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Acoustic Cardiography and Heart Failure: Advancing Diagnosis and Treatment

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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_3 for detecting acute decompensated heart failure. Acoustic cardiography offers a cost-efficient, easy-to-use method to optimize the devices used in cardiac resyncronization 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 resyncronization therapy device optimization. (CHF. 2006;12(4 suppl 1):2–7) ©2006 Le Jacq

Heart 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.[1]

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.[2]

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.[3–5] The addition of devices such as implantable cardioverter-defibrillators and pacemakers have also proven beneficial.[6] Some HF

W. Frank Peacock, MD;[1] Alex Harrison, MD;[2] Alan S. Maisel, MD[3]
From the Department of Emergency Medicine, Cleveland Clinic, Cleveland, OH;[1] the Division of Cardiology, Department of Medicine, University of California, Irvine Medical Center, Orange, CA;[2] and the Department of Medicine, Veterans Affairs San Diego Healthcare System and University of California, San Diego, San Diego, CA[3]
Address for correspondence: Alex Harrison, MD, Division of Cardiology, Department of Medicine, University of California, Irvine, 101 The City Drive, Building 53, Route 81, Room 100, Orange, CA 92868-4080
E-mail: alexharrisonmd@hotmail.com

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 ≤35%), and intraventricular conduction delay (e.g., QRS >120 milliseconds).[7–11] 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[12]; 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.[13] 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.[7–11] 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[14] first described abnormal diastolic cardiac sounds in the literature in 1880. With relatively

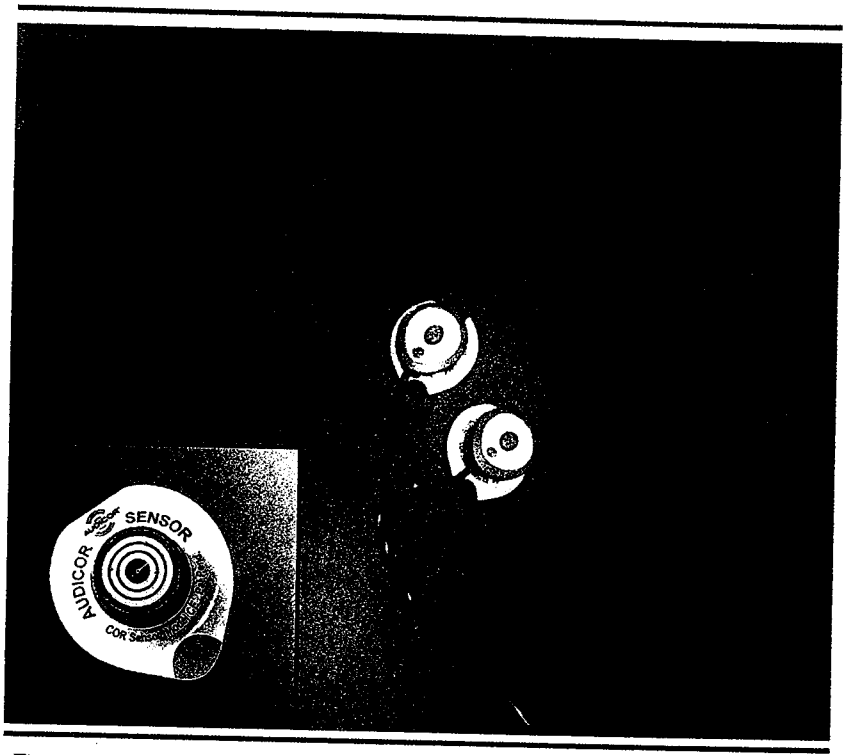

Figure 1. Placement of the AUDICOR sensors (Inovise Medical, Inc., Portland, OR)

normal heart rates, S_3, also known as a ventricular gallop, occurs 0.12–0.16 sec after the S_2 in early diastole.[15] 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.[16] 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.[17]

The auscultated S_3 and S_4 have long been used as clinical signs of heart disease with both diagnostic and prognostic importance.[18–23] However, the value of these physical findings has been diminished by reports of poor accuracy and a large degree of interobserver variability.[24,25] 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.[26] 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,[27–30] and results of phonocardiography have been used to determine the accuracy of physician auscultation.[25] 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.[31,32] 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

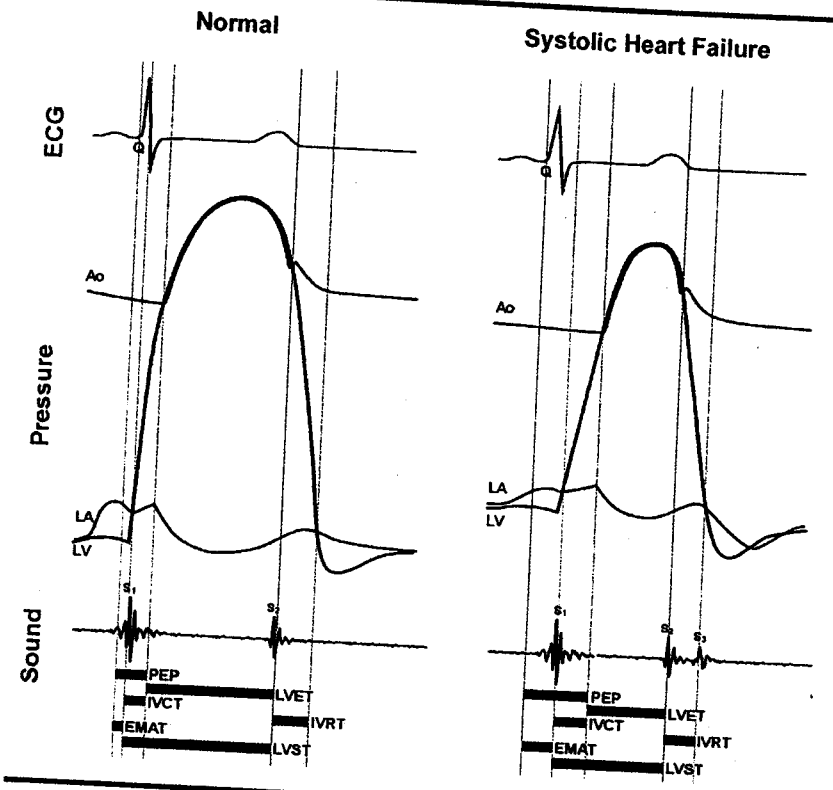

Figure 2. Heart sounds and systolic time interval data provided by the AUDICOR device (Inovise Medical, Inc., Portland, OR). (Pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR data.) ECG=electrocardiogram; Ao=aorta; LA=left atrium; LV=left ventricle; PEP=pre-ejection 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.[33]

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).[34,35] 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,[35] 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 electromechanical activation time correlates with measures of cardiac contractility (dP/dt).[35,36] 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.[37] 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.[2] 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.[22] Studies have demonstrated

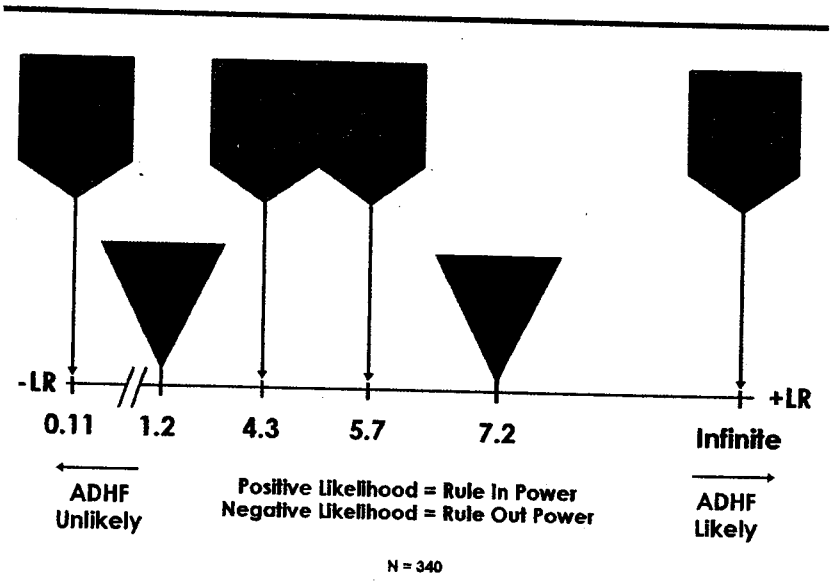

Figure 3. Synergy between acoustic cardiography–detected S_3 and B-type natriuretic peptide (BNP) (pg/mL). ADHF=acute decompensated heart failure; LR=likelihood ratio

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.[38,39] 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;[2] however, the nondiagnostic 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.[39]

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.[39]

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[40,41] 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_3 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.[42] 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_3 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_3 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.[13] 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.[7–11]

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.[43] 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).[12] 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_1, indicating ventricular systole and closure of the mitral valve. In doing so, the LV systolic time—the interval from S_1 to S_2—can be maximized, which has been shown to correlate well with maximizing ejection fraction.[33] In addition, the strength of the S_3, 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[43] 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.[1,2] 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.[3,4] 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.[5] 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.[5,6] Later, through the work of Aubrey Leatham[7] 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[8,9] in the 1960s (with the correlation of abnormal systolic time intervals [STIs] with left ventricular [LV] dysfunction), auscultative and phonocardiographic bedside diagnosis came into its golden age.[7–11] 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.[12,13] 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,

Sanjiv J. Shah, MD;[1] Andrew D. Michaels, MD, MAS[2]
From the Division of Cardiology, Department of Medicine, University of California, San Francisco, San Francisco, CA;[1] and the Division of Cardiology, Department of Medicine, University of Utah, Salt Lake City, UT[2]
Address for correspondence: Andrew D. Michaels, MD, MAS, Division of Cardiology, Department of Medicine, University of Utah, 30 North 1900 East, Room 4A100, Salt Lake City, UT 84132-2401
E-mail: andrew.michaels@hsc.utah.edu

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_1 interval); LVST=left ventricular systolic time (S_1-S_2 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_3 and V_4 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_3) and the duration of STIs.

The S_3 is a low-pitched sound that occurs in early diastole, approximately 120–160 milliseconds after the S_2, during rapid LV filling.[14] The AUDICOR system determines the presence of the S_3, and, based on the intensity and persistence of the sound, provides a value of S_3 strength with a range of 1–10. If this value equals or exceeds 5.0, the algorithm declares that an S_3 is present.

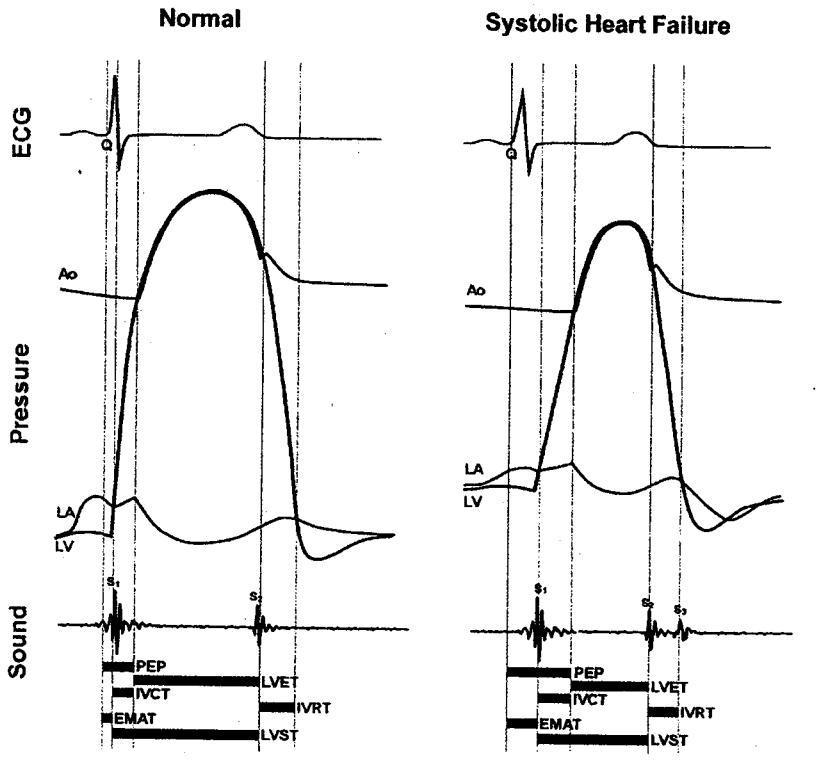

Figure 1. Illustration of systolic time intervals in relation to the cardiac cycle depicted via electrocardiographic (ECG) and pressure waveforms (pressure waveforms are displayed here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data.). Traditional 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_1 interval) and the isovolumic contraction time (IVCT). The AUDICOR system measures the EMAT and left ventricular systolic time (LVST; S_1-S_2 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_1 interval), isovolumic contraction time (IVCT), pre-ejection period (PEP), LV ejection time (LVET), and electromechanical systole (Q-S_2 interval). The PEP is comprised of

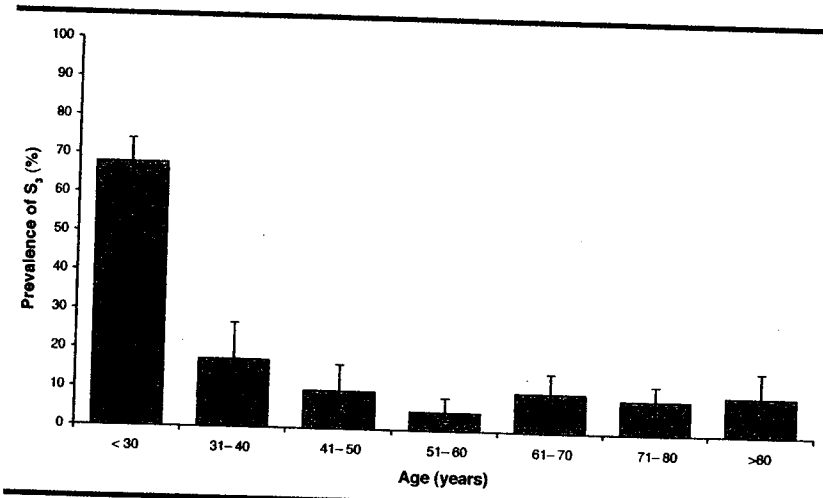

Figure 2. Prevalence of the S_3 by age in asymptomatic individuals. Prevalence of the S_3 decreases markedly in subjects older than 30 years. Adapted with permission from *Congest Heart Fail.* 2005;11:242–247.[16]

the EMAT and the IVCT, and the Q-S_2 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.[15] It is the PEP/LVET ratio that has been most used to diagnose LV dysfunction.[10,15]

Of note, the STIs measured by the AUDICOR system are different from those conventionally measured. The AUDICOR system measures the Q-S_1, Q-S_2, and S_1-S_2 (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.[16] determined the prevalence of the S_3 (Figure 2). Using these same recordings, 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_3 by decade of age. There is a high prevalence of physiologic S_3 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_3 has diagnostic and prognostic value in a variety of conditions, including LV dysfunction,[17–21] valvular heart disease,[22,23] acute myocardial infarction,[24] and in the perioperative period.[25] Phonocardiography has traditionally been the gold standard for detection of the S_3, 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 cardiohemic system, resulting in the S_3.[24,26–28] 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_3 becomes audible.[26] These hemodynamic conditions increase the deceleration rate of early mitral inflow, a finding that has been associated with the S_3.[29–31]

Using the AUDICOR system, we sought to better understand the test characteristics and physiology of the phonocardiographic S_3 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_3. The sensitivities of the S_3 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_3 detected by the AUDICOR system is highly specific in detecting LV dysfunction.[32]

In the same cohort of 90 patients, we hypothesized that tissue Doppler imaging would provide insight into the physiology of the pathologic S_3. 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.[33,34] 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_3.

In this study, we found that subjects with an S_3 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_3 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_3 (p=0.009).[35] In addition, E/E′ was independently associated with S_3 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_3 and E/E′. Based on these findings, the pathologic S_3 seems to be due to abrupt deceleration of high-pressure mitral inflow acting in concert with decreased velocity of the mitral annulus.

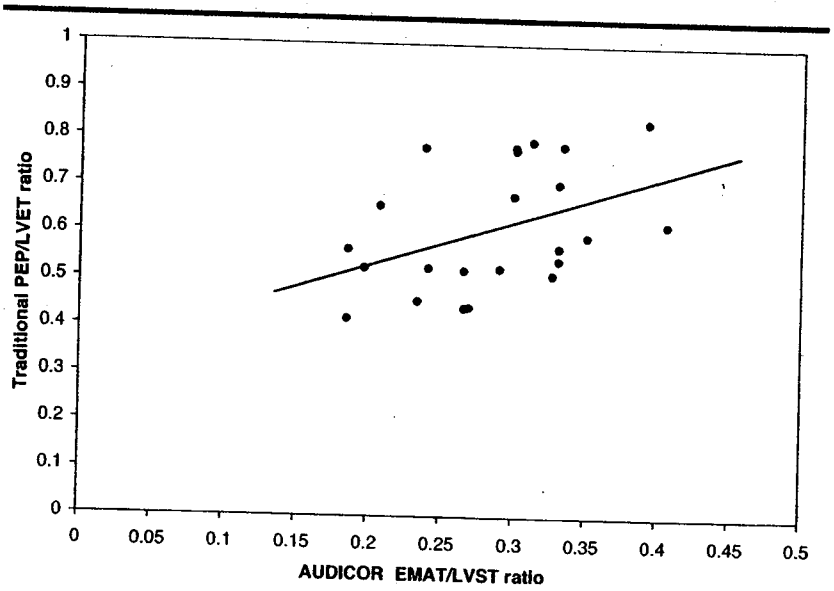

Figure 3. Scatterplot of traditional systolic time intervals (STIs) (pre-ejection period [PEP]/left ventricular ejection time [LVET]) and AUDICOR (Inovise Medical, Inc., Portland, OR) STIs (electromechanical activation time [EMAT]/left ventricular systolic time [LVST]). The AUDICOR and traditional STI 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,[8] using Q-S_1 and Q-S_2 measurements to derive the EMAT/LVST ratio.

