CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Audible Coronary Artery Stenosis

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ABSTRACT

OBJECTIVE: Hemodynamically significant coronary artery stenoses generate turbulent blood flow patterns that manifest as intracoronary murmurs. This study aims to evaluate the performance of modern acoustic detection of these murmurs by acoustic signals captured from patients undergoing gold standard comparative coronary angiography.

METHODS: We prospectively studied 156 patients undergoing elective coronary angiography, excluding those with acute coronary syndrome, prior chest surgery, or significant valvular disease. Acoustic signals were captured before arterial access. Angiographic degree of stenosis in each coronary artery was graded blinded to clinical and acoustic data. Acoustic data were analyzed blinded to clinical and angiographic data, categorizing subjects as "normal," "diseased," or "inconclusive." Of 156 patients examined, 123 generated analyzable data.

RESULTS: Angiographically significant stenosis (≥50%) prevalence was 52% (18%, 23%, 11% with 1-, 2-, 3-vessel disease, respectively). Acoustic detection sensitivity and specificity for stenosis ≥50% in any vessel were 0.70 and 0.80, respectively (negative predictive value, 0.71; positive predictive value, 0.79). Acoustic detection optimally identified stenosis ≥50% with an area under the curve of 0.75. For stenosis ≥50% in major vessels only (left main, proximal-mid left anterior descending, proximal-mid circumflex, proximal-mid right coronary), prevalence was 46%; sensitivity and specificity were 0.72 and 0.76, respectively (negative predictive value, 0.76; positive predictive value, 0.72; area under the curve, 0.76).

CONCLUSIONS: Acoustic signal patterns and modern analysis techniques may be used to identify intracoronary murmurs generated by hemodynamically significant coronary artery stenoses in all major vessels. Further investigation is warranted to compare the clinical performance of this modality with current noninvasive approaches that evaluate patients at risk for atherosclerotic and obstructive coronary artery disease.

 • *The American Journal of Medicine (2016) 129, 515-521*

KEYWORDS: Acoustic cardiography; Intracoronary murmur; Stenosis; Turbulence

Normal coronary arterial blood flows in a laminar orientation and reaches maximal velocity during diastole.[1,2] Stenotic segments disrupt flow patterns as blood accelerates through and disassembles on lesional exit. As flow velocity exceeds laminar thresholds, turbulence manifests and produces an intracoronary murmur.

Methods to characterize these turbulent flow conditions in coronary arteries have evolved on the basis of a fundamental understanding of fluid dynamics. Turbulent flow exerts fluctuating stresses on coronary arterial walls, transmitting vibrations as acoustic pressure wave signals. These signals are predictably detectable within specified frequency ranges.[3,4] In large arteries, such as carotids, a portion of the acoustical emission from stenosis-related turbulence manifests in the frequency range audible to the human ear, clinically described as "bruits." However, most of the acoustic signal spectrum of stenosis-related turbulence is complex and beyond the range

Funding: The majority of the trial costs were provided by the University of Minnesota Cardiovascular Division. AUM Cardiovascular, Inc provided partial support for a research nurse during the trial.

Conflict of Interest: EC was provided with partial support by AUM for work as a research nurse and training to use the device used in the subsequent TURBULENCE (CLINICAL EVALUATION OF THE CADENCE DEVICE IN DETECTION OF CORONARY ARTERY DISEASES) trial, which is the pivotal trial for the AUM device that followed the feasibility trial. RFW holds stock options in AUM Medical related to work performed after this study was completed and to protocol development and subsequent management of the TURBULENCE (CLINICAL EVALUATION OF THE CADENCE DEVICE IN DETECTION OF CORONARY ARTERY DISEASES) trial.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2016.01.015

of unassisted human auscultation. Bruits from coronary artery stenosis (ie, intracoronary murmurs) have been described historically (ie, Dock's murmur), but are rarely appreciated with a standard stethoscope and human ear.[5] Competing acoustic signals may be generated from intracardiac valvular abnormalities and adjacent organs (ie, lung expansion), and low-frequency 200 Hz sounds may be secondary to flow variation, aortic translational movement, and ventricular filling. Moreover, the acoustic insulation of the chest, intervening intrathoracic tissue, and overlying soft tissue may diminish the amplitude of acoustic signals generated from stenotic coronary artery segments.[6]

As of yet, no modern study has validated the use of acoustic detection of coronary artery stenosis in at-risk patients undergoing catheter-based coronary angiography.[2,7] In this study, we sought to evaluate the performance of modern acoustical detection to identify intracoronary murmurs corresponding to significant coronary artery stenoses as confirmed by gold standard coronary angiography.

