Recognizing Unrecognized Risk
The Evolving Role of Ventricular Functional Assessment in Population-Based Studies

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he rapid evolution of advanced cardiac imaging technologies has resulted in enhanced detection of subclinical disease with the potential for early implementation of therapeutic strategies and reduction in subsequent morbidity and mortality. Noninvasive assessment of ventricular function can provide evidence of prevalent coronary artery disease and cardiomyopathy and could supplant electrocardiography (ECG), the traditional marker of unrecognized myocardial infarction (UMI), in population screening. An appreciation of past efforts in this field is useful in understanding the potential future trajectories of these technologies.

Unrecognized Myocardial Infarction
Ever since Herrick’s initial description of classic angina in 1912, it has been known that incident myocardial infarction (MI) will go unrecognized in a substantial portion of the population. Patients with UMI either recall symptoms that are atypical of MI or have no recollection of any event at all. Initially, autopsy findings and, later, ECG evidence indicated that “silent” MIs were frequent in hospitalized populations. These observations were later extended to a free-living cohort with the first epidemiological data reported from the Framingham Heart Study in 1959 by Stokes and Dawber.1 These investigators noted that 21% of subjects with new ECG-documented MI on biennial serial examinations had either atypical symptoms that were not clearly related to MI or no apparent ischemia-related complaints. Kannel and Abbott2 later observed that new Q-wave infarctions detected on biennial Framingham examinations over a 30-year follow-up period were unknown to 28% of the men and 35% of the women who experienced them, with approximately half of these MIs unaccompanied by discernible symptoms on further investigation. More impressive still was the fact that after MI diagnosis, the 10-year death rate was at least as great in subjects with UMI as in those with recognized infarction (45% versus 39%). As shown in the Table, these results have been confirmed by reports from other investigators in locations ranging from Honolulu and Reykjavik to Israel and the Bronx, with UMI prevalence rates largely related to age and ranging from approximately 4% to 44% of all infarctions.3,4 Remarkably, with the exception of the Israeli Ischemic Heart Disease Study, all-cause death rates were similar in recognized MI and UMI in all of these reports.

Because of practical considerations, epidemiological investigations have relied on the relatively inaccurate measures of patient testimony, medical history, and ECG for the diagnosis of prevalent or incident MI. Although ECG is an inexpensive, safe, and expedient medium, the test characteristics of ECG are problematic because of limitations in sensitivity and, to a lesser degree, specificity. When the diagnostic criteria are based on Q waves, sensitivity is limited as these are detected in only half of all infarctions documented by delayed gadolinium-enhanced magnetic resonance imaging (Gd-MRI), the current imaging “gold standard” for MI diagnosis.5 The presence of a Q wave correlates best with overall size rather than with the transmural characteristics of the infarct,6,7 which leads to underdiagnosis of smaller infarcts. In addition, Cox8 demonstrated ECG reversion to normal of 5.6% of Q-wave infarctions over a 4-year period, which can further hamper sensitivity. Finally, most population-based studies fail to account for posterior infarcts in their diagnostic criteria by ignoring the development of right precordial R waves. Although less of an issue, the specificity of ECG MI diagnosis can be reduced by “pseudo-infarct patterns” found in conditions such as hypertrophic cardiomyopathy, emphysema, right ventricular hypertrophy, and infiltrative cardiomyopathy.9 The inclusion of repolarization abnormalities in diagnostic criteria will also serve to impair specificity. Despite these diagnostic vagaries, the ECG diagnosis of UMI will remain a part of the standard screening procedure simply because of its low cost and ease of use. However, imaging techniques that directly address cardiac pathology may be more predictive of outcome than ECG because they improve sensitivity without reducing specificity.

