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Monitoring the Sequelae of Coronary Microembolization on Myocardium Using Noninvasive Imaging (Review)

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Abstract

Acute myocardial infarction (AMI) is a leading cause of death worldwide. It has been clinically classified into 1) ischemic from a primary coronary event (e.g., plaque rupture or thrombotic occlusion), 2) ischemic from a supply-and-demand mismatch and c) ischemic from a percutaneous coronary interventions (PCI). Catheter-based PCI has been frequently used as an alternative to conventional bypass surgery for patients at high risk. However, this method of treatment is associated with microvascular obstruction (MVO) by dislodged microemboli that results in left ventricular (LV) dysfunction/remodeling, perfusion deficits, microinfarction and arrhythmia. The contributions of microemboli after revascularization of AMI have been acknowledged by major cardiac and interventional societies. Recent studies showed that Emboli Detection and Classification (EDAC) Quantifier offers increased sensitivity and capability for detecting dislodged coronary microemboli during PCI. Coronary microembolization can be detected directly by monitoring intramyocardial contrast opacification on contrast echocardiography, increasing F-18 fluorodeoxyglucose (FDG) uptake on positron emission tomography, loss/diminution of signal on first pass perfusion and hypoenhanced zone on contrast enhanced magnetic resonance imaging (MRI) and multidetector computed tomography (MDCT) and indirectly by ST-segment elevation on electrocardiography (ECG). The relations between volumes/sizes of microemboli, visibility of microinfarct, myocardial perfusion and LV function are still under intensive discussions. Non-invasive imaging can play important role in assessing these parameters. This review shed the light on the techniques used for detecting coronary microemboli, microvascular obstruction and microinfarct and the short- and long-term effects of microemboli on LV function, structure and perfusion.

Keywords

Coronary Artery Disease, Coronary Emboli, Interventions, Magnetic Resonance Imaging and

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1. Introduction

One in six deaths among Americans is caused by coronary artery disease [1]. Treatment of acute myocardial infarction (AMI) includes revascularization therapy using bypass surgery, balloon angioplasty or stenting. Microvascular obstruction (MVO) is an established complication of revascularization therapy for AMI. A recent study, however, showed that MVO is ischemic injury and not exclusive to revascularization therapy [2]. Furthermore, MVO was observed in a wide range of diseases such as valvular disease, endocarditis, cardiomyopathy with mural thrombus and arrhythmias [3]-[9]. It has also been reported in patients with hypertension, diabetes [10], systemic lupus erythematosus [11] and sickle cell disease [12]. Thus, early detection of dislodged coronary microemboli and visualization of microinfarct are necessary for preventing and treating the side effects of coronary microemboli.

The European Society of Cardiology [13] advocates four reperfusion strategies for acute ST-segment elevation myocardial infarction (STEMI): primary percutaneous coronary interventions (PCI), thrombolysis, rescue coronary angioplasty and late PCI (>12 hours after symptoms). Investigators found that the total volume of microemboli dislodged from ruptured plaque is a key event in formation of MVO, microinfarction, LV dysfunction [10] [14]-[18], arrhythmia [19] [20] and sudden death [16] [21] [22]. Okamura *et al.* found that distal embolization occurs at high frequently (87%) during PCI procedure and the number of microemboli is the greatest after stenting [23], because hard stent mash crushes plaque, squeezes plaque particles through the gaps between stent struts. Mechanical obstruction of the microvessel lumen by microemboli (leukocytes, erythrocytes, fibrin and platelet thrombi) and endothelial damage underly the formation of MVO. The exact time course of changes leading to patchy or diffuse MVO, however, are unknown because endothelial damage is induced by intracellular calcium overload, opening of the mitochondrial permeability transition pore, the release of oxygen free radicals and tumor necrosis factor. The variability of atherosclerosis plaque content, type of stent and degree of mechanical compression explain the difference in myocardial response. Kleinbongard *et al*. [24] recently showed that stent implantation into atherosclerotic plaques releases vasoactive agents (such as serotonin, thromboxane and tumor necrosis factor (TNFα) that contribute to further impairment in myocardial perfusion. These findings were confirmed in multiple studies that showed substantial number of patients with AMI experience major cardiac events after PCI [25]-[34] and these events continued during follow-up [35]-[39].

Myocardial ischemia/reperfusion and coronary microemboli impact not only the myocardium but also coronary microvessels. MVO is the most severe form of reperfusion injury [40], which is resulted primarily from debris [41], platelet aggregates [42], vasoconstriction [24] and/or damaged vascular endothelium [43]. MVO can happen during primary and elective PCI. Investigators found that MVO is a complex pathologic process and the main components are distal atherothrombotic embolization, ischemic injury, reperfusion injury and susceptibility of coronary microcirculation to injury [44]-[46]. Increased local release of platelet- and endothelium-derived microemboli into the coronary microvessels has also been identified in patients undergoing primary PCI for AMI and correlated to indices of MVO, such as TIMI frame count, myocardial blush grade and electrocardiogram ST-segment resolution [47].

2. Microemboli and Cardiac Injury Biomarkers

Measurements of plasma creatine kinase and troponin I are routinely used before and after coronary interventions to provide evidence of myocardial injury [48] [49]. Clinical and experimental studies have reported close relationship between MR-defined large infarct size and serum level of creatine kinase MB and troponin I [50] [51]. However, this relationship seems not be robust in NSTEMI patients with small infarct size [52].

An experimental study showed that the concentrations of troponin I (0.52 ± 0.28 ng/ml) and creatine-kinase MB (1670 ± 370 U/L) in animals received 16 mm^3 were not sigificantly different from animals received 32 mm^3 (creatine-kinase = 1060 ± 235 U/L and troponin I = 0.68 ± 0.4 ng/ml) at 24 hrs, suggesting that that creatine kinase MB and troponin I have limited sensitivity for differentiating the effects of different microemboli volumes [53]. Another short coming of cardiac injury biomarkers is demonstrated in the kinetics of creatine kinase

MB and troponin I. Investigators found that both injury biomarkers are significantly higher at 18 - 24 hours compared with controls or baseline data. However, there was no significant difference in creatine-kinase-MB or troponin I levels between solely microembolized myocardium and AMI superimposed with similar volume of microemboli. At 68 - 72 hours, creatine-kinase-MB returned to baseline level, while troponin I remained high in animals subjected to double insult compared with single insult [54].

Mehran *et al.* found after PCI that plaque burden, measured on intravascular ultrasound (IVUS), closely correlated with the elevation of creatine-kinase MB [55] [56]. The DEDICATION trial, evaluating patients randomized to distal protection using a filter wire protection device versus standard PCI without distal protection, showed no significant difference in cardiac biomarker elevation [57]. Kunadian *et al.* [58] confirmed these data in meta-analysis study, where the use of distal protection devices resulted in no decrease of early mortality or recurrent myocardial infarction rate.

