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An Overview of the Consequences of Distal Coronary Microembolization on Left Ventricular Function, Perfusion and Viability

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ABSTRACT

Annually, an estimated 1,285,000 *in-patient angioplasty procedures,* 1,471,000 *inpatient diagnostic cardiac catheterizations and* 68,000 *inpatient defibrillator implantations are performed. The direct and indirect cost of cardiovascular diseases for* 2007 *is approximately $*431.8 *billion. The occurrence of plaque rupture with subsequent microemboli of atherosclerotic and thrombolytic debris into small coronary vessels has been confirmed. Microinfarction results from microemboli that are shed following coronary interventions. The aims of this review are to:* 1) *detect heterogeneous microinfarction using viability imaging,* 2) *characterize the consequences of distal coronary microembolization on left ventricle function and perfusion and* 3) *illustrate the progress of non-invasive imaging modalities in assessing distal coronary microembolization.*

Keywords*: *Distal Coronary Microemblolization, Microinfarct, Left Ventricular Function, Cardiac Imaging

1. Introduction

Ischemic heart disease is the leading cause of death with an estimated 60 million cases each year and cost the healthcare system approximately $186 billion. Clinical studies have shown that 42% of patients experience major cardiac events such as heart failure and sudden death after coronary intervention [1-6]. Microemboli, liberated during percutaneous coronary intervention (PCI), have been a well-recognized phenomenon in daily clinical practice. This phenomenon is not limited to PCI but includes a wide range of diseases, including valvular disease, prosthetic valve, endocarditis, cardiomyopathy, mural thrombus, arrhythmias and during heart-lung-bypass in patients with congenital heart disease [7-13]. This pathology is also seen in patients with hypertension, diabetes [14], systemic lupus erythematosus [15] and sickle cell disease [16]. Clinical manifestations that could plausibly be associated with microinfarction include unstable anginal episodes that do not meet diagnostic criteria for acute homogeneous myocardial infarction and non–Q wave infarcts. Microinfarction may be subclinical in some patients but the cumulative effect of repetitive microinfarction could eventually result in evident deterioration of cardiac structure and function.

Given the vast patient population who experience embolic events, surprisingly little is known of the relationship between microinfarction, left ventricular (LV) function and arrhythmia. The American College of Cardiology and the European Society of Cardiology recently recognized the detrimental consequences of clinical coronary microemboli in their 2007 guidelines [17]. High incidences (30-50%) of defects on myocardial perfusion scintigraphy have been detected after PCI with optimally implanted stents [18-21] and these events continued during follow-up [22-26]. Investigators found that the size and number of emboli dislodged from ruptured plaque is likely a key event in formation of microinfarction [27]. Several studies have identified distal coronary microemboli as the underlying etiology of LV dysfunction [14,17,28-30] and sudden death [29,31,32]. Coronary microemboli have also been recognized as a major source of arrhythmia, which may result in sudden death [33,34]. Currently, there is intensive work on providing reliable non-invasive diagnostic techniques that can be used to visualize microinfarction caused by distal coronary microemboli and assess the efficacy of new therapies and devices designed to treat or prevent microembolization. Such techniques should have the ability to

quantify the effects of distal coronary microemboli on left ventricular function, perfusion and viability.

The aims of this review are to: 1) detect heterogeneous microinfarction using viability imaging, 2) characterize the consequences of distal coronary microembolization on left ventricle function and perfusion and 3) illustrate the progress of non-invasive imaging modalities in assessing distal coronary microembolization.

2. Distal Coronary Microembolization

Distal coronary microemboli and microinfarction has been identified at autopsy in patients with acute coronary syndromes who died of sudden cardiac death [35-42]. Okamura et al used an intracoronary Doppler guide wire to visualize and count microemboli during PCI in patients. The investigators found that the size of microemboli ranges between 47.16 to 2503.48 μm [43]. Other investigators found that the size of microemboli in patients after sudden cardiac death due to coronary intervention averaged 250 μm [44]. It was also found that size and volume of microemboli has a different impact on myocardial perfusion [45].

