Published in final edited form as:

Int J Cardiovasc Imaging. 2015 April ; 31(4): 881–888. doi:10.1007/s10554-015-0619-9.

Coronary microcirculation changes in non-ischemic dilated cardiomyopathy identified by novel perfusion CT

Wayne L. Miller,

Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA

Thomas R. Behrenbeck,

Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA

Cynthia H. McCollough,

Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN, USA

Eric E. Williamson,

Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN, USA

Shuai Leng,

Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN, USA

Timothy L. Kline, and

Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

Erik L. Ritman

Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

Erik L. Ritman: elran@mayo.edu

Abstract

Intramyocardial microvessels demonstrate functional changes in cardiomyopathies. However, clinical computed tomography (CT) does not have adequate spatial resolution to assess the microvessels. Our hypothesis is that these functional changes manifest as altered heterogeneity of the spatial distribution of arteriolar perfusion territories. Our goal was to determine whether the spatial analysis of perfusion CT could clinically detect changes in the function and structure of the intramyocardial microcirculation in a non-ischemic dilated cardiomyopathy (DCM). Two groups were studied: (1) a Control group (12 male plus 12 female) with no risk factors nor evidence of coronary artery disease, and (2) a DCM group (12 male plus 12 female) with left ventricular ejection fraction 40 % and no evidence of coronary artery disease. Using the CT scan, the LV free

© Springer Science+Business Media Dordrecht 2015

Correspondence to: Erik L. Ritman, elran@mayo.edu.

Conflict of interest The authors do not have any conflict of interest. All co-authors are employed by the Mayo Clinic. The authors have control of the primary data and allow the journal to review their deidentified data if requested.

Ethical standards The human studies were approved by the Institutional Review Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

wall thickness and its radius of curvature were measured. The DCM group was sub divided into those with LV free wall thickness <11.5 mm and those with thickness ≥ 11.5 mm. In the myocardial opacification phase of the CT scan sequence, myocardial perfusion (F) and intramyocardial blood volume (Bv) for multiple intramyocardial regions were computed. No significant differences between the groups were demonstrable in overall myocardial F or Bv. However, the myocardial regional data showed significantly increased spatial heterogeneity in the DCM group when compared to the Control group. The findings demonstrate that altered function of the subresolution intramyocardial microcirculation can be quantified with myocardial perfusion CT and that significant changes in these parameters occur in the DCM subjects with LV wall thickness greater than 11.5 mm.

Keywords

Dilated cardiomyopathy; Heart failure; Coronary artery disease; Myocardial microcirculation; Regional myocardial blood flow

Introduction

Dilated cardiomyopathy (DCM) is generally considered to be a disease process of the myocardium leading to ventricular systolic dysfunction without a causative contribution of impaired myocardial blood flow. This perspective is commonly supported by the demonstration of angiographically normal coronary arteries and normal epicardial coronary artery blood flow. However, more recently, changes in the coronary microcirculation blood flow, particularly due to abnormalities in coronary artery endothelial dysfunction involving resistance and conductance vessels, have been advanced as factors contributing to the impaired myocardial function [1–4]. Endothelial dysfunction in the setting of myocardial remodeling and systolic dysfunction has also been associated with an adverse prognosis [5, 6]. The issue of the role of changes in the myocardial microcirculation as a causative factor or as an effect of myocardial dysfunction is yet to be clarified. Further, the means of quantitation of abnormalities in coronary blood flow in the clinical setting have been limited most generally to invasive techniques such as coronary angiography with its associated risks. Therefore, a non-invasive method to measure myocardial microcirculation blood flow and flow reserve would likely be highly useful in the clinical evaluation of patients with DCM, particularly early onset DCM when focused therapy could potentially be most beneficial in slowing or reversing the disease process. Thus, the aim of our study was to utilize a computed tomography (CT) perfusion imaging analysis approach that was previously validated and standardized [7] to identify and characterize abnormalities in the structure and perfusion of the coronary microcirculation in patients with DCM relative to subjects without DCM. Our hypothesis is that the disturbed function of myocardial arterioles in DCM manifests as altered heterogeneity of the spatial distribution of arteriolar perfusion territories (of the order of 0.1–0.01 mm³ volume).