Unrecognized Left Ventricular Dysfunction
For more than 2 decades, echocardiography has been incorporated into prospective epidemiological assessment of cardiovascular risk in the United States and Europe, and a substantial body of literature has accrued describing the prevalence and prognosis of depressed systolic function in subjects who may or may not have knowledge of associated functional limitations. As in the case of UMI, congestive
heart failure (CHF) symptoms may exist in but may not be recognized by individuals displaying depressed contractile patterns on imaging studies. Thus, it may be preferable to similarly label this scenario “unrecognized left ventricular dysfunction” (ULVD) instead of the commonly applied term “asymptomatic left ventricular dysfunction.” ULVD diagnosis was originally based on M-mode echocardiography–determined left ventricular (LV) fractional shortening or derived LV ejection fraction (EF) with the use of the Teicholz cubed formula. M-mode echocardiography, which images only a thin slice of the anteroseptal and posterolateral basal LV walls, can provide accurate assessment of global function when ventricular wall motion abnormalities are diffuse and equivalent but can be extremely inaccurate when segmental wall motion abnormalities (SMAs) are limited to areas beyond those interrogated by the narrow beam of ultrasound or affect only the basal segments. Despite this major limitation, early reports indicated that M-mode echocardiography could detect ULVD and predict development of CHF. Vasan and colleagues at Framingham\(^\text{10}\) observed that increments in both LV diastolic and systolic height-indexed chamber dimensions predicted incident CHF over an 11-year follow-up period (adjusted hazard ratio [HR] 1.47 for diastolic dimension) in a middle-aged cohort free from known heart failure or coronary disease. Although global systolic function determined by LV fractional shortening did not predict CHF in Framingham subjects, investigators from the Cardiovascular Health Study\(^\text{11}\) later noted that reduced fractional shortening was present in 5.5% of the cohort at baseline and that this did not foretell incident CHF, with an adjusted relative risk of 2.51 for every 10-unit decline in shortening.

Cardiovascular Health Study investigators have also performed qualitative assessment of 2-dimensional echoes and found borderline LV systolic function (estimated EF 45% to 54%) in 5.4% and impaired EF (\(<45\%\)) in 2.6% of this elderly cohort (age \(>65\) years).\(^\text{12}\) Both levels of impaired EF predicted cardiovascular (adjusted HRs 2.08 and 2.13, respectively) and all-cause death (1.25 and 1.83), with trends toward prognostic significance for incident nonfatal MI and stroke as well. In a similar assessment of qualitative EF estimates in the middle-aged Framingham cohort, Wang and coworkers\(^\text{13}\) reported that 3.0% of subjects without symptoms or history of CHF (6.0% of men and 0.8% of women) had an estimated EF \(<50\%\). When subjects with subjectively determined EF were partitioned into groups with either mild (40% to 50%) or moderate–severe (\(<40\%\)) degrees of dysfunction, those with greater impairment had reduced rates of CHF-free survival (age- and sex-adjusted HRs of 3.9 and 8.5, respectively) as well as all-cause death (1.9 and 5.0). In fact, survival curves for moderate–severe ULVD approached those of subjects with symptomatic heart failure. These findings were similar to those observed in free-living subjects in Copenhagen, where the survival rate was reduced (HR 4.6 over 2 years of follow-up) in subjects with baseline EFs \(<40\%\) regardless of whether they had heart failure symptoms.\(^\text{14}\)

### The Strong Heart Study

Until now, epidemiological imaging studies have failed to address the prognostic potential of regional wall motion abnormalities and have instead focused on analogues of EF that provided a more generalized assessment of ventricular function. In this issue of *Circulation*, Cicala and associates\(^\text{15}\) examine the prevalence and prognostic significance of echocardiographic segmental and global wall motion abnormalities in American Indian subjects enrolled in the Strong Heart Study who had no history of coronary artery disease (CAD), stroke, or CHF. Subjects, who were 45 to 74 years of age, were also excluded if there was evidence of Q-wave MI at baseline, which further limited the possibility of UMI in this overweight, diabetes-prone population. Nevertheless, 5% of subjects still displayed echocardiographic evidence of regional myocardial dysfunction in a coronary distribution consistent with UMI. After significant major CAD risk factors and M-mode echocardiography–determined EF were

