Possible Detection of Atherosclerotic Coronary Calcification by Two-dimensional Echocardiography

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SUMMARY Using two-dimensional echocardiography, a technique was developed for digitizing reflected acoustic signals and performing variable signal processing. This resulted in accentuation of differences in focal reflectivity of target tissues and improved ultrasonic tissue characterization. Study of a learning population of 200 patients demonstrated abnormal specular reflections from the proximal left coronary artery in patients with coronary artery disease. A prospective study of 100 patients was then performed to test the reliability of this method in predicting the presence of significant stenosis. Abnormal echocardiograms were a highly sensitive (94%) but less specific (65%) indicator of significant atherosclerosis of the left coronary system. One-third of patients studied had fluoroscopically identifiable coronary calcification, and 95% had abnormal echocardiograms. We postulate that our echocardiographic findings may be secondary to the presence of small amounts of coronary calcification. Echocardiographic tissue differentiation, therefore, may prove to be a noninvasive means of evaluating patients for coronary atherosclerosis.

Two-dimensional echocardiography has been demonstrated to be a possible tool for examining the proximal left coronary artery. This technique has been used to describe the normal left main, left anterior descending and left circumflex coronary anatomy. In addition, decreases in coronary artery luminal diameter secondary to atherosclerotic cardiovascular disease have been visualized. Despite the desirability of noninvasively selecting patients with atherosclerotic lesions of the proximal left coronary artery, two-dimensional echocardiography has not been extensively used for this purpose because of several technical difficulties. The size of these vessels lies near the limit of resolution of echocardiography, particularly in a population of coronary patients. Variations in normal coronary anatomy are well recognized, including differences in the length of the left main coronary artery (LMCA) and the size and number of vessels present at its division. These structures move with ventricular systole relative to the ultrasonic plane. Because of the current technical limitations in directly visualizing the LMCA, we have attempted to create a technique to analyze variations in tissue properties of this region by means other than direct visualization. The goal of this research is to develop a method to accentuate the differences between sound reflected from atherosclerotic and from normal tissue. This report describes the development of such a technique. The results of an initial prospective study using this method for the identification of coronary artery disease (CAD) in a large clinical population are presented. In addition, a basis for the change in reflectivity produced by atherosclerosis is presented and the potential clinical role of this type of research discussed.

Methods To evaluate the effect of digital signal processing on the ability of echocardiography to detect changes in focal reflectivity produced by atherosclerosis, a commercially available, two-dimensional echocardiographic scanner was modified at Indiana University
The basic system included a Smith Kline Instruments (Ekosector I) mechanical sector scanner with a pulse repetition rate of 3200 Hz. The probe contained a 2.25-MHz transducer oscillated through a 30° arc at a scan rate of 60/sec, yielding a line density of 54 lines/30° field. Two-dimensional images were recorded by direct ultrasonic recording on a videotape Sanyo VTC 7100 cassette recorder and these were available for subsequent redisplay and analysis in real-time, slow motion, or single-frame format.

Because of the wide range of acoustic signal amplitude encountered in clinical echocardiography (120 db), the basic system had to be modified before addition of a fast analog-to-digital converter.* Typical display devices used in current equipment are capable of recording only about 20 db of this range and photographic techniques, such as Polaroid film, limit the dynamic range to 10 db. In order for more of the 120-db range to be included in analog-to-digital conversion, dynamic range compression was required. Initially, reflected acoustic signals were processed through a log preamplifier to accentuate the signals of lowest amplitude, which would normally be lost in the recording and playback process (fig. 1A). This ultrasonic scale was then processed through a fast analog-to-digital converter, which included 10 shades of gray. Because of the initial preamplification and dynamic range compression, a larger portion of the low-amplitude echoes were included in the lowest two shades of gray on the digital scale. Gain and reject controls could be adjusted such that these signals formed a uniform gray background. Reflected signals of mid-range amplitude were displayed in a linear fashion and occupied approximately three shades of gray on the digital scale (fig. 1B). These signals appeared similar in conventional studies and in digitally processed scans. A variable function signal transformer was then available for further electronic processing of signals in the higher-amplitude range. The operator could select curves ranging from log to linear to exponential; the latter is shown in figure 1C. Reflected acoustic signals were then reconverted from digital-to-analog and displayed on an oscilloscope in the standard fashion. Processed images could be viewed on-line and in real-time throughout the study.