Materials and methods

Patient selection

This study was reviewed and approved by Mayo Clinic Institutional Review Board. All study subjects were selected to be between 45 and 55 years of age. The control group had no cardiac-related symptoms, and with no clinical history of coronary artery disease. The DCM group had a left ventricular ejection fraction (LVEF) $\geq 40\%$, minimal or no coronary calcification (<100 Agatston units by screening coronary calcium scan) [8], and no history or electrocardiographic (ECG) evidence of myocardial infarction. Potential study participants were also excluded if they were in atrial fibrillation or had additional risk factors, e.g., smoking, hypertension or diabetes. Additional exclusion criteria were serum creatinine >1.5 mg dL⁻¹, allergy to intravenous (IV) contrast, renal disease (proteinuria >1 g per 24 h, hematuria, pyrexia, history of glomerulonephritis), pregnancy or lactating, or exposure to IV contrast in previous 48 h. All subjects were consented prior to the screening CT scan.

Imaging

A SOMATOM Definition Flash dual-source CT scanner (Siemens Medical Solutions, Forchheim, Germany) was used for scanning the subjects. Each CT image consists of small voxels, each with a gray scale proportional to the X-ray attenuation coefficient (μ). The scanner's accuracy and sensitivity is frequently calibrated to ensure that this value is reproducible in different subjects. In clinical CT scanner images, the gray scale is expressed as Hounsfield Units (HU) = $1000 [\mu(\text{tissue}) - \mu(\text{water})] / [\mu(\text{water})]$. Table 1 summarizes the scanning parameters used in this study. Subjects were scanned without drugs to slow the heart rate. Mid ventricular heart sections were scanned using prospective ECG gated scanning during diastole. At heart rates less than or equal to 60 beats per minute (bpm) the heart was scanned every heart cycle during the passage of the intravascular contrast bolus through the LV, but at rates exceeding 60 bpm the heart was scanned every other heart beat. Patients were coached in the use of an interactive breath control device system (bellows) [9] in order to keep their diaphragm in the same position and hence to ensure that the subjects' heart position did not change throughout the 30 s scan sequence. A peripherally injected bolus of contrast medium was used to generate time attenuation curves (TAC) to estimate, intramyocardial blood volume (Bv) and myocardial perfusion (F) [10]. The ECG-triggered scans were obtained during diastole in order to limit heart movement during each scan, as well as to image the heart at a state of maximum F [11] and Bv [12]. The nonionic contrast agent used contained 350 mg mL⁻¹ of iodine and was injected at a volume of 0.25 mL kg⁻¹ into the antecubital vein at 5 mL s⁻¹. The 0.25 mL kg⁻¹ contrast dose was a tradeoff between the need for minimal contrast burden as well as an attempt to shorten the duration of the cointravascular contrast bolus transit through the heart. The shorter the bolus duration the more accurate the estimated F and Bv values [13]. However, we had to maintain a sufficient concentration of the bolus so that the peak deflection of TAC within the smallest myocardial nROI was at least twice the CT image noise. Six seconds after start of the injection the X-ray of the CT scanner was turned on for the 30 s ECG gated scan protocol. Subjects were asked to hold their breath for at least 30 s during which they were asked to keep the diaphragm at the same level by watching the light emitting diode (LED) indicator

of thoracic circumference. Following the scan, the amount of beat to beat motion of the LV free wall epicardial/lung interface motion was measured in the CT images to confirm the subjects' adherence to the breath-holding regime.

Computing LV wall thickness and curvature

The end-diastolic LV free wall was outlined manually when peak opacification of the LV chamber occurred. The myocardial wall thickness (T) was measured at right angles to the endo- and epicardial surfaces at multiple points along the wall and an average value was determined. The wall curvature (R) at that point in the wall was computed from a circular arc fitted to the endocardial surface of the wall. The ratio of wall thickness to radius of curvature is an index of LV wall stress (σ) as derived from the Laplace's Law ($P \times R = \sigma \times T$, i.e., $\sigma/P = R/T$), where P is the transmural pressure. We chose the upper limit of left ventricular free-wall thickness to be 11.5 mm based on the published ultrasound [14–16] and MRI [15] data.

