

# Congestive Heart Failure®

july • august 2006

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**FOR SPECIALISTS AND PRIMARY CARE CLINICIANS TREATING HEART FAILURE**

## Acoustic Cardiography and Heart Failure: Advancing Diagnosis and Treatment

### **review paper**

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### **original papers**

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**Supplement to Congestive Heart Failure**

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## REVIEW PAPER

# The Utility of Heart Sounds and Systolic Intervals Across the Care Continuum

*Acoustic cardiography is an exciting, new, easy-to-use, modernized technology that incorporates already proven techniques of phonocardiography. Application of acoustic cardiography to clinical practice can improve diagnosis and management of heart failure patients. Its clinical use should help address some of the need for robust, inexpensive, and widely accessible technology for proactive heart failure diagnosis and management. Acoustic cardiographically recorded measurements have been correlated with both cardiac catheterization and echocardiographically determined hemodynamic parameters. Heart sounds captured by acoustic cardiograms have proven to assist clinicians in assessing dyspneic patients in the emergency department by utilizing the strong specificity of an S<sub>3</sub> for detecting acute decompensated heart failure. Acoustic cardiography offers a cost-efficient, easy-to-use method to optimize the devices used in cardiac resynchronization therapy. The rapidly and easily obtainable information gathered by acoustic cardiography should foster its more widespread use in diagnosis and treatment of heart failure, including cardiac resynchronization therapy device optimization. (CHF. 2006;12[4 suppl 1]:2-7) ©2006 Le Jacq*

**H**art failure (HF) currently affects over 5 million Americans, with roughly 500,000 new cases each year. It accounts for 12–15 million office visits and 6.5 million hospital days annually. Despite new and improved treatments, HF results in 300,000 deaths each year as a primary or contributory cause. The rapid growth of HF has made it a disease of epidemic proportions that has a tremendous clinical and financial impact on the US health care system. With 5-year mortality rates approaching 50%, it is the most common cause of hospitalization in patients older than 65 years and is the single most expensive diagnosis in the United States. In 2001, there were almost one million hospital discharges for decompensated HF, at a cost of more than \$20 billion. The average hospital loses more than \$1000 per HF admission.<sup>1</sup>

HF care in 2006 has shown dramatic progress over the past several years, and many more options are currently available than was the case as recently as the early 1990s. With the discovery and clinical application of new biomarkers, such as B-type natriuretic peptide (BNP) and the rapidly expanding field of implantable devices, HF care has become an emergent subspecialty within the field of cardiology. However, despite the progress made within the HF arena, there remains significant unmet clinical need. Because HF occurs most frequently in the elderly, a population with many simultaneous comorbidities, it can be a challenging diagnosis in the emergency department (ED). Moreover, since its most common presentation is dyspnea, a symptom that is common to many diseases,

misdiagnosis is routine. Even in the BNP era, accurate diagnosis of acute decompensated HF (ADHF) at ED presentation remains difficult. BNP has aided in “ruling out” ADHF with its high negative predictive value, but due to the limited positive predictive value and specificity of abnormal BNP values, problems with accurately “ruling in” ADHF persist. Results from a large prospective blinded study have shown that 18.5% of ED HF diagnoses are inaccurate.<sup>2</sup>

Medical therapies, such as angiotensin-converting enzyme inhibitors, β blockers, and spironolactone, have led to marked improvements in both symptom control and overall survival in patients with HF.<sup>3–5</sup> The addition of devices such as implantable cardioverter-defibrillators and pacemakers have also proven beneficial.<sup>6</sup> Some HF

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patients benefit from simultaneous pacing of both ventricles (biventricular, or BiV, pacing) or of one ventricle in patients with bundle branch block. This approach is referred to as cardiac resynchronization therapy (CRT) and is recommended in advanced HF (usually New York Heart Association class III or IV), severe systolic dysfunction (e.g., ejection fraction  $\leq 35\%$ ), and intraventricular conduction delay (e.g., QRS  $> 120$  milliseconds).<sup>7–11</sup> The rationale behind CRT is that it improves pump performance and reverses ventricular remodeling. Importantly, when BiV pacing is used, the delay between atrial and ventricular stimulation (the AV delay) should be adjusted to achieve the maximum attainable cardiac output. Studies have suggested that the optimal AV delay can be defined by Doppler echocardiography<sup>12</sup>; however, this is a limited resource in many environments.

Unfortunately, expensive and highly programmable CRT devices have been shown in real-world practice to have a 30% nonresponder rate.<sup>13</sup> This may be largely attributable to the fact that only 10% of CRT devices are optimized and is in stark contrast to the randomized controlled clinical trials that led to the approval of CRT devices.<sup>7–11</sup> There continues to be a tremendous need for robust, inexpensive, widely accessible, and easy-to-use technology that is highly specific for proactive HF diagnosis and management.

Heart sounds and systolic time intervals recorded in an acoustic cardiogram may improve the areas of weakness in the current HF era and have proven valuable in assisting clinical diagnostic and management challenges encountered during HF care.

## Heart Sounds and Systolic Time Intervals

Auscultation of heart sounds has been a diagnostic tool employed by clinicians to detect abnormalities associated with cardiac dysfunction for centuries. Potain<sup>14</sup> first described abnormal diastolic cardiac sounds in the literature in 1880. With relatively

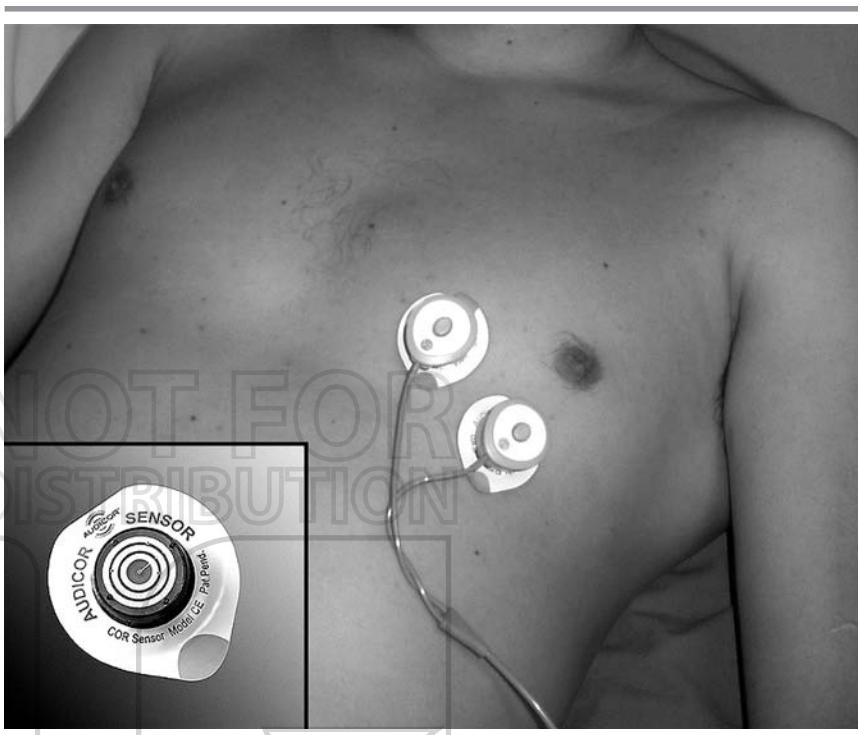


Figure 1. Placement of the AUDICOR sensors (Inovise Medical, Inc., Portland, OR)

normal heart rates,  $S_3$ , also known as a ventricular gallop, occurs 0.12–0.16 sec after the  $S_2$  in early diastole.<sup>15</sup> The most likely explanation for the extra sound producing the  $S_3$  is that vigorous and excessively rapid filling of blood into a stiff ventricle is suddenly halted, causing vibrations audible as the  $S_3$ .<sup>16</sup> The  $S_4$ , also known as an atrial gallop, occurs after P-wave onset and before the  $S_1$  in the cardiac cycle. The  $S_4$  occurs as blood enters a relatively noncompliant ventricle late in diastole because of atrial contraction and causes vibrations of the left ventricular (LV) muscle, mitral valve apparatus, and LV blood mass.<sup>17</sup>

The auscultated  $S_3$  and  $S_4$  have long been used as clinical signs of heart disease with both diagnostic and prognostic importance.<sup>18–23</sup> However, the value of these physical findings has been diminished by reports of poor accuracy and a large degree of interobserver variability.<sup>24,25</sup> In addition, it has been well documented that physician physical examination skills have deteriorated and are not emphasized during training as much as they once were.<sup>26</sup> The phonocardiogram has

traditionally been the gold standard tool for the detection of extra heart sounds because it produces objective data that is reproducible and quantifiable. Phonocardiography has been used to understand the mechanisms and associated clinical characteristics of diastolic sounds,<sup>27–30</sup> and results of phonocardiography have been used to determine the accuracy of physician auscultation.<sup>25</sup> In addition to providing objective measures of heart sounds, phonocardiography used in conjunction with a carotid pulse tracing allows for the collection of valuable data about systolic time intervals.<sup>31,32</sup> While phonocardiography provides reliable and objective information, obtaining the data has proven difficult, timely, and cumbersome and requires a technician with specialized skill to operate the device. Consequently, its use has been supplanted by echocardiography.

With the invention of new technology, the phonocardiogram has recently been reincarnated as a newer modern version of the older proven technique. This newly renovated phonocardiogram is called an acoustic cardiogram. By replacing the standard  $V_3$  and  $V_4$

**Table.** Definitions of Diastolic Time Intervals

ABBREVIATION	CARDIAC CYCLE TERMINOLOGY	DEFINITION
EMAT	Electromechanical activation time	Time from the Q-wave onset to mitral valve closure ( $S_1$ )
LVST	Left ventricular systolic time	Time from mitral valve closure ( $S_1$ ) to aortic valve closure ( $S_2$ ); includes the IVCT
PEP	Pre-ejection period	Time from Q-wave onset to aortic valve opening; includes the IVCT
LVET	Left ventricular ejection time	Time when the left ventricle is actively ejecting blood into the aorta (time from aortic valve opening to aortic valve closure)
IVRT	Isovolumic relaxation time	Time when the left ventricle relaxes during early diastole before any filling occurs (time after the aortic valve closes and before the mitral valve opens)
IVCT	Isovolumic contraction time	Time during contraction of the ventricle after the mitral valve closes and before the aortic valve opens

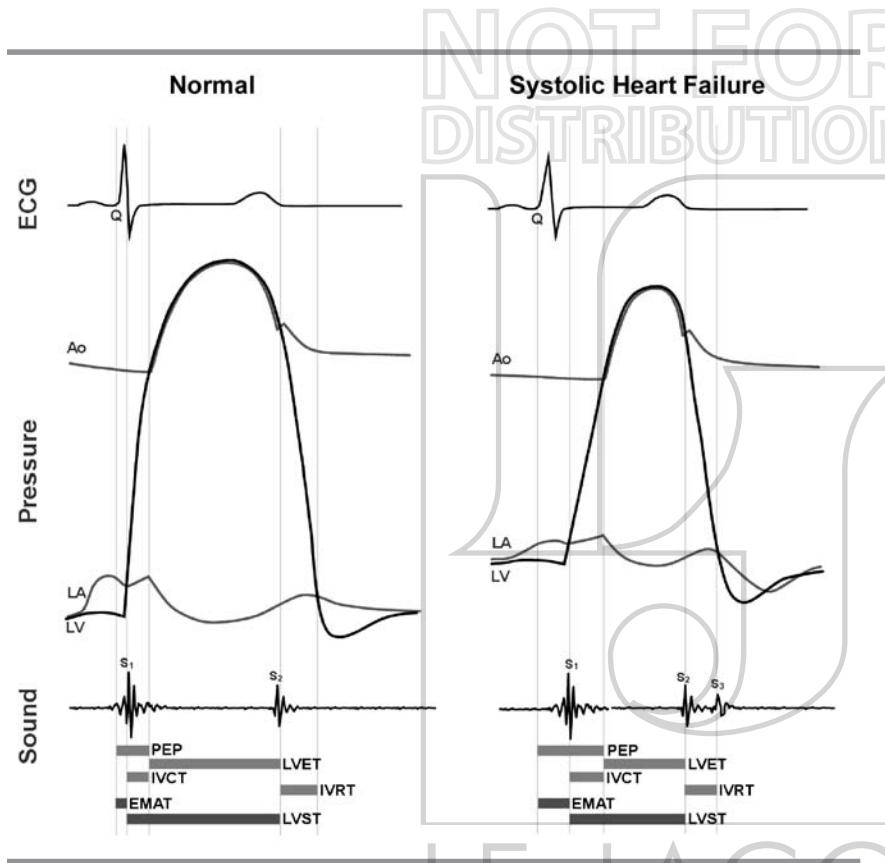


Figure 2. Heart sounds and systolic time interval data provided by the AUDICOR device (Inovise Medical, Inc., Portland, OR). (Pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR data.) ECG=electrocardiogram; Ao=aorta; LA=left atrium; LV=left ventricle; PEP=pre-ejection period; LVET=left ventricular ejection time; IVCT=isovolumic contraction time; IVRT=isovolumic relaxation time; EMAT=electromechanical activation time; LVST=left ventricular systolic time

leads with newly designed sensors, both sound and electrical information can be gathered. To process the acoustic cardiogram data, Inovise Medical, Inc. (Portland, OR) has developed the AUDICOR technology. This is a system that records, stores, displays, and algorithmically interprets the simultaneous digital electrocardiographic

(ECG) and acoustical data (Figure 1). The strengths of this system are that it does not require a pulse sensor, works in noisy environments (e.g., in an ED where accurate auscultation may be difficult), and has relatively forgiving sensor placement. Computer algorithms allow for rapid, reproducible, and objective data to be generated and analyzed

for prompt clinical use. Acoustic cardiography can provide objective measurements of heart sounds as well as valuable information about systolic time intervals that have proven useful in a variety of clinical settings (Figure 2, Table). A detailed investigation and discussion of the hemodynamic correlates of the  $S_3$  and systolic time interval follows in this supplement.<sup>33</sup>

### Acoustic Cardiography and Its Correlation to Gold Standards

Acoustic cardiography is a validated, rapid, and noninvasive means to assess cardiac hemodynamics. It has been compared with cardiac catheterization, an invasive procedure that represents the gold standard of cardiac hemodynamics. Acoustic cardiography has also been compared with echocardiography, a similarly noninvasive method to assess cardiac hemodynamics. However, both cardiac catheterization and echocardiography are much more costly, time-consuming, and highly limited resources.

Recent studies demonstrated the relationship between various measurements of cardiac hemodynamics. In one report, 100 subjects each underwent acoustic cardiography, echocardiography, BNP measurement, and left heart catheterization within a 4-hour period. These studies demonstrated that there was a strong association between the presence of an  $S_3$  and a number of parameters, including the incidence of HF diagnosis, depressed LV ejection fraction, elevated LV end-diastolic pressure, abnormal ventricular

relaxation, and tissue Doppler imaging assessments indicative of ventricular dysfunction (e.g., increased deceleration rate of early mitral valve inflow patterns).<sup>34,35</sup> While BNP values performed well in predicting the absence of HF, they fared poorly in predicting depressed LV ejection fraction and elevated LV end-diastolic pressure. Therefore, acoustic cardiography can help "rule in" certain diagnoses with its high specificity for ventricular dysfunction and abnormal cardiac hemodynamics,<sup>35</sup> thus supplementing the clinical impression in precisely the range where BNP performs poorly. In addition, systolic time interval data have proven to correlate well with hemodynamic measures: the LV systolic time correlates well with the LV ejection fraction, and the electro-mechanical activation time correlates with measures of cardiac contractility ( $dP/dt$ ).<sup>35,36</sup> This easily and rapidly obtainable information has been proven to assist clinicians in assessing dyspneic patients in the ED and in other areas of HF management and could be widely implemented to help proactive HF diagnosis and management.

## Clinical Applications of Acoustic Cardiography

**Emergency Department.** Although HF may be readily diagnosed in its advanced stages, it can be difficult to diagnose clinically in its earlier stages.<sup>37</sup> HF has many nonspecific signs and symptoms that can present diagnostic and management ambiguities. Also, the ED can be a challenging environment for detecting an  $S_3$  by routine auscultation. Even in the BNP era, an accurate diagnosis of ADHF within the ED remains poor, with 18.5% of cases of ADHF being undiagnosed.<sup>2</sup> Recent studies evaluating the clinical utility of acoustic cardiography in the ED setting have found that the detection of  $S_3$  is significant and aids physicians in accurate diagnosis. While not sensitive enough to be used as a screening tool, the detection of an  $S_3$  is highly specific for abnormal cardiac function.<sup>22</sup> Studies have demonstrated

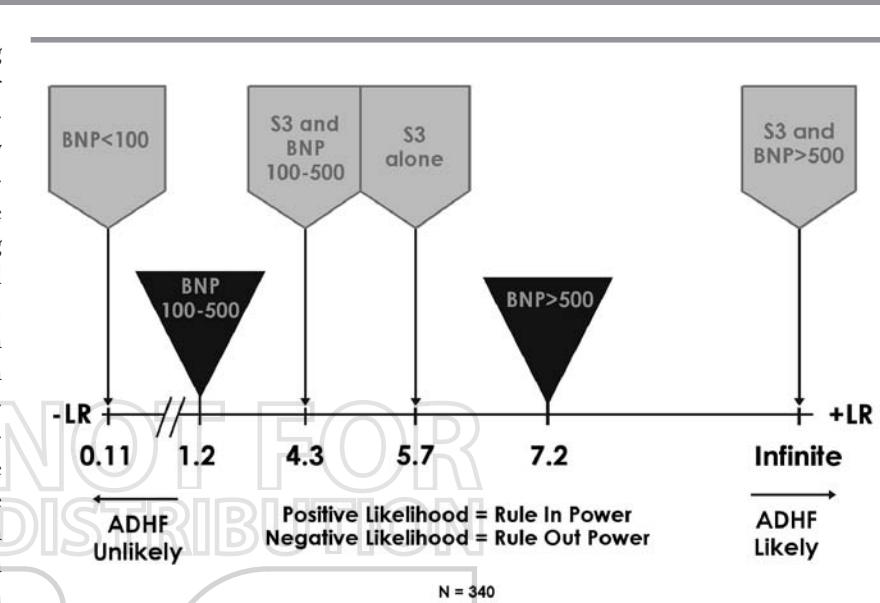


Figure 3. Synergy between acoustic cardiography-detected  $S_3$  and B-type natriuretic peptide (BNP) (pg/mL). ADHF=acute decompensated heart failure; LR=likelihood ratio

the additive information garnered by  $S_3$  heart sounds detected by acoustic cardiograms and the combined utility it serves with BNP values when evaluating dyspneic patients in the ED.<sup>38,39</sup> These studies illustrate that an  $S_3$  detected by acoustic cardiography is highly specific for ADHF and is ideally suited for use in combination with BNP to improve diagnostic accuracy in ED patients with dyspnea of unclear etiology (Figure 3).

The implementation of BNP testing has improved the diagnostic accuracy of detecting ADHF;<sup>2</sup> however, the non-diagnostic values of BNP between 100–500 pg/mL, the range referred to as the "gray zone," are found in an important portion of dyspneic patients. Acoustic cardiography has been shown to help resolve a significant amount of these indeterminate BNP values and can substantially improve the diagnostic evaluation of patients with gray-zone BNP values. In doing so, acoustic cardiography can increase the confidence with which physicians initiate treatment for clinically significant ADHF, as recently corroborated by M. Zuber, MD (unpublished data, May 2006). Moreover, the presence of an  $S_3$  in combination with a BNP value  $> 500$  pg/mL virtually assures the presence of

ADHF as depicted by the infinite positive likelihood ratio in Figure 3.<sup>39</sup>

The clinical advantages of an early accurate diagnosis of ADHF are apparent. Interestingly, there appears to be a significant fiscal penalty for an inaccurate initial ED diagnosis missing HF when it is present. According to a study appearing later in this supplement, patients who were misdiagnosed as non-ADHF (most often chronic obstructive pulmonary disease and pneumonia) at ED presentation accrued hospital charges that were significantly higher than those correctly diagnosed: \$10,508 vs. \$7977, respectively. The difference of more than \$2500 represented a 32% increase in charges and resulted in a near doubling of the financial loss experienced by the hospital.<sup>39</sup>

Because acoustic cardiography can be performed at the time of the ECG (a test routinely obtained within minutes in the ED as compared with central laboratory testing, which can take hours), it can help solve some of the unmet clinical need for more rapid and accurate diagnosis. As a result, fewer missed diagnoses, more rapid and accurate initial diagnoses, and valuable risk assessment should allow prompt initiation of appropriate treatment and

early risk stratification. This translates to better clinical outcomes and more economically sound delivery of health care. The Acute Decompensated Heart Failure National Registry (ADHERE) database<sup>40,41</sup> has collected data on over 100,000 patient cases and has taught us that earlier diagnosis and initiation of appropriate treatment renders better outcomes and more cost-efficient care. A review and analysis of the existing literature surrounding acoustic cardiography and its role in assisting ED diagnosis of ADHF appears in this supplement, along with original articles and case studies demonstrating the powerful utility of this application.

**Inpatient Hospital Setting.** The appearance, disappearance, or change in the S<sub>3</sub> intensity in response to maneuvers or therapies, e.g., vasodilators or diuretics, has been well studied. Dynamic changes may reveal significant information about clinical status regarding treatment response.<sup>42</sup> The baseline data obtained in the ED may then be utilized to assist in determining therapeutic efficacy throughout a patient's hospital stay. As well, while few data currently exist for diagnosing ADHF that occurs as a secondary event during a hospitalization, one could speculate that having a baseline or BNP and acoustic cardiogram on admission could significantly aide in this diagnosis. Should an elevation in BNP occur and/or an S<sub>3</sub> appear that was not initially present, the diagnosis of a new, or exacerbation of an existing, cardiac dysfunction should be considered and investigated. Similarly, knowledge of the dry weight acoustic status at discharge could help at follow-up and subsequent outpatient assessments.

**Outpatient Cardiology Offices and HF Clinics.** The utility of acoustic cardiograms in outpatient settings for monitoring has been hypothesized as a means to detect early signs of ADHF, because an S<sub>3</sub> occurs before the onset of symptoms. This may potentially help to identify patients who require prompt medical intervention, as opposed to the

more stable patient for whom a routine check-up with an HF nurse practitioner or physician's assistant could be scheduled. In doing so, early adjustments in medications and/or further evaluation may help prevent an episode of ADHF requiring hospitalization. This rapidly and easily obtainable information can be gathered at the time of arrival at the clinician's office when baseline vital signs and ECG are recorded. This information is much easier and faster to obtain than any laboratory test, including the BNP value, which requires phlebotomy and laboratory analysis.

