Published in final edited form as:

Heart Fail Rev. 2017 July ; 22(4): 455–464. doi:10.1007/s10741-017-9628-1.

Role of PET to Evaluate Coronary Microvascular Dysfunction in Non-ischemic Cardiomyopathies

Paco E. Bravo, MD, Marcelo F. Di Carli, MD, and Sharmila Dorbala, MD, MPH

Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, the Noninvasive Cardiovascular Imaging Program, Departments of Medicine (Cardiology) and Radiology, Cardiac Amyloidosis Program, Department of Medicine, Brigham and Women's Hospital, Boston, MA

Abstract

Coronary microvascular dysfunction (CMD) can result from structural and functional abnormalities at the intramural and small coronary vessel level affecting coronary blood flow autoregulation, and consequently leading to impaired coronary flow reserve. CMD often co-exists with epicardial coronary artery disease, but is also commonly seen in patients with various forms of heart disease, including dilated, hypertrophic and infiltrative cardiomyopathies. CMD can go unnoticed without any symptoms, or manifest as angina, and/or dyspnea, and contribute to the development of heart failure, and even sudden death especially when co-existing with myocardial fibrosis. However, whether CMD in non-ischemic cardiomyopathy is a cause or an effect of the underlying cardiomyopathic process, or whether it can be potentially modifiable with specific therapies, remains incompletely understood.

Keywords

coronary microvascular dysfunction; non-ischemic cardiomyopathy; coronary flow reserve; cardiac PET

Introduction

Increased availability of positron emission tomography (PET) scanners, PET perfusion tracers, and advanced software tools have fueled an exponential growth in cardiac PET. Extensive literature supports the powerful role of perfusion defects and left ventricular ejection fraction (LVEF) on PET myocardial perfusion imaging (MPI) to accurately diagnose obstructive coronary artery disease (CAD) and to stratify risk. Peak hyperemic myocardial blood flow (MBF) and coronary flow reserve (CFR, stress/rest MBF) quantified by PET provide insights into coronary microvascular function. Coronary microvascular

Correspondence to: Sharmila Dorbala, MD, MPH, Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Cardiovascular Division, Department of Medicine, Heart & Vascular Center, Brigham and Women's Hospital, 70 Francis Street, Shapiro 5th Floor, Room 128, Boston, MA 02115, Tel: 617-732-6290, sdorbala@partners.org.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest

Paco E. Bravo declares that he has no conflict of interest.

Marcelo Di Carli declares that he has no conflict of interest.

dysfunction (CMD) is an integral feature of ischemic and several of the non-ischemic cardiomyopathies. In this paper, we critically review the literature on the utility of cardiac PET in the evaluation of CMD in individuals with non-ischemic cardiomyopathy.

Role of PET in the Evaluation of CMD

The coronary microvasculature, the small vessels that perfuse the myocardium, are comprised of the coronary prearterioles ($<500\ \mu\text{m}$) and arterioles ($<100\ \mu\text{m}$). These microvessels are dynamic and metabolically responsive with alterations in vascular tone matching myocardial oxygen needs.[1] Release of H_2O_2 through diseased coronary arteries has been implicated in a proinflammatory environment potentiating myocardial fibrosis and hypertrophy (Figure 1), which may be pathophysiologically relevant in non-ischemic cardiomyopathies[1].

Dysfunction of the coronary microvasculature can result from a variety of structural or functional alterations with downstream effects, and, irrespective of underlying etiology, will impair hyperemic MBF. Imaging of microvascular structural alterations is currently challenging, due to the limits of spatial resolution of the imaging techniques. However, hyperemic MBF can be accurately imaged using invasive or noninvasive techniques, and has emerged as one of the robust metrics for CMD. Noninvasively measured MBF at rest, during maximal hyperemia, and coronary vasodilatory capacity estimated by CFR (ratio of peak hyperemic MBF to rest MBF) are increasingly being used in clinical practice. Presently, MBF can be quantified noninvasively using radionuclide imaging, cardiac magnetic resonance (CMR), or contrast echocardiography, but, PET is the mostly commonly used and validated technique. With most modern PET scanners, MBF can be obtained during routine PET MPI acquisition with O-15 water, N-13 ammonia, or Rubidium-82. MBF by each of these tracers has been well validated by microsphere studies in animals and found to be highly reproducible. Several easy to use software programs are commercially available to quantify MBF and CFR. MBF and CFR quantified by PET is, thus, the technique with the greatest wealth of evidence and the most widely used method for evaluation of CMD.