There have been relatively few studies, however, aimed specifically at assessing microinfarction, perfusion and function after PCI. Angelini et al indicated, "Little attention has thus far been given to the detection and prevention of microembolization [46]." Heusch *et al.* [47] reported that "Quantitative information on microinfarction is missing: the size and number of microemboli and associated microinfarction in a given heart or perfusion territory have not been reported so far." A recent study relates the volume of microemboli to myocardial damage [28]. In our studies we defined microinfarction on cardiac magnetic resonance (CMR)/multi-detector computed tomography (MDCT)/histochemical stain as a bright, small, unstained and necrotic lesion (1-7 mm^2) within the area at risk. Invasive studies in animal models have shown LV dysfunction after delivery of embolic materials into coronary arteries [17,27,34,47-51]. The discrepancy between the damage and disproportional LV contractile dysfunction has been demonstrated [52]. Dörge *et al.* [53] found, 8 hrs after delivery of 42 um microspheres into the left circumflex coronary artery in swine model, that there was significant decrease in systolic wall thickening and an increase in LV end-diastolic pressure. The observed decrease in LV function was disproportionate to the extent of the myocardial damage. LV dysfunction has been attributed to the release of tumor necrosis factor (TNF)-α [33]. The effects of distal coronary microemboli have been investigated extensively using highly invasive methods and after administration of substantially higher load than seen clinically [17,34,47-50].

2.1. Characterization of Distal Coronary Microembolization

2.1.1. Microscopic Investigations

The most common form of distal coronary microemboli is atherosclerotic plaque. Atherosclerotic plaque is shed downstream into the microvasculature of the myocardium causing microinfarction. The earliest evidence of microembolization and microinfarction came from autopsy of patients who have died of sudden cardiac death [29,31,32]. These studies found that platelet microembolization can be one of the causes of acute coronary syndrome in patients. Post-mortem study of patients who died from sudden cardiac death revealed that microemboli are more common in vessels with plaque erosion than plaque rupture [54]. Microembolization is associated with invasion of polymorphonuclear leukocytes, monocytes and macrophages as inflammatory response [29,32,53,55,56]. Histopathology confirmed the presence of single and multiple microemboli in various diameter blood vessels which are surrounded by various extents of microinfarction. Embolized microvasculature showed endothelial sloughing and fibrin as contributors of microvascular obstruction, these changes were associated with edema and inflammatory cells out of the microvessels [55-59].

2.1.2. Non-Invasive Imaging

Microinfarct imaging is a challenge because of the low spatial resolution of conventional diagnostic scanners and motion artifacts. Cardiac magnetic resonance (CMR) and multi-detector computed tomography (MDCT) techniques are associated with unique imaging properties that define the achievable spatial and temporal resolutions and exhibit variable sensitivity and specificity to cardiac pathologies [60-67]. Multiple factors must also be considered when determining the most appropriate modality for a specific application, such as cost, availability in health care centers, patient tolerance, and contraindications.

CMR and MDCT imaging are noninvasive techniques that offers image contrast and tissue characterization. Today, they are accepted methods to quantify extent and severity of structural changes and in few cases to monitor response of therapies. CMR imaging has been used extensively to assess these parameters in clinical studies on large myocardial infarct and there has also been a few clinical studies describing these parameters following microembolization [28,30,55,56,68-71]. Cine MR imaging showed regional dysfunction in the embolized subregion compared to remote myocardium. These regional

changes led to increase in LV volumes and decease in ejection fraction and cardiac output in the acute [72], but not chronic phase [59].

The advantages of CMR imaging are its potential to provide near simultaneous information on cardiac anatomy, function, perfusion and viability. CMR imaging has proven to be an extremely sensitive method for detecting microinfarction (as low as 2 g) [68,73,74]. This technology 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 CMR imaging after PCI; 2) the lack of administration of nephrotoxic iodinated contrast media; 3) CMR imaging 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) CMR imaging has the potential to measure 3D strain at rest and dobutamine stress; and 7) acquisition of images in any plane negates the need for post imaging reconstruction of images. Recent clinical studies showed a link between MR visualization of microinfarction and impaired myocardial perfusion [68,75]. Selvanayagam et al examined myocardial perfusion and necrosis serially after percutaneous coronary intervention with a validated, quantitative MR technique [30] and found that myocardial perfusion is reduced in segments with irreversible injury after PCI. CMR applications have been hampered by several technical issues, namely motion, magnetic field inhomogeneity, magnetization transfer saturation and sequence parameters.