Initial clinical experience was gained with this system by retrospectively studying a learning population of 200 patients after coronary angiography. Preliminary observations in patients with known CAD suggested that exponential processing of high-amplitude reflected signals was most beneficial in discriminating patterns of reflectivity from atherosclerotic as opposed to normal coronary arteries. With this form of processing, a greater portion of the digital scale is allocated to signals at the higher end of the amplitude scale. The use of approximately five shades of gray for the oscilloscopic display of these signals allowed them to be better differentiated. Using this method, distinct patterns of focal reflectivity were noted from the proximal left coronary artery in patients with atherosclerotic cardiovascular disease. High-amplitude specular reflections were noted in the region of the LMCA, proximal left anterior descending coronary artery (LAD) or proximal left circumflex coronary artery (LCCA). These specular reflections, termed high-intensity echoes (HIEs), were not felt to arise from the aorta because they were seen to be lateral to the aorta and of brighter intensity. Similarly, they were from cardiac and not pulmonary structures, as they were reproducible within any given portion of the cardiac cycle and demonstrated systolic motion paralleling aortic motion.

After these distinct HIEs were noted in studies of a learning population of patients with CAD, a prospective study was undertaken to test the reliability of this method as a predictor of atherosclerotic cardiovascular disease. The study group included 100 consecutive patients undergoing coronary angiography at the Indiana University Hospital. All patients underwent left-heart catheterization and coronary angiography using standard catheterization techniques. Coronary angiography was considered to be positive for significant atherosclerosis if any portion of the LMCA, LAD, or LCCA had a decrease in luminal diameter of at least 50%. Coronary angiograms were analyzed by independent observers without knowledge of the echocardiographic findings.

Coronary angiography revealed that 34 patients (37.8%) had no angiographically demonstrated coronary lesions. Fifty-three patients (59%) were found to have significant obstructions of some portion of the left coronary artery, with or without lesions of the right coronary artery; 11 of these 53 had significant

*In conjunction with the Fortune Fry Research Laboratory, Indianapolis Center for Advanced Research, Indianapolis, Indiana.
obstruction of the LMCA and 42 had lesions in the LAD or LCCA and a normal LMCA. Five of the latter 42 patients had significant obstructions of the LAD distal to the first septal perforator or of the LCCA distal to the first marginal branch, while in 37 the lesion was located proximally. Three patients in the study (3.3%) had significant obstructive lesions of the right coronary artery, without significant disease in the left coronary artery. The goal of this study was to determine the value of echocardiography in detecting lesions of the left coronary artery, so these three patients were considered as angiographic negatives. Ten of the original 100 patients were subsequently excluded echocardiographically (see Results section) and are excluded from these demographic data.

At catheterization, 11 patients had significant valvular heart disease. Of the 34 cases without CAD, four had calcific aortic stenosis, one had calcific mitral stenosis, and one had a normally functioning Starr-Edwards aortic prosthesis. Three of the 53 patients with CAD had coexistent valvular aortic stenosis. The 10 patients excluded echocardiographically included two patients with aortic stenosis.

Each patient undergoing cardiac catheterization was also evaluated for the presence or absence of significant coronary calcification. Cineangiograms were retrospectively reviewed and the region of the left and right coronary arteries evaluated both during contralateral contrast injection and in the frames immediately preceding ipsilateral injection. Small, discrete areas of calcification near obstructing lesions, larger masses of calcification, and diffuse calcification of vessel segments were all considered as positive.

Each patient had an echocardiogram performed before cardiac catheterization. First, for the purposes of orientation, the patients had a routine examination. The patients were placed in the left lateral decubitus position and the echocardiographic probe placed at the left sternal border in the third or fourth intercostal space. The scanning plane was aligned parallel to the short axis of the aorta and scanned caudad and cephalad to locate the ostium of the LMCA, as previously described. The probe was then rotated clockwise until the scan was aligned parallel to the long axis of the LMCA. The degree of rotation required varied somewhat in each patient. This two-dimensional echocardiographic plane is demonstrated in figure 2, and a representative scan of a normal LMCA is shown in figure 3. The single-frame images selected for illustrations contain only a portion of the data lines available during the real-time display and therefore do not provide a true reproduction, and this problem is compounded by the use of instant-copy film. In addition, the ability to continually sweep the narrow angle transducer provides necessary orientation during the real-time study. These difficulties in providing adequate still-frame illustrations are generally appreciated.

Having identified the region of the proximal left coronary artery, reflected signals were then processed using the previously described format (fig. 1). The resultant processed image was recorded in real time. Gain and reject controls were appropriately adjusted such that low-intensity signals formed a uniform gray background, specular reflections (from the aorta, pulmonary artery and interatrial septum) in the mid-range of the digital scale were displayed as on a conventional study, and higher-amplitude signals were exponentially processed (fig. 3). Each digitally processed scan was interpreted jointly before cardiac catheterization by two observers. The study was considered positive if either observer felt that abnormal HIEs were present during the real-time study in the region of the left coronary artery. Bright ultrasonic reflections were not considered as a positive test if they occurred in the anterior or posterior aorta or in the region of the right coronary artery. In the former case, bright specular reflections were frequently noted in normal subjects. The tricuspid annulus also was found to produce false positives frequently in the region of the right coronary artery.

