Mini Review

Integration of Non-Invasive Imaging in Characterizing Consequences of Coronary Artery Microembolization

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Abstract
Coronary microembolization occurs in spontaneous atherosclerosis plaque rupture, valvular disease, endocarditis, arrhythmias, heart-lung bypass surgery, congenital heart disease, hypertension, diabetes, systemic lupus erythematosus and sickle cell disease. Coronary microembolization can also be induced by therapeutic coronary interventions. High intensity transient signals (HITS) derived from Doppler guide wire has the potential to count coronary microemboli in real-time during percutaneous coronary intervention (PCI). Both non-invasive magnetic resonance imaging (MRI) and computed tomography (CT) have the potential for assessing regional perfusion and left ventricular (LV) function after PCI. The visibility of micro infarct on MRI and CT after administration of contrast media, however, is limited and depends on technical and biological factors. Both MRI and CT modalities underestimate total micro infarct size compared with microscopy. MR images revealed that the presence of coronary microemboli in pre-existing large infarct delays the healing process and magnifies LV remodeling. Chronological preclinical studies revealed that coronary microemboli migrate into the extravascular space leading to natural revascularization. Despite current standard of care, existing methods and therapies do not prevent coronary embolization and completely reverse their deleterious effects.

INTRODUCTION
A recent report from the American Heart Association showed that every minute more than one person suffers from myocardial ischemia [1]. Most of the patients undergo coronary revascularization to reduce infarct size, limit onset of heart failure and improve clinical outcome. Coronary microembolization occurs in spontaneous atherosclerosis plaque rupture, valvular disease, endocarditis, arrhythmias, heart-lung bypass surgery, congenital heart disease, hypertension, diabetes, systemic lupus erythematosus and sickle cell disease [2-5]. Coronary microembolization can also be induced by therapeutic coronary interventions.

Coronary microembolization describes a process where aggregated dislodged platelets and atherothrombotic debris induce microvascular obstruction, inflammation and micro infarction. Cuculi et al showed that 5-30% of the patients suffered from coronary embolization after PCI [6]. And the effects on myocardium varied from non-symptomatic to sudden death [3,7,8]. The range of size of coronary microemboli retrieved is 47–2503μm. This review addresses the use of non-invasive magnetic resonance imaging (MRI) and computed tomography (CT) in characterizing the short- and long-term consequences of coronary artery microemboli on myocardial structure and function.

Cardiac imaging
On the contrary, acute and scar large infarct can be detected 1) directly on positron emission tomography (PET) and single-photon emission computed tomography (SPECT) and 2) indirectly on electrocardiography (EGC), cardiac injury biomarkers, ventriculography, and echocardiography. PET, SPECT and echocardiography have been the clinical modalities for assessing myocardial perfusion and viability, while intravascular imaging methods, such as optical coherence tomography (OCT) and intravascular ultrasound (IVUS), characterize plaque composition (large necrotic cores, high plaque volume, thin-capped fibroatheroma) [9-11]. It should be noted that visualization and quantification of coronary microemboli and myocardial microinfarct is still clinically challenging using these methods because of their poor sensitivity. Table 1 summarizes
T1- and T2-mapping images showed increases in native T1- and T2-relaxation times in MI compared with remote myocardium and a greater decrease in T1-relaxation time after administration of MR contrast media[24, 25]. These new imaging sequences need to be tested yet in patients with myocardial microinfarct.

Computed tomography imaging

Computed tomography (CT) is another noninvasive coronary artery and myocardial imaging modality. CT is a faster, more widely available, and less expensive imaging technique than MRI. This imaging technique has also been used for visualizing microinfarct and detecting LV dysfunction in microembolized LAD artery territory in swine model [26-29]. We defined the effects of tube voltages of 80kV and 120kV on the measurement of myocardial microinfarct 3 days after delivering 32mm3 microemboli in the LAD coronary artery [27]. Multislice CT images revealed inconsistency in visualizing microinfarct caused by this volume and microemboli sizes using tube voltages of 80kV and 120kV. The extent of microinfarct was not significantly different between the two tube voltages and histochemical stain at postmortem. The potential of CT in measuring micro infarct was tested in swine subjected to a combination of 90min LAD coronary occlusion and microembolization (32mm3, 40-120μm) followed by reperfusion [30]. CT imaging was performed at 3 days then sacrificed in subgroup of animals or 3 days and 5 weeks then sacrificed. Micro infarct mass was quantified on cine and delayed contrast enhancement CT. MRI, cardiac injury biomarkers, macroscopic histochemical TTC staining and histopathologic staining were used as independent references. Delayed contrast enhancement CT delineated micro vascular obstruction zone embedded in myocardial infarct and micro infarct specks resulting from persistent MVO by deposited micro emboli in micro vessels of peri-infarct zone. Bland-Altman test showed close agreements between the masses of myocardial infarct measured on delayed contrast enhancement CT/MRI and macroscopic histochemical TTC staining, but not between these modalities and microscopy. CT also showed the infarct resorption (healing) between 3 days and 5 weeks (13.4 ± 0.5 g and 9.8 ± 0.5 g, P < 0.017). In another