CLINICAL SIGNIFICANCE

- This report validates the performance of modern acoustic detection and analysis of intracoronary murmurs corresponding to hemodynamically significant coronary artery stenoses in all major vessels.
- The clinically relevant comparison with gold standard, catheter-based coronary angiography yields sensitivity and specificity detecting stenoses ≥50% at 0.70 and 0.80, respectively (negative predictive value, 0.71; positive predictive value, 0.79).
- Audible coronary artery stenosis may support decision-making toward further diagnostic testing of suspected atherosclerotic and obstructive coronary artery disease.

MATERIALS AND METHODS

Patient Selection

The study population comprised 156 patients aged 18 to 89 years who were referred for elective coronary angiography on the basis of chest pain, anginal equivalent, or preoperative evaluation, with or without positive or indeterminate stress testing at the University of Minnesota Medical Center from April 2004 to March 2011 (with institutional review board approval). Patients with acute coronary syndromes, prior open chest surgery (including coronary bypass surgery), and known significant valvular disease (categorized as a prior diagnosis of moderate to severe insufficiency or stenosis) were excluded from the study.

Study Protocol

On arrival to the cardiac catheterization laboratory, informed consent was obtained. In the supine position, patients underwent targeted auscultation using an advanced digital electronic stethoscope (3M Littman Electronic Stethoscope, Model 4000, St. Paul, Minnesota) applied to 6 previously defined anterior thoracic sites (Figure 1). Acoustic signals were obtained in the 20 to 2000 Hz range for 8-second loop intervals recorded at each of the 6 positions, yielding voltage-based time domain data (Supplementary Figure 1A-C, available online).

After the acoustic data recording, patients underwent standard catheter-based coronary angiography. Multiple views of the right and left coronary arteries were recorded in 1024 × 1024 pixel format at 15 to 30 frames per second and stored for later analysis. Intracoronary nitroglycerine was administered before angiography or after the first angiographic run, as per standard clinical indications (Figure 2).

The following additional data were recorded at the time of coronary angiography: hemoglobin and hematocrit concentration, platelet count, electrolyte panel, serum creatinine concentration, body mass index, and prior echocardiographic or stress test results, including left ventricular ejection fraction, wall motion abnormalities, evidence of infarction or ischemia, and valvular abnormalities.

Angiographic Analysis

An experienced angiographer blinded to the results of the acoustical analysis and ultimate clinical outcome reviewed all angiograms. Coronary anatomy was divided into 16 segments per the American Heart Association's standardized coronary map.[8] The maximal percent diameter stenosis by visual estimate in each segment was recorded in deciles (eg, <10% stenosis, 10%-19% stenosis, 20%-29% stenosis). The presence of Thrombolysis in Myocardial Infarction 0, 1, or 2 flow distal to a stenotic lesion was recorded. The presence of intermittent systolic coronary compression >50% ("myocardial bridging") was recorded.

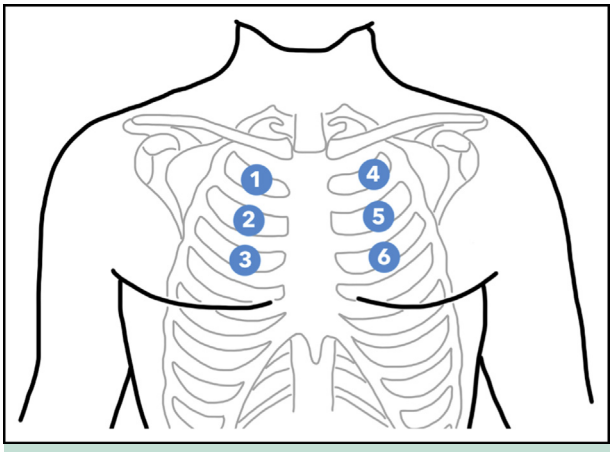

Figure 1 Auscultation sites. Six serial measurements obtained at each of the labeled anterior thoracic sites in 8-second loops.

