ORIGINAL ARTICLE

Early onset of left ventricular regional asynchrony in arteries with sub-clinical stenosis

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Background. Asynchrony has been reported to be a marker of ischemic-induced left ventricular dysfunction, the magnitude of which correlates with extent of epicardial coronary disease. We wished to determine whether normal-appearing arterial territories with mild degrees of asynchrony have lower ^{82}Rb PET absolute myocardial blood flow (MBF) and/or lower myocardial flow reserve (MFR).

Methods and Results. Data were examined retrospectively for 105 patients evaluated for known/suspected CAD who underwent rest/regadenoson-stress ^{82}Rb PET/CT and quantitative coronary angiography. Rest and stress absolute MBF and MFR were quantified from first-pass ^{82}Rb PET curves. Regional relative myocardial perfusion summed stress score (SSS), summed rest score (SRS), regional phase bandwidth (BW), and regional semi-quantitative asynchrony visual scores of (Asynch) were assessed. We found that in apparently normal arteries (SSS < 4, SRS < 4 and stenosis < 70%), those with abnormally low MFR < 2.0 compared to those with MFR ≥ 2.0 had larger phase BW (186 ± 79° vs 158 ± 67°, P = .02), and more visually apparent Asynch (5.7 ± 4.2 vs 3.9 ± 3.6, P = .02), which was associated with increasing stenosis values (ρ = 0.44, P < .0001).

Conclusion. A subgroup of coronary territories with normal relative perfusion and normal or non-obstructive coronary disease may have reduced MFR, which is signaled physiologically by a mild degree of left ventricular asynchrony. (J Nucl Cardiol 2021;28:1040–50.)

Key Words: Physiology of myocardial/coronary perfusion • myocardial ischemia and infarction • PET • myocardial blood flow • dyssynchrony • microvascular dysfunction

Abbreviations	
Asynch	Asynchrony measure
BW	Bandwidth
CAD	Coronary artery disease
EF	Ejection fraction
LAD	Left anterior descending
LCX	Left circumflex
LV	Left ventricle
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
PET	Positron emission computed tomography
RCA	Right coronary artery

INTRODUCTION

PET/CT pharmacologic stress myocardial perfusion imaging is a highly effective technology for diagnosing hemodynamically significant obstructive coronary disease (CAD).[1] CAD can be identified by qualitative evaluation of relative tracer uptake or comparison to a known database.[2] PET accuracy is improved by using quantified rest and stress absolute myocardial blood flow (MBF) and myocardial flow reserve (MFR = stress MBF/rest MBF).[3]

In studies of PET accuracy, x-ray contrast arteriography is often the accepted reference standard, defined as per cent luminal stenosis. Coronary arteries are considered abnormal and flow-limited for stenosis $\geq 70\%$. However, lesser degrees of discrete epicardial stenosis may be associated with abnormal regional flow and wall motion abnormalities,[4] due to obstruction at three other anatomic levels: (1) diffuse non-critical epicardial coronary stenoses; (2) microvascular coronary disease, affecting arterioles below the level of angiographic resolution; and (3) endothelial dysfunction in the production of local vasodilators such as nitric oxide and impairment in sympathetic innervation.[5] Coronary microvascular disease and endothelial dysfunction may reduce blood flow, manifested by reduced MFR, and produce wall motion abnormalities and ventricular dysfunction.[6]

An ''ischemic cascade'' or constellation of sequential cardiac mechanical events has been postulated to occur in response to ischemia resulting from oxygen supply/demand imbalance, including altered diastolic and systolic function, ECG changes, and angina.[7] Since oxygen extraction by myocardium is near maximal at rest, metabolic alterations must derive from inadequate coronary blood flow.[5] Left ventricular (LV) asynchrony is an additional marker of ischemic-induced LV dysfunction,[8] and the magnitude of asynchrony induced by pharmacologic stress correlates directly with extent of epicardial coronary disease.[9] Decreasing regional MBF and MFR induces progressively more pronounced asynchrony.[10]

There has been increased recognition that myocardial perfusion imaging studies with minimal heterogeneity, previously interpreted as normal, may be associated with major adverse acute coronary events during long-term follow-up.[11] Events may occur even with summed stress score (SSS) < 4 or low scores for total perfusion deficit.[12] Quantitation of flow in such patients may be helpful in elucidating their risk.[13]

The hypothesis of this investigation is that subtle abnormalities of ventricular function, primarily manifest as abnormal LV synchrony, serve as an early identifier of ischemic LV dysfunction. Asynchrony might be detected even when LV relative perfusion scores are within accepted normal limits, and rigorous anatomic angiographic analysis reveals only subcritical coronary stenosis. We wished to determine whether normal-appearing arterial territories with mild degrees of asynchrony have lower MBF and/or lower MFR.