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**UMI Incidence, Prevalence, and Mortality in 12 Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Age, y</th>
<th>Cohort Description</th>
<th>ECG Method</th>
<th>Incidence*</th>
<th>Prevalence, %</th>
<th>UMI, %</th>
<th>Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Collaborative Study Group</td>
<td>3049</td>
<td>39–59</td>
<td>Company employees</td>
<td>Manual</td>
<td>2.2</td>
<td>1.1</td>
<td>23</td>
<td>...</td>
</tr>
<tr>
<td>Israeli Ischemic Heart Disease Study</td>
<td>9509</td>
<td>40–69</td>
<td>Civil servants</td>
<td>Computer/manual</td>
<td>3.6</td>
<td>Excluded</td>
<td>40</td>
<td>1.7 RMI higher</td>
</tr>
<tr>
<td>MR FIT Study</td>
<td>12666</td>
<td>35–57</td>
<td>Intermediate risk for CAD</td>
<td>Minn code/manual</td>
<td>N/A</td>
<td>Excluded</td>
<td>25</td>
<td>...</td>
</tr>
<tr>
<td>Honolulu Heart Study</td>
<td>7331</td>
<td>45–68</td>
<td>Japanese-American men</td>
<td>Manual</td>
<td>0.7</td>
<td>N/A</td>
<td>33</td>
<td>4–5 No difference</td>
</tr>
<tr>
<td>Framingham Study</td>
<td>5127</td>
<td>30–62</td>
<td>CAD excluded</td>
<td>Manual</td>
<td>2.2</td>
<td>Excluded</td>
<td>25</td>
<td>4–5 No difference</td>
</tr>
<tr>
<td>Bronx Aging Study</td>
<td>390</td>
<td>75–85</td>
<td>Elderly Bronx residents</td>
<td>Manual</td>
<td>24</td>
<td>6.4</td>
<td>44</td>
<td>7.1 No difference</td>
</tr>
<tr>
<td>Reykjavik Study (males)</td>
<td>9141</td>
<td>33–79</td>
<td>Icelandic men</td>
<td>Minn code/manual</td>
<td>0.5–3.2</td>
<td>0.5–2.8</td>
<td>32</td>
<td>3–5 No difference</td>
</tr>
<tr>
<td>Reykjavik Study (females)</td>
<td>9773</td>
<td>33–79</td>
<td>Icelandic women</td>
<td>Minn code/manual</td>
<td>0.4–2.2</td>
<td>0.5</td>
<td>33</td>
<td>...</td>
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<tr>
<td>Cardiovascular Health Study</td>
<td>5888</td>
<td>∼72</td>
<td>Ambulatory, age &gt;65 y</td>
<td>Novacode/manual</td>
<td>N/A</td>
<td>3.4</td>
<td>22</td>
<td>3.6 No difference</td>
</tr>
<tr>
<td>HERS</td>
<td>2763</td>
<td>∼67</td>
<td>Postmenopausal women with CAD</td>
<td>Novacode/manual</td>
<td>1</td>
<td>N/A</td>
<td>4</td>
<td>...</td>
</tr>
<tr>
<td>ARIC Study</td>
<td>12843</td>
<td>45–65</td>
<td>CAD excluded</td>
<td>Minn code/manual</td>
<td>0.8</td>
<td>Excluded</td>
<td>20</td>
<td>...</td>
</tr>
<tr>
<td>Rotterdam Study</td>
<td>5148</td>
<td>61–75</td>
<td>Suburban residents</td>
<td>MEANS/manual</td>
<td>3.8</td>
<td>N/A</td>
<td>43</td>
<td>...</td>
</tr>
</tbody>
</table>

MR FIT indicates Multiple Risk Factor Intervention Trial; HERS, Heart and Estrogen/progestin Replacement Study; ARIC, Atherosclerosis Risk In Communities; RMI, recognized myocardial infarction; Minn, Minnesota; NA, not applicable, and MEANS, Modular ECG Analysis System.