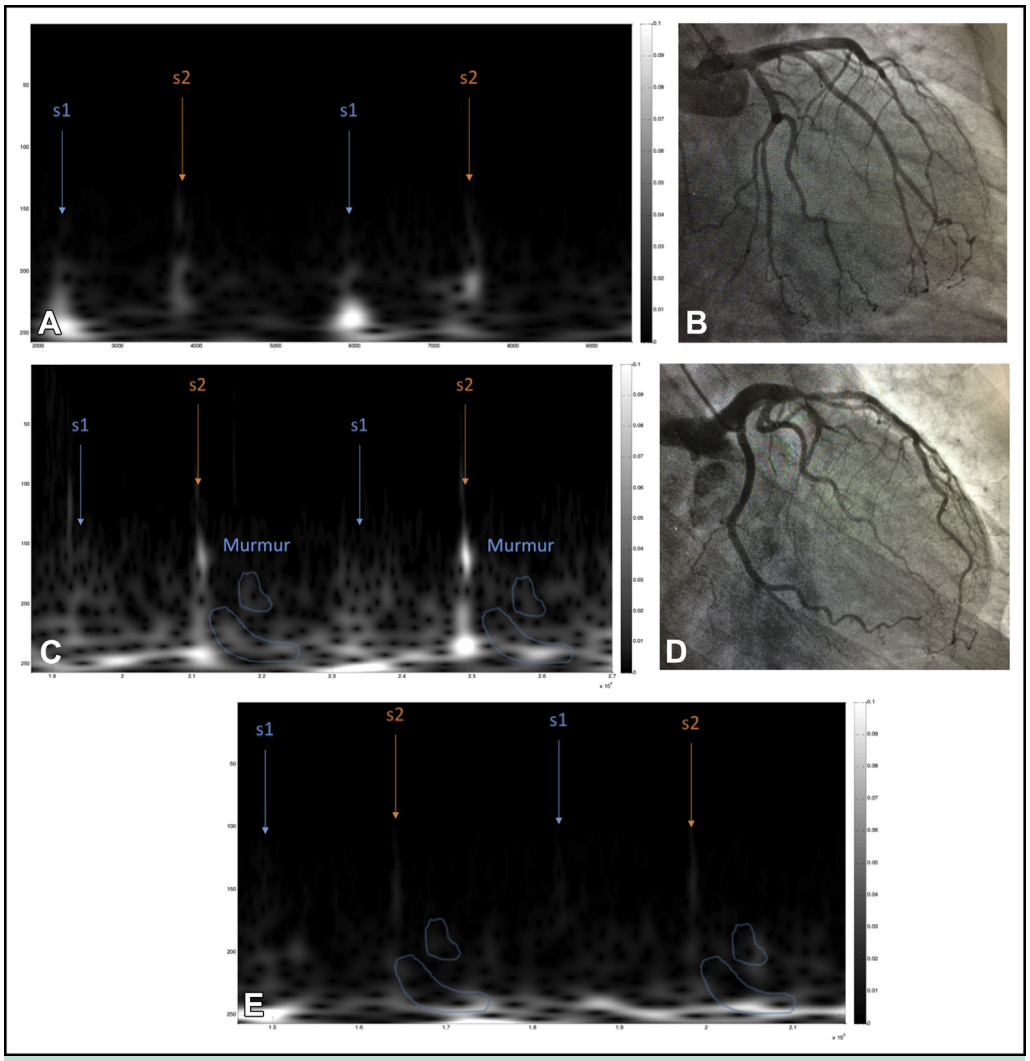

Figure 2 Acoustic spectral displays and corresponding angiograms. Patient #36: (**A**) no discernable intracoronary murmur signal is detected between S1 and S2 sounds; angiogram (**B**) demonstrates normal appearing coronary anatomy. Patient #52: (**C**) intracoronary murmur signal detected at approximately 175 to 250 Hz range between valve closure sounds S1 and S2; angiogram (**D**) demonstrates a distinct significant coronary stenosis of the proximal left anterior descending coronary artery in the right anterior oblique caudal projection. Postangioplasty acoustic recording (**E**) demonstrates no discernable residual intracoronary murmur, corresponding to treatment of stenosis.

Acoustical Recording and Analysis

The acoustic signal was recorded using an advanced digital electronic stethoscope (3M Littman Electronic Stethoscope, Model 4000). Loop interval recordings were stored in lossless digital format. Data recordings were then digitally transferred and analyzed by an acoustical engineer blinded to clinical and angiographic data. The acoustical engineer determined signal data integrity before spectral analysis. Acoustic signal detection analyses of recordings were categorized as "normal," "diseased," or "inconclusive" on the basis of predefined summation scoring thresholds.

Technical Analysis

Acoustic signaling data were acquired in a "time domain" format in 8-second continuous loop recordings using the commercially available advanced digital electronic stethoscope (3M Littman Electronic Stethoscope, Model 4000) as the transducer. These data were then digitally transferred from the recording device to a PC computer equipped with MATLAB 2011a (MathWorks, Inc, Natick, Mass). Patient "time domain" data were then translated to a "frequency domain" format to test the detection algorithm.

The data processing algorithm applied included 2 phases: preprocessing and testing. **Supplementary Figure 2** (available online) demonstrates sequences for testing. In both phases, raw acoustic signaling data collected from patients were preprocessed to subtract ambient noise. Signal quality was then evaluated in both time and frequency domains. In the event that data quality was considered unacceptable, it was removed from the training

and testing data sets. These data were included in the "inconclusive" data set.