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[8,9] 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.[15] 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.[8–10,36,37] 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.[36–42] More recent studies have shown an association between N-terminal pro-BNP and abnormal STIs.[43]

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,[8] 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_2 (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_3 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_3 and STIs) was superior to S_3, 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.[44] 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_3 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.[45] 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,[46–48] optimization of CRT is an area of active investigation, because refining patient selection, increasing response rates, and controlling costs are of prime importance.[49] Baker and colleagues[50] 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_3 and abnormal STIs. This technology has provided insight into the physiology of the S_3 and the correlation of S_3 and STIs with abnormal cardiac hemodynamics. Since the S_3 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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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 ≥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.
(CHF. 2006;12[4 suppl 1]:14–18) ©2006 Le Jacq

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.[1] 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.[2] 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_3 and V_4 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.[3] 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

Michel Zuber, MD;[1] Peter Kipfer, MD;[2] Christine Attenhofer Jost, MD[3]
From the Cardiology Outpatient Clinic, Othmarsingen, Switzerland;[1] the Cardiology Outpatient Clinic, Frauenfeld, Switzerland;[2] and Cardiovascular Center Zürich, Klinik im Park, Zürich, Switzerland[3]
Address for correspondence: Michel Zuber, MD, Bahnhofstrasse 8, 5504 Othmarsingen, Switzerland
E-mail: michel.zuber@bluewin.ch

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.[4]

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_3 and for various systolic parameters. The system evaluates the possible presence of an S_3 by measuring the intensity and persistence of the energy of sounds that have the appropriate frequency and timing for an S_3. It expresses the resultant value in the range of 1–10 and declares S_3 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_1. 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_1 to the aortic component of the S_2. 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.

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_3 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_3

	S_3 Absent (N=129)	S_3 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 $p<0.05$

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%

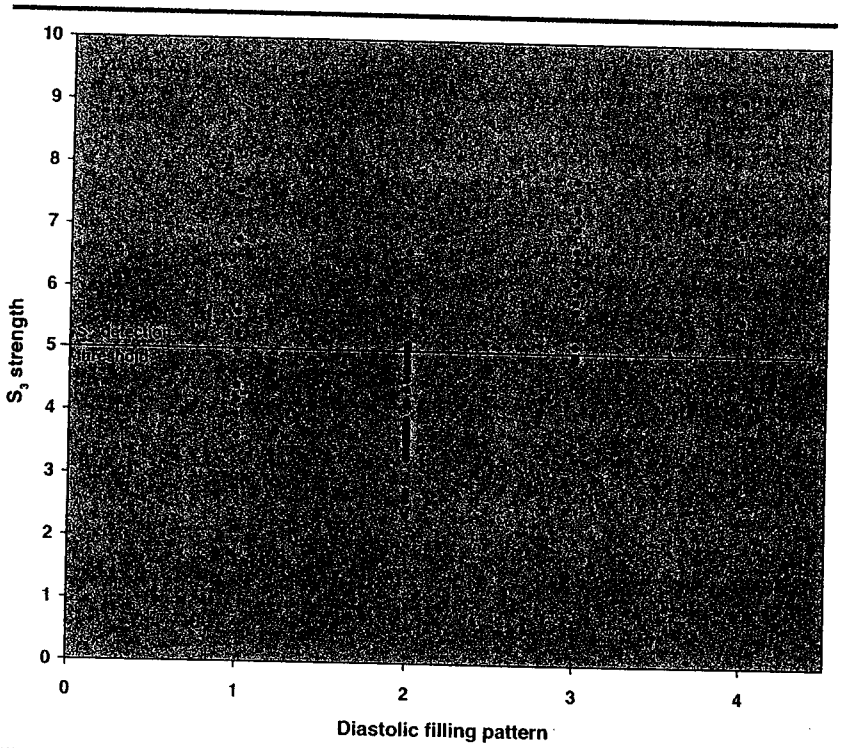

Figure 1. S_3 strength vs. diastolic filling pattern in patients with left ventricular ejection fraction <50%. 1=normal filling; 2=delayed relaxation; 3=pseudonormal pattern; 4=restrictive pattern

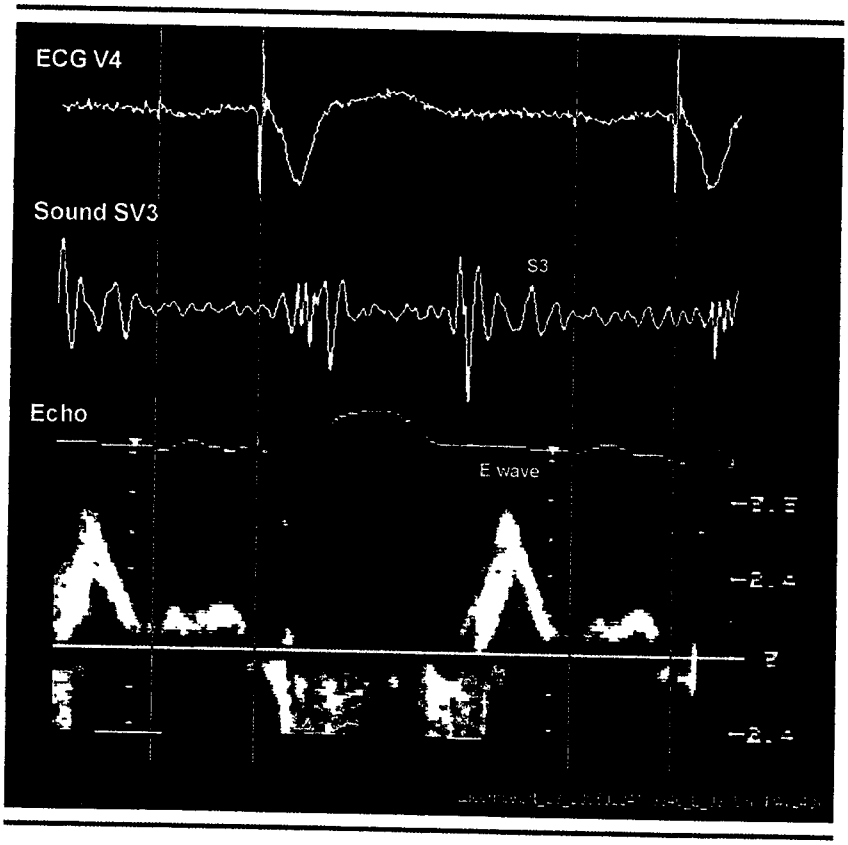

Figure 2. Temporal relationship between the S_3 and a prominent E wave

(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_3, 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_3 was absent vs. those in which it was present. It shows that the patients with an S_3 have a lower mean LVEF and higher LV diastolic dimensions. Regarding parameters of LV filling, the patients with an S_3 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_3. Especially noteworthy is the finding that the prevalence of the S_3 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_3 strength to exceed the detection threshold. Conversely, of all the patients with pseudonormal or restrictive filling

Table III. Comparisons of Findings Among the Four Diastolic Filling Patterns in Patients With Left Ventricular (LV) Ejection Fraction <50%

	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_3 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_3. 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_3 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%.

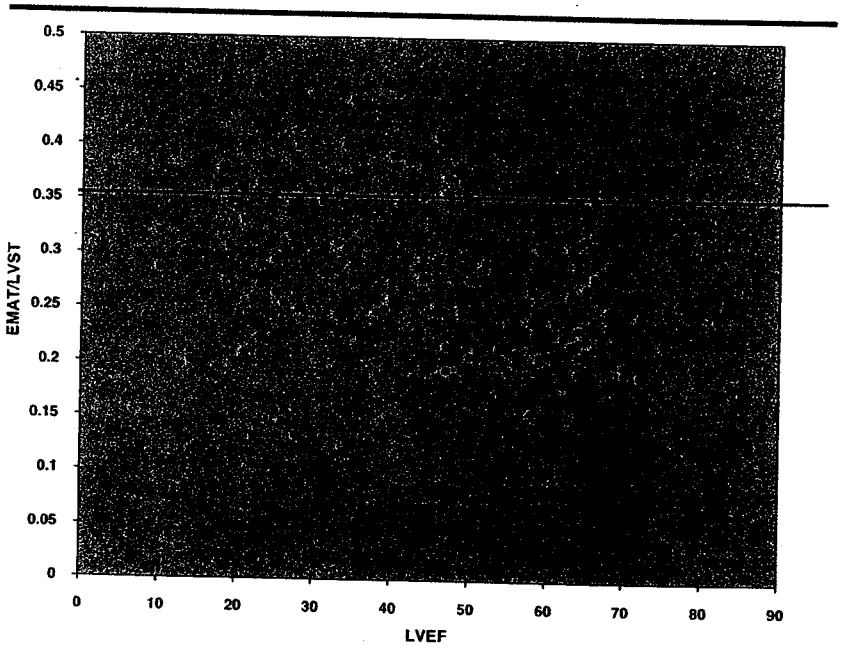

Figure 3. Electromechanical activation time (EMAT)/left ventricular systolic time (LVST) vs. left ventricular ejection fraction (LVEF) (%)

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 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.[5] Abnormal diastolic heart sounds, especially the S_3, have long been associated with hemodynamic abnormalities that underlie heart failure.[3,6,7]

Generation and Occurrence of the S_3. Our findings are consistent with the observations of others that the S_3 is specific, but not highly sensitive, for heart failure associated with LVSD.[3,6,7] The S_3 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_3. 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.

Due to the influence of heart rate on LVET and PEP, researchers developed regression formulas to study indexed values.[8,9] 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).[10–12] LVEF was shown to be highly correlated with PEP/LVET and useful in diagnosing heart failure.[8,11] 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.[13]

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 synonymous 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_3 and V_4 positions. The acoustic cardiographic data include the S_3 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.[1]

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_{max}), using manometer-tipped catheters in 22 patients and fluid-filled catheters

Markus Roos, MD; Stefan Toggweiler, MD; Michel Zuber, MD; Peiman Jamshidi, MD; Paul Erne, MD
From the Division of Cardiology, Kantonsspital Luzern, Lucerne, Switzerland
Address for correspondence: Paul Erne, MD, Head of Division of Cardiology, Kantonsspital Luzern, 6004 Luzern, Switzerland
E-mail: paul.erne@ksl.ch

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_{max} (mm Hg/sec)	1348±468
S_3 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_{max}=maximum contractility	

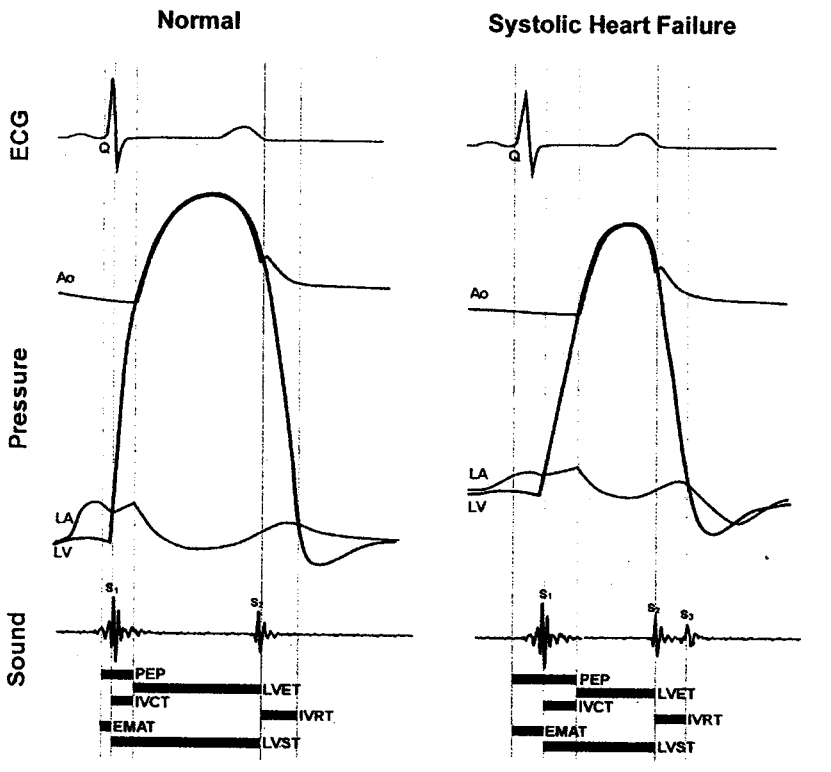

Figure 1. Relationship of traditional systolic time intervals to acoustic cardiographic systolic parameters (normal vs. systolic heart failure) (pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data). ECG=electrocardiogram; 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 analyzed by the computerized AUDICOR algorithm using measurements generated for the S_3 and for various systolic parameters. The system evaluates the possible presence of an S_3 by measuring the intensity and persistence of the energy of sounds that have the appropriate frequency and timing for an S_3. It expresses the resultant value in the range of 1–10 and declares an S_3 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_1. 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_1 to the aortic component of the S_2. 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_3 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_{max} <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 ≥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.

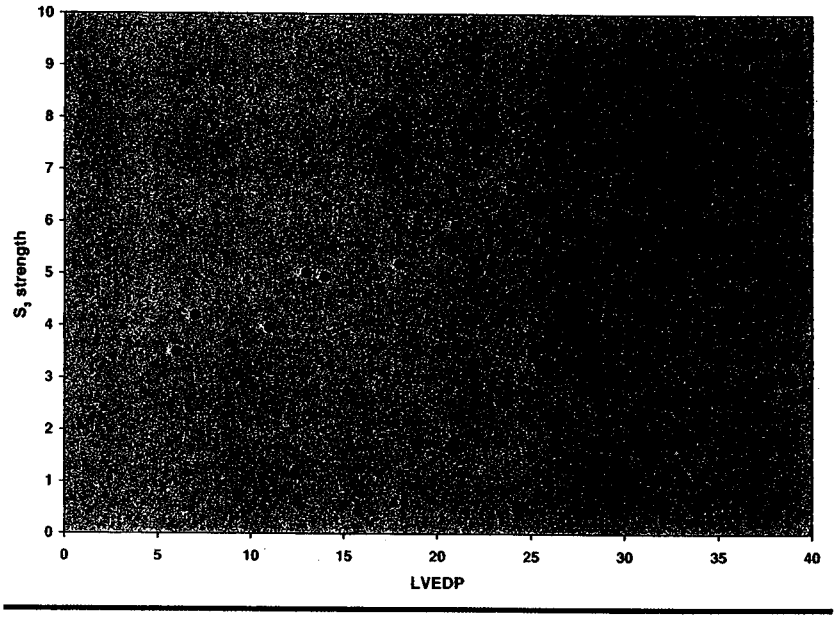

Figure 2. S_3 strength vs. left ventricular end-diastolic pressure (LVEDP) in the patients with left ventricular systolic dysfunction; pre-ventriculogram recordings. Filled circles=left ventricular systolic time (LVST) <45% of R-R interval (R=0.982; p<0.0001); empty circles=LVST >45% of R-R interval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

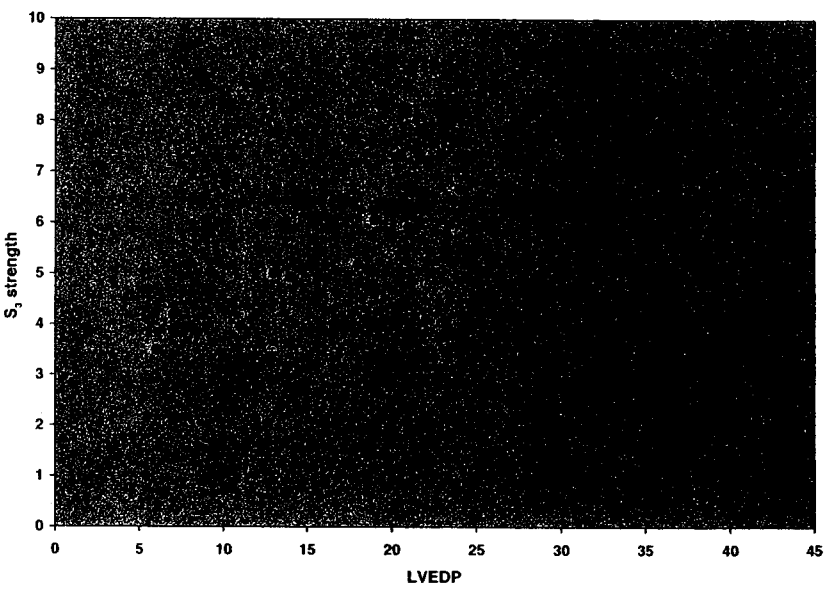

Figure 3. S_3 strength vs. left ventricular end-diastolic pressure (LVEDP) in the patients with left ventricular systolic dysfunction and left ventricular systolic time <45% of R-R interval. Filled circles=pre-ventriculogram (R=0.982; p<0.0001); empty circles=post-ventriculogram (R=0.956; p<0.025)

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 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 illustrates the value of expressing evidence 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