3. Coronary Microemboli

Spontaneous coronary microembolization occurs at any time in diseased arteries despite antiplatelet therapy. Coronary microembolization has been confirmed in patients who died from sudden cardiac death [16] [22] and the average size of microemboli was ~250 μm [59]. Okamura *et al.* found on IVUS that the size of microemboli ranges between 47 - 2503 μm [60]. The size and number of detached emboli is key in the formation of MVO zone in AMI, patchy microinfarction, LV dysfunction [10] [14]-[18], arrhythmia [19] [20] and sudden death [16] [21] [22].

MVO refers to suboptimal regional perfusion of infarct-related artery in the presence of patent epicardial coronary circulation. Investigators found that sponteneous plaques and debris are more common in arteries with plaque erosion than plaque rupture [61]. Cardiologists also observed that acute ST-elevation myocardial infarction (STEMI) results from coronary atherosclerotic plaque disruption.

Furthermore, coronary microemboli is considered to be inevitable during PCI revascularization of obstructive atherosclerotic plaque [62], because plaques and debris are disrupted during the passage of guide-wires, positioning of the balloon and stent implant. Differentiation of spontaneous from procedural microembolization is difficult because patients arrive to the hospital with pre-existing AMI related to coronary thrombi and PCI revascularization is also associated with microthrombi. Pathological analyses revealed that coronary thrombi consist of platelets, erythrocytes and fibrin, and often contain atherosclerotic inflammatory cells [63] [64]. Microscopic examination revealed that platelet aggregation could be one of the causes of acute coronary syndrome in patients [16] [21] [22]. Additionally, a recent study by Khan *et al.* showed that the formation of MVO is not exclusive to revascularization therapy [2].

Boese *et al.* found an association between plaque composition and post-procedural microinfarction [65]-[67]. The components of microemboli, endothelial sloughing, edema and fibrin plugging have significant impact on myocardial perfusion [65] [68]-[72] and may be on the invasion of polymorphonuclear leukocytes, monocytes and macrophages to the extracellular space [16] [22] [70] [72] [73].

4. Microemboli Visualization

Direct and indirect evidence of microembolization during PCI comes from distal protection device and IVUS-system, which reported embolic particle sizes and a typical reversal of systolic flow, delayed diastolic component and visualization of microemboli [74]-[76]. Microemboli create countable signals on the IVUS display due to the higher reflection of sound waves compared to the blood cells. The microembolic signals appear as short-duration, unidirectional, high-intensity signals within the flow spectrum on the fast Fourier transform spectral display.The intensity of the backscatter signal is processed into gray scale with a spatial resolution of 150 μm at a frame rate of 10 - 30 frames/s. This new technique can also identify and quantify various plaque components in patients [77]-[81]. It can detect features associated with plaque vulnerability, such as an eccentric pattern; the presence of an echolucent core, probably representing the lipid-rich core; positive vessel wall remodeling, defined by the expansion of the overall vessel without compromising the lumen [82]; presence of thrombi [83]-[85]; lumen narrowing [84]; and a spotty pattern of calcifications [86]. Thus, Doppler ultrasound technique became the gold standard method to quantify microemboli in real-time.

MRI and MDCT, positron emission tomography (PET) and single photon emission computed tomography

(SPECT) are associated with unique imaging properties and exhibit variable sensitivity and specificity to cardiac pathologies [87]-[94]. Cardiovascular MRI and MDCT scanners offer a higher spatial resolution than nuclear medicine techniques. MRI based on 3D datasets is considered the gold standard for volumetric and functional analysis of cardiac chambers. In addition, MRI is a versatile technique that has the ability to assess viability on delayed contrast enhancement, LV function on cine, 3D strain with saturation tagged and phase contrast velocity encoded sequences and perfusion on first pass contrast media [95].

MRI, MDCT have been used for detecting microinfarct [71] [96]-[99]. These noninvasive methods can be used alternatively in patients with contraindications to iodinated or gadolinium-based contrast agents. MRI has inherent strengths over the other clinically approved modalities that include: 1) the absence of radiation exposure, which is a strong motivation to further work on implementing MRI after PCI; 2) the lack of administration of nephrotoxic iodinated contrast media; 3) MRI is the method of choice for assessment of LV function and myocardial viability; 4) signal intensity differences of nearly 2 - 5 fold were identified between viable and non-viable myocardium; 5) serial assessments; 6) the potential to measure three dimensional (3D) strain at rest and dobutamine stress; and 7) acquisition of images in any plane negates the need for post imaging reconstruction of images. The advantages of using MDCT include: a) MDCT angiography is the method of choice for direct visualization of coronary calcium and atherosclerosis; b) the presence of LV assist devices do not preclude the performance of MDCT imaging; c) the relatively fast acquisition time (7 - 10 min) compared with cardiac MRI (45 min), leads to patient's comfort as well as cost and time savings; d) scanning of claustrophobic or uncooperative patients; e) less technical and personnel requirements for MDCT studies; f) life-support and physiologic-monitoring equipment can be placed close to MDCT scanners and g) iodinated contrast media provide linear relationship between attenuation and concentration on first pass perfusion MDCT [100].

5. Microvascular Obstruction and Microinfarction

The coronary artery tree consists of large epicardial arteries and microvessels. The range of epicardial coronary artery diameter varies between a few millimeters to 400 - 500 μm and these vessels are visible on the current imaging modalities, but not microvessels between 8 - 120 μm. Advanced real-imaging techniques helped in accurately determining coronary artery diameter that led to reduce the use of oversized stent or higher pressures resulting in emboli being sloughed into the lumen of the artery.

Galiuto classified microvascular damage after revascularization into structural (irreversible) and functional (reversible), where the structural damage is related to damage of microvascular walls; conversely, the functional damage is related to edema and cellular plugging [101]. De Maria *et al.* showed the similarity in the sequelae of spontaneous and procedural distal microembolization [62]. Jaffe *et al.* described two pattens of MVO, namely zonal MVO located in the core of pre-existing infart (primery PCI) and patchy MVO located in ischemic myocardium (elective PCI) [44]. A schematic figure shows both patterns of infarcts in pre-existing infart superimposed with microemboli (**Figure 1**). Microinfarct has been recognized on MRI in patients after PCI [15] [17] [95]. Visualization of patchy microinfarct on contrast enhanced MRI and MDCT depends on multiple factors; namely spatial resolution, extent of microinfarct and imaging time after embolization (**Figure 2**).

In experimental animal studies, MRI and MDCT demonstrated microinfarct, result from patchy MVO, as differentially enhanced speck with heterogeneou pattern in the ischemic-related artery [53]. Acute microinfarct on histochemical and histological stains was defined as unstained necrotic speck (0.7 - 7 mm^2 in size) and patchy violate-blue myocytes surrounding obstructed microvessels, respectively (**Figure 3**) [53].

Investigators also assessed the sensitivity of MRI and MDCT techniques in visualizing patchy microinfarct using different volumes/sizes of microemboli and determined the cutoff of microemboli volume that provides reproducible visible microinfarct [53] [54] [102]-[105]. We found that both visible and non-visible microinfarct on MRI and MDCT have short- and long-term side effects [53] [54] [104] [105].