CMD in Non-ischemic Cardiomyopathies

Coronary microvascular dysfunction can coexist with several cardiovascular diseases. Camici and colleagues have classified CMD into four types depending on the presence or absence of epicardial CAD and myocardial diseases: Type 1, no myocardial disease or CAD, Type 2, myocardial disease without CAD, Type 3, CAD and type 4, iatrogenic[2, 3]. In this review, we focus on Type 2 CMD—myocardial disease without CAD i.e., non-ischemic cardiomyopathy associated with dilated cardiomyopathy, hypertrophic cardiomyopathy and infiltrative cardiomyopathy (Fabry's disease or amyloidosis). CMD is frequent in individuals with non-ischemic cardiomyopathy (Table 1). It may cause minimal symptoms in some patients or manifest as chest pain, dyspnea and/or ischemic electrocardiographic changes in the absence of obstructive epicardial CAD. Whether CMD in non-ischemic cardiomyopathy is a cause or an effect of the underlying cardiomyopathic process is not known; but, CMD has been associated with worsening systolic and diastolic function, worsening heart failure,

sudden death, and poor clinical outcomes. Importantly, CMD is potentially modifiable with some of the heart failure therapies.

Dilated Cardiomyopathy

Dilated cardiomyopathy is myocardial dysfunction in the absence of CAD. CMD in dilated cardiomyopathy portends worse prognosis (Table 1). Dilated myocardial phenotype and a multitude of myocardial histological changes may be responsible for CMD in dilated cardiomyopathy. The volume fraction of myofibrils is reduced[4] and myocardial fibrosis is increased[4], when compared to ischemic cardiomyopathy[5], or control hearts[6]. Myocardial capillary density is decreased significantly[5, 6], but without prominent changes in the arterioles.

Peak vasodilator hyperemic MBF and CFR are reduced in individuals with dilated cardiomyopathy (Table 1, Figure 2) even prior to onset of symptomatic heart failure (1.91 ± 0.76 ml/gm/min) when compared to healthy subjects (3.78 ± 0.86 ml/gm/min)[7]. CMD is partly mediated by high resting sympathetic tone, with reduced coronary vascular resistance at rest and blunted flow response to cold stress[8]. Regional flow heterogeneity with relatively reduced perfusion to the septum in relation to the lateral wall, as well as regional metabolic and contraction changes, are observed in individuals with LBBB[9, 10]; but, these changes appear to be independent of perfusion or CMD[11].

Neglia et al.[7] showed that reduced peak hyperemic MBF of < 1.36 ml/gm/min is an independent predictor of death (relative risk 3.5), and development or progression of heart failure in individuals with dilated cardiomyopathy. Similarly, Majmudar et al.[12] showed that a composite event of cardiac death, heart failure hospitalization, aborted sudden death or late revascularization was two-fold higher in individuals with non-ischemic cardiomyopathy and CFR < 1.65 compared to CFR > 1.65 .

Investigators have evaluated the modifiability of CMD in dilated cardiomyopathy using a variety of heart failure therapies. Angiotensin converting enzyme inhibitors, widely used in the management of heart failure, appear to improve CMD via a NO and a bradykinin mediated mechanism in an animal model of tachycardia-mediated cardiomyopathy[13]. Similarly, in a prospective randomized placebo controlled study of 16 subjects, peak hyperemic MBF improved 6 months after carvedilol therapy (1.67 ± 0.63 to 2.58 ± 1.04 , $p < 0.001$) compared to placebo (1.80 ± 0.84 to 1.77 ± 0.60 , NS)[14]. Cardiac resynchronization therapy is also promising to improve LVEF fraction in dilated cardiomyopathy; in one study, wall stress, peak hyperemic MBF, and CFR improved along with LVEF and wall stress[15]. However, establishing a direct link between improvement in CMD from the various advanced heart failure therapies and survival benefit may be difficult to establish.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a sarcomeric disease characterized by a hypertrophic myocardial phenotype. Symptoms of chest pain, heart failure, and sudden death in HCM have been attributed to CMD. CMD with associated myocyte ischemia has been postulated

as common mechanism underlying arrhythmias and sudden death in hypertrophic cardiomyopathy[16]. Although the predominant mechanism responsible for CMD in hypertrophic cardiomyopathy is felt to be structural remodeling of the arterioles and myocardial fibrosis, other mechanism such as increased LV mass[17], capillary rarefaction[18], extrinsic compressive forces[17], compression of the septal perforator arteries, myocyte disarray, and spasm have also been implicated[18]. The intra mural vessel walls are hypertrophied due to proliferation of smooth muscles and collagen in the media (and intima) causing luminal narrowing[18, 19].

Interestingly, coronary microvascular function is not impaired in carriers of hypertrophic cardiomyopathy mutations, despite early evidence of impaired energetics[20], but is often abnormal in hypertrophic cardiomyopathy patients (Figure 3), even with mild or no symptoms. Compared to controls, peak hyperemic MBF (1.50 ± 0.69 vs. 2.71 ± 0.94 ml/min/gm, $P < 0.001$) and CFR (1.80 ± 0.70 vs. 2.70 ± 0.90 , $P < 0.001$) are substantially reduced in hypertrophic cardiomyopathy (Table 1). However, CMD is not invariably present in all patients with HCM. Previous studies have demonstrated that patients with HCM have a wide range of CFR at diagnosis; where some patients present with normal CFR (implying relatively preserved or just minimally impaired coronary microvascular function), and others with severely reduced CFR (consistent with significant CMD) [21].