#### CRT and Outpatient Optimization.

One of the most exciting and promising new uses of acoustic cardiography is its rapid and easy use in CRT optimization. Expensive and highly programmable CRT devices have been shown in real-world practice to have a 30% nonresponder rate, which may be largely attributable to the fact that only 10% of CRT devices are optimized.<sup>13</sup> This is in stark contrast to the randomized controlled clinical trials that led to the approval of CRT devices for treating HF. All of these trials implemented optimization strategies.<sup>7-11</sup>

The paucity of CRT optimization in clinical practice stems from the labor- and time-intensive echocardiography protocols. These procedures are costly and require an expensive echocardiogram machine and a skilled echocardiographer. Acoustic cardiography offers a cost-efficient, easy-to-use method to optimize CRT patients. Acoustic cardiography has been compared with other optimization techniques employing echocardiographic protocols and has proven comparable.<sup>43</sup> In this study, 22 CRT patients had independently obtained recommendations for best AV delays through echocardiography and acoustic cardiography, revealing that both technologies yield equivalent clinical results. Echocardiographic optimization strategies attempt to achieve optimal AV delay by coordinating the end of the A wave (indicating the end of the atrial contribution of LV filling) with the onset of systolic mitral

regurgitant flow (indicating the onset of ventricular contraction).<sup>12</sup> Acoustic cardiography can optimize the settings of the CRT device by creating the shortest electromechanical activation time, defined as the time from the onset of the QRS complex (ventricular depolarization), to the S<sub>1</sub>, indicating ventricular systole and closure of the mitral valve. In doing so, the LV systolic time—the interval from S<sub>1</sub> to S<sub>2</sub>—can be maximized, which has been shown to correlate well with maximizing ejection fraction.<sup>33</sup> In addition, the strength of the S<sub>3</sub>, as measured by AUDICOR, can be minimized, thereby lowering LV end-diastolic pressure if initially above the detection threshold. All of this can be performed easily, rapidly, at the point of care, and without the need for expensive devices and skilled technicians. A detailed analysis of benefits of acoustic cardiography in CRT optimization appears later in this supplement, along with the echocardiography equivalency study<sup>43</sup> and case studies demonstrating the applicability of this technique in CRT optimization.

The easy-to-use and rapidly obtainable information gathered by acoustic cardiography should foster more widespread CRT optimization. This could allow for real-world experience with CRT to approach the success rates seen in the large randomized controlled trials.

#### Summary and Conclusions

Acoustic cardiography is an exciting new modernized technology implementing the already proven techniques of phonocardiography and systolic time intervals. When applied to clinical practice, acoustic cardiography can improve diagnosis and management of HF patients. Its clinical use should help address some of the need for robust, inexpensive, widely accessible, and easy-to-use technology for proactive HF diagnosis and management. Heart sounds and systolic time intervals captured by acoustic cardiograms have proven valuable in assisting clinical diagnostic and management challenges encountered in HF care.

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## ORIGINAL PAPER

# Hemodynamic Correlates of the Third Heart Sound and Systolic Time Intervals

*Bedside diagnostic tools remain important in the care of patients with heart failure. Over the past two centuries, cardiac auscultation and phonocardiography have been essential in understanding cardiac pathophysiology and caring for patients with heart disease. Diastolic heart sounds ( $S_3$  and  $S_4$ ) and systolic time intervals have been particularly useful in this regard. Unfortunately, auscultation skills have declined considerably, and systolic time intervals have traditionally required carotid pulse tracings. Newer technology allows the automated detection of heart sounds and measurement of systolic time intervals in a simple, inexpensive, noninvasive system. Using the newer system, the authors present data on the hemodynamic correlates of the  $S_3$  and abnormal systolic time intervals. These data serve as the foundation for using the system to better understand the test characteristics and pathophysiology of the  $S_3$  and systolic time intervals, and help to define their use in improving the bedside diagnosis and management of patients with heart failure. (CHF. 2006;12[4 suppl 1]:8–13) ©2006 Le Jacq*

With the advent of increasingly complex diagnostic modalities in cardiovascular medicine, it is remarkable that simple bedside diagnostic tests such as cardiac auscultation and electrocardiography (ECG) remain essential.<sup>1,2</sup> Bedside diagnosis is invaluable because of the importance of rapid diagnosis and triage, the continual constraints on health care resources, and the improvement in outcomes that occurs when proper diagnostic decisions are made early in the course of treatment. This is especially true in the diagnosis and treatment of heart failure, because the epidemic of heart failure continues to grow and because its manifestations can be protean.<sup>3,4</sup> Cardiac auscultation and the timing of heart sounds have been central to bedside noninvasive diagnosis of heart failure over the past century.

Cardiac auscultation began long before Theophile Laennec's fortuitous discovery of the stethoscope in

1818; descriptions of cardiac sounds date back to Hippocrates' writings, circa 400 BC.<sup>5</sup> However, it was not until the latter half of the 19th century and the early 20th century, with the description and timing of heart sounds and murmurs and the rise of phonocardiography, that the full potential of cardiac auscultation was realized. During that important time, Carl Pierre Potain described the  $S_3$ , and Willem Einthoven, Otto Frank, and Carl Wiggers played key roles in the development of modern phonocardiography, with its graphic depiction of heart sounds.<sup>5,6</sup> Later, through the work of Aubrey Leatham<sup>7</sup> and William Evans in the late 1940s (with the creation of a novel phonocardiogram with the additional capability of recording simultaneous carotid pulse tracings and ECG data) and Weissler and colleagues<sup>8,9</sup> in the 1960s (with the correlation of abnormal systolic time intervals [STIs] with left ven-

tricular [LV] dysfunction), auscultative and phonocardiographic bedside diagnosis came into its golden age.<sup>7–11</sup> Within the realm of auscultation and phonocardiography, both the  $S_3$  and STIs have been among the most useful and best-studied diagnostic tools.

## Methodology and Definitions

Although bedside cardiac diagnosis remains important, the practice of the cardiac physical examination has deteriorated significantly over time.<sup>12,13</sup> In addition, although STIs historically have provided a rapid bedside diagnostic method to evaluate LV function, the need for skilled personnel and simultaneous carotid pulse tracings has limited the usefulness of this method, especially after the emergence of echocardiography.

Newer technology allows the automated detection of heart sounds and the measurement of STIs in a simple,

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**Table.** Third Heart Sounds and Systolic Time Intervals in Asymptomatic Individuals by Age

AGE (YR)	N	EMAT (ms)	%EMAT*	LVST (ms)	%LVST*	EMAT/LVST
<30	171	73.2±10.8	8.0±1.7	339±25	36.7±5.5	0.22±0.04
<40	253	73.7±11.3	8.2±1.8	338±28	37.3±5.1	0.22±0.04
31–40	86	74.4±12.1	8.7±1.9**	335±33	38.7±4.0**	0.22±0.05
41–50	114	77.2±14.9**	8.7±2.5**	343±31	38.0±5.8	0.23±0.06
51–60	210	82.2±17.8**	9.1±2.4**	344±29**	38.0±5.1	0.24±0.06**
61–70	189	82.4±15.9**	9.7±2.6**	340±30	40.0±4.0**	0.25±0.06**
71–80	289	86.0±18.4**	9.7±2.5**	348±35**	38.9±4.3**	0.25±0.07**
>80	130	85.9±16.1**	9.8±3.1**	342±47	38.9±7.2**	0.25±0.06**
≥40	941	83.3±17.2**	9.5±2.6**	344±34**	38.7±5.1**	0.25±0.06**

Data are presented as mean ± SD. EMAT=electromechanical activation time (Q-S<sub>1</sub> interval); LVST=left ventricular systolic time (S<sub>1</sub>-S<sub>2</sub> interval); \*%EMAT and %LVST refer to the percentage of each interval as a portion of the total cardiac cycle duration (R-R interval); \*\*p<0.05 compared with group younger than 40 years. Data source is Inovise Medical, Inc., Portland, OR, on file.

inexpensive system (AUDICOR, Inovise Medical, Inc., Portland, OR). This acoustic cardiograph records, stores, displays, and interprets simultaneous digital ECG and heart sound data, using unique dual-purpose sensors that acquire both electrical and acoustic data from the V<sub>3</sub> and V<sub>4</sub> positions. The AUDICOR system's computerized algorithm uses wavelet-based signal processing techniques combined with a hidden Markov model to identify normal and abnormal heart sounds, and it determines the timing of heart sounds in the cardiac cycle by comparing the sounds to the onset of the P wave and QRS complexes in the simultaneously recorded ECG. The algorithm was developed using files annotated by phonocardiography experts, and it has been clinically validated using Doppler echocardiography and invasive hemodynamic data from patients with a variety of cardiac abnormalities. The AUDICOR system produces a variety of measurements, including the presence and strength of heart sounds (such as the S<sub>3</sub>) and the duration of STIs.

The S<sub>3</sub> is a low-pitched sound that occurs in early diastole, approximately 120–160 milliseconds after the S<sub>2</sub>, during rapid LV filling.<sup>14</sup> The AUDICOR system determines the presence of the S<sub>3</sub>, and, based on the intensity and persistence of the sound, provides a value of S<sub>3</sub> strength with a range of 1–10. If this value equals or exceeds 5.0, the algorithm declares that an S<sub>3</sub> is present.

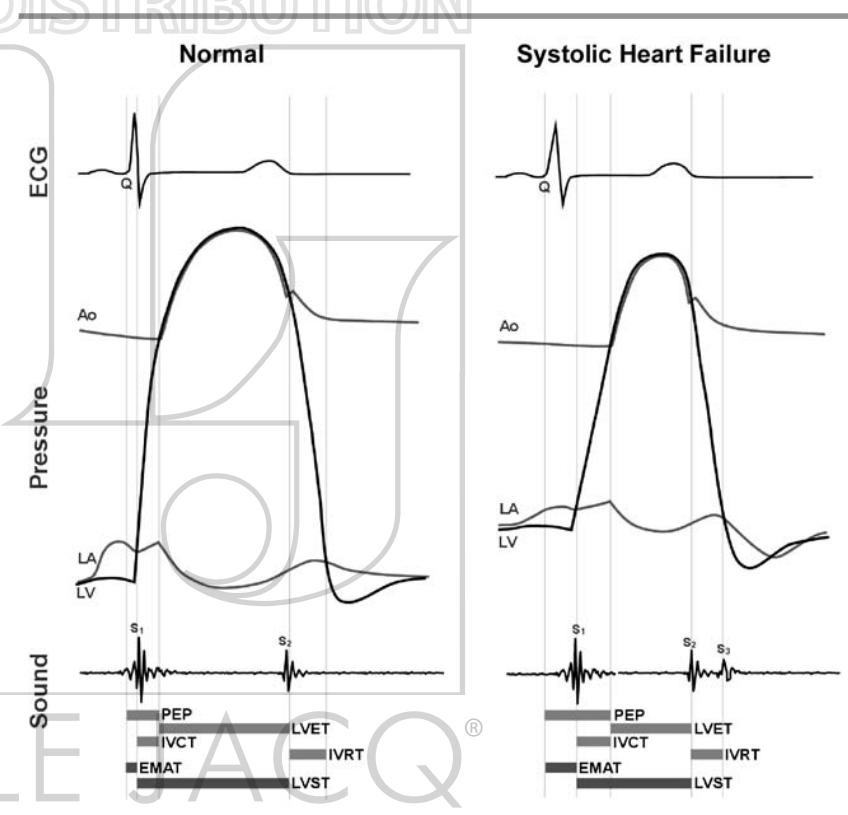
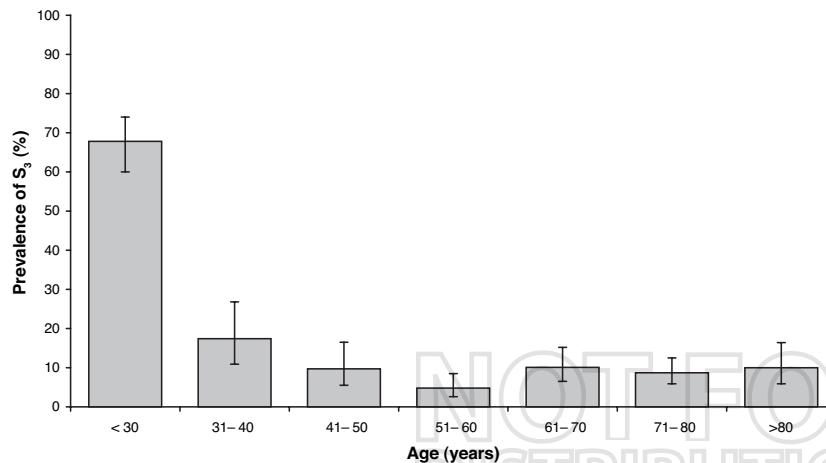


Figure 1. Illustration of systolic time intervals in relation to the cardiac cycle depicted via electrocardiographic (ECG) and pressure waveforms (pressure waveforms are displayed here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data.). Traditional systolic time intervals include the pre-ejection period (PEP) and the left ventricular ejection time (LVET). The PEP encompasses the electromechanical activation time (EMAT; Q-S<sub>1</sub> interval) and the isovolumic contraction time (IVCT). The AUDICOR system measures the EMAT and left ventricular systolic time (LVST; S<sub>1</sub>-S<sub>2</sub> interval). Isovolumic relaxation time (IVRT) may be measured by invasive left heart catheterization or echocardiography. Ao=aorta; LA=left atrium; LV=left ventricle

Figure 1 displays the conventional LV STIs, which include the electromechanical activation time (EMAT; Q-S<sub>1</sub> interval), isovolumic contrac-

tion time (IVCT), pre-ejection period (PEP), LV ejection time (LVET), and electromechanical systole (Q-S<sub>2</sub> interval). The PEP is comprised of



**Figure 2.** Prevalence of the S<sub>3</sub> by age in asymptomatic individuals. Prevalence of the S<sub>3</sub> decreases markedly in subjects older than 30 years. Adapted with permission from *Congest Heart Fail*. 2005;11:242–247.<sup>16</sup>

the EMAT and the IVCT, and the Q-S<sub>2</sub> is comprised of the PEP and LVET. Another important STI measurement is the PEP/LVET ratio. Since the PEP and LVET intervals vary equally at heart rates <110 bpm, the PEP/LVET ratio avoids the necessity of employing a heart-rate correction to the STIs.<sup>15</sup> It is the PEP/LVET ratio that has been most used to diagnose LV dysfunction.<sup>10,15</sup>

Of note, the STIs measured by the AUDICOR system are different from those conventionally measured. The AUDICOR system measures the Q-S<sub>1</sub>, Q-S<sub>2</sub>, and S<sub>1</sub>-S<sub>2</sub> (LV systolic time [LVST]) intervals. In the traditional method, the PEP contains the IVCT, whereas in the AUDICOR method, the LVST contains the IVCT. Since the AUDICOR system does not measure PEP, it avoids the necessity of obtaining carotid pulse tracings, which allows for AUDICOR's rapid bedside use with minimal training. The AUDICOR system also calculates the %EMAT and %LVST, which describe each interval as a percentage of the entire cardiac cycle (R-R interval).

### Prevalence and Normal Ranges

Using previously collected data from a cross-sectional sample, Collins et al.<sup>16</sup> determined the prevalence of the S<sub>3</sub> (Figure 2). Using these same record-

ings, the normal ranges of STIs using the AUDICOR system were calculated. The study sample comprised 1194 individuals (age, 57.8±20.3 years; range, 18–94 years; 732 [61.3%] women) who were all asymptomatic from a cardiac standpoint. Figure 2 shows the prevalence of the S<sub>3</sub> by decade of age. There is a high prevalence of physiologic S<sub>3</sub> in individuals up to the age of 30 years, after which there is a rapid decline, with <10% prevalence in asymptomatic older subjects. The Table lists the mean STIs per decade. The EMAT, LVST, and EMAT/LVST all increase slightly with age.

### Hemodynamic Correlates

**Third Heart Sound.** The S<sub>3</sub> has diagnostic and prognostic value in a variety of conditions, including LV dysfunction,<sup>17–21</sup> valvular heart disease,<sup>22,23</sup> acute myocardial infarction,<sup>24</sup> and in the perioperative period.<sup>25</sup> Phonocardiography has traditionally been the gold standard for detection of the S<sub>3</sub>, a finding that was thought to be highly sensitive and specific for LV dysfunction. Physiologically, it is thought that an abrupt limitation of LV inflow during early diastole causes vibration of the entire cardiovascular system, resulting in the S<sub>3</sub>.<sup>24,26–28</sup> An increase in mitral inflow in early diastole, followed by a rapid cessation of that inflow, appears to be the

ideal setting in which the pathologic S<sub>3</sub> becomes audible.<sup>26</sup> These hemodynamic conditions increase the deceleration rate of early mitral inflow, a finding that has been associated with the S<sub>3</sub>.<sup>29–31</sup>

Using the AUDICOR system, we sought to better understand the test characteristics and physiology of the phonocardiographic S<sub>3</sub> in a cohort of 90 patients undergoing cardiac catheterization. All patients underwent computerized phonocardiographic heart sound analysis with the AUDICOR system, B-type natriuretic peptide (BNP) testing, echocardiography, and invasive LV pressure measurement within a 4-hour period. Mean LV end-diastolic pressure and BNP were higher, and LV ejection fraction (LVEF) was lower, in those with an S<sub>3</sub>. The sensitivities of the S<sub>3</sub> to detect abnormalities in LV function were only 30%–50%. However, specificity for detecting elevated LV end-diastolic pressure, elevated BNP, and decreased LVEF were high, at 92%, 87%, and 92%, respectively. Therefore, although it has limited sensitivity, the S<sub>3</sub> detected by the AUDICOR system is highly specific in detecting LV dysfunction.<sup>32</sup>

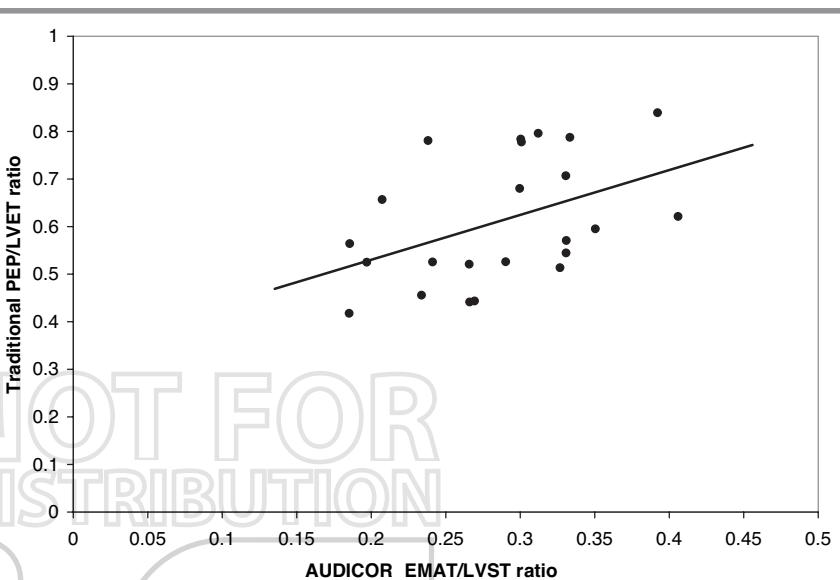
In the same cohort of 90 patients, we hypothesized that tissue Doppler imaging would provide insight into the physiology of the pathologic S<sub>3</sub>. Tissue Doppler imaging determines the velocity of myocardium, and the ratio of early mitral inflow to early diastolic velocity of the mitral annulus (E/E') has been shown to correlate with LV filling pressures.<sup>33,34</sup> Since E/E' takes into account the volume and pressure of mitral inflow (E) as well as stiffness of the myocardium (E'), we hypothesized that the E/E' ratio would be independently associated with the S<sub>3</sub>.

In this study, we found that subjects with an S<sub>3</sub> had higher BNP ( $p=0.0008$ ), higher LV early- and mid-diastolic filling pressures ( $p<0.0001$ ), and higher LV end-diastolic filling pressures ( $p=0.009$ ). On echocardiography, we found that those with an S<sub>3</sub> had lower LVEF ( $p=0.0006$ ), and higher E velocity ( $p=0.002$ ), E deceleration time

( $p=0.003$ ), and E/E' ( $p<0.0001$ ). On multivariate analysis, we found that of the echocardiographic parameters, only E/E' was independently associated with the S<sub>3</sub> ( $p=0.009$ ).<sup>35</sup> In addition, E/E' was independently associated with S<sub>3</sub> when controlling for LV filling pressures at any point during diastole ( $p<0.02$  for all points in diastole). This is an important finding, because it shows that elevated filling pressure alone does not account for the association between S<sub>3</sub> and E/E'. Based on these findings, the pathologic S<sub>3</sub> seems to be due to abrupt deceleration of high-pressure mitral inflow acting in concert with decreased velocity of the mitral annulus.

**Systolic Time Intervals.** The STIs were the first quantitative, noninvasive method for determining LV function. Realizing that the timing of events in the cardiac cycle was previously neglected in the study of LV performance, Weissler and colleagues<sup>8,9</sup> studied and popularized the use of STIs in detecting LV dysfunction. Although they found that the PEP increases and LVET decreases with LV dysfunction, these parameters varied with heart rate, necessitating a correction factor. In addition, since PEP increases with both increased QRS duration and increased IVCT (due to diminished rate of pressure rise during isovolumic contraction), prolongation of the PEP may not be an indicator of LV dysfunction in patients with intraventricular conduction delay.<sup>15</sup> The ratio of PEP/LVET, which has been shown to be less sensitive to heart rate and changes in QRS duration, is therefore best suited to diagnose LV dysfunction.

Abnormal STIs have been shown to predict decreased cardiac output, stroke volume, and LVEF, and increased LV end-diastolic volume.<sup>8-10,36,37</sup> In the past, STIs were used for evaluation of LV performance in cardiomyopathy, coronary disease, hypertension, valvular heart disease, and in the study of clinical pharmacology.<sup>36-42</sup> More recent studies have shown an association between N-terminal pro-BNP and abnormal STIs.<sup>43</sup>



**Figure 3.** Scatterplot of traditional systolic time intervals (STIs) (pre-ejection period [PEP]/left ventricular ejection time [LVET]) and AUDICOR (Inovise Medical, Inc., Portland, OR) STIs (electromechanical activation time [EMAT]/left ventricular systolic time [LVST]). The AUDICOR and traditional STI ratios are significantly correlated ( $p=0.037$ ), but the correlation is modest ( $r=0.44$ ). Patient-level data extracted from *Circulation*, 1968;37:149-159,<sup>8</sup> using Q-S<sub>1</sub> and Q-S<sub>2</sub> measurements to derive the EMAT/LVST ratio.

As stated earlier, the AUDICOR system measures and calculates the EMAT/LVST, and not the PEP/LVET ratio. Using subject-level data from a previously published study,<sup>8</sup> we found that the EMAT/LVST ratio is modestly but significantly correlated to the PEP/LVET ( $r=0.44$ ;  $p=0.037$ ) (Figure 3). However, since only a modest correlation between the two ratios was found, we sought to verify that the AUDICOR-derived STIs, and particularly the EMAT/LVST, continue to be useful in diagnosing LV dysfunction.