Also of clinical significance is patchy MVO at the peri-infarct zone, where, this zone contains an admixture of viable and nonviable myocytes that provides a suitable environment for the development of LV arrhythmia [106] [107]. The mechanism underlying hypokinesia in the peri-infarction zone is not well defined. Several hypotheses have been proposed, including changes in mechanical load leading to cellular hypertrophy and dysfunction [108], reduced coronary reserve [109], increased systolic wall stress [110], oxidative stress, and inflammation [111]. Microscopic examination of the peri-infarct zone revealed sporadic non-patent microvessels microemboli.

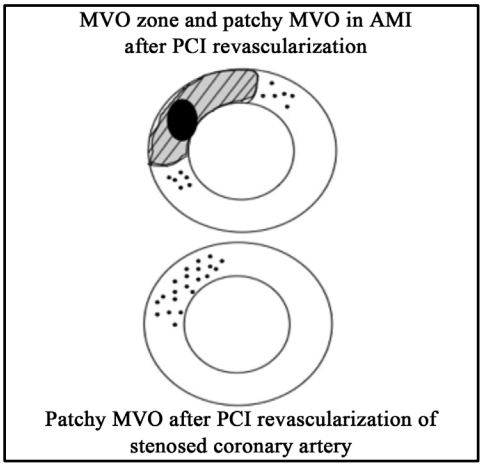

Figure 1. The two types of MVO are: MVO zone in the core of AMI (dark zone) and the patchy MVO (dotted) after PCI revascularization of stenosed coronary artery without infarct.

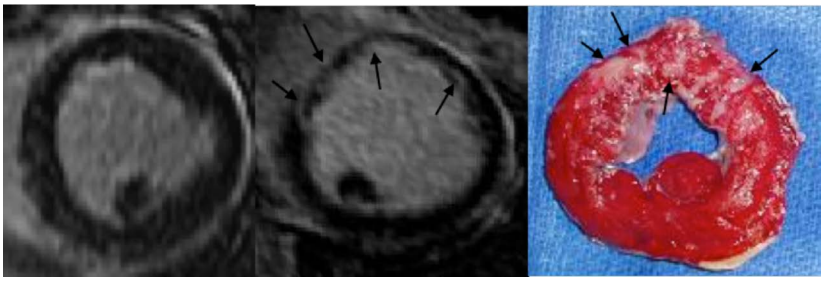

Figure 2. Contrast enhanced MR images of myocardial microinfarct acquired at 1hr (left) and 7 days after coronary embolization (middle). The speck of microinfarct are visible at 7 days (arrows), but not at 1hr, after embolization. A corresponding left ventricle section stained with a triphenyltetrazolium chloride stain shows patchy microinfarct at 7 days (arrows, right).

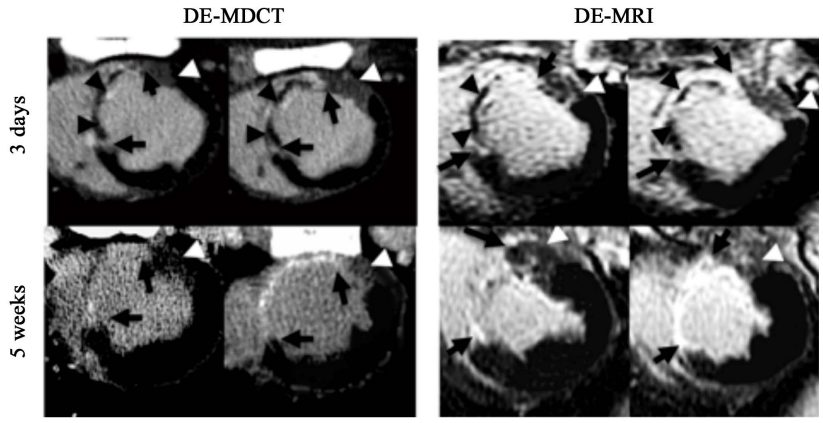

Figure 3. Contrast enhanced MDCT (left block) and MRI (right block) were obtained from a representative animal subjected to myocardial infarct superimposed with microembolization. At 3 days (top row), the images showed hyperenhanced MI (black arrows), hypoenhanced MVO (black arrowhead) and moderately patchy microinfarct at the peri-infarct zone (white arrowhead). At 5 weeks (bottom row), both imaging modalities showed wall thinning in MI (black arrows), moderately enhanced microinfarct at the peri-infarct zone (white arrowhead) and hypertrophy in remote myocardium.

Unlike microscopy, MRI and MDCT indirectly demonstrated sporadic MVO by visualization patchy microinfarct.

6. Microemboli and Infarct Healing

Our understanding of coronary microvasculature in patients has been limited partly due to inability to non-invasively visualize the anatomy of microvascular bed and its complicated functional pathways. On the other hand, acute and scar myocardial infarct are discriminated on noninvasive imaging. Choi *et al.* [112] and Inkangisorn *et al.* [113] monitored the healing of myocardial infarct on delayed contrast enhanced MRI. They found a decline of 27% - 31% in the extent of myocardial infarct over the course of 2 months in patients. Furthermore, myocardial infarct is associated with MVO [114], which occurs in 40% - 60% of patients treated by PCI. Other investigators found that the extent of myocardial infarct on MRI decreases by 21% - 30% in humans during the first week following treatment for STEMI [115], while MVO reduced by 48% in humans [116] and 67% in animals [117].

In recent studies, we found that MVO zone in AMI delays infarct healing, accentuates LV remodeling and hypertrophy of romote myocardium compared with infarct with negligable MVO [118] (**Figure 4**). The difference in the speed of healing is most likely related to slow delivery of nutrients and inflammatory cells to remove the debris [119] [120], while the accentuation in LV hypertrophy is compensatory to infarct thinning and buldging. Infarct size [121] [122] and MVO [60] [121] [123] [124] are powerful predictors of adverse LV remodelling and prognosis.

7. Microemboli and Perfusion

PCI partially restores flow in the infarct-related artery with persistent ST-segment elevation, abnormal myocardial blush grade and abnormal TIMI frame count, due to distal embolization [125]. Lund *et al.* [126] observed