Results

Using conventional two-dimensional echocardiographic techniques, the ostium of the LMCA could be adequately identified in 90 of 100 (90%) patients. In 10 patients, the echocardiogram was felt to be technically inadequate, and the patients were excluded from the study. Data for the remaining 90 patients are listed in table 1. Sixty-three patients were found to have abnormal HIEs in the region of the left coronary artery. Fifty of these 63 patients (79%) had significant angiographic lesions in the left coronary artery. Eleven had obstruction of the LMCA, 34 had lesions in the proximal LAD or proximal LCCA without left main narrowing, and five had obstructions distal to the first septal perforator or the first obtuse marginal
Table 1. Relationship of Echocardiography to Coronary Artery Disease*

<table>
<thead>
<tr>
<th></th>
<th>Echo HIE</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cath</td>
<td>+</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>L. CAD</td>
<td>-</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63</td>
<td>90</td>
</tr>
</tbody>
</table>

\[p < 0.001 \text{ by chi-square test.}\]

Abbreviations: HIE = high-intensity echo; Cath = catheterization; L. CAD = left coronary artery disease; Sens = sensitivity; Spec = specificity; Pred V = predictive value.

Three of the 50 patients with CAD had calcific aortic stenosis. Figure 5 demonstrates HIEs in the region of the left coronary artery and thickening of the aortic valve in one of these patients. As in the case of unprocessed scans, the Polaroid copies of these still frames do not provide all of the data available during the real-time study.

Thirteen of the 63 patients (21%) with echocardiographic findings of abnormal HIEs had no demonstrable angiographic obstructions of the left coronary artery. Of these 13 echocardiographic false positives, three patients had significant obstructions of the right coronary artery as an isolated lesion. Two of these 13 patients had calcific aortic stenosis and one patient had calcific mitral stenosis.

Twenty-seven of 90 patients (30%) had no abnormal branch. Representative processed echocardiograms are demonstrated in figures 4 and 5.

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Twenty-seven of 90 patients (30%) had no abnormal branch. Representative processed echocardiograms are demonstrated in figures 4 and 5.
HIEs on two-dimensional echocardiography. Twenty-four of these patients were later found to be angiographically normal. Of this group of 24 echocardiographic true negatives, two patients had calcific aortic stenosis and one patient had a normally functioning Starr-Edwards aortic valve prosthesis. Three of the 27 patients with normal echocardiograms were found to have significant angiographic obstruction of the left coronary artery (false negatives).

The correlation between the echocardiographic demonstration of abnormal HIEs and significant angiographic obstruction of the left coronary artery is demonstrated in table 1. HIEs on the processed image were found to be a significant predictor of angiographic lesions \(p < 0.001\). The sensitivity of this method was demonstrated to be 94% and the specificity was 65%. The resultant predictive value was 79%.

To assess the relationship between the presence of echocardiographic HIEs and coronary calcification, cineangiograms were reviewed. Thirty-one of 90 patients (33.3%) were noted to have coronary calcification by cardiac fluoroscopy. Of these, 30 patients had significant angiographic lesions of the left coronary artery; one patient had no CAD, but did have calcific aortic stenosis. Twenty-three of 59 patients (39%) without coronary calcification were found to have significant angiographic lesions. The presence of fluoroscopically identifiable calcium was found to be an insensitive (57%) but highly specific (97%) predictor of significant CAD by angiography (table 2).

The echocardiographic results of patients with fluoroscopically identifiable calcification of the left coronary artery were considered separately. Of these 31 patients (table 3), 28 had abnormal HIEs identified on the two-dimensional study. All 28 of these patients had significant angiographic obstructions of the left coronary system. Two patients with fluoroscopically calcified left coronary arteries and angiographically significant obstructions had normal two-dimensional echocardiograms (false negatives). The final patient in this group was an echocardiographic true negative.

Eleven of the original 100 patients had calcific valvular heart disease or a valvular prosthesis. Two of these patients were among the 10 excluded because of an inadequate echocardiogram. The echocardiographic and angiographic results of the other nine patients are listed in table 4. Six of these nine patients had abnormal HIEs. Three of these six patients had CAD and three represented echocardiographic false positives. The remaining three patients had normal echocardiograms and were angiographically normal. In a setting of calcific valvular heart disease or a prosthesis, the specificity appeared decreased, although too few patients were studied to show statistical significance.