Table 1: Currently available methods for coronary microemboli counting (Doppler imaging) and myocardial microinfarct detection (Magnetic resonance imaging, computed tomography, cardiac injury biomarkers and biopsy).

<table>
<thead>
<tr>
<th>Methods</th>
<th>Features</th>
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<tbody>
<tr>
<td>Doppler imaging</td>
<td>1) Quality and interpretation of the image highly depends on the skill of the user.</td>
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<td></td>
<td>2) Limited by the presence of air and calcified tissues.</td>
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<td>Magnetic resonance imaging</td>
<td>1) Relatively slow and noninvasive</td>
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<td></td>
<td>2) Needs injection of a contrast medium, which may cause rare allergy</td>
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<td></td>
<td>3) MR scanners cause some people to feel claustrophobic</td>
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<tr>
<td>Computed tomography imaging</td>
<td>1) Quick and noninvasive</td>
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<td></td>
<td>2) Involves exposure to ionizing radiation</td>
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<td></td>
<td>3) Needs injection of a contrast medium, which causes kidney problems or allergy</td>
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<tr>
<td>Cardiac injury biomarkers</td>
<td>1) Minimally invasive</td>
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<tr>
<td></td>
<td>2) Lacks of sensitivity for microinfract</td>
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<td></td>
<td>3) Time dependent after PCI</td>
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<tr>
<td>Myocardial biopsy</td>
<td>1) Invasive</td>
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<td></td>
<td>2) Not recommended in patients after PCI</td>
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<td>3) Suffers from sampling error</td>
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the main techniques and their features in detecting coronary microemboli and myocardial microinfarct.

NON INVASIVE IMAGING METHODS

Doppler imaging

This imaging technique uses high-frequency sound waves to produce moving images. Porto et al. [4,5,12], were the first to count coronary microemboli in real-time during PCI using high intensity transient signals (HITS) derived from Doppler guide-wire. They combined cardiac injury biomarkers, delayed contrast enhanced MRI (DE-MRI) and intravenous ultrasound and coronary angiography to explore peri-procedural myocardial necrosis after percutaneous coronary stenting in 64 native vessels from 52 consecutive patients. They found good correlation between microemboli volume and microinfarct size on DE-MRI. Similar finding was documented experimentally [13].

Magnetic resonance imaging

The recent advancements of high field MR scanners and sequences allowed scientists and clinicians to explore minor pathologic changes in myocardium, including myocardial microinfarct. Using MRI, Breuckmann et al. [14], indicated that a threshold of 5% is necessary for visualization of microinfarct. Preclinical studies showed myocardial microinfarct on MRI (Figure 1), that resulted in a significant decrease in regional contractility and global dysfunction. Some animals showed no evidence of visible microinfarct, but regional and global dysfunction on MRI. Histo chemical staining and microscopy confirmed the presence of microinfarct in macroscopically non visible microinfarct, which explains LV dysfunction seen on MRI (Figure 2), [15,16]. Kwong et al. [17], reported that small infarct (1.4% of LV mass) identified on DE-MRI portended a sevenfold increased risk for major adverse cardiac events in patients.

More recently, investigators showed that T1 mapping MRI sequences had the potential to demonstrate regional T1 changes associated with myocardial edema and diffused fibrosis [18-24]. T1- and T2-mapping images showed increases in native T1- and T2-relaxation times in MI compared with remote myocardium and a greater decrease in T1-relaxation time after administration of MR contrast media[24, 25]. These new imaging sequences need to be tested yet in patients with myocardial microinfarct.
Figure 1 Long and short axis view delayed contrast enhancement MR images obtained from an animal subjected to LAD coronary artery embolization (top images) show patchy microinfarct (top row, black arrows). Lower MRI images show MVO zones (black arrowhead) in the core of the infarct (white arrows) and patchy microinfarct at the peri-infarct zone (white arrowhead) in an animal subjected to 90min LAD occlusion/microembolization/revascularization.