*Incidence per 1000 patient-years.
controlled for, SMAs still conferred a 2.5-fold risk for any cardiovascular event (MI, stroke, incident CAD, or CHF) and a 2.6-fold greater risk for cardiovascular death. SMAs were predictive of each of the separate cardiovascular events except for stroke, and the latter may have been due to the low number of incident events over the 7-year follow-up period. When compared with subjects with known CAD and those without CAD who had normal wall motion, patients with SMAs displayed an intermediate risk for one of the outcomes within the predefined cardiovascular event cluster. In the smaller group of subjects with global wall motion abnormalities, a similar risk for cardiovascular events (adjusted HR 2.4) was found, although this was powered entirely by the high rate of incident CHF in this group. Though not significantly different, risk for cardiovascular death tended to be even higher in subjects with global dysfunction than in those with SMAs. It is disappointing that the qualitative stratification strategy for classifying SMA severity, as outlined in Cicala and colleagues’ Methods, is never pursued and that the authors fail to indicate whether there is a relationship between SMA severity/distribution and clinical outcome. In addition, the criteria for assigning subjects into the category of “global dysfunction” are a bit nebulous.

The report by Cicala et al is noteworthy for several reasons. First, to our knowledge it is the first population-based study in which SMAs and global hypokinesis have been analyzed separately and apart from measures of overall systolic function. The result is that SMAs, and not global dysfunction, appear to predict incident vascular disease. Perhaps even more interesting is the notion that SMAs in a coronary distribution, presumably a result of CAD in most cases, do not appear to carry the same predictive power for cardiovascular morbidity as does a history of CAD. As discussed above, multiple studies have indicated that recognized and unrecognized Q-wave MIs carry similar prognoses in terms of risk for death. Thus it might also be expected that echocardiographic UMI might have the same ability to predict cardiovascular events as a history of CAD, but this was not the case in this investigation.

Probably the best explanation for the apparent limitation in predictive value displayed by echocardiography is that it is a more sensitive test for prevalent CAD than is ECG. As discussed above, Q-wave infarctions, which are the major predictive marker in most ECG studies, are known to represent larger infarcts, which in turn may be indicative of more severe coronary and other forms of vascular disease. Because subjects with Q-wave MIs at baseline were excluded from analysis, those with larger infarcts, presumably carrying a more ominous prognosis, may have been filtered out, thereby leaving a select population with only echocardiographic abnormalities resulting in a lower risk for cardiovascular events.

Management of ULVD
The predictive value of ventricular functional imaging reported by the Strong Heart investigators suggests an increasingly important role for 2-dimensional echocardiography or allied technologies in population screening. In addition, this report serves to underline the importance of aggressive investigation of unsuspected ULVD detected in the clinical laboratory. This is where a line of caution must be drawn, however, because the discovery of ULVD will inevitably lead to further cardiac evaluation, which may be expensive, time consuming, uncomfortable, or even dangerous for the patient. Therefore, early ascertainment of ULVD should be a major requirement before more aggressive diagnostic procedures involving radiation exposure risks or invasive investigation are undertaken.

ULVD Ascertainment
Wall motion assessment is one of the most challenging aspects of echocardiography. This fact is supported by the wide variation in normal EFs reported in patients without known cardiac disease. For example, whereas McDonagh et al reported a mean EF of 47% in a healthy, middle-aged Scottish population, Redfield et al noted an EF of 64% in a population of similar age without known cardiac disease. Limitation in accurate endocardial edge identification, particularly in apically acquired windows, has plagued epidemiologists for decades and is one reason that the antiquated, though often more reliable, M-mode technology continues to be used in population studies. The relatively recent advent of harmonic imaging, continued overall improvement in instrument quality, and the use of contrast media when endocardial definition requires enhancement will help to improve study accuracy in this area. With these advances, all of which are currently available in clinical labs, accurate 2-dimensional quantification of EF and improved identification of SMAs are possible on a routine basis and may be feasible on an epidemiological basis. In any event, qualitative assessment of reduced EF, especially in “borderline” cases, ideally should be accompanied by quantification, preferably by using a biplane method with carefully drawn endocardial borders. Failure to visualize such borders should trigger the implementation of contrast imaging for enhanced accuracy or implementation of an alternative imaging modality.