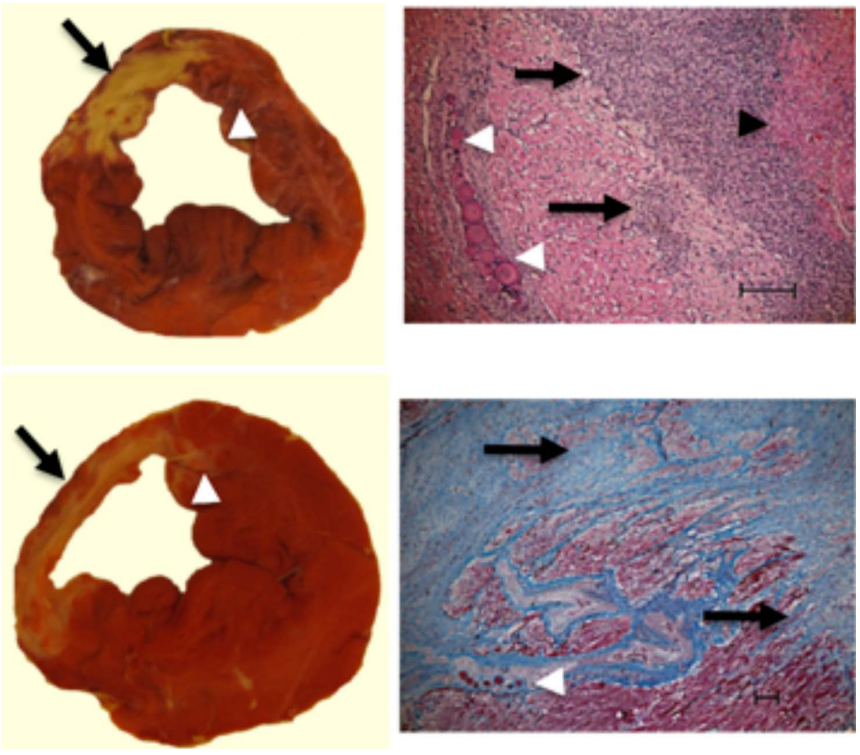

Figure 4. Histochemical TTC stain shows the difference in wall thickness and extent of MI between 3 days (top row, group II) and 5 weeks (bottom row, group III). Histopathological stains (Hematoxylin/eosin and Masson trichrome) show the peri-infarct zone and scar infarct over the course of 5 weeks. Black arrow = infarct, black arrowhead = hemorrhage, white arrowhead = microemboli obstructing blood vessels.

that the perfusion in AMI is spatially and temporally complex with regions of hyperaemia, low flow and MVO. Selvanayagam *et al*. [17] observed a decline in perfusion reserve in myocardial segments that showed new microinfarct resulted from microemboli after PCI. Porto *et al.* [15] used ultrasonography and delayed contrast-enhanced imaging after PCI for determining the relationship between the extent of microinfarct and plaque volumes. A positive correlation was found between the two parameters.

Several studies showed the perfusion deficit in embolized myocardium [70] [71] and increase in epicardial coronary flow [73], which was linked to the release of adenosine in ischemic myocardium [18] [127]. Experimental studies confirmed the persistent regional perfusion deficit in AMI, patchy microinfarct (**Figure 5**) [54] [71] and AMI superimposed with microemboli [54], which are reflected on perfusion indices (max upslope, max signal intensity/attenuation and time to peak). **Table 1** shows the regional changes in peak signal attenuation and signal intensity on MDCT (in Hounsfield units) and MRI (in arbitrary units), respectively) as a function of time in animals subjected to 90 min LAD occlusion plus microembolization and reperfusion. The perfusion data show the deficits in perfusion of the infarct and peri-infarct myocardium over time compared to remote myocardium.

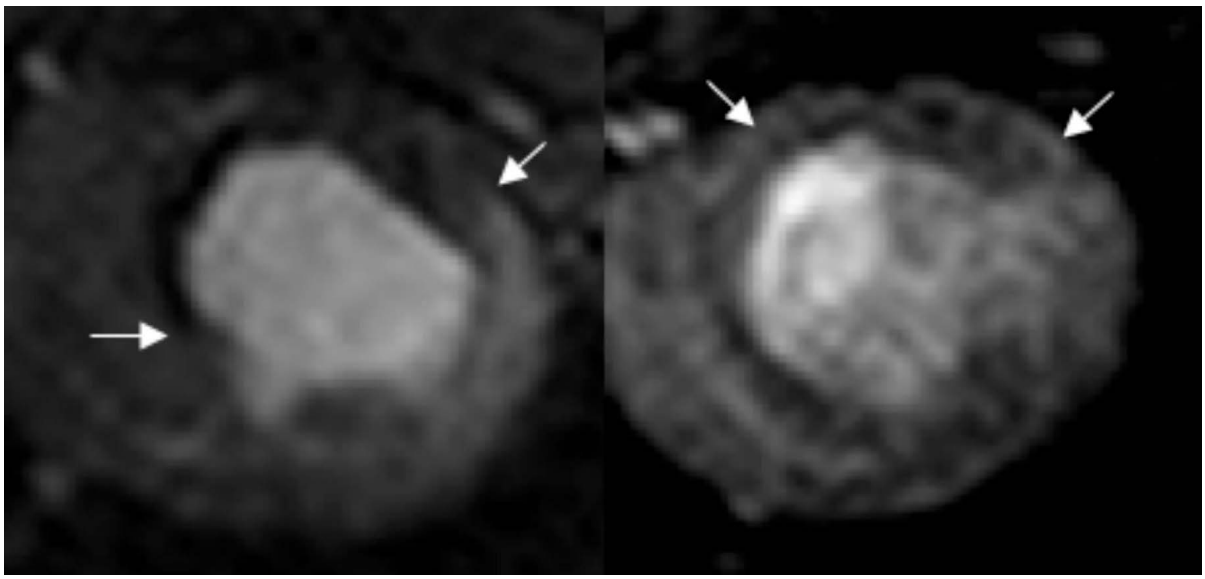

Figure 5. Myocardial perusion deficits (arrows) are shown at the peak of remote myocardial enhancemet at 1 (left) and 7 (right) days after coronary embolization in swine model.

Table 1. MDCT peak signal attenuation Hounsfield units (HU) of animals subjected to LAD occlusion/reperfusion plus microembolization ischemic insult at 3 days and 5 weeks of Groups II and III.

	Group II 3 days	Group III 3 days	Group III 5 weeks
MDCT			
Remote myocardium	150 ± 7	123 ± 3	115 ± 1*†
Peri-infarct zone	89 ± 7$^{\#}$	104 ± 4$^{\#}$	114 ± 3$^{*\dagger\#}$
Infarct	61 ± 7$^{\dagger\S\#}$	88 ± 4$^{\dagger\S\#}$	89 ± 1$^{\dagger\S\#}$
MRI			
Remote myocardium	1432 ± 77	1442 ± 67	1515 ± 195
Peri-infarct zone	1041 ± 72$^{\#}$	966 ± 31$^{\#}$	1277 ± 71$^{*\dagger\#}$
Infarct	806 ± 58$^{\dagger\S\#}$	732 ± 58$^{\dagger\S\#}$	1017 ± 79$^{*\dagger\S\#}$

$^{*}P < 0.02$ compared with 3 days of the same cohort; $^{\dagger}P < 0.01$ compared with animals in Group II; $^{\S}P < 0.02$ compared with border zone myocardium, $^{\#}P < 0.02$ compared with remote myocardium.

8. Microemboli and LV Function

The most clinically used methods for assessing LV function are dobutamine echo-contractile reserve, contrast echo (wall motion) and MRI (wall 3D strain). Quantifying LV function is a powerful predictor of mortality in patients with coronary artery disease [60] [121]. Invasive methods demonstrated the deleterious effects of microembolization on regional and global LV function [18] [128]. The observed changes in LV function were disproportional to the extent of microinfarct.

