Screening for Left Ventricular Systolic Dysfunction: Is Imaging a Solution?

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To address the heart failure burden, our focus needs to shift to disease prevention. Strategies to initially screen for heart failure precursors such as asymptomatic left ventricular systolic dysfunction have been evaluated, including clinical scores, the 12-lead electrocardiogram, and natriuretic peptides. However, their specificity limits their broad application as screening tools in asymptomatic populations. High-quality images are now available from hand-carried cardiac ultrasound devices, at a fraction of the capital cost of standard echocardiography with favorable diagnostic performance, especially when experienced staff perform the imaging. Questions that remain to be addressed include how we should select the target population to screen, who should perform the screening studies, how much training is required, and how often screening studies should be performed. (J Am Coll Cardiol Img 2010;3:421–8) © 2010 by the American College of Cardiology Foundation

Despite modest reductions in mortality over the last 2 decades, there has been little change in the age-adjusted incidence of heart failure in community-based cohorts; hence, overall and age-adjusted prevalence rates continue to rise (1,2). Current treatment strategies are usually applied at later stages in the disease trajectory, with modest health outcome gains. Our focus needs to shift to an earlier stage, to allow disease prevention and early detection of patients before they develop clinical congestive heart failure. Echocardiographic markers associated with an increased risk of developing heart failure include left ventricular systolic dysfunction (LVSD), left ventricular (LV) diastolic dysfunction, increased LV mass, and increased left atrial size (3–5). This review will focus on asymptomatic LVSD, which holds the most promise as a potentially modifiable echocardiographic risk factor.

The Diagnostic Assessment Framework: How Should We Evaluate the Benefit of Diagnostic Tests?

An ideal diagnostic test should be safe, accurate, clinically effective, and cost effective. Fineberg et al. (6) initially proposed a hierarchical approach to the evaluation of diagnostic imaging technologies subsequently extended by others, including appraisal of technical efficacy, diagnostic accuracy, impact on diagnostic thinking, therapeutic planning and patient outcomes, and societal considerations (7). Diagnostic accuracy refers to the ability of the test to distinguish the presence or absence of disease. Relevant measures include sensitivity, specificity, and measures related to receiver-operator-characteristic curves. To be clinically effective, the information provided by the test should result in a change in both the clinician’s diagnostic thinking (by raising or lowering pre-test
A B B R E V I A T I O N S  
AND ACRONYMS

ACE = angiotensin-converting enzyme
ECG = electrocardiogram
HCU = hand-carried cardiac ultrasound
LV = left ventricular
LVSD = left ventricular systolic dysfunction

What Is the Prevalence of Asymptomatic LVSD?

Using the heart failure classification proposed by the American College of Cardiology and the American Heart Association, asymptomatic structural heart disease (stage B) was 2.8-fold more common than symptomatic heart failure (stages C and D) in a community-based sample of residents age ≥45 years (10). This forms the basis for incident heart failure cases in the future. Furthermore, depending on the population studied and the cutoff chosen to define LVSD, approximately 2% to 8% of adults have LVSD, of whom approximately one-half have no prior or current history of heart failure (Table 1). Men are 2 to 3 times more likely to be affected with a strong age predilection. In selected high-risk groups such as patients with vascular disease or diabetes mellitus, up to 20% may have LVSD (11).

What Are the Morbidity and Mortality Associated With Asymptomatic LVSD?

Longitudinal cohort studies have demonstrated a 3- and 8-fold increased risk of developing heart failure in individuals with mild and moderate to severe asymptomatic LVSD, respectively (12). In the SOLVD (Studies of Left Ventricular Dysfunction)-Prevention study, 15.8% of individuals with asymptomatic LVSD died within 37 months, with approximately 90% of these being cardiovascular deaths (13). In the Framingham cohort, individuals with asymptomatic LVSD had a 60% higher risk of dying (Fig. 2) (12). Most of these deaths were attributed to vascular disease (40% coronary artery disease, 21% other vascular disease), with 43% of the coronary artery disease deaths being sudden. Importantly, 56% of the individuals with asymptomatic LVSD who died did not develop antecedent heart failure, indicating that waiting for someone to develop symptomatic heart failure may be a missed opportunity to intervene and potentially avoid premature death.

Can We Improve Outcomes in Individuals With Asymptomatic LVSD?