Computing Bv and F from the myocardial time attenuation curve (TAC)

The TAC were generated from the average HU value within a selected Region of Interest (ROI) within the CT images obtained from the sequential scans obtained during a single breath-hold. In this study we used a gamma variate curve fit to the TAC data. The effect of CT image noise on the smoothness of the TAC can be greatly reduced by fitting the CT-based data with a gamma variate curve [17]. Gamma-variate curves describe the change in contrast concentration in the LV chamber as:

$$C(t) = ct^a \times \exp(-t/b), \quad (1)$$

where $C(t)$ is the contrast medium concentration as a function of time, which is represented by the CT numbers in Hounsfield units (HU) above the background CT value, t is the time (in seconds) beginning at the appearance of the TAC, and a , b , and c are the curve-fitting parameters (derived by the fitting procedure).

It has been shown that a single gamma variate curve well describes the LV and aortic curves, but the myocardial curve is best represented by the superposition of an intravascular component and an extravascular component (caused by contrast in the extravascular space resulting from the permeability of the capillary endothelium) as:

$$C(t) = ct^a \times [\exp(-t/b) + d \times \exp(-t/h)], \quad (2)$$

where the intravascular component is described by the $ct^a \exp(-t/b)$ component and was used in our analysis of the myocardial perfusion and intramyocardial Bv. Using the derived gamma-variate curves, the Bv was calculated as the ratio of the area under the myocardial TAC divided by the area under the LV chamber TAC. F was also derived from the gamma variate curves as described elsewhere [18].

Myocardial perfusion (F) was computed and confirmed by the method described using an Electron Beam CT scanner using dogs [19] and pigs [20]. Use of helical multislice CT using pigs [18] form the basis for the quantification of F and Bv in this current study.

Analysis of the spatial heterogeneity of F and Bv

To calculate the index of spatial heterogeneity of F and Bv, the master ROI over the LV free wall was subdivided into a number of nested transmural ROIs (nROIs) within the master ROI. These nROI were of equal area (or volume if multiplied by thickness of myocardium within a single CT slice image). As different subjects had different heart sizes, the area of the master ROI would differ for each subject. This ROI was subdivided into multiple nROI. We developed computer software to accomplish this goal to avoid subjective error and reduce processing time. Each one of the nROIs is then used to generate its own myocardial TAC. The minimum allowable size of the nROI was established by examining the role of CT image noise in this analysis. Increasingly smaller nROI regions were analyzed within the left ventricular chamber (where no microscopic perfusion defects exist). Hence, any variation in CT image gray scale of the LV chamber is primarily due to CT image noise. The analysis was performed on a CT image at peak contrast enhancement for the left ventricular chamber. The point at which this 'random noise' equals or exceeds the variation seen within the opacified myocardium was used to determine the lower limit for nROI size—below which the CT noise dominates over the TAC signal.

As illustrated in Fig. 1, the master ROI over the LV wall was divided into 4, 8 and 16 nROI (each of the individual 16 nROIs being not less than the minimum size as "allowed" by the noise analysis). When the myocardial TACs were computed for each nROI, then the F and Bv were calculated for each nROI. The mean (M) and standard deviation (SD) were then calculated for the values obtained for each set of nROI of the same size. These data were then used to calculate the slope and offset (bias) of the linear regression of the scatter plot $\text{Log}(\text{SD}/\text{M})$ vs $\text{Log}(\text{size of one nROI})$. The slope of this regression would be -0.5 if the distribution of hypoperfused territories is random [21] and would be 0.0 if the distribution is homogeneous. Slope values between these extremes are consistent with the local correlation between perfusion territories. The above analysis was performed in the up to fourteen 4.8 mm thick CT slices in each subject.

As shown in a simulation by Behrenbeck et al. [7] the impact of microperfusion territory size on the nROI analysis is a decrease in bias of the regression with decreasing microperfusion territory size. In that simulation, there was no change in regression slope because the spatial distribution is random in that simulation.