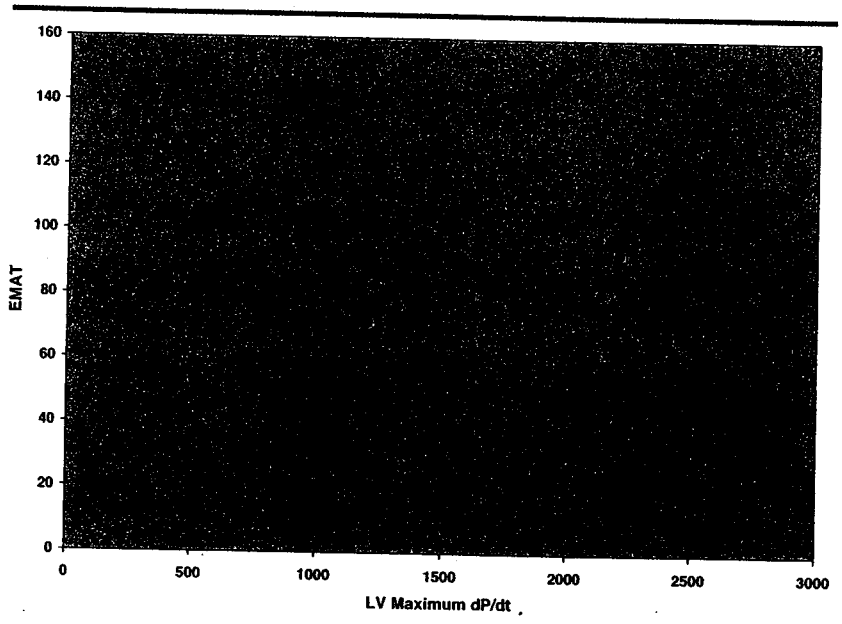

Figure 4. Relationship of electromechanical activation time (EMAT) to left ventricular (LV) maximum contractility (dP/dt) in the patients with left ventricular systolic dysfunction ($R=-0.961$; $p=0.063$)

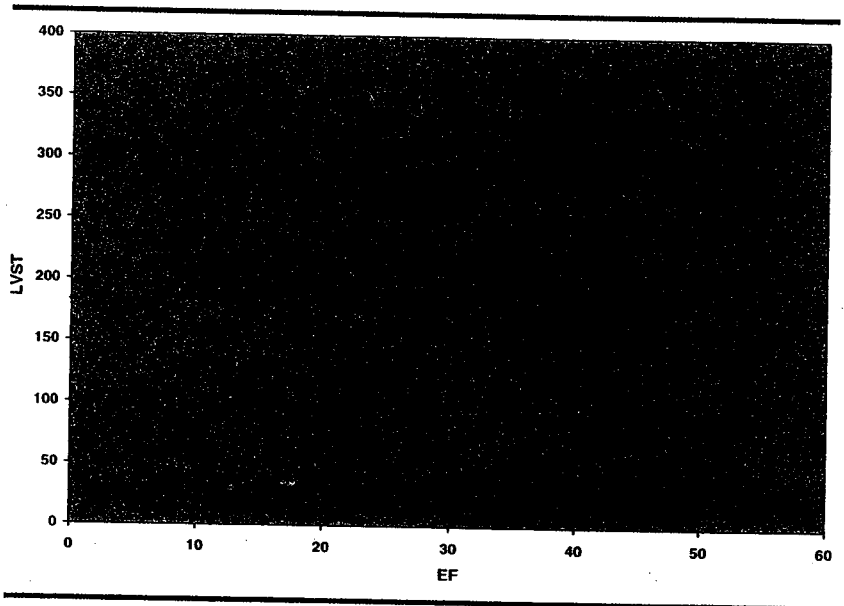

Figure 5. Left ventricular systolic time (LVST) vs. ejection fraction (EF) in patients with left ventricular systolic dysfunction, by heart rate subgroups. R is nonsignificant for each subgroup. Filled circles=heart rate ≤75 bpm; empty circles=heart rate >75 bpm

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.[2]

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.[3] 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.[3] 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.[4] 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.[5] 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.[6–9] 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.[10] 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 performed, 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

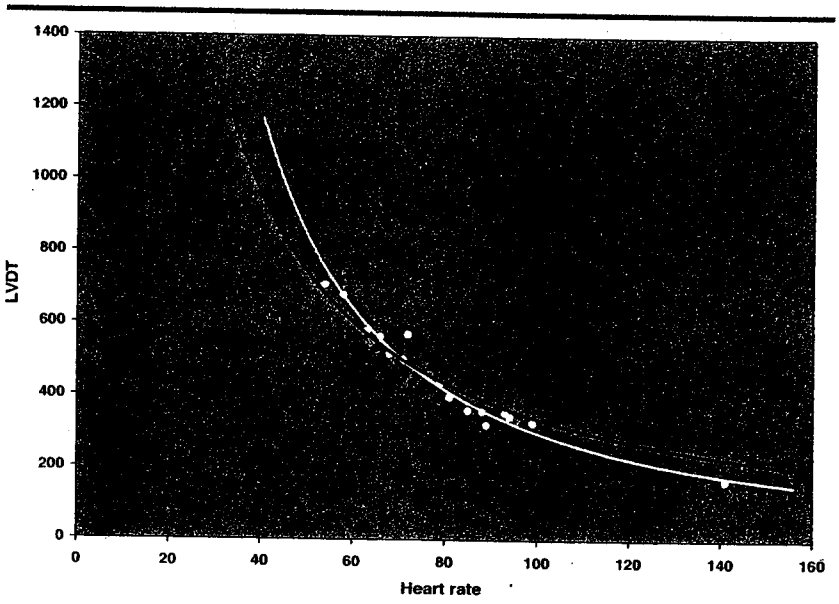

Figure 6. Left ventricular diastolic time vs. heart rate in patients without vs. with left ventricular systolic dysfunction, defined as ejection fraction (EF) <50%. Black=EF ≥50% (R=–0.952; $p<0.0001$); white=EF <50% (R=–0.985; $p<0.0001$)

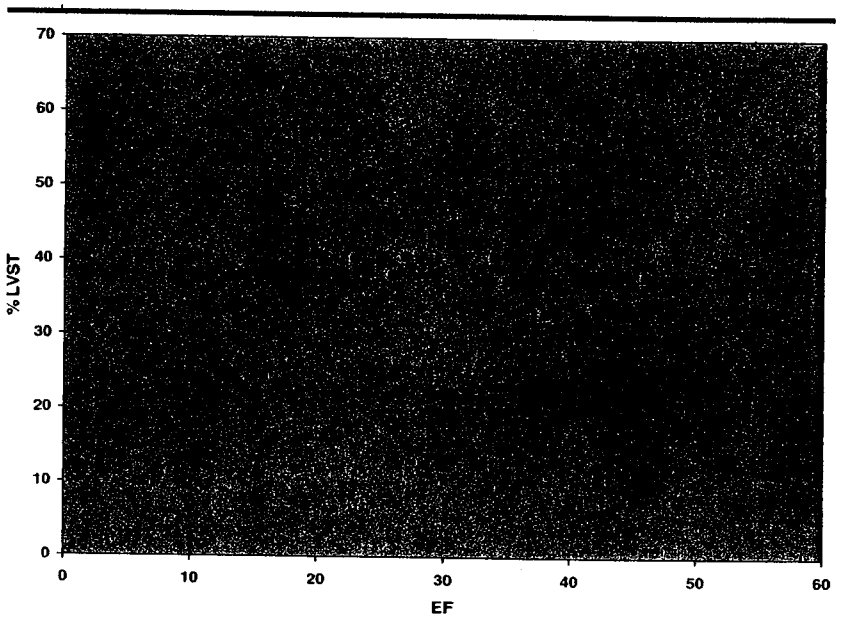

Figure 7. Relationship between left ventricular systolic time as a percentage of the R-R interval (%LVST) and ejection fraction (EF) in patients with left ventricular systolic dysfunction, by heart rate subgroups. Filled circles=heart rate ≤75 bpm; empty circles=heart rate >75 bpm

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.[11] 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.[5]

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 transmitral 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 ± SD of 17±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 ≤20 milliseconds. Furthermore, the echocardiographic transmitral 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.[1,2]

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_3 and V_4 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_3 strength: a measurement of the overall acoustic energy of the S_3 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_1. 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_1 to S_2. This interval is reduced in patients with LV dysfunction.

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

Ayesha Hasan, MD;[1] William T. Abraham, MD;[1] Lori Quinn-Tate, RN, MN;[2] Lei Brown, RDCS, RVT;[2] Ali Amkieh, MD[2]
From the Division of Cardiology, The Ohio State University, Columbus, OH;[1] and the Heart & Vascular Clinic, Louisiana Heart Hospital, Lacombe, LA[2]
Address for correspondence: Ayesha Hasan, MD, Division of Cardiovascular Medicine, The Ohio State University, 473 West 12th Avenue, Room 200 DHLRI, Columbus, OH 43210
E-mail: ayesha.hasan@osumc.edu

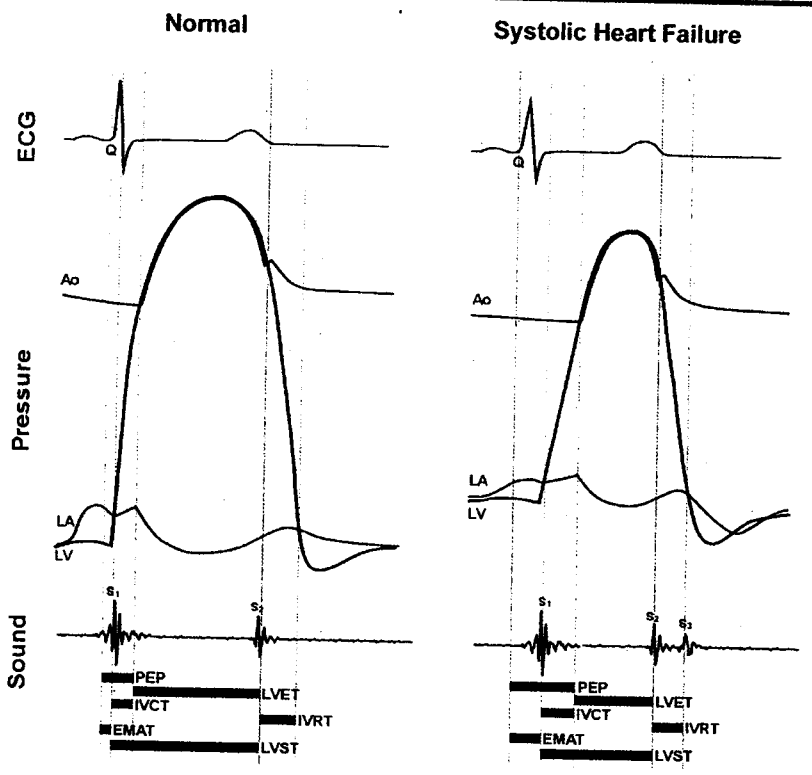

Figure 1. Relationship of traditional systolic time intervals to acoustic cardiographic systolic parameters (normal vs. systolic heart failure). (Pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data.) ECG=electrocardiogram; 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

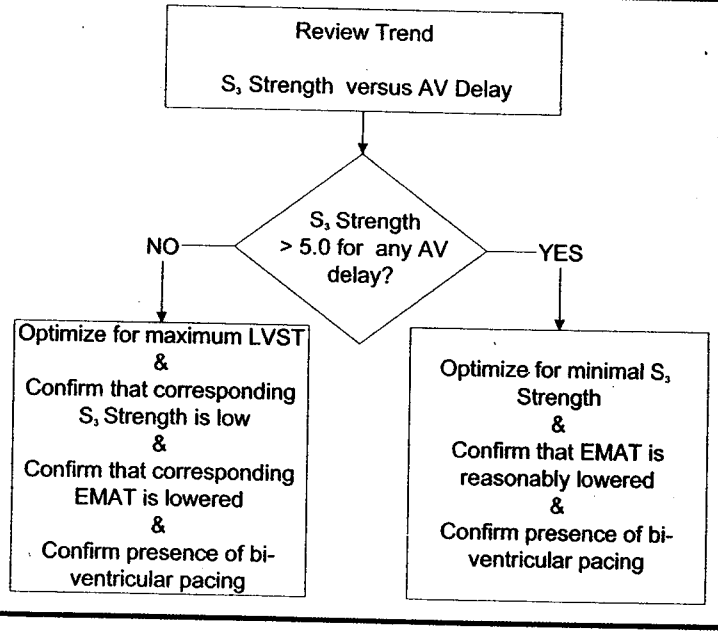

Figure 2. Flow chart used to determine the best atrioventricular (AV) delay during cardiac resynchronization therapy optimization using acoustic cardiography. LVST=left ventricular systolic time; EMAT=electromechanical activation time

hemodynamic abnormalities known to be associated with heart failure.[3,4] In particular, the comparison of acoustic cardiography parameters with relevant hemodynamic parameters obtained during left heart catheterization studies have shown that: 1) S_3 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.[5]

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

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

Subject No.	Doppler Echo	Δ (Echo, Acoustic)	Acoustic Cardiography		
			Consensus	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 ± SD	168±53	17±16	175±50	175±50	177±50

Δ=difference

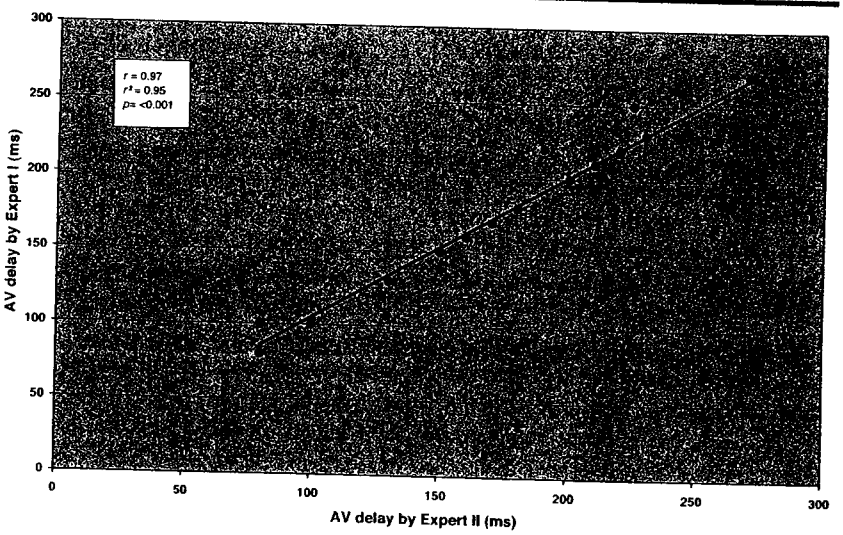

Figure 3. Relationship of the recommended atrioventricular (AV) delays obtained through independent, blinded over-read of the AUDICOR TS (Inovise Medical, Inc., Portland, OR) trends by two clinical experts

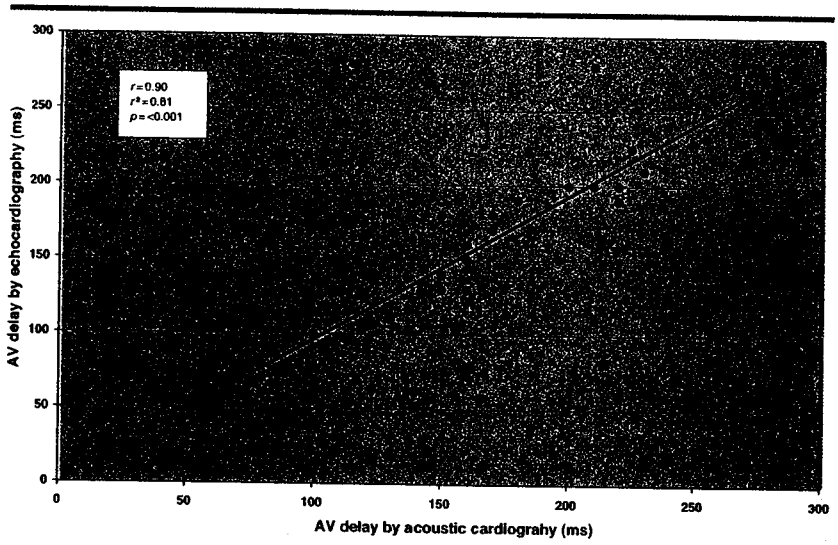

Figure 4. Relationship of recommended atrioventricular (AV) delays obtained through echocardiography and acoustic cardiography (consensus over-read) patient evaluation

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.[5,6] 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 milliseconds and for 21 (95.5%) subjects within 40 milliseconds, while the discrepancy for one patient was 70 milliseconds. A review of the Doppler transmitral flow images for subjects where the discrepancy was >30 milliseconds 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±53 milliseconds, and for the acoustic cardiography-based analysis it was 175±50 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.[1] Using the Doppler transmitral 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.[1] 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.[7] In particular, in postimplantation patients, the reduction in LVEDP is important to support the reverse remodeling process.[8]

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.[5] have shown, the S_3 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_3 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.[5,6] In particular, in the latter patients, the S_3 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.[5,9]

The relationship among EMAT, LVST, and the Doppler transmitral 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 transmitral 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 transmitral 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 transmitral 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 transmitral flow pattern. In this case, the acoustic cardiogram trend offers clear guidance to the best AV setting (per Figure 2, low S_3 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_3 strength