MATERIALS AND METHODS

Patients

We conducted a retrospective investigation of an unselected population of patients who were evaluated between 1/1/2010 and 12/31/2016 for known/suspected CAD. Data of 105 patients (age 69 ± 13 years; 42 females; 63 males) were analyzed. All patients had coronary arteriography that was technically adequate for quantitation, and ^{82}Rb rest and regadenoson-stress PET studies with determination of MBF. Mean time difference between PET and angiography was 138 ± 388 days, with no cardiac events (e.g., PCI or MI) between PET and angiography. 39% of patients had a history of PCI, 22% had a history of MI, and 24% had a history of CABG.

The Institutional Review Board approved this retrospective study and the requirement to obtain informed consent was waived. All data were handled in compliance with the Health Insurance Portability and Accountability Act of 1996.

Angiography Digital cines were reviewed by expert angiographers at a core laboratory (Boston Clinical Research Institute, BCRI, Boston, MA), who quantified stenosis by

planimetry using ''PlusPlus'' software (Sanders Data Systems, Palo Alto, CA). Arteries with at least a 20% stenosis were quantified as to exact percent stenosis. Lesions in vessels < 2.0 mm in diameter were not assessed unless the lesion was in a vascular segment that was the primary conduit of circulation for any myocardial wall/segment, or if the artery segments would be ≥ 2.0 mm in diameter if fully perfused.

For each patient, the three major coronary arterial territories (LAD, LCX, and RCA) were given a score based on the most severe stenosis in the major artery in that territory. In cases in which more than one lesion was identified in a territory, the value of the stenosis of the most severe lesion was recorded. For each territory in which there was no stenosis of ≥ 20% visualized, a value of 0% stenosis was adopted.

PET Data Collection

The PET data acquisition protocol followed standard published guidelines.[14] As the pharmacologic testing agent was regadenoson, patient preparation included the standard recommended duration of fasting, abstention from caffeine, and withholding of cardiac medications.[15] At rest, 0.94-1.22 GBq (35-45 mCi) of ^{82}Rb was infused from a strontium-rubidium generator over 20-30 seconds. At peak pharmacologic stress 50-60 seconds following initiation of regadenoson injection, a similar activity was injected over approximately 20-30 seconds.[16] Blood pressure, heart rate, and cardiac rhythm were monitored and recorded throughout imaging and pharmacologic testing. PET/CT studies were acquired on a GE Discovery VCT 64 PET/CT in 2D mode (N = 74) or on a GE D710 PET/CT 64-slice CT system in 3D mode (N = 31). Data acquired in 3D mode were corrected for prompt gamma rays.[17]

All data were acquired in gated list mode and reconstructed by OSEM (20 subsets; 2 iterations; z-axis filter = ''standard''; post-filter = 2.57 mm FWHM), as recommended by the manufacturer. Attenuation correction of tomograms was performed as part of iterative image reconstruction using CT data. First-pass data subsequently were re-binned as 20 3-second frames, 5 12-second frames, and 7 30-second frames. From the equilibrium phase of the study, myocardial perfusion portions of data were re-binned as gated tomograms at 8 frames/R-R interval, with non-gated equilibrium images formed by summing the gated tomograms.

Regional Myocardial Perfusion Computation

Semi-automated software (Emory Cardiac Toolbox, ''ECTb,'' Emory University, Atlanta, GA) computed MBF from dynamic first-pass data.[18] A 1-tissue compartment, 1 rate constant (microsphere analog) model with spillover effects described tracer uptake in myocardial tissue. Algorithms automatically identified blood pool and myocardial tissue voxels. Curves sampled at blood pool locations were corrected for myocardial activity ''spill over'' caused by LV contraction, respiration, and imperfect spatial resolution. Rest and stress MBF and MFR values were obtained for each of the three main arterial territories. MFR < 2.0 was considered abnormal.[19]

From equilibrium data, rest and stress LVEF and volumes were calculated using ECTb. These algorithms also applied ^{82}Rb-specific normal limits to equilibrium images to obtain LV relative perfusion scores for perfusion polar maps for three main arterial territories, including SSS, summed rest scores (SRS), and summed difference scores (SDS) generated by an artificial intelligence-driven approach.[20]

Apparently normal arteries were defined by conventional criteria as those with territorial SRS < 4 and territorial SSS < 4 and stenosis < 70%.

Coronary territories were then assigned to one of the three following classes: (Artery Class1) apparently normal arteries with low relative perfusion scores (SSS and SRS < 4) and insignificant 0%-20% stenosis; (Artery Class2) apparently normal arteries with low relative perfusion scores (SSS and SRS < 4) and with 20%-69% stenosis; (Artery Class3) arteries with significant stenosis: ≥ 70% stenosis.