Statistical analysis

The statistical characteristics of overall group parameters, overall LV myocardium values, and regional myocardial Bv and F data were analyzed with the software package Matlab (R2011b, The MathWorks, Natick, MA). Values are presented as mean and SD ($M \pm \text{SD}$) and percent or number in category. A *t* test was performed to compare both the Control to DCM groups, as well as compare male to female within the same group. In the case of the regional myocardial Bv and F data, for each subject a regression line was computed. The slope and intercept were considered as individual measurements for each group. The results were deemed significant when $P < 0.05$.

Results

Subject characteristics

In total, fifty-three subjects were screened. Of these, five subjects were excluded resulting in the analysis of forty-eight, age matched, participants. In the Control group the average AU score was 4.1 ± 7.9 for the males and 0.0 for all females. For the DCM group the average score for the males was 13.7 ± 30.0 and for the females was 1.6 ± 4.4 . Of the candidates for the DCM group 1 female and 2 males were excluded because their calcium scores exceeded 100 AU. Of the subjects recruited, 12 men and 12 women were included for both the DCM group and the Control group. Table 2 lists the clinical characteristics and demographics for the study cohort. Plasma lipids were within normal range according to NCEP III guidelines [22] for the 'Control' and the "DCM" group.

Subject X-ray dose

The CT scans resulted in a total patient X-ray dose (assuming the conversion factor described in Ref. [23]) of 9.12–11.59 mSv when the heart was scanned at every sequential heart cycle and 6.77–8.71 mSv when the heart was scanned every other heart cycle.

Determination of minimum size of the myocardial region of interest

Analysis to determine the lower limit for a useful nROI volume gave a lower bound of 15 mm^3 (i.e., $1.77 \times 1.77 \text{ mm}^2$ in-plane area) for the smallest nROI size that could be used in the analysis in order to prevent significant corruption by CT image noise.

Regional CT image analysis values of LV myocardium

Because the scans obtained at <60 bpm were obtained for every heart cycle but in those with >60 bpm every other heart cycle, we regenerated the TAC of the <60 bpm by taking every other TAC value. The area under those regenerated curves differed from the original (every heart cycle) curve by only 1.3 % which has a similar magnitude effect on the computed F and Bv values. The fitted TAC of the transient passage of myocardial intravascular contrast show both the different peak deflections of the TAC in the different nROIs (of the same size) and of the baseline value. Table 3 summarizes the stroke volume, intramyocardial Bv and myocardium perfusion (F) for each sex and group. Figure 2 shows the regression analysis findings for the spatial heterogeneity of Bv of both groups as well as the breakdown for the cardiomyopathy subjects with LV wall thickness less than 11.5 and more than 11.5 mm left ventricular hypertrophy (LVH). The feature of note is that the slope both the male and female of the DCM groups are significantly ($P < 0.05$) more negative than the Control group, consistent with the DCM group having decreased local correlation between perfusion territories. The bias in DCM males is lower than in the Control males, consistent with decreased arteriolar perfusion territory volume. There is no significant difference for the females.

Because some of the subjects had non-zero coronary calcium scores (albeit all were selected to have scores of <100 Agatston Units) the comparison of the "LVH" to the Control group was repeated without those subjects with any evidence of coronary calcification. The analysis showed that there was no statistically significant difference to the prior analysis of

differences in the slopes or biases of the log/log regressions between Control, and cardiomyopathy, subjects for both male-to-male and female-to-female comparisons.

Because there were significant differences in body weight and heart rate (those with HR ≤ 60 bpm had a scan every heart cycle whereas those with HR > 60 bpm were scanned every other heart cycle) within each group we reanalyzed the data for just those with body weight between 70 and 90 kg and those with heart rates ≤ 60 bpm. Within those limits there was no statistically significant difference (t test) of body weight or heart rate between the groups. Also, the analysis within those limits did not show any significant differences between the regression slopes ($P > 0.05$) for F and Bv spatial heterogeneity in the females and in the male subsets within the Control and DCM groups relative to the analysis involving all subjects in each group.

Table 4 summarizes the LV free wall thickness/wall radius of curvature (an index of wall stress) for each sex in each group. Except for the males with wall thickness greater than 11.5 mm in the DCM group both sexes showed significant increases in the wall stress index within each of the groups.