In a study of 81 patients undergoing cardiac catheterization and echocardiography, we used the AUDICOR system to study the relationship between STIs and parameters of LV dysfunction. EMAT ( $r=-0.51$ ;  $p<0.0001$ ), EMAT/LVST ( $r=-0.41$ ;  $p=0.0001$ ), and Q-S<sub>2</sub> ( $r=-0.39$ ;  $p=0.0003$ ), correlated with LVEF, but not LV filling pressure. Since STIs, as measured by the AUDICOR system, appear to be more closely related to LVEF, and the S<sub>3</sub> appears to be more closely related to elevated LV filling pressures, we developed an LV dysfunction index using the

AUDICOR-derived data. We found that this index had an area under the receiver operator characteristic curve (c-statistic) of 0.89 (95% confidence interval, 0.81–0.98) for the detection of LV dysfunction (defined as LVEF <50% and LV end-diastolic pressure >15 mm Hg). Test characteristics of the AUDICOR-derived index (which combined S<sub>3</sub> and STIs) was superior to S<sub>3</sub>, EMAT, LVST, or EMAT/LVST alone in detecting LV dysfunction.

## Future Directions

The AUDICOR system has the potential to provide further assistance in determining underlying cardiac pathophysiology and in the diagnosis and management of patients with heart failure. Recently, Chen et al.<sup>44</sup> described a noninvasive method for determining LV end-systolic elastance, a measurement that has traditionally required cumbersome invasive measurement with a conductance catheter and occlusion of the inferior vena cava. The noninvasive measurement described by Chen and colleagues requires echocardiographic, sphygmomanometric, and STI data,

the latter of which could be measured with the AUDICOR system. Thus, the AUDICOR system may be able to play a role in determining LV end-systolic elastance, a load-independent measure of LV stiffness, which may be useful in future studies of ventricular-vascular coupling.

The addition of AUDICOR-derived data such as the S<sub>3</sub> and abnormal STIs to BNP testing may also assist in the diagnosis of LV dysfunction. Preliminary data from a study of 90 patients undergoing cardiac catheterization, echocardiography, BNP, and AUDICOR testing show that in the range of 100–500 pg/mL, BNP has poor discriminatory value in the diagnosis of LV dysfunction. However, the addition of AUDICOR data to BNP significantly improves the positive and negative likelihood ratios for ruling

in and ruling out LV dysfunction, especially in the gray zone of BNP levels of 100–500 pg/mL.<sup>45</sup> Thus, the AUDICOR system could potentially be used to improve the emergency diagnosis of heart failure.

Finally, AUDICOR analysis of heart sounds and STIs may have yet another role in the field of cardiac resynchronization therapy (CRT). Although a number of studies have shown clinical improvement and mortality benefit with CRT,<sup>46–48</sup> optimization of CRT is an area of active investigation, because refining patient selection, increasing response rates, and controlling costs are of prime importance.<sup>49</sup> Baker and colleagues<sup>50</sup> recently reported their findings of altered STIs in a study of patients pre- and post-treatment with CRT. Therefore, monitoring STIs pre- and post-CRT and using this data to

help optimize CRT is another potential use of the system.

## Conclusions

Bedside diagnosis remains a vital tool in the diagnosis and treatment of heart failure. The AUDICOR system provides a simple, inexpensive, and quantitative method to determine the presence of the S<sub>3</sub> and abnormal STIs. This technology has provided insight into the physiology of the S<sub>3</sub> and the correlation of S<sub>3</sub> and STIs with abnormal cardiac hemodynamics. Since the S<sub>3</sub> appears to be highly specific for elevated LV end-diastolic pressure, and abnormal EMAT/LVST appears to be specific for low LVEF, the combination of the two in the AUDICOR system may be particularly helpful in improving the bedside diagnosis and management of heart failure patients.

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A large, light gray graphic of the letters 'J' and 'Q' is centered on the page. The letter 'J' is positioned at the top left, and the letter 'Q' is positioned below it, partially overlapping the 'J'. Both letters are rendered in a bold, rounded font. They are set against a white background which is enclosed within a thin black rectangular border.



## ORIGINAL PAPER

# Systolic Dysfunction: Correlation of Acoustic Cardiography With Doppler Echocardiography

*For detection of left ventricular (LV) systolic dysfunction in the outpatient setting, simultaneous electrocardiographic and heart sound data have been shown to be helpful. In 161 patients with suspected or known cardiac disease, echocardiography and acoustic cardiography were performed. Acoustic cardiographic parameters correlated to echocardiography included: presence or absence of  $S_3$ , electromechanical activation time (EMAT), LV systolic time (LVST), and EMAT/LVST. LV ejection fraction was  $\geq 50\%$  in 82 patients ( $S_3$  present in 9.8%) and  $< 50\%$  in 79 patients ( $S_3$  present in 30.4%; the  $< 50\%$  group also had a greater EMAT, EMAT/LVST, and lower mean LVST [ $p < 0.05$ ]). Patients with an  $S_3$  had a lower ejection fraction, larger mean left atrial and LV dimensions, and an increased proportion of diastolic dysfunction. Acoustic cardiography allows reliable detection of the  $S_3$ , which correlates with echocardiographic evidence of impaired LV function, and the EMAT/LVST ratio reflects reduced ejection fraction, providing an affordable, accessible means to assess LV dysfunction in the outpatient setting.*

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The ability to detect left ventricular systolic dysfunction (LVSD) is important because it frequently provides the pathophysiologic substrate for heart failure, a major cause of disability and death. Although echocardiographic and radionuclide studies are noninvasive tests used to measure left ventricular (LV) function, these tests are expensive and are not always readily available.<sup>1</sup> Consequently, a reliable, convenient, and cost-effective method to detect impaired LV function is desirable. To address this problem, physicians have widely adopted other tests for heart failure, such as the measurement of B-type natriuretic peptide (BNP). However, the inverse relationship between sensitivity and specificity for heart failure across the commonly encountered range values of BNP has limited the diagnostic value of this test.<sup>2</sup> To provide a more suitable diagnostic method, Inovise Medical, Inc. (Portland, OR)

has developed the AUDICOR system. This is a system that records, stores, displays, and algorithmically interprets simultaneous digital electrocardiographic (ECG) and sound (i.e., acoustic cardiographic) data, including the  $S_3$ , by using proprietary, dual-purpose sensors placed in the V<sub>3</sub> and V<sub>4</sub> positions. Previous work has shown that the  $S_3$  identified algorithmically by AUDICOR has high specificity for detecting hemodynamic evidence of heart failure and is diagnostically superior to auscultation.<sup>3</sup> Since the system records acoustic cardiographic data throughout the entire cardiac cycle, it permits the measurement of systolic time intervals (STIs) as diagnostic parameters in addition to the  $S_3$ .

The purpose of this study was to investigate the relationships of acoustic cardiographic findings to Doppler echocardiographic evidence of LVSD in patients with known or suspected heart disease.

## Methods

**Subjects.** We enrolled 171 ambulatory patients who had been referred to a cardiology clinic for Doppler echocardiographic evaluation of known or suspected cardiac disease. Of these, we excluded 10 patients for the following reasons: three were missing acoustic cardiograms, two lacked sufficient echocardiographic data to evaluate LV function, three were missing BNP data, and two had acoustic cardiograms that were not analyzable due to poor quality. The analyses were performed on the remaining 161 patients.

All patients gave written informed consent before enrollment in the study, which was approved by the local medical ethics committees of Aargau and Zurich, Switzerland.

Within 1 hour of the Doppler echocardiographic study, each patient had acoustic cardiographic data recorded and BNP (Biosite Triage, Biosite, Incorporated, San Diego, CA) and

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serum creatinine (Roche Diagnostics Reflotron, Hoffman-La Roche, Basel, Switzerland) measured.

**Echocardiographic Data.** Following the guidelines of the American Society of Echocardiography, each patient had a complete two-dimensional and Doppler echocardiographic examination. The investigators who interpreted the Doppler echocardiographic findings were blinded to other clinical and acoustic cardiographic data. We defined LVSD as LV ejection fraction (LVEF) of <50%. LV diastolic function was evaluated using the diastolic filling pattern and tissue Doppler examination of the lateral mitral annulus (for E') to determine the E/A ratio, E/E' ratio, the deceleration time of the E wave, and the pulmonary venous flow pattern. Diastolic function was graded as normal, delayed relaxation, pseudonormal, or restrictive. It can be difficult to categorize patients into a diastolic filling group due to inconsistent Doppler data and length of atrial reversal in some patients—for example, those with mitral insufficiency. The presence of elevated LV filling pressure was determined using the method described by Ommen and Nishimura.<sup>4</sup>

**Acoustic Cardiogram Data.** A 10-second AUDICOR recording was obtained from each patient and analyzed by the computerized algorithm using measurements generated for the S<sub>3</sub> and for various systolic parameters. The system evaluates the possible presence of an S<sub>3</sub> by measuring the intensity and persistence of the energy of sounds that have the appropriate frequency and timing for an S<sub>3</sub>. It expresses the resultant value in the range of 1–10 and declares S<sub>3</sub> to be present in a patient if the value equals or exceeds five. Electromechanical activation time (EMAT) is measured by the algorithm as the time from the onset of the Q wave to the mitral component of the S<sub>1</sub>. The value of EMAT in milliseconds reflects the time required for the left ventricle to generate sufficient force to close the

**Table I.** Comparison of Findings in Patients With Left Ventricular (LV) Ejection Fraction ≥50% vs. <50%

	LV EJECTION FRACTION	
	≥50% (N=82)	<50% (N=79)
LV ejection fraction (%)	62±7	34±10*
Age (yr)	66±13	63±12
Heart rate (bpm)	63±10	67±13*
Left bundle-branch block (%)	1.2	21.5*
QRS duration (ms)	101±17	129±31*
B-type natriuretic peptide (pg/mL)	110±176	214±249*
E/A	0.96±0.48	1.01±0.74
E/E'	7.0±3.4	9.9±4.5*
Deceleration time (ms)	214±55.0	201±63.5
Diastolic filling pattern (%)		
Normal	20.0	14.9
Delayed relaxation	69.3	64.2
Pseudonormal	9.3	14.9
Restrictive	1.3	6.0
S <sub>3</sub> present (%)	9.8	30.4*
Electromechanical activation time (EMAT) (ms)	84±13	100±20*
LV systolic time (LVST) (ms)	361±33	345±35*
EMAT/LVST	0.23±0.04	0.3±0.07*

Data are mean ± SD except as noted. \*Significant at p<0.01

**Table II.** Comparison of Doppler Echocardiographic Findings in Patients Without vs. With an Electronically Detected S<sub>3</sub>

	S <sub>3</sub> ABSENT (N=129)	S <sub>3</sub> PRESENT (N=32)
Left ventricular ejection fraction (%)	51±17	40±14*
Left atrial dimension (mm)	22±5	25±8
Left ventricular end-diastolic dimension (mm)	53±9	60±10*
E/A	0.8±0.4	1.6±1.0*
E/E'	7.8±4.1	10.0±4.4**
Deceleration time (ms)	213±56	180±68
Elevated left ventricular end-diastolic pressure (%)	16.9	63.6*
Abnormal diastolic filling pattern (pseudonormal or restrictive) (%)	7	52*

Data are mean ± SD except as noted. \*Significant at p<0.01; \*\*significant at p<0.05

mitral valve. LV systolic time (LVST) is measured as the time from the mitral component of the S<sub>1</sub> to the aortic component of the S<sub>2</sub>. The ratio EMAT/LVST was computed as the simple ratio of these two components.

**Statistical Analyses.** Continuous data are reported as mean ± SD. Categoric data are presented as percentages of their respective subgroups. We tested the null hypothesis for the continuous variables using the Student *t* test and for the dichotomous variables using chi-square analysis.

## Results

The mean age was 64.4±12.8 years (range, 19–88 years), and 109 (68%) were male. Mean BNP was 161±221 pg/mL (range, 4–1270 pg/mL). Eighteen patients (11%) had left bundle-branch block, and 25% had a QRS duration ≥130 milliseconds (mean, 115±29 milliseconds; range, 80–221 milliseconds). An LVEF of <50% was present in 79 patients; the mean was 49%, ranging from 10% to 82%. The remainder of the findings are shown in the tables and figures.

Table I shows that among the 161 study patients, 82 had LVEF ≥50%

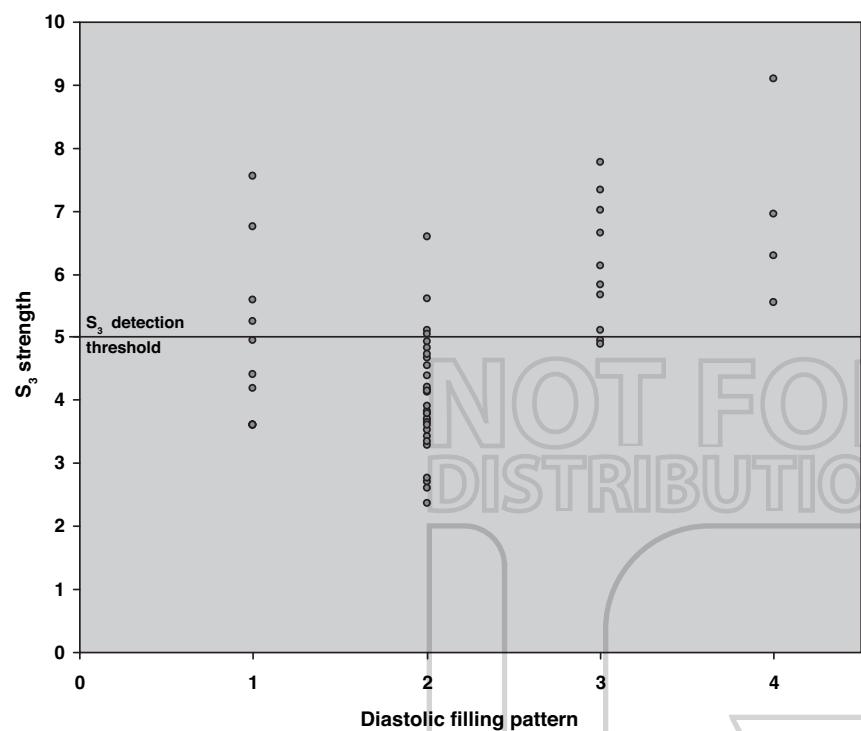


Figure 1. S<sub>3</sub> strength vs. diastolic filling pattern in patients with left ventricular ejection fraction <50%. 1=normal filling; 2=delayed relaxation; 3=pseudonormal pattern; 4=restrictive pattern

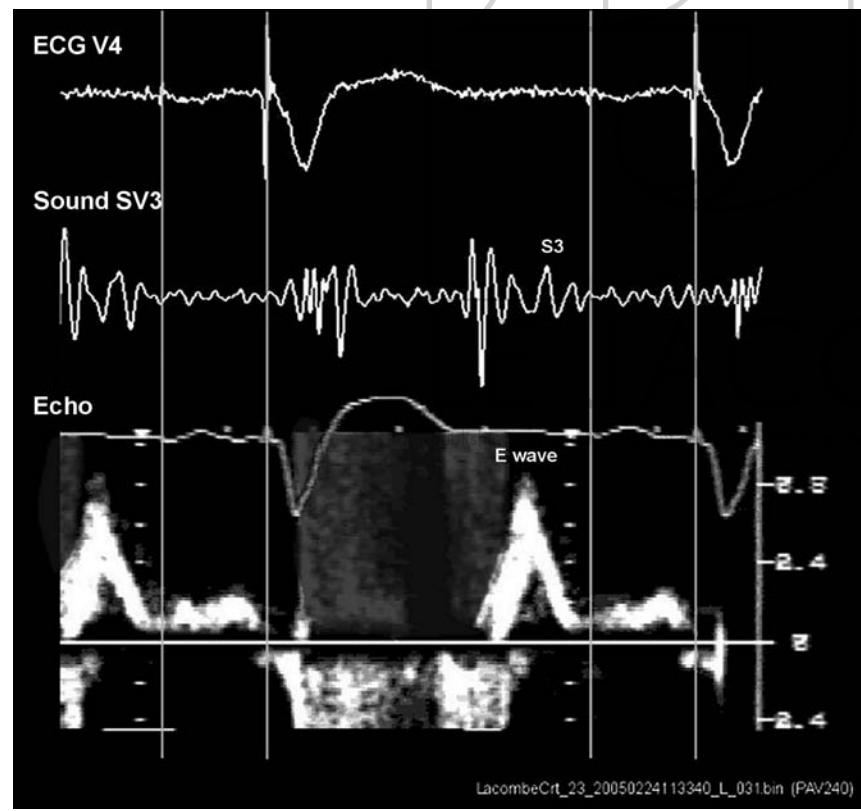


Figure 2. Temporal relationship between the S<sub>3</sub> and a prominent E wave

(group A) and 79 had LVEF <50% (group B). Although we did not perform the study in an acute setting, the patients in group B had higher mean heart rates and levels of BNP. In addition, the patients in group B had greater mean QRS durations, with a higher prevalence of left bundle-branch block. Although the mean E/A ratios were similar, group B had a higher mean E/E'. The patients in group B had significantly higher proportions of pseudonormal and restrictive filling patterns. Regarding the acoustic cardiogram parameters, the patients in group B had a higher prevalence of electronically detected S<sub>3</sub>, a greater mean EMAT and EMAT/LVST, and a lower mean LVST.

Table II compares the echocardiographic findings in all the patients in which an electronically detected S<sub>3</sub> was absent vs. those in which it was present. It shows that the patients with an S<sub>3</sub> have a lower mean LVEF and higher LV diastolic dimensions. Regarding parameters of LV filling, the patients with an S<sub>3</sub> have greater mean E/A and E/E' ratios and a higher proportion of abnormal diastolic filling patterns.

Table III shows the differences in the findings in Group B for each of the four types of filling patterns. In general, the patients with abnormal diastolic filling tend to be older, have wider QRS complexes, a higher prevalence of left bundle branch block, higher mean values of BNP, a lower mean LVEF, a higher mean E/E' ratio, a higher prevalence of elevated left ventricular end-diastolic pressure, and a higher prevalence of S<sub>3</sub>. Especially noteworthy is the finding that the prevalence of the S<sub>3</sub> is by far the lowest in the patients with the pattern of delayed relaxation and the highest in the patients with a pseudonormal and restrictive filling patterns.

Figure 1 graphically demonstrates these relationships. It shows that only four patients with delayed LV relaxation had sufficient S<sub>3</sub> strength to exceed the detection threshold. Conversely, of all the patients with pseudonormal or restrictive filling

	FILLING PATTERN			
	NORMAL (N=10)	DELAYED RELAXATION (N=43)	PSEUDONORMAL (N=10)	RESTRICTIVE (N=4)
Age (yr)	53.8±15.2	65.7±9.1*	65.2±10.0	66.3±14.2
Heart rate (bpm)	63.1±17.8	67.6±10.2	65.4±14.8	72.3±16.8
Left bundle branch block (%)	10.0	23.3	30.0	25.0
QRS duration (ms)	117±25	130±33	138±33	132±28
B-type natriuretic peptide (pg/mL)	147±133	171±214	466±238*	348±217*
LV ejection fraction (%)	42.6±5.7	33.3±10.9*	28.1±6.7*	30.8±8.1*
E/A	1.2±0.4	0.7±0.2*	1.5±0.2	3.1±1.6*
E/E'	7.8±1.7	9.3±4.8	14.4±3.0*	12.1±1.6*
Elevated LV end-diastolic pressure (%)	11.1	17.6	100*	100*
S <sub>3</sub> present (%)	40	9.3*	80	100.0*
Electromechanical activation time (EMAT) (ms)	96±26	100±19	98±13	114±24
LV systolic time (LVST) (ms)	351±35	348±36	343±35	326±22
EMAT/LVST	0.28±0.09	0.29±0.06	0.29±0.05	0.35±0.07

Data are mean ± SD except as noted. \*Significant at  $p<0.05$  compared with the normal filling group

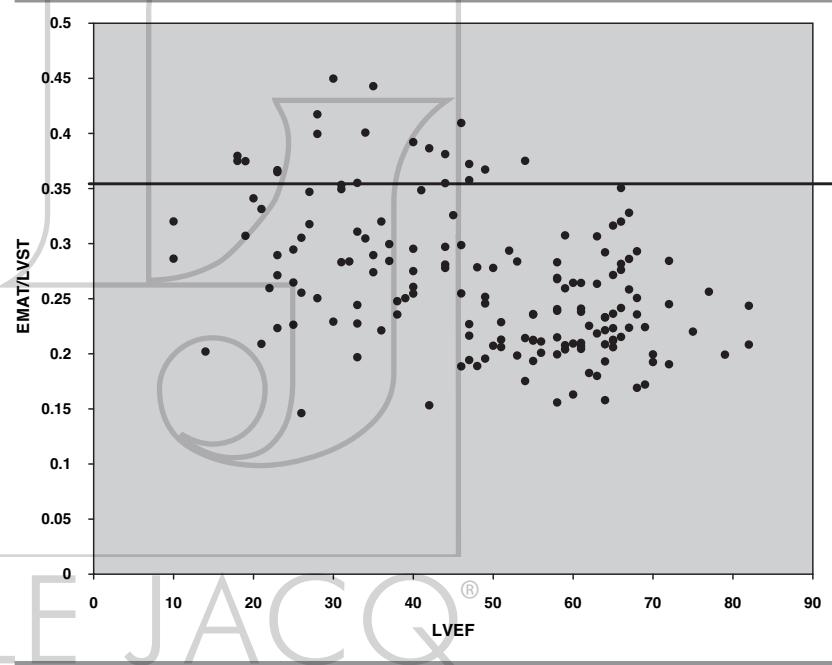
patterns, conditions characterized by vigorous early passive diastolic filling patterns, only two patients failed to exceed this detection threshold.

Figure 2 also demonstrates the relationship between vigorous early diastolic filling, i.e., a prominent E wave, and the S<sub>3</sub>. It represents an example of simultaneous acoustic cardiogram and Doppler echocardiographic recordings in a patient with an atrioventricular sequential pacemaker. The figure shows that the S<sub>3</sub> occurs immediately following the peak of a prominent E wave.

Figure 3 demonstrates the ability of a systolic acoustic cardiogram parameter to discriminate between patients with vs. without LVSD. It shows that values of LVST/EMAT ratio >0.35 are highly specific for LVEF <50%.