**Discussion**

The major application of ultrasound to clinical cardiology has been its use in determining the position

![Figure 5](http://circ.ahajournals.org/)

*processed scans from two patients. (left) This patient is normal. (right) high-intensity echoes (Abn HIEs) are seen at the aortic valve (AV) and left coronary artery in a patient with aortic stenosis and coronary artery disease.*
and motion of intracardiac structures. However, a variety of disciplines demonstrate that more extensive analysis of acoustic signal may provide information about tissue properties of target organs. For example, a characteristic change in acoustic impedance of myocardium has been noted after experimental infarction. In the field of ophthalmology, semiquantitative comparisons of the amplitude of components of acoustic signals from intraocular structures has allowed identification of 25–30 separate histologic types of eye pathology. Tissue characterization using ultrasound has also been used to study atherosclerosis. Interrogation of sections of excised femoral artery with high-frequency transducers has demonstrated characteristic patterns of acoustic reflection from normal intima, fibro-fatty plaques, and calcified plaques. Similar methods have been applied to high resolution B-mode scanners to demonstrate atherosclerotic lesions in the thoracic aorta of experimental animals. Thus, the feasibility of detecting both early and late changes of atherosclerosis has been demonstrated using a variety of ultrasonic techniques.

An initial purpose of this study was to develop equipment that allowed variable processing of reflected ultrasound to determine if digital signal processing would allow improved tissue characterization. A technique has been described that uses dynamic range compression to incorporate the entire range of signal amplitude encountered in clinical echocardiography. In addition, a variable function transformer is available with which the operator can select the form of signal processing most applicable to the target tissue. This equipment was then used in the study of a learning population of patients who underwent coronary angiography to determine if specific alterations in reflectivity secondary to CAD were detectable. In this study, characteristic changes in reflective patterns were noted in the region of the proximal left coronary artery. Furthermore, exponential processing of these larger-amplitude signals on the digital scale allowed them to be clearly discriminated from surrounding cardiac structures. This pilot study, therefore, demonstrated the feasibility of performing ultrasonic tissue interrogation of the proximal left coronary artery in humans using a commercially available echocardiographic sector scanner to detect coronary atherosclerosis.

Having demonstrated this potential, a prospective study was undertaken to determine the sensitivity and specificity of this form of tissue characterization of the proximal left coronary artery in detecting atherosclerotic lesions. In this study, technically adequate echocardiograms of the region of the proximal left coronary artery could be obtained in 90% of subjects. This probably represents a significantly higher success rate than could be achieved by attempts at direct visualization of the lumen of the proximal coronary arteries. Using digital signal processing, abnormal HIEs were noted in 50 of the 53 patients with coronary lesions documented by catheterization. The method of signal processing used in this study is only an initial prototype, is not quantitative, and will certainly be modified with further investigation. Nonetheless, these results suggest that techniques using echocardiographic tissue identification may become a sensitive means of screening patients for coronary atherosclerosis.

The exact anatomic cause for the change in the interaction of ultrasound with atherosclerotic tissue is not known. One likely source, however, is the presence of calcification within coronary plaques. The presence of coronary calcification by fluoroscopy has previously been recognized as a fairly specific means for screening patients for atherosclerotic cardiovascular disease. The extent of coronary calcification, furthermore, can be semiquantitatively correlated with the severity of coronary artery disease. In this study, 30 of the 31 patients with calcified coronary arteries also had angiographically significant lesions (table 2). The site of coronary calcification in this study was uniformly within the proximal coronary artery. This is consistent with reports in the literature.

### Table 3. Relationship of Echocardiography to Coronary Artery Disease in Patients with Calcified Coronary Arteries

<table>
<thead>
<tr>
<th>Echo HIE</th>
<th>Cath</th>
<th>L. CAD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Sens</td>
<td>95%</td>
<td>100%</td>
<td>Pred V</td>
</tr>
</tbody>
</table>

*p < 0.1 by chi-square test.

Abbreviations: HIE = high-intensity echo; Cath = catheterization; L. CAD = left coronary artery disease; Sens = sensitivity; Spec = specificity; Pred V = predictive value.

### Table 4. Relationship of Echocardiography to Coronary Artery Disease in Patients with Valvular Heart Disease

<table>
<thead>
<tr>
<th>Echo HIE</th>
<th>Cath</th>
<th>L. CAD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Sens</td>
<td>100%</td>
<td>50%</td>
<td>Pred V</td>
</tr>
</tbody>
</table>

*p = NS by chi-square test.

