Microvascular dysfunction in infiltrative cardiomyopathies

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Infiltrative heart diseases are characterized by myocardial tissue alterations leading to mechanical dysfunction which in turn develops into bi-ventricular congestive heart failure. Also the coronary microvasculature undergoes significant remodeling and dysfunction. The effects of the unbalance of the mechanical cross-talk between cardiac muscle and vessels and of the impairment of vasodilatory function can be measured non-invasively by means of positron emission tomography and cardiac magnetic resonance. (J Nucl Cardiol 2019;26:200–7.)

Key Words: Coronary artery disease • vasodilator stress • cardiomyopathy • coronary blood flow

INTRODUCTION

A number of patients affected by infiltrative heart diseases not only have myocardial tissue alterations which lead to mechanical dysfunction developing into bi-ventricular congestive heart failure[1] but show also a significant coronary microvascular remodeling[2,3] and dysfunction (CMD). Amyloidosis and Anderson-Fabry disease are the two conditions most frequently associated with CMD; while at present, there is very limited evidence of microvascular involvement in the inflammatory infiltration of sarcoidosis.

FUNCTIONAL ANATOMY OF THE CORONARY CIRCULATION

Large epicardial coronary arteries are mainly conductance vessels surrounded by adipose tissue; their wall is made of three layers (adventitia, media, and intima) and diameter ranges from approximately 500 μm to 2 to 5 mm.[4] Epicardial coronaries are capacitance vessels that accumulate elastic energy during systole, which is converted into kinetic energy at the beginning of diastole. This mechanism enhances the reopening of intramyocardial thin walled vessels that are squeezed closed by systolic contraction. Smaller <500 μm intramural coronary arteries are resistance vessels that regulate myocardial perfusion and compose the microcirculation. Small arteries have diameters ranging from approximately 100 to 500 μm, account for 20% microcirculatory resistance:[5] their specific function is to maintain pressure at the origin of arterioles within a narrow range to buffer sudden changes in perfusion pressure or flow. Proximal small arteries (500 to 150 μm) are more responsive to changes in flow, while the smaller and distal arterioles (150 to 100 μm) are more responsive to changes in pressure. Arterioles with diameter less than 100 μm are the most distal compartment and account for 40% of microcirculatory resistance: they are the site of metabolic regulation, as their tone is influenced by metabolites produced by surrounding cardiac myocytes.[6–8] All the components of microcirculation collectively regulate myocardial perfusion by a balance of mechanisms including: extravascular compressive forces, diastolic interval duration, coronary perfusion pressure, local metabolic factors, endothelial function, neuro-humoral factors, arterial oxygen tension, and content.

Anginal pain[9] and CMD[8,10] are present in various cardiomyopathies with different structural and functional mechanisms. CMD is an important element of disease progression and outcome (Tables 1, 2).[11,12]

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Microvascular function can only be assessed indirectly through invasive measurements of coronary flow velocity[13,14] or non-invasive myocardial blood flow (MBF) and coronary flow reserve (CFR).[4] CMD is diagnosed through the measurement of the impairment of the increase of MBF in response to vasoactive stimuli. Positron emission tomography (PET) is at present the most accurate technique clinically available to measure myocardial perfusion.[4,15] Nowadays, cardiovascular magnetic resonance (CMR) can be used for research purposes to measure absolute myocardial perfusion.[16,17] A reduced CFR is a marker of CMD only in the absence of obstructive stenoses of the epicardial arteries, which have to be ruled out when studying patients with suspected infiltrative diseases.

AMYLOIDOSIS AND MICROVASCULAR DYSFUNCTION

Cardiac amyloidosis is characterized by the extracellular deposition of insoluble fibrils composed of misfolded proteins. This broad term describes a family of both inherited and acquired forms of the disease. There are more than 30 recognized human proteins that can deposit as amyloid and amyloidosis is classified by the protein precursor.[18] The four major subtypes of amyloidosis are summarized in Table 3.

