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Impairment of Subendocardial Perfusion Reserve and Oxidative Metabolism in Non-Ischemic Dilated Cardiomyopathy

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Abstract

Background—Cardiac magnetic resonance (CMR) and [^{11}C] acetate positron emission tomography (PET) were used to assess the hypothesis that patients with nonischemic dilated cardiomyopathy (NIDCM) have decreased subendocardial perfusion reserve and impaired oxidative metabolism, consistent with the concept of “energy starvation” in heart failure (HF).

Methods and results—CMR myocardial perfusion was evaluated in 13 NIDCM patients and 15 control subjects with coronary risk factors and normal myocardial perfusion. The NIDCM patients underwent [^{11}C] acetate PET. The myocardial perfusion index (MPI) was calculated as the normalized rate of myocardial signal augmentation following gadolinium contrast injection. Hyperemic transmural, subendocardial and subepicardial MPI were reduced in NIDCM compared to control subjects [0.13 vs. 0.18 ($P < 0.001$), 0.13 vs. 0.17 ($P < 0.001$), and 0.13 vs. 0.17 ($P = 0.008$), respectively]. The subendocardial perfusion reserve was 1.59 ± 0.21 vs. 1.86 ± 0.32 for the subepicardium ($P = 0.002$) demonstrating reduced perfusion reserve. The myocardial oxidative metabolic rate (k_{mono}) per unit demand (rate-pressure product) was reduced proportional to perfusion reserve ($P = 0.02$)

Conclusions—Impaired subendocardial perfusion reserve in NIDCM confirmed results previously attained only in animal models. Impaired perfusion and impaired oxidative metabolism are consistent with subendocardial energy starvation in HF.

Introduction

The heart failure (HF) syndrome due to nonischemic dilated cardiomyopathy (NIDCM) is associated with high rates of morbidity and mortality[1]. Left ventricular (LV) hypertrophy, hemodynamic overload, and increased wall stress [2] lead to increased myocardial energy demand while decreased capillary density [3], and a likely increased transcapillary pressure gradient, reduce myocardial substrate supply. The combination of these factors is postulated to produce excess energy demand compared to supply and to deplete myocardial high-energy phosphate stores [4–6]. This chronic state of supply-demand energy imbalance has

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Disclosures

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been termed myocardial “energy starvation” and has been postulated to contribute to the pathophysiology of congestive HF.

In normal dogs, subendocardial blood flow is reduced relative to subepicardial blood flow in response to maximal hyperemia [7, 8], and this finding is accentuated in heart failure models [9–11]. This attenuated maximal flow response in the subendocardium has been associated with chronic fibrosis which is greatest in the endocardial layers [11]. The severity of reduced myocardial blood flow is a predictor of poor prognosis in patients with NIDCM [12]. Reduced transmural myocardial blood flow at baseline and during hyperemia has been demonstrated by positron emission tomography (PET) in patients with compensated NIDCM [13], but PET cannot differentiate subendocardial from subepicardial flow. However, first-pass contrast cardiac magnetic resonance (CMR) imaging can demonstrate subendocardial and subepicardial perfusion [14] and has been validated in animal models against microsphere-assessed blood flow [15–17]. This approach has demonstrated subendocardial hypoperfusion during the intravenous administration of adenosine in patients with syndrome X [18] and with coronary atherosclerosis [19].

The monoexponential decay rate of [^{11}C] acetate using PET (k_{mono}) has been validated as an estimate of myocardial oxidative metabolism in dogs [20], healthy male volunteers [21] and patients with NIDCM [22] and correlates closely with myocardial oxygen consumption [20, 22–25]. We have demonstrated an imbalance of energy supply (k_{mono}) vs. demand (judged by the systolic rate-pressure product) in patients with NIDCM compared to normal subjects [26]. The relation of LV minute work to k_{mono} , described by the work-metabolic index (WMI) has shown reduced LV pump efficiency in heart failure [22, 27, 28].

Based on CMR’s capacity to define subendocardial perfusion, we employed CMR with [^{11}C] PET imaging to assess the hypothesis that patients with NIDCM have reduced subendocardial perfusion reserve plus impaired myocardial oxidative metabolism, a combination consistent with an imbalance of energy supply- to demand ,and hence “energy starvation”.