## Discussion

Despite recent advances, such as pro-BNP assays and cardiac resynchronization therapy, diagnosis and treatment of systolic dysfunction with clinical heart failure and its underlying abnormalities remain challenging. There is a continued need for simple, low-cost tests that aid in initial heart failure diagnosis and monitoring patient progress. Our data show that such tests should include the detection of abnormal diastolic sounds and the



**Figure 3.** Electromechanical activation time (EMAT)/left ventricular systolic time (LVST) vs. left ventricular ejection fraction (LVEF) (%)

measurement of STIs. Although no longer as widely used as they have been in the past, STIs have recently been validated as a method to detect and monitor LV dysfunction in conjunction with cardiac resynchronization therapy.<sup>5</sup> Abnormal diastolic heart sounds, especially the S<sub>3</sub>, have long been associated with hemodynamic abnormalities that underlie heart failure.<sup>3,6,7</sup>

**Generation and Occurrence of the S<sub>3</sub>.** Our findings are consistent with the observations of others that the S<sub>3</sub> is specific, but not highly sensitive, for heart failure associated with LVSD.<sup>3,6,7</sup> The S<sub>3</sub> is believed to occur during the rapid, passive phase of ventricular filling early in diastole. The kinetic energy of the incoming blood is transduced into the acoustical energy associated with an S<sub>3</sub>. While it is tempting

to dichotomize "systolic" and "diastolic" heart failure, the data shown in Table III and in Figure 1 show that many patients with LVSD also have delayed diastolic relaxation. In this group, only 9.3% of the patients with LVSD had an  $S_3$ , compared with 80% and 100%, respectively, of the patients with Doppler echocardiographic evidence of vigorous passive early inflow. Figure 2 illustrates the close temporal relationship between the peak of this early inflow and an  $S_3$ . Therefore, patients with impaired early diastolic filling, even in the presence of LVSD, would not be expected to have an  $S_3$ .

**Systolic Time Intervals.** Consequently, it would be desirable to have parameters for detecting ventricular dysfunction in addition to the  $S_3$ . A possible set of diagnostic parameters that can fulfill this role are STIs. Traditionally, STIs required the recordings of the ECG, phonocardiogram, and the carotid pulse tracing. The resultant diagnostic parameters included electromechanical systole (Q onset to  $S_2$ ), LV ejection time (LVET), and pre-ejection period (PEP, the time from Q onset to beginning of ejection from the left ventricle). PEP consists of both the EMAT and the isovolumetric contraction time (IVCT). Since the measurement of these intervals required manual measurements of analog recordings, the process was time-consuming and labor intensive.

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Due to the influence of heart rate on LVET and PEP, researchers developed regression formulas to study indexed values.<sup>8,9</sup> However, the ratio of PEP/LVET has been shown to be less sensitive to heart rate. Normal ranges have been established for the STIs, and values outside the normal range have been correlated with LV dysfunction (cardiac output, stroke volume, LV end-diastolic pressure).<sup>10–12</sup> LVEF was shown to be highly correlated with PEP/LVET and useful in diagnosing heart failure.<sup>8,11</sup> As a result of LVSD, the LVET shortens and the PEP lengthens, primarily due to a diminished rate of LV pressure rise during isovolumetric contraction.<sup>13</sup>

The parameters of systolic function that the AUDICOR system provides are similar to the traditional STIs. The difference is that PEP contains IVCT, whereas EMAT does not. The AUDICOR LVST contains IVCT, whereas LVET does not. Since the AUDICOR system generates both EMAT and LVST, it does not matter in which of these two parameters the IVCT is included. Furthermore, the AUDICOR system is advantageous because its recordings can be obtained as easily as a standard ECG, and a computerized algorithm makes the measurements on the digital data that generate these recordings.

The data in Table I show that not only the electronically recorded  $S_3$ , but also the systolic parameters

EMAT, LVST, and EMAT/LVST, discriminate between patients with vs. without LVSD. Thus, the array of systolic and diastolic parameters that acoustic cardiogram parameters provide increases the likelihood of detection of LVSD.

**Limitations of the Study.** The number of patients in this study is relatively small, particularly when separate analyses are performed for the patients in groups A and B. Therefore, our findings should be corroborated on a larger set of data. The diagnosis of heart failure is of great clinical interest, and ventricular dysfunction and heart failure are not synonymous. However, the detection of LVSD in the appropriate clinical context is very important in the process of diagnosing heart failure.

## Conclusions

We conclude that acoustic cardiography allows reliable detection of the  $S_3$ , and the ratio EMAT/LVST, and these parameters correlate with echocardiographic evidence of LV dysfunction. This could be a helpful, affordable, and easily accessible means to assess patients with dyspnea in the outpatient setting.

We also conclude that in patients with LVSD, a filling pattern of impaired relaxation is common and diminishes the prevalence of the  $S_3$ . Therefore, the use of parameters of systolic function is a useful adjunct to the evaluation of these patients.

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## ORIGINAL PAPER

# Acoustic Cardiographic Parameters and Their Relationship to Invasive Hemodynamic Measurements in Patients With Left Ventricular Systolic Dysfunction

*Data obtained at cardiac catheterization were used to evaluate the utility of acoustic cardiographic data in assessing the hemodynamic abnormalities associated with left ventricular systolic dysfunction (LVSD). Thirty-seven patients (mean age, 62.6 years) underwent catheterization, and hemodynamic data were recorded. Acoustic cardiographic recordings were obtained using a system that records and algorithmically interprets diastolic heart sounds and parameters analogous to traditional systolic time intervals. Seventeen patients had LVSD (defined as ejection fraction <50%). The 17 patients with LVSD composed the cohort for analysis. There were strong associations between acoustic cardiographic parameters and left ventricular end-diastolic pressure, ejection fraction, and maximum contractility. Heart rate tended to influence the strength of these correlations. The authors conclude that acoustic cardiographic data can be used in the evaluation of patients with known or suspected LVSD, and specifically in the selection of patients for cardiac resynchronization therapy and the optimization of the settings of implanted resynchronization devices. (CHF. 2006;12(4 suppl 1):19–24) ©2006 Le Jacq*

Despite recent advances in its management, the prevalence of heart failure is increasing as the population ages, and heart failure remains a major cause of disability and death. The optimal management of heart failure requires not only its accurate diagnosis, but reliable methods to determine with specificity the hemodynamic abnormalities in individual patients. These determinations will permit the most effective treatment to be selected for each patient. Similarly, it is important to be able to measure the effectiveness of such treatment and to determine whether it should modified in any way. To benefit as many patients as possible, the methods of evaluation of hemodynamic function should be safe, reliable, widely available, and cost-effective.

Although left ventricular systolic dysfunction (LVSD) is not synony-

mous with the clinical entity of heart failure, the demonstration of LVSD in the appropriate clinical context, e.g., a patient with acute or chronic dyspnea, is strong *prima facie* evidence that systolic heart failure is responsible for the patient's symptoms. A technology that could facilitate the detection of LVSD is the AUDICOR test (Inovise Medical, Inc., Portland, OR). The AUDICOR system records, stores, displays and algorithmically interprets simultaneous digital electrocardiography (ECG) and sound (i.e., acoustic cardiographic) data by using proprietary dual-purpose sensors placed in the V<sub>3</sub> and V<sub>4</sub> positions. The acoustic cardiographic data include the S<sub>3</sub>, recorded during diastole and various other parameters that are closely related to the traditional systolic time intervals. These are established methods for evaluating cardiac function.<sup>1</sup>

In the present study, we tested the hypothesis that acoustic cardiographic parameters are quantitatively related to invasive measurements of left ventricular (LV) cardiac function.

## Methods

**Subjects.** We enrolled 37 patients (33 men) with a mean age of 62.6 years (range, 42–79 years), who had been referred to the Kantonsspital Luzern, Lucerne, Switzerland. All cardiac catheterizations were performed in the postabsorptive state and under mild sedation. The hemodynamic measurements obtained included measurements of LV ejection fraction (LVEF), LV end-diastolic pressure (LVEDP), pulmonary capillary wedge pressure, and LV contractility (dP/dt) and maximum contractility (dP/dt<sub>max</sub>), using manometer-tipped catheters in 22 patients and fluid-filled catheters

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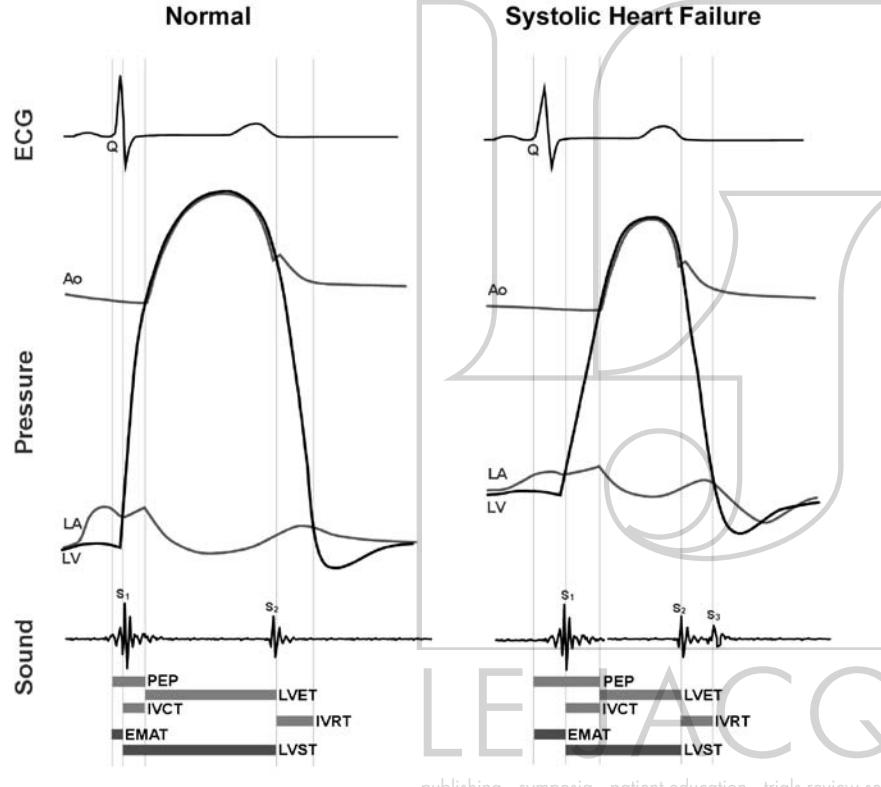
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**Table.** Demographic, Hemodynamic, and Acoustic Cardiographic Characteristics of the Patients With Left Ventricular (LV) Systolic Dysfunction (n=17)

Age (yr)	60±10
Heart rate (bpm)	81±20
Left bundle branch block (%)	5.9
QRS duration (ms)	130±40
LV ejection fraction (%)	32±11
LV end-diastolic pressure (mm Hg)	17±8
LV dP/dt <sub>max</sub> (mm Hg/sec)	1348±468
S <sub>3</sub> present (%)	41.2
Electromechanical activation time (EMAT) (ms)	93±25
LV systolic time (LVST) (ms)	329±31
EMAT/LVST	0.28±0.07

Data are presented as mean ± SD except where indicated otherwise.

dP/dt<sub>max</sub> = maximum contractility



**Figure 1.** Relationship of traditional systolic time intervals to acoustic cardiographic systolic parameters (normal vs. systolic heart failure) (pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data). ECG=electrocardiogram; Ao=aorta; LA=left atrium; LV=left ventricle; PEP=pre-ejection period; LVET=left ventricular ejection time; IVCT=isovolumic contraction time; IVRT=isovolumic relaxation time; EMAT=electromechanical activation time; LVST=left ventricular systolic time

in 15 patients. Acoustic cardiographic recordings were also obtained from all patients, and each recording was judged technically adequate for analysis. All parameters except the LVEF were measured both before and immediately after the left ventriculogram.

We defined LVSD as an LVEF <50%. We confined the analysis of the data to the patients who met this criterion.

**Acoustic Cardiographic Data.** A 10-second AUDICOR recording was obtained from each patient and ana-

lyzed by the computerized AUDICOR algorithm using measurements generated for the S<sub>3</sub> and for various systolic parameters. The system evaluates the possible presence of an S<sub>3</sub> by measuring the intensity and persistence of the energy of sounds that have the appropriate frequency and timing for an S<sub>3</sub>. It expresses the resultant value in the range of 1–10 and declares an S<sub>3</sub> to be present in a patient if the value equals or exceeds five. Electromechanical activation time (EMAT) is measured by the algorithm as the time from the onset of the Q wave to the mitral component of the S<sub>1</sub>. The value of EMAT (in milliseconds) reflects the time required for the left ventricle to generate sufficient force to close the mitral valve. LV systolic time (LVST) is measured as the time from the mitral component of the S<sub>1</sub> to the aortic component of the S<sub>2</sub>. The parameter EMAT/LVST is computed as the simple ratio of these two components. Percent EMAT (%EMAT) and percent LVST (%LVST) are computed as the EMAT or LVST divided by the dominant R-R interval. The %EMAT and %LVST are used in recognition of the heart rate dependency of these variables. Figure 1 illustrates these parameters and their relationships to the traditional systolic time intervals in a normal ventricle and in LVSD.

**Statistical Analyses.** Pearson correlation coefficients and two-tailed *p* values were calculated to demonstrate the strength of associations between pairs of acoustic cardiographic and independent hemodynamic variables.

## Results

Seventeen patients had LVSD as defined. The Table shows the demographic, hemodynamic, and acoustic cardiographic characteristics of these patients.

Figure 2 shows data from the pre-left ventriculogram tracings and reveals that in patients with LVSD and in whom the %LVST is <45%, there is a strong linear relationship between LVEDP and S<sub>3</sub> strength. However, in the patients whose %LVST is >45%,

the relationship between  $S_3$  strength and LVEDP is much weaker.

Figure 3 shows the stability of the relationship between LVEDP and  $S_3$  strength. It displays data from the pre- and post-left ventriculogram tracings in patients with LVSD and LVST <45%. The effects of the left ventriculogram had a negligible influence on the relationship between LVEDP and  $S_3$  strength.

Figure 4 shows that in patients with LVSD, values of EMAT >100 milliseconds are associated with LV dP/dt<sub>max</sub> <1000 mm Hg/sec. It therefore demonstrates the relationship between an additional acoustic cardiographic parameter and another fundamental measure of LV function.

Figure 5 reveals that in patients with LVSD, LVST increases as LVEF increases. However, if the heart rate exceeds 75 bpm, the LVST is generally shorter at any value of LVEF than it is at slower heart rates.

Figure 6 shows that the quantitative relationship between LV diastolic time (LVDT) and heart rate differs in patients with vs. without LVSD. In each group of patients, LVDT falls as the heart rate increases. However, especially at heart rates  $\geq 70$  bpm, the LVDT at each heart rate tends to be shorter in patients with LVSD vs. without LVSD.

Figure 7 demonstrates that in contrast to LVST (Figure 5), the values of %LVST decrease as LVEF increases. This is because of the higher heart rates that often prevail in patients with low LVEF. More specifically, Figure 7 also shows that patients with LVSD have higher values of %LVST at each increment of ejection fraction if their heart rates exceed 75 bpm than do patients with slower heart rates.

## Discussion

Our data show that acoustic cardiographic parameters are quantitatively related to invasive measurements of ventricular function. In patients with LVSD, there is a positive linear relationship between  $S_3$  strength and LVEDP (Figure 2). In addition, Figure

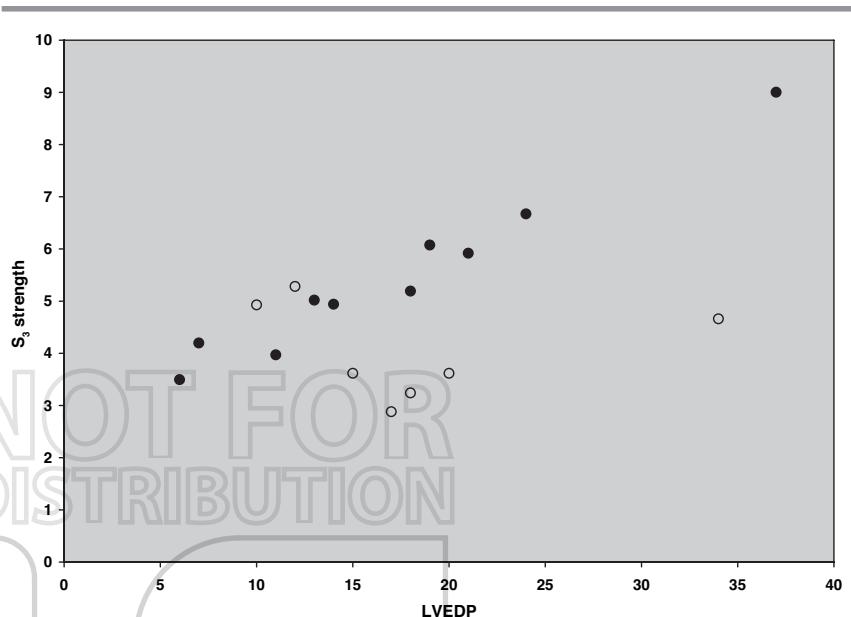


Figure 2.  $S_3$  strength vs. left ventricular end-diastolic pressure (LVEDP) in the patients with left ventricular systolic dysfunction; pre-ventriculogram recordings. Filled circles=left ventricular systolic time (LVST) <45% of R-R interval ( $R=0.982$ ;  $p<0.0001$ ); empty circles=LVST >45% of R-R interval ( $R=-0.071$ ;  $p=0.881$ )

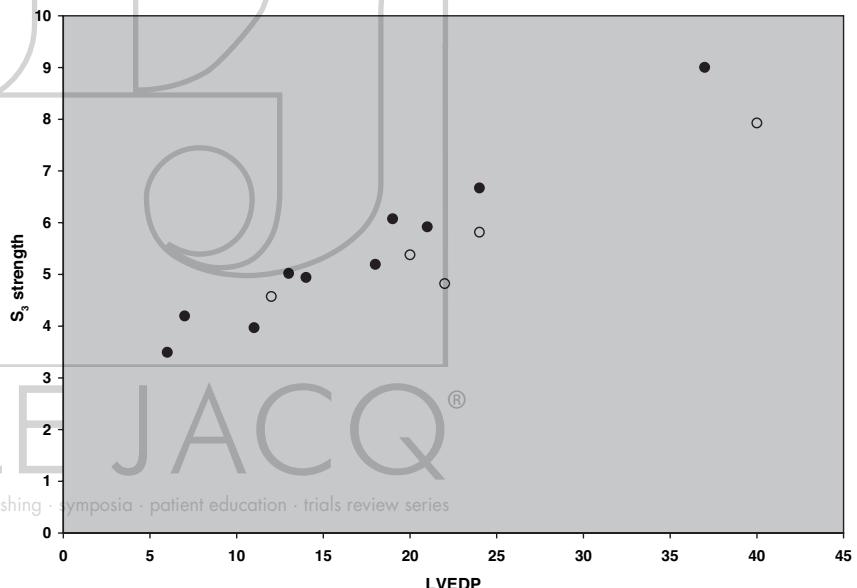


Figure 3.  $S_3$  strength vs. left ventricular end-diastolic pressure (LVEDP) in the patients with left ventricular systolic dysfunction and left ventricular systolic time <45% of R-R interval. Filled circles=pre-ventriculogram ( $R=0.982$ ;  $p<0.0001$ ); empty circles=post-ventriculogram ( $R=0.956$ ;  $p<0.025$ )

3 reveals that despite the perturbations imposed by a rapid injection of angiographic dye into the left ventricle, the linear relationship between  $S_3$  strength and LVEDP persists. This relationship between  $S_3$  strength and LVEDP persists. This relationship between  $S_3$  strength and LVEDP persists.

dence of an  $S_3$  as a continuous variable. This is more robust than treating it as a dichotomous variable, as is the case for  $S_3$  detection by auscultation.

As also shown in Figure 2, however, the linear relationship between

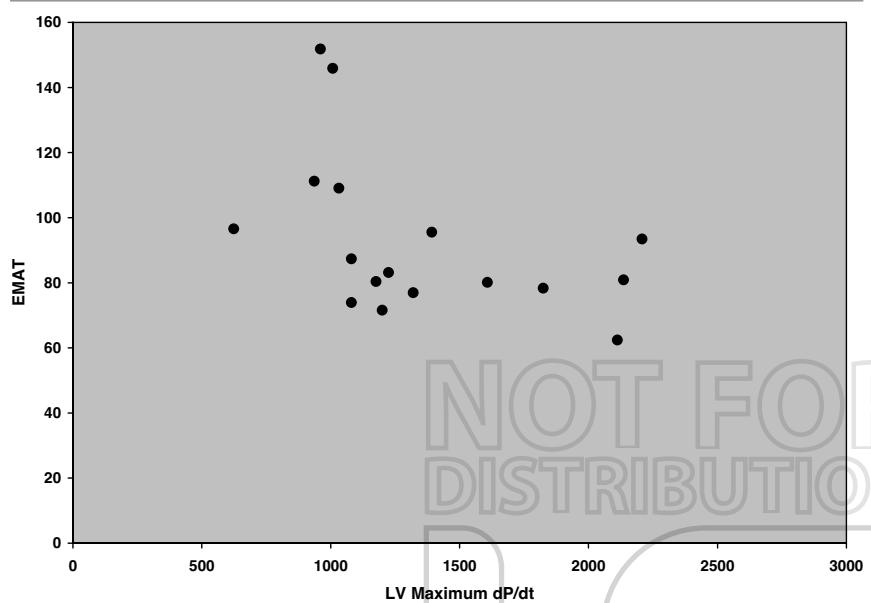


Figure 4. Relationship of electromechanical activation time (EMAT) to left ventricular (LV) maximum contractility ( $dP/dt$ ) in the patients with left ventricular systolic dysfunction ( $R=-0.961$ ;  $p=0.063$ )

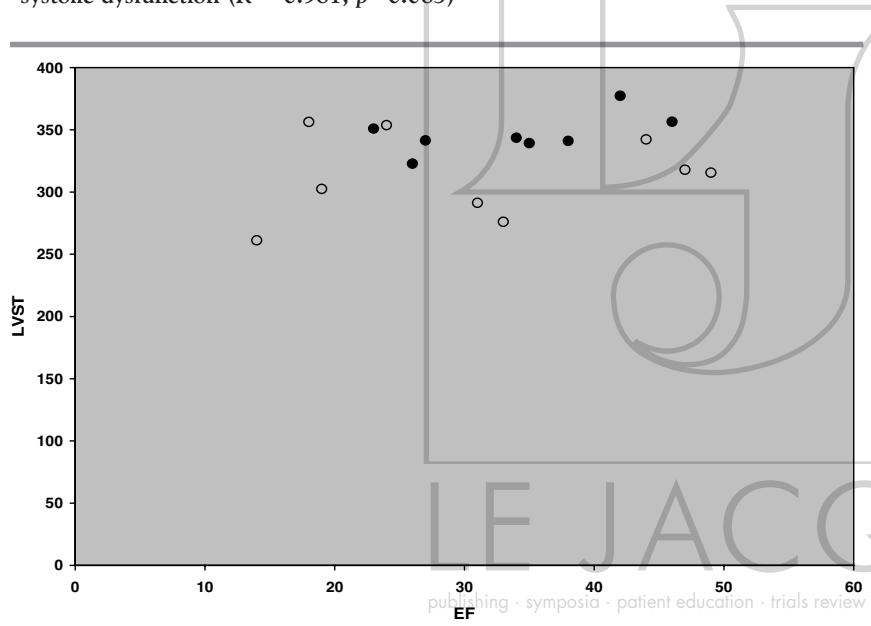


Figure 5. Left ventricular systolic time (LVST) vs. ejection fraction (EF) in patients with left ventricular systolic dysfunction, by heart rate subgroups.  $R$  is nonsignificant for each subgroup. Filled circles=heart rate  $\leq 75$  bpm; empty circles=heart rate  $> 75$  bpm

$S_3$  strength and LVEDP disappears if the LVST exceeds 45% of the cardiac cycle. A likely explanation for this is that an increase in LVST occurs at the expense of the proportion of time spent in diastole. A reduction in the duration of diastole can prevent early passive diastolic filling of the ventricle from being sufficiently vigorous

to produce an  $S_3$ . This is because both the isovolumic relaxation and the active filling periods impinge on the time available for passive filling. This, in turn, helps explain why, despite its high specificity for heart failure in the appropriate clinical setting, the corresponding sensitivity of the  $S_3$  for systolic dysfunction is only moderate.<sup>2</sup>

Despite the presence of LVSD, many patients may have sufficient impairment of early passive diastolic filling to prevent an  $S_3$  from occurring. An implication of these observations is that if a patient with heart failure has a detectable  $S_3$ , a goal of therapy would be to reduce its strength. However, if the patient does not have an  $S_3$ , an alternate goal would be to modify the %LVST appropriately.