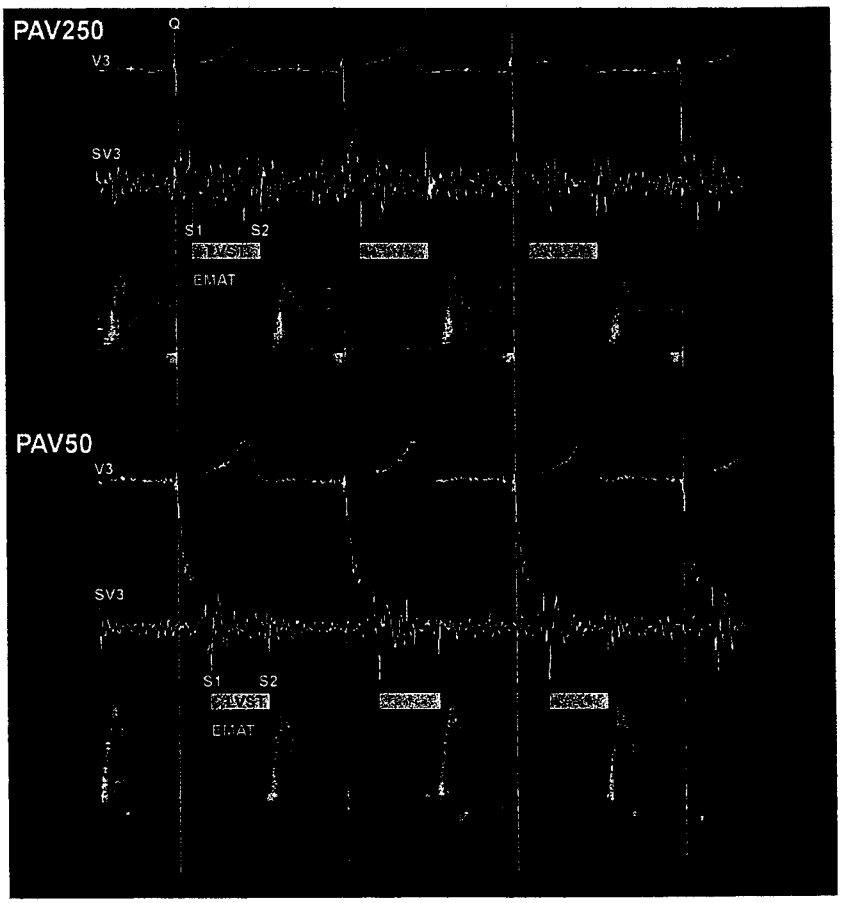

Figure 5. Illustration of electrocardiographic, AUDICOR (Inovise Medical, Inc., Portland, OR) systolic time intervals (electromechanical activation time [EMAT], left ventricular systolic time [LVST]), and echo Doppler transmitral flow pattern in a cardiac resynchronization therapy patient for short and 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 transmitral 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 transmitral 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

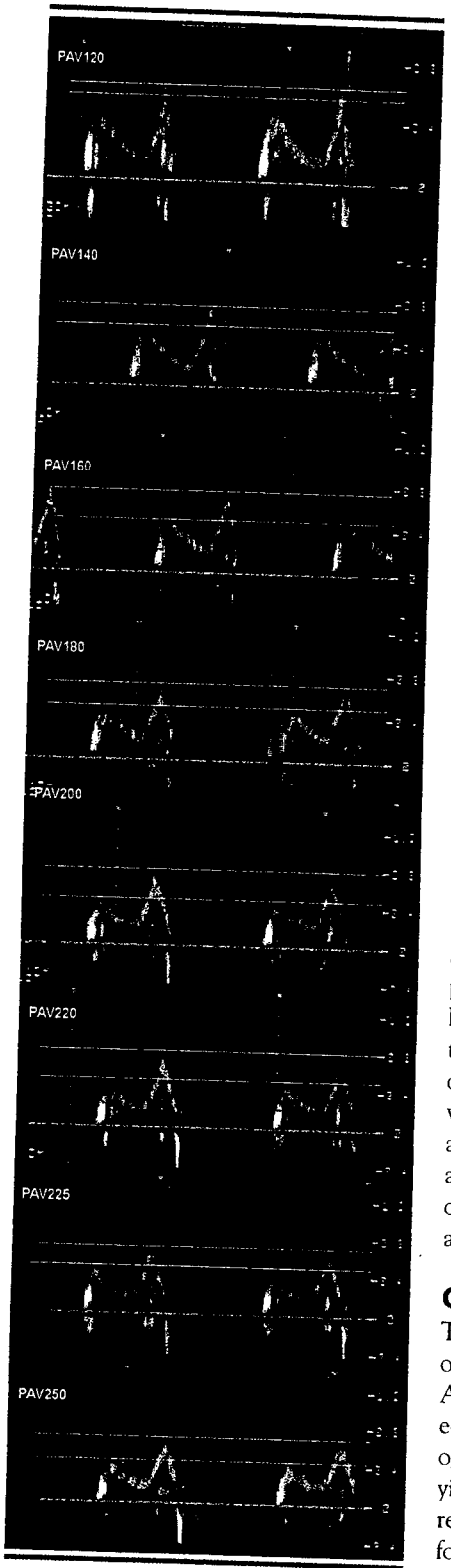

Figure 6. Echocardiographic Doppler transmitral flow pattern for all of the atrioventricular delays tested in study subject number 3

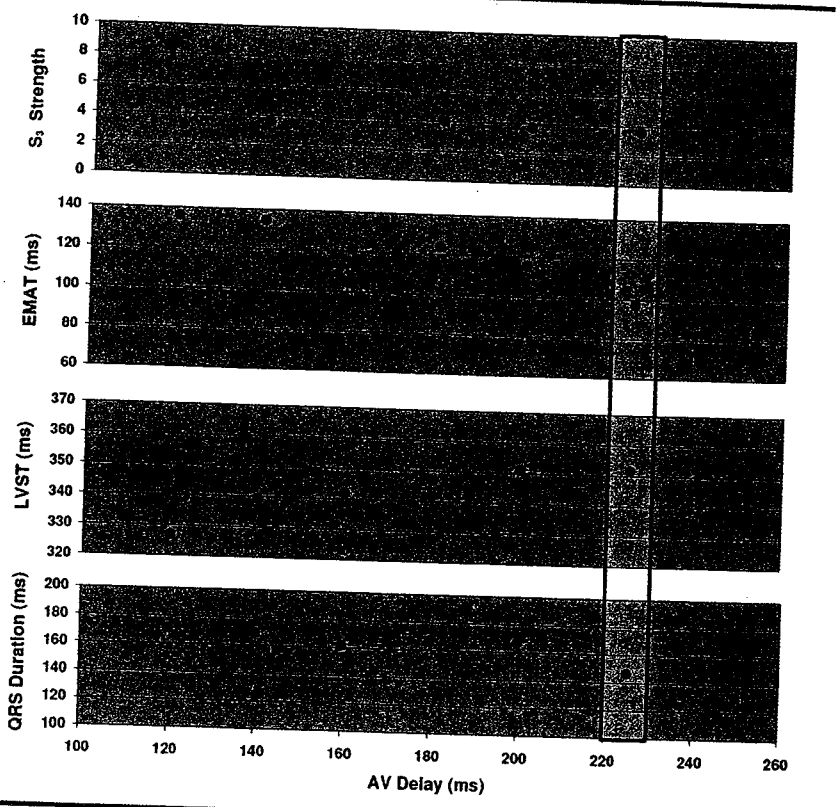

Figure 7. Trend showing the acoustic cardiogram values for all of the atrioventricular (AV) delays tested in study subject number 3. EMAT=electromechanical activation time; LVST=left ventricular systolic time

tested, and therefore it cannot be concluded that the recommended AV 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±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 transmitral flow patterns.

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ORIGINAL PAPER

Clinical and Economic Benefits of Using AUDICOR S_3 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_3 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_3 was highly specific (94%) for ADHF and was valuable in combination with BNP values to improve the diagnostic accuracy in undifferentiated emergency department dyspenic 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.[1] Chest radiography, while helpful when demonstrating signs of congestion, is often nondiagnostic, especially in patients with an acute exacerbation of chronic HF.[2–4]

The introduction of B-type natriuretic peptide (BNP) has been useful for excluding HF in acutely dyspneic ED patients, with its high sensitivity when concentrations are <100 pg/mL. However, the specificity of BNP is poor (76%) at this level.[5] 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%.[6–8] 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%.[2,9,10] The addition of an S_3 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.[11]

The consequences of HF misdiagnosis are significant and well documented. The Acute Decompensated HF National Registry (ADHERE database)[12,13] 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

W. Frank Peacock, MD;[1] Alex Harrison, MD;[2] Donald Moffa, MD[1]
From the Department of Emergency Medicine, Cleveland Clinic, Cleveland, OH;[1] and the Division of Cardiology, Department of Medicine, University of California, Irvine Medical Center, Orange, CA[2]
Address for correspondence: Alex Harrison, MD, Division of Cardiology, Department of Medicine, University of California, Irvine, 101 The City Drive, Building 53, Route 81, Room 100, Orange, CA 92868-4080
E-mail: alexharrisonmd@hotmail.com

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.[11,14] 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[11,14] 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.[15,16] 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[11,14] 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.,[11] 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.[11,14,16] 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 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.[17] 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.[12,13]

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.

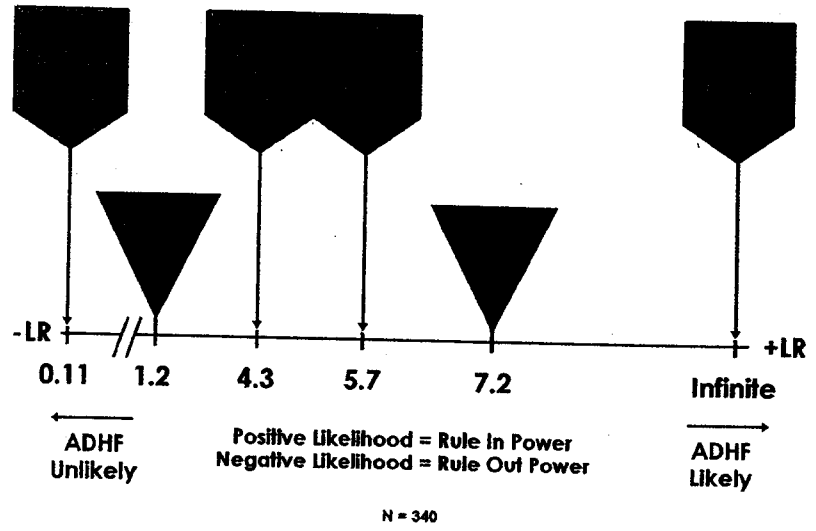

Figure. Positive likelihood ratio (LR) for primary acute decompensated heart failure (ADHF) generated by each and combined clinical variables. BNP=B-type natriuretic peptide (pg/mL)

Limitations

The limitations of this study are similar to those reported in our previous work.[11,14] 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. 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.[16]

Conclusions

Our findings suggest that an S_3 is highly specific for ADHF. The high specificity and positive LR of an S_3 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_3 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_3 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

Cardiac 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.[1–5] 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.[6] This has mainly been done using parameters obtained by Doppler echocardiography, but also by measuring left ventricular (LV) dP/dt_{max}.[7–11] 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_3 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.[12,13] 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^2 (normal <134 g/m^2). 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 electrophysiology 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.[14] 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_3 and V_4 positions. For each CRT AV and VV

Stefan Toggweiler, MD; Michel Zuber, MD; Paul Erne, MD
From the Division of Cardiology, Kantonsspital Luzern, Lucerne, Switzerland
Address for correspondence: Paul Erne, MD, Head of Division of Cardiology, Kantonsspital Luzern, 6004 Luzern, Switzerland
E-mail: paul.erne@ksl.ch

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_{max} (cm/sec)	71	66	37
A_{max} (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_3, the EMAT (the interval from the onset of the Q wave of the electrocardiogram to the S_1), and the LV systolic time (the interval from S_1 to S_2). 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 (Aplio). 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.[15] 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,[16] 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.[17] 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 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.

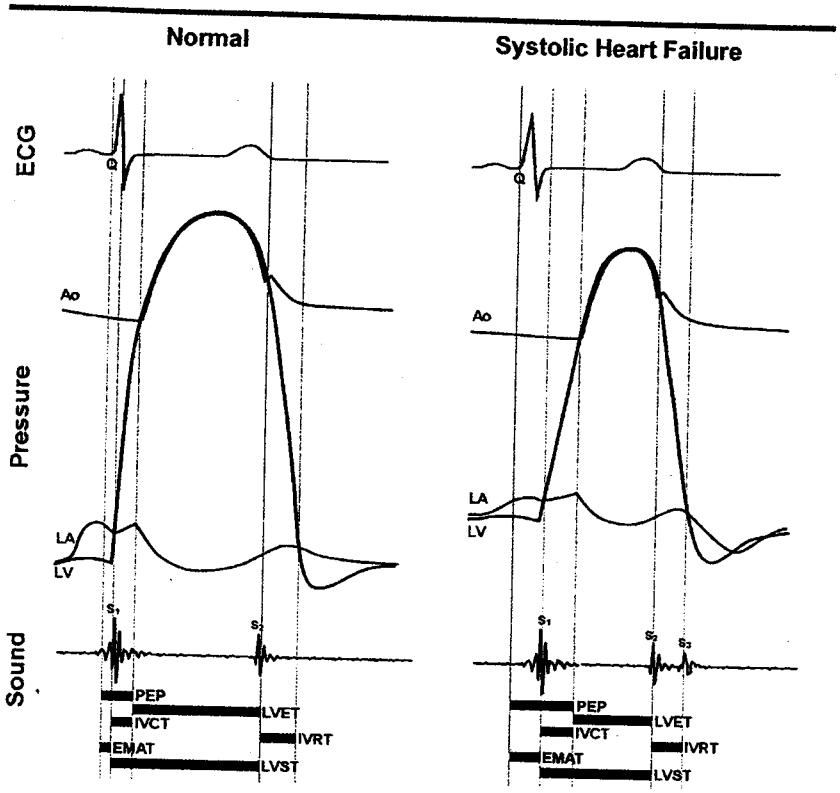

Figure. Schematic of acoustic cardiography and left ventricular pressure tracings for a normal patient and a heart failure patient showing a phonocardiographic S_3, an increased electromechanical activation time (EMAT) ($Q–S_1$), reduced left ventricular systolic time (LVST) ($S_1–S_2$), and a higher 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

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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.[1,2] Despite the array of diagnostic tests available to physicians, as many as 18% of ED patients with acute HF are misdiagnosed.[3,4] 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.[5] 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.[6,7]

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.[8] 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_3 with the assistance of proprietary dual-purpose sensors placed in the V_3 and V_4 positions. Previous work has shown that data from acoustic cardiograms are highly specific for the hemodynamic abnormalities known to be associated with HF.[9]

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_3 or S_4 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 P_{O_2} of 68, an O_2 saturation of 92%, and a P_{CO_2} 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_3.

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_2 and her oxygenation worsened. Despite these therapeutic efforts, the patient died in the hospital and her family declined a request to perform an autopsy.

W. Frank Peacock, MD
From the Department of Emergency Medicine, The Cleveland Clinic Foundation, Cleveland, OH
Address for correspondence: W. Frank Peacock, MD, Department of Emergency Medicine (E19), The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195
E-mail: peacocw@ccf.org

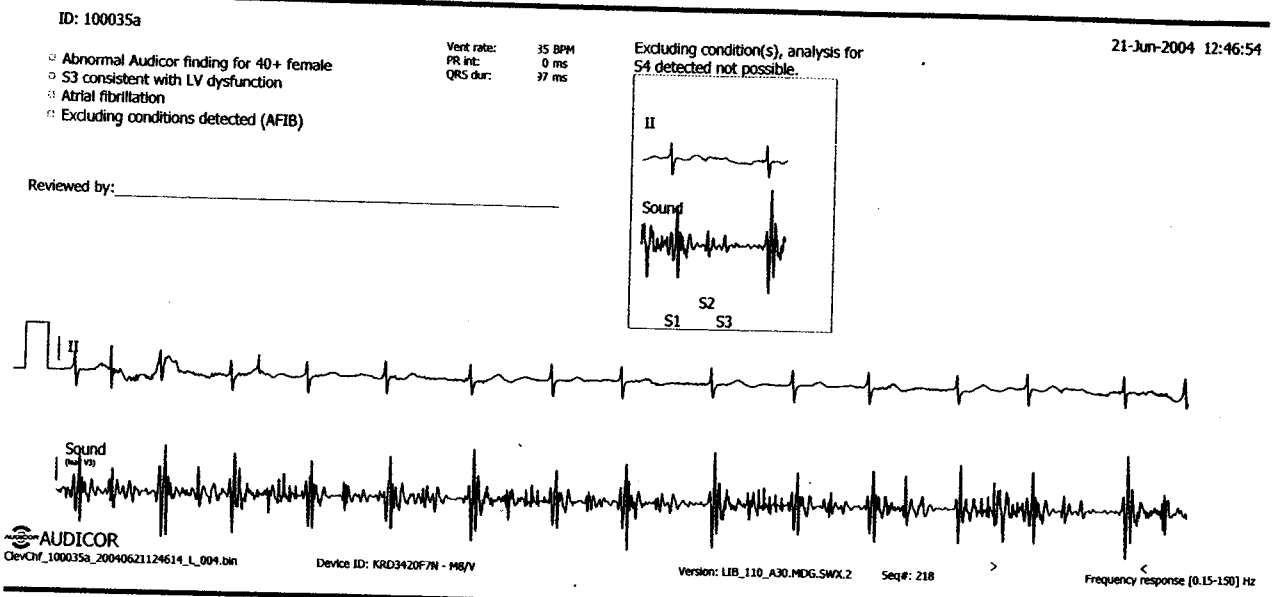

Figure. AUDICOR report showing an S_3

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 artifactually 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.[10]

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).[11,12] 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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The Combined Utility of an S3 Heart Sound and B-Type Natriuretic Peptide Levels in Emergency Department Patients With Dyspnea

SEAN P. COLLINS, MD, MSc,[1] CHRISTOPHER J. LINDSELL, PhD,[1] W. FRANK PEACOCK, MD,[2] VIRGINIA D. HEDGER, PhD,[1] JEFF ASKEW, MD,[3] DANIEL C. ECKERT, MD,[3] AND ALAN B. STORROW, MD[4]

Cincinnati, Ohio; Cleveland, Ohio; Nashville, Tennessee

ABSTRACT

Background: Emergency department (ED) patients with undifferentiated dyspnea are a diagnostic dilemma. We hypothesized that electronic detection of an S3 would be more accurate in determining decompensated heart failure than physician auscultation, and that combining electronic heart sounds with B-type natriuretic peptide (BNP) would provide additional decision making information to the emergency physician, especially in the BNP indeterminate range (100–500 pg/mL).