Studies in subjects with LVSD following myocardial infarction with or without heart failure mandate the use of beta-adrenergic receptor blockers and either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers to retard progressive adverse LV remodeling and improve outcomes (14). There is also randomized controlled trial evidence from the SOLVD-Prevention investi-
Investigators that ACE inhibitors reduced the combined end point of death or hospitalization for heart failure in patients with asymptomatic LVSD over 3 years of follow-up (13). Despite most subjects being prescribed open-label ACE inhibitors after the study was completed, there was a significant mortality benefit over 11 years in those subjects who were randomized to receive ACE inhibitor therapy in the original study (Fig. 3) (15). This is particularly relevant given that most individuals with LVSD in the community are not taking ACE inhibitors (16). Furthermore, in patients with vascular disease, antiplatelet therapy, statins, and revascularization may reduce the risk of recurrent ischemic events and subsequent adverse LV remodeling (14).

Table 1. Prevalence of LVSD in Community Surveys Involving More Than 1,000 Subjects

<table>
<thead>
<tr>
<th>Study (Ref #)</th>
<th>Sample Size</th>
<th>Age Range (yrs)</th>
<th>Mean Age (yrs)</th>
<th>LVSD Definition</th>
<th>Prevalence (%)</th>
<th>Proportion Symptom-Free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardin et al. (17) (U.S.)</td>
<td>5,201</td>
<td>≥65</td>
<td>73</td>
<td>Abnormal</td>
<td>3.7</td>
<td>—</td>
</tr>
<tr>
<td>McDonagh et al. (19) (Scotland)</td>
<td>1,467</td>
<td>25–74</td>
<td>50</td>
<td>EF ≤30%</td>
<td>2.9</td>
<td>48</td>
</tr>
<tr>
<td>Schunkert et al. (20) (Germany)</td>
<td>1,566</td>
<td>25–75</td>
<td>50</td>
<td>EF &lt;48%</td>
<td>2.7</td>
<td>42</td>
</tr>
<tr>
<td>Mosterd et al. (21) (the Netherlands)</td>
<td>2,267</td>
<td>55–95</td>
<td>66</td>
<td>FS ≥25%</td>
<td>3.7</td>
<td>60</td>
</tr>
<tr>
<td>Davies et al. (22) (England)</td>
<td>3,960</td>
<td>≥45</td>
<td>61</td>
<td>EF &lt;40%</td>
<td>1.8</td>
<td>47</td>
</tr>
<tr>
<td>Devereux et al. (18) (U.S.)</td>
<td>3,184</td>
<td>45–74</td>
<td>60</td>
<td>EF &lt;40%</td>
<td>2.9</td>
<td>72</td>
</tr>
<tr>
<td>Redfield et al. (23) (U.S.)</td>
<td>2,042</td>
<td>≥45</td>
<td>63</td>
<td>EF ≤40%</td>
<td>2.0</td>
<td>47</td>
</tr>
<tr>
<td>Abhayaratna et al. (24) (Australia)</td>
<td>1,275</td>
<td>60–86</td>
<td>69</td>
<td>EF ≤40%</td>
<td>2.1</td>
<td>22</td>
</tr>
</tbody>
</table>

EF = ejection fraction; FS = fractional shortening; LVSD = left ventricular systolic dysfunction.
bility status in treatment efficacy studies and as the reference standard in diagnostic accuracy studies, it would seem reasonable to infer clinical effectiveness with strategies that improve our ability to detect LVSD. However, most individuals with asymptomatic LVSD in the community would not have been eligible for the SOLVD-Prevention trial, in which middle-aged men with coronary artery disease and moderate to severe LVSD dominated (13). That being said, it is generally accepted that this indication for ACE inhibitors should be applied broadly, given the consistent demonstration of efficacy in studies that enrolled subjects with LVSD (14).

How Should We Screen for Asymptomatic LVSD?

In asymptomatic populations with low disease prevalence, diagnostic screening tests with high specificity and positive predictive value are preferred to allow a rule-in strategy, thereby minimizing false positives and unnecessary downstream testing. The low prevalence of LVSD in the general community (17–24), the inability of a physical examination to reliably detect LVSD (25), and the limited availability of standard echocardiography mandate a selective approach to identify which individuals should undergo echocardiography. Three options that have been widely evaluated are the use of clinical risk factors, the 12-lead electrocardiogram (ECG), and plasma natriuretic peptide levels.