Methods

Study Design and participants

This study was part of a prospective interventional study investigating the effects of mineralocorticoid receptor antagonism on myocardial energy starvation. We studied 13 patients with newly diagnosed NIDCM who were recruited from Vanderbilt University Medical Center and the Nashville Veterans Affairs Medical Center between 2008 and 2010. Eligible participants were between the ages of 18 and 80 years old, of any ethnic background and either sex, New York Heart Association Functional Class II-IV, with an echocardiographic LVEF of 35% or less and serum potassium level less than 5.0 while on medical therapy for heart failure (including stable beta-adrenergic blockade and an angiotensin converting enzyme inhibitor or angiotensin receptor blocking drug for a minimum of 3 months). *Participants were enrolled during a trial of maximum medical therapy prior to possible device implantation.* Individuals with a need for an implantable cardioverter-defibrillator or re-synchronization therapy device and those with evidence of prior myocardial infarction on ECG, a positive stress test or coronary artery disease with 50% or greater stenosis in a major epicardial artery at angiography were excluded. Further exclusion criteria included severe chronic obstructive airway disease precluding adenosine use, creatinine > 2.5 mg/dl, glomerular filtration rate < 30 ml/min, uncontrolled atrial fibrillation, current spironolactone therapy and physician preference. A retrospective review of CMR studies disclosed 15 subjects who had undergone CMR with adenosine and gadolinium infusion for chest pain assessment who often had several risk factors for

coronary artery disease but no evidence of significant coronary artery disease on review of medical records and no structural heart disease or perfusion abnormalities on CMR. These subjects had normal systolic function and served as a control group. The study was approved by the Vanderbilt and Nashville Veterans Affairs Institutional Review Boards, and all patients provided written informed consent.

Cardiac MRI

Cardiac MRI was performed using a commercially available 1.5-T Siemens Magentom Avanto scanner (Erlangen, Germany). Patients were scanned using a phased-array torso receiver coil. The imaging protocol consisted of two parts: cine imaging for ventricular volume and function; contrast-enhanced first pass imaging for myocardial perfusion.

Following localizer images to identify the location of the heart within the thorax, cine imaging was first performed aligned to the horizontal and vertical long-axis of the heart from which a stack of contiguous short axis cine images of the LV were acquired. Typical acquisition parameters for cine images were: field of view (FOV) 300×340 mm, matrix 156×192 , slice thickness (SL) 8 mm, flip angle (FA) 80° and adjusted downwards depending on the specific absorption rate, echo time (TE) 1.1 msec, bandwidth (BW) 930 Hz/pixel, and usually 30 phases per cardiac cycle to maintain repetition time (TR) below 50 msec. Parallel imaging was employed using the generalized autocalibrating partially parallel acquisition (GRAPPA) technique with an acceleration factor of 2. The typical scan time was < 15 sec per slice. Following cine imaging, myocardial perfusion imaging was performed during the peak hyperemic effect of adenosine and under resting conditions. Adenosine (140 mcg/kg/min) was infused intravenously over 4 – 6 minutes. At two minutes into the adenosine infusion, 0.1 mmol/kg gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, IN) was injected intravenously. First pass imaging of the wash-in of Gd-DTPA through the LV myocardium was performed in 3 short axis imaging planes positioned in mid myocardial segments of the LV using a saturation-recovery turbo fast low angle shot (FLASH) gradient echo sequence. All three short axis images were acquired with each R-R interval over 50 consecutive heart beats starting with the injection of Gd-DTPA in order to capture the initial wash-in of Gd-DTPA through the myocardium. Typical acquisition parameters for first pass images were: FOV 320×400 mm, matrix 116×192 , SL 8 mm, slice gap 8 mm, FA 12° , TE 1.1 msec, TR 160–190 msec, BW 930 Hz/pixel, and GRAPPA acceleration factor 2. Following a 5 min delay, contrast-enhanced first pass imaging was repeated under resting conditions with a second intravenous injection of 0.1 mmol/kg Gd-DTPA (total combined dose 0.2 mmo/kg Gd-DTPA). Ten minutes following the initial injection of Gd-DTPA, short axis myocardial late gadolinium enhancement imaging was performed using both single-shot inversion recovery (IR) and phase sensitive inversion recovery (PSIR) true FISP imaging. Typical acquisition parameters for first pass images were: FOV 270×360 mm, matrix 108×192 , SL 8 mm, FA 50° , TE 1.1 msec, TR 700 msec, BW 1200 Hz/pixel. IR and PSIR images were acquired every other cardiac cycle. To properly select the optimal inversion time (TI) delay, a TI “scout” sequence acquired at the ten-minute mark in a single short axis imaging plane using the above parameters and with progressively longer TI times. The optimal TI was visually determined as the time delay when the myocardium appeared darkest. The average TI for IR imaging was 220–280 msec. PSIR imaging is less sensitive to TI and the TI was set to 300 msec for all PSIR acquisitions.