The reasons for this heterogeneity of CFR in HCM are not completely understood but appear to be multifactorial. Firstly, a pre-determined or inherited component is likely to play a role. This was suggested by Olivotto et al[22], in a study where the investigators observed significantly lower peak MBF (1.7 ± 0.6 ml/min/g vs. 2.4 ± 1.2 ml/min/g; $P < 0.02$) by PET as well as higher prevalence of myocardial late gadolinium enhancement (LGE, 96 vs. 67%, $P = 0.038$) by cardiac magnetic resonance (CMR) in patients testing positive for myofilament-encoding genes compared to genotype-negative HCM patients despite similar baseline characteristics, including maximal LV wall thickness, between groups [22]. This study suggested a genetic predisposition for the development of intramural CMD in HCM.

The degree of LV hypertrophy is also an important predictor of CMD. Several authors have observed an inverse correlation between stress-MBF (and thus CFR) measured by PET or CMR and maximal LV wall thickness in HCM [17, 21, 23], myocardial mass indexed to body surface area[17], and serum NT pro BNP (a marker of increased myocardial wall stress)[17]. Ex-vivo studies have provided additional morphologic and histopathologic correlations in this respect [18, 24, 25]. Tanaka et al. observed that the percentage of luminal narrowing of intramural coronary vessels was inversely correlated with heart weight and myocyte size in the LV septum and free wall during necropsies of individuals with HCM[18]; and Krams et al. described an inverse relationship between normalized coronary arteriolar lumen and degree of LV hypertrophy in myectomy specimens of HCM patients[25]. Nevertheless, while CMD is clearly more pronounced in myocardial segments with hypertrophy[23], segments without hypertrophy also demonstrate CMD[26] implicating mechanisms beyond myocardial hypertrophy.

Arteriolar remodeling is most prominent in regions with fibrosis suggesting a possible causal role leading to fibrosis[18]; intramural arteriolar remodeling in myocardial samples from

infants support this being a developmental abnormality. In fact, impaired CFR and myocardial ischemia are also significantly more prevalent in the presence of myocardial LGE on CMR (Figure 4), a marker of myocardial fibrosis in HCM [23, 27, 28]. In the absence of LGE, patients with HCM usually exhibit normal to low-normal CFR, whereas in the presence of LGE, CFR varies widely with approximately 50% of symptomatic patients demonstrating reduced CFR (<2.0) in some series[28]. Post-mortem studies have yielded similar findings[18, 19]. Baron et al. evaluated 48 necropsies of patients with HCM and observed a significantly higher frequency of small vessel disease changes in myocardium tissue sections that exhibited moderate or severe fibrosis (74%) compared to sections with mild or no fibrosis (30%)[19]. Subendocardial perfusion is particularly impaired suggesting a role for extravascular compressive forces in addition to reduced capillary density[17, 23]. Although LV out flow tract gradient may increase myocardial wall stress and is independently associated with worse clinical outcomes[29], a gradient at rest or provoked by amyl nitrate, is not an independent predictor of peak hyperemic MBF[17, 21, 29]. In conjunction, these data highlight the close inter-relation that exists between CMD, genetic-predisposition, LV hypertrophy and fibrosis in HCM.

Finally, CMD in individuals with hypertrophic cardiomyopathy signals future risk of LV systolic dysfunction,[30] with a peak hyperemic MBF < 1.11 ml/gm/min portending a 7.5 fold risk of developing LVEF $< 50\%$, or remodeling. These individuals also carry a poor prognosis with a 20-fold increased relative risk (95% CI, 2.4 to 167.8; $P=0.003$) of poor clinical outcomes (composite end-point of death, progressive heart failure to NYHA class 3 or 4, and ventricular tachyarrhythmias necessitating ICD[29].

Fabry's disease

Anderson Fabry's disease is an X-linked lysosomal storage disease that is caused by a loss of function mutation in the GLA gene that encodes for alpha galactosidase A. It is characterized by deposition of glycosphingolipid in the heart, skin, kidneys, and nerves causing organ dysfunction and premature mortality[31]. A seminal cardiac pathology in Fabry's cardiomyopathy is globotriaosylceramide deposition in myocytes with vacuolization[32]. These deposits may activate a variety of signaling pathways leading to hypertrophy, apoptosis, necrosis and fibrosis, which increase coronary vascular resistance, myocardial oxygen demand, and cause CMD[33]. CMD has the potential to cause myocardial fibrosis in Fabry's Disease[34]. Although CMD is more severe among those with LV hypertrophy, it is also seen in women and among individuals without LV hypertrophy[33]; these authors thus, propose that in addition to capillary rarefaction, and microvascular compression, pathologies related to LV hypertrophy, endothelial dysfunction from the storage of glycosphingolipids, dysregulation of the nitric oxide pathway, and microvascular remodeling may contribute to CMD in Fabry's disease[33]. Also, on intravascular ultrasound imaging patients with Fabry's disease demonstrate diffuse hypoechoic coronary plaques with greater lipid cores compared to control individuals[35].