Regional LV Wall Thickening Computation

ECTb algorithms reported wall thickening (WT) abnormality values ranging from 0 (normal) to 4 (most severe) in each of the 17 segments of LV WT polar maps. WT was quantified for rest and stress for each of the 3 major territories by summing all of the non-zero scores within those territories.

Regional LV Bandwidth Computations

Rest and stress systolic and diastolic phase parameters and visual displays were computed from equilibrium gated tomograms (ECTb SyncTool).[21] Phase histograms depicting frequency of occurrence of contractions at each phase of the R-R interval were color coded to polar maps displaying the phase at which maximum contraction occurred (Figures 1A and 1B). Similar phase histograms and polar maps were generated for regional diastolic relaxation (Figures 1C and 1D). SyncTool algorithms reported only global values of phase standard deviation and phase bandwidth (BW), which quantifies the amount of the R-R interval over which 95% of systolic contractions and 95% of diastolic relaxations occur. To obtain territorial values of these parameters, algorithms were written in IDL V 8.2 to analyze polar maps converted to jpg files. Each pixel was scaled from a minimum of 0 to a maximum of 360 to span the range of angles and tabulated in one of 3 arrays to correspond to the locations in the map that corresponded to the 3 main territories, with locations defined in the same way as the indicated boundaries that are routinely displayed on polar maps of relative perfusion and MBF.