The use of clinical characteristics incorporated into a multivariable logistic regression model to detect individuals with LVSD applied to the Framingham cohort had an area under the receiver-operator-characteristic curve of 0.75 in men and 0.72 in women; however, this model did incorporate 12-lead ECG findings and would be difficult to use in clinical practice (26). The 12-lead ECG has been shown to be highly sensitive in identifying LVSD in some but not all studies (27). However, it lacks the specificity and therefore the positive predictive value to be useful as a screening tool, with most studies reporting specificities below 80% (27).

In symptomatic patients, recent meta-analyses have demonstrated that plasma natriuretic peptides are better indicators of clinical heart failure than of LVSD (28,29). This reflects their correlation with raised intracardiac filling pressure, which occurs in LVSD and various other forms of heart disease (30). Studies that have focused on the isolated detection of LVSD in asymptomatic individuals have been heterogeneous, with indications of publication bias in at least 1 systematic review (27–29). In part, this may be explained by the different populations evaluated, the various assays and thresholds used to define abnormal levels, and the different cutoffs used to define the reference standard (i.e., “any” or “moderate to severe” LVSD). In an economic evaluation based upon the diagnostic performance of plasma natriuretic pep-
tides in the Framingham cohort (26) and health outcome data extrapolated from randomized controlled trials (13), it appeared that screening for LVSD may be cost effective, provided the prevalence of LVSD was at least 1% in the target population (Fig. 4) (31). However, by far, the majority of individuals with abnormal natriuretic peptide levels will have normal LV systolic function, which limits the use of natriuretic peptide levels as a screening tool for LVSD in asymptomatic individuals (32). Attempts to improve the specificity by incorporating clinical variables, the 12-lead ECG, measurement of urinary natriuretic peptide levels, and additional inflammatory biomarkers have met with variable success (27,33,34).

It has been argued that limiting the use of natriuretic peptides to the detection of LVSD ignores their full diagnostic and prognostic utility. Raised natriuretic peptide levels in individuals with normal LV systolic function (who are labeled as “false positives”) may indicate other pathology such as LV diastolic dysfunction, atrial fibrillation, coronary artery disease, valvular heart disease, or cardiomyopathy (30,32). However, it is not clear whether further investigation and treatment of such pathology in the context of screening in an asymptomatic population will lead to better outcomes. Given that the accepted reference standard to identify subjects with LVSD is an imaging method, another approach to screening is to perform a focused and limited imaging study to answer the specific question being asked.

**Hand-Carried Cardiac Ultrasound (HCU) Devices to Screen for Asymptomatic LVSD**

Given the limited availability and cost of standard echocardiography, portable HCU devices providing high image quality at substantially reduced capital cost have been developed, with some recent handheld devices weighing <1 kg. Although a number of studies have addressed how HCU may reduce diagnostic error when performed in addition to physical examination (35), there has been growing interest in evaluating its role as a screening tool in community-based populations (36–38). The sensitivity and specificity of HCU to identify LVSD is approximately 90% when performed by experienced operators (36–38). In a consecutive series of 533 subjects, the comparative diagnostic performance

![Figure 4. Impact of Prevalence of Low EF on the Cost Effectiveness of Screening for Men and Women Using BNP Followed by Echocardiography in Those With a Positive Test](image)

The cost-effectiveness (C-E) ratio drops below $100,000 per quality-adjusted life year (QALY) gained at a prevalence over 0.5% and drops below $50,000 at a prevalence over 1%. For any given prevalence of disease, the C-E ratio is lower for women because the accuracy of B-type natriuretic peptide (BNP) levels is slightly greater for women than men. Open circles — men (BNP vs. no screen); closed circles — women (BNP vs. no screen). Reprinted, with permission, from Heidenreich et al. (31). EF — ejection fraction; LV — left ventricular.
favored HCU compared with the 12-lead ECG and plasma natriuretic peptide levels, driven largely by its higher specificity (Table 3) (38). A further small improvement in specificity was achieved by performing HCU only in those individuals who had either an abnormal 12-lead ECG or elevated natriuretic peptide levels, but at the expense of a reduction in sensitivity. The reduction in unnecessary downstream testing driven by the higher positive predictive value of HCU makes this a cost-effective method to determine which patients should have a standard echocardiogram, especially when performed in subjects at the highest risk of developing LVSD, such as those with vascular disease, diabetes mellitus, or previous heavy alcohol exposure (Table 3) (38).