CMD is prevalent in Fabry's disease, with angina or chest pain reported in about 19% of men and women (not on therapy) and in 24–30% of women and men on enzyme replacement therapy[36]. Myocardial perfusion reserve was significantly lower in Fabry's

disease patients compared to control patients (dipyridamole O-15 water PET, CFR 3.3 ± 1.2 vs. 4.5 ± 3.6 , $p = 0.02$ [37]; and adenosine O-15 water PET 1.41 ± 0.39 vs. 3.03 ± 0.85 , $p < 0.0001$ [38]). But, with enzyme replacement therapy, despite significant reduction in plasma concentrations of globotriaosylceramide, CFR did not improve in one study after approximately 10 months of therapy[38], and failed to improve in another study at 6months, and 12 months post-therapy [39]. Similarly, systolic and diastolic parameters evaluated by CMR and echocardiography did not change even after 24 months of therapy[40]. These studies suggest that other mechanisms may be involved in cardiac manifestations of Fabry's disease.

Amyloidosis

Cardiac amyloidosis is part of a systemic protein misfolding disorder resulting in deposits of amyloid fibrils (misfolded proteins) in the myocardial interstitium and in the perivascular spaces. Cardiac amyloidosis can be broadly classified into light chain amyloidosis (AL, a plasma cell dyscrasia) and transthyretin amyloidosis (ATTR). ATTR amyloidosis is of two types: ATTRwt, a wild type disease of aging or ATTRmt, a familial autosomal dominant disease resulting from a mutation of the TTR gene. Cardiac involvement is common in AL disease and ubiquitous in ATTR disease and is the most likely cause of heart failure and death in these patients. Myocardial dysfunction in amyloidosis is mediated via at least two mechanisms: 1) amyloid deposits and 2) circulating light chain related toxicity in individuals with AL[41].

Angina without epicardial CAD has been well-described in individuals with amyloidosis[42]. Perivascular amyloid deposits[43], intracoronary amyloid deposits[44], interstitial amyloid deposits with increased LV mass[43], restrictive heart failure and high LV filling pressures, autonomic neuropathy, and endothelial dysfunction may account for CMD in amyloidosis[43]. Interstitial and perivascular amyloid deposits may compress coronary microvessels thereby increasing coronary microvascular resistance. Increased LV mass may reduce capillary density and decrease diastolic perfusion from high LV filling pressures. Autonomic dysfunction, a well-known manifestation of amyloidosis, may also result in vasomotor dysfunction[41].

From a symptom perspective, angina pectoris can be the first manifestation of cardiac amyloidosis. This became evident in a study of Suwaida et al[42], in which they investigated 153 patients with chest pain and angiographically normal coronary arteries and performed invasive CFR assessment using Doppler flow wires, and infusions of intracoronary adenosine and acetyl choline to test microvascular and endothelial dysfunction respectively. CFR was calculated as the ratio of hyperemic to basal average peak velocity of the distal vessel. Of the 153 patients studies, 5 individuals (CFR range, 1.6 to 2.3) were subsequently diagnosed with systemic AL amyloidosis (9–48 months later), suggesting that coronary microvascular dysfunction may precede overt cardiac amyloidosis by several months to years. In another study, brachial artery flow mediated dilation was substantially reduced in individuals with AL cardiac amyloidosis[45]. The results of these two studies are supported by ex vivo studies demonstrating that exposure to AL proteins impaired smooth muscle

relaxation in human arterioles from atrial and adipose tissue[46], and thus laid the foundation for the possibility of AL-mediated coronary microvascular dysfunction.

In a prospective study, cardiac structure on echocardiography and coronary microvascular function (rest and vasodilator stress N-13 ammonia) was prospectively evaluated in 21 individuals with cardiac amyloidosis (15 AL, 6 ATTR) without epicardial CAD[47]. Minimal coronary vascular resistance was markedly increased (111 ± 40 ml/g/min/mm Hg vs. 70 ± 19 ml/g/min/mm Hg; $P < 0.004$) and stress MBF (0.85 ± 0.29 ml/g/min vs. 1.85 ± 0.45 ml/g/min, $P < 0.0001$) and CFR (1.19 ± 0.38 vs. 2.23 ± 0.88 , $P < 0.0001$) were substantially reduced in subjects with amyloidosis compared to subjects with hypertensive LV hypertrophy. Minimal coronary vascular resistance and CFR were linearly related to parameters of diastolic dysfunction (e' , $r = 0.41$, $P = 0.002$; e' , $r = 0.49$, $P = 0.008$, respectively), and subclinical systolic dysfunction (longitudinal strain, $r = 0.48$, $P = 0.01$; $r = -0.44$, $P = 0.03$, respectively). CMD from amyloid deposits may potentially explain a greater vulnerability of these individuals to ischemia and subclinical impairment of LV systolic function. Notably, MBF and CFR improved remarkably in two individuals with active AL-CMP and hematological and clinical response at 6 months, despite no change in LV wall thickness, implying reversibility of CMD and supporting a role for light chain toxicity in CMD (Figure 5).