AL (or primary) and ATTR types are the most common forms of cardiac amyloidosis, representing together the 98% of all cases.[2,3] Amyloid may deposit within any component of the heart: myocardium, vessels, valves, endocardium and epicardium, and parietal pericardium. Vascular involvement is more often observed in the AL-type in parallel with a marked interstitial deposition of circulating free light chains.[19] Amyloid fibrils either surround individual myocytes or accumulate in clumps (nodular pattern more common in ATTR); this patchy deposition involves especially the subendocardial and midwall regions (Figure 1). Amyloid modulates interstitial matrix composition and tissue remodeling by disabling the balance of matrix metalloproteinases and their inhibitors.[20] Over time, a number of myocytes may become atrophic[21,22] and replacement fibrosis ensues.[2] By means of CMR Fontana et al. reported that ATTR amyloid deposits were larger than AL amyloid deposits and were associated with a significant increase in cell volume. By contrast, myocytes were of normal size in patients with AL.[22] In agreement with metabolic studies in isolated myocytes[23] the authors suggest that AL amyloid fibrils may be cardiotoxic and the increase in ventricular wall thickness could be ascribed mainly to replacement of dead myocytes and expansion of extracellular volume.[16] These changes of the left ventricular (LV) wall architecture decrease LV compliance and

Table 1. Classification of coronary microvascular dysfunction

Type	Clinical setting	General aspects
Type 1: in the absence of myocardial diseases and obstructive CAD	CV risk factors Microvascular angina	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states). It is at least partly reversible
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy Dilated cardiomyopathy Anderson-Fabry disease Amyloidosis Myocarditis Aortic stenosis	This type is found in primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular). It is sustained in most instances by adverse remodeling of intramural coronary arterioles. It can be severe enough to cause myocardial ischemia and yields an independent prognostic value. It remains unclear whether medical treatment may reverse some cases
Type 3: in obstructive CAD	Stable angina Acute coronary syndrome	This type may occur in the context of either stable CAD or acute coronary syndromes and can be sustained by numerous factors. It is more difficult to identify than the first two types
Type 4: iatrogenic	PCI Coronary artery grafting	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction and/or distal embolization

CAD, coronary artery disease; *CV*, cardiovascular; *PCI*, percutaneous coronary intervention
Modified from References[11] and [12]

Table 2. Mechanisms of coronary microvascular dysfunction

Alterations	Pathologic conditions
Structural	
Luminal obstruction	Microembolization in acute coronary syndromes or after recanalization, *amyloidosis*
Vascular wall infiltration	*Amyloidosis*, *Anderson-Fabry disease*
Vascular remodeling	Hypertrophic cardiomyopathy, arterial hypertension
Vascular rarefaction	Aortic stenosis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	CV risk factors, *amyloidosis*
Dysfunction of smooth muscle cell	Hypertrophic cardiomyopathy, arterial hypertension, microvascular angina
Autonomic dysfunction	Coronary recanalization, *amyloidosis*
Extravascular	
Extravascular compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension, *amyloidosis*
Reduction in diastolic perfusion time	Aortic stenosis

CV, cardiovascular
Modified from Reference[11]

systolic/diastolic function thus resulting in increased LV filling pressure and extravascular compressive forces.[24] The wall of the epicardial arteries, mainly the adventitia, can be infiltrated although significant luminal obstruction rarely occurs.[25] On the other hand, in AL-type intramural microvasculature is altered in up to 90% of patients (less frequently so in senile amyloidosis).[19,26] Amyloid deposition first occurs in the tunica media progressing towards the adventitia and the intima until total obstruction occurs[3,27] (Figure 2). Severe microvascular obstruction may lead to focal ischemia, microinfarctions, and replacement fibrosis aggravating LV dysfunction.[24,26] Both cardiomyocytes and endothelial cells show increased oxidative stress.[28] In atrial coronary arterioles, a brief exposure to light-chain proteins causes microvascular toxicity increasing superoxide and peroxynitrite levels which blunt endothelial mediated vasodilation.[29] Altogether, pathogenetic mechanisms of CMD in amyloidosis include structural changes of intramyocardial arteries (infiltration, thickening of the vascular wall with impingement on the vessel lumen causing obstruction,[3,27] functional abnormalities (imbalance of autonomic regulation[30,31] and endothelial dysfunction)[29] and extravascular factors (perivascular and interstitial amyloid deposits resulting in increased LV mass and extramural compression,[2] decreased LV compliance, increased diastolic LV filling pressure[8] (Figure 3).