Discussion

Magnetic Resonance Imaging (MRI) has been used to detect fibrosis in the myocardial wall and used as an indicator of some cardiomyopathies. The method involves quantifying delayed enhancement of the myocardium following an injection of a gadolinium-based contrast agent [24]. Although MRI is also used to establish the spatial distribution of myocardial perfusion [25]. These two methods seem to correlate well with the presence of some cardiomyopathies but the scan duration required to generate these data is probably too long for routine clinical use. It is also not clear that sufficiently small regions of interest within the myocardium can be used to provide meaningful indication of the spatial heterogeneity of patchy fibrosis and/or perfusion. An advantage of CT is its speed while maintaining high spatial resolution.

The findings of this study reveal that differences in regression bias and slope magnitudes reflect differences in intra-myocardial arteriolar function. A more negative slope is consistent with a more random distribution of perfused territories. More random distributions are consistent with contiguous perfusion territories not being sensitive to the perfusion (or non-perfusion) of their neighboring perfusion territories. This sets the stage for larger areas with poor perfusion. The intersection of the DCM and Control regressions is an index of the areas of arteriolar perfusion territories in the DCM subjects. The perfusion territory areas (or volume multiplied by CT image slice thickness) in females are smaller than in the males. These areas are larger than the perfusion territories in subjects with presymptomatic coronary atherosclerosis [7]. These results are consistent with the DCM patients having larger arterioles involved than the arterioles affected in early atherosclerosis. Malyar et al. [26] showed in pigs that the perfusion territory of a terminal arteriole (< 0.03 mm lumen diameter) was about 0.3 mm in diameter and the territory of an arteriole of the order of 0.2 mm lumen diameter has a perfusion territory of approximately 2 mm diameter. As summarized by Kuo et al. [27] the terminal arterioles are particularly sensitive to

pressure, metabolites, and agonists—whereas the larger arterioles are more sensitive to flow. These results are consistent with early atherosclerosis being mediated by changes in the endothelium (which is of increased impact in the terminal arterioles versus the larger arterioles in DCM being more affected by the smooth muscle which is of increased functional significance in the larger arterioles). Our results and their interpretation are consistent with other studies [28] which suggest that coronary microvascular abnormality is an important feature in DCM. The myocardial regional data showed significantly increased spatial heterogeneity in the DCM group when compared to Control group.

This study demonstrates an analysis of the microcirculation of cardiomyopathy patients at the level of the arterioles which, up to now, has involved only invasive techniques. Up to now, non-invasive direct assessment of the coronary microcirculation has not been clinically possible, thus there has not been a universally adopted therapy for these patients.

Our model would allow assessment of reversibility of the microvascular component of DCM and could help in demonstrating the transition to irreversible and possible structural heart disease. The nested Region-of-Interest analysis method does indicate the sub-resolution differences in perfusion distribution. As indicated in Fig. 2, the difference in the regression slope of the DCM group is consistent with a tendency for the spatial distribution in the DCM group to be more random than in the Control group. In the Control group the local correlation could be due to any one active perfusion territory providing adequate perfusion to its neighboring perfusion territories. This effect would likely result in “discouragement”, i.e., less perfusion of contiguous territories as adjacent territories supply sufficient nutrients, which would be at odds with the chances of some of the contiguous perfusion territories being active if the spatial distribution was purely random.

In an effort to minimize invasiveness only 0.25 mL contrast per kg (i.e., on average, 20 mL) was injected intravenously over 5 s. It is doubtful that the contrast volume can be further reduced, but it is likely that the X-ray exposure can be further reduced. This would require additional application of post-scan image analysis noise-reduction approaches.

Because differences of body weight could influence CT image noise due to differences in X-ray attenuation and beam hardening, and because differences in TAC curve sampling intervals (due to scans occurring every heart cycle at 60 bpm vs. every second heart cycle at >60 bpm) could affect the fidelity of the curve analysis, we also performed analysis in a subset of subjects so as to minimize these plausible impacts. As we could show no differences ($P>0.05$) from the analysis of the entire group, we conclude that even the smallest nested ROI was still large enough to render the “photon noise” component of the overall CT image noise insignificant for our analysis. Moreover, the lack of impact of the TAC sampling intervals is consistent with the relatively long duration of the TAC (greater than the 4 s injection duration) rendered these sampling differences insignificant.