More recently MDCT has been introduced to quantify viability and perfusion in large myocardial infarction [76-80] as well as acute and chronic microinfarction [59,72]. Viability MDCT imaging demonstrated the heterogeneous pattern of microinfarction, which is totally different from wave-front homogeneous large infarct, described by Jennings *et al.* [81]. Cine MDCT imaging demonstrates the decline in ejection fraction and increase in volumes as well as the perfusion deficit after bolus contrast injuction in micrembolized hearts [59,72].

The potential advantages of using MDCT include: 1) MDCT angiography is the method of choice for direct visualization of the coronary arteries, coronary calcium and atherosclerosis in its earliest stages; 2) the presence of LV assist devices do not preclude the performance of MDCT imaging; 3) the relatively fast acquisition time (7–10min) compared with cardiac MRI (45min), leads to cost and time savings; 4) scanning of claustrophobic or uncooperative patients; 5) less technical and personnel requirements for MDCT studies; 6) life-support and physiologic-monitoring equipments can be placed close to CT scanner and 7) CT contrast media provide linear relationship between attenuation and concentration on first pass perfusion MDCT [82]. In current practice, however, some of the inherent challenges for using MDCT imaging in ischemic heart disease include: i) exposure to radiation precludes serial assessment; ii) limited to stress-test (contractile reserve); iii) poor detection of edema in acute phase; and iv) extensive image post processing. It should be noted that other technologies, such as PET and SPECT imaging have low spatial resolution; therefore they are limited in visualizing microinfarction.

3. Consequences of Microembolization

Experimental studies have shown greater LV dysfunction in the microembolized territory than would be expected from the final extent of microinfarction [33,56]. The most likely explanation for the severe contractile dysfunction is rather the inflammatory reaction to microembolization and microinfarction. Heusch and co-workers have shown that the reasons for the contractile dysfunction are the release of tumour necrosis factor (TNF) α [83] and a myofibrillar oxidation [84]. Accordingly, investigators used non-specific anti-inflammatory glucocorticoid methylprednisolone [51], specific TNF-α antibodies [33], and the non-specific anti-oxidants ascorbic acid [84] for preventing the deleterious effects of coronary microembolization on LV dysfunction. These therapies showed some beneficial effects. Another study showed that TNF-α has an active role in protecting the myocardium from the formation of microinfarction after microembolization [83] and blocking TNF-α cause an increase in the extent of microinfarction [85]. Microinfarction, caused by the large volume of dislodged microemboli, can be detected at 24 hours by the release of biochemical markers of myocardial injury; such as creatine kinase and troponin [17,86].

Clinical studies also identified coronary microemboli as a potential cause of left ventricular dysfunction in the absence of an atherosclerotic obstruction of an epicardial coronary artery [29,34]. Data confirmed that microinfarction activates arrhythmogenesis [34] and causes sudden death in patients [54]. Selvanayagam *et al* [87] found in 152 patients that even small amounts of procedure-related myocardial injury are associated with poor clinical outcome. Investigators found that 2-5% of LV microinfarction causes disproportional LV dysfunction [88]. Based on the results found in experimental animals [59,72], we documented that the mortality rate is dependent on the volume of microemboli. A volume of 16 mm^3 of 40-120 μm microemboli caused no death in the first 72 hours after microembolization, whereas a volume

of 66 mm^3 of the same sizes of microemboli caused 25% mortality within the first 24 hours.

Microemboli may be one of the causes of mismatch between blood flow in the epicardial coronary arteries and LV function; a phenomenon which has been clinically observed after PCI [89,90]. The incidence of microembolization from coronary plaques vary from 30% [32], 54% [54] to 81% [44]. The highest incidence was seen in patients who had recent PCI or thrombolysis [44]. In patients who underwent PCI, Selvanayagam *et al.* found a new area of infarct in 28% of patients after the procedure on contrast enhanced CMR imaging [69]. However, in half of the patients the new infarct after coronary intervention was interpreted to be caused by occluded side-branches, resulting in a 12% incidence of microinfarction possibly caused by microembolization [28].

The occurrence of plaque rupture with subsequent microemboli of atherosclerotic and thrombolytic debris into small coronary vessels has been confirmed [32,91] and that emboli sizes differ widely [92,93]. The direct and indirect clinical evidence for microemboli during PCI comes from distal protection devices [94-96] and elevation of creatine-kinase [97], respectively. The elevation of cardiac injury enzymes occurs in 10-40% of patients after PCI [34,46,68,98]. A follow-up study [53] 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 creatine-kinase levels were elevated > 2 times the upper normal range compared with patients whose creatine-kinase were not elevated. Such observations have been confirmed by subsequent studies [27,48,49,53].