Regional LV Visual Asynchrony Analysis

Visual asynchrony scoring of coronary territories was performed using a method previously described by our laboratory.[22] A medical imaging physicist and a cardiologist independently graded regional asynchrony on a 5-point scale while viewing rest and stress systolic and diastolic phase histograms and polar maps. The lowest score (0 = ''normal'') was assigned to a territory if rest and stress systolic phase
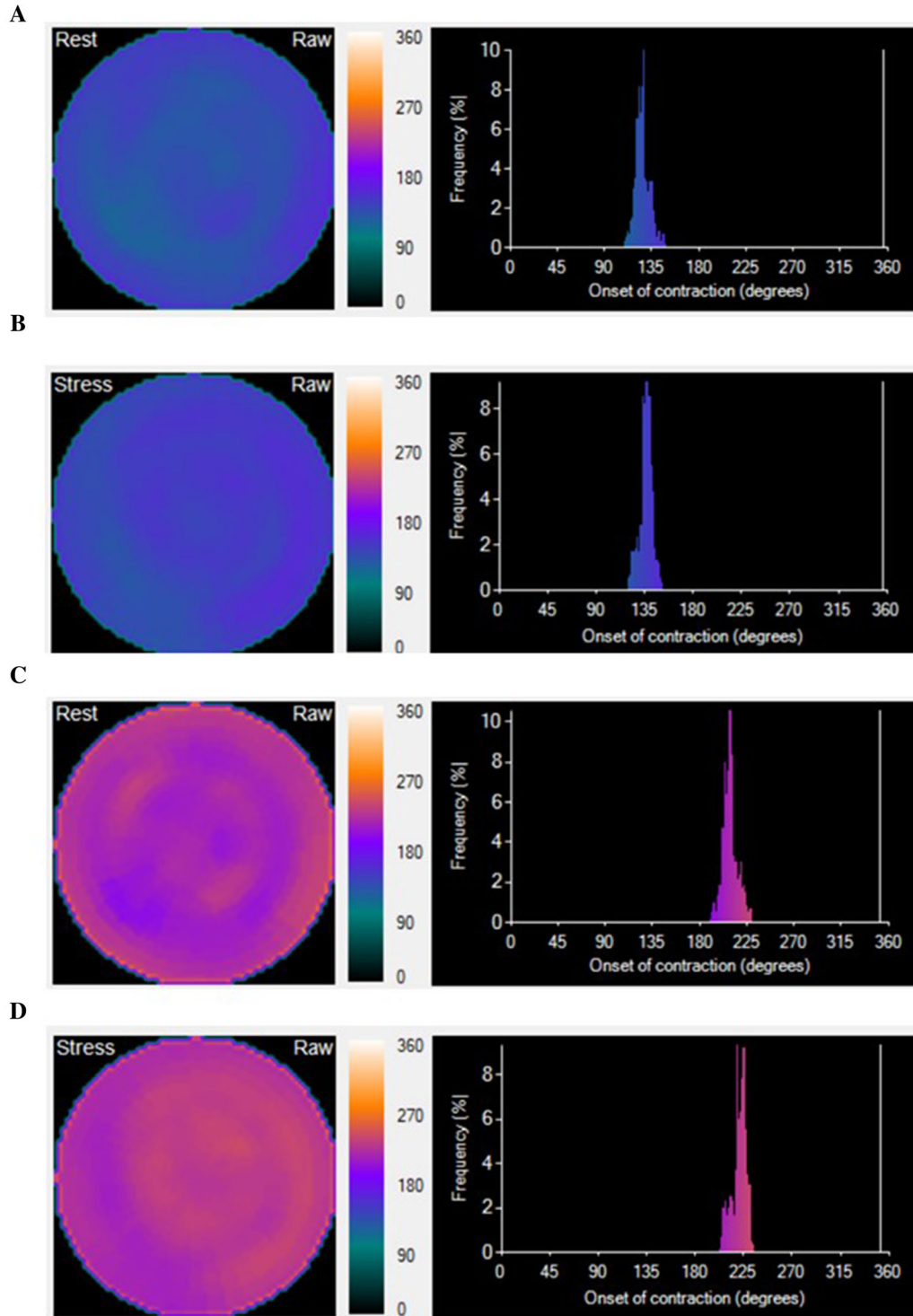
Figure 1. Systolic contraction phase polar maps and phase histograms at rest (**A**) and stress (**B**) and diastolic relaxation phase polar maps and phase histograms at rest (**C**) and stress (**D**) for a patient with LAD, LCX, and RCA stenosis < 20%, regional SSS of 0, 0, and 0, regional SRS of 0, 0, and 0, regional MFR of 3.8, 3.7, and 3.7, regional visual asynchrony scores of 0, 0, and 0, and regional phase BW values of 79°, 66°, and 66°.
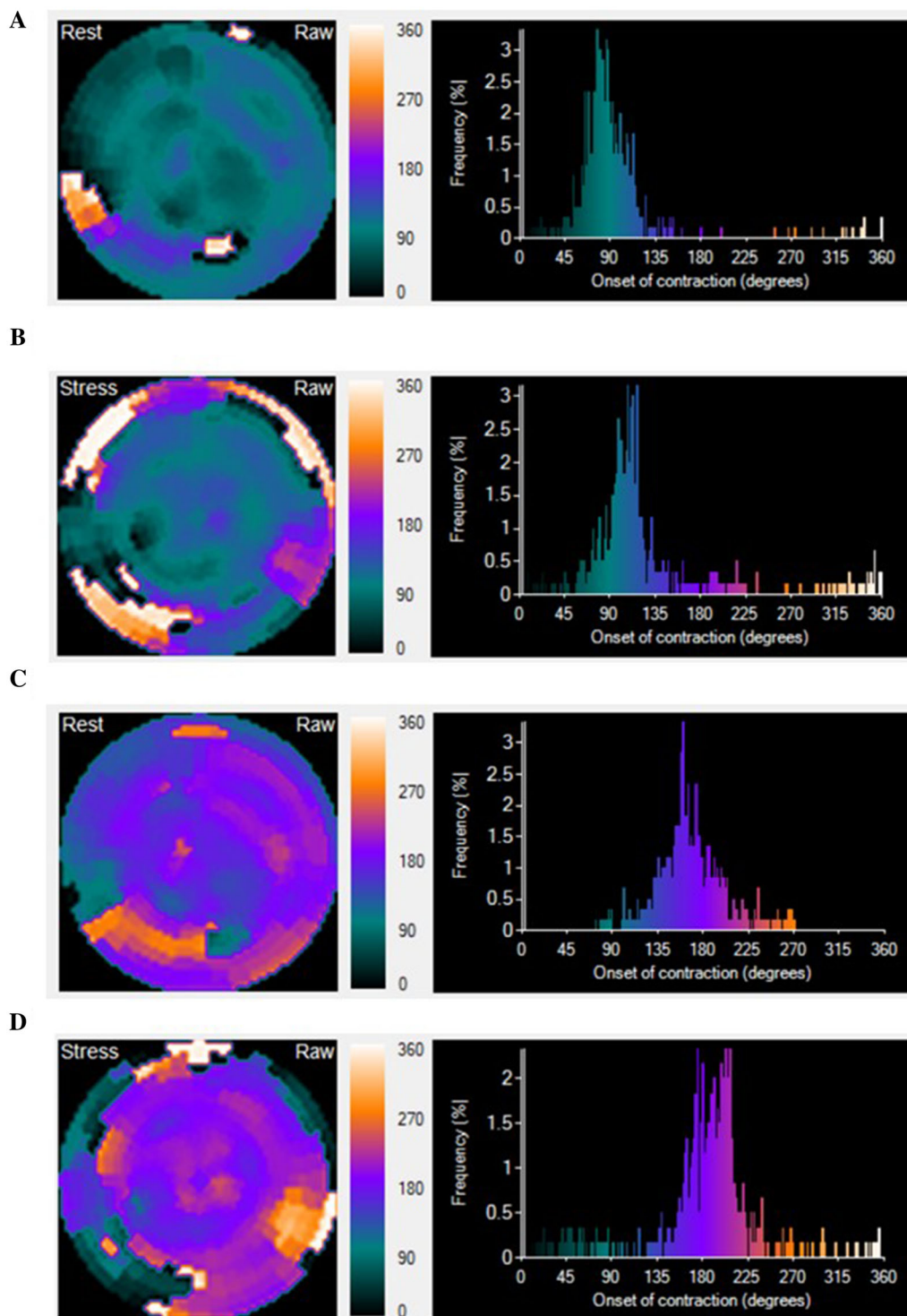
Figure 2. Systolic contraction phase polar maps and phase histograms at rest (**A**) and stress (**B**) and diastolic relaxation phase polar maps and phase histograms at rest (**C**) and stress (**D**) for a patient with LAD, LCX, and RCA stenosis of 48%, 42%, and 0%, regional SSS of 0, 0, and 0, regional SRS of 0, 0, and 0, regional MFR of 1.29, 2.29, and 2.08, regional composite visual asynchrony scores of 10, 9, and 10, and regional composite BW values of 177°, 227°, and 187°.