Conclusion

This study demonstrates in human subjects that subresolution spatial distribution at the microcirculatory level can be quantified with perfusion CT and that significant changes in

spatial heterogeneity of intramyocardial Bv and myocardial perfusion occur in subjects with DCM.

Acknowledgments

The authors would like to thank the following personnel. Dr. Jodie Christner and Ms. Maria Shiung; Study Coordinator, Jennifer Alkhamis; CT Techs—Lisa L. Jorgenson, Emily Sheedy, Katherine Steele, Cynthia Walfoort, Nikkole Weber; CT Nurses—Laurie Claeys, Susan Persons, Susan Inman Radenz and William Stromme; and the Division of Engineering, Aaron Treat, Ms. Renae M. Forsman, Bruce W. Gustine, and Ms. Diane R. Eaker and Delories C. Darling. This study was funded in part by NIH Grants HL72255 and UL1TR000135.

References

1. Bitar F, Lerman A, Akhter MW, Hatamizadeh P, Janmohamed M, Khan S, Elkayam U. Variable response of conductance and resistance coronary arteries to endothelial stimulation in patients with heart failure due to non-ischemic dilated cardiomyopathy. *J Cardiovas Pharm Therap*. 2006; 11:197–202.
2. Spoladore R, Fiscaro A, Faccini A, Camici PG. Coronary microvascular dysfunction in primary cardiomyopathies. *Heart*. 2013;10.1136/heartjnl-2013-304291
3. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007; 356:830–840. [PubMed: 17314342]
4. Treasure CB, Vita JA, Cox DA, Fish RD, Gordon JB, Mudge GH, Colucci WS, Sutton MG, Selwyn AP, Alexander RW. Endothelium-dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. *Circulation*. 1990; 81:772–779. [PubMed: 2306829]
5. Neglia D, Michelassi C, Trivieri MG, Sambucetti G, Giorgetti A, Pratali L, Gallopin M, Salvadori P, Sorace O, Carpeggiani C, Poddighe R, L'Abbate A, Parodi O. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. *Circulation*. 2002; 105:186–193. [PubMed: 11790699]
6. Cecchi F, Olivetto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med*. 2003; 349:1027–1035. [PubMed: 12968086]
7. Behrenbeck TR, McCollough CH, Miller WL, Williamson EE, Leng S, Kline TL, Ritman EL. Early changes in myocardial microcirculation in asymptomatic hypercholesterolemic subjects: as detected by perfusion CT. *Ann Biomed Eng*. 2014; 14(42):515–525. [PubMed: 24232745]
8. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantitation of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990; 15:827–832. [PubMed: 2407762]
9. Carlson SK, Felmle JP, Bender CE, Ehman RL, Classic KL, Hu HH, Hoskin TL. Intermittent-mode CT fluoroscopy-guided biopsy of the lung or upper abdomen with breath-hold monitoring and feedback: system development and feasibility. *Radiology*. 2003; 229:906–912. [PubMed: 14657321]
10. Rumberger, JA.; Bell, MR.; Feiring, AJ.; Marcus, ML.; Behrenbeck, T.; Ritman, EL. Measurement of myocardial perfusion using fast computed tomography. In: Marcus, M.; Schelbert, HR.; Skorton, DJ.; Wolf, GL., editors. *Cardiac imaging: a companion to Braunwald's Heart Disease*. WB Saunders Company; Philadelphia: 1991. p. 688-702.
11. Sabiston DC, Gregg DE. Effect of cardiac contraction on coronary blood flow. *Circulation*. 1957; 15:14–20. [PubMed: 13396921]
12. Liu YH, Bahn RC, Ritman EL. Dynamic intramyocardial blood volume: evaluation with a radiological opaque marker method. *Am J Physiol*. 1992; 263:H963–H967. [PubMed: 1415624]
13. Mullani N, Gould KL. First pass measurements of regional blood flow using external detectors. *J Nucl Med*. 1983; 24(7):577–581. [PubMed: 6602868]
14. Kanza RE, Higashino H, Kido T, Kurata A, Salto M, Sugawara Y, Mochizuki T. Quantitative assessment of regional left ventricular wall thickness and thickening using 16 multidetector-row