Recent clinical studies showed the perfusion deficit in embolized myocardium [55,59] and increase in epicardial coronary flow [53]. The increase in epicardial flow at rest has been linked to release of adenosine from myocardium not affected by the microemboli [27,99]. However, at stress a decreased coronary reserve is seen because the microvascular obstruction in the microembolized territory. The perfusion deficit in the microembolized territory is ameliorated with time and at one week the decrease has partially recovered [55,59].

Other investigators suggested that distal coronary microemboli might be one of the causes to inadequate flow in the epicardial vessels despite apparently successful revascularization in patients treated with PCI for ST-elevation myocardial infarctions [100]. CMR imaging, using first-pass perfusion, high-resolution viability and cine, could provide further insights to the pathophysiology behind this pathology [101].

Our recent studies (unpublished data) demonstrated that microinfarction is surrounded by edematous peri-infarction zone (viable and nonviable), which might be the cause of arrhythmia [102]. The arrhythmogenic effects of the peri-infarction zone have been confirmed in recent clinical studies [103-105]. The proposed pathophysiological explanation is that the tissue heterogeneity with re-entrant ventricular tachycardia is promoted in patchy infarcts with interwoven bundles of myocytes [103,106].

4. Cardiac Protection

Catheter-based coronary intervention has been introduced as an alternative to conventional surgery for patients with high risk due to comorbidities and age. Catheter-based coronary intervention is performed while the heart is beating and coronary flow is not interrupted. Coronary plaques and debris are disrupted during the passage of the guide wire, positioning of the balloon and stent implantations. When oversized stent or higher pressures are used, strain on the plaque would increase, resulting in microemboli being sloughed into the lumen of the artery through stent struts, thereby increasing the risk for distal microinfarction. Based on the histological analysis of retrieved debris, the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial, showed visible debris in 78% of patients [107]. Thus, the use of distal protection devices in capturing emboli seems to be very attractive.

Several protection devices have been proposed to prevent distal emboli, including proximal or distal protection devices and thrombectomy catheters [94,108,109]. Distal protection devices are non-occlusive devices that are positioned distal to the target lesion to filter emboli sloughed into the lumen of the artery during PCI. The results of randomized trials on adjunctive mechanical devices to prevent distal emboli, however, are conflicting. Initial results in a non-randomized trial have been promising [96]. Distal protection devices, such as the FilterWire EZ System, have been shown to reduce the incidence of microinfarction and adverse cardiac events in patients undergoing saphenous vein graft interventions [110]. Patel et al. revealed that distal protection devices reduce microcirculation damage and improve LV function in patients [110]. In a recent study, it was found that thrombus aspiration during PCI reduces the number of distal coronary microemboli and hence cellular damage [111]. Others suggested that the impact of these devices on myocardial perfusion and clinical outcome in patients remains limited [112]. There have been considerable advances in developing devices and therapies for minimizing the effects of microemboli during coronary inter-

vention and improving microvascular function [43,46,95, 113,114].

Other therapeutic approaches include the use of glycoprotein IIb/IIIa inhibitors. Previous studies have provided evidence of the beneficial effect of glycoprotein IIb/IIIa receptor inhibitors on the microvasculature [115,116]. The glycoprotein IIb/IIIa inhibitor, tirofiban, is a synthetic, non-peptide inhibitor acting at glycoprotein (GP) IIb/IIIa receptors in platelets. Specific platelet glycoprotein IIb/IIIa receptor inhibitors with powerful antiplatelet aggregation properties have been found to attenuate no-reflow [116,117]. The exact cause of this beneficial effect is, however, unclear. Yang et al found that tirofiban is very effective in improving perfusion of infarcted myocardium [118]. These findings support the concept that endothelial protection, apart from platelet inhibition, contributes to the efficacy of tirofiban on cardiac perfusion.

In conclusion, early detection, characterization and treatment of microinfarction reduce morbidity and mortality. The ability to non-invesively monitor the effects of distal coronary microemboli could have profound implications on patient management after coronary intervention or in other diseases associated with distal coronary microembolization. Non-invesive imaging may be useful in assessing the effectiveness of new devices and therapies designed to capture microemboli and reduce the microinfarction effects on left ventricular function, perfusion and viability, respectively.

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