV dysfunction or HF, showed that both longitudinal and circumferential strain rate were independent predictors of outcomes after AMI. Moreover, only circumferential strain rate was a predictor of LV remodeling, whereas global and radial strain rate were not [36], suggesting that preserved circumferential function might prevent ventricular enlargement after AMI. In the case of post-AMI HFpEF, it is hypothesized that circumferential and radial strains are relatively preserved in the initial process in order to maintain LVEF. This could be the reason why no association was found between GCS or global radial strain and LV remodeling in post AMI patients with HFpEF in the study performed by Hsiao et al [37] (fig 2).

Normal, stunned or infarcted?

Furthermore, there is data suggesting that STE could distinguish between normal, stunned and infarcted myocardium. Bachner-Hinzen et al (study performed on ten pigs) demonstrated that circumferential strain was able to predict which segments will eventually become infarcted and which will be stunned. Moreover, when stunning resolved, peak circumferential strain was an indicator of transmural strain. Thus, CS detects ischemia and reperfusion, while RS only detects ischemia at the acute stage of MI [40].

Transmural versus non-transmural AMI

Measurement of GCS can differentiate between subendocardial and transmural infarction [41-46]. Chan et al demonstrated that circumferential strain was preserved, while longitudinal strain was reduced in subendocardial infarcts. On the other hand, both circumferential and longitudinal strain were reduced in transmural infarcts. There was no difference in radial strain [41]. Becker et al found that circumferential strain had the highest sensitivity and specificity in distinguishing transmural from non-transmural infarction [43]. Recently, a study using layer specific STE analysis, demonstrated that both circumferential and longitudinal strains of endocardial, mid myocardial and epicardial layer can distinguish infarcted from non-infarcted segments and differentiate non-transmural from transmural AMI [6].

GLS in the prediction of post-AMI ventricular arrhythmias

Prediction and prevention of ventricular arrhythmias and sudden cardiac death early after AMI has been a challenge. Haugaa et al confirmed the role of myocardial deformation in the prediction of ventricular arrhythmias [47]. The Defibrillator in Acute Myocardial Infarction Trial could not demonstrate a survival advantage of implantable cardioverter defibrillator (ICD) implantation within 40 days in AMI patients with an $LVEF \leq 35\%$ [48]. Ersbøl et al demonstrated additional information on longitudinal strain to LVEF in the early phase of AMI for identifying patients who might benefit from ICD implantation [49]. Therefore, GLS might be included next to LVEF in the LV evaluation of AMI patients.

Regional strain of the LV

Regional contraction is not only influenced by reduced contractility of the affected myocardium, but also by tension from the surrounding segments. Therefore, when ischemia occurs, shortening of the myocardial fibers decreases during LV ejection, and early systolic lengthening associated with post-systolic shortening can be observed in the ischemic myocardium. Strain param-

Fig 1. Left ventricular global longitudinal strain (GLS) in two post AMI patients: a) Calculated LVEF was 55%. Left and right upper corner: curves derived from apical four-, three-, and two-chamber views show a reduced regional longitudinal strain in the anterior septal wall of a patient with LAD occlusion, 3 days after PCI. ESL, PSS and reduced LPSS can be noticed in the affected segments (red - basal, blue - mid, purple - apical segment of the anterior septum), with a normal aspect in the non-affected segments; right bottom: bull's eye plot with a mildly reduced GLS (-17.3%) and visualization of the affected wall; b) Calculated LVEF was 45%. Left and right upper corner: curves derived from apical four-, three-, and two-chamber views show a severely reduced regional longitudinal strain in the anterior, septal and inferior walls of a patient with anterior AMI 5 months after PCI and multi-vessel coronary artery disease. ESL and reduced LPSS can be noticed in the majority of the segments, while PSS is present in few segments (sign of chronic infarction); right bottom: bull's eye plot with significantly reduced GLS (-4.9%) and visualization of the affected walls (ESL = early systolic lengthening, PSS = post-systolic shortening, LPSS = longitudinal peak systolic strain, ESS = end-systolic strain).

Fig 2. Mildly reduced regional circumferential strain (basal and apical segments) in a patient with anterior STEMI with distal left anterior descending coronary artery occlusion and multi-vessel coronary artery disease, 3 days after PCI: a) at the level of the mitral valve; b) at the level of the papillary muscles; c) at the level of the apex. LVEF was 52%.

Fig 3. Regional longitudinal strain: a) curves derived from 4 chambers view in a normal patient; b) curves derived from 3 chambers view in a patient with anterior STEMI, 2 days after PCI. LPSS coincides with ESS in this case and is reduced in the affected segments. Moreover, ESL and PSS can be noticed in the segments with a reduced LPSS. LVEF was 55% (ESL = early systolic lengthening, PSS = post-systolic shortening, LPSS = longitudinal peak systolic strain, ESS = end-systolic strain)

eters can characterize ischemic dysfunction by showing reduction in the peak systolic strain, low systolic shortening, presence of systolic lengthening (SL) and post-systolic shortening (PSS) (fig 3).