- computed tomography: comparison with cine magnetic resonance imaging. *Radiat Med.* 2007; 25:119–126. [PubMed: 17450336]
15. Basavarajaiah S, Wilson M, Naghavi R, Whyte G, Turner M, Sharma S. Physiological upper limits of left ventricular dimensions in highly trained junior tennis players. *Br J Sports Med.* 2007; 41:784–788. [PubMed: 17957014]
  16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber qualification: a report from the American Soc of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, branch of the European Soc of Cardiology. *J Am Soc Echocardiogr.* 2005; 18(12):1440–1463. [PubMed: 16376782]
  17. Thompson HK Jr, Starmer CF, Whalen RE, McIntosh H. Indicator transit time considered as a gamma variate. *Circ Res.* 1964; 14:502–515. [PubMed: 14169969]
  18. Daghini E, Primak AN, Chade AR, Zhu X, Ritman EL, McCollough CH, Lerman LO. Evaluation of porcine myocardial microvascular permeability and fractional vascular volume using 64-slice helical computed tomography (CT). *Invest Radiol.* 2007; 42:274–282. [PubMed: 17414522]
  19. Schermund A, Bell MR, Lerman LO, Ritman EL, Rumberger JA. Quantitative evaluation of regional myocardial perfusion using fast X-ray computed tomography. *Herz.* 1997; 22(1):29–39. [PubMed: 9088938]
  20. Mohlenkamp S, Beighley PE, Pfeifer EA, Behrnebeck TR, Sheedy PF, Ritman EL. Intramyocardial blood volume, perfusion and transit time in response to embolization of different sized microvessels. *Cardiovasc Res.* 2003; 57:843–852. [PubMed: 12618246]
  21. Bassingthwaite JB, Bever RP. Fractal correlation in heterogeneous systems. *Physica D Nonlinear Phenom.* 1991; 53:71–84.
  22. NCEP III Guidelines. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA.* 2001; 285:2486–2497. [PubMed: 11368702]
  23. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. *Circulation.* 2007; 116:1290–1305. [PubMed: 17846343]
  24. Ismail TF, Prasad SK, Pennell DJ. Prognostic importance of late gadolinium enhancement cardiovascular magnetic resonance in cardiomyopathy. *Heart.* 2012; 98:438–442. [PubMed: 22128204]
  25. Ugander U, Oki AJ, Hsu L-Y, Kellman P, Greiser A, Aletras AH, Sibley CT, Chen MY, Bandettini WP, Arai AE. Extracellular volume imaging by magnetic resonance imaging provides insight into overt and subclinical myocardial pathology. *Eur Heart J.* 2012; 33:1268–1278. [PubMed: 22279111]
  26. Malyar NM, Gössl M, Beighley PE, Ritman EL. Relationship between arterial diameter and perfused tissue volume in myocardial microcirculation—a micro-CT based analysis. *Am J Physiol Heart Circ Physiol.* 2004; 286:H2386–H2392. [PubMed: 14670815]
  27. Kuo L, David MJ, Chilian WM. Endothelial modulation of arteriolar tone. *NIPS.* 1992; 7:5–9.
  28. Neglia D, L'Abbate A. Coronary microvascular dysfunction and idiopathic dilated cardiomyopathy. *Pharmacol Rep.* 2005; 57(Suppl):151–155. [PubMed: 16415496]

Fig. 1.

Left panel A tomographic image through the mid cardiac region during passage of the bolus of contrast agent through the left ventricular chamber. *Right panel* Shows the outlined LV free wall and its sub division into 16 transmural nested regions of interest. The larger nested ROIs consist of the addition of sets of two contiguous ROIs for the 8 and sets of four contiguous ROIs for the 4 nested ROIs used in the analysis. A TAC was generated for each of the 4, 8 and 16 nested ROIs

Fig. 2.