Methods and Results: We collected demographic, clinical, and laboratory data in a convenience sample of ED patients presenting with signs or symptoms of acute decompensated heart failure between September 2003 and June 2004. The electronic presence of an S3 or S4 was determined using the Audicor system, a validated device that algorithmically detects S3 and S4 heart sounds. Two independent reviewers determined the presence or absence of acute decompensated heart failure (primary HF) based on chart review, while blinded to BNP and Audicor results. Test characteristics were determined with 95% confidence intervals. Of 422 enrolled patients, 343 had complete data and were included in the final analysis. Median age was 61 years, 54% were female, and 48% were white. The sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of an electronic S3 for primary HF were 34% (26% to 43%), 93% (89% to 96%), 66% (57% to 74%), 7% (4% to 11%), and 70% (65% to 75%) and for physician auscultation were 16% (11% to 24%), 97% (93% to 99%), 84% (76% to 89%), 3% (2% to 7%), and 66% (61% to 71%). The addition of an Audicor S3 to intermediate BNP levels improved the positive LR from 1.3 to 2.9; the positive predictive value from 53% to 80%.

Conclusion: An S3 is highly specific for primary HF and it is ideally suited for use in combination with BNP to improve diagnostic accuracy in ED patients with dyspnea of unclear etiology.

Key Words: Dyspnea, Emergency department, BNP, S3.

Emergency department (ED) patients with undifferentiated dyspnea present a challenging diagnostic dilemma. Traditional means of heart failure diagnosis, including history and physical examination, are often unreliable.[1] Ancillary tests such as chest radiography, although helpful when demonstrating signs of congestion, are often nondiagnostic, especially in patients with an acute exacerbation of chronic heart failure.[2–4] Recently, introduction of B-type natriuretic peptide (BNP) has been useful for excluding heart failure in acutely dyspneic ED patients. Although highly sensitive below 100 pg/mL, the specificity of BNP is poor (76%) at this level.[5] To be useful as a confirmatory marker of heart failure, specificity must be high. Specificity does not rise above 90% until BNP levels are higher than 400 to 500 pg/mL.[6–8] This results in an indeterminate zone (100–500 pg/mL), where BNP levels are neither sufficiently sensitive to be used as a screening test nor sufficiently specific to be useful in "ruling in" heart failure. This may contribute to the misdiagnosis rate for acute decompensated heart failure (primary HF) of between 10 and 20%.[2,9,10] The addition of a second more specific test to indeterminate BNP levels could affect decision making in heart failure patients.

From the [1]Department of Emergency Medicine and [3]Department of Internal Medicine, Division of Cardiology, University of Cincinnati, Cincinnati, Ohio; [2]Department of Emergency Medicine, The Cleveland Clinic, Cleveland, Ohio and [4]Department of Emergency Medicine, Vanderbilt University, Nashville, Tennessee.

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Reprint requests: Sean P. Collins, MD, University of Cincinnati, Department of Emergency Medicine, 231 Albert Sabin Way, ML 0769, Cincinnati, OH 45267.

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Auscultated diastolic heart sounds, specifically the S3, have been associated with elevated left ventricular end-diastolic pressure and decompensated heart failure.[1,11–13] They are highly specific for HF, which makes them an ideal confirmatory marker that could complement the use of BNP. However, the auscultated S3 is notoriously insensitive to elevated pulmonary capillary wedge pressure and detection of primary HF.[14,15] Compounding the difficulty of S3 detection by auscultation is the loud ED environment and confounding illnesses such as chronic obstructive pulmonary disorder and obesity that make detection difficult. Preliminary research suggests that an electronically detected S3 has at least moderate sensitivity while maintaining high specificity for detection of an elevated left ventricular end-diastolic pressure and decreased ejection fraction.[16]

Electronic methods of identifying heart sounds can potentially improve detection of an S3 or S4 compared with auscultation. We have previously reported the prevalence of an electronically detected S3 and S4 in ED patients with suspected HF,[17] but did not evaluate the diagnostic test characteristics because of limitations of the criterion standard for HF. The aim of this study was to use a valid criterion standard for evaluating the diagnostic test characteristics of an electronically detected S3 or S4 and an auscultated S3 and S4 in ED patients with signs and symptoms of acute decompensated HF. We further sought to determine the combined diagnostic utility when electronically detected heart sounds were added to BNP levels. We hypothesized that the electronic detection of heart sounds would improve diagnostic accuracy for decompensated HF when compared with physician auscultation of the third and fourth heart sound. In addition, we hypothesized that combining electronic heart sounds with BNP would provide additional decision-making information to the emergency physician.

Methods

Study Design and Setting

This study was a prospective convenience sample of patients at 4 emergency departments who presented with signs or symptoms of decompensated heart failure between September 2003 and June 2004, detailed methods for which have been previously reported.[17] Briefly, patients were identified as potential participants if they were older than 18 years of age, had an electrocardiogram (ECG) ordered, had signs or symptoms of heart failure (dyspnea, extremity edema, fatigue), and had provided written informed consent. Patients were excluded if an ECG had been performed and more than 1 hour had passed since they had received vasodilators or diuretics for acute heart failure. Patients with pacemakers or in atrial fibrillation were not excluded from enrollment. Institutional review board approval was obtained at all enrolling hospitals.

Methods of Measurement

On completion of enrollment, clinical study assistants collected demographics, medical history, and electronic heart sound data using the Audicor device (Audicor, Inovise Medical, Portland, OR). The treating physician, blinded to electronic heart sound data, documented the presence or absence of jugular venous distension, lower extremity edema, and an S3 or S4 detected by auscultation before receiving laboratory and radiology results. Chest radiography, as interpreted by radiology staff, laboratory variables, BNP levels (all 4 centers used the Triage BNP meter, Biosite, Inc), 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. The study assistants obtained 30-day follow-up by telephone interview. The death registry (Social Security Administration 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 S3 or S4 was determined using the Audicor system, an ECG accessory device that replaces the standard V3 and V4 leads with leads for collecting both sound and electrical data. Sound data from both leads are analyzed using a signal processing algorithm to search for the S3 and S4. The algorithm has been validated by comparison to blinded, consensus over read of heart sound tracings by expert phonocardiographers, and in clinical studies comparing the algorithm to hemodynamic measurements obtained during left heart catheterization.[16,18] For study purposes, the Audicor was placed on subjects by a trained clinical study assistant. Acoustical data were collected for a 10-second period, saved to CD, and shipped to Inovise Medical for processing. This differs fundamentally from our previous work where a 4-minute recording was analyzed in detail using state-of-the-art signal processing techniques to best elucidate the prevalence of the S3. Use of a stand-alone 10-second sampling period reflects the use of the Audicor device in practice and is most appropriate for estimating the sensitivity and specificity of the measure. Raw data were supplied to Inovise Medical to allow for signal processing using the most updated algorithm. The presence or absence of an S3 or S4 was recorded in an electronic spreadsheet (Microsoft Excel, Microsoft Corp, Redmond, WA) and subsequently linked to the clinical data for analysis.

Criterion Standard for Heart Failure

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 study assistants to remove all heart sound data and BNP values. Two senior cardiology fellows determined the patient's HF status during their acute ED presentation. Information available to the fellows included the subject's entire medical record from the ED and inpatient stay including ancillary testing and laboratory results. HF status was defined as primary acute decompensated heart failure (primary HF), secondary heart failure (secondary HF), and non–heart failure (non-HF). Primary HF was defined as acutely decompensated HF. Secondary HF was determined to occur when a patient presented to the ED with a condition other than HF but had a medical history of HF. Non-HF was determined to occur when a patient was judged not to have HF and not have a medical history of HF. If the cardiologist's reviews were discordant, the diagnosis was adjudicated by the principal investigator after reviewing the discrepant chart and having a formal meeting with both reviewers.

CME Questions

Todd C. Kerwin, MD, CME Editor
Winthrop Cardiology Associates, Mineola, NY

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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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 transmitral 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

CME Answer Grid

1.	❑T ❑F	5.	❑T ❑F	9.	❑T ❑F	13.	❑T ❑F
2.	❑T ❑F	6.	❑T ❑F	10.	❑T ❑F	14.	❑T ❑F
3.	❑T ❑F	7.	❑T ❑F	11.	❑T ❑F	15.	❑T ❑F
4.	❑T ❑F	8.	❑T ❑F	12.	❑T ❑F	16.	❑T ❑F

CME Evaluation

	Agree				Disagree
1. My knowledge was enhanced by this activity.	1.__	2.__	3.__	4.__	5.__
2. The activity helped to clarify issues specific to heart failure patients.	1.__	2.__	3.__	4.__	5.__
3. The information obtained from this exercise will have an impact on my care of patients.	1.__	2.__	3.__	4.__	5.__
4. The format of the exercise was useful.	1.__	2.__	3.__	4.__	5.__

5. Suggestions for future topics:

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This activity is sponsored by Winthrop-University Hospital and is supported by an unrestricted educational grant from Inovise Medical, Inc.

Primary Data Analysis

Data are described using median and range for continuous data and frequencies and percents for categorical data. Between-group comparisons used the Mann-Whitney U test for 2 groups, the Kruskall-Wallis test for multiple groups, or chi-square tests, as appropriate. Concordance between cardiologist reviews was assessed using Cohen's kappa. Measures of diagnostic accuracy (sensitivity, specificity, likelihood ratios, and predictive values) are reported with 95% confidence intervals. To determine the impact of combining an S3 and BNP for prediction of primary HF, likelihood ratios were calculated from the slope of the receiver operator characteristic curves. This methodology allows for understanding how the presence of an S3 should impact decision making when BNP is in the indeterminate range. Three intervals of BNP were considered in combination with an Audicor S3: (1) negative, BNP <100 pg/mL; (2) indeterminate, BNP 100–500 pg/mL; and (3) positive, BNP >500 pg/mL. Analyses were performed using SPSS v13.0 (SPSS Inc, Chicago, IL) and Microsoft Excel (Microsoft Corporation).

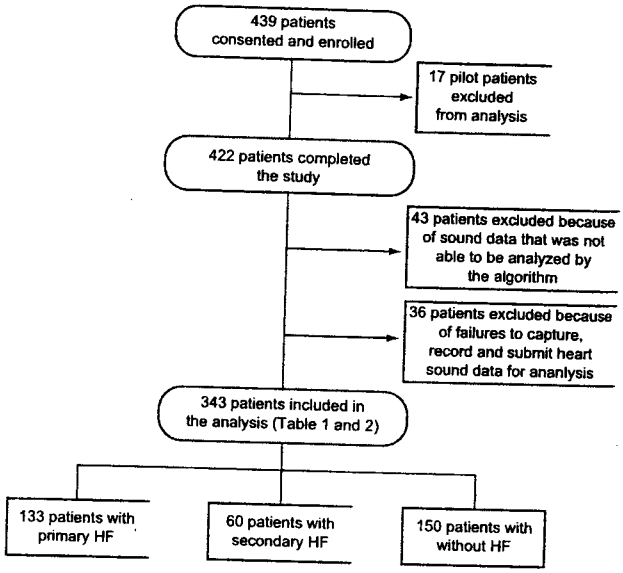

Fig. 1. Patient enrollment and data analysis.

Results

Characteristics of Study Subjects

Of 439 subjects enrolled, 17 were pilot subjects on whom the study protocol and acoustical algorithm were tested prior to final revisions (Fig. 1). Of the remaining 422 patients, 343 were included in the primary analysis. There were 36 patients excluded because of failures to capture, record, and submit heart sound data for analysis, and 43 with heart sound data that could not be analyzed because of excluding conditions for the algorithm (S3: ventricular rhythm/tachycardia, heart rate >115, PR interval <120 ms; S4: all of the S3 excluders plus junctional rhythm, ventricular pacing, and atrial fibrillation/flutter/tachycardia). The 79 patients that were excluded were similar to those patients included in the analysis (Table 1). Of the patients included in this analysis, there were 133 (38.7%) patients with primary HF, 60 (17.4%) patients with secondary HF, and 150 non-HF patients (43.6%). The reviewers agreed 86.0% of the time on the presence of primary HF (kappa = 0.77). In those cases in which there was a disagreement, the case was adjudicated as primary HF in 37.5%, secondary HF in 52.1%, and non-primary HF in 10.4%.

Median age was 61 years (range 20 to 97 years), 54% were female, and 48% were white (Table 1). A previous diagnosis of HF was present in 48%. The median BNP level in patients with primary HF was 697 pg/mL (range 5 to 5000) ($P < .001$ when compared with all others). Those with secondary HF had a median BNP of 94 pg/mL (range 5 to 5000) ($P = .001$ when compared with primary HF and $P = .001$ when compared with patients with no HF), whereas non-HF patients had a median BNP of 48 pg/mL (range 5 to 688). Of the 100 patients with primary HF and a previous ejection fraction documented, 53 had an ejection fraction of less than 40%. Twenty-three percent of patients with Primary HF had no signs of congestion on chest x-ray. An Audicor S3 was detected in 33.8% (26.0% to 42.6%) of primary HF patients. When subjects had heart sound recordings performed before treatment, 33.3% (24.0% to 44.1%) had an S3, whereas 34.9% (21.5% to 51.0%) had an S3 present when heart sound recordings were performed after treatment.

Diagnostic Test Characteristics of the S3

The diagnostic test characteristics of the Audicor and physician auscultation for prediction of primary HF are shown in Table 2. For diagnosing primary HF within the entire patient population, the sensitivity, specificity, positive, and negative predictive value and diagnostic accuracy of an electronic S3 for primary HF were 34% (26% to 43%), 93% (89% to 96%), 66% (57% to 74%) 7% (4% to 11%), and 70% (65% to 75%) and for physician auscultation were 16% (11% to 24%), 97% (93% to 99%), 84% (76% to 89%), 3% (2% to 7%), and 66% (61% to 71%). When only those patients who were sampled before administration of vasodilators or diuretics were considered (n = 275), the sensitivity, specificity, positive, and negative predictive value and diagnostic accuracy of the Audicor S3 did not change significantly; sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 33% (24% to 44%), 94% (89% to 97%), 71% (55% to 84%), and 74% (68% to 77%), respectively. Finally, the test characteristics of the Audicor S3 and the auscultated S3 did not change significantly when the patients with secondary HF were eliminated (primary HF vs. non-HF only).

Diagnostic Test Characteristics of the S4

Although the S4 has not previously been considered to be as specific for primary HF as an S3, we investigated its test

Table 1. Demographics, History, Physical Examination, and Diagnostic Test Results for All Enrolled Subjects, Stratified by Heart Failure Status

	No HF n = 150		Secondary HF n = 60		Primary HF n = 133		*P* value	Included patients n = 343		Excluded patients n = 79		*P* value
Age	55	(20, 95)	68	(39–93)	69	(30–97)	<.001	61	(20–97)	61	(31–92)	.821
Race												
Caucasian	80	(53.3)	25	(41.7)	61	(45.9)	.235	166	(48.4)	40	(50.6)	.803
Other	70	(46.7)	35	(58.3)	72	(54.1)		177	(51.6)	39	(49.4)	
Sex												
Male	63	(42.0)	26	(43.3)	70	(52.6)	.176	159	(46.4)	44	(55.7)	.137
Female	87	(58.0)	34	(56.7)	63	(47.4)		184	(53.6)	35	(44.3)	
Medical history												
CHF	6	(4.0)	44	(73.3)	114	(85.7)	<.001	164	(47.8)	41	(51.9)	.534
CAD	31	(20.7)	24	(40.0)	61	(45.9)	<.001	116	(33.8)	28	(35.4)	.793
Hypertension	71	(47.3)	43	(71.7)	100	(75.2)	<.001	214	(62.4)	50	(63.3)	1.000
VHD	11	(7.3)	25	(41.7)	64	(48.1)	<.001	100	(29.2)	22	(27.8)	.891
Cardiomyopathy	3	(2.0)	17	(28.3)	45	(33.8)	<.001	65	(19.0)	22	(27.8)	.090
Prior abnormal ejection fraction[a]	0	(0.0)	7	(38.9)	24	(53.3)	<.001	31	(38.3)	8	(42.1)	.798
Systolic blood pressure	140	(80–220)	142	(68–215)	148	(85–257)	.021	142	(68–257)	134	(69–219)	.030
Diastolic blood pressure	80	(39–136)	82	(37–124)	83	(39–167)	.184	82	(37–167)	79	(47–133)	.568
Heart rate	90	(54–140)	82	(25–114)	91	(44–142)	.062	90	(25–142)	93	(58–158)	.026
Respiration rate	20	(11–40)	20	(10–44)	22	(12–44)	.008	20	(10–44)	20	(12–85)	.839
Oxygen saturation	98	(57–100)	96	(78–100)	96	(72–100)	<.001	97	(57–100)	97	(60–100)	.745
Temperature	97.7	(96.0–102.8)	98	(96.6–100.3)	97.5	(95.0–101.2)	.026	97.7	(95.0–102.8)	97.6	(94.1–104.0)	.211
BMI	28.0	(14.6–86.3)	28.8	(12.2–78.3)	27.3	(15.1–76.7)	.454	28.0	(12.2–86.3)	31.5	(14.8–65.7)	.048
Creatinine clearance	97.9	(9.9–520.8)	65.1	(8.4–318.8)	58.8	(5.4–255.7)	<.001	76.9	(5.4–520.8)	75.8	(6.7–384.6)	.995
Symptoms												
JVD	7	(4.7)	6	(10.0)	43	(32.6)	<.001	56	(16.5)	14	(18.7)	.613
Peripheral edema	43	(28.7)	20	(33.3)	83	(63.4)	<.001	146	(42.8)	42	(53.8)	.079
Dyspnea	118	(78.7)	51	(85.0)	128	(96.2)	<.001	297	(86.6)	68	(86.1)	.857
Orthopnea	36	(24.0)	22	(36.7)	91	(68.4)	<.001	149	(43.4)	32	(41.0)	.800
PND	20	(13.3)	16	(26.7)	52	(39.7)	<.001	88	(25.8)	27	(34.6)	.123
Congestion on x-ray	20	(13.5)	25	(42.4)	103	(77.4)	<.001	148	(43.5)	39	(49.4)	.380
BNP	48	(5–688)	94	(5–5000)	697	(5–5000)	<.001	271	(5–5000)	273	(5–4690)	.819
Auscultation												
S3	5	(3.4)	2	(3.3)	21	(16.4)	<.001	28	(8.4)	9	(12.3)	.268
S4	4	(2.7)	3	(5.0)	8	(6.3)	.354	15	(4.5)	2	(2.8)	.748
Audicor												
S3	9	(6.0)	5	(8.3)	45	(33.8)	<.001	59	(17.2)	0	(0.0)	—
S4	18	(12.8)	7	(13.7)	18	(17.6)	.557	43	(14.6)	0	(0.0)	—

Data are given as medians and ranges or as frequencies and percents.