Noninvasive MRI showed that coronary microemboli cause super-acute (1 hour) acute (3 days), subacute (7 days) and chronic (5 - 8 weeks) impairment in regional and global LV function [54] [69] [73] [129] [130]. It was found that global and regional LV impairment 3 days after LAD microembolization with 16 mm^3 volume and 40 - 120 μm diameters is comparable to 90 min left anterior descending (LAD) coronary artery occlusion/reperfusion, despite the substantial difference in the extents of myocardial damage (6.5% ± 0.6% LV mass versus 12.6% ± 1.2%, $P < 0.001$) (**Figure 6**). Other experimental MRI and MDCT studies demonstrated the greater decline in ejection fraction and increase in LV volumes in pre-existing MI with large MVO compared with similar extents of myocardial damageand negligable MVO [104] [105] [118]. Furthermore, animals with negligable MVO showed moderate recovery in ejection fraction over the course of 5 weeks, but not in animals with large MVO.

In 1995, Pfeffer described the complexity of dimensional changes in the LV after AMI [131]. Early techniques for assessing myocardial strain were invasive and included implantable metal [132] or radiopaque [133] markers. Recently, investigators found that cine, tagged and velocity-encoded phase contrast MR pulses have the pontential for quantifying 3 dimensional (3D) LV strain (radial, circumferential and longitudinal) [69] [130] (**Figure 7** and **Figure 8**). These indices are independent of ejection fraction, wall motion or myocardial oxygen consumption [134].

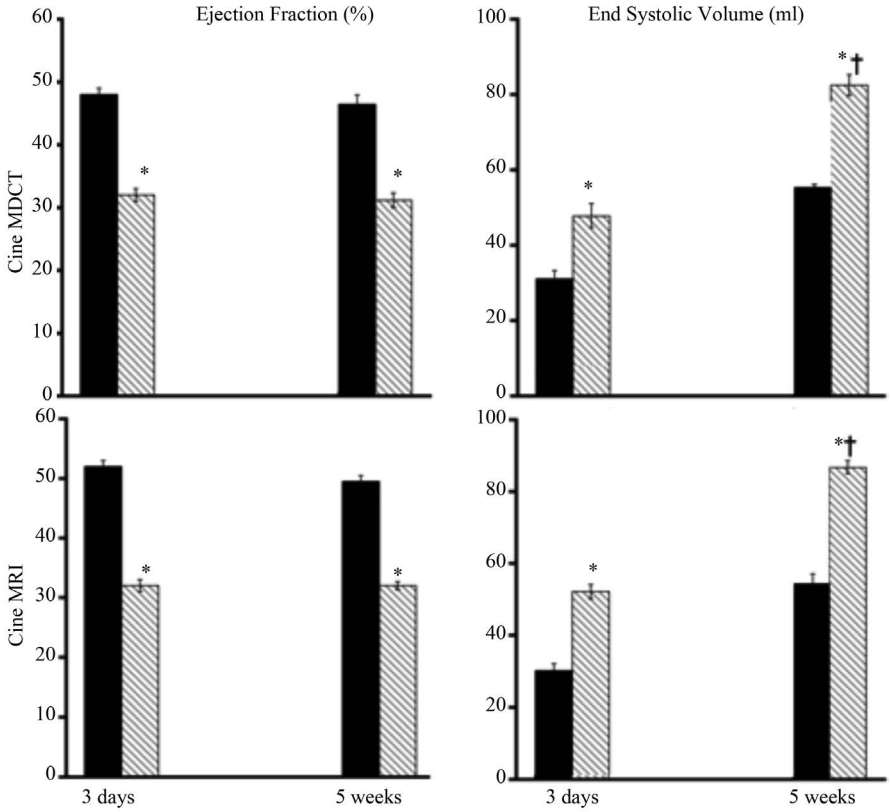

Figure 6. Ejection fraction (%) and end systolic volume (ml) in Groups I (black column) and III (striped column) measured on cine MDCT (top row) and MRI (bottom row). MI superimposed with microembolization showed persistent decline in ejection fraction (left blocks) and increase in end systolic volume (right blocks). Similar changes in ejection fraction and end systolic volume were observed on both modalities. $^{*}P < 0.02$ compared with Group I. $^{\dagger}P < 0.02$ compared with the same cohort at 3 days.

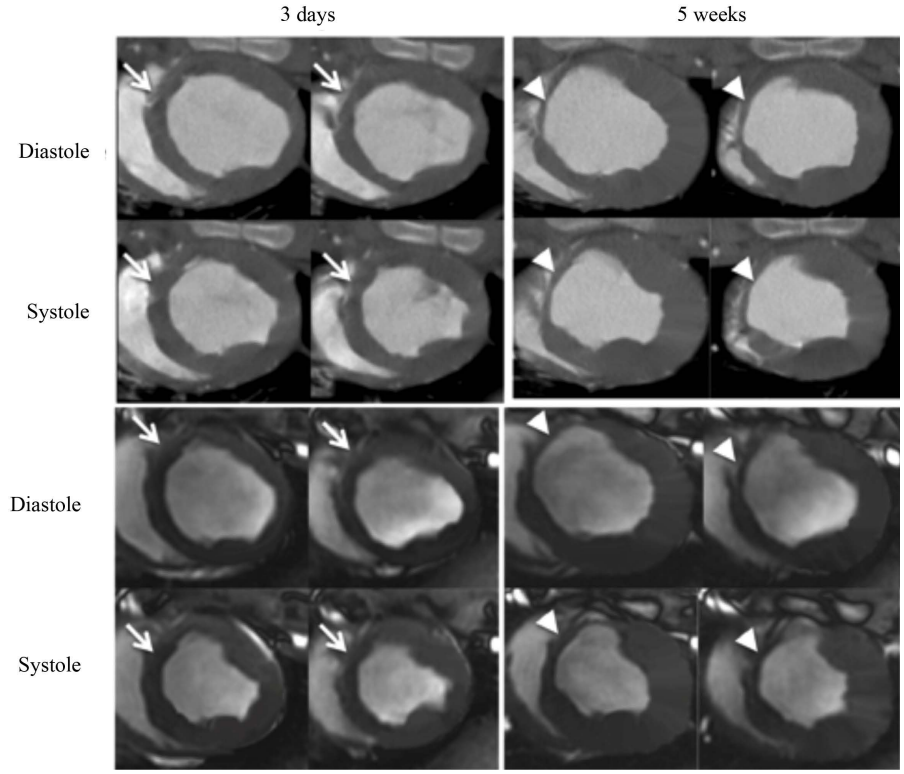

Figure 7. Cine MDCT (top blocks) and MRI (bottom blocks) acquired at 3 days (left blocks) and 5 weeks (right blocks) after embolization of the LAD coronary artery. MDCT and MRI show the lack of systolic wall thickening in the LAD territory at 3 days and 5 weeks. The LAD region (arrows) showed no thinning at 3 days, but at 5 weeks. Compensatory hypertrophy was evident at 5 weeks in remote myocardium.