histograms were narrow peaks centered near 1/3 R-R, and diastolic phase histograms were narrow peaks centered near 2/3 R-R, along with rest and stress phase maps displaying uniform contraction throughout that territory. The highest score (4 = ''markedly asynchronous extensive territory'') was assigned to a territory if phase histograms were broad or scattered and corresponded to a large % of contractions occurring out of phase for a large extent of that territory. For each reader, a composite value of visual regional phase asynchrony (Asynch) was formed, generated by summing all systolic and diastolic rest and stress visual territorial scores, for which the highest possible value was 16 per territory. All scoring was performed by both readers without access to other clinical or computed information. The purpose of defining the semi-quantitative visual Asynch parameter in this way was to quantify observers' perceptions of unusual-appearing patterns in systolic or diastolic, rest or stress phase relationships while viewing phase polar maps and phase histograms generated by the ECTb algorithms. Examples in which anomalies sometimes are even more striking in diastolic relaxation than in systolic contraction phase maps and phase histograms illustrate the reason that we summed visual scores for all four phase types of systolic, diastolic, rest, and stress visual scores (Figure 2).

Statistical Analysis

Analyses were performed using ''MedCalc'' commercially available statistical analysis software.[23] Values are reported as means ± one standard deviation. Continuous variables were assessed by the χ^2 test to determine normality of distribution. ANOVA assessed whether there were differences among continuous variables by artery class, and assessed whether there were differences among continuous variables, and automatically applied Bonferroni corrections for comparisons among multiple categories. The unpaired or paired t test, as appropriate, compared values between groups for continuous variables that were normally distributed; otherwise, the Mann-Whitney or Wilcoxon test was used. χ^2 Analysis of proportions compared ratios. Linear regression determined whether there were significant associations among continuous variables, for which Pearson correlation coefficients (r) were generated. Rank correlation determined strength of association between continuous and discrete variables, for which Spearman's correlation coefficients (ρ) were generated. Inter-observer agreement for Asynch scores was assessed by the χ^2 test for contingency tables. For all tests, probability (P) < .05 was defined as statistically significant, or as adjusted by Bonferroni corrections.

RESULTS

Coronary Artery Classification

315 Coronary arterial territories were assessed for the 105 patients. There were 174 arteries with undetectable stenosis (stenosis < 20%), 72 arteries with 25%-69% stenosis, and 69 arteries with 70%-100%

stenosis. Thus, there were 246 arteries with stenosis < 70%. Including relative perfusion considerations (SSS < 4 and SRS < 4), by conventional criteria there were 122 Class1 arteries with low relative perfusion scores and 0%-20% stenosis, 56 Class2 arteries with low relative perfusion scores and stenoses ranging from 25% to 69%, and 69 Class3 arteries with low relative perfusion scores and significant stenoses ranging from 70% to 100%.

Mean QRS duration was 0.11 ± 0.03 seconds, and there were no QRS duration differences among artery classes (P = .13).

Regional Myocardial Perfusion

Rest MBF was higher for apparently normal arteries than abnormal arteries (0.86 ± 0.59 vs 0.77 ± 0.38, P < .001), as was stress MBF (2.03 ± 1.23 vs 1.29 ± 0.84, P < .001), so that regional MFR was higher for apparently normal than abnormal arteries (2.54 ± 1.18 vs 1.79 ± 1.13, P < .001). Nonetheless, 35% (63/178) of apparently normal arteries had territorial MFR below 2.00. Those arteries had a mean MFR value of 1.58 ± 0.27, for which the minimum was 0.98 (Table 1). Despite having normal relative perfusion scores, and similar quantified stenosis values, apparently normal arteries with MFR < 2.00 had lower stress MBF, larger phase BW (186 ± 79° vs 158 ± 67°, P = .02), and a larger Asynch score (5.7 ± 4.2 vs 3.9 ± 3.6, P = .02), compared to apparently normal arteries with MFR ≥ 2.00. WT scores did not differ between the groups (Table 1).