Figure 2 The plot shows the decrease in LV ejection fraction as a function of microemboli volume.

study, Carlsson et al. [26], indicated that multi detector CT is sensitive modality to depict microinfarct in the embolized territory at 7-8 weeks after delivering 250,000 (40-120μm) micro emboli.

Jablonowski et al. [29], assessed myocardial extracellular volumes in normal myocardium, contiguous infarct and micro infarct. They found that the fractional distribution volume was 24% in viable myocardium, 36% in micro infarct after delivery of 16mm$^3$ micro emboli, 41% in microinfarct after delivery of 32mm$^3$, 55% in large infarct after 90min LAD occlusion/revascularization and 56% after 90min LAD occlusion/revascularization with delivery of 32mm$^3$ micro emboli. The microscopic measurements confirmed CT data. Measurements of fractional distribution volume in ischemic and non-ischemic heart disease has been recently reviewed using MRI and CT [31].

On micro-CT, Malyar et al., identified in vitro the patchy pattern...
of perfusion in microembolized myocardium and attributed it to a random distribution and clustering of microemboli in micro vessels [32]. Myocardial extracellular volume was also determined in patients on dual-energy equilibrium contrast enhanced CT and compared with equilibrium contrast enhanced MRI. The extracellular volume in healthy subjects was (34.48% ± 8.97 for CT and 34.18% ± 8.98 for MRI) and showed good agreement, with a small bias and acceptable 95% limits of agreement compared with MRI[33]. Compared with healthy subjects, patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, amyloidosis, and sarcoidosis had significantly higher myocardial extracellular volumes on dual-energy equilibrium contrast-enhanced CT. Thus, investigators suggested that CT might be a potential approach in the clinical assessment of diffuse myocardial fibrosis, particularly in patients with contraindications to MRI.

Coronary microembolization

Myocardial Function: Two-dimensional echocardiography with Doppler is the common method for assessing regional and global function of the LV. However, echo cardiographic measurements present with several limitations, mainly with regard to through plane motion and poor acoustic windows. MRI and CT offers great advantage over echocardiography by providing a set of contiguous long axis and short axis LV/RV slices (Figures1,2). Previous studies showed that cine MRI sequences provide variable information on cardiac mass, LV/RV volumes and 3 dimensional LV strains (radial, circumferential and longitudinal) after microembolization [13,34-37]. Carlsson et al. [34, 35], demonstrated MRI the deleterious effects of coronary embolization on regional LV radial strain at 1 hour and 1 week in swine model. In another study, Carlsson et al. [26], indicated that multi detector CT is sensitive modality to determine regional and global LV dysfunction in the LAD territory at 7-8 weeks after delivering microemboli.

On cine MRI the effects of two microemboli volumes (16mm³ and 32mm³) on LV ejection fraction were determined (Figure 2), [15]. It was also found that the effect of 32mm³ microemboli on radial stain was broader (involved at least 4 segments in basal, mid and apical MRI slices) than 16mm³ microemboli. We also explored experimentally the effects of different microemboli volumes (16mm³ and 32mm³) on LV function in preexisting AMI [15]. Animals subjected to LAD occlusion/coronary microembolization/revascularization showed early microvascular obstruction (Figures1,2) and dysfunction (Figure 4), and later greater LV wall thinning, decrease in ejection fraction and increase in end-systolic volume than controls or animals subjected to LAD occlusion/revascularization only. Quantitative analysis showed a total of 576 segments with systolic wall thickening were graded as normal, with a thickening of more than 30% (192, 112, and 64 segments in control, LAD occlusion/revascularization, and microemboli in preexisting AMI groups, respectively); hypokinetic, with 10%–29% thickening (48 and 48 segments in LAD occlusion/revascularization, and microemboli in preexisting AMI groups, respectively); akinetic, 0%–9% (32 and 32 segments, respectively); and dyskinetic, −10% to 0%
0 and 48 segments, respectively). Dyskinesis and paradoxical systolic-wall thinning were observed only in LAD occlusion/microembolization/revascularization group.