The circumferential and longitudinal strain on MRI were evaluated in control animals and compared with animals subjected to different ischemic insults; namely solely coronary microembolization, solely LAD occlusion for 90 min followed by reperfusion and 90 min LAD coronary occlusion plus microembolization and reperfusion in a swine model [130]. MRI studies were performed 3 days affter coronary interventions (**Figures 9-11**). It was found that the impairment in LV circumferential strain and dyssynchrony is comparable between 32 mm^3 coronary microemboli and 90 min occlusion/reperfusion of the same infarct-related artery, despite the difference in the extents of myocardial damage. Furthermore, microemboli caused significant decrease in peak systolic strain rate of remote myocardium. The comparable LV dysfunction in these animals suggests that mechanisms other than the extent of myocardial damage govern LV dysfunction [135], such as the release of tumor necrosis factor (TNF)-α [19] and other inflammatory mediators [136] [137]. Solely microembolized and AMI superimposed with microemboli showed slower systolic strain rate than LAD occluded/reperfused territory, suggesting disproportion between myocardial damage and circumferential strain. In remote myocardium, peak systolic strain rate was significantly decreased in microembolized and combined insult animals, but not in occluded/reperfused animals, compared with controls. Similar to peak systolic strain rate, peak diastolic strain rate in remote myocardium was significantly decreased in animals subjected to microembolization or combined interventions, but not in LAD occluded/reperfused animals. Cine and tagged MRI sequences provided evidence that peak strain and time to peak strain (TTPS) are early predictors of dysfunction. Recent studies showed that the complex contraction pattern of the heart and alterations to this pattern due to various cardiac pathologies could be determined using tagged cine MRI [11]-[13].

9. Clinical Studies

Evidence on coronary microembolization in patients came from intravascular imaging, detailing a relationship between plaque volume reduction in the diseased coronary artery after PCI with reduced myocardial reperfusion

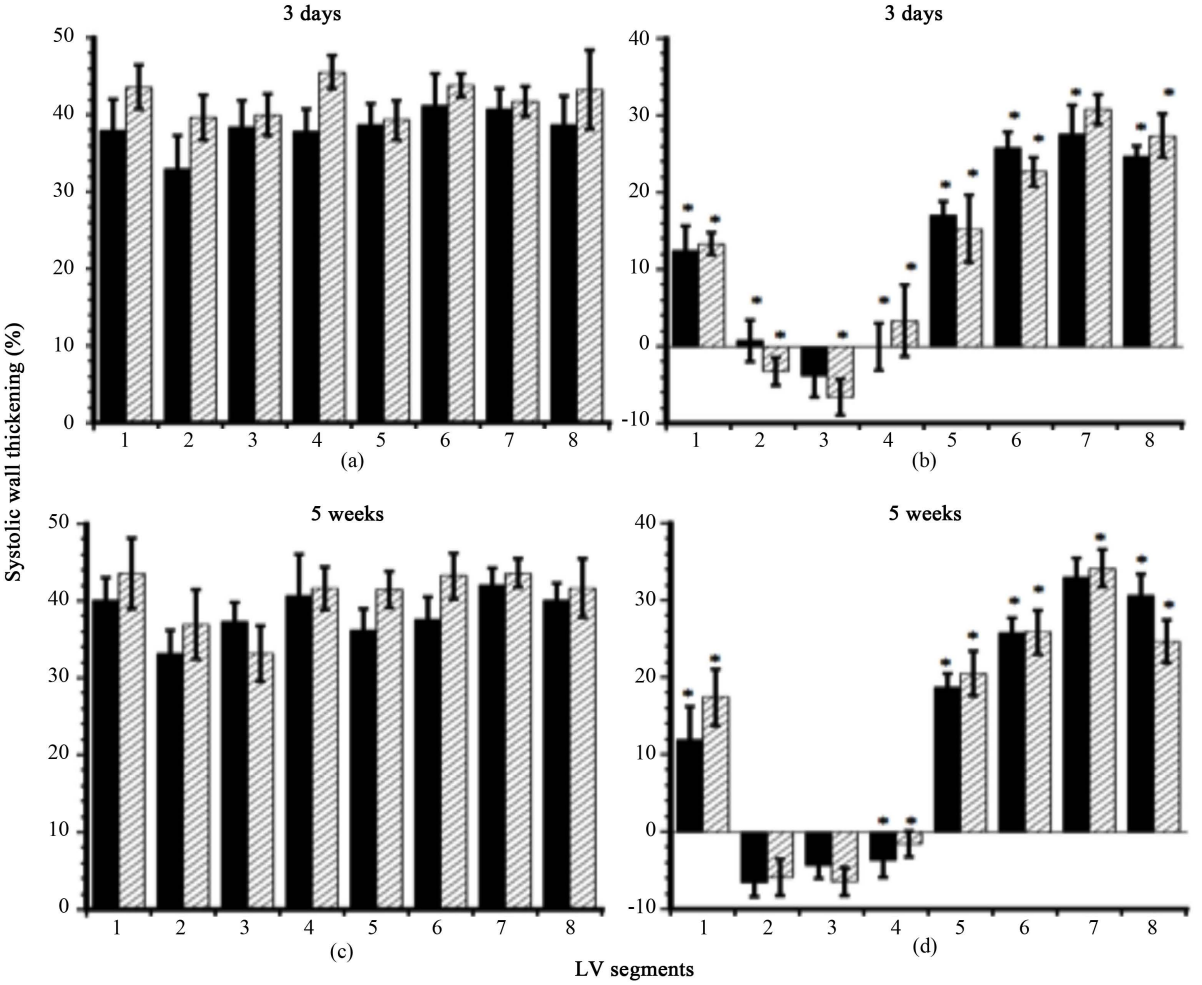

Figure 8. Systolic wall thickening in slices above (a) and (c) and below (b) and (d) the site of occlusion/microembolization/reperfusion at 3 days (top row) and 5 weeks (bottom row) in Group III. Each LV slice was divided to 8 segments and the segments with dysfunctional LAD territory are located in segments 2, 3 and 4. Similar magnitudes of changes in systolic wall thickening were obtained on MDCT (black bars) and MRI (striped bars). $^{*}P < 0.02$ compared with remote myocardium.