**Limitations of the Evidence**

The best method to screen for asymptomatic LVSD is still not clear, with multiple or sequential biomarker strategies and HCU holding the most promise (33,34,36–38). HCU appears to be cost effective; however, a number of questions remain. What is the ideal target population? Screening high-risk populations appears most appropriate (38), but what is the best method to identify these individuals, and should we include age and sex descriptors? Who should perform HCU? The procedure is highly dependent on the operator, and its widespread application may be limited by the finite number of experienced sonographers. Operators with limited echocardiography experience have been trained in standardized programs as short as 3 hours to perform and interpret focused echocardiograms with moderate sensitivity to detect LVSD; however, these studies have largely involved physicians and medical students, who are unlikely to be involved in widespread screening programs (39). Nonetheless, this could allow for opportunistic screening of high-risk patients when they present for clinical evaluation. Furthermore, in a small study of diabetic outpatients, nurses trained to use HCU correctly identified all cases of LVSD, although the false-positive rate was relatively high (40). Whichever method is chosen, appropriate quality control processes need to be established to ensure consistent training, skills maintenance, and acceptable diagnostic accuracy.

Should we restrict screening to the detection of asymptomatic moderate to severe LVSD? Mild LVSD and diastolic dysfunction are also associated with increased morbidity and mortality (5,12). However, it is not clear whether treating this would lead to better outcomes in asymptomatic populations. How often should we screen? This will drive cost effectiveness and will be influenced by the incident rate of LVSD in the target population. Finally, screening for asymptomatic LVSD has not been evaluated in a randomized controlled trial; however, a linked evidence approach seems reasonable, given the evidence that we can improve outcomes in subjects with asymptomatic LVSD (13–15).

**Conclusions**

The impact of treating symptomatic heart failure on overall disease burden is likely to be limited unless treatment is combined with methods to reduce the frequency of incident heart failure in the community. One method to do this is to screen for recognized precursors of heart failure such as asymptomatic LVSD. A number of strategies have

| Table 3. The Diagnostic Accuracy and Cost Effectiveness of the 12-Lead ECG, NTproBNP, and HCU,* or Their Combination in Detecting LVSD, With Standard Echocardiography as the Reference Standard |
|-----------------|---------------------------------|-----------------|-----------------|
| **Strategy**    | **General Population (n = 734)** | **High-Risk Group (n = 761)** |
|                 | Sensitivity | Specificity | Cost per Case of LVSD Detected (€) | Sensitivity | Specificity | Cost per Case of LVSD Detected (€) |
| ECG abnormal    | 92          | 78          | 1,614                        | 90          | 64          | 1,006                        |
| NTproBNP level abnormal | 80          | 88          | 1,501                        | 76          | 70          | 1,096                        |
| ECG or NTproBNP level abnormal | 96          | 72          | 2,412                        | 94          | 49          | 1,485                        |
| ECG and NTproBNP level abnormal | 76          | 94          | 1,912                        | 73          | 85          | 1,104                        |
| HCU abnormal    | 93          | 97          | 1,101                        | 97          | 93          | 683                          |
| HCU abnormal after ECG abnormal | 87          | 98          | 884                         | 83          | 96          | 649                          |
| HCU abnormal after NTproBNP level abnormal | 87          | 98          | 913                         | 70          | 97          | 712                          |

*HCU was performed in 533 consecutive subjects. †High-risk refers to individuals with a history of ischemic heart disease, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, or heavy alcohol usage. Modified, with permission, from Galasko et al. (38).

ECG = electrocardiogram; HCU = hand-carried cardiac ultrasound; LVSD = left ventricular systolic dysfunction; NTproBNP = N-terminal pro-B-type natriuretic peptide.
been evaluated, including the use of clinical scores, the 12-lead ECG, natriuretic peptide levels, and more recently, HCU. The HCU holds promise as a screening tool in asymptomatic subjects, with a high specificity if HCU is performed by experienced sonographers. However, the technique is highly operator dependent, which may limit its broader application in resource-constrained environments. That being said, it seems likely that screening for asymptomatic LVSD will have a greater impact on disease burden than our current approach of waiting for individuals to develop clinical heart failure before deciding who and when to treat.

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