Regional LV Function

Regarding visual Asynch scores, there was good agreement between the two readers (χ^2 = 334.8, P < .0001), with contingency coefficient = 0.72 (P < .001).

In quantifying regional phase parameters, the mean number of pixels sampled per arterial territory was 4,732 ± 847, consistent with 128 transaxial sections having been reconstructed as 128 × 128 matrices, so that the numbers of sampled polar map phase values per territory were on the order of 128 × 128/3. Regional phase standard deviation reflected regional territorial phase BW so closely that only BW values were further analyzed (r = .97).

Table 2 compares apparently normal arteries with stenosis 0%-20% to those with stenosis of 20%-69%. Relative perfusion scores, MFR and WT were similar between the two groups. Regional phase BW was lower in apparently normal arteries with < 20% stenosis compared to 20%-69% stenosis (158 ± 71° vs 182 ± 72°, P = .02), as were visual Asynch scores

Table 1. Regional myocardial perfusion and function in apparently normal arterial territories subdivided by normal and abnormal regional myocardial flow reserve (MFR)

	MFR < 2.0 (N = 63)	MFR ≥ 2.0 (N = 115)
Stenosis (%)	16 ± 24	14 ± 23
Rest MBF	1.06 ± 0.84	0.75 ± 0.35*
Stress MBF	1.61 ± 1.10	2.25 ± 1.25*
MFR	1.58 ± 0.27	3.08 ± 1.15*
SRS	0.6 ± 1.1	0.5 ± 1.1
SSS	1.1 ± 1.4	0.6 ± 1.3*
SDS	0.5 ± 0.9	0.1 ± 0.3*
WT	0.67 ± 1.43	0.50 ± 1.60
BW (°)	186 ± 79	158 ± 67*
Asynch	5.7 ± 4.2	3.9 ± 3.6*

MFR, myocardial flow reserve; *MBF*, myocardial blood flow; *SRS*, summed rest score; *SSS*, summed stress score; *SDS*, summed difference score; *WT*, wall thickening; *BW*, bandwidth; *Asynch*, asynchrony
*$P < .05$ vs MFR < 2.0

Table 2. LV territorial absolute and relative perfusion measures for apparently normal arteries with stenosis 0%-20% and 20%-69% and low relative perfusion scores compared to arteries with significant stenosis ≥ 70%

Parameter	Artery Class1 SRS < 4 and SSS < 4 and stenosis < 20% (N = 122)	Artery Class2 SRS < 4 and SSS < 4 and stenosis = 20%-69% (N = 56)	Artery Class3 stenosis > 70% (N = 69)
Stenosis (%)	0 ± 0	47 ± 13*	91 ± 10*[†]
Rest MBF	0.91 ± 0.61 (mL·g^{-1}·min^{-1})	0.77 ± 0.53 (mL·g^{-1}·min^{-1})	0.77 ± 0.38 (mL·g^{-1}·min^{-1})
Stress MBF	2.15 ± 1.31 (mL·g^{-1}·min^{-1})	1.75 ± 0.98 (mL·g^{-1}·min^{-1})	1.29 ± 0.84* (mL·g^{-1}·min^{-1})
MFR	2.57 ± 1.23	2.50 ± 1.79	1.79 ± 1.13*[†]
SRS	0.6 ± 1.1	0.5 ± 1.0	2.9 ± 3.6*[†]
SSS	0.9 ± 1.4	0.6 ± 1.2	5.9 ± 5.9*[†]
SDS	0.2 ± 0.6	0.2 ± 0.6	3.1 ± 4.0*[†]
WT	0.5 ± 1.3	0.7 ± 1.9	3.9 ± 5.4*[†]
BW (°)	158 ± 72	182 ± 71*	209 ± 80*
Asynch	3.9 ± 3.7	5.9 ± 4.3*	9.1 ± 4.6*[†]

SSS, summed stress score; *SRS*, summed rest score; *SDS*, summed difference score
*$P < .025$ vs Artery Class1; [†]$P < .025$ vs Artery Class2

(3.9 ± 3.7 vs 5.9 ± 4.3, $P = .002$, Figure 3; Table 2). Regional Asynch scores had significant rank correlation with regional BW ($\rho = 0.74$, $P < .0001$). Of all variables tested, Asynch scores correlated most strongly with continuous values of stenosis ($\rho = 0.44$, $P < .0001$).