Least squares, best fit, regressions to the fractal analysis Bv results for all subjects within each group. The *left panels* are for females and the *right panels* are for males. The *upper panels* are for those DCM subjects with LV wall thickness less than 11.5 mm and the *lower panels* for those DCM subjects with LV wall thickness greater than 11.5 mm. Each panel has a regression for the DCM and the entire control group

Table 1

CT scan and reconstruction parameters for cardiac perfusion

Parameter	Details
Scan type	Sequential
Collimator	32×1.2 mm
kVp	120
mAs per rotation	90
Phase start (% of QRS to QRS interval)	60 %
Total scan sequence duration	30 s
Start of scan after start of IV injection	6 s
Temporal resolution	75 ms
Contrast medium concentration	350 mg Iodine mL ⁻¹
Contrast injection rate	5 cc s ⁻¹
Amount of contrast injected	0.25 mL kg ⁻¹
Site of injection	Antecubital vein
Reconstruction kernel	B25
Reconstructed image thickness	4.8 mm
Reconstructed image interval	2.4 mm
Voxel size	$0.39 \times 0.39 \times 4.8$ mm ³

Table 2

Summary of group parameter values

Parameter	Female control	Female DCM	Male control	Male DCM
Number of subjects—total	12	12	12	12
Mass (kg)	69.7 ± 13.7	76.0 ± 19.0	86.6 ± 9.1	94.0 ± 14.0
Number (70–90 kg)	4 (78.3 ± 6.0)	4 (79.5 ± 7.0)	7 (80.2 ± 5.4)	7 (80.5 ± 6.6)
Heart rate for group (bpm)	60.7 ± 7.6	65.2 ± 6.9	61.0 ± 11.3	59.2 ± 6.6
Number (<60 bpm)	6 (54.2 ± 4.4)	2 (57.5 ± 0.7)	6 (54.7 ± 3.1)	5 (53.8 ± 2.9)
Age (years)	45.4 ± 4.0	49.0 ± 5.0	45.8 ± 5.5	48.0 ± 4.0
LDL (mg dL ⁻¹)	86.3 ± 24.6 ^{a,b}	113.0 ± 29.0	93.8 ± 17.7 ^{a,b}	123.0 ± 31.1
HDL (mg dL ⁻¹)	62.3 ± 12.3 ^b	54.8 ± 15.0	47.1 ± 11.7 ^b	41.8 ± 13.0
Triglycerides (mg dL ⁻¹)	89.8 ± 41.3 ^a	146.0 ± 82.0	100.0 ± 26.5	172.0 ± 131.0
C-react protein (mg dL ⁻¹)	0.31 ± 0.28	0.24 ± 0.20	0.12 ± 0.11	0.26 ± 0.26
Interleukin-6 (pg dL ⁻¹)	2.2 ± 1.8	1.9 ± 0.9	1.2 ± 0.9	2.1 ± 1.7
Calcium score (Agatston)	0.0 ± 0.0	1.6 ± 4.4	4.1 ± 7.9	13.7 ± 3.0

^aDenotes statistical difference between Control and DCM^bDenotes statistical difference between across sex

Table 3

CT image analysis-based parameters

Parameter	Female control	Female DCM	Male control	Male DCM
Stroke volume (mL/BMI)	4.3 ± 2.0	4.2 ± 1.5	4.9 ± 2.9	4.3 ± 1.5
Myocardial blood volume (myocardium volume fraction)	0.11 ± 0.54	0.12 ± 0.04	0.10 ± 0.02	0.12 ± 0.04
Myocardial perfusion ($\text{ML min}^{-1} \text{cm}^{-3}$)	0.92 ± 0.54	1.12 ± 0.51	0.82 ± 0.18	0.92 ± 0.21

Table 4

LV wall thickness/long axis radius of free wall curvature

Group	<11.5 mm LV wall thickness	>11.5 mm LV wall thickness	<i>P</i>
Female control	0.24 ± 0.03	0.35 ± 0.003	0.005
Female DCM	0.25 ± 0.03	0.31 ± 0.06	0.051
Male control	0.21 ± 0.03	0.26 ± 0.03	0.080
Male DCM	0.21 ± 0.01	0.25 ± 0.04	0.026

No statistically significant differences between females and between males at the same wall thickness group