A clinical study showed that longitudinal strain measured on cine MRI correlated well with infarct size [38]. Suhail et al. [36], found that cine and tagged MRI sequences can demonstrate the decline in LV and RV circumferential and longitudinal strains in microinfarct. Compensatory increase in longitudinal strain of RV free wall was also observed in response to microemboli. From these preclinical studies, it was concluded that coronary microemboli with or without AMI core causes complex myocardial injury and ventricular dysfunction that were not replicable in solely AMI. Saeed et al. [27], demonstrated that the changes in LV function are dependent on the volume of microemboli in the absence of AMI core. CT images acquired at end diastole and end systole showed impaired systolic wall thickening in microembolized LAD territory as compared with remote myocardium (Figure 2). Regional dysfunction leads to significant reduction in percent LV ejection fraction.

Myocardial perfusion

The severity and extent of myocardial ischemia is a key to decision-making for coronary revascularization. With commencing myocardial ischemia, a cascade of cellular, functional and electrocardiographic events ensues. Thallium-201 scintigraphy studies demonstrated that large coronary artery stenosis causes myocardial ischemia [39,40]. First pass MRI perfusion detected myocardial perfusion deficits at the microvascular level in patients after PCI [4,41]. This imaging sequence has the potential to detect perfusion deficits as early as 1 hour after embolization and the territory fed by embolized artery appeared as hypo enhanced zone (Figure 5) shows the perfusion deficit in the LAD territory in swine mode.

Selvanyagam et al. [42], used first pass perfusion and DE-MRI to demonstrate perfusion deficits and new microinfarct 24 hours after PCI. Choi et al. [43], found an association between perfusion deficits and microinfarct size in patients after PCI.In an experimental study, Mohlenkamp et al. [44], also investigated the changes in coronary microcirculation (intramyocardial microvascular blood volume, perfusion, transit time and pattern of microvascular injury) in response to different sizes of microemboli. The investigators observed that 100μm microspheres resulted in patchy plugging, while 10μm microspheres induced contiguous hemorrhagic myocardial injury. Investigators found that maximum up slope, maximum signal intensity and time to the peak data obtained from first pass MRI perfusion are the best indices to quantify the severity of the deficits [13,15,34,45]. Saeed et al. [27], also tested the potential of CT in assessing the acute effects (3 days after LAD embolization) of 16mm³ (40-120μm) coronary microemboli on myocardial perfusion using the above perfusion indices 3 days after intervention. This imaging modality confirmed the MR data in showing the perfusion deficits. Carlsson et al. [26], indicated that CT is also sensitive modality to depict the perfusion deficits in scar microinfarct 7-8 weeks after LAD embolization.

Cardiac injury biomarkers

Cardiac injury occurs when there is disruption of cell membrane integrity that results in the loss of intracellular creatine kinase MB (CK-MB), troponin I, myoglobin, heart-type fatty acid binding protein, and lactate dehydrogenase and their rise in the blood. Clinical studies revealed that elevation of those biomarkers in the blood is indicative of myocardial injury [46,47]. In a study designed to define the significance of peri-procedural troponin rise, investigators studied 50 subjects after coronary intervention [47]. They found differential enhancement in 29% and a strong correlation between troponin rise and mass of new infarct. A large meta-analysis of 23230 patients with stable or unstable angina undergoing PCI with follow-up for 6–34 months compared with the data from healthy volunteers showed a close relationship between CK-MB concentration and mortality rate, even at a minor increase of CK-MB 1–3× conferring a relative risk of death of 1.5 (95% CI 1.2 to 1.8) [48].

Investigators also found in swine model that plasma concentrations of creatine-kinase MB and troponin I were significantly higher after delivery of 16 mm³ and 32 mm³ microemboli to the LAD coronary artery after 24 hours PCI compared with baseline, but there was no significant difference in troponin I or creatine-kinase between the groups [49]. After 72 hours, however, the concentration of troponin I was significantly higher in animals that received large volume, suggesting that
this analytical method is not sensitive and specific enough to differentiate mass of microinfarct based on the volume of microemboli.

**Myocardial biopsy**

Unlike cardiac injury biomarkers, microscopic examination confirms the obstruction coronary microvessels by microemboli. It is a gold standard method for confrming myocardial necrosis, but it suffers from sampling error. Gu et al. [8], observed under light and electron microscope the damage of vascular endothelium and myocardium in the territory of microembolized microvessels by automicrothrombotic particles. Other investigators showed at the cellular level that monocytes/macrophages dominate the cellular infiltrates for the first 2 weeks after MI and participate in wound healing [50, 51]. On the other hand, biopsy is not recommended in patients after PCI.