For the control subjects images were not obtained during resting conditions. All images were corrected for surface coil intensity variation using a normalization filter. The LV end diastolic volume, end systolic volume, stroke volume, LVEF, LV mass, LV mass index (defined as LV mass [grams]/body surface area [m^2]) were calculated using system

software. and the LV peak systolic wall stress (WS) was calculated using a previously described method for thick walled spheres [29].

$$WS = P / [(V_{lum} + V_{myo}) / V_{lum}]^{2/3} - 1$$

where V_{lum} = ventricular inner volume, V_{myo} = ventricular myocardial wall volume and P = systolic arterial pressure.

The rate-pressure product (RPP) was calculated as HR x systolic blood pressure (SBP) (beats per minute × mmHg). Myocardial enhancement occurred during the transit of Gd-DTPA through the heart, and the myocardial perfusion index (MPI) was calculated using software (CMR tools, London U.K.) [18], as the maximum slope of the time-intensity curve of myocardial enhancement according to the following equation:

$$MPI = \text{Maximum slope(myocardium)} / \text{Maximum slope(left ventricular cavity)}$$

This yielded a normalized upslope of myocardial enhancement as a quantitative estimate of myocardial enhancement among various subjects as previously described [30, 31]. The myocardium was automatically divided into subendocardial and subepicardial regions. The MPI was calculated for transmural myocardium, subendocardium, and subepicardium at rest and during adenosine infusion. The myocardial perfusion reserve index (MPRI) was calculated using the following equation:

$$MPRI = MPI(\text{during hyperemia}) / MPI(\text{during rest})$$

PET data acquisition and analysis

Within 2 hours of the CMR study, the rate of LV oxidative metabolism was assessed with [^{11}C] acetate. The patient lay supine in a hybrid PET/CT scanner (GE Discovery STE, GE Health care, WI). The heart rate and systemic blood pressure were recorded at baseline and every 5 minutes during data acquisition. A low-dose CT scan was obtained for attenuation correction, followed by intravenous bolus administration of [^{11}C] acetate (0.286 mCi/Kg). ECG-gated images were acquired in list mode for 30 minutes and were reformatted into images of 12 frames of 10 seconds each, 8 frames of 30 seconds, 4 frames of 60 seconds, 2 frames of 300 seconds, and 1 frame of 600 seconds. A second, similar CT scan was acquired at the end of the data collection.

The [^{11}C] acetate images were processed after CT attenuation correction. Regions of interest over the LV blood pool and the LV myocardium on the last [^{11}C] image were applied to all other frames in the study. The count data were expressed as counts/pixel. The blood pool and activity were plotted vs. time. The monoexponential clearance rate, defined as k_{mono} , was determined by least squares fitting of the linear portion of the time-activity curve [32]. This estimate of LV oxidative metabolism correlates closely with myocardial oxygen consumption [20, 22–25]. The heart rate (HR) and systolic blood pressure (SBP) were averaged over the period of data acquisition. The rate-pressure product (RPP) was calculated as HR x systolic blood pressure (SBP) (beats per minute × mmHg). The work-metabolic index (WMI), a measurement of LV efficiency, was calculated as: $WMI = (LVSVI \times SBP \times HR) / k_{mono}$, where LVSVI is LV stroke volume index (stroke volume per square meter) [22].