Conclusions

Individuals with non-ischemic cardiomyopathies manifest varying degrees of CMD, with a greater magnitude of CMD in hypertrophic heart diseases compared to dilated cardiomyopathy. CMD may be the result of the underlying cardiomyopathic process, but in turn may potentiate myocardial fibrosis and dysfunction. Myocardial ischemia from CMD may predispose some of these individuals to the occurrence of sudden cardiac death. Strategies that improve CMD may be important modifiable targets for therapy to improve outcomes in individuals with non-ischemic cardiomyopathies.

Acknowledgments

Sharmila Dorbala has received grants from the National Institutes of Health (R01 HL 130563) and the American Heart Association (16 CSA 28880004), and grants from Astellas Pharma.

Funding

This work was supported in part by a grant from the National Institutes of Health (1T32HL094301, Dr. Bravo) and (1R01HL130563, Dr. Dorbala).

References:

1. Gutterman DD, Chabowski DS, Kadlec AO, Durand MJ, Freed JK, Ait-Aissa K, et al. The Human Microcirculation: Regulation of Flow and Beyond. *Circ Res* 2016;118:157–72. [PubMed: 26837746]
2. Spoladore R, Fiscaro A, Faccini A, Camici PG. Coronary microvascular dysfunction in primary cardiomyopathies. *Heart* 2014;100:806–13. [PubMed: 23904360]
3. Camici PG, Crea F. Coronary microvascular dysfunction. *The New England journal of medicine* 2007;356:830–40. [PubMed: 17314342]

4. Schwarz F, Mall G, Zebe H, Blickle J, Derks H, Manthey J, et al. Quantitative morphologic findings of the myocardium in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;51:501–6. [PubMed: 6218745]
5. Abraham D, Hofbauer R, Schafer R, Blumer R, Paulus P, Miksovsky A, et al. Selective downregulation of VEGF-A(165), VEGF-R(1), and decreased capillary density in patients with dilative but not ischemic cardiomyopathy. *Circ Res* 2000;87:644–7. [PubMed: 11029398]
6. Mosseri M, Schaper J, Admon D, Hasin Y, Gotsman MS, Sapoznikov D, et al. Coronary capillaries in patients with congestive cardiomyopathy or angina pectoris with patent main coronary arteries. Ultrastructural morphometry of endomyocardial biopsy samples. *Circulation* 1991;84:203–10. [PubMed: 2060096]
7. Neglia D, Parodi O, Gallopin M, Sambuceti G, Giorgetti A, Pratali L, et al. Myocardial blood flow response to pacing tachycardia and to dipyridamole infusion in patients with dilated cardiomyopathy without overt heart failure. A quantitative assessment by positron emission tomography. *Circulation* 1995;92:796–804. [PubMed: 7641359]
8. Drzezga AE, Blasini R, Ziegler SI, Bengel FM, Picker W, Schwaiger M. Coronary microvascular reactivity to sympathetic stimulation in patients with idiopathic dilated cardiomyopathy. *J Nucl Med* 2000;41:837–44. [PubMed: 10809200]
9. Nowak B, Stellbrink C, Schaefer WM, Sinha AM, Breithardt OA, Kaiser HJ, et al. Comparison of regional myocardial blood flow and perfusion in dilated cardiomyopathy and left bundle branch block: role of wall thickening. *J Nucl Med* 2004;45:414–8. [PubMed: 15001681]
10. Ono S, Nohara R, Kambara H, Okuda K, Kawai C. Regional myocardial perfusion and glucose metabolism in experimental left bundle branch block. *Circulation* 1992;85:1125–31. [PubMed: 1537110]
11. Masci PG, Marinelli M, Piacenti M, Lorenzoni V, Positano V, Lombardi M, et al. Myocardial structural, perfusion, and metabolic correlates of left bundle branch block mechanical derangement in patients with dilated cardiomyopathy: a tagged cardiac magnetic resonance and positron emission tomography study. *Circ Cardiovasc Imaging* 2010;3:482–90. [PubMed: 20463209]
12. Majmudar MD, Murthy VL, Shah RV, Kolli S, Mousavi N, Foster CR, et al. Quantification of coronary flow reserve in patients with ischaemic and non-ischaemic cardiomyopathy and its association with clinical outcomes. *Eur Heart J Cardiovasc Imaging* 2015;16:900–9. [PubMed: 25719181]
13. Nikolaidis LA, Doverspike A, Huerbin R, Hentosz T, Shannon RP. Angiotensin-converting enzyme inhibitors improve coronary flow reserve in dilated cardiomyopathy by a bradykinin-mediated, nitric oxide-dependent mechanism. *Circulation* 2002;105:2785–90. [PubMed: 12057995]
14. Sugioka K, Hozumi T, Takemoto Y, Ujino K, Matsumura Y, Watanabe H, et al. Early recovery of impaired coronary flow reserve by carvedilol therapy in patients with idiopathic dilated cardiomyopathy: a serial transthoracic Doppler echocardiographic study. *J Am Coll Cardiol* 2005;45:318–9. [PubMed: 15653035]
15. Knaapen P, van Campen LM, de Cock CC, Gotte MJ, Visser CA, Lammertsma AA, et al. Effects of cardiac resynchronization therapy on myocardial perfusion reserve. *Circulation* 2004;110:646–51. [PubMed: 15302806]
16. Dilsizian V, Bonow RO, Epstein SE, Fananapazir L. Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993;22:796–804. [PubMed: 8102625]
17. Knaapen P, Germans T, Camici PG, Rimoldi OE, ten Cate FJ, ten Berg JM, et al. Determinants of coronary microvascular dysfunction in symptomatic hypertrophic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2008;294:H986–93. [PubMed: 18156203]
18. Tanaka M, Fujiwara H, Onodera T, Wu DJ, Matsuda M, Hamashima Y, et al. Quantitative analysis of narrowings of intramyocardial small arteries in normal hearts, hypertensive hearts, and hearts with hypertrophic cardiomyopathy. *Circulation* 1987;75:1130–9. [PubMed: 3552306]
19. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural (“small vessel”) coronary artery disease in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;8:545–57. [PubMed: 3745699]
20. Timmer SA, Germans T, Brouwer WP, Lubberink M, van der Velden J, Wilde AA, et al. Carriers of the hypertrophic cardiomyopathy MYBPC3 mutation are characterized by reduced myocardial