Frequency-dependent features were extracted from the estimated raw acoustic signal spectrum and compared with prespecified frequency bands identified in related acoustic studies.[9] In the "classification" training step, both extracted signal features and angiographically confirmed patient information were used to train a statistical classifier to differentiate normal from abnormal coronary acoustic information. In the "turbulence detection" step, extracted features were transferred to the pretrained classifier, and the "normal/diseased" detection result was output to generate the detection report. The final detection result represented an averaged summation of the support vector machine result for each scan location.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (25th, 75th percentile). Categoric variables are presented as frequency and percentage. Diagnostic test statistics and receiver operating characteristic (ROC) curves were calculated for comparing the acoustic result with the angiographic result. Multivariable logistic regression models were used to investigate possible associations between clinical and demographic variables, and agreement between acoustic and angiographic results. All analyses were performed using Stata Version 12 (StataCorp LP, College Station, Tex).

RESULTS

Patient Population

A total of 156 patients were enrolled after meeting inclusion criteria. Of these patients, 123 (79%) produced acoustical signal recordings sufficient for analysis and 33 (21%) produced acoustical signal recordings deemed incomplete for analysis. Reasons for incomplete recordings included excessive ambient noise from the clinical setting, incomplete number of sites captured (ie, only 5/6 sites acquired or interpreted because of technical limitations, eg, patient already draped), and data transfer error.

Patient demographics and angiographic disease distribution of the study patients are shown in **Table 1**. The population was primarily male (55%), aged 60 ± 13 years, and overweight (body mass index 30 ± 6 kg/m^2). Common serum laboratory tests were within normal ranges (hemoglobin 13.7 ± 1.8 g/dL, serum creatinine 1.0 ± 0.2 mg/dL). Left ventricular performance ranged from mildly abnormal to normal (ejection fraction 55% ± 13%). Traditional atherosclerotic risk factors were broadly represented by hypertension (68%), history of cigarette smoking (60%), hyperlipidemia (50%), family history of premature coronary artery disease (42%), and diabetes (30%).