Statistical Analysis

Continuous variables are presented as a mean $\pm$ standard error of the mean. Tables represent mean and corresponding 95% confidence intervals (CI). Differences were compared using the Student's *t*-test and paired *t*-test when applicable. Echocardiographic visual estimates of ejection fraction were recorded as a 5 unit range and were allocated to the midpoint of the range for statistical purposes. Categorical variables were compared using the chi-square test. All analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois), statistical significance was judged as 2 tailed $P < 0.05$.

Results

There were 13 patients with NIDCM and 15 control subjects. The latter had normal LVEF, normal LV wall motion and no LV hypertrophy. Among the control subjects, 11 had hypertension, 7 had hyperlipidemia and 5 had non-insulin dependent diabetes mellitus. The frequency of these risk factors was similar to the NIDCM patients (Table 1). Medication usage between the two groups differed with all NIDCM taking an ACE-I or ARB and betablocker while control subjects were taking a combination of ACE-I, ARB, betablocker and calcium channel blockers. All the patients with NIDCM, had perfusion data at rest and during adenosine infusion, and all the control subjects had perfusion data during adenosine infusion. The LVEF by echocardiography and by CMR was much lower in NIDCM than control, as expected by study design. The LVEF by CMR averaged 15 units more than by echo in both NIDCM and control subjects. The LV mass index and LV wall stress were much greater in patients with NIDCM than control subjects. The hemodynamic results (Table 2) indicate a lower diastolic blood pressure at rest (69mmHg vs 79mm Hg, $P = 0.035$) but no significant difference in RPP at rest in the NIDCM patients and the control subjects. The RPP was slightly lower during adenosine infusion in the NIDCM patients as compared to controls ($P = 0.048$), however, the increase in RPP between rest and adenosine infusion was not statistically different (2280 vs 2893 $P = 0.46$) between NIDCM and control subjects, demonstrating a comparable increase in myocardial demand.

Cardiac catheterization was performed in 11 NIDCM patients (Table 3) with right heart hemodynamic data in 8. The mean right atrial pressure and pulmonary capillary wedge or LV end diastolic pressures were elevated. The LVEF by contrast ventriculography was severely depressed. Coronary angiography showed no evidence of significant coronary atherosclerosis.

Figure 1 shows representative still frame short axis images at the peak appearance of Gd-DTPA during the first circulation of Gd-DTPA in a control subject and in a patient with NIDCM, plus an illustration of the method for segmental analysis and a representative signal intensity- time curve. A circumferential zone of reduced density in the subendocardium is present in the NIDCM patient. The circumferential nature of this finding and its persistence on recirculation of Gd-DTPA both indicate that this finding is an indicator of hypoperfusion rather than an imaging artifact.

There was no late gadolinium myocardial enhancement consistent with macroscopic fibrosis in any of the participants' images.

Comparison of hyperemic MPI

During the peak hyperemic effect of adenosine, the transmural MPI was in NIDCM was 0.13 ± 0.01 , which was lower compared to the peak MPI of 0.18 ± 0.01 in control subjects ($P < 0.001$). The subendocardial MPI in NIDCM during adenosine infusion was significantly less than in control subjects 0.13 ± 0.01 vs. 0.18 ± 0.01 , ($P < 0.001$) (Table

4 and Figure 2). Similarly, the subepicardial MPI in NIDCM during the infusion was significantly less than in control subjects 0.13 ± 0.01 vs. 0.18 ± 0.01 , $P = 0.008$).

Subendocardial vs. Subepicardial MPI in NIDCM

At rest, there was no significant difference between the MPI in the subendocardium and subepicardium in the NIDCM patients, 0.084 ± 0.01 vs. 0.073 ± 0.01 ($P = 0.074$). During adenosine infusion, the mean MPI increased significantly in the subendocardium from 0.084 ± 0.01 to 0.13 ± 0.01 ($P < 0.001$) and in the subepicardium from 0.073 ± 0.01 to 0.13 ± 0.01 ($P = 0.006$).

Myocardial perfusion reserve and metabolism in NIDCM

Figure 3 shows the MPRI for transmural, subendocardial and subepicardial myocardium in NIDCM. The transmural MPRI, an overall marker of increased flow above baseline was 1.73 ± 0.23 , the corresponding subendocardial MPRI of 1.59 ± 0.21 was significantly lower than the subepicardial MPRI of 1.86 ± 0.32 ($P = 0.002$).