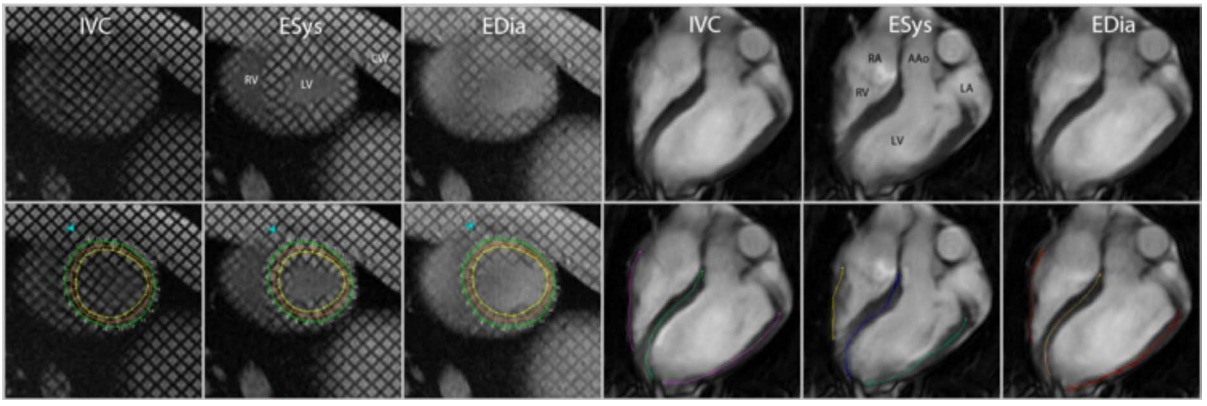

Figure 9. Representative tagged and cine MR images utilizing tracing Method. Top row demonstrates short-axis and long-axis MRI images, while bottom row demonstrates images after tracing of the myocardium using *HARP*. Left three columns are cine tagged MRI and right three columns are cine MRI. IVC = Isovolumetric Contraction, ESys = End Systole, EDia = End Diastole, LV = Left Ventricle, RV = Right Ventricle, CW = Chest Wall, RA = Right Atrium, LA = Left Atrium, AAo = Ascending Aorta.

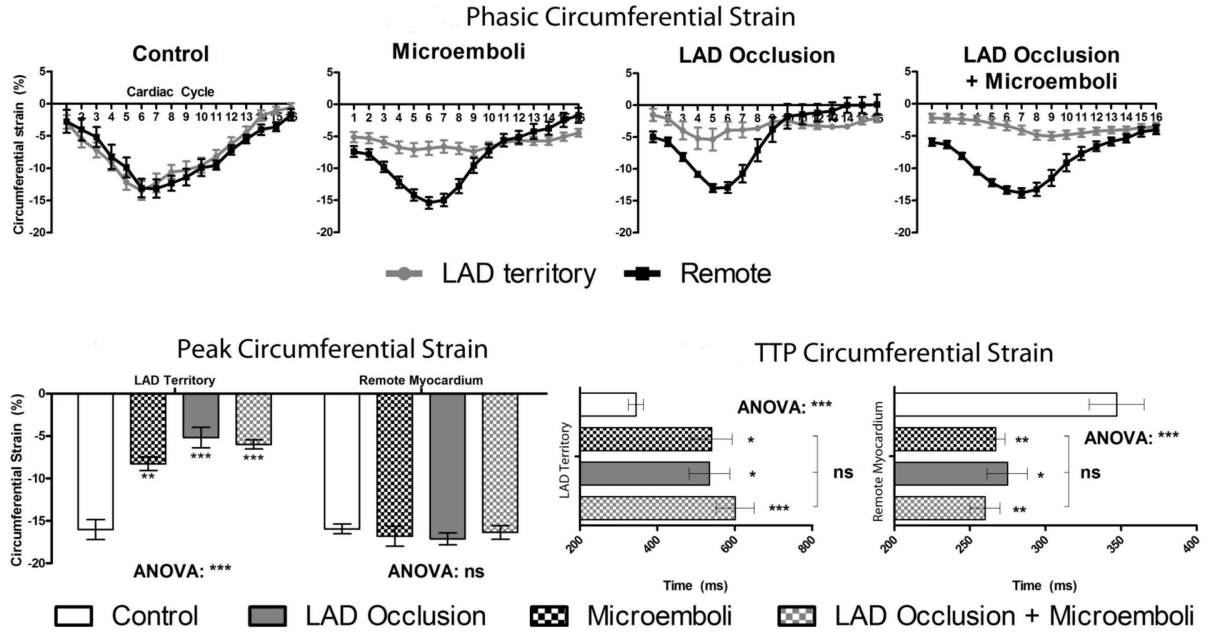

Figure 10. Top row: Phasic circumferential strain peak and rate during R-R interval in LAD territory and remote myocardium of control and animals subjected to microembolization, 90 min LAD occlusion/reperfusion and the combination. A significantly decreased peak circumferential strain was observed in the LAD territory compared with remote myocardium in all coronary interventions ($P < 0.001$). Bottom left: Bars show average peak circumferential strain. ANOVA showed significant decrease in strain of the LAD territory 3 days after interventions compared with controls. Remote myocardium showed no significant difference between interventions and control. Bottom right: Bars show significant variation in time to peak circumferential strain between remote and LAD territory TTPS. Remote myocardium showed decreased TTPS for all interventions, while the LAD territory demonstrated increase. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

[138] and formation of new infarction and MVO in patients [15] [139]. The occurrence of plaque rupture with subsequent microemboli of atherosclerotic and thrombolytic debris into small coronary vessels has been confirmed [22] [140]. Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial reported visible debris in 78% of patients [141]. Bahrmann *et al.* demonstrated that the incidence of procedure associated non-ST elevation myocardial infarction is correlated to the frequency of Doppler-detected microemboli [76] [142].

Clinical studies showed substantial difference in the incidence of microembolization from coronary plaques from 30% [22], 54% [61] to 81% [143]. In half of the patients the additional infarct after PCI was interpreted to be caused by occluded side branches, resulting in a 12% incidence of microinfarction caused by microembolization [15]. Recent studies showed the capability of MRI and MDCT to detecting microinfarct (>2 g) [71] [96]-[99]. Selvanayagam *et al.* found a new area of infarct in 28% of patients after the procedure using contrast enhanced cardiac MRI [144]. The highest incidence was seen in patients who had recent PCI or thrombolysis [143]. Coronary microemboli are considered the primary causes of contractile dysfunction and arrhythmogenesis in the absence of an atherosclerotic obstruction of an epicardial coronary artery [16] [20]. Cardiac MRI has been implemented in measuring perfusion in patients after PCI [17] [145].

Coronary microemboli may explain the cause of mismatch between blood flow in the epicardial coronary arteries and LV function; a phenomenon which has been clinically observed after PCI [146] [147]. Selvanayagam *et al.* [145] found in 152 patients that even small amounts of procedure-related myocardial injury are associated with poor clinical outcome and concluded that 2% - 5% of LV infarct causes disproportional LV dysfunction [110]. Other studies have shown coronary microemboli cause persistent LV dysfunction (heart failure) and in some cases sudden death [25] [26].