- efficiency in the absence of hypertrophy and microvascular dysfunction. *Eur J Heart Fail* 2011;13:1283–9. [PubMed: 22021246]
21. Bravo PE, Pinheiro A, Higuchi T, Rischpler C, Merrill J, Santaularia-Tomas M, et al. PET/CT assessment of symptomatic individuals with obstructive and nonobstructive hypertrophic cardiomyopathy. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2012;53:407–14.
 22. Olivotto I, Girolami F, Sciagra R, Ackerman MJ, Sotgia B, Bos JM, et al. Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofibrillar gene mutations. *J Am Coll Cardiol* 2011;58:839–48. [PubMed: 21835320]
 23. Petersen SE, Jerosch-Herold M, Hudsmith LE, Robson MD, Francis JM, Doll HA, et al. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. *Circulation* 2007;115:2418–25. [PubMed: 17452610]
 24. Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. *Heart* 2000;84:476–82. [PubMed: 11040002]
 25. Krams R, Kofflard MJ, Duncker DJ, Von Birgelen C, Carlier S, Kliffen M, et al. Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodeling of the coronary microcirculation. *Circulation* 1998;97:230–3. [PubMed: 9462521]
 26. Camici P, Chiriac G, Lorenzoni R, Bellina RC, Gistri R, Italiani G, et al. Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography. *J Am Coll Cardiol* 1991;17:879–86. [PubMed: 1999624]
 27. Sotgia B, Sciagra R, Olivotto I, Casolo G, Rega L, Betti I, et al. Spatial relationship between coronary microvascular dysfunction and delayed contrast enhancement in patients with hypertrophic cardiomyopathy. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 2008;49:1090–6.
 28. Bravo PE, Zimmerman SL, Luo HC, Pozios I, Rajaram M, Pinheiro A, et al. Relationship of delayed enhancement by magnetic resonance to myocardial perfusion by positron emission tomography in hypertrophic cardiomyopathy. *Circulation Cardiovascular imaging* 2013;6:210–7. [PubMed: 23418294]
 29. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriac G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med* 2003;349:1027–35. [PubMed: 12968086]
 30. Olivotto I, Cecchi F, Gistri R, Lorenzoni R, Chiriac G, Girolami F, et al. Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2006;47:1043–8. [PubMed: 16516091]
 31. Marian AJ. Challenges in the Diagnosis of Anderson-Fabry Disease: A Deceptively Simple and Yet Complicated Genetic Disease. *J Am Coll Cardiol* 2016;68:1051–3. [PubMed: 27585510]
 32. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. *Heart* 2007;93:528–35. [PubMed: 17401074]
 33. Tomberli B, Cecchi F, Sciagra R, Berti V, Lisi F, Torricelli F, et al. Coronary microvascular dysfunction is an early feature of cardiac involvement in patients with Anderson-Fabry disease. *Eur J Heart Fail* 2013;15:1363–73. [PubMed: 23818648]
 34. Sheppard MN. The heart in Fabry's disease. *Cardiovasc Pathol* 2011;20:8–14. [PubMed: 19919901]
 35. Kovarnik T, Mintz GS, Karetova D, Horak J, Bultas J, Skulec R, et al. Intravascular ultrasound assessment of coronary artery involvement in Fabry disease. *J Inher Metab Dis* 2008;31:753–60. [PubMed: 18998239]
 36. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, et al. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J* 2007;28:1228–35. [PubMed: 17483538]
 37. Kalliokoski RJ, Kalliokoski KK, Sundell J, Engblom E, Penttinen M, Kantola I, et al. Impaired myocardial perfusion reserve but preserved peripheral endothelial function in patients with Fabry disease. *J Inher Metab Dis* 2005;28:563–73. [PubMed: 15902560]