As shown in Figure 4, the decreased force of LV contraction revealed by a low  $dP/dt_{max}$  is associated with a prolonged EMAT. Thus, EMAT is an additional diagnostic parameter that can discriminate between patients with intact vs. impaired LV systolic function. As a measure of LV function,  $dP/dt_{max}$  is especially relevant because it is highly sensitive to abnormalities of contractility.<sup>3</sup> Since  $dP/dt_{max}$  typically occurs during isovolumic contraction, it is not affected by alterations in afterload unless especially severe LVSD is present or if aortic diastolic pressure is very low. Conversely,  $dP/dt_{max}$  is very sensitive to changes in preload, especially if contractility is increased.<sup>3</sup> Measuring  $dP/dt_{max}$  is most useful for evaluating directional changes in contractility during interventions in which acute changes in preload can be assessed.

Patients with LVSD tend to have shorter LVSTs because ventricles with impaired contraction require more time to generate enough force to open and keep open the aortic valve. As shown in Figure 5, LVST is related to LVEF, and this relationship is affected by the patient's heart rate. At higher heart rates, the LVST is generally shorter at each level of LVEF because of the diminished time for diastolic filling at these rates. Figure 6 confirms this by demonstrating the relationship between LVDT (the complement of LVST) and heart rate in patients with vs. without LVSD. Above a heart rate of about 70, patients with LVSD generally spend less time in diastole for each increment in heart rate than do patients without LVSD. Compounding this effect on the Starling mechanism,

as Meiler et al.<sup>4</sup> showed, such a reduction in the time for diastolic filling can reduce subendocardial perfusion and further impair ventricular function in patients with heart failure. In a therapeutic application of these principles, Baker et al.<sup>5</sup> studied systolic and diastolic time intervals in 11 patients before and after implantation of cardiac resynchronization therapy (CRT) devices. They found that appropriate settings of the CRT devices shortened LV systole and concomitantly lengthened diastole.

As Figure 1 indicates, the rationales upon which the systolic acoustic cardiographic parameters are based are similar to that of traditional systolic time intervals. Abnormal systolic time intervals have been correlated with measures of LV dysfunction such as low cardiac output, stroke volume, and LV end-diastolic volume. The relation between the pre-ejection period and LV ejection time was shown to be highly correlated with LVEF and to be useful in diagnosing heart failure.<sup>6-9</sup> As a result of LV failure, the LV ejection time shortens and the pre-ejection period lengthens, primarily due to a diminished rate of LV pressure rise during isovolumic contraction.<sup>10</sup> These changes are respectively analogous to a shortening of LVST and prolongation of EMAT. Determination of the traditional systolic time intervals required labor-intensive measurements by experts who examined analog tracings of the simultaneously recorded ECG, phonocardiogram, and carotid pulse. In contrast, the acoustic cardiographic parameters are obtained through automated measurements of digital data and require no more time or effort to record than does a standard ECG.

As suggested above, one of the applications for which acoustic cardiography is particularly well-suited is CRT. CRT devices are intended to improve the hemodynamic status of patients with systolic heart failure by permitting the adjustment of the atrioventricular and/or ventriculoventricular intervals of implanted pacemakers. If properly per-

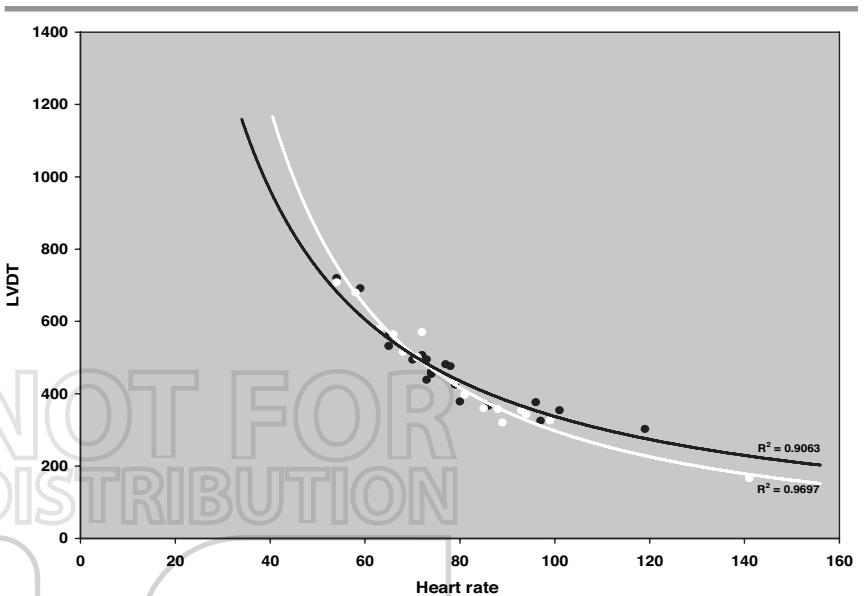


Figure 6. Left ventricular diastolic time vs. heart rate in patients without vs. with left ventricular systolic dysfunction, defined as ejection fraction (EF) <50%. Black=EF ≥50% ( $R=-0.952$ ;  $p<0.0001$ ); white=EF <50% ( $R=-0.985$ ;  $p<0.0001$ )

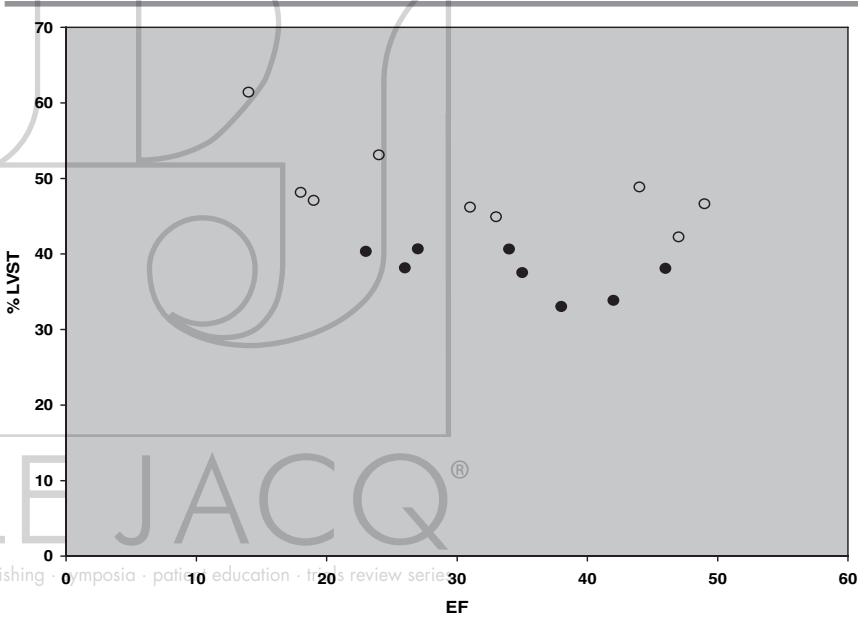


Figure 7. Relationship between left ventricular systolic time as a percentage of the R-R interval (%LVST) and ejection fraction (EF) in patients with left ventricular systolic dysfunction, by heart rate subgroups. Filled circles=heart rate ≤ 75 bpm; empty circles=heart rate > 75 bpm

formed, these adjustments can improve cardiac efficiency by optimizing the timing and sequence of cardiac activation. However, before selecting a patient for CRT, it is first necessary to determine that LVSD is a plausible explanation of the symptoms. Not only can pulmonary

disease mimic the symptoms of heart failure, but not all cases of heart failure are associated with LVSD. Therefore, when they are available, echocardiographic, radionuclide, and angiographic tests of LVEF are often used. Although tests such as the echocardiogram and

radionuclide studies can be used to confirm the presence of LVSD, their high cost and limited availability make them unsuitable for widespread use as screening tests.<sup>11</sup> Also, although the echocardiogram has been used to help optimize pacemaker settings following implantation of the CRT device, its use in this context is cumbersome, time-consuming, and highly dependent on the skill of the operator. As shown by their ease of use and their quantitative

relationships to well-accepted invasive measures of LV function, acoustic cardiographic parameters could be ideal for CRT optimization.<sup>5</sup>

**Limitations of the Study.** The number of patients in this study is small, and the findings must be corroborated using a larger set of data. A larger set of data will also be required to determine appropriate heart rate corrections for the various acoustic cardiographic parameters.

## Conclusions

We conclude that easily obtained acoustic cardiographic data may be used to detect and assess the severity of LVSD, as shown by the relationship of acoustic cardiographic data to invasive measurements of LV function. Acoustic cardiography can also be applied in the selection of patients for CRT and the optimization of the settings of implanted CRT devices.

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## ORIGINAL PAPER

# Optimization of Cardiac Resynchronization Devices Using Acoustic Cardiography: A Comparison to Echocardiography

*Optimization of pacemaker settings for cardiac resynchronization therapy (CRT) remains challenging and problematic. Several noninvasive methods are offered to customize the programmed parameters for individual patients, but so far only echocardiographic imaging has established itself as an accepted method. The authors examined the value of acoustic cardiography as a fast and more cost-efficient alternative to established echocardiographic imaging techniques for the optimization of CRT devices. The atrioventricular delay in 22 subjects with implanted CRT devices was independently optimized using echocardiography (Doppler transmural flow) as well as acoustic cardiography, and the recommended settings from each method were later compared. Doppler echocardiography and acoustic cardiography recommendations matched within a mean value  $\pm$  SD of  $17 \pm 16$  milliseconds and gave a correlation coefficient of  $r=0.90$  ( $p<0.001$ ). In 17 of the 22 cases (77.3%), the difference between echocardiographic and acoustic cardiogram CRT optimization results was  $\leq 20$  milliseconds. Furthermore, the echocardiographic transmural flow pattern was not significantly different for the setting independently chosen by the echocardiographic expert and the acoustic cardiographer for the cases with a difference of  $>20$  milliseconds (22.7%). In addition, it took less time for the acoustic cardiogram to collect sufficient information to make a recommendation, and it was found that the acoustic cardiogram data trend is easier to interpret. (CHF. 2006;12[4 suppl 1]:25–31) ©2006 Le Jacq*

To maximize the benefits of cardiac resynchronization therapy (CRT), a fast and cost-effective method of atrioventricular (AV) delay optimization that also fits into the standard pacemaker follow-up workflow is desirable. Despite the clinical acceptance of echocardiography in CRT optimization, practical aspects such as availability, time, cost, and the need for a well-trained echocardiographer limit the application of AV optimization to only a small percentage of CRT patients. This, in turn, may limit the effectiveness of CRT, since key outcome studies demonstrating the benefits of CRT routinely utilized such techniques of AV optimization.<sup>1,2</sup>

A promising, fast, and inexpensive method for device optimization in CRT

is acoustic cardiography. One approach to acoustic cardiography (AUDICOR, Inovise Medical, Inc., Portland, OR) records, stores, displays, and algorithmically interprets simultaneous electrocardiographic (ECG) and acoustic data. These data are collected using proprietary ECG/sound sensors placed in the standard precordial V<sub>3</sub> and V<sub>4</sub> positions, i.e., near the left ventricular (LV) apex. The assessment of cardiac function is achieved by the detection and automated analysis of systolic and diastolic heart sounds and their temporal relationships to the ECG. The primary acoustic cardiography parameters of relevance for the management of systolic heart failure are (see also Figure 1):

- S<sub>3</sub> strength: a measurement of the overall acoustic energy of the S<sub>3</sub>,

in a 10-second time interval. This parameter exhibits values in a range of 0–10 units.

- Electromechanical activation time (EMAT): the interval in milliseconds measured from the onset of the QRS complex to the mitral component of the S<sub>1</sub>. This parameter reflects the time required for the left ventricle to generate sufficient force to close the mitral valve and shows an increased value in patients with systolic heart failure.
- LV systolic time (LVST): the interval in milliseconds measured from S<sub>1</sub> to S<sub>2</sub>. This interval is reduced in patients with LV dysfunction.

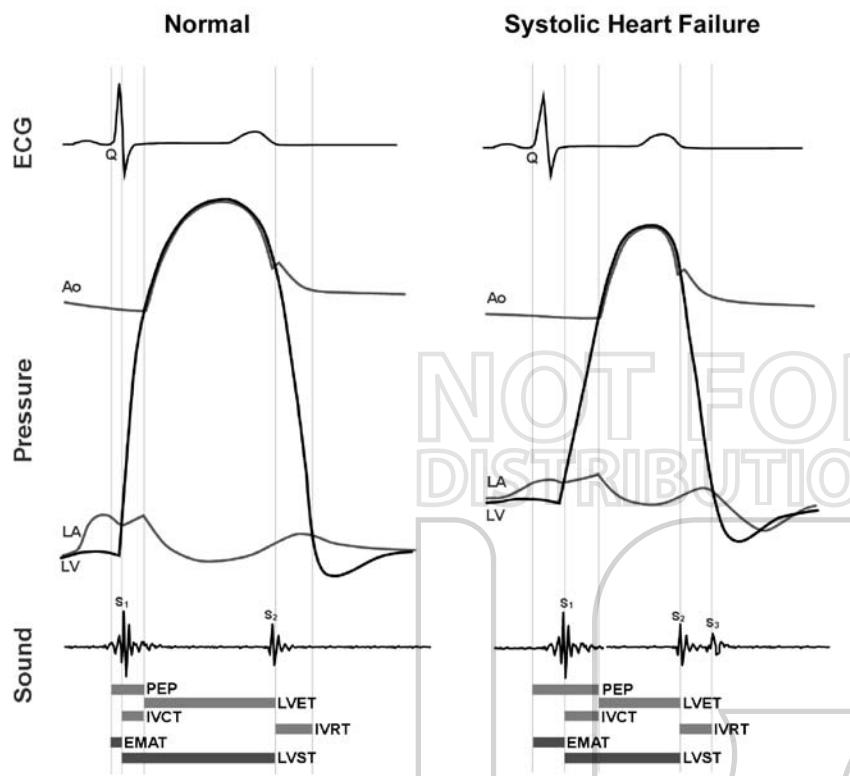
Previous studies have shown that acoustic cardiography accurately detects clinical heart failure and specific

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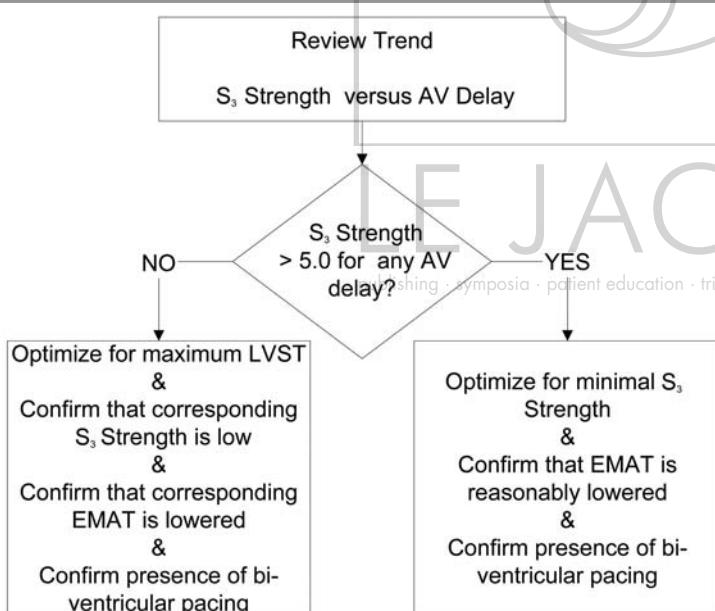
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**Figure 1.** Relationship of traditional systolic time intervals to acoustic cardiographic systolic parameters (normal vs. systolic heart failure). (Pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data.) ECG=electrocardiogram; Ao=aorta; LA=left atrium; LV=left ventricle; PEP=pre-ejection period; LVET=left ventricular ejection time; IVCT=isovolumic contraction time; IVRT=isovolumic relaxation time; EMAT=electromechanical activation time; LVST=left ventricular systolic time



**Figure 2.** Flow chart used to determine the best atrioventricular (AV) delay during cardiac resynchronization therapy optimization using acoustic cardiography. LVST=left ventricular systolic time; EMAT=electromechanical activation time

hemodynamic abnormalities known to be associated with heart failure.<sup>3,4</sup> In particular, the comparison of acoustic cardiography parameters with relevant hemodynamic parameters obtained during left heart catheterization studies have shown that: 1) S<sub>3</sub> strength correlates well with the absolute value of the LV end-diastolic pressure (LVEDP); 2) a prolonged EMAT is associated with reduced LV maximum contractility; and 3) reduced LVST values correlate to reduced LV ejection fraction (LVEF) in patients with systolic dysfunction.<sup>5</sup>

We tested the hypothesis that acoustic cardiography provides a fast, easy-to-use, and, therefore, cost-effective method to optimize CRT settings, and that acoustic cardiogram parameters produce very similar recommendations for the best AV delay settings in CRT devices compared with established echocardiographically-guided optimization methods.

## Methods

**Patient Population.** Twenty-two subjects (14 men; mean age, 72 years; range, 62–87 years), mean preimplantation LVEF of 25% (range, 10–40%), mean current LVEF of 37% (range, 15%–68%) with implanted CRT devices scheduled for an echocardiographically guided AV optimization were included in the study.

Exclusion criteria for participation in the study were the presence of atrial fibrillation or any other pacemaker-related issue at the time of presentation that would have prevented a successful AV delay optimization using echocardiography.

All subjects fulfilled the classic criteria for receiving CRT at the time of implantation. All patients had a CRT device implanted for at least 3 months and had undergone at least one echocardiographically guided AV optimization before enrollment in this study.

**Study Design.** After written patient consent was obtained, all subjects underwent a regular follow-up of their pacemaker/implantable cardioverter-defibrillator before optimization of their AV delay.

**Doppler Echocardiography.** The echocardiographic studies were performed with a Hewlett Packard (Palo Alto, CA) 4500 Ultrasound system in Doppler transmural flow mode. For the echocardiographically guided AV optimization, patients were placed in the left lateral position. The selection of the appropriate AV delays to test, as well as the total range and separation between the temporarily programmed AV delays, were determined by the clinician based on clinical judgment. For each temporarily programmed AV delay, an echocardiographic image of the Doppler transmural flow pattern was recorded on videotape, then analyzed and recorded in the patient chart. At the end of the recording, the clinician determined the best AV delay for the patient based on the review of all echocardiographic images and noted the optimal settings in the patient chart.

**Acoustic Cardiography.** After completion of the echocardiographically guided AV optimization, the subject was placed in the supine position and connected to an AUDICOR TS device to record and trend acoustic cardiographic parameters. The subject's AV delays were temporarily changed and programmed to the same temporary settings as used during the echocardiographic evaluation. For each temporary AV delay, a full 10-second AUDICOR test was recorded, analyzed for the  $S_3$  strength, EMAT, and LVST, and trended against the AV delay changes. After taking all AUDICOR tests, the patient's AV delay was permanently programmed based on the results of the echocardiographic evaluation.