In the past decades, a few studies have indirectly investigated CMD in a limited number of patients with biopsy-proven AL-type amyloidosis complaining of chest pain. Stress-induced wall motion abnormalities have been shown despite the absence of obstructive epicardial coronary artery disease (CAD) with contrast echocardiography.[23] The reduction of coronary velocity flow reserve, measured by means of intracoronary Doppler wire, has been reported by Al Suwaidi et al.[32]

PET tracers have been developed for the detection of amyloid deposits in the heart,[33,34] and only recently few studies have measured myocardial perfusion. Dorbala and Colleagues[10] using $^{13}NH_3$ quantified MBF, CFR, and minimal coronary vascular resistance in a cohort of symptomatic patients with amyloidosis and without epicardial CAD compared with matched hypertensive subjects with LV hypertrophy. The amyloid group showed significantly reduced MBF both at rest and during hyperemia with a lower CFR, paralleled by an increase of minimal coronary resistance irrespective of the LV mass or amyloidosis subtype. It is conceivable that the reduction of resting MBF can be the result of highly heterogeneous tissue composition determining different flow rates in each tissue compartment, i.e., higher in normal tissue and lower in scar tissue. The tracer uptake in a given myocardial region reflects the average uptake and hence average flow in this mixture of normal and infiltrated/fibrotic tissue.[35]

CMR combines tissue characterization and semi-quantitative assessment of perfusion: presence of late gadolinium enhancement and increased T1 relaxation time represent interstitial space expansion due to amyloid infiltration[36]. Li and co-workers[22] using 3 T CMR

Table 3. Four major amyloidosis subtypes

Amyloid type	Precursor protein	Distribution	Etiology	Associated disease
AL	Immunoglobulin light chain	Systemic and localized	Acquired	Plasma cell dyscrasia
ATTR	Transthyretin (TTR)	Systemic	Acquired (senile) and hereditary	Mutation of TTR or accumulation of wild type (senile)
AA	Serum amyloid A	Systemic	Acquired	Chronic inflammation
Aβ2M	β2-microglobulin	Systemic	Acquired and hereditary	Chronic hemodialysis

in AL-cardiac amyloidosis patients recently reported a decrease in the first-pass parameters perfusion slope and Max Signal Intensity compared to normal controls. Moreover, regional impairment of perfusion was proportional to impairment of LV systolic function.[37]

The coexistence of chronic renal failure may limit the use of gadolinium containing CMR contrast agents.

ANDERSON-FABRY DISEASE AND MICROVASCULAR DYSFUNCTION

Anderson-Fabry disease is caused by an X-linked inherited deficiency of lysosomal α-galactosidase A. The glycosphingolipid deposition determines multiorgan damage with renal, cardiac and cerebrovascular involvement.[38] Cardiac symptoms including palpitations, angina and dyspnoea are reported in approximately 40-60% of patients with Fabry disease. Globotriaosylceramide deposits are present in myocytes, conduction tissue, vascular endothelium, smooth muscle cells and valve tissue.[39] The myocardium shows a series of secondary changes, above all myocyte hypertrophy, and the resultant hypertrophic phenotype is a ''phenocopy'' of hypertrophic cardiomyopathy.[40] Progressive myocardial scarring and deterioration of LV function occurs in a significant proportion of patients.[41] The compound of myocyte hypertrophy, replacement fibrosis, hypertrophy,[42] and proliferation of smooth muscle and endothelial cells narrowing intramural arteries[43] all contribute to raise coronary vascular resistance and increase myocardial oxygen demand. PET studies with $[^{15}O]H_2O$[44,45] have shown a significant reduction of hyperemic MBF and CFR and an increase in minimal coronary resistance [44] in Fabry patients compared with healthy controls. Tomberli et al.[46] investigated the role of gender and LV hypertrophy with $^{13}NH_3$ and found a marked impairment of microvascular function, i.e., a 60% reduction in hyperemic MBF, irrespective of Fabry cardiomyopathy and LV hypertrophy. Albeit the phenotype is almost exclusively present in males these investigators found that females without LV hypertrophy had a significant degree of CMD, which could be the only sign of the disease.