Blood Flow in Apparently Normal Arteries

Considering only apparently normal arteries, ROC analysis of Asynch and BW values to discriminate between arteries with stenosis values ≥ 20% (Figure 2) from those arteries judged to have no recognizable stenosis (Figure 1) yielded threshold values of Asynch > 6 and BW > 165°. Using these as the discrimination thresholds, both resting MBF and stress MBF were

significantly higher for Asynch $\leq$ 6 vs those with Asynch > 6, and for BW $\leq$ 165° vs BW > 165°, and stenosis was less, despite similar regional MFR (Table 3). Relative perfusion measures were similar for these Asynch and BW categories (Table 3), which was predictable considering that our definitions of apparently normal arteries were those with SRS < 4 and territorial SSS < 4 and stenosis < 70%.

DISCUSSION

The goal of this research was to determine whether pharmacologic stress-induced mild LV dysfunction, manifest as either wall thickening abnormalities or asynchrony, might identify an ischemic response in patients with non-critical coronary stenosis, but who might have diffuse non-obstructive or microvascular CAD. Our findings indicate that in coronary arterial territories with normal relative qualitative perfusion, a previously described index of LV asynchrony[22] was significantly increased (greater asynchrony) in coronary artery territories with reduced stress myocardial blood flow and reduced flow reserve. Worsened asynchrony was more likely in arteries with an average stenosis of 20%-69% (mean 47%) than 0%-20%. LV systolic dysfunction, assessed by wall thickening index, did not appear to discriminate between arteries with a lower flow reserve (< 2.0) or between the two levels of subcritical coronary stenosis.

Stress-induced changes in asynchrony have been used increasingly to identify ischemic heart disease and quantify its extent. While pharmacologic stress reduces asynchrony in normal subjects,[24] more recently it has been demonstrated that stress-induced asynchrony differentiates ischemic vs non-ischemic cardiomyopathy,[8] and that degree of asynchrony correlates with extent of CAD.[9] A prior study in patients with normal PET MPI scans showed that systolic asynchrony improved with stress in groups with normal or severely abnormal overall LV function, despite their having a significant prevalence of CAD.[25] However, coronary anatomy was not described in that work, and diastolic asynchrony was not evaluated, as in the current study. Other studies have shown that increasing degrees of asynchrony identify multi-vessel CAD on SPECT MPI,[9] suggesting that asynchrony should be related to blood flow.[13] Our study used stress-induced asynchrony to attempt to distinguish coronaries with modest degrees of non-critical obstruction from those without. Our results indicate that mild degrees of worsening asynchrony may serve as a marker of territories with early ischemia despite normal qualitative perfusion.

MFR reflects total resistance across the coronary vasculature.[26] The anatomic level giving rise to

pharmacologic stress-induced mild ischemic LV asynchrony in our patients cannot be precisely defined. The fact that asynchrony was associated with MFR < 2.0 and mean coronary stenosis of 47% suggests that it may arise from diffuse non-obstructive CAD, with diffuse luminal narrowing. Base-to-apex perfusion gradients characteristic of non-obstructive arterial narrowing may co-exist with other regions of severe epicardial stenosis.[27] Alternatively, mild ischemia may arise in the microvasculature, the coronary pre-arterioles, and arterioles (< 100-400 μm) which provide a large portion of overall coronary resistance.[28] These vessels normally auto-regulate to maintain myocardial blood supply. Disease states, such as diabetes and hypertension that may cause arteriolar remodeling, impede autoregulation leading to local myocardial hypoxia. Endothelial dysfunction, through inhibition of vasodilating mediators such as nitric oxide, can reduce local oxygen delivery leading to ischemia. Pathophysiologic changes at any or all of these anatomic levels may cause ischemia and LV asynchrony in the absence of an identifiable ''critical stenosis'' in the epicardial vasculature.

A scan showing normal relative myocardial perfusion is felt to confer a good long-term prognosis. However, patients with normal scans may have a significant event rate. For PET, an MFR value < 2.0 identifies a group of patients with normal-appearing perfusion imaging who are at increased risk for MACE.[29] For SPECT imaging, the REFINE-SPECT study reviewed scans and events (4.5 years of follow-up) in nearly 20,000 patients.[12] A normal scan, or a SSS = 0, conferred a 1.3%-2.0% MACE rate. In our study, normal relative perfusion, with mild worsening of asynchrony was associated with MFR < 2.0, and non-obstructive CAD which was more advanced. Whether mild stress-induced asynchrony can help further categorize the risk for events in patients with normal perfusion scans will require further study.