After the patient was discharged, two clinical specialists trained in interpreting acoustic cardiographic trends were asked to independently review the data and produce a recommended AV delay. The specialists were blinded to the patient information as well as the echocardiographic data and recommended AV setting. Based on the results of echocardiographic and hemodynamic studies of the relationship between the absence of an  $S_3$  with impaired

**Table.** Echocardiographic (Echo) and Acoustic Cardiographic Optimal Atrioventricular Delay Setting Recommendations (ms) for All Study Subjects

SUBJECT No.	$\Delta$ (ECHO, ACOUSTIC)		ACOUSTIC CARDIOGRAPHY		
	DOPPLER ECHO	ACOUSTIC		EXPERT I	EXPERT II
1	130	30	160	160	160
2	60	20	80	80	80
3	225	0	225	225	250
4	100	0	100	100	100
5	150	10	160	160	160
6	210	20	230	230	230
7	160	0	160	160	160
8	140	10	150	150	150
9	190	30	220	190	220
10	280	70	210	240	210
11	200	20	220	220	220
12	200	20	220	220	220
13	130	20	150	150	150
14	180	10	170	170	170
15	230	40	270	270	270
16	200	10	210	210	210
17	200	0	200	200	200
18	180	30	150	150	150
19	70	10	80	80	100
20	170	0	170	170	170
21	110	20	130	130	130
22	190	10	180	180	180
Mean $\pm$ SD		168 $\pm$ 53	17 $\pm$ 16	175 $\pm$ 50	175 $\pm$ 50
$\Delta$ =difference					

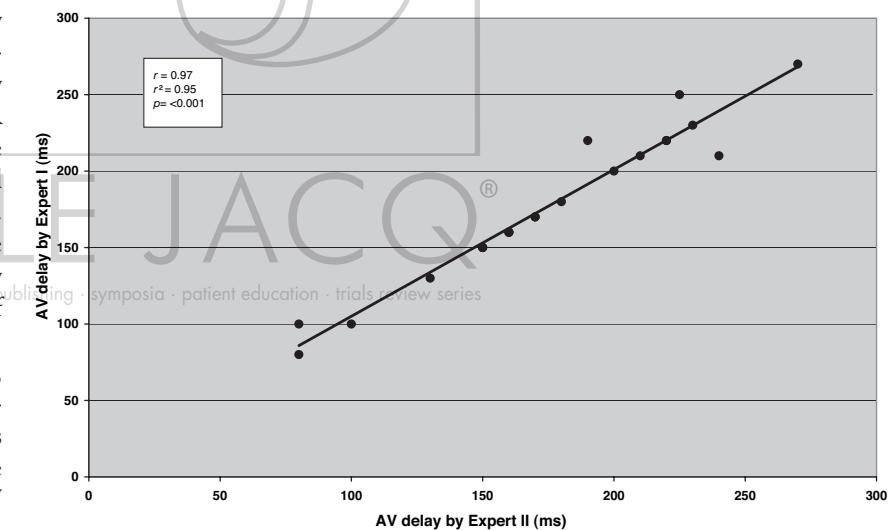
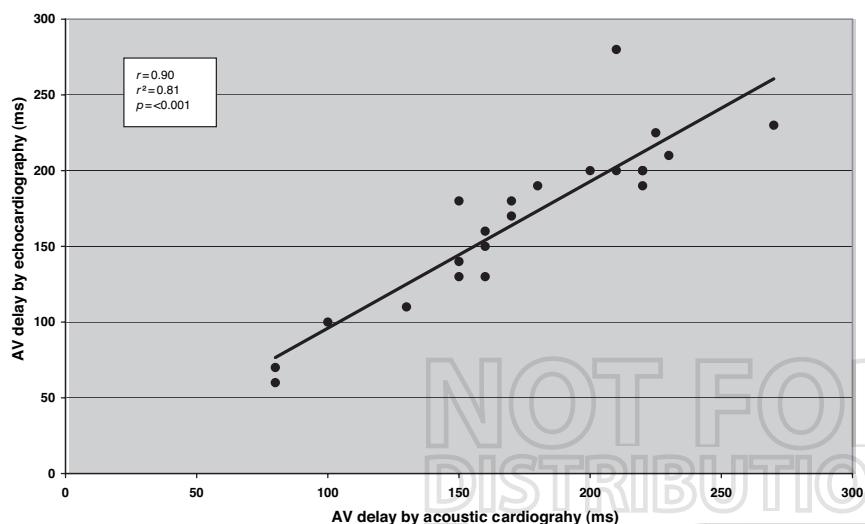


Figure 3. Relationship of the recommended atrioventricular (AV) delays obtained through independent, blinded over-read of the AUDICOR TS (Inovise Medical, Inc., Portland, OR) trends by two clinical experts

relaxation in diastole (E/A < 1.0), the LVEDP in LV systolic dysfunction, and the strength of an  $S_3$  correlating well with the relationships between LVST and



**Figure 4.** Relationship of recommended atrioventricular (AV) delays obtained through echocardiography and acoustic cardiography (consensus over-read) patient evaluation

LVEF, and EMAT and LV contractility, the flow chart in Figure 2 was devised and used by the two clinical specialists in interpreting the acoustic cardiographic trends for the various AV delays per patient.<sup>5,6</sup> In those cases where the specialists disagreed with respect to the recommended AV setting, the disagreement was documented, and both were asked to agree on a recommended consensus AV setting by reviewing the blinded data together.

**Statistical Analyses.** The recommendation for a best AV delay (as obtained through the individual review of the acoustic cardiography trends and the consensus recommendation) were compared against the final AV delays obtained through the echocardiographically guided procedure. Correlation coefficients for the over-read results from the two clinical specialists, as well as for the comparison between acoustic cardiography and echocardiography recommendations, were calculated using standard linear regression analysis. Significance was determined by  $p<0.05$ .

## Results

**Comparison of AV Delays Recommended by the Two Reviewers.** The Table contains the detailed AV delay recommendations for all subjects based

on the independent interpretation of the two experts in acoustic cardiography, and Figure 3 shows the correlation between the AV delays recommended by the two reviewers. There was excellent agreement between the two reviewers ( $r=0.97$ ;  $p<0.001$ ). For the settings about which both experts initially disagreed, the corresponding acoustic cardiogram parameters did not differ significantly.

**Comparison of AV Delays Recommended by Acoustic Cardiography and Echocardiography.** The Table shows the echocardiographically and acoustic cardiographically determined AV settings as well as the difference between both methods for each subject. For the 22 subjects included in the study, recommendations from both methods matched for 17 (77.3%) subjects within 20 ms and for 21 (95.5%) subjects within 40 ms, while the discrepancy for one patient was 70 ms. A review of the Doppler transmitral flow images for subjects where the discrepancy was  $>30$  ms revealed that the differences for the AV settings picked by one or the other optimization method were marginal at best.

Figure 4 shows the correlation of the echocardiography and acoustic cardiography AV delay recommendations for all

subjects. The correlation coefficient is  $r=0.90$  ( $p<0.001$ ). The mean value for the echocardiography-based recommendation was  $168\pm53$  milliseconds, and for the acoustic cardiography-based analysis it was  $175\pm50$  milliseconds, which is not significantly different.

## Discussion

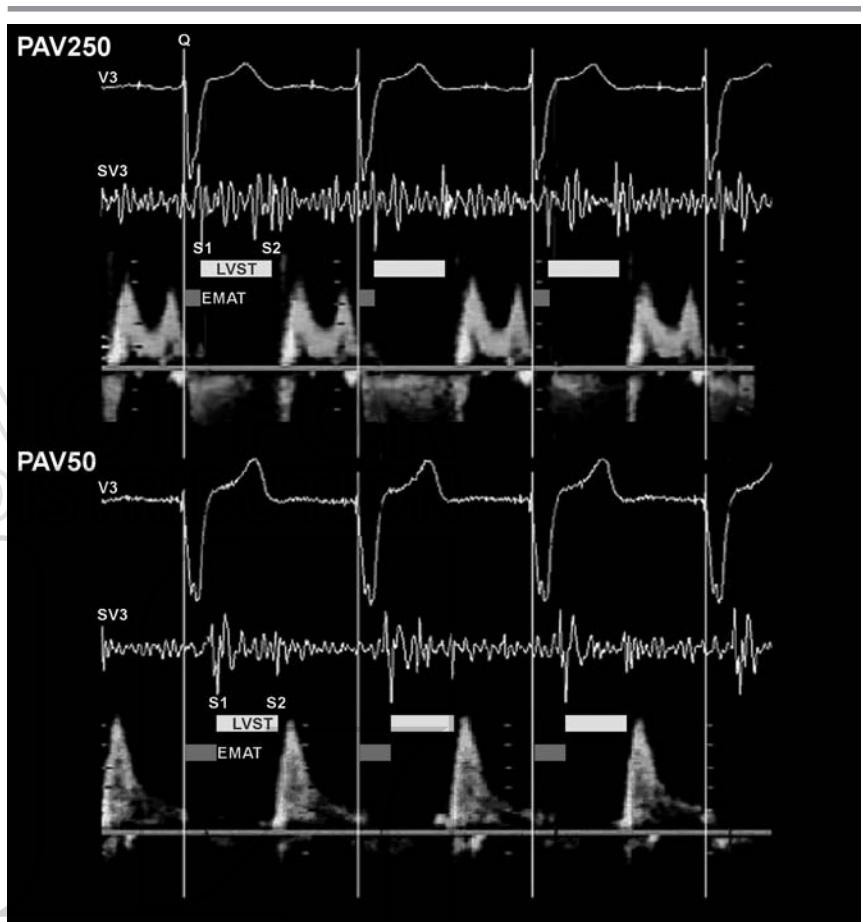
The key focus during AV optimization is to maximize preload through optimal synchronization of the atrial contribution to LV filling at the onset of LV systole.<sup>1</sup> Using the Doppler transmural flow pattern to optimize the AV delay, the most common approach is to improve the passive inflow pattern (maximize E-wave height and width, if possible, and reduce the deceleration time) and to increase the atrial contribution to LV filling through maximizing the A-wave height and width, as well as its timing with respect to the mitral valve closure.<sup>1</sup> The achieved increase in preload leads to two positive effects: 1) an increase in effective filling pressure, with a consequent increase in LV end-diastolic volume and increase in stroke volume via the Frank-Starling mechanism; and 2) an overall reduction in LVEDP, and thereby improvements in the LV diastolic function as reflected by changes in the E/A ratio and, potentially, a reduction in diastolic dysfunction class.<sup>7</sup> In particular, in postimplantation patients, the reduction in LVEDP is important to support the reverse remodeling process.<sup>8</sup>

It was shown in left heart catheterization studies that acoustic cardiographic parameters correlate well with relevant hemodynamic parameters that are key in the optimization of CRT devices in patients with systolic heart failure. As Roos et al.<sup>5</sup> have shown, the S<sub>3</sub> strength is correlated in a linear fashion to LVEDP, and therefore can be used to optimize preload in CRT patients. As shown in Doppler echocardiographic and catheterization studies on patients with systolic heart failure, the strength of the S<sub>3</sub> can be reduced by either severely impaired passive filling at high heart rates or in

patients with an abnormal relaxation pattern, with an E/A ratio of  $<1.0$ .<sup>5,6</sup> In particular, in the latter patients, the S<sub>3</sub> strength might not show sufficient variation during the AV optimization, so one can obtain additional guidance for the AV optimization through systolic time intervals, namely EMAT and LVST. EMAT will increase with a reduction in LV maximum contractility, while LVST decreases with a reduction in LVEF.<sup>5,9</sup>

The relationship among EMAT, LVST, and the Doppler transmural flow pattern in CRT patients is illustrated in Figure 5. For short AV times, the atrial contribution to LV filling is often reduced due to the closure of the mitral valve before the end of the atrial systole. As a result, the peak of the A wave in the transmural flow pattern is strongly reduced and, in some cases, the A wave is truncated by the closure of the mitral valve. In this situation, EMAT is strongly prolonged and LVST is reduced. For longer, more optimal AV times, the peak of the A wave in the transmural flow pattern is increased to its maximum point and the tail end of the A wave is aligned with the closure of the mitral valve. In this setting, EMAT will be shortened, while LVST is lengthened.

As an example, Figure 6 shows the Doppler transmural flow patterns and Figure 7 shows the acoustic cardiographic trend for one of the patients in this study. In this case, both the echocardiographically guided optimization as well as the acoustic cardiographic evaluation yielded conclusions that the best setting for that subject is an AV delay of 225 milliseconds. Advanced pattern recognition skills are needed to identify the best AV setting through the Doppler transmural flow pattern. In this case, the acoustic cardiogram trend offers clear guidance to the best AV setting (per Figure 2, low S<sub>3</sub> strength [ $<5.0$ ], so the best setting is determined through the maximum LVST and a low EMAT, while making sure that the setting is not too close to the intrinsic PR interval). Note that the low S<sub>3</sub> strength



**Figure 5.** Illustration of electrocardiographic, AUDICOR (Inovise Medical, Inc., Portland, OR) systolic time intervals (electromechanical activation time [EMAT]), left ventricular systolic time [LVST]), and echo Doppler transmural flow pattern in a cardiac resynchronization therapy patient for short and long atrioventricular (AV) delays. With a shorter AV delay, there is fusion of the E and A wave, resulting in reduced passive filling (shorter diastolic filling time). With a longer AV delay, there is separation of the E and A waves, with atrial contraction ending with onset of systole or QRS.

is consistent with the pattern of E/A  $<1.0$  in the transmural flow patterns.

The simplicity of interpreting the acoustic cardiographic trends is underscored by how closely the two clinical specialists who interpreted the acoustic cardiogram trends produced similar recommended AV delays for the enrolled subjects.

Besides being virtually equivalent to measuring Doppler transmural flow for optimization of CRT, acoustic cardiography has the advantages of being less time consuming for the physician and less burdensome for the patient. For example, AV optimization using acoustic cardiography took no longer than 15 minutes for any of the

patients, whereas echocardiography required more than an hour for several of the patients. In addition, unlike the case for performing echocardiography, obtaining the acoustic cardiographic data does not require the patient to be lying in an uncomfortable left lateral position for a prolonged period. It is likely that by providing greater ease and comfort to physicians and their patients, adopting acoustic cardiography will lead to wider acceptance of the optimization of CRT devices.

**Limitations of the Study.** This study has certain limitations. During the echocardiographic evaluation, only a limited number of AV settings were

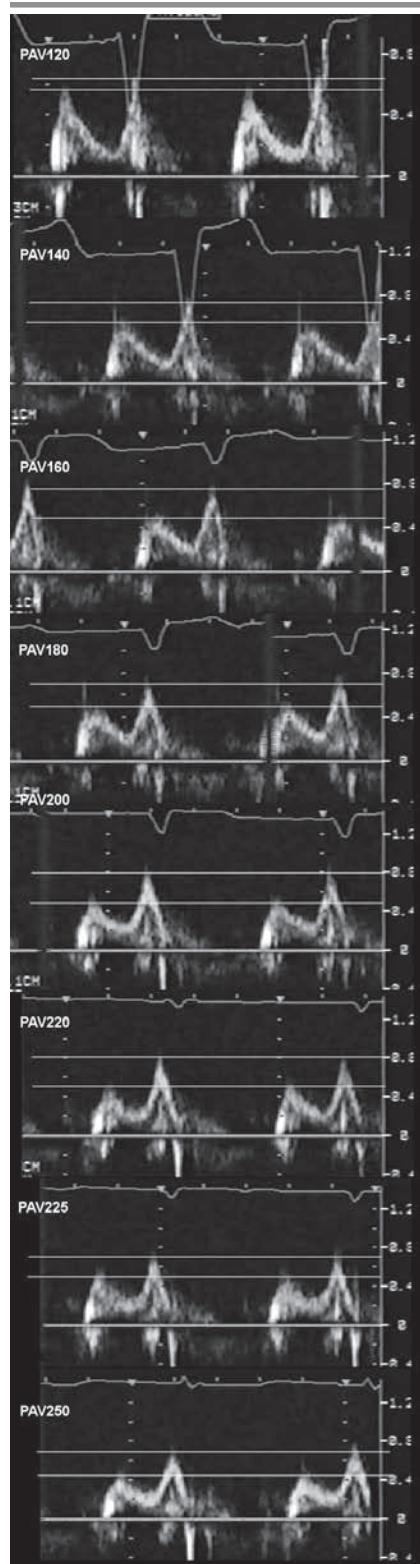


Figure 6. Echocardiographic Doppler transmural flow pattern for all of the atrioventricular delays tested in study subject number 3

tested, and therefore it cannot be concluded that the recommended AV

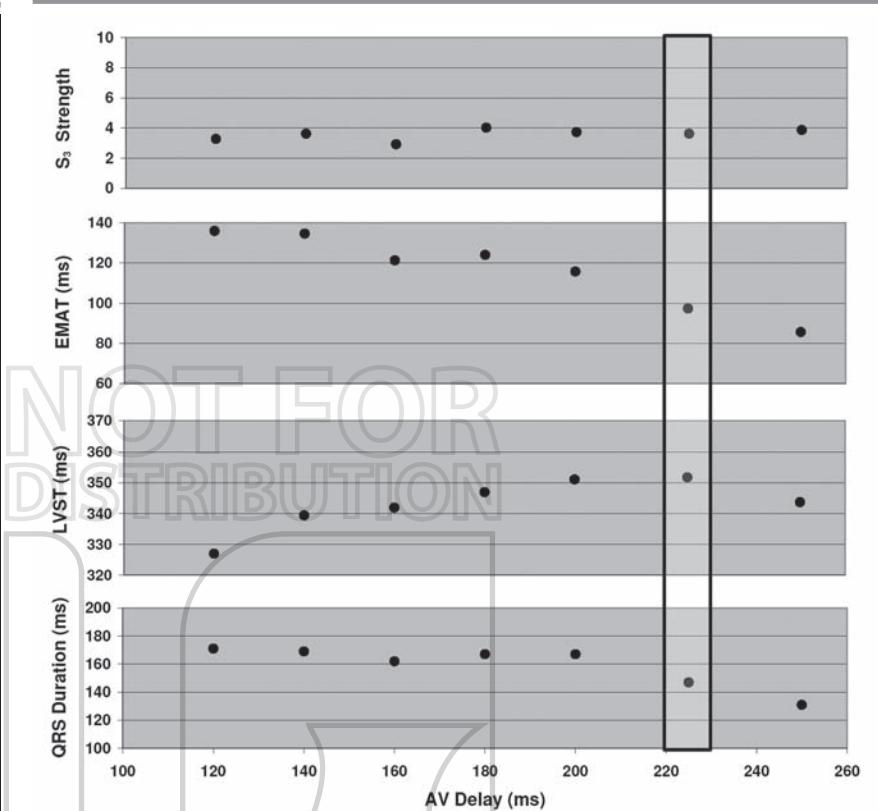


Figure 7. Trend showing the acoustic cardiogram values for all of the atrioventricular (AV) delays tested in study subject number 3. EMAT=electromechanical activation time; LVST=left ventricular systolic time

setting is the only valid one for the patient. Most of the patients had been benefitting from the CRT implantation for over 6 months and, as a result of successful reverse remodeling, the variations in the mitral flow velocity and acoustic cardiogram parameters are less than would be expected had optimization been performed before any reverse remodeling occurred.

## Conclusions

The comparison of independently obtained recommendations for best AV delays in 22 CRT patients through echocardiography and acoustic cardiography shows that both technologies yield equivalent clinical results. The recommended final settings matched for all patients within a mean value of  $17 \pm 16$  milliseconds and resulted in a correlation coefficient of  $r=0.90$ . The observation that an optimal AV delay of a value other than the “out-of-the-box” or preprogrammed setting of around 100 milliseconds was found in

most patients underscores the need to perform AV optimization in all patients. Acoustic cardiography is not only a fast, easy-to-use, and cost-effective method to optimize CRT, but it also has clinical utility in CRT optimization similar to Doppler-echocardiographic evaluations based on the transmural flow patterns.

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A large, light gray graphic of the letters 'J' and 'Q' is centered on the page. The letter 'J' is positioned on the left, and the letter 'Q' is on the right, with their stems overlapping. Both letters are enclosed within a thin rectangular border. Below this graphic, the word 'JACQ' is written in a large, bold, light gray sans-serif font. A registered trademark symbol (®) is located at the top right corner of the 'Q'. At the bottom right corner of the 'Q', there is a small, faint copyright symbol (©). The overall design is minimalist and modern.



## ORIGINAL PAPER

# Clinical and Economic Benefits of Using AUDICOR S<sub>3</sub> Detection for Diagnosis and Treatment of Acute Decompensated Heart Failure

*Because many of the signs and symptoms of acute decompensated heart failure (ADHF) are nonspecific (e.g., dyspnea), accurate diagnosis can be challenging. Highly specific indicators of ADHF can assist in early and accurate diagnosis, therefore providing a potential for better outcomes and cost efficiency. Demographic, clinical, laboratory, and electronically detected S<sub>3</sub> data (Inovise Medical, Inc., Portland, OR) were collected in 340 emergency department patients with suspected ADHF. After hospital discharge, two blinded cardiologists determined whether ADHF was present. Total hospital charges were also recorded. The overall ED misdiagnosis rate was 14.0%, of which over 90% were a failure to recognize ADHF when it was present. The S<sub>3</sub> was highly specific (94%) for ADHF and was valuable in combination with BNP values to improve the diagnostic accuracy in undifferentiated emergency department dyspneic patients. Misdiagnosed ADHF patients accrued over \$2500 more in hospital charges than patients correctly diagnosed with ADHF, a 32% increase.*

(CHF. 2006;12(4 suppl 1):32–36) ©2006 Le Jacq

Patients presenting to the emergency department (ED) with undifferentiated dyspnea represent a challenging diagnostic dilemma. Because heart failure (HF) occurs most frequently in the elderly, a population with many simultaneous comorbidities, it can be a difficult diagnosis. And, since its most common presentation is dyspnea, a symptom that is common to many diseases, misdiagnosis is not unusual. The diagnostic accuracy of history and physical examination for HF is often unreliable.<sup>1</sup> Chest radiography, while helpful when demonstrating signs of congestion, is often nondiagnostic, especially in patients with an acute exacerbation of chronic HF.<sup>2–4</sup>

The introduction of B-type natriuretic peptide (BNP) has been useful for excluding HF in acutely dyspneic ED patients, with its high sensitiv-

ity when concentrations are <100 pg/mL. However, the specificity of BNP is poor (76%) at this level.<sup>5</sup> BNP levels become useful as a confirmatory marker of an acute HF exacerbation only when levels are >500 pg/mL, when its specificity rises above 90%.<sup>6–8</sup> Thus, an indeterminate “gray zone” between 100–500 pg/mL exists where BNP levels are neither sufficiently sensitive to be used as a screening test, nor sufficiently specific to “rule in” HF. This may contribute to the high acute decompensated HF (ADHF) misdiagnosis rate, estimated in the range of 10–20%.<sup>2,9,10</sup> The addition of an S<sub>3</sub> detected by the AUDICOR system (Inovise Medical, Inc., Portland, OR) as a second, more specific test to gray-zone BNP levels has been shown to improve accurate initial diagnosis and decision making in HF patients.<sup>11</sup>

The consequences of HF misdiagnosis are significant and well documented. The Acute Decompensated HF National Registry (ADHERE database)<sup>12,13</sup> has collected data on more than 100,000 patient cases and has demonstrated that earlier diagnosis and initiation of appropriate treatment is associated with fewer intensive care unit (ICU) admissions, shorter hospitalizations, fewer invasive procedures, and lower acute mortality. By emphasizing more rapid and accurate initial diagnosis of ADHF in the ED, better clinical outcomes and more economically sound delivery of health care will follow.

We sought to further elaborate on the addition of electronically detected heart sounds to the diagnostic armamentarium of the ED physician who treats patients with undifferentiated

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dyspnea or other symptoms suggestive of HF. We hypothesized that the electronic detection of heart sounds would improve diagnostic accuracy for ADHF, especially in diagnostically challenging subgroups, and wanted to assess the fiscal impact of inaccurate initial HF diagnoses.

## Methods

**Study Design and Setting.** Between September 2003 and June 2004, a prospective convenience sample was obtained in 340 patients who presented with signs or symptoms of decompensated HF at four EDs. Detailed methods and descriptions of the analysis have been previously reported.<sup>11,14</sup> Subjects were evaluated for potential participation if they were older than 18, had an electrocardiogram (ECG) ordered, and had signs or symptoms of ADHF (dyspnea, extremity edema, fatigue). Subjects were excluded if more than 1 hour had passed since they had received vasodilators or diuretics for ADHF. All subjects gave written informed consent, and the Institutional Review Board approved the study at all enrolling hospitals.