Figure 4 shows the method for determining k_{mono} and a comparison of k_{mono} to RPP in our current NIDCM patients vs. normal subjects from our prior work [26]. In the NIDCM patients the mean k_{mono} was $0.041 \text{ min}^{-1} \pm 0.005$ and the mean RPP was 7140 beats per $\text{min} \times \text{mmHg}$ resulting in the ratio of $k_{\text{mono}}/\text{RPP}$ of $5.9 \times 10^{-6} \text{ min}^{-1}/\text{beats min} \times \text{mmHg}$. This is significantly less than the value of 8.5×10^{-6} in the normal subjects ($P = 0.001$). In NIDCM the mean WMI was $3.3 \times 10^6 \text{ ml} \times \text{mmHg}/\text{m}^2$. Figure 5 shows the relationship between $k_{\text{mono}}/\text{RPP}$ and subendocardial MPRI in the anterior wall segment shown in Figure 1. (This segment is considered the most free of potential artifact.) There was a significant relationship between the impairment in this index of supply vs. demand and impairment in subendocardial vasodilator reserve.

Discussion

Summary of results

To our knowledge, this is the first published work that demonstrates and compares subendocardial and subepicardial perfusion reserve in patients with NIDCM. This was feasible because of the superior spatial resolution of CMR to differentiate these regions, as opposed to transmural myocardial blood flow and blood flow reserve using PET or catheter-based techniques. The principal findings were 1) lower transmural, subendocardial, and subepicardial myocardial perfusion in NIDCM patients compared to control subjects during adenosine infusion, 2) greater impairment of perfusion reserve in the subendocardium compared to the subepicardium in NIDCM and 3) impaired oxidative metabolism and LV pump efficiency in NIDCM. This impaired vasodilator reserve plus impaired oxidative metabolism provide support for the “energy starvation” hypothesis.

Our findings of attenuated subendocardial perfusion reserve correspond to reports of endothelial dysfunction prior to the onset of heart failure in dogs [33], microvascular remodeling in rats [34], severe impairment of subendocardial perfusion reserve in a canine heart failure model [10, 11] impaired dilatation of coronary microvasculature in patients [35–37] and reduced transmural perfusion reserve in patients with NIDCM using PET [12, 13, 38, 39].

According to the energy starvation hypothesis, LV hypertrophy and subendocardial ischemia [10, 11, 40] are considered the anatomical and physiological basis for metabolic stress [4, 6] in the LV subendocardium. Such a state is postulated to lead to reduced subendocardial energy stores [6], creating a vicious cycle with reduced subendocardial contractility, leading

to progressive LV dysfunction, elevation of LV end diastolic pressure and further reduction of subendocardial perfusion. Our patients with NIDCM had LV hypertrophy, greater systolic LV wall stress, and impaired subendocardial perfusion reserve compared to control subjects. All these support the concept of subendocardial energy starvation in NIDCM.

Comparison to control subjects

The control subjects included individuals with cardiovascular risk factors that may slightly reduce baseline and hyperemic myocardial blood flow [41, 42] and therefore this does not allow a direct comparison between truly normal subjects and the NIDCM patients in this study. Nevertheless, the results do permit the comparison between non-ischemic individuals with and without LV systolic dysfunction and with similar coronary risk factor profiles. In spite of a likely, slight impairment in myocardial blood flow in our control subjects with a moderately high prevalence of coronary risk factors, we still found significant differences in the MPI between these subjects and the NIDCM patients during adenosine infusion. Wang et. al. studied a group of clinically normal subjects with coronary risk factors similar to our control subjects in the Multiethnic Study of Atherosclerosis [41]. No perfusion abnormalities were found on CMR at rest or during adenosine infusion, similar to our control subjects. The global transmural myocardial blood flow averaged 1.01 ml/g/min, and the hyperemic flow averaged 3.02, a perfusion reserve that was far greater than in our NIDCM patients. The blunted, transmural hyperemic response we found with MPRI (1.73) is also much less than in previously reported CMR studies of normal subjects with coronary artery disease (MPRI = 2.8)[43]. Similar results were found using a flow wire technique in patients with chest pain and normal coronary arteries [40] and with [^{13}N] ammonia in actually normal subjects [13].