The discovery of definite ULVD, whether regional or global, should trigger an etiologic search, initially in the realm of CAD. In the case of asymptomatic SMAs, the presence of wall thinning, absence of systolic wall thickening, and enhanced reflectivity in a typical coronary distribution provide adequate evidence for prior infarction. If only regional hypokinesis is apparent, the presence of confounding conditions such as conduction defects, right ventricular volume overload, and postoperative changes should be excluded. Performance of one of the newer quantitative echocardiographic methods designed to assess strain, such as tissue Doppler strain rate imaging or myocardial speckle tracking, may also be of value. The ability of strain rate imaging to distinguish nontransmural from transmural MI and normal myocardium has been documented in both animal and clinical studies, and threshold values with excellent test characteristics have been documented by Zhang and colleagues.

If echocardiographic studies are less than definitive or the technology is unavailable, confirmation of infarction may be obtained with delayed-enhancement Gd-MRI or possibly contrast-enhanced multislice computed tomography. Gd-MRI can accurately document transmural or even subendo-
cardial infarction.\textsuperscript{4,7} In the case of global ventricular dysfunction, a cardiomyopathy workup should also include an initial investigation of possible CAD. Gd-MRI assessment may again prove useful, as there is evidence that in up to 87% of cases the technique can distinguish ischemic from nons ischemic pathologies.\textsuperscript{22} Another reasonable approach would be to pursue conventional or computed tomographic angiography to search for triple-vessel or left main CAD. In the interest of avoiding radiation exposure, our preference is to pursue MRI first and to proceed with computed tomographic angiography only if there is evidence of infarction or if the results are not definitive.

**Therapeutic Approaches**

If evidence of UMI is observed in a single-vessel distribution and no additional wall motion abnormalities are detected, then there is no clear indication for further investigation and aggressive medical intervention with statins, antiplatelet agents, and probably β-blockade should be pursued. It might be argued that imaging-based stress testing should be included in this algorithm, but until there is evidence that treatment of what would be considered “silent myocardial ischemia” has an outcome benefit, this is not presently indicated.

In the case of unrecognized global LV dysfunction, if CAD is discovered, then invasive evaluation and possibly revascularization may be indicated on the basis of appropriate anatomy and evidence of myocardial viability. In any case, the initiation of angiotensin-converting enzyme inhibition or receptor blockade is supported by the results from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial, in which subjects without symptoms of heart failure and EFs <35% took almost 3 times as long to develop CHF symptoms when treated with enalapril compared with placebo-assigned controls (8.3 versus 22.3 months).\textsuperscript{23} It should be noted that subjects in the Prevention arm of SOLVD were known to have existing cardiac disease, although they were not currently being treated with heart failure medications. Furthermore, there was an EF-dependent treatment effect, and treatment-assigned subjects with EFs in the 33% to 35% range received a benefit of only borderline significance. Thus, it is not certain that similar treatment of asymptomatic subjects screened for ULVD with mild or moderate EF reduction would result in outcome benefits equivalent to those seen in SOLVD.

**Epidemiological Applications**

Finally, it is unknown whether advanced imaging technologies that pose no radiation risk should play a major role in selective population risk screening. Enhanced detection of CAD with the use of tissue Doppler strain rate imaging or myocardial speckle tracking has yet to be reported in an epidemiological setting. Early strides are, however, being made in the epidemiological application of MRI. A recent report by Kwong and coworkers\textsuperscript{24} indicated that Gd-MRI evidence of even small amounts of myocardial necrosis conferred increased risks for major adverse cardiac events and cardiovascular death (HR 8.3 and 10.9) when compared with the presence of SMAs (HR 4.8 and 6.2) in subjects with suspected but undocumented CAD. The ongoing Multi-Ethnic Study of Atherosclerosis (MESA) has already documented subtle abnormalities of ventricular function related to carotid intimal thickness that may represent subclinical evidence of CAD.\textsuperscript{25} Finally, Gd-MRI is being used to assess prevalence and prognosis of UMI in a subgroup of the Aging Gene/Environment Susceptibility (AGES)–Reykjavik Study. Although the accuracy of technology such as this in detecting ULVD and UMI could lead to a quantum leap in cardiovascular risk assessment, only trials targeted at the treatment of high-risk subjects with ULVD can truly determine whether the benefits of advanced imaging implementation in population screening will justify the significant costs.

**Disclosures**

None.

**References**


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