**Methods of Measurement.** The methods of measurement are the same as those in our previous work<sup>11,14</sup> and are explained as follows. After study enrollment, clinical study assistants (CSAs) collected demographic data, past medical history, and electronic heart sound data using the AUDICOR device. The treating physician, blinded to electronic heart sound data, documented the presence or absence of jugular venous distension, lower extremity edema, and an  $S_3$  detected by auscultation before receiving laboratory and radiology results. Chest radiography (as interpreted by radiology staff), laboratory variables, BNP levels, automated ECG results, in-hospital data, and in-hospital events were collected by chart review. A study nurse, blinded to AUDICOR results, performed the chart review using a standardized data collection form with predetermined data definitions. CSAs obtained 30-day

follow-up by telephone interview. The Social Security Administration's Death Master File online service and medical records were reviewed for all patients. All clinical data were double entered into an electronic database for subsequent analysis.

The presence of an  $S_3$  was determined using the AUDICOR system, an acoustic cardiogram that replaces the standard  $V_3$  and  $V_4$  leads with sensors for collecting both sound and electrical data. Sound data from both leads are analyzed using a signal-processing algorithm to detect the  $S_3$ . The algorithm has been validated by comparison to blinded consensus over heart sound tracings read by expert phonocardiographers and in clinical studies comparing the algorithm to hemodynamic measurements obtained during left heart catheterization.<sup>15,16</sup> For study purposes, the AUDICOR sensors were placed on subjects by a trained CSA. Acoustic cardiographic data were collected for a 10-sec time period, saved to a compact disc, and shipped to Inovise Medical, Inc. for processing. Raw data were supplied to allow for signal processing using the most updated algorithm. The presence or absence of an  $S_3$  was recorded in an electronic spreadsheet (Microsoft Excel, Microsoft Corporation, Redmond, WA) and subsequently linked to the clinical data for analysis.

**Methods for Cost Analysis.** The CSAs obtained the total hospital charges for each subject's hospital stay from the hospital billing department. In addition, the final discharge diagnosis-related group (DRG) coded was obtained from the coding department for each subject. This allowed a cost analysis based on the presence or absence of an accurate initial ED diagnosis and an assessment of any consequent fiscal outcomes.

**Criterion Standard for HF.** The criterion standard for ADHF is the same as that stated in our previous work<sup>11,14</sup> and is explained as follows. On completion of all data collection, and 9

months after the final patient follow-up was completed, the entire medical record for each enrolled patient was copied. The records were reviewed by CSAs to remove all heart sound data and BNP values. Then, two board-prepared cardiologists reviewed all the available documentation to determine the patient's HF status during their acute ED presentation. HF status was defined as HF present (primary HF) and non-HF (non-HF). Primary HF was defined as ADHF. Non-HF was determined to occur when a patient was judged not to have HF or to have a medical history of HF, but to be well compensated at presentation. If the cardiologist's reviews were discordant, the diagnosis was adjudicated by the principal investigator.

**Primary Data Analysis.** Data are described using median and range for continuous data and frequencies and percents for categoric data. Measures of diagnostic accuracy (sensitivity, specificity, and likelihood ratios [LRs]) are reported with 95% confidence intervals. Positive LRs were calculated by positive LR = sensitivity / (1-specificity) = (true positive / (true positive + false negative) / (false positive / (false positive + true negative)).

**Subgroup Analysis.** Analysis was also performed on various subgroups. The entire dataset was divided into three challenging subgroups based on clinically relevant diagnostic and risk stratification parameters. Group 1 consisted of subjects who were misdiagnosed as non-HF by ED physicians but were later determined by the cardiologist panel to have ADHF. Group 2 consisted of subjects having a BNP value <500 pg/mL and at least one of the following: no history of HF, history of chronic obstructive pulmonary disease (COPD), prior ejection fraction (EF) >40%, or no prior admissions for HF. Group 3 was defined as patients who, irrespective of BNP values, had at least one of the following: no history of HF, history of COPD, prior EF >40%, or no prior admissions for HF. Finally, data

**Table I.** Sensitivity, Specificity, and Positive Likelihood Ratio (LR) for Various Assessments of Heart Failure

	$S_3$	BNP 100–500 pg/mL	BNP >500 pg/mL	$S_3$ AND BNP 100–500 pg/mL	$S_3$ AND BNP >500 pg/mL
n	340	250	250	250	250
Sensitivity (% [95% CI])	38.2 (30.3–46.7)	29.6 (22.3–38.1)	63.2 (54.5–71.1)	10.4 (6.2–17.0)	28.0 (20.9–36.4)
Specificity (% [95% CI])	93.3 (89.1–96)	74.4 (66.1–81.2)	91.2 (84.9–95.0)	97.6 (93.2–99.2)	100 (97.0–100)
Positive LR (95% CI)	5.7 (3.3–9.9)	1.2 (0.77–1.7)	7.2 (4.0–12.8)	4.3 (1.3–14.8)	Infinite

BNP=B-type natriuretic peptide; CI=confidence interval

**Table II.** Sensitivity, Specificity, and Positive Likelihood Ratio (LR) for an  $S_3$  in Predicting Heart Failure (HF) in Challenging Subgroups

	ED DIAGNOSIS OF NON-HF (43 OF 248 MISDIAGNOSED)	EITHER NO HF HISTORY, POSITIVE COPD HISTORY, PRIOR EF >40%, OR NO PRIOR HF ADMISSIONS AND BNP <500 pg/mL	EITHER NO HF HISTORY, POSITIVE COPD HISTORY, PRIOR EF >40%, OR NO PRIOR HF ADMISSIONS
n	248	152	306
Sensitivity (% [95% CI])	37.2 (24.4–52.1)	30.8 (18.6–46.4)	35.2 (27.3–45.5)
Specificity (% [95% CI])	93.2 (88.9–95.9)	93.8 (87.8–97.0)	94.1 (90–96.6)
Positive LR (95% CI)	5.4 (2.9–10.3)	5.0 (2.1–11.7)	6.1 (3.3–11.1)

ED=emergency department; COPD=chronic obstructive pulmonary disease; EF=ejection fraction; BNP=B-type natriuretic peptide; CI=confidence interval

were analyzed for the presence of an  $S_3$  and a BNP value within the gray zone of 100–500 pg/mL.

## Results

**Subject Demographics.** The 340 subjects had a median age of 61 years (range, 20–97 years); 54% were women, and 48% were white. A previous diagnosis of HF was present in 48% of patients. One hundred subjects had an EF measurement available, of which 31 (31%) were abnormal (EF <40%). ADHF was determined by the cardiologist panel to be present in 131 subjects (38.5%). All 340 subjects underwent AUDICOR  $S_3$  detection. Only 250 subjects had a BNP value determined as its assessment and was at the discretion of the ED physician and not mandated by the study protocol.

**Diagnostic Test Characteristics of BNP and the  $S_3$ .** The sensitivity, specificity, and positive LR for detecting ADHF by use of the  $S_3$  alone, BNP

in the gray zone and exceeding 500 pg/mL, and in combinations of the  $S_3$  and BNP are presented in Table I. A schematic of the positive LR generated by each and combined clinical variables is depicted in the Figure.

The analysis of an  $S_3$  in detecting HF in diagnostically challenging patients showed a similar performance to that of the subjects as a whole, with sensitivity in the mid-30% range and specificity in the low 90% range (Table II).

**AUDICOR  $S_3$  for Misdiagnosis Correction.** As previously reported by Collins et al.,<sup>11</sup> the overall ED misdiagnosis rate was 14%. Of the 47 misdiagnosed cases, 43 were due to a failure to diagnose ADHF when it was present. Had the AUDICOR  $S_3$  been used as the sole diagnostic criterion among the 43 patients ultimately defined as having primary HF, 15 (34.9%) would have been correctly diagnosed as having primary HF. Two of these patients were sent home, 12 were admitted

to a non-ICU setting, and one was admitted to the ICU. Similarly, had the AUDICOR  $S_3$  been used as the sole diagnostic criterion for primary HF, 14 of the 206 patients (6.8%) that were correctly diagnosed as non-HF would have been incorrectly classified as having primary HF. Of these 14 patients, 10 were discharged home and four were admitted to a non-ICU setting. However, of these 14 subjects with a false-positive  $S_3$  suggesting ADHF, four had a history of known HF (with two having documented depressed EF), two were younger than 40 (when an  $S_3$  can be physiologic), and eight had numerous other severe disease comorbidities.

**Cost Analysis.** The median hospital charges for subjects with HF correctly diagnosed in the ED was \$7977 (N=88), compared with \$10,508 (N=43) for subjects with HF that were misdiagnosed in the ED; a difference of more than \$2500 and a 32% increase in charges. Of the 43 patients with HF who were misdiagnosed in the ED, 15 (35%) had an  $S_3$  detected by AUDICOR.

Evaluating the final discharge DRG coded for the 43 subjects who were misdiagnosed with something other than ADHF in the ED revealed that nine of the 43 could not be analyzed because they were not admitted. Ten of the remaining 34 subjects were coded for disease processes less severe and with less reimbursement than ADHF: pneumonia (five subjects), COPD (two subjects), chest pain (two subjects), and hypertension (one subject).

## Discussion

This study corroborates the results of previous analyses showing that the presence of an  $S_3$  is highly specific for ADHF.<sup>11,14,16</sup> One could propose, given the >93% specificity of an  $S_3$  for ADHF, that when an  $S_3$  is detected in an ED patient with signs and symptoms of decompensated HF, very little further diagnostic testing may be required before treatment can be initiated. This is especially true if a BNP level exceeds 500 pg/mL, since the positive LR for ADHF with this combination ( $S_3$  and BNP >500 pg/mL) was infinite. Our findings suggest that the high specificity of the AUDICOR  $S_3$  alone is a useful adjunct and is complementary to BNP measurement. While indeterminate BNP levels (100–500 pg/mL) had a poor positive LR for predicting ADHF (1.2; 95% confidence interval, 0.77–1.73), the presence of an AUDICOR  $S_3$  in these subjects increased the positive LR to 4.3 (95% confidence interval, 1.3–14.8).

Highly specific tests are useful because their positive LRs and positive predictive values help “rule in” specific diagnoses. The high specificity of the AUDICOR  $S_3$  can be helpful to diagnose HF when it is suspected in acutely dyspneic ED patients. Among the subjects who had an ED misdiagnosis and were subsequently found to have presented with ADHF, over one third could have been appropriately diagnosed and treated in the ED had an AUDICOR  $S_3$  been utilized. This should be balanced, however, given the approximately 7% false-positive rate observed, and each case should be analyzed individually within the clinical context.

Of particular clinical relevance is the fact that the strong specificity of an AUDICOR  $S_3$  to predict ADHF persisted in the challenging diagnostic subgroups. Some have postulated that an  $S_3$  is present only in severe cases of ADHF where the clinical signs and symptoms of HF are already apparent. This was not the case in our study. Of the 43 missed diagnoses of ADHF in the ED, 15 (35%) had an  $S_3$  present. These cases were sufficiently subtle

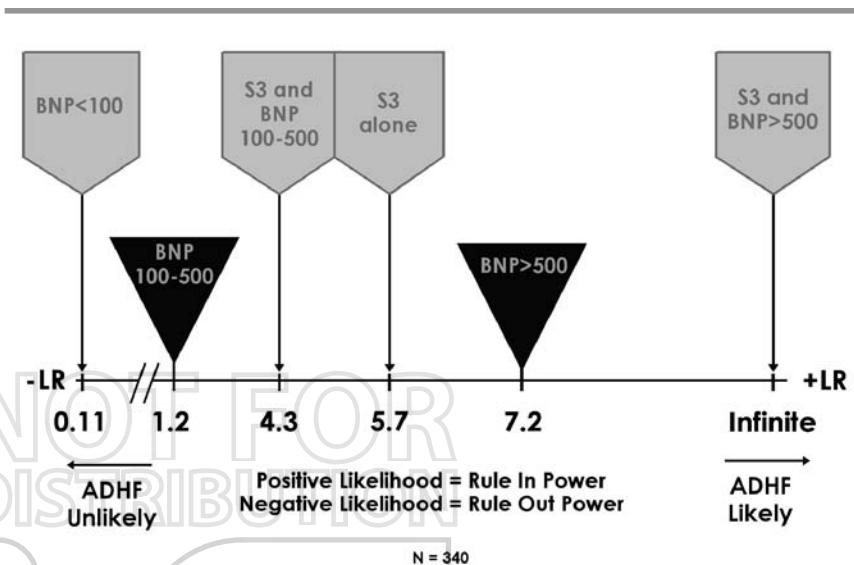


Figure. Positive likelihood ratio (LR) for primary acute decompensated heart failure (ADHF) generated by each and combined clinical variables. BNP=B-type natriuretic peptide (pg/mL)

or complicated such that the correct diagnosis of ADHF went unrecognized in the ED. In addition, an  $S_3$  proved highly specific and useful in diagnosing ADHF in subjects who had either no prior history of HF, had a history of COPD, had a prior EF >40%, or had no previous admissions for HF, and an indeterminate BNP of <500 pg/mL. It is also important to note the positive LR of an  $S_3$  alone (5.7) in detecting ADHF, because in real-time, an AUDICOR-detected  $S_3$  will likely become known 60 minutes before a BNP result can return, even under optimal circumstances. It has been demonstrated in large clinical trials that the average turn-around time for laboratory tests in the ED is 63 minutes for point-of-care platforms and 116 minutes for centrally processed laboratory tests.<sup>17</sup> This positive LR for an  $S_3$  alone could allow physicians an early and more accurate diagnosis of ADHF to allow for initiation of appropriate treatment. In doing so, the earlier diagnosis and initiation of appropriate treatment may provide the opportunity for better clinical outcomes and more cost-efficient care.<sup>12,13</sup>

Examining the fiscal impact of a misdiagnosis of ADHF in the ED suggests opportunities for improved

accuracy. Hospital charges for those incorrectly diagnosed as having non-primary HF (most often pneumonia or COPD), when they actually presented with ADHF, were significantly higher than those who were correctly diagnosed with ADHF; \$10,508 vs. \$7977, respectively. This difference of more than \$2500 represents a 32% increase in charges. The difference in cost becomes magnified when one considers that the national average reimbursement for the HF DRG is approximately \$5000, thus making the missed diagnosis a near doubling of the fiscal loss for the hospital.

In addition, the assessment of the final discharge DRG in the misdiagnosed HF patients revealed that 10 of 34 (29.4%) were incorrectly labeled and undercoded. The 10 miscoded subjects, who were later determined to have originally presented with ADHF, were coded for less severe diagnoses. Misdiagnoses included pneumonia, COPD, chest pain, and hypertension, which have national reimbursement rates of roughly \$4900, \$4100, \$2350, and \$2600, respectively. This creates a potential scenario where even greater fiscal losses accrue for a hospital since these misdiagnoses represent a functional down-coding of the HF population.

## Limitations

The limitations of this study are similar to those reported in our previous work.<sup>11,14</sup> This study enrolled an observational cohort of patients with signs or symptoms of HF. We are only able to report the test characteristics of heart sounds in patients that are representative of our sampling. There is a possibility that, due to selection bias, the true test characteristics of abnormal heart sounds in ED patients with primary HF are different than those we have reported.

Work-up bias could also be present; patients who were considered low-risk based on initial signs and symptoms may have had fewer subsequent tests.

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This lack of testing could have resulted in a missed diagnosis of primary HF. Furthermore, those patients who were considered too unstable to consent and be enrolled by the treating physician may have had different heart sound test characteristics. However, increased severity of illness, likely due to worse underlying HF, would have likely increased the yield of our test characteristics since previous work has demonstrated the high specificity for detecting elevated left ventricular end-diastolic pressure.<sup>16</sup>

## Conclusions

Our findings suggest that an S<sub>3</sub> is highly specific for ADHF. The high specificity

and positive LR of an S<sub>3</sub> may allow physicians to make an early and accurate diagnosis of ADHF so that appropriate therapy can be instituted in a timely manner. Furthermore, the use of the highly specific S<sub>3</sub> appears to be ideally suited for use in combination with BNP to improve diagnostic accuracy in ED patients with undifferentiated dyspnea. In this analysis, the S<sub>3</sub> proved highly specific for diagnosing ADHF even in challenging subsets of patients. There is a demonstrable clinical benefit for increased accuracy in early diagnosis of ADHF, and it appears that there is also a significant fiscal penalty for inaccurate initial diagnosis that misses ADHF when it is present.

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## CASE REPORT

# Optimization of Atrioventricular and Interventricular Delay With Acoustic Cardiography in Biventricular Pacing

**C**ardiac resynchronization therapy (CRT) improves hemodynamic and echocardiographic parameters, symptoms, quality of life, morbidity, and mortality in patients with medically refractory congestive heart failure associated with a prolonged QRS duration.<sup>1–5</sup> To fully exhaust the benefits of CRT, it is important to optimize atrioventricular (AV) and interventricular (VV) conduction delays to achieve optimal mechanical synchronization of the heart chambers.<sup>6</sup> This has mainly been done using parameters obtained by Doppler echocardiography, but also by measuring left ventricular (LV) dP/dt<sub>max</sub>.<sup>7–11</sup> However, an experienced echocardiographer and a stable patient are needed to get reproducible results. These examinations are time-consuming, and no standard parameter for optimization is yet available. For these and cost reasons, even today, only a minority of CRT devices are optimized after implantation. Acoustic cardiography (AUDICOR, Inovise Medical Inc., Portland, OR) has been developed to measure time intervals very precisely and with reproducible results. Due to the fact that the strength of the S<sub>1</sub> and the electromechanical activation time (EMAT) correlate well with LV function, we used acoustic cardiography for optimizing the VV and AV delays in a patient with a biventricular pacemaker.<sup>12,13</sup> Five weeks after this optimization, we also investigated the

effects on the Doppler echocardiographic parameters, B-type natriuretic protein (BNP) value, and the functional capacity of this patient.

## Case Report

A 67-year-old man presented with New York Heart Association (NYHA) class II dyspnea and a markedly reduced ejection fraction (EF) of 28% following a prior aortic valve replacement in 2001, at which time his EF was normal. The electrocardiogram showed a left bundle branch block morphology and a QRS duration of 180 milliseconds. Doppler echocardiography revealed a VV contraction delay of 40 milliseconds, measured as the difference between the onset of the pulmonary ejection wave and the aortic ejection wave, and an intraventricular septal-posterolateral delay of 200 milliseconds measured with displacement imaging and autotracking (Aplio, Toshiba Medical Systems, New York, NY). There was eccentric LV hypertrophy with an end-diastolic diameter of 67 mm (normal <60 mm) and an LV mass index of 212 g/m<sup>2</sup> (normal <134 g/m<sup>2</sup>). The patient had known arterial hypertension, which was medically well controlled. No malignant arrhythmias were induced during electrophysiology studies, and a biventricular pacemaker device (Stratos LV, BIOTRONIK, Inc., Berlin, Germany) was implanted. The coronary sinus was cannulated using an electrophysi-

ology catheter, and the optimal posterolateral vein could be identified and cannulated. Postimplantation, medical therapy consisted of an angiotensin-converting enzyme inhibitor, a β blocker, spironolactone, loop diuretics, digoxin, and amiodarone. The patient was orally anticoagulated due to reduced LV function. Medical therapy was not changed during the observation period. There were no clinical signs of congestive heart failure postimplantation.

The patient was enrolled in our CRT optimization program 5 weeks after the implantation. The AV delay was set at 120 milliseconds, and simultaneous ventricular pacing was programmed to a baseline VV setting. Rate-dependent shortening of the AV interval was turned off because the benefit of this feature has been questioned recently in biventricular pacemakers.<sup>14</sup> During optimization and the follow-up period, the patient was in sinus rhythm. Sitting blood pressure was 93/70 mm Hg. Cardiac examination showed no clinical signs of congestive heart failure. After the baseline programming, the patient was sent home for 6 weeks. Eleven weeks postimplantation, the patient's CRT device was optimized using acoustic cardiography (AUDICOR technology). The acoustic cardiography data were obtained using AUDICOR sensors attached to the V<sub>3</sub> and V<sub>4</sub> positions. For each CRT AV and VV

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**Table.** Doppler Echocardiography Data and End Points With Intrinsic Conduction, Standard, and Optimized Programming\*

PROGRAMMING	INTRINSIC	AV 120 ms, VV 0 ms	AV 160 ms, VV -40 ms
Sitting blood pressure (mm Hg)	—	93/70	109/55
Functional NYHA class	—	II	II
QRS duration (ms)	186	186	187
Heart rate during echocardiography (bpm)	62	70	70
dP/dt of mitral regurgitation continuous wave Doppler spectrum (mm Hg/sec)	744	800	865
VTI LVOT (cm)	11.1	14.3	12.5
E <sub>max</sub> (cm/sec)	71	66	37
A <sub>max</sub> (cm/sec)	65	58	64
E/A	1.08	1.13	0.58
A duration (ms)	131	100	127
E deceleration time (ms)	304	193	427
VV delay (ms)	141	85	28
Ejection fraction (three-dimensional, %)	27	32	45
End-diastolic volume (mL)	106	112	132
End-systolic volume (mL)	78	77	73
Tmsv 6 (ms)	335	143	35
Tmsv 12 (ms)	335	474	35
Exercise capacity (W)	—	103	115
Maximum oxygen uptake (mL/min/kg)	—	22.4	26.9
B-type natriuretic protein (ng/L)	—	99	69

AV=atrioventricular; VV=interventricular; NYHA=New York Heart Association; VTI=velocity time integral; LVOT=left ventricular outflow tract; Tmsv 6/12=time to minimal systolic volume of basal (6) and basal/midventricular segments (12) in three-dimensional echocardiography volume. \*Both biventricular stimulation settings were programmed 6 weeks before measuring all data, whereas for intrinsic values, the pacemaker was set to VVI with a base rate of 30 bpm just before examination.

delay combination, a full AUDICOR test (10-second data recording) was recorded and analyzed, and the results were trended for interpretation. The recorded data included the presence and strength of the S<sub>1</sub>, the EMAT (the interval from the onset of the Q wave of the electrocardiogram to the S<sub>1</sub>), and the LV systolic time (the interval from S<sub>1</sub> to S<sub>2</sub>). Forty-five different settings were programmed for evaluation using the AUDICOR data (with possible combinations of 100, 125, 150, 175, 200, 225, 250, 275, and 300 milliseconds for AV delays and RV40, RV20, 0, LV20, and LV40 milliseconds for VV delays). Then, Doppler echocardiographic and AUDICOR data were collected for the baseline programming and intrinsic conduction without pacing. The Doppler echocardiographic parameters are summarized in the Table.