Comparison to normal physiology and heart failure

In normal dogs under resting conditions, subendocardial blood flow is slightly greater than subepicardial flow [7, 8], and subendocardial flow increases less than subepicardial flow during maximal hyperemia. These findings are much more pronounced in animal models of LV hypertrophy and decompensated heart failure in which subendocardial flow reserve is near exhaustion [10, 11].

In patients with NIDCM, PET has shown reduced transmural myocardial blood flow reserve [13, 38] associated with high LV wall stress and an abnormal oxygen consumption pattern [38]. Using the coronary flow wire technique, there are similar findings of reduced transmural coronary flow reserve in patients with NIDCM [37, 40]. Our finding of a mean increase of 68% in transmural MPI corresponds closely to PET data in NIDCM [13]. Reduced perfusion reserve has been associated with reduced myocardial capillary density in biopsy specimens [3] which is a possible mechanism for these alterations in myocardial blood flow. Our CMR results demonstrate that the subendocardium is predominantly responsible for the reduced transmural perfusion reserve in NIDCM.

We compared our results in patients with NIDCM to the patients with cardiac Syndrome X reported by Panting, et al. who used similar CMR acquisition, measurement and analysis techniques [18]. Our patients showed a modest increase in both subendocardial and subepicardial MPI with adenosine, while Syndrome X patients had no significant change in subendocardial MPI with adenosine.

Metabolism

The metabolic data support the concept of energy starvation. The k_{mono} results and the ratio, $k_{\text{mono}}/\text{RPP}$, in our current patients were reduced compared to our prior normal subjects [26]. The current k_{mono} results were similar to our prior patients with NIDCM [26] and to those in

the literature [21, 22, 28]. Importantly, we found a positive relation between $k_{\text{mono}}/\text{RPP}$ (an index of supply vs. demand) and subendocardial MPRI (Fig. 5) such that reduced metabolic rate per unit demand was associated with less vasodilator reserve. These results suggest (but cannot prove) a causative relationship between subendocardial perfusion and L V oxidative metabolism.

Limitations

- 1) Due to the retrospective collection of the control data, the control subjects did not have resting MPI performed. Thus, we could not estimate their MPRI. Nevertheless, the NIDCM patients had significantly lower MPI than our control subjects during adenosine infusion. Further, the literature supports much lower MPRI in NIDCM than in normal subjects [13, 43] as well as in those with chest pain and coronary risk factors [41, 43].
- 2) Participants in the study were enrolled during a trial of maximum medical therapy for HF, and hence represent a population of patients relatively early in the course of HF. This time frame allowed for the performance of CMR. We acknowledge that the findings may not represent individuals later in the disease process. 3) We acknowledge the limitation of an historical control group in this study. However, coronary risk factors were similar between the NIDCM and control subjects (Table 1), which reduces the possibility of these being confounding factors. While there might be concern that calcium blocking drugs (CCB) in the control subjects might increase the adenosine stress MPI and enhance the difference in MPI between NIDCM and control subjects, we compared the MPI of the 5 subjects with CCB to the 10 without CCB and found no difference between these subgroups (0.178 ± 0.02 SD vs. 0.182 ± 0.01 , respectively, $P=\text{NS}$) (data not shown). Concern might also be raised about the role of LVH and of a history of hypertension (HTN) in our patients with NIDCM compared to the control subjects. Our patients with NIDCM had LVH by MRI and the control subjects did not. The recent CMR literature shows that MPRI was not affected by the LV mass index in a group of patients with controlled hypertension, some with and some without LVH [44]. These investigators also found that MPI was greater in patients with HTN than in normal subjects, regardless of LVH. In light of this, we analyzed our data for subsets of HTN and no HTN. We found there was no statistically significant difference in adenosine MPI between control subjects with a history of HTN (0.19) vs. without (0.18) ($P=0.535$). Further, we found no significant differences in the MPI of NIDCM patients' with a history of HTN (0.138) vs. without (0.12) ($P=0.34$). Thus, we believe that these data support the comparisons of our NIDCM patients to our cohort of control subjects, many of whom had treated HTN and none of whom had LVH.
- 4) There was sex inequality between the NIDCM and control groups with a disproportionately greater number of women in the control cohort, but this would be unlikely to affect our results since prior studies have shown no sex difference in RPP, transmural or regional blood flow in normal subjects during hyperemia [45, 46]. 3) There were a relatively small number of participants in this study, but in spite of this we found highly significant differences in the myocardial perfusion indices between NIDCM and control subjects.