Distribution of maximal angiographic stenosis in any major vessel is shown in **Supplementary Figure 3** (available online). By defining ≥50% diameter stenosis of a coronary segment as significant, the prevalence of significant stenosis at angiography was 52% (n = 64; 18%, 22%, and 11% with 1, 2, and 3-vessel disease). Three patients revealed a total occlusion of a single vessel and no other significant disease. Focal lesions were not differentiated from serial lesions. No significant coronary stenosis was demonstrated in 48% of the study group. No patient in this cohort demonstrated isolated left main coronary stenosis.

A total of 69 male patients and 54 female patients were included in this study. Angiographically confirmed significant coronary artery disease was identified in 38 male patients (55.1%) and 26 female patients (40.7%) (**Supplementary Figure 4**, available online).

Accuracy of Acoustic Detection of Coronary Artery Stenosis

The overall accuracy of acoustic detection in correctly identifying coronary artery stenoses is shown in **Table 2**. The greatest accuracy was noted for detection of a coronary artery diameter stenosis of 50% or greater. The sensitivity and specificity for acoustic detection of a coronary artery diameter stenosis ≥50% in any vessel were 0.70 and 0.80, respectively (negative predictive value [NPV], 0.71; positive predictive value [PPV], 0.79; ROC area under the curve [AUC], 0.75).

When coronary artery stenoses were defined as 70% rather than 50%, the sensitivity and specificity of acoustic detection were 0.69 and 0.71, respectively (NPV, 0.75; PPV, 0.64). When patients with isolated total occlusions were excluded, the area under the ROC was essentially unchanged (0.74) for all levels of stenosis. However, when only major coronary vessels were considered, stenoses were more reliably identified (ROC AUC, 0.76; $P = .43$ vs all vessels).

Detection of multivessel coronary artery disease (2- and 3-vessel involvement with ≥50% diameter stenosis) yielded lower accuracy, with a sensitivity and specificity of 0.67 and 0.64, respectively (PPV, 0.48; NPV, 0.79).

ROC curves (**Supplementary Figure 5**, available online) illustrate the relationship between the maximal percent stenosis in any coronary artery and the acoustic test result. The test generated 73% maximal accuracy in detecting arteries with a diameter stenosis ≥50% (ROC AUC, 0.74). The sensitivity, specificity, PPV, and NPV are shown in **Table 2**.

DISCUSSION

This study demonstrated that modern acoustic detection and spectral analysis of signals corresponding to intracoronary murmurs may reliably identify significant coronary artery stenoses in patients with risk factors for, and ultimately confirmed to have, coronary artery disease. With sensitivity and specificity for stenosis ≥50% at 0.70 and 0.80, respectively (NPV, 0.71; PPV, 0.79), acoustic detection

Table 1 Patient Characteristics (n = 123)

	Maximum Stenosis in Any Vessel				
	<20% (n = 27)	20%-49% (n = 32)	50%-69% (n = 10)	≥70% (n = 54)	All (n = 123)
Age (y)	53 ± 12	61 ± 14	62 ± 9	62 ± 12	60 ± 13
Male	9 (33%)	22 (66%)	6 (60%)	32 (58%)	69 (55%)
BMI (kg/m^2)	30.3 ± 7.3	30.5 ± 5.7	30.2 ± 8.4	29.8 ± 6.0	30.1 ± 6.3
Hgb (mg/dL)	13.5 ± 1.4	13.6 ± 1.8	14.6 ± 1.5	13.6 ± 2.1	13.7 ± 1.8
Creatinine (mg/dL)	0.9 (0.8, 1.0)	0.9 (0.8, 1.2)	0.9 (0.7, 1.0)	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)
EF (%)	56 ± 10	59 ± 13	54 ± 17	51 ± 14	55 ± 13
Hypertension	12 (44%)	26 (76%)	9 (90%)	39 (71%)	86 (68%)
Diabetes	4 (15%)	10 (30%)	2 (20%)	22 (40%)	38 (30%)
Smoking (ever)	18 (67%)	19 (56%)	8 (80%)	30 (55%)	75 (60%)
Hyperlipidemia	7 (26%)	18 (53%)	7 (70%)	31 (56%)	63 (50%)
Family history of CAD	9 (33%)	14 (41%)	6 (60%)	24 (44%)	53 (42%)