[a]Prior ejection fraction available for 100 patients—abnormal ejection fraction defined as less than 55%. JVD, jugular venous distention; CHF, congestive heart failure; CAD, coronary artery disease; VHD, valvular heart disease; PND, paroxysmal nocturnal dyspnea; BNP, brain natriuretic peptide.

Table 2. Diagnostic Test Characteristics of an Audicor-Detected and Auscultated S3 and S4

	Auscultation				Electronic detection			
	S3		S4		S3		S4	
	n = 335		n = 334		n = 343		n = 294	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present
No HF + secondary HF	200	7	200	7	196	14	167	25
Primary HF	107	21	119	8	88	45	84	18
Prevalence of HF	38.2	(33.0–43.7)	38.0	(32.8–43.5)	38.8	(33.6–44.2)	34.7	(29.3–40.5)
Prevalence of heart sound	8.4	(5.7–12.0)	4.5	(2.6–7.5)	17.2	(13.4–21.7)	14.6	(10.9–19.3)
Accuracy	66.0	(60.6–71.0)	62.3	(56.8–67.5)	70.3	(65.1–75.0)	62.9	(57.1–68.4)
Sensitivity	16.4	(10.7–24.2)	6.3	(3.0–12.4)	33.8	(26.0–42.6)	17.6	(11.1–26.7)
Specificity	96.6	(92.9–98.5)	96.6	(92.9–98.5)	93.3	(88.8–96.2)	87.0	(81.2–91.2)
PPV	83.6	(75.8–89.3)	93.7	(87.6–97.0)	66.2	(57.4–74.0)	82.4	(73.3–88.9)
NPV	3.4	(1.5–7.1)	3.4	(1.5–7.1)	6.7	(3.8–11.2)	13.0	(8.8–18.8)
FPR	75.0	(54.8–88.6)	53.3	(27.4–77.7)	76.3	(63.1–86.0)	41.9	(27.4–57.8)
FNR	65.1	(59.5–70.4)	62.7	(57.1–68.0)	69.0	(63.2–74.3)	66.5	(60.3–72.3)

PPV, positive predictive value; NPV, negative predictive value; FPR, false-positive rate; FNR, false-negative rate.

characteristics as well. The Audicor S4 had an overall accuracy of 63% (57% to 68%), 18% sensitivity (11% to 27%), 87% specificity (81% to 91%), 82% PPV (73% to 89%), and 13% NPV (9% to 19%) for primary HF within the entire patient population (Table 2). The auscultated S4 had an overall accuracy of 62% (57% to 68%), 6% sensitivity (3% to 12%), 97% specificity (93% to 99%), 84% PPV (76% to 89%), and 3% NPV (2% to 7%). When primary HF was compared to only non-HF, the test characteristics of an Audicor or auscultated S4 did not change significantly.

Audicor S3 Among Patients With a False-Negative ED Diagnosis

The overall ED misdiagnosis rate was 14.0% (10.6% to 18.2%). Of the 48 cases, 44 of them were a failure to diagnose HF when it was present. Had the Audicor S3 been used as the sole diagnostic criterion among the 44 ultimately considered having primary HF, 15 (34.1%; 20.9% to 50.0%) would have been correctly diagnosed as having primary HF (Table 3). Two of these patients were sent home, 12 were admitted to a non–intensive care unit setting, and 1 was admitted to the intensive care unit. Similarly, had the Audicor S3 been used as the sole diagnostic criterion for primary HF, 14 of the 206 patients (6.8%; 3.9% to 11.4%) that were correctly diagnosed as nonprimary HF would have been incorrectly classified as primary HF. Of these 14, 10 were discharged home and 4 were admitted to a non–intensive care unit setting.

Combined Diagnostic Accuracy of BNP and S3

Obtaining a BNP value was at the discretion of the treating physician; 205 patients had a BNP measurement within 2 hours of presentation. The diagnostic test characteristics of BNP in its "indeterminate zone" (100 to ≤500) both in isolation and in combination with an Audicor S3 were calculated for prediction of Primary HF. A BNP level in this range had an interval likelihood ratio of 1.3 and a PPV of 54.3% (95% CI 42.0–66.1%) when the S3 was not considered. When the Audicor S3 was present, the interval likelihood was 2.9 and the PPV was 80.0% (95% CI 51.4–94.7%) (Fig. 2).

Discussion

Our study is the first to quantify the diagnostic test characteristics of an S3 in ED patients with acutely decompensated HF. Our results suggest that the presence of an S3 is highly specific for decompensated HF. With more than 93% specificity, one could argue that when an S3 is detected in an ED patient with signs and symptoms of decompensated HF, very little further diagnostic testing is required before treatment can be initiated. Further, our findings suggest that the high specificity of the Audicor S3 is a useful

Table 3. ED Diagnosis Compared With Final Diagnosis Stratified by the Presence of an Audicor S3

		Audicor S3		
ED diagnosis	Final diagnosis	Absent (n = 284, 83%)	Present (n = 59, 17%)	Total (n = 343)
Nonprimary HF (n = 250, 73%)	Primary HF	29 (8.5%)	15 (4.4%)	44 (12.8%)
	Nonprimary HF	192 (60.0%)	14 (4.1%)	206 (60.1%)
Primary HF (n = 93, 27%)	Primary HF	59 (17.2%)	30 (8.7%)	89 (25.9%)
	Nonprimary HF	4 (1.2%)	0 (0.0%)	4 (1.2%)

ED, emergency department; HF, heart failure.

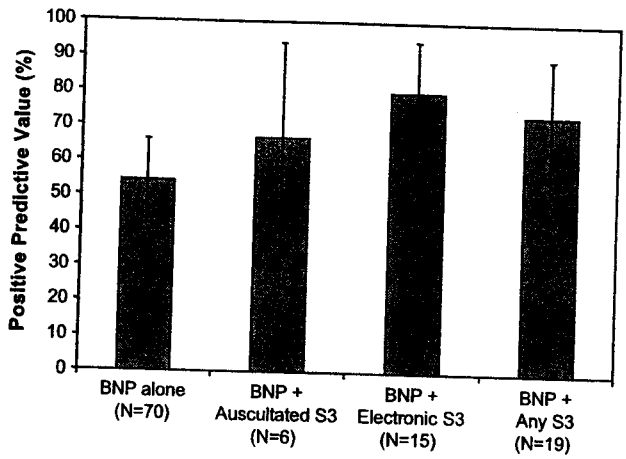

Fig. 2. Bar graph showing the positive predictive value (±95% confidence intervals) of B-type natriuretic peptide in the range 100 to 500 pg/mL with and without consideration of the presence of an S3.

complement to BNP. The presence of an Audicor S3 in a patient with an indeterminate BNP level (100 to 500 pg/mL) increases the positive likelihood ratio from 1 to 3 and increases the PPV from 54% to 80%.

A highly specific test such as the Audicor S3 may be helpful to "rule in" HF. Among those without an ED diagnosis of primary HF, but who were subsequently found to have presented with HF, about one third could have been more appropriately diagnosed in the ED. This should be balanced, however, with the approximately 7% false-positives observed.

In our previous analyses, we found the prevalence of S3 to change significantly with treatment with vasodilators or diuretics.[17] We did not find this to be the case in this analysis (33.3% to 34.9% vs 57.6% to 28.6%). The most likely explanation for the different findings is that the Audicor sampling technique was different for each analysis. In prior reports, we used an algorithm that selected the best 10-second sound sample from a 4-minute continuous recording. In the current study, we used a 10-second sample that was recorded at the bedside by the device as it is used in clinical practice. It is possible the 4-minute recording was more likely to detect a subtle, low-frequency S3 than the 10-second recording. Another possible explanation is that the proportion of patients with a detectable S3 after treatment increased with the new gold standard. As a result, the small number of primary HF patients that did not have an S3 when sampled after treatment were minimized by the majority of patients that did have an S3 heart sound after treatment. Finally, patients did not serve as their own controls in this study; no subject had heart sounds sampled both before and after treatment. Future studies will address this issue by sampling primary HF patients both before and after treatment to determine the effect of treatment on the persistence of the S3.

Interestingly, the diagnostic accuracy of the S3 did not change dramatically when we removed patients with secondary HF from the analysis. These patients are often the most difficult subgroup to diagnose accurately in the ED. Determining whether patients with a history of HF are acutely decompensated when presenting signs and symptoms could be attributed to a number of pathophysiologic processes (eg, decompensated HF, pulmonary embolism, chronic obstructive pulmonary disease) is often difficult. That the diagnostic ability of the S3 was not affected by the cohort of patients with secondary HF is encouraging; the presence of an S3 in this cohort is likely from an acute exacerbation of their heart failure (primary HF).

It is not surprising that the diagnostic accuracy and overall test characteristics of the S4 were less encouraging than the S3. An S4 is often present in many other disease states (hypertension, coronary artery disease) and is less specific than an S3 for elevated left ventricular end diastolic pressure.[16] Further, 15% to 30% of patients older than age 50 have been shown to have electronically detected S4s.[19]

Limitations

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, because of selection bias, the true test characteristics of abnormal heart sounds in ED patients with primary HF is different than that which we have reported. Further, the high prevalence of HF (and thus high pretest likelihood of primary HF) in the primary HF cohort may have diminished the usefulness of both BNP and the S3.

The treating physician's impression of the presence of primary HF may have biased their interpretation of the presence for abnormal heart sounds. They may have been more likely to listen closely for an S3 in patients who had other features (jugular venous distension, pulmonary rales, and lower extremity edema) consistent with primary HF. This bias could have resulted in an increased specificity of auscultation.

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

Finally, there was a large proportion of patients that were excluded because of poor sound tracing quality or because heart sound data was not completely captured. This could have led to bias in the results for heart sound test characteristics. However, the excluded and included patients were similar with regard to proportion of pertinent medical

history, physical examination findings, signs of congestion on chest x-ray, and BNP levels. If patients were unable to have heart sounds captured because of increased severity of their illness and inability to cooperate for heart sounds recording, one would expect that this would bias results to the null; those patients with increased severity of disease would be expected to have significantly elevated left ventricular end-diastolic pressure, resulting in a greater proportion of S3s detected. Missing data from these patients would likely cause a decrease in both sensitivity and specificity.

Conclusion

In summary, our findings suggest that an S3 is highly specific (93%) for decompensated heart failure in ED patients and, when present, the treating physician should strongly consider primary HF to be present. Furthermore, the use of the S3 may be complementary to BNP, especially when BNP levels are in the indeterminate zone (100–500 pg/mL).

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Sean P. Collins MD, Christopher J. Lindsell PhD, W. Frank Peacock IV, Virginia D. Hedger PhD, MS, RN, Alan B. Storrow MD

W.B. SAUNDERS

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Original Contributions

The effect of treatment on the presence of abnormal heart sounds in emergency department patients with heart failure☆

Sean P. Collins MD[a,*], Christopher J. Lindsell PhD[a], W. Frank Peacock IV[b], Virginia D. Hedger PhD, MS, RN[a], Alan B. Storrow MD[a]

[a]*Department of Emergency Medicine, University of Cincinnati, Cincinnati, OH 45267-0769, USA*
[b]*Ohio State University, Department of Emergency Medicine, Cleveland Clinic Foundation, Cleveland, OH 44195, USA*

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Abstract

Objective: We sought to assess the proportion of ED patients with an electronically detected S_3 or S_4, determine the relation of these heart sounds to heart failure (HF), and analyze how the proportion changes with ED treatment.

Methods: Heart sounds were assessed in ED patients with suspected HF. The presence or absence of HF and whether treatment with diuretics or vasodilators had occurred were recorded.

Results: Three hundred seventy-six patients had complete data. The proportion of patients with an S_3 and an S_4 was significantly higher for those with HF compared with those without ($P < .001$). Of 59 patients with HF evaluated before treatment, 57.6% had an S_3 and 35.6% had an S_4. For the 35 patients with HF evaluated after treatment, the proportions of both S_3 and S_4 were lower (28.6% and 8.6%, respectively; $P \leq .0064$).

Conclusions: This study suggests the proportion of patients with an electronically detected S_3 in HF is more than 50%, and that its presence is affected by prior treatment with diuretics or vasodilators.

1. Background

Patients with decompensated heart failure (HF) represent an increasing proportion of ED patients with dyspnea. In 2002, there were approximately 1 million hospital discharges for HF, most of which originated in the ED [1]. The poor diagnostic accuracy of history and physical examination findings has been well documented [2,3]. Although left bundle branch block and Q waves are highly specific electrocardiographic (ECG) findings for left ventricular dysfunction, their lack of sensitivity make them poor screening tools [4,5]. Alveolar and interstitial edema on chest radiography can be diagnostic for acute decompensated HF, but up to 20% of patients with HF lack signs of congestion [6,7]. Because of the paucity of highly accurate ED screening tools, a definitive diagnosis of HF is often determined after hospital admission. Reliable detection

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* Corresponding author. Tel.: +1 513 558 8079; fax: +1 513 558 5791.
E-mail address: sean.collins@uc.edu (S.P. Collins).

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of abnormal diastolic heart sounds (S_3 or S_4) may be a useful addition to the emergency physician's battery of diagnostic tests.

Third and fourth heart sounds have been described in the literature as far back as the late 1800s [8]. The third heart sound (S_3), also known as a ventricular gallop, occurs 0.12 to 0.16 seconds after the second heart sound in early diastole [9]. The most likely explanation for this extra sound is that excessively rapid filling of a stiff ventricle is suddenly halted, causing vibrations audible as the third heart sound [10]. The fourth heart sound (S_4), also known as an atrial gallop, occurs after P-wave onset and before the first heart sound in the cardiac cycle. It is produced in late diastole because of atrial contraction causing vibrations of the left ventricular muscle, mitral valve apparatus, and left ventricular blood mass [11].

The detection of an S_3 is often considered normal in adolescents and young adults, but its detection after the age of 40 years is usually considered abnormal and indicative of left ventricular dysfunction [12-14]. The reported prevalence of an S_4 in healthy individuals is variable, ranging from 11% [14] to 75% [15-21]. Recent research suggests that the detection of either an S_3 or S_4 is relatively uncommon in the general population, and the occurrence of either sound should prompt further investigation [22].

An auscultated S_3 is notoriously insensitive for elevated pulmonary capillary wedge pressure and acute decompensated HF [23]. Compounding the difficulty of S_3 or S_4 detection is the loud ED environment, confounding illnesses such as chronic obstructive pulmonary disease and obesity that make detection difficult, and the inability of the patient to tolerate being placed in the ideal examining position (recumbent) because of their orthopnea. Electronic methods of identifying heart sounds can potentially improve detection of an S_3 or S_4, compared with auscultation by the examining physician. Preliminary research suggests that an *electronically detected* S_3 has at least moderate sensitivity (39%) and high specificity (96%) for detection of an elevated left ventricular end-diastolic pressure [24]. The aim of *this study* was to compare the proportion of electronically detected S_3's or S_4's in ED patients with acute decompensated HF (Primary HF) to those without acute decompensated HF (Non-HF). We hypothesized the presence of an electronically detected S_3 or S_4 would be higher in patients with Primary HF than Non-HF. The focus of *this article* is to describe the proportion of patients with an electronically detected S_3 or S_4, and describe the impact of treatment on the detection of these sounds.

2. Methods

2.1. Study design and setting

This study was a prospective observational study of ED patients who presented with signs or symptoms of decompensated HF between September 2003 and June 2004. Patients were enrolled by clinical study assistants (CSAs) at 4 urban EDs (patient volume ranging from 35 000 to 85 000 visits), 2 of which were academic departments with active residency programs, and 2 of which were community centers with ED residents rotating through the ED. Institutional review board approval was obtained at all enrolling hospitals.