Summary and Conclusions

To our knowledge, this is the first demonstration of reduced subendocardial perfusion and perfusion reserve in patients with NIDCM. These data enhance the results of prior studies that could only demonstrate reduced transmural perfusion. Further, we have documented a correlation between perfusion reserve and oxidative metabolism, such that less perfusion reserve is related to reduced oxidative metabolism per unit demand. . These data support the energy starvation hypothesis. The combination of LV hypertrophy and excess systolic wall

stress in our NIDCM patients augments myocardial demand at a time of reduced myocardial perfusion reserve and impaired oxidative metabolism. Together, this supply-demand mismatch is postulated to cause subendocardial “energy starvation” in NIDCM, leading to reduced contractility and worsening of the condition. Possibly, strategies aimed towards reducing energy starvation may favorably improve LV performance and metabolism in heart failure.

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Figure 1.

Mid ventricular short axis images of a control subject (A) and NIDCM patient (B) at peak arrival of gadolinium contrast within myocardium during adenosine infusion.. A circumferential rim of endocardial hypoenhancement is demonstrated in B. (C) Anterior segment of mid ventricular short axis image divided into endocardium (green) and epicardium (red). (D) Signal intensity vs. time plots of first-pass wash-in of contrast into LV (solid black), endocardium (solid green) and epicardium (solid red). The slope of the appearance of contrast is denoted by dashed lines. NIDCM=nonischemic dilated cardiomyopathy, LV=left ventricle

Figure 2.
Comparison of transmural, subendocardial and subepicardial myocardial perfusion index (MPI) in NIDCM and control subjects during adenosine infusion.

Figure 3.
Comparison of transmural, subendocardial and subepicardial MPRI in NIDCM

Figure 4.

A. Serial cardiac images following $[^{11}C]$ acetate injection, with monoexponential decay rate (k_{mono}). B. Relation of k_{mono} to systolic rate-pressure product (RPP). There is a linear relation between k_{mono} and RPP in normal subjects [$k_{mono}(min^{-1}) = 0.034 \times 10^{-6} + RPP(3.156 \times 10^{-6})$, $R = 0.81$, $P = 0.03$]. In comparison to normal subjects, nearly all NIDCM patients had reduced k_{mono} that would be expected for the level of RPP, and the relationship between k_{mono} and RPP was not significant ($P = 0.54$).

Figure 5.

Relation between ratio $k_{\text{mono}}/\text{RPP}$ and subendocardial MPRI (myocardial perfusion reserve index) segment shown in Fig. 1, where $k_{\text{mono}} (\text{min}^{-1})/\text{RPP} (\text{beats per min} \times \text{mmHg}) = 1.44 \times 10^{-6} + \text{MPRI} (2.745 \times 10^{-6})$, $R = 0.63$, $P = 0.02$]. Please see text for explanation and abbreviations.

Table 1

Characteristics of patients with NIDCM and controls

	NIDCM Mean (95% CI)	Control Subjects Mean (95%CI)	P value
Subjects	13	15	
Sex (male/female)	9/4	2/13	0.03
Age (years)	48 (42–54)	56.1 (49–63)	0.07
Body Surface Area (m ²)	2.1 (1.9–2.3)	1.9 (1.7–2.0)	0.095
Ejection Fraction by Echocardiography (%)	22 (17–26)	57 (53–60)	<0.001
Ejection Fraction by CMR (%)	37 (32–41)	71 (66–75)	<0.001
Left Ventricular Mass (grams)	182 (156–207)	94 (86–102)	<0.001
Left Ventricular Mass Index (grams/ m ²)	87 (78–95)	49 (45–53)	<0.001
Left Ventricular Wall Stress (kPA)	142.9 (120–165)	106 (84–127)	0.006
Medications <i>n</i> (%)			
ACE-I/ARB	13 (100)	8 (54)	0.07
BB	13 (100)	3 (20)	<0.001
CCB	0 (0)	5 (33)	0.044
Cardiovascular risk Factors <i>n</i> (%)			
HTN	7 (53)	11 (73)	0.43
DM	4 (31)	5 (33)	0.89
HLD	6 (46)	7 (46)	0.98