38. Elliott PM, Kindler H, Shah JS, Sachdev B, Rimoldi OE, Thaman R, et al. Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. *Heart* 2006;92:357–60. [PubMed: 16085718]
39. Kallikokoski RJ, Kantola I, Kallikokoski KK, Engblom E, Sundell J, Hannukainen JC, et al. The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease. *J Inherit Metab Dis* 2006;29:112–8. [PubMed: 16601877]
40. Koskenvuo JW, Hartiala JJ, Nuutila P, Kallikokoski R, Viikari JS, Engblom E, et al. Twenty-four-month alpha-galactosidase A replacement therapy in Fabry disease has only minimal effects on symptoms and cardiovascular parameters. *J Inherit Metab Dis* 2008;31:432–41. [PubMed: 18509742]
41. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. *J Am Coll Cardiol* 2016;68:1323–41. [PubMed: 27634125]
42. Al Suwaidi J, Velianou JL, Gertz MA, Cannon RO, 3rd, Higano ST, Holmes DR, Jr., et al. Systemic amyloidosis presenting with angina pectoris. *Ann Intern Med* 1999;131:838–41. [PubMed: 10610629]
43. Dorbala S, Vangala D, Bruyere J, Jr., Quarta C, Kruger J, Padera R, et al. Coronary microvascular dysfunction is related to abnormalities in myocardial structure and function in cardiac amyloidosis. *JACC Heart Fail* 2014;2:358–67. [PubMed: 25023822]
44. Neben-Wittich MA, Wittich CM, Mueller PS, Larson DR, Gertz MA, Edwards WD. Obstructive intramural coronary amyloidosis and myocardial ischemia are common in primary amyloidosis. *Am J Med* 2005;118:1287.
45. Modesto KM, Dispenzieri A, Gertz M, Cauduro SA, Khandheria BK, Seward JB, et al. Vascular abnormalities in primary amyloidosis. *Eur Heart J* 2007;28:1019–24. [PubMed: 17430997]
46. Migrino RQ, Truran S, Gutterman DD, Franco DA, Bright M, Schlundt B, et al. Human microvascular dysfunction and apoptotic injury induced by AL amyloidosis light chain proteins. *Am J Physiol Heart Circ Physiol* 2011;301:H2305–12. [PubMed: 21963839]
47. Dorbala S, Vangala D, Bruyere J, Jr., Quarta C, Kruger J, Padera R, et al. Coronary Microvascular Dysfunction Is Related to Abnormalities in Myocardial Structure and Function in Cardiac Amyloidosis. *JACC Heart failure* 2014.
48. van den Heuvel AF, van Veldhuisen DJ, van der Wall EE, Blanksma PK, Siebelink HM, Vaalburg WM, et al. Regional myocardial blood flow reserve impairment and metabolic changes suggesting myocardial ischemia in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2000;35:19–28. [PubMed: 10636254]
49. Range FT, Paul M, Schaefers KP, Acil T, Kies P, Hermann S, et al. Myocardial perfusion in nonischemic dilated cardiomyopathy with and without atrial fibrillation. *J Nucl Med* 2009;50:390–6. [PubMed: 19223407]

Figure 1. Microvascular dysfunction may potentiate hypertrophy, fibrosis and atherosclerosis. In health (left panel), a balance of NO (nitric oxide), prostacyclin (PGI₂), and epoxyeicosatrienoic acids (EETs) and low levels of hydrogen peroxide support a quiescent nonproliferative state. With onset of disease (right panel), hydrogen peroxide released from the microvasculature can create a proinflammatory environment and lead to hypertrophy, fibrosis, and atherosclerosis. Figure reproduced with permission from reference.[1]

Figure 2. Transthoracic echocardiography and rest-regadenoson N-13 ammonia PET/CT in a 75 year-old male with idiopathic non-ischemic dilated cardiomyopathy.

Patient initially presented with syncope due to sustained ventricular tachycardia.

Echocardiography showed a severely dilated left ventricle with severely reduced systolic function. Cardiac PET showed no definite evidence of vasodilator-induced myocardial ischemia. However, global peak hyperemic myocardial blood flow was moderate to severely reduced, and coronary flow reserve was mildly impaired. Invasive coronary angiography demonstrated normal epicardial coronary arteries. Overall, findings were consistent with a form of non-ischemic dilated cardiomyopathy with associated coronary microvascular dysfunction.

Figure 3. Rest-Regadenoson N-13 ammonia PET/CT in a 22 yr old man with hypertrophic cardiomyopathy

A 22 yr old man with known hypertrophic cardiomyopathy without LVOT obstruction and ongoing chest discomfort was referred for rest and regadenoson N-13 ammonia PET/CT for evaluation of coronary microvascular dysfunction. Stress and rest images are shown in alternate rows with short axis images (top two rows) from apex to base (left to right), horizontal long axis images (middle two rows) from the inferior to the anterior wall (left to right), and vertical long axis images (bottom two rows) from the septum to the lateral wall (left to right). On the right bottom panel, stress, rest, and reversibility polar plots (top row) and summed stress, summed rest and summed difference scores are shown (bottom panel). LVEF declined from 56% at rest to 39% after vasodilator stress. Peak hyperemic myocardial blood flow and coronary flow reserve (CFR) were substantially reduced for age. Coronary CT angiography shows normal epicardial coronary arteries with prominent myocardial crypts in the mid portion of the anterior wall.