The septal-posterolateral intraventricular delay was measured with new displacement imaging software with

autotracking. Displacement curves are used by integrating myocardial Doppler velocities of the medial and lateral mitral annulus, thus forming an apical four-chamber view (Aprio). A full-volume acquisition of the left ventricle (transthoracic three-dimensional echocardiography) was analyzed offline to create global and segmental time-volume curves. A systolic dyssynchrony index was created based on the dispersion of times to minimum volume for each segment (iE 33 system, Philips Medical Systems, Andover, MA). BNP was measured after a resting period of at least 1 hour and, thereafter, symptom-limited spiroergometry was performed. The patient was discharged with the optimized AV and VV delays for another 6 weeks using the lowest EMAT as a surrogate for optimal contractility and timing (right ventricular stimulation 40 milliseconds before LV stimulation and an AV delay of 250 milliseconds). Because the

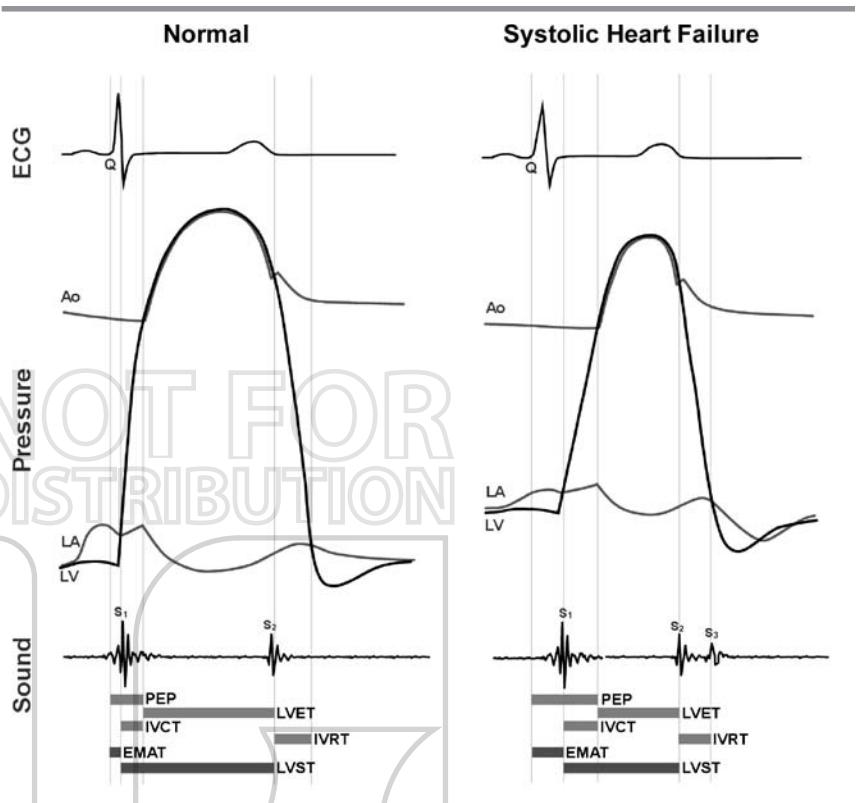
best parameter combination could not be programmed permanently in the Stratos LV, optimization was performed by programming a VV delay of -40 milliseconds and the highest possible AV delay of 160 milliseconds. Seventeen weeks postimplantation, AUDICOR and echocardiographic data were taken again, BNP was measured, and symptom-limited spiroergometry was carried out.

Doppler echocardiographic data and results from the other examinations with intrinsic, standard, and optimized programming are shown in the Table. Maximum exercise capacity was 103 W with standard programming and 115 W with optimized programming. Oxygen uptake rose from 22.4 mL/min/kg to 26.9 mL/min/kg. Three-dimensional EF increased from 32% to 45%, and better synchronization was obvious just by looking at the apical four-chamber view. In addition, the BNP value decreased from 99 ng/L to 69 ng/L.

## Discussion

Encouraging studies comparing AUDICOR data with invasive measurements obtained during LV catheterization indicate that EMAT correlates with  $dP/dt_{max}$  in subjects with signs of dyssynchrony (i.e., wide QRS complexes) and LV systolic time correlates with EF.<sup>15</sup> Thus, EMAT was used as a primary parameter to determine the best AV/VV delay combination (Figure). The hypothesis that minimizing EMAT might be beneficial is supported by the work of Jansen and colleagues,<sup>16</sup> which showed that the time to onset of systolic velocity measured with tissue Doppler imaging might be a better parameter to predict reverse remodeling than the time to peak velocity. In this case, we were able to achieve a better hemodynamic state through optimized programming, and exercise capacity, maximum oxygen uptake, and ejection fraction were improved by achieving better synchronization. Also, the BNP level decreased, indicating lower filling pressure after optimized delays, although the patients remained in NYHA class II before pacemaker implantation and throughout the entire observation period. The relatively low BNP value (<100 ng/L) before delay optimization documents the optimal medical therapy in these patients.<sup>17</sup> Therefore, this case report also underlines that clinical judgment alone is not sufficient for evaluating the effects of synchronization therapy.

In comparison with Doppler echocardiography, optimization of biventricular pacing seems to be achievable through



**Figure.** Schematic of acoustic cardiography and left ventricular pressure tracings for a normal patient and a heart failure patient showing a phonocardiographic  $S_3$ , an increased electromechanical activation time (EMAT) ( $Q-S_1$ ), reduced left ventricular systolic time (LVST) ( $S_1-S_2$ ), and a higher left ventricular diastolic pressure. ECG = electrocardiogram; Ao = aorta; LA = left atrium; LV = left ventricle; PEP = pre-ejection period; LVET = left ventricular ejection time; IVCT = isovolumic contraction time; IVRT = isovolumic relaxation time

the fast and easy use of acoustic cardiography (AUDICOR device), yielding results that are easy to interpret, and importantly, independent of the person operating the device. This case report indicates the potential of this new acoustic cardiography approach to optimizing biventricular pacemakers for heart failure therapy. However, there might be a remodeling process following not just

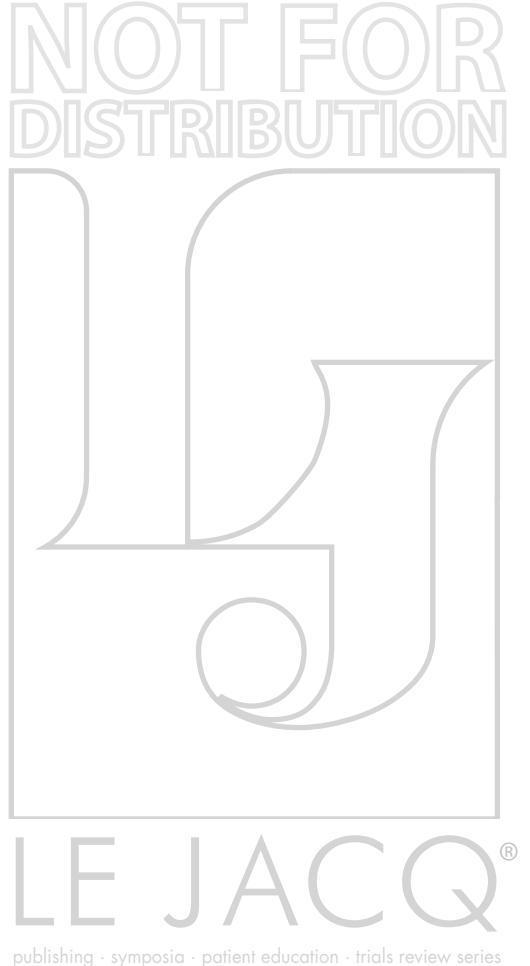
CRT implantation, but also changes to the AV and VV interval programming. We therefore suggest waiting several weeks before carrying out exercise tests after optimizing AV and VV delays.

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## CASE REPORT

## Acoustic Cardiography in the Differential Diagnosis of Dyspnea

The prevalence of heart failure (HF) is increasing as the US population ages and large numbers of patients with acute HF present to the emergency department (ED) each year.<sup>1,2</sup> Despite the array of diagnostic tests available to physicians, as many as 18% of ED patients with acute HF are misdiagnosed.<sup>3,4</sup> When HF coexists with diseases such as chronic obstructive pulmonary disease (COPD) or pneumonia, its diagnosis is missed in the prehospital environment in as many as 46% of patients.<sup>5</sup> The prompt and accurate detection of HF is important because the early provision of appropriate treatment significantly reduces mortality and the duration and cost of hospitalization.<sup>6,7</sup>

B-type natriuretic peptide (BNP) is often used to evaluate patients with possible HF, but its lack of specificity in commonly encountered ranges of values has limited its diagnostic usefulness.<sup>8</sup> To improve the diagnosis of acute and chronic HF, Inovise Medical, Inc. (Portland, OR) has developed the AUDICOR test. This is a system that records, stores, displays, and algorithmically interprets simultaneous digital electrocardiography (ECG) and sound. The device records both the cardiographic and acoustic data and the S<sub>3</sub> with the assistance of proprietary dual-purpose sensors placed in the V<sub>3</sub> and V<sub>4</sub> positions. Previous work has shown that data from acoustic cardiograms are highly specific for the hemodynamic abnormalities known to be associated with HF.<sup>9</sup>

This case study illustrates how data from an acoustic cardiogram can improve the ability to detect HF in the presence of multiple possible causes of dyspnea.

## Case Description

A 75-year-old obese African-American woman with a remote and recent history of cigarette smoking, chronic atrial fibrillation, coronary artery disease including previous coronary bypass surgery, type 2 diabetes mellitus, and systemic and pulmonary hypertension presented to the ED of the Cleveland Clinic Foundation with increasing dyspnea and chest tightness. At the time of her presentation, the patient had been hospitalized at a subacute nursing care facility for management of an exacerbation of COPD. During this hospitalization, she was noted to have developed hemoptysis and increasing requirements for supplemental oxygen. Consequently, she was transported to the ED for further evaluation and possible readmission to a general medicine service. Her medications included albuterol, atenolol, glyburide, and prednisone.

Physical examination at the time of her evaluation revealed that she was afebrile, but tachycardic and tachypneic (heart rate, 101 bpm; respiratory rate, 30 BPM; blood pressure, 130/79 mm Hg). She was in moderate respiratory distress and was using her accessory muscles of respiration. Examination of her lungs showed

diffuse wheezes and right-sided basilar rales. Cardiac examination revealed a rapid, irregular heart rate and a 2/6 systolic murmur but no S<sub>3</sub> or S<sub>4</sub> by auscultation. The abdominal examination was unremarkable and the extremities showed bilateral 2+ pitting edema.

Laboratory evaluation was remarkable for a white blood cell count of 24.8 and hemoglobin of 6.6. Arterial blood gases on a 40% Venturi mask revealed a PO<sub>2</sub> of 68, an O<sub>2</sub> saturation of 92%, and a PCO<sub>2</sub> of 59. The BNP was 200 pg/mL. The chest x-ray showed moderate cardiomegaly, a particularly dense infiltrate in the right upper lobe, and a more diffuse infiltrative pattern possibly compatible with generalized pulmonary edema. The 12-lead ECG indicated atrial fibrillation, possible prior anteroapical myocardial infarction, an indeterminate QRS axis, borderline low voltage, persistent precordial S waves, and nonspecific ST-T abnormalities. An acoustic cardiogram was obtained using the AUDICOR device, which revealed an S<sub>3</sub>.

The patient was admitted to the medical service and treated with broad-spectrum antibiotics, multiple transfusions, repeat doses of furosemide, corticosteroids, and bronchodilators. Despite the use of bilevel positive airway pressure and high-flow oxygen, she continued to retain CO<sub>2</sub> and her oxygenation worsened. Despite these therapeutic efforts, the patient died in the hospital and her family declined a request to perform an autopsy.

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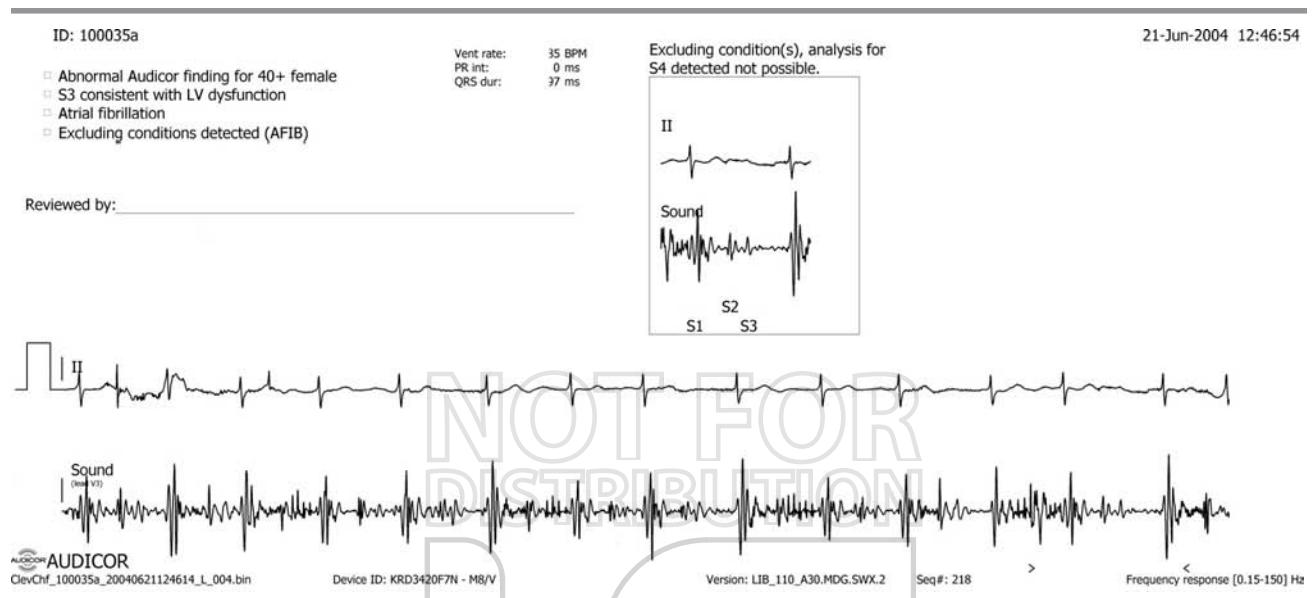


Figure. AUDICOR report showing an  $S_3$

## Discussion

This patient had several possible coexisting causes of her worsening dyspnea, none of which were mutually exclusive. First, she had a known history of cigarette smoking and previously diagnosed COPD. The use of her accessory muscles of respiration and the presence of peripheral edema (possibly due to cor pulmonale) and hypercapnia also support this diagnosis.

Second, pulmonary hemorrhage, possibly secondary to carcinoma of the lung, may have contributed to the patient's dyspnea. Her history of smoking and the dense infiltrate in the upper lobe of her right lung support the diagnosis of lung cancer. Related to a hemorrhage, severe anemia may also have contributed to her shortness of breath.

Although she was afebrile, the patient's very high white blood cell count, together with pulmonary infiltrates, suggests that pneumonia may also have been present. Alternatively, the combination of leukocytosis and severe anemia raises the possibility of a blood dyscrasia such as leukemia.

HF is another prominent possibility as a cause of dyspnea. Her pedal edema suggests that diagnosis, but may have been due to cor pulmonale from COPD rather than biventricular failure. The radiographic findings of cardiomegaly and diffuse bilateral pulmonary infiltrates are compatible with HF, but the infiltrates may have been caused by pneumonia or pulmonary hemorrhage. Although her BNP was abnormal, it was only mildly elevated, which may have been caused by acute ischemia as suggested by her history of coronary disease and her complaint of chest tightness. Also, obesity (weight, 180 lb) may have artificially lowered her BNP. The patient had several underlying diseases that could have caused HF. Besides having coronary artery disease and a history of systemic hypertension, she had a systolic murmur (possible papillary muscle dysfunction) and atrial fibrillation. The combination of hypoxemia and severe anemia may have also worsened her myocardial ischemia, leading to a further decrease in left

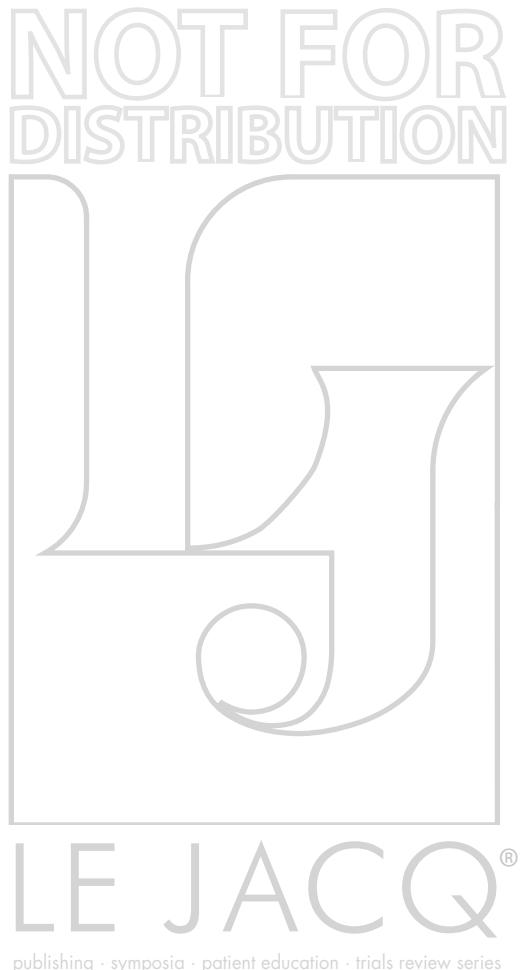
ventricular function. HF could have been further exacerbated by atenolol and by the multiple transfusions the patient had received. Although an  $S_3$  was not detected by auscultation, the AUDICOR test revealed that an  $S_3$  was present (Figure). An  $S_3$  has been shown to be highly specific for HF in the appropriate clinical context.<sup>10</sup>

Although this patient had a number of possible causes of dyspnea, the presence of an electronically detected  $S_3$  makes the presence of HF very likely. For example, previous studies have shown that the electronically detected  $S_3$  in the presence of even slightly elevated BNP greatly increases the likelihood that HF is present (positive likelihood ratio 1.2 for BNP in the 100–500 pg/mL range, 4.3 positive likelihood ratio for  $S_3$ , and a BNP in the 100–500 pg/mL range).<sup>11,12</sup> The identification of HF in a patient with multiple severe illnesses is especially important, since the appropriate treatment of HF reduces patients' overall clinical burden.

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# CME Questions

**Todd C. Kerwin, MD, CME Editor**

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**INSTRUCTIONS FOR COMPLETING THIS FORM:** Read the papers and answer *all* the true/false questions that follow. Please place your selection on the answer grid. **YOU MUST ALSO COMPLETE THE CME EVALUATION SECTION** and return the form within 6 months of the papers' publication to receive credit. Letters of credit will be mailed to participants biannually.

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**EDITOR DISCLOSURES:** Dr. Kerwin is on the Speaker's Bureau for Aventis and Takeda Pharmaceuticals.

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**OBJECTIVE AND TARGET AUDIENCE:** All health care practitioners are eligible to receive credit. At the conclusion of this activity, participants should be able to: 1) summarize the important points discussed in the paper reviewed; 2) identify patients to whom the paper is relevant; 3) modify management practices as new information is learned; and 4) identify deficiencies in their knowledge base.

## Peacock, Harrison, and Maisel (pages 2–7)

1. In the appropriate clinical setting, the detection of an  $S_3$  is highly specific for abnormal cardiac function.
2. The majority of cardiac resynchronization therapy (CRT) devices implanted in clinical practice are optimized.

## Shah and Michaels (pages 8–13)

3. The  $S_3$  occurs early in systole.
4. Abnormal systolic time intervals correlate with other markers of left ventricular (LV) dysfunction.

## Zuber, Kipfer, and Jost (pages 14–18)

5. The presence of an  $S_3$  is specific, but not highly sensitive for LV systolic dysfunction.
6. The presence of impaired relaxation in patients with LV systolic dysfunction reduces the prevalence of an  $S_3$ .

## Roos, Toggweiler, Zuber, et al. (pages 19–24)

7. The data in this study do not support a correlation between acoustic cardiography and invasive hemodynamic data.
8. Heart rate appears to have no effect on the ability to detect an  $S_3$  in patients with LV dysfunction.

## Hasan, Abraham, Quinn-Tate, et al. (pages 25–31)

9. The current standard for optimizing atrioventricular (AV) delay is analysis of the Doppler transmural flow pattern by echocardiography.
10. The study showed poor correlation between echocardiography and acoustic cardiography in optimizing the AV delay.

## Peacock, Harrison, and Moffa (pages 32–36)

11. The use of acoustic cardiography to assess for the presence of an  $S_3$  did not appear to aid in the diagnosis of acute decompensated heart failure when combined with a clinical evaluation and B-type natriuretic peptide (BNP) levels.
12. The accurate diagnosis of emergency department patients with dyspnea appears to result in cost savings.

## Toggweiler, Zuber, and Erne (pages 37–40)

13. The echocardiographic parameters for interventricular (VV) optimization of CRT devices are well established and standardized.
14. Electromechanical activation time obtained by acoustic cardiography may be useful in determining the best AV/VV settings.

## Peacock (pages 41–43)

15. The misdiagnosis of emergency department patients with dyspnea rarely occurs.
16. BNP levels are both highly sensitive and specific when used to diagnose the etiology of dyspnea.



CME Answers are available on the Congestive Heart Failure page at [www.lejacq.com](http://www.lejacq.com)

## CME Answer Grid

- |  |  |   |   |
|--|--|---|---|
| 1. <input type="radio"/> T <input type="radio"/> F | 5. <input type="radio"/> T <input type="radio"/> F | 9. <input type="radio"/> T <input type="radio"/> F  | 13. <input type="radio"/> T <input type="radio"/> F |
| 2. <input type="radio"/> T <input type="radio"/> F | 6. <input type="radio"/> T <input type="radio"/> F | 10. <input type="radio"/> T <input type="radio"/> F | 14. <input type="radio"/> T <input type="radio"/> F |
| 3. <input type="radio"/> T <input type="radio"/> F | 7. <input type="radio"/> T <input type="radio"/> F | 11. <input type="radio"/> T <input type="radio"/> F | 15. <input type="radio"/> T <input type="radio"/> F |
| 4. <input type="radio"/> T <input type="radio"/> F | 8. <input type="radio"/> T <input type="radio"/> F | 12. <input type="radio"/> T <input type="radio"/> F | 16. <input type="radio"/> T <input type="radio"/> F |

## CME Evaluation

- |  | Agree                    |                          | Disagree                 |                          |                          |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. My knowledge was enhanced by this activity.   | 1. <input type="radio"/> | 2. <input type="radio"/> | 3. <input type="radio"/> | 4. <input type="radio"/> | 5. <input type="radio"/> |
| 2. The activity helped to clarify issues specific to heart failure patients.               | 1. <input type="radio"/> | 2. <input type="radio"/> | 3. <input type="radio"/> | 4. <input type="radio"/> | 5. <input type="radio"/> |
| 3. The information obtained from this exercise will have an impact on my care of patients. | 1. <input type="radio"/> | 2. <input type="radio"/> | 3. <input type="radio"/> | 4. <input type="radio"/> | 5. <input type="radio"/> |
| 4. The format of the exercise was useful.  | 1. <input type="radio"/> | 2. <input type="radio"/> | 3. <input type="radio"/> | 4. <input type="radio"/> | 5. <input type="radio"/> |
| 5. Suggestions for future topics:  |                          |                          |                          |                          |                          |

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