CMR = Cardiac Magnetic Resonance Imaging

ACE-I/ARB = Angiotensin converting enzyme inhibitor or angiotensinogen receptor blocker

BB= Beta-blocker

CCB = Calcium channel blocker

HTN = Hypertension

DM= Diabetes Mellitus

HLD = Hyperlipidemia

Table 2

Hemodynamics of patients with NIDCM and control subjects at rest and during adenosine

	NIDCM Mean (95% CI)	Control Subjects Mean (95% CI)	P value
Rest			
SBP	122.5 (111.6–132.4)	131.2 (121.9–140.1)	0.18
DBP	69.0 (62.5–75.5)	78.8 (71.9–85.7)	0.035
HR	66.2 (60.8–71.6)	70.8 (65.1–76.5)	0.22
RPP	8101(7210–8989)	9296 (8370–10221)	0.057
Adenosine			
SBP	122.5 (112.9–132.6)	134.9(124.8–144.9)	0.076
DBP	68.0 (62.0–73.9)	76.7 (66.5–86.8)	0.14
HR	84.9 (77.8–92.0)	90.3 (82.6–97.8)	0.28
RPP	10381(9253–11508)	12189 (10738–13639)	0.048
RPP difference between rest and adenosine	2281(1150–3409)	2893 (1566–4219)	0.46

SBP = Systolic blood pressure

DBP = Diastolic blood pressure

HR = Heart rate

RPP = Rate pressure product (systolic blood pressure $\times$ heart rate)

Table 3

Cardiac catheterization results and hemodynamics of NIDCM patients

	Mean (95% CI)	No. of patients
Mean right atrial pressure (mmHg)	8 (4.0–11.6)	8
Systolic pulmonary artery pressure (mmHg)	37 (26.5–47.5)	8
Diastolic pulmonary artery pressure (mmHg)	22 (11.1–31.0)	8
Mean pulmonary artery pressure (mmHg)	27 (17.6–36.3)	8
Pulmonary artery wedge pressure (mmHg)	18 (9.9–26.0)	8
Cardiac Output * (L/min)	4.1 (2.4–5.7)	7
Cardiac Index * (L/min/m ²)	2.3 (1.4–3.2)	8
LVSP (mmHg)	112 (94.1–130.0)	8
LVEDP or PCWP (mmHg)	21 (14.4–27.5)	11
Ejection Fraction estimated by Contrast ventriculography (%)	24 (17.4–30.5)	9
Coronary angiography findings	No significant Coronary artery disease**	10

* Cardiac output was measured using the thermal dilution method during right heart catheterization

** No lesions greater than 50% luminal diameter reduction in any vessel

NIDCM = Non- Ischemic Dilated Cardiomyopathy

LVSP = Left Ventricular Systolic Pressure

LVEDP = Left Ventricular End Diastolic Pressure

PCWP = Pulmonary Capillary Wedge Pressure

Table 4

Myocardial perfusion index in NIDCM and controls

		NIDCM (n=13) Mean (95%CI)	Control Subjects (n=15) Mean (95%CI)	P value
Transmural	Rest	0.079 (0.065–0.093)	Not performed	
	Adenosine infusion	0.13 (0.12–0.15)	0.18 (0.17–0.19)	< 0.001
	P value	< 0.0001		
Endocardium	Rest	0.084 (0.066–0.10)	Not performed	
	Adenosine infusion	0.13 (0.110–0.150)	0.18 (0.161–0.199)	< 0.001
	P value	< 0.001		
Epicardium	Rest	0.073 (0.062–0.084)	Not performed	
	Adenosine infusion	0.13 (0.11–0.15)	0.18 (0.16–0.2)	0.008
	P value	0.006		

NIDCM = Non- Ischemic Dilated Cardiomyopathy