Longitudinal peak systolic strain (LPSS) and end-systolic strain

Original Task Force recommendations in standardization of deformation suggested that end-systolic strain was able to evaluate systolic function more accurately than LPSS, due to the fact that peak systolic strain can show normal values when marked PSS is present in ischemic segments. Despite these findings, subsequent inter-vendor analysis reports recommended the use of LPSS in the evaluation of systolic dysfunction [50,51].

Kalam et al suggests that global LPSS (GLPSS) is superior to LVEF in detection of ischemia. The reason is the localization of longitudinal fibers in the sub-endocardial layer, which is the first one affected by ischemia [12]. Another study demonstrated that GLPSS is useful in the evaluation of transmural injury in the setting of a first AMI [36].

Systolic lengthening (SL) and duration of the early systolic lengthening (DESL)

Myocardium affected by ischemia tends to stretch during early systole before the onset of systolic shortening (when the pressure rises in the LV), because of its reduced ability in generating active force. After the acute event, viable myocardium progressively recovers, whereas necrotic segments preserve the same pattern of SL. DESL is a novel parameter, which reflects the time fibers remain stretched. Smedsrud et al demonstrated the superiority of DESL over GLPSS in identifying patients with significant coronary artery disease. A value of DESL > 58 ms had good sensitivity and specificity in detecting significant coronary artery disease [20,21]. DESL also correlated with the infarct size and was able to distinguish coronary occlusions from non-occlusions. Moreover, Zahid et al demonstrated that this parameter successfully identified NSTEMI patients with no visible scar on magnetic resonance [52].

Detection of post-AMI viable myocardium is a prognostic factor of remodeling and HF. When a myocardial segment has a SL > 40% of systole there is a high probability of no recovery. Furthermore, when more than 4 segments show this pattern of prolonged SL, there is a high probability of no recovery of the LV function [53].

Post-systolic strain, post-systolic shortening (PSS) and post-systolic index (PSI)

Post-systolic strain and PSS have been proposed as markers of viability in some studies. PSS occurs in both viable and necrotic myocardium. In viable myocardium, it is attributed to the interaction between ischemic and sur-

rounding myocardium, due to passive recoil. In the latter case, it is associated with SL and occurs when LV pressure is falling down during isovolumic relaxation [54].

Pislaru et al demonstrated that PSS parameters are the most specific in differentiating ischemic from non-ischemic ischemia during acute coronary occlusion [55]. On the other hand, it might be difficult to assess ischemic alterations in a previously damaged myocardium. Claus et al showed that PSS was not present in chronic infarction, suggesting that increased myocardial stiffness can diminish PSS caused by passive recoil [56].

What seems to remain an open issue is which direction of strain should be analyzed in order to assess PSS in STE. LS are the most frequently used, but the acquisition is less reliable in apical segments because of technical difficulties. This may interfere with the accuracy of diagnosing anterior AMI.

The post-systolic index represents the ratio between the amplitude of PSS to total shortening and it is calculated as (PSS-ESS)/peak strain or maximum strain change. It was shown to be effective in distinguishing ischemic from non-ischemic segments in association with PSS [57]. Furthermore, PSI increased significantly in graded coronary flow reduction, even when PSS did not decrease [55,58]. It still remains a question how to differentiate between physiologic and pathologic PSI. Moreover, the cut-off values of PSI are still unclear.

Tarkelsen et al concluded that PSS by tissue Doppler imaging was not a marker of viability in STEMI patients after revascularization [58]. Despite these findings, several other studies demonstrated that PSS was a marker of viability, and moreover a predictor of systolic recovery. Eek et al showed that PSS assessment before revascularization in NSTEMI patients predicted systolic recovery and HF [59]. The findings were confirmed by Hosokawa et al (in post-STEMI patients treated with PCI) [60] and Song et al (with stress echocardiography after AMI) [61]. Furthermore, Brainin et al found that PSS in the septal wall was associated with an increased risk of HF [54]. This is due to the fact that myocardial fibers in this zone suffer greatest deformation during systole and are exposed to the highest wall stress. PSS measured by STE was found to be an independent predictor of HF [62].

In conclusion speckle tracking echography represents a very useful, non-invasive method in the early diagnosis of LV remodeling after an acute myocardial infarction, with a high prognostic value in predicting subsequent HF development, which might be prevented with the early initiation of adequate therapy.

Conflict of interest: none

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