SARCOIDOSIS AND MICROVASCULAR DYSFUNCTION

The most common site of infiltration of sarcoid granulomas in the myocardium is the LV free wall followed by the septum, right ventricle, and atria. The granulomatous inflammation damages the myocytes and patchy replacement fibrosis appears as soon as the myocyte integrity is affected whilst coronary arteries rarely show structural changes.[47] In a relatively large

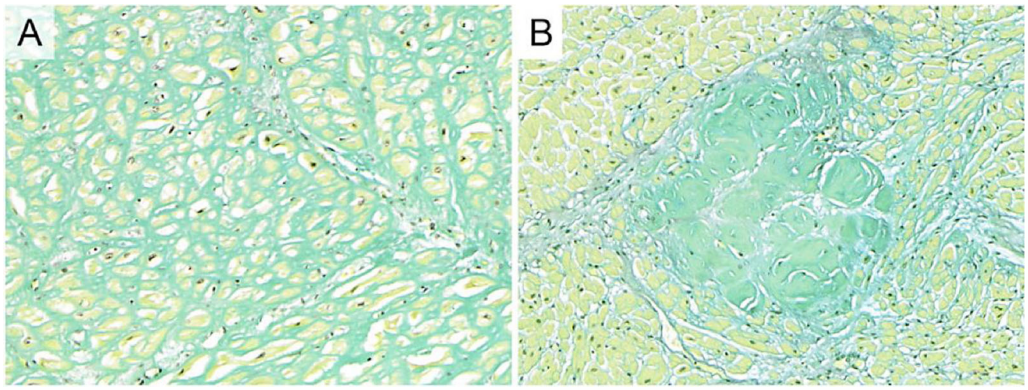

Figure 1. Histopathologic deposition patterns of cardiac amyloidosis. (**A**) Pericellular interstitial deposition amyloid fibrils surround individual myocytes; (**B**) Nodular interstitial deposition more common in ATTR-type amyloid (sulfated alcian blue stains, with original magnification ×200). From Reference[2] with permission.