The mass of microinfarct on MRI, CT imaging, macroscopic histochemical staining and microscopy were compared 3 days after LAD embolization using 16mm$^3$ and 32mm$^3$ of 40-120μm microemboli [52]. Microscopy provided higher spatial resolution for measuring necrotic myocardium. MRI, CT and histochemical staining significantly underestimated the mass of microinfarct compared with microscopy.

The use of iron particles, as MR contrast medium, showed promise in noninvasively identifying and quantifying temporal changes in myocardial inflammation in patients with AMI [53]. Monitoring macrophages/monocytes infiltration might be useful for predicting clinical outcomes and treatment efficacy. Chronic microinfarct can be differentiated microscopically from acute microinfarct by remodeled blood vessels, lack of inflammatory cells and the presence of fibrotic tissue [37,49,54].

It has been shown that slow infarct healing can lead to LV remodeling, rupture and death [55]. AMI territories with microvascular obstruction showed slow infarct healing (resorption) compared with AMI without microvascular obstruction. The slow healing process led to increase in LV volumes and compensatory hypertrophy at 5 weeks after embolization of AMI [37]. Furthermore, MRI and histologic study demonstrated that the resorption of microinfarct is faster than large infarct [49]. The decline in microinfarct and MI core at 5 weeks was 60% and 25%, respectively [49,56]. Choi et al [57], and Inkangisorn et al [58] found in patients a decline in infarct size by 27% and 31%, respectively, 2 months after infarction.

Additional microscopic observations in myocardial microinfarct are: 1) apoptotic bodies [13, 59], 2) calcium deposits [13] and 3) migration of intravascular microembol to interstitial space (Figure6). Reactive oxygen species have been shown to exert direct inhibitory effects on myocardial function in vivo [60]. Grutzendler et al., showed that microemboli are cleared from the microvasculature by either hemodynamic pressure or angiography, in which emboli were engulfed by the endothelium and trans located through the microvascular wall [61]. The engulfment of emboli by the endothelial membrane projections leads to reestablishment of blood flow, vessel sparing and salvaged ischemic tissues. On the other hand, this phenomenon may limit the use of microemboli therapy in treating tumors or occluding severely injured blood vessels.

**Microinfarct treatment**

The ability of glucocorticoid in reducing myocardial inflammation after coronary embolization has been experimentally tested by Chen et al. [62]. Investigators found that glucocorticoid improves LV function after coronary embolization through the suppression of transforming growth factor-beta 1 (TGF-β1)/Smad3 and connective tissue growth factor. Jin et al. [63], used MRI for determining the effect of glucocorticoid on microembolized coronary artery. They found a less dysfunction in regional wall motion in treated than untreated 6 hours after coronary microembolization, where glucocorticoid treatment ameliorated myocardial dysfunction (88.6 ± 7.6%) compared with untreated group (47.7 ± 4.7%; P< 0.001). The systolic wall-thickening index was 96.3 ± 8.2% at the baseline. The LV ejection fraction decreased from 49.9 ± 3.5% at baseline to 34.6 ± 3.7% at 6 hours (P< 0.001) in the control group, which was significantly less in treated group from 47.1 ± 3.8% to 42.5 ± 3.9% (P< 0.001). Furthermore, Ma et al found glucocorticoid attenuates LV remodeling caused by coronary microemboli [64].

Other experimental study revealed that phosphatase and tensin homolog deleted on chromosome ten (PTEN) were proteins regulating inflammation and apoptosis [65]. This protein is highly expressed in reperfused acute MI and it enhances inflammation after embolization [65]. Investigators found that inhibition of PTEN improved myocardial function by attenuating myocardial apoptosis [66]. Wang et al. [67], provided evidence that atorvastatin inhibits myocardial apoptosis in swine model of coronary microembolization by regulating PTEN/Akt signaling pathway.

**SUMMARY**

This review shows the integration of multi-imaging modalities in visualizing coronary microemboli (Doppler imaging) and assessing the effects of coronary microembolization on myocardial structure, function and healing (MR and CT imaging). These imaging techniques hold promise as noninvasive methods of assessing and monitoring myocardial microinfarct evolution after therapeutic interventions. The visibility of microinfarct on MRI and CT is still limited and depends on technical issues (such as optimization of MR images, elimination of motion artifacts, slice thickness and contrast media) as well as biological issues (such as age of the microinfarct (edematous or fibrotic) and microemboli sizes and volume). Both MRI and CT need improvement in spatial resolution. Additionally, it is of paramount importance to develop innovative techniques for preventing coronary microemboli formation and treating strategies.

**REFERENCES**