Values are mean ± standard deviation, median (25th, 75th percentile), or n (%).
Summary statistics calculated with all available data.
BMI = body mass index; CAD = coronary artery disease; EF = ejection fraction; Hgb = hemoglobin.

performs sufficiently to assist in the decision-making process toward potential further diagnostic testing.

Clinical Implication: Comparison with Current Noninvasive Evaluation for Coronary Artery Disease

Current noninvasive modalities that detect the presence of myocardial ischemia as a surrogate to coronary artery stenoses include exercise stress electrocardiogram, exercise stress echocardiography, nuclear myocardial perfusion imaging, and positron emission tomography computed tomography (CT) scanning. The sensitivity and specificity of these tests range considerably from approximately 68% to 91% and 73% to 88%, respectively.[10,11] These modalities rely to varying degrees on technical constraints of rapid ventricular rate and arrhythmias that may affect image gating, potential need for beta-blockade to increase diastolic duration to improve image acquisition, potential need for pharmacologic vasodilation, and technical support and cost associated with implementation. Although this study did not directly compare patients' acoustic findings with the results of these other commonly used modalities, a comparative clinical trial currently is under way.

History

The concept of cardiac acoustic signal spectral analysis was first introduced in 1955, primarily as a means to reveal cardiac murmur characteristics and to better understand congenital heart disease pathophysiology.[7,12] Further advances in this technology were applied to the detection and characterization of carotid artery stenosis.[13,14] Considerably deeper and further from the skin surface, however, coronary artery diastolic murmurs were later appreciated and characterized using advanced computer-based signal processing techniques to identify unique spectral characteristics.[2,5,15-17] Ultimately, detection algorithms evolved such that intracoronary murmurs associated with coronary artery flow and stenoses could be analyzed for characteristic acoustic signal frequency patterns.[2,17]

Prior Studies

Feasibility experiments have generated refined detection algorithms to identify coronary artery stenoses on the basis of mechanical modeling, canine in vivo testing, and limited human studies.[2,15-19] Semmlow et al[2] reported an early human study evaluating the performance of an acoustic signal detection method among 12 patients with angiographically confirmed coronary artery disease and 12 age-matched controls. In the context of sample-size limitation,

Table 2 Diagnostic Test Statistics

Definition of Significant CAD (% Stenosis in Any Vessel)	Sensitivity	Specificity	PPV	NPV	Accuracy
≥50%	0.70	0.80	0.79	0.71	73%
≥70%	0.69	0.71	0.64	0.75	70%
≥50% (modified)*	0.69	0.77	0.75	0.72	73%
≥50% (in major vessel)	0.72	0.74	0.70	0.77	73%

CAD = coronary artery disease; NPV = negative predictive value; PPV = positive predictive value.
*Excludes 3 patients with a totally occluded vessel and no other significant disease.

albeit with 92% true-positive tests, patients with significant coronary artery disease were noted to generate frequency spectral pattern components in the range of 120 to 200 Hz. Patient selection of their cohort was based on angiographic findings with limitations of study size and absence of analysis of relevant potentially confounding acoustic variables.

Makaryus et al[7] reported a study evaluating performance measures of a coronary acoustic signal detection method in patients undergoing coronary CT angiography. Of the 161 patients who completed the study protocol, 19 (12%) demonstrated CT angiography evidence of significant coronary artery disease with >50% coronary artery stenosis, 17 of whom were positively identified by acoustic signal pattern recognition. The majority of patients in their study (142 of the 161 completed; 88%) demonstrated nonobstructive or no coronary artery disease (<50% coronary artery stenosis), 82 of whom were deemed to have no coronary artery disease (sensitivity 89.5%, specificity 57.7%). Inherent in their study was the low to moderate pretest probability of coronary artery disease, which was justification for the use of a noninvasive diagnostic modality. A notable limitation to their study was the low number of patients with CT angiography evidence of coronary artery disease (n = 19).