The clinical evidence for microembolization after PCI came from the elevation of creatine-kinase in 10% - 40% of patients [20] [74] [96] [148] [149]. A follow-up study in patients who underwent coronary angioplasty or coronary atherectomy found that the relative risk of cardiac death is increased 2.2-fold in patients whose

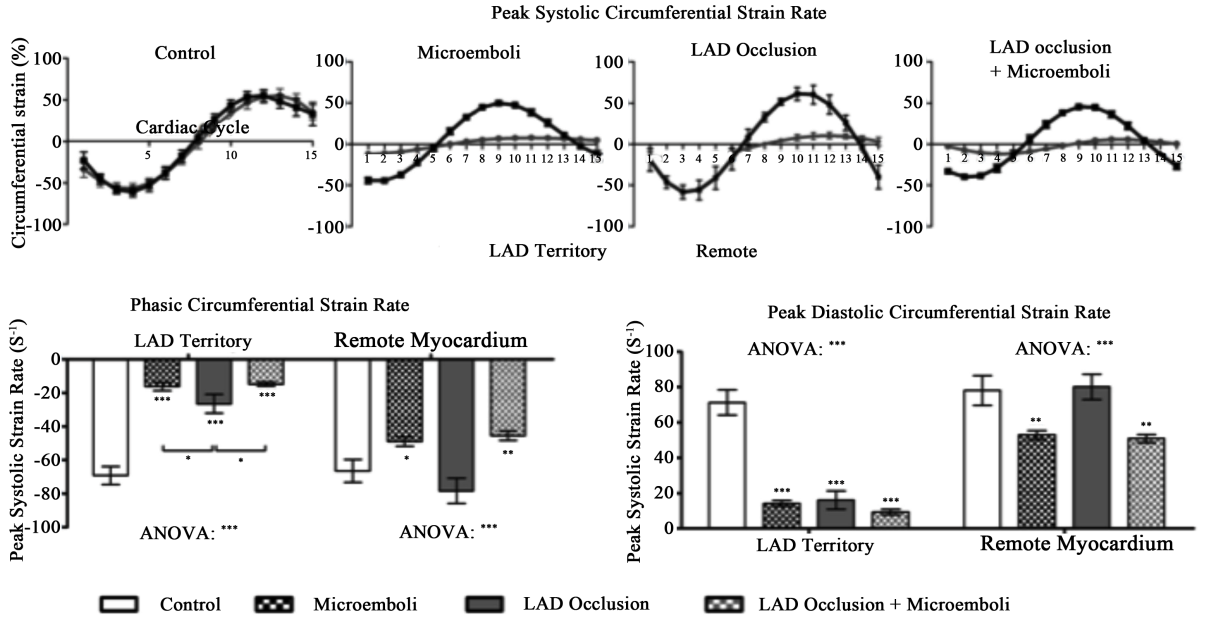

Figure 11. Top row: Circumferential strain rate curves. In control animals, remote myocardium and LAD territory have identical curves, while remote vs. LAD territory in all interventions were significantly different ($P < 0.001$). Bottom left: The LAD territory showed significantly decreased systolic strain rate in LAD territory for all interventions, with microembolized and combined groups significantly less than solely LAD occlusion. Remote myocardium showed only a decrease in microembolized and combined groups. Bottom right: The LAD territory demonstrated significantly decreased diastolic strain rate in LAD territory for all interventions. Remote myocardium again showed only significant decrease in microembolized and combined groups. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ [130].

creatine-kinase levels were elevated >2 times the upper normal range compared with patients whose creatine-kinase were not elevated [73]. Such observations have been confirmed by subsequent studies [18] [73] [150] [151].

Recent clinical studies showed a link between MR visualization of microinfarction and impaired myocardial perfusion [95] [96]. Selvanayagam *et al.* examined myocardial perfusion and necrosis serially after PCI with a validated, quantitative MR technique [17] and found that myocardial perfusion is reduced in segments with infarct after PCI. Investigators also reported that patchy microinfarct at the peri-infarct zone might be an arrhythmogenic substrate [107] [152]-[154]. The proposed pathophysiological explanation is that the tissue heterogeneity with re-entrant ventricular tachycardia is promoted in patchy infarcts with interwoven bundles of myocytes [107] [155].

10. Microemboli and Myocardial Protection

The clinical impact of microemboli on patients with STEMI is evident. Distal protection devices and thrombectomy catheters are widely used to minimize coronary microembolization. These devices are positioned distal to the target lesion to filter emboli sloughed into the lumen of the artery during PCI. Depending on the pore size of these filters, they catch emboli down to a certain size of particles, while allowing continuous blood flow during the procedure. Most of these filters have a pore size of 100μm or larger, which can allow smaller particles to go to microvessels with the possibility of microinfarct. There have been considerable advances in developing distal protection devices, thrombectomy catheters and therapies for minimizing the effects of microemboli during coronary interventions [60] [74] [156]-[161]. Distal protection devices, such as the Filter Wire System, have been shown to reduce the incidence of microinfarction and adverse cardiac events in patients undergoing saphenous vein graft interventions [162]. Other investigators found that it also improve microcirculation and LV function in patients [162] [163]. Others questioned its effectiveness in filtering microemboli because cardiac complications are observed after utilization of the filters [58] [164]. The impact of these devices on myocardial perfusion and clinical outcome in patients remains limited [164]. The absence of benefits with the

use of distal filter wire protection devices could be explained by the low sensitivity of the assay methods, the fact that such devices can themselves induce distal embolization when crossing highly thrombotic lesions or may not be effective in filtering microemboli which is related to the large pores (~120 μm) of these filters that allow the passage of <120 μm microemboli.

Another approach to reduce coronary microemboli is to use therapeutic drugs or anti-platelet agents. The glycoprotein IIb/IIIa inhibitors are synthetic, non-peptide inhibitor acting at glycoprotein (GP) IIb/IIIa receptors in platelets. Junghans *et al.* found that glycoprotein IIb/IIIa receptor antagonist tirofiban reversibly suppressed HITS (microemboli) in the cerebrovascular circulation [165]. Others found this class of therapy inhibitors MVO [166] [167]. Yang *et al.* found in infarction that tirofiban is very effective in improving myocardial perfusion via vascular endothelial protection [168]. These findings support the concept that endothelial protection, apart from platelet inhibition, contributes to the efficacy of tirofiban on myocardial perfusion. Despite the adverse outcomes associated with microembolization, proven targeted therapies remain elusive. The presented data that obtained from controlled studies may activate the development of new devices and therapies for preventing microembolization and treating microinfarct, respectively. MRI and MDCT are useful noninvasive techniques for guiding interventional procedures and assessing the effects of microemboli and therapies.

11. Conclusion

The sequellae of changes in coronary arteries and myocardium after microembolization has been documented in experimental animals and patients subjected to coronary interventions. Non-invasive imaging modalities can play important role in assessing the short- and long-term effects of coronary microemboli on cardiac function, perfusion and viability. Non-invasive imaging may also help in assessing the efficacy of newer distal filtration devices and therapies in patients.

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Abbreviations

Acute Myocardial Infarction (AMI)
Percutaneous Coronary Interventions (PCI)
Microvascular Obstruction (MVO)
Left Ventricular (LV)
Emboli Detection and Classification (EDAC)
F-18 Fluorodeoxyglucose (FDG)
Magnetic Resonance Imaging (MRI)
Multidetector Computed Tomography (MDCT)
Electrocardiography (ECG)
ST-Segment Elevation Myocardial Infarction (STEMI)
No ST-Segment Elevation Myocardial Infarction (NSTEMI)
Tumor Necrosis Factor (TNFα)
Intravascular Ultrasound (IVUS)
Positron Emission Tomography (PET)
Single Photon Emission Computed Tomography (SPECT)
Three Dimensional (3D)
Left Anterior Descending (LAD)
Time to Peak Strain (TTPS)
Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD)
Glycoprotein (GP)

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