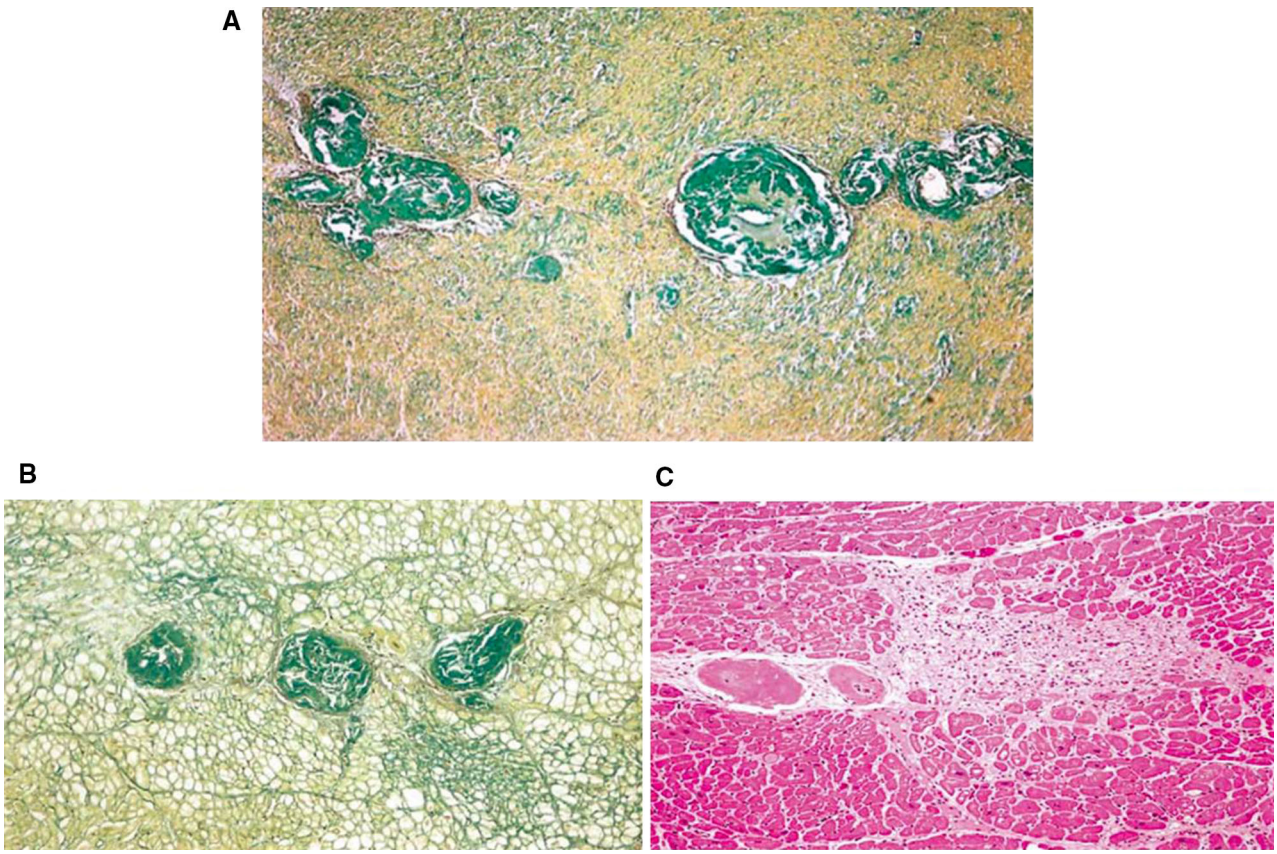

Figure 2. Pathologic features of obstructive amyloidosis in intramural coronary arterioles and myocardial tissue. (**A**) Severe obstruction in several vessels (sulfated alcian blue stain; magnification ×40). (**B**) Chronic myocardial ischemia (vacuolated myocytes) associated with adjacent multifocal amyloidosis (sulfated alcian blue stain; magnification ×100). (**C**) Chronic myocardial ischemia (*arrow*, healed microinfarct) associated with obstructed arterioles (*dotted arrow*) (hematoxylin-eosin stain; original magnification ×100). From Reference[27] with permission.