Figure 4. Cardiac magnetic resonance and rest-regadenoson N-13 ammonia PET/CT in a patient with apical-variant hypertrophic cardiomyopathy.

Patient is a 40 year-old male who presented with significant exertional chest pain, and functional class III. He had angiographically normal epicardial coronary arteries. However, cardiac magnetic resonance (CMR) imaging revealed classic appearance of apical-variant hypertrophic cardiomyopathy with significant late gadolinium enhancement (LGE) mostly confined to the hypertrophic apex. On further evaluation, N-13 ammonia PET showed evidence of significant vasodilator-induced ischemia and coronary microvascular dysfunction particularly at the apex.

Figure 5. Rest-Dipyridamole N-13 ammonia PET/CT in a 68 yr old man with light chain amyloidosis.
A 68 yr old man with known systemic and cardiac light chain amyloidosis was referred for evaluation of coronary microvascular dysfunction as part of a research study. Epicardial CAD was excluded by coronary CT angiography. Rest and dipyridamole stress N-13 ammonia PET/CT was performed at baseline (Panel A) and followup images 6 months after completion of chemotherapy (Panel B). Perfusion images are displayed as described in Figure 3. Peak hyperemic myocardial blood flow and coronary flow reserve (CFR) were substantially reduced at baseline and improved significantly on follow-up (although still abnormal).

Table

Myocardial blood flow by PET in individuals with dilated, hypertrophic, amyloid cardiomyopathy or Fabry's disease compared to controls

First Author	Year	Tracer	Stressor	N	Cohort	Rest MBF (ml/gm/min)	Peak MBF (ml/gm/min)	CFR	Controls, N	Rest MBF (ml/gm/min)	Peak MBF (ml/gm/min)	CFR
DCM												
Van den Heuvel[48]	2000	N-13	DIPY	22	DCMP	1.02 ± 0.21	1.66 ± 0.36	1.72 ± 0.21	Healthy, 22	1.02 ± 0.16	2.80 ± 1.04	2.71 ± 0.10
Neglia[7]	1995		DIPY	22	DCMP	0.69±0.23	1.53±0.79	2.22±0.89	Healthy, 12	1.04±0.22	3.67±0.97	3.63±0.97
Range[49]	2009	O-15	ADO	12	DCMP+AF	0.82 ± 0.31	1.32 ± 0.93	1.68±0.94	DCMP+SR, 18	1.13 ± 0.31	2.52±1.20	2.1 ± 1.01
									Control+SR, 22	1.14 ± 0.2	3.57±0.88	3.37 ± 0.88
Masci[11]	2010	N13	DIPY	11	DCMP+LBBB	0.50 ± 0.07	0.94±0.20	1.83±0.50	DCMP, no LBBB, 7	0.54 ± 0.12	0.87±0.26	1.80±0.63
Majmudar[12]	2015		ADO, DIPY, REG	128	Nonischemic CMP	0.95 ± 0.38	1.65 ± 0.77	1.82 ± 0.73	Ischemic CMP, 382	0.87 ± 0.40	1.20 ± 0.56	1.46 ± 0.59
HCM												
Cecchi[29]	2003	N13	DIPY	51	HCM	0.84 ± 0.31	1.50±0.69	1.8±0.7		1.0±0.23	2.71±0.94	2.7±0.9
				12	Controls							
Knaapen[17]	2008	O-15	ADO	18	HCM	0.92±0.25	2.26±0.97	2.66±1.32		1.30±0.38	2.93±0.64	3.26±1.05
				10	Controls							
Timmer[20]	2011	O-15	ADO	15	HCM carriers	1.19±0.34	3.87±0.75	3.37±0.71		1.18±0.32	3.96±0.86	3.64±0.92
				11	Controls							
Bravo[21]	2011	N-13	DIPY	33	Nonobstructive HCM	1.04±0.33	1.58±0.49	1.62±0.57	Obstructive HCM	0.9±0.14	1.72±0.46	1.90±0.31
									Latent HCM	0.89±0.14	1.97±0.32	2.27±0.51
FD												
Elliott[38]	2006		DIPY	10	Fabry's	0.99±0.17	1.37 ± 0.32	1.41 ± 0.39	Controls, 24	1.17±0.25	3.44 ± 0.78	3.03±0.85
Kallioski[37]	2005	O-15	DIPY	15	Fabry's			3.3±1.2	Controls, 30			4.4±1.6
Tomberli[33]	2013	N-13	DIPY	30	Fabry's		1.8±0.5		Controls, 24		3.2±0.5	
Amyloidosis												
Dorbatal[43]	2014	N-13	DIPY	31	Amyloidosis	0.59±0.15	0.85±0.29	1.19±0.38	LVH, 10	0.88±0.23	1.85±0.45	2.23±0.88

DCMP = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LBBB = left bundle branch block; DIPY = dipyridamole; ADO = adenosine; REG = regadenoson; N-13 = N-13 ammonia, O-15 = O-15 water; SR= sinus rhythm; LVH = LV hypertrophy