2.2. Selection of participants

The CSAs screened ED bedside charts and interviewed ED patients to determine potential candidates for enrollment. Potential candidates were discussed with the treating physician to confirm suitability. Inclusion criteria were the following: (1) signs or symptoms of decompensated HF (dyspnea, lower extremity edema, fatigue, jugular venous distension, or orthopnea); (2) an ECG ordered as part of their ED workup; (3) willing and able to provide informed consent; (4) age $\geq$18 years; and (5) able to be reached by phone for follow-up. Patients were excluded if more than 1 hour had passed since they received vasodilator or diuretic treatment. These exclusion criteria were selected to maximize capture of heart sounds before, or shortly after, medication administration.

2.3. Methods of measurement—data collection and processing

On completion of enrollment, CSAs prospectively collected demographics and past medical history. The treating physician completed a data collection form before receiving laboratory and radiology results on which they documented the presence or absence of jugular venous distension, lower extremity edema, and an S_3 or S_4 detected by auscultation. The CSAs then obtained electronic acoustic heart sound data using the Audicor device (Audicor, Inovise Medical, Portland, Ore). Electronic data were stored on CD for subsequent signal processing. Physicians were blinded to electronic acoustic data.

Chest radiography results, as interpreted by radiology staff, laboratory variables, b-type natriuretic peptide (BNP) levels, automated ECG results, inhospital data (previous ejection fraction [EF] documented by echocardiogram, nuclear medicine scan, left and right heart catheterization, inhospital cardiac testing and therapeutics, and hospital discharge diagnosis) and inhospital events (cardiac arrest, death, and intubation), were collected by chart review. A study nurse, blinded to Audicor results, performed chart review. A standardized data collection form with predetermined data definitions was used to abstract data.

Thirty-day follow-up was obtained by telephone interview by the CSAs. We used our standard follow-up procedure in which 3 attempts by phone to contact the patient, 2 attempts to contact a patient's alternative contact, a medical record review, and death registry review are conducted. The death registry (Social Security Administration Death Master File Online Service) and medical records

were reviewed for all patients whether they are contacted so as to obtain details of any self-reported events. In the case of conflicting data, the data available in the medical record were recorded on the case report form. Once forms were completed, data were double entered into the study database.

2.4. Methods of measurement—electronic heart sounds analysis

The presence of an S_3 or S_4 was determined using the Audicor system during the patient's ED stay. Electronic heart sounds were acquired before, or just after vasodilator or diuretic treatment. No patient had heart sounds recorded both before and after vasodilator or diuretic treatment. The system is designed as an accessory to standard ECG machines and replaces V_3 and V_4 leads with dual leads for collecting both sound and acoustical data. Sound data from both leads are analyzed for the presence of abnormal diastolic heart sounds using a signal processing algorithm. In combination with an ECG algorithm, the system provides a diagnostic statement that reflects the combined ECG and acoustic findings (Fig. 1).

The Audicor algorithm for detection of heart sounds has been cleared by the FDA after submission of performance results comparing the Audicor algorithm to a blinded, consensus overreading of heart sound tracings by expert phonocardiographers [25]. This algorithm has subsequently been validated in clinical studies comparing the algorithm detection of the S_3 and S_4 both to (1) hemodynamic measurements obtained during left heart catheterization and (2) visual overreading of the sound tracing [24-27]. The S_3 has been found to be moderately sensitive (41%) and highly specific (92%) for elevated left ventricular end-diastolic pressure.

Each of the CSAs was trained before patient enrollment. Continued training was conducted throughout to maximize data quality and proper use of the Audicor. For study purposes, the Audicor was placed on subjects by the CSA. Acoustical data were collected a for a 4-minute period, saved to CD, and shipped to Inovise Medical for signal

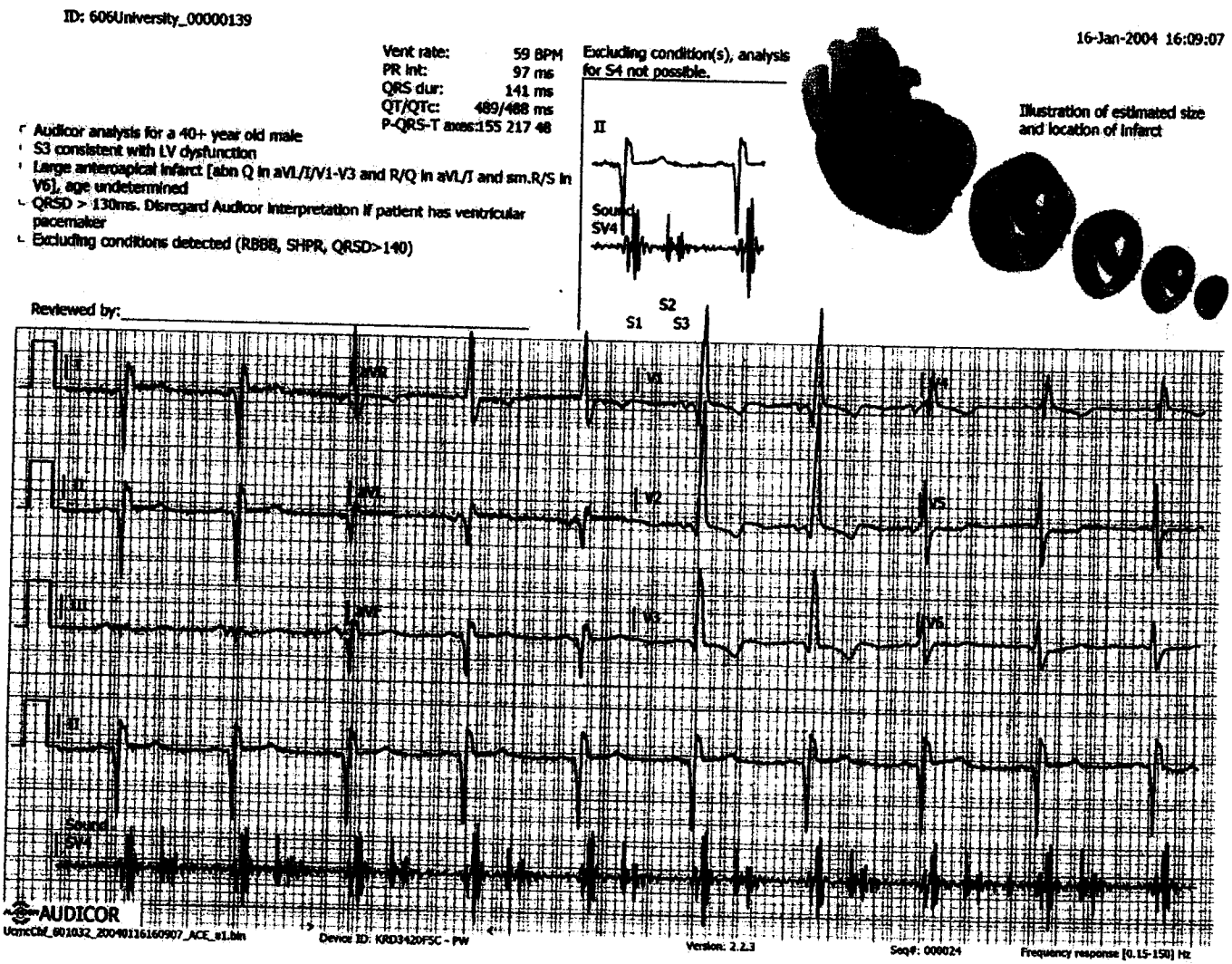


Fig. 1 Printout of the Audicor ECG. In addition to the electrical information, there is visual and typed sound information displayed.

Table 1 Demographics, history, physical examination, and diagnostic test results for all enrolled subjects and stratified by discharge diagnoses

	Non-HF		Secondary HF		Primary HF		All patients	
	n = 268		n = 43		n = 110		N = 421	
Demographics								
Age (IQR)	58	(46-69)	71	(56-80)	71	(56-79)	[illegible]	[illegible]
Men	122	(45.5)	21	(48.8)	60	(54.5)	[illegible]	[illegible]
White	135	(50.4)	19	(44.2)	52	(47.3)	[illegible]	[illegible]
Past medical history								
Previous EF >40%	41	(80.4)	6	(40.0)	13	(39.4)	[illegible]	[illegible]
Previous EF <40%	10	(19.6)	9	(60.0)	20	(60.6)	[illegible]	[illegible]
History of HF	73	(27.2)	35	(81.4)	97	(88.2)	[illegible]	[illegible]
History of CAD	69	(25.7)	19	(44.2)	56	(50.9)	[illegible]	[illegible]
History of hypertension	150	(56.0)	33	(76.7)	80	(72.7)	[illegible]	[illegible]
Clinical findings								
Dyspnea on exertion	222	(82.8)	36	(83.7)	106	(96.4)	[illegible]	[illegible]
Jugular venous distension	22	(8.4)	12	(27.9)	36	(32.7)	[illegible]	[illegible]
Peripheral edema	94	(35.3)	26	(60.5)	68	(62.4)	[illegible]	[illegible]
Diagnostic tests								
No congestion on chest x-ray†	194	(73.2)	15	(34.9)	22	(20.0)	[illegible]	[illegible]
Congestion on chest x-ray	71	(26.8)	28	(65.1)	88	(80.0)	[illegible]	[illegible]
Median BNP level (pg/mL)(IQR)	66	(21-179)	485	(209-1000)	744	(439-1640)	[illegible]	[illegible]

Columns refer to the total number and the percentage of patients unless otherwise indicated. CAD, coronary artery disease [illegible]

† Congestion on chest x-ray was indicated by any of the following: alveolar pulmonary edema, interstitial edema, and pulmonary vascular congestion.

processing. A computerized algorithm was used to select the highest quality 10-second sample from the 4 minute continuous recording. The selection was based on (1) the signal-to-noise ratio of energy within the S_1 and S_2 region compared with regions where valid heart sounds are not present; and (2) the presence of conditions that do not allow heart sound analysis, such as high heart rates and atrial fibrillation (preventing S_4 analysis). Where a 10-second period of data that met these criteria could not be found, the data were classified as unanalyzable. Using the highest quality data segment allows for computing the most accurate heart sound detection possible.

The presence or absence of an S_3 or S_4 was recorded in an electronic spreadsheet (Microsoft Excel, Microsoft Corp, Redmond, Wash), along with the ECG interpretation generated using the Audicor algorithm. This algorithm

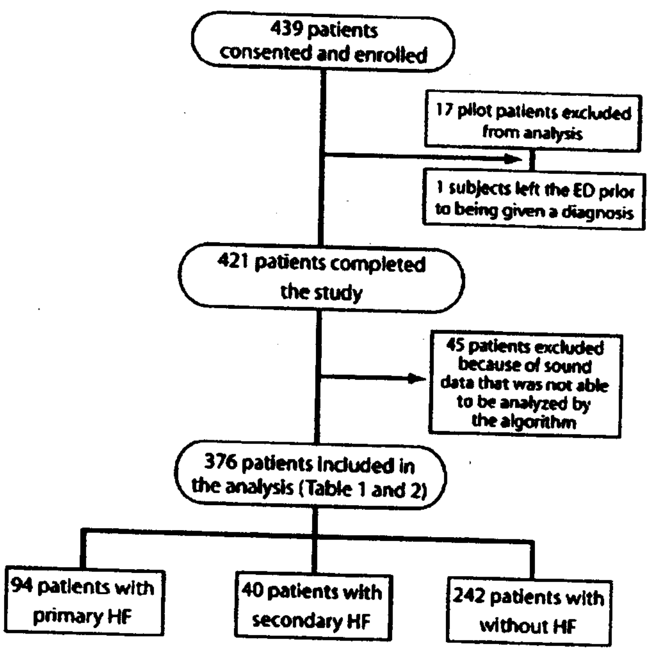


Fig. 2 Flow diagram of patient enrollment and analysis.

incorporates advanced automated detection of prior myocardial infarction, acute myocardial infarction, and left ventricular hypertrophy [28-31]. The Audicor data were subsequently linked to the clinical data for analysis.

3. Primary variables

The 3 variables evaluated in this study were the following: (1) the presence or absence of *abnormal heart sounds* detected by the Audicor algorithm; (2) the patient's HF status; and (3) whether *vasodilator or diuretic treatment was administered* before heart sounds sampling. The presence or absence of heart sounds was determined by the Audicor algorithm, as defined above. The presence or absence of HF was defined as a primary discharge diagnosis of acute decompensated HF (Primary HF), a secondary discharge diagnosis of HF (Secondary HF), or a non-HF discharge diagnosis (Non-HF). A secondary discharge diagnosis of HF (Secondary HF) refers to any discharge diagnosis of HF that is not a primary discharge diagnosis. Physicians were allowed to use any diagnostic technique as per their standard practice, to confirm or rule out the diagnosis of HF. This included chest x-ray, BNP measurement, and echocardiography. The gold standard for the presence or absence of HF was based on the following: (1) the discharge summary as provided by the emergency physician for patients discharged home from the ED or the observation unit and (2) the inpatient discharge summary for patients admitted to the hospital. Prior treatment being administered was defined as the administration of any vasodilator or diuretic before obtaining heart sound data. This was determined through prospective data collection and confirmed by retrospective chart review.

4. Primary data analysis

Data are described using median and range for continuous data and frequencies and percentages for categorical data. The proportion of patients with an S_3 or S_4 in Primary, Secondary, and Non-HF patients was computed, with 95% confidence intervals. The proportion of patients with electronically detected heart sounds was compared between patients with Primary HF and Non-HF, and between patients who received treatment and those who did not receive treatment before data acquisition using χ^2 tests. Analyse have been performed using SPSS version 12.0 (SPSS Inc, Chicago, Ill) and Microsoft Excel (Microsoft Corporation).

5. Results

5.1. Characteristics of study subjects

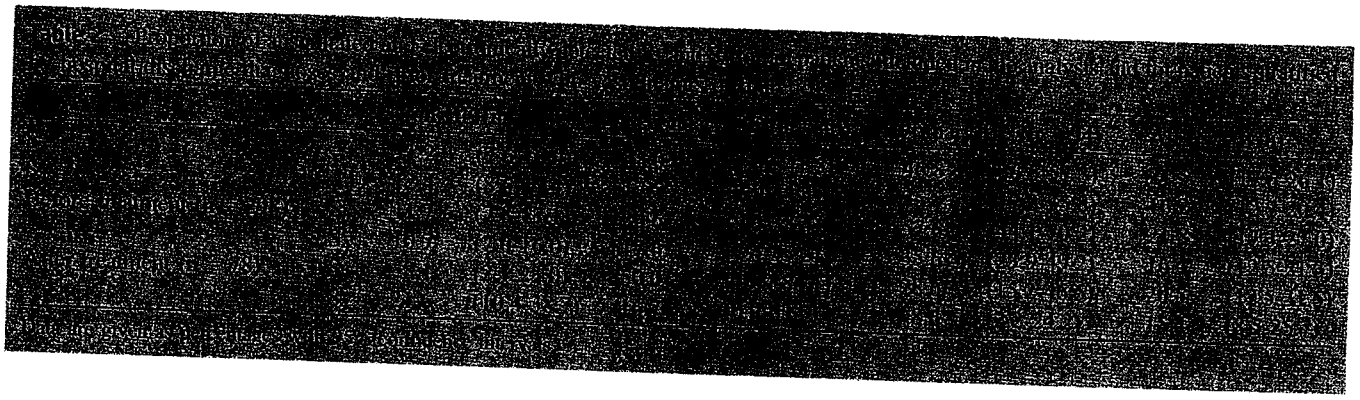
Of 439 subjects enrolled, 17 were pilot subjects on whom the study protocol and acoustic algorithm were tested before final revisions. One subject left the ED before being given a diagnosis. These subjects are not included in any analyses. The remaining 421 subjects are described in Table 1, stratified by final diagnosis.

Median age was 61 years (interquartile range [IQR] 48 to 75 years), 51.8% were women, and 48.9% were white. A previous diagnosis of HF was present in 48.7%. Median BNP levels in patients with Primary HF were 764 pg/mL (IQR 459 to 1640 pg/mL). Those with Secondary HF had a median BNP of 485 pg/mL (IQR 209 to 1000 pg/mL), and those with Non-HF had a median BNP of 66 pg/mL (IQR 21-179 pg/mL). Of patients with Primary HF and a previous EF documented, 60.6% had an EF of less than 40%. Twenty percent of patients with Primary HF had no signs of congestion on chest x-ray.

5.2. Main results

5.2.1. Proportion of patients with an S_3 or S_4

Of the 421 patients, 376 were included in this analysis (Fig. 2). Forty-five patients were excluded because of sound data that were missing or not having been analyzed. Of the patients included in this analysis, there were 94 patients with Primary HF, 40 patients with Secondary HF, and 242 Non-HF patients. With the exception of race, the 45 patients who were excluded had similar demographics, past medical history, clinical findings, diagnostic test results, and proportion of Primary HF diagnoses when compared with those patients included in the analysis ($P > .142$). Excluded patients were more likely to be white than included patients ($P = .039$).



The proportion of patients with an S_3 detected by Audicor in Primary HF was 46.8% (95% CI, 36.5%-57.3%), compared with 25.0% (95% CI, 13.2%-41.5%) in Secondary HF and 11.2% (95% CI 7.6-16.0%) in Non-HF (Table 2). Similarly, those patients with Primary HF were more likely to have an Audicor-detected S_4 (25.5% [95% CI, 17.3%-35.8%]) than those patients with Secondary HF (17.5% [95% CI, 7.9%-33.4%]) and Non-HF diagnoses (12.4% [95% CI, 8.6%-17.4%]). Overall, the proportion of patients with an S_3 and an S_4 were higher for Primary HF than Non-HF patients ($P < .001$).