Limitations

Our study is limited by a restricted number of patients, but has the advantage of studying a population selected only on the basis of having technically adequate PET imaging and angiograms. Other investigations that combined PET MPI and angiography included larger populations,[30] but relied on qualitative analysis of angiograms, rather than the detailed quantitative analysis used in the present study. It also would have been desirable to relate asynchrony to a physiologic descriptor of coronary stenosis severity, such as fractional flow reserve, but this was beyond the scope of the current study.[26]

Table 3. LV territorial absolute and relative perfusion measures for apparently normal arteries with lower and higher regional phase bandwidth (BW) and regional visual asynchrony (Asynch) scores

Parameter	BW ≤ 165° (N = 101)	BW > 165° (N = 77)	Asynch ≤ 6 (N = 127)	Asynch > 6 (N = 51)
Stenosis (%)	10 ± 20	20 ± 25*	12 ± 22	23 ± 26†
Rest MBF	1.05 ± 0.70 (mL·g⁻¹·min⁻¹)	0.64 ± 0.28* (mL·g⁻¹·min⁻¹)	0.97 ± 0.65 (mL·g⁻¹·min⁻¹)	0.61 ± 0.27† (mL·g⁻¹·min⁻¹)
Stress MBF	2.42 ± 1.29 (mL·g⁻¹·min⁻¹)	1.50 ± 0.97* (mL·g⁻¹·min⁻¹)	2.26 ± 1.22 (mL·g⁻¹·min⁻¹)	1.42 ± 1.06† (mL·g⁻¹·min⁻¹)
MFR	2.55 ± 1.22	2.59 ± 1.13	2.62 ± 1.21	2.37 ± 1.08
SRS	0.6 ± 1.1	0.6 ± 1.1	0.6 ± 1.1	0.5 ± 1.0
SSS	0.9 ± 1.4	0.8 ± 1.3	0.8 ± 1.4	0.7 ± 1.2
SDS	0.3 ± 0.7	0.2 ± 0.4	0.3 ± 0.7	0.2 ± 0.4

*$P < .05$ vs BW ≤ 165°; †$P < .05$ vs Asynch ≤ 6
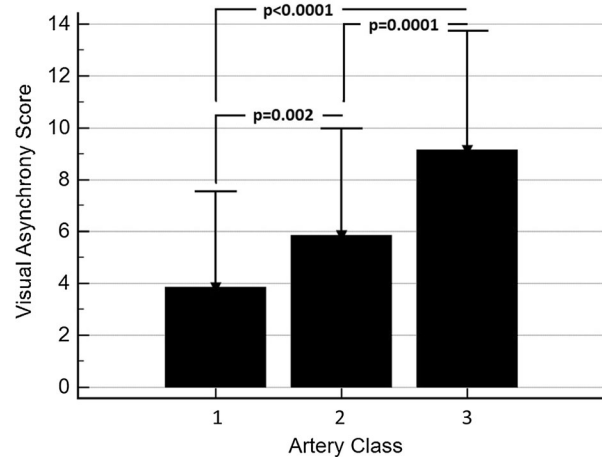
Figure 3. Regional visual asynchrony scores vs artery class.

We combined visual systolic and diastolic asynchrony scores into a semi-quantitative parameter designed to achieve the maximal sensitivity for detecting mild degrees of regional asynchrony. Studies on the ischemic cascade suggest that either systolic or diastolic dysfunction may occur early after the initiation of ischemia.[7] Our process of assigning scores to quantify visual impressions of asynchrony magnitude is similar to the well-accepted practice of clinicians' grading of relative myocardial perfusion. Both our quantitative (BW) and semi-quantitative visual asynchrony parameters were limited in that they did not identify whether the preponderance of mild asynchrony was systolic or diastolic in origin. Nevertheless, our semi-quantitative visual approach has been previously validated, and yielded good agreement between observers, supporting the validity of our observations.

CONCLUSIONS

Patients with coronary artery disease may have angiography that shows non-obstructed vessels, with normal regional perfusion. The majority of these territories have quantified rest and stress myocardial perfusion and perfusion reserve that are normal, but a sizeable percentage have subnormal MFR. This finding appears to correlate with angiographic anatomy which, though non-obstructive, has a higher percent stenosis than vessels with normal MFR, and with mild abnormalities of overall systolic and/or diastolic LV synchrony. These data suggest that systolic and diastolic asynchrony may help define coronary arterial territories which are apparently normal by relative perfusion criteria, but which have low perfusion reserve and the potential for demonstrating stress-induced ischemia. Consequently, it is advisable to measure regional

MBF, MFR, and regional asynchrony for patients with suspected CAD.

NEW KNOWLEDGE GAINED

A subgroup of coronary territories with normal relative perfusion and normal or non-obstructive coronary disease may have reduced MBF and/or reduced MFR, which is signaled physiologically by a mild degree of left ventricular asynchrony.

Disclosures

No other potential conflicts of interest relevant to this article exist.

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