Technical Considerations of Acoustic Detection

Our study cohort of patients referred for catheter-based angiography includes a predominant sample of patients with coronary artery stenoses, permitting a clinically relevant assessment of acoustic detection accuracy. Moreover, the finding of an optimal detection threshold at 50% diameter stenosis is consistent with experimental findings in animal models showing that turbulence, pressure decrease, and a reduction in hyperemic flow begin to occur at this level of stenosis.[20-22] Accordingly, the acoustic signal of coronary stenosis would be predicted to be present in vessels with at least 50% stenosis and absent in vessels without 50% stenosis.

Particularly for coronary artery stenoses, acoustic signal processing algorithms begin by isolating the diastolic segment of coronary artery flow, often between 200 and 300 ms after the S2 heart sound to support the discrimination between "normal" and "diseased."[16,17] Two resonance frequency peaks commonly are observed corresponding to intrinsic arterial properties of both normal and stenotic vessels. Although acoustic mechanical waves travel at frequencies ranging from 20 to 20,000 Hz, those arising from coronary artery stenosis turbulence range broadly from 110 to 800 Hz.[16]

Uninterrupted laminar flow corresponds to a low-frequency spectral peak that may be excited by pressure fluctuations. High-frequency spectral energy generally increases as the degree of stenosis increases.[18,19,23,24] With severe stenoses approaching 95% occlusion, acoustic signals may be attenuated by low blood flow. Although acoustic signaling patterns may recognize arterial occlusions as small as 25% of reference vessel diameter,[23-25] this was not evaluated in our study.

Prior studies have validated elimination of background noise (particularly valve closure sounds corresponding to S1 and S2) to facilitate detection of coronary occlusion, as well as targeted acoustic enhancement of diastolic coronary sounds.[6,12,15-17] Many algorithms optimize signal-to-noise ratios by averaging multiple diastolic periods' data for frequency spectral analysis.[25] The preprocessing algorithm used in this study does not eliminate valve closure sounds; however, low-level background noise (eg, voices and ambient noise) is removed as 1 component of data preprocessing. Electrocardiogram data are captured, and acoustic data from both systole and diastole are used in the data analysis. In addition, the algorithm was trained using data collected from patients representing variable ranges of age, body mass index, gender, and coronary artery disease states (eg, diffuse disease, serial lesions, bifurcations).

The training patient acoustic data were mapped into multidimensional decision spaces. Of note, decision spaces were not created for individual coronary vessels, and as such, vessel specificity is not possible. The decision spaces did not separate data according to specific peak frequency band; rather the data were mapped and compared by dimension, incorporating time and frequency analysis. The frequency analysis was limited to the 40 to 1000 Hz range, reflecting the frequency bands of interest, particularly noting prior validation of left anterior descending coronary artery stenosis spectral peaks occurring in the 40 to 80 Hz range.[26] The patients in this study were tested against these multidimensional spaces, and a "best fit" was subsequently calculated.

Study Limitations

Blood flow impairment and distinction of significant coronary artery stenoses are limited in quantification by angiography alone. Accordingly, angiographic analysis may have misclassified lesions such that some of the false-positive acoustic detections were in fact true-positives. Likewise, some of the negative acoustic classifications might have represented false-negatives due to angiographic misclassification. Nevertheless, acoustic detection agreed remarkably with the angiographic findings. Future studies will refine the accuracy of acoustic detection using physiologic parameters of coronary flow impairment, such as fractional flow reserve.

Although our study included 65 of 123 patients (51%) with analyzable acoustic data and angiographically confirmed stenoses ≥50% in at least 1 vessel, study size remains a limitation. However, the results observed within this constraint serve as an indicator of the reliability of this modality with adequate acoustic signal capture and suggest that larger studies are warranted.

We did not find an association between the accuracy of acoustic detection and a number of theoretically