Abbreviations: HIE = high-intensity echo; Cath = catheterization; L. CAD = left coronary artery disease; Sens = sensitivity; Spec = specificity; Pred V = predictive value.
in which coronary calcification was uniformly found to occur within the proximal 3 cm of the coronary
tree,13,14 with the LAD being the most frequently in-
volved vessel.15 14 This proximal portion of the cor-
monary artery may explain the presence of HIEs in 50
patients, one must consider the 13 patients with abnor-
mal echocardiograms and no significant obstructions
by angiography. Scans were interpreted as positive if
any abnormal HIEs were present. Further experience
may allow recognition of false-positive patterns. For
example, six of these patients had other sources that
could have represented specular ultrasonic reflectors.
Two patients had calcific aortic stenosis, and one
patient had calcific mitral stenosis. As demonstrated
in table 4, tissue characterization of the proximal left
coronary artery appears to be of limited value in the
setting of calcific valvular heart disease or a valvular
prosthesis. An additional three of the 13 patients were
found by angiography to have isolated obstruction of
the right coronary artery. These patients could have
had early atherosclerotic changes of the left coronary
system without significant angiographic obstruction.
Nonetheless, this technique presently tends to over-
diagnose significant CAD of the left coronary artery.

Thus, these techniques may prove valuable if used in conjunction for the screening of
patients for CAD. In this study, for example, of the
three patients with false-negative echocardiograms,
the diagnosis of CAD could have appropriately been
suspected due to the identification of coronary
calcification by fluoroscopy in two (tables 2 and 3).
The site of maximal angiographic obstruction con-
sistently corresponded to the site of fluoroscopically
identified coronary calcification. However, the loca-
tion of the abnormal HIEs by two-dimensional tech-
niques did not always correspond to this region. Of the
50 patients with CAD and abnormal HIEs overlying
the LMCA, LAD or LCCA, 45 patients had
angiographically demonstrated obstructions in the
proximal system (11 LMCA, 34 proximal LAD or
LCCA). Five patients, however, had distal
angiographic obstructions with proximal echocar-
diographic abnormalities. Thus, the abnormal HIE on
the two-dimensional study could have represented
either the visualization of an adjacent plaque either in
the aorta or in the distal coronary artery, as a result of
the beam width of the echocardiographic scan, or it
could have represented the detection of early changes
in the proximal coronary artery in association with a
distal angiographically significant obstruction.
The hypothesis that these focal changes in ul-
trasonic reflectivity could be secondary to calcium can
be supported by the prior recognition of calcification of
other intracardiac structures using echocar-
diography. For example, ultrasonic examination of
the aortic valve and aortic root in patients with calcific
aortic stenosis has shown characteristic increases in
ultrasonic reflections from the valve leaflets.15, 16 This
finding has been helpful in making the qualitative
diagnosis of acquired aortic stenosis. Similarly,
valvular calcification with rheumatic mitral stenosis
has been recognized.17, 18 In addition, echocar-
diography has been helpful in further defining the
syndrome of calcification of the mitral valve annulus.19, 20

While calcium within an atherosclerotic left cor-

While calcium within an atherosclerotic left cor-
patients with CAD, significant differences exist in the experimental basis of these two techniques. Positive treadmill exercise tests are produced by alterations in the ST-T segment of the ECG because of an imbalance between myocardial oxygen supply and demand. False-positive treadmill exercise examinations are known to occur in the presence of factors that alter the ST-T segment of the ECG independent of this imbalance, such as digitalis, hypokalemia, ventricular hypertrophy and intraventricular conduction abnormalities. In contrast, tissue characterization using echocardiography attempts to detect changes in focal reflectivity of ultrasound by the target tissue. Because echocardiography attempts to identify changes in tissue histology rather than the adequacy of myocardial perfusion, however, these two techniques may well provide complementary data.22

In summary, the use of digital processing of ultrasonic signal for the purpose of tissue interrogation of the proximal left coronary artery in humans using two-dimensional echocardiography appears to be promising. In a selected group of patients, this initial method demonstrated adequate sensitivity and fair specificity for predicting the presence of CAD. These results are preliminary. However, the feasibility of this type of research has been demonstrated and further investigation in this area appears warranted. While the anatomic source for abnormal ultrasound reflection is not known, the presence of calcium in the vessel appears to be a likely source. This form of investigation has the potential not to replace other techniques of evaluating patients for coronary ischemia, but to become an independent and correlative means of evaluating patients for the presence or absence of coronary artery disease.

References
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Circulation. 1980;62:1046-1053
doi: 10.1161/01.CIR.62.5.1046

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/62/5/1046