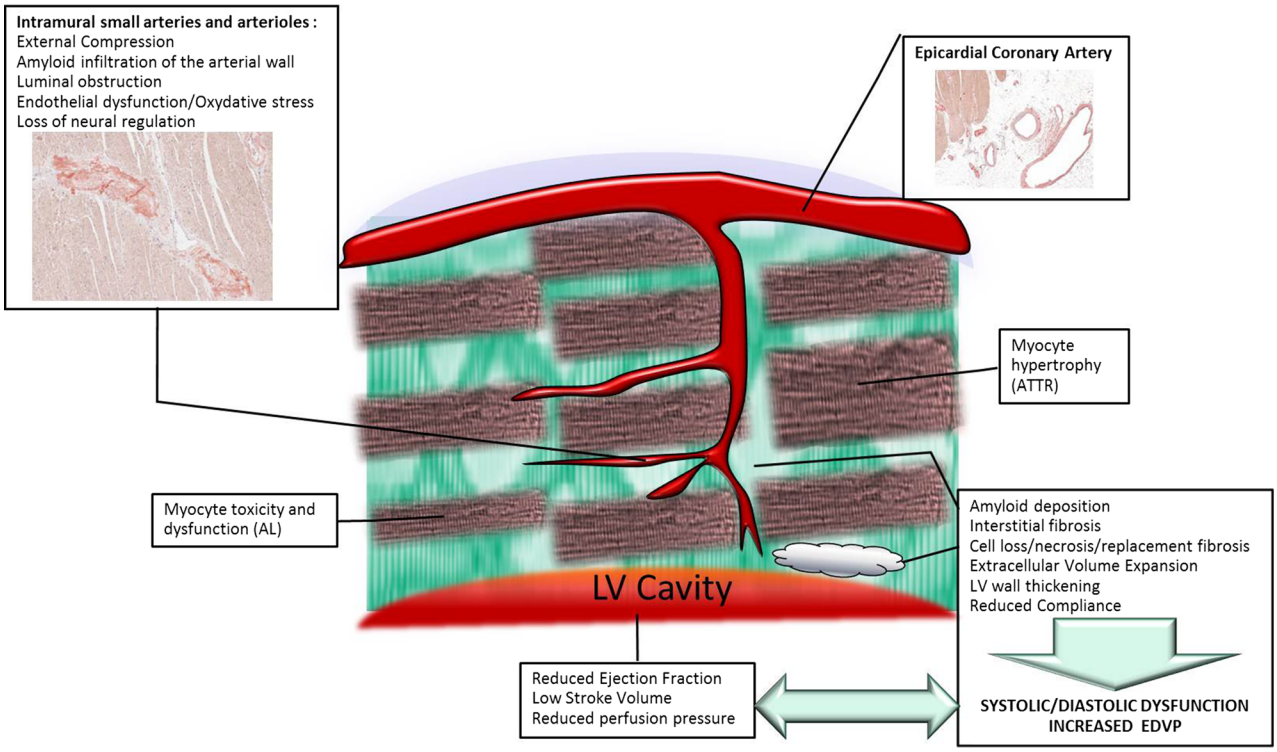

Figure 3. Mechanisms of microvascular dysfunction in amyloidosis. Amyloid deposits induce oxidative stress affecting myocytes and their contractile function. Low stroke volume, stiffened LV wall, external compressive forces, and high end-diastolic ventricular pressure (EDVP) impair diastolic filling of coronary vessels. Epicardial vessels are usually spared. Amyloid infiltration of the intramural vasculature progresses form the tunica media to the adventitia and the intima leading to microvascular obstruction. In AL, amyloidosis light-chain proteins increase oxidative stress and induce endothelial dysfunction and apoptotic injury of endothelial cells. Subendocardial foci of ischemia, microinfarctions, and replacement fibrosis, further contribute to myocardial dysfunction and, in case of involvement of the conduction system, cardiac electrical disorders. Inserts from Yagishita A, et al. Circ J 73,1349-1351 (2009) with permission.

cohort of patients with sarcoidosis, Blankstein and co-workers have reported that patients who had abnormalities (visually assessed) in both myocardial perfusion with ^{82}Rb and metabolism with ^{18}F-FDG had a fourfold increase in the annual rate of cardiac death and sustained ventricular arrhythmias.[48]

Systemic inflammation is known to impair microvascular function[49–51] and there is increasing awareness of the involvement of the coronary microcirculation in sarcoidosis. A recent study by Kruse at al using $^{13}NH_3$ PET analyzed myocardial perfusion and flow reserve before and after immune-suppressive therapy in a retrospective cohort of patients.[52] Resting MBF was unaffected by the presence of abnormal ^{18}F-FDG uptake, while hyperemic MBF and CFR were significantly lower in areas of abnormal ^{18}F-FDG uptake paralleled by higher coronary resistance. In a more advanced stage of the disease, with both perfusion and ^{18}F-FDG uptake abnormalities, the loss of vasodilatory capacity was extended also to regions with normal ^{18}F-FDG uptake, suggesting a diffuse impairment of microvascular function which could precede the myocardial tissue structural alterations. After a follow-up of 2.5 years, positive response to immune-suppressive therapy preserved microvascular function whereas non-responders showed a further impairment of CFR.[52]

Hybrid CMR tissue characterization and ^{18}F-FDG in combination can characterize different stages of the disease (necrosis, fibrosis, and active inflammation).[53] If a perfusion defect detected with SPECT or visually at PET can be attributed to replace fibrosis, these recent studies quantifying MBF and CFR point at a functional CMD in sarcoidosis attributable to the negative effects of inflammatory cytokines, TNF-α, and oxidative species in endothelium-mediated CMD.[8] CMD is just a facet of this protean disease; nevertheless, the

impairment of vasodilatory capacity can be a warning of the lethal progression of the cardiac involvement and seems to purport a prognostic value.[52]

CONCLUSIONS

CMD is an important contributor in the pathophysiology of infiltrative cardiomyopathies, in particular in amyloidosis and Anderson-Fabry disease. In the past few years, imaging techniques gained a central role in the quantitative assessment of microvascular dysfunction in patients suffering from these conditions. These new findings lend further support to both the clinical and prognostic importance of CMD.

Disclosure

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter discussed in this manuscript.

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