Of 59 patients with a primary HF diagnosis evaluated before treatment with diuretics or vasodilators, 34 (57.6% [95% CI, 44.1-70.2]) had an S_3 and 21 (35.6% [95% CI, 23.9-49.2]) had an S_4 (Fig. 3). For the 35 patients with a primary HF diagnosis evaluated after treatment with diuretics or vasodilators, the proportions of both S_3 (10 [28.6% {95% CI, 15.2-46.5}]) and S_4 (3 [8.6% {95% CI, 2.2-24.2}]) were lower ($P \leq .0064$). For the 205 patients with a non-HF diagnosis evaluated before treatment with diuretics or vasodilators, 24 (11.7% [95% CI, 7.8-17.1]) had an S_3 and 22 (10.7% [95% CI, 7.0-16.0]) had an S_4. For the 37 patients with a non-HF diagnosis evaluated after treatment with diuretics or vasodilators, 3 (8.1% [95% CI, 2.1-23.0]) had an S_3, whereas 8 (21.6% [95% CI, 10.4-38.7]) had an S_4. The proportion of non-HF patients with an S_3 and S_4 did not differ significantly before and after treatment with diuretics or vasodilators ($P = .522$ and $P = .0643$, respectively).

6. Limitations

Although this observational cohort study shows the proportion of patients with and without HF who have an S_3 or an S_4 and how treatment affects the proportion, several limitations remain. Hospital discharge diagnosis is often reflective of ED presentation and reason for hospitalization, but it may not always accurately reflect the acute ED presentation. This can result in misclassification bias. For example, patients may present to the ED in acute decompensated HF and receive appropriate treatment, including vasodilators and diuretics. By the time the admitting team examines the patient, often several hours later, the patient may be compensated, leading to a hospital discharge diagnosis not reflective of their ED presentation. If the same person had had an S_3 and/or S_4 present at the time of heart sound sampling/auscultation, it would decrease the specificity of an S_3 or S_4 for identification of Primary HF. The corollary could also be true; those patients who developed HF while in the hospital may have been given a hospital discharge diagnosis of Primary HF, although when they presented to the ED and had heart sound recording performed, they did not have Primary HF. This could have decreased the sensitivity of the S_3 and S_4 for diagnosing Primary HF.

Workup bias could also be present; patients with Primary HF who were considered low-risk may have had fewer tests and no definitive diagnosis of HF because of the lack of testing.

This study enrolled an observational cohort of patients with signs or symptoms of HF. We are only able to report the proportion of patients with abnormal heart sounds and not the true prevalence. There is a possibility that, because of selection bias, the true prevalence of abnormal heart sounds in ED patients with Primary HF is different from the proportion that we have reported.

Finally, there was likely a component of selection bias present. Those patients who were more acutely ill were more likely to be treated earlier and have heart sounds sampled after treatment had begun. However, we would expect that those that are more acutely ill (with higher end-diastolic pressure) would be more likely to have abnormal heart sounds present. Their lack of abnormal heart sounds after treatment may be a greater indication of the hemodynamic changes (decreased end-diastolic pressure) that occur with vasodilators and diuretics.

Patients were either sampled before treatment or after treatment, but not both. We have assumed that among patients sampled after treatment, the pretreatment proportion with an S_3 would have been similar to those sampled

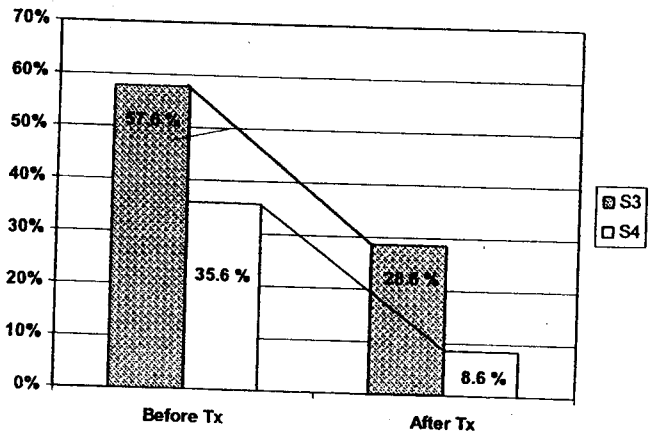


Fig. 3 Affect of treatment on proportion of patients with electronically detected heart sounds.

before treatment. It is possible this group had either a greater or smaller proportion with a pretreatment S_3, decreasing our confidence in the finding that the S_3 decreases after treatment.

7. Discussion

Our study is the first to quantify the proportion of ED patients with Primary HF that have an electronically detectable S_3 and S_4. We show that more than 50% of patients with Primary HF have an S_3 before treatment with vasodilators or diuretics and that ED treatment with these medications may decrease the prevalence of an S_3 and S_4. These findings make sense from a physiologic standpoint. An S_3 and S_4 are thought to be reflective of poor ventricular relaxation resulting in raised end-diastolic pressure. Administration of vasodilators and diuretics results in a decrease in preload, afterload, and intravascular volume, all of which would lead to a decrease in end-diastolic pressure and S_3/S_4 resolution.

We found a smaller proportion of S_3's and S_4's in those patients with Secondary HF compared with Primary HF. This is expected; although the patients with Secondary HF carry a history of HF, the main focus of their therapy during hospitalization was not HF. In compensated patients with HF, with normal or near-normal preload and afterload, a decreased proportion of S_3's and S_4's relative to Primary HF would be expected. The proportion of Non-HF patients with S_3's and S_4's is consistent with previous studies of abnormal heart sounds in asymptomatic individuals [22]. In an observational cohort of 1329 asymptomatic individuals, 15% to 30% of patients older than age 50 years have been shown to have electronically detected S_4's. It has been suggested that these findings are due to the effects of aging and essential hypertension on ventricular stiffness [20]. Between 20% and 35% of asymptomatic patients younger than age 40 years may have an S_3 present because of a healthy hyperdynamic left ventricle. This likely contributes to the number of S_3's and S_4's in the Non-HF group.

Of note, there were 37 Non-HF patients (18.6%) that were treated with nitrates or vasodilators. There are several possible explanations for this. The ED misdiagnosis rate for Primary HF has been suggested to be between 10% and 20%, consistent with our findings in this study [7,32]. Secondly, there may have been patients who presented with Primary HF who were adequately treated by the emergency physician. At the time of evaluation by the admitting team, the patient's Primary HF signs and symptoms had improved, resulting in a Non-HF hospital discharge diagnosis. Finally, several patients may have had S_3's and S_4's because of other disease processes. Other disease processes such as acute coronary syndrome are also associated with an S_3 and S_4.

Until recently, physicians have had relatively poor screening tools for HF. Physical examination has been traditionally unreliable [2,3]. Similarly, chest radiography misses 20% of echocardiogram-proven cardiomegaly, and many patients with chronic HF will have elevated wedge pressures and acute decompensation despite a lack of congestion on chest x-ray [6,7,33]. As a result, a definitive diagnosis of HF is often obtained after the patient is admitted to the hospital and has undergone echocardiography, right heart catheterization, or both. The paucity of screening tools most likely contributes to the 10% to 20% ED misdiagnosis rate for Primary HF [7,32]. Our diagnostic ability has improved with the introduction of natriuretic peptides. Although these markers have high sensitivity at their recommended cutoff of 100 pg/mL, they have relatively poor specificity for Primary HF when only modestly elevated (100-500 pg/mL) [34-36]. As a result, natriuretic peptides are good when used to rule out HF, but their increased number of false positives, especially at intermediate levels, makes them poor rule-in markers.

The S_3 has been reported to be a highly specific marker of raised end-diastolic pressure and Primary HF [23,24]. It might be suggested that these 2 diagnostic tests could be complementary—combining the high sensitivity of BNP with the high specificity of the S_3. Those patients with a BNP below 100 pg/mL are highly unlikely to have Primary HF. Those patients with a modestly elevated BNP (100-500 pg/mL) and an S_3 present would be highly likely to have Primary HF. However, those patients with a BNP in the indeterminate zone and no S_3 present may require further workup. Future heart sound studies will need to prospectively evaluate this relationship. Furthermore, previous studies suggest patients with Primary HF and an S_3 may have a worse prognosis, have increased lengths of stay, and consume more hospital resources than those patients with Primary HF who lack an S_3 [37,38].

In summary, our study suggests that an S_3 is present in more than 50% of patients with Primary HF before treatment and that treatment may have a significant clinical effect on the presence of abnormal heart sounds. Emergency physicians need to consider the possibility of prior treatment with vasodilators and diuretics when using the presence of an S_3 or S_4 as a diagnostic strategy in the dyspneic ED patient.

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ORIGINAL PAPER

Prevalence of the Third and Fourth Heart Sound in Asymptomatic Adults

The prevalence of abnormal diastolic heart sounds in asymptomatic adults has been the subject of great debate. The authors determined the prevalence of an electronically detected S_3 and S_4 in 1329 asymptomatic adults between the ages of 18 and 94. The authors also investigated the relationship between abnormal diastolic heart sounds, age, and electrocardiography. The overall prevalence of S_3 was 10.0% [95% confidence interval [CI], 8.1%–12.2%], S_4 was 15.6% [95% CI, 13.2%–18.2%], and both S_3 and S_4 were 3.5% [95% CI, 2.4%–5.0%]. Using multinomial logistic regression, increasing age was found to decrease the odds of an S_3 being heard [odds ratio, 0.96; 95% CI, 0.95–0.96] and increase the odds of an S_4 being heard [odds ratio, 1.04; 95% CI, 1.03–1.05]. We conclude that the prevalence of an S_3 is increased earlier in life, that an S_4 is less common than previous studies suggest, and that its detection, even in the elderly, should not be ignored. [CHF. 2005;11:242–247] ©2005 CHF, Inc.

Extra diastolic heart sounds are produced as a result of increased stiffness and decreased compliance of the left ventricle (LV). The third heart sound (S_3) occurs 0.12–0.16 seconds after the second heart sound in early diastole (Figure 1).[1] Of the many proposed theories, the most likely explanation is that excessive rapid filling of a stiff ventricle is suddenly halted, causing vibrations that are audible as S_3.[2] The fourth heart sound (S_4) occurs after P wave onset and before the first heart sound in the cardiac cycle. It is produced in late diastole as a result of atrial contraction causing vibrations of the LV muscle, mitral valve apparatus, and LV blood mass.[3] The atrial and ventricular "gallop" has been described in the literature dating back to the late 1800s.[4] The ventricular gallop is recognized as an S_3. The atrial gallop is synonymous with an S_4.

The detection of an S_3 is often considered "normal" in adolescents and young adults, while its detection after the age of 40 is usually considered abnormal and indicative of LV dysfunction.[5–7] The incidence of an S_4 in acute ischemia and acute infarction approaches 100%.[8]

The prevalence of these sounds, especially the S_4, in healthy individuals has been a subject of great debate. Previous phonocardiographic studies have found a prevalence of S_4 from as low as 11%[9] to as high as 75%,[10] as well as many values in between.[11–16] The vast majority of these studies enrolled fewer than 300 subjects and suffered from enrollment bias because many of the subjects had been referred for cardiac workup, including left-sided and right-sided heart catheterization.

The goals of our study are twofold: 1) to determine the prevalence of an S_3 and S_4 in a large asymptomatic population using a computerized algorithm that analyzes acoustical data; and 2) to determine if there is an association between abnormal diastolic heart sounds, age, and electrocardiographic (ECG) findings.

Methods

This study was a cross-sectional observational cohort study of a convenience sample of asymptomatic persons. The Western Institutional Review Board, Olympia, WA, approved the study.

Subject Enrollment. A total of 1511 subjects were recruited from two colleges near Portland, OR; a community center outside Portland; a hospital outpatient clinic (Willamette Valley Medical Center); and several senior citizen centers. Subjects were screened by a research nurse who obtained consent and a brief cardiac history and determined whether the subjects had any acute

Sean P. Collins, MD;[1] Patricia Arand, PhD;[2] Christopher J. Lindsell, PhD;[3] W. Frank Peacock IV, MD;[4,5] Alan B. Storrow, MD[1]
From the Department of Emergency Medicine[1] and the Institute of Health Policy and Health Sciences Research,[3] University of Cincinnati, Cincinnati, OH; Inovise Medical, Inc., Portland, OR;[2] the Department of Emergency Medicine, Ohio State University, Columbus, OH;[4] and The Cleveland Clinic Foundation, Cleveland, OH[5]
Address for correspondence: Sean P. Collins, MD, Assistant Professor, Department of Emergency Medicine, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267-0769
E-mail: sean.collins@uc.edu
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cardiovascular complaints. Potential subjects were not enrolled if acute cardiovascular complaints were indicated. Baseline demographic information was recorded on all subjects.

Recording the Heart Sounds. Electrodes were placed on each subject in a standard 12-lead configuration, except for Audicor (Inovise Medical, Inc., Portland, OR) sensors (capable of both ECG and acoustic signal detection), which were placed in the V_3 and V_4 positions (Figure 2). The V_3 sensor was positioned in the fourth intercostal space at the midclavicular line. The V_4 sensor was positioned midway between V_3 and V_5, the latter of which was in the fifth intercostal space in the anterior axillary line. Cardiac acoustic and standard 12-lead ECG data were recorded simultaneously. The subject was supine or in a semi-Fowler's position and asked to relax, breath normally, and refrain from speaking during a 10–180-second continuous recording. The data collection was performed with custom data collection systems based on the Hewlett-Packard XLi cardiograph (Hewlett-Packard Company, Palo Alto, CA) with sampling rates at either 4000 or 1000 samples per second and digital files stored for later processing. All of the sound and electrical data were run through the same version of the ECG and sound algorithms, independent of the system on which the data was collected. All recorded data was filtered and downsampled to the same sampling rate (500 samples per second) and then processed through identical data streams.

The 12-lead ECGs were analyzed using a commercial computerized algorithm (Audicor) for the presence of cardiac disease, specifically the presence of LV hypertrophy, prior myocardial infarction (MI), acute MI, and ischemia. Patients with multiple findings on ECG were given only one diagnosis, according to a priority ordering of findings: acute MI, prior MI, ischemia, LV hypertrophy, abnormal, borderline, and normal.

Phonocardiographic evidence of heart sounds was determined by computerized algorithm. The algorithm has been validated in prior studies comparing the detection of S_3 and S_4 to hemodynamic measurements obtained at cardiac catheterization.[17] Briefly, both channels (V_3 and V_4) are analyzed by the algorithm for the presence of abnormal diastolic heart sounds, using the ECG as a timing marker, and frequency content appropriate for the gallops, and the results are combined for the final statements. The results of this analysis are then displayed on the paper printout of the ECG.

Statistical Analysis. Data are described using median and range for age and frequencies and percent for all other variables. For computing prevalence, the sound data constitute a multinomial distribution with mutually exclusive findings of no sounds, S_3 only, S_4 only, or both S_3 and S_4. This distribution arises from a function of the algorithmic interpretation of the heart sounds. The detection of either heart sound is not necessarily an independent event. Both gallops may be identified during a period of potential acoustic overlap. When this occurs, since it is not possible to algorithmically categorize the finding as a discrete S_3 or S_4, it is reported as the combination. For this reason, exact 95% confidence intervals for multinomial proportions have been used to estimate variance of the prevalence estimates. Prevalence estimates of the S_3 and S_4 do not include findings of both S_3 and S_4. Multinomial logistic regression has been used to evaluate relationships between predictor variables and the presence or absence of the various heart sounds. Analyses have been performed using StatXact version 6 (Cytel Software Corporation, Cambridge MA) and SPSS version 12.0 (SPSS Inc., Chicago IL).

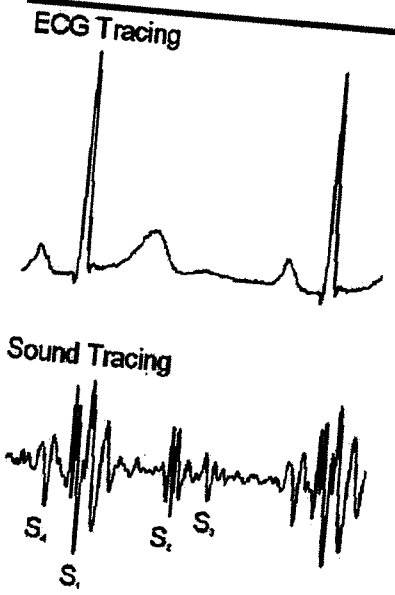

Figure 1. Location of heart sounds in the cardiac cycle. ECG=electrocardiographic

Results

We recorded heart sounds in 1511 subjects between 18 and 99 years of age (median, 63 years). There were 182 subjects excluded from the analysis because of: dextrocardia (1), missing demographic information (3), ventricular pacing (47), other ECG abnormalities in which heart sounds were not able to be analyzed (52) (e.g., Wolff-Parkinson-White syndrome, second-degree heart block), and atrial fibrillation or flutter (79). Of the remaining 1329 subjects included in analyses, 35.7% (474) were ambulatory seniors, 31.5% (418) were from the hospital outpatient clinic, 20.2% (269) were asymptomatic adults, 11.4% (152) were college students, and 1.2% (16) did not fit into any of these categories. Women comprised 59.1% (786) of the subjects. Population characteristics are given in Table I for the entire cohort and for subjects within each group.

The overall prevalence of S_3 was 10.0% (95% confidence interval [CI], 8.1%–12.2%); the prevalence of S_4 was 15.6% (95% CI, 13.2%–18.2%), and the prevalence of both S_3 and S_4 was 3.5% (95% CI, 2.4%–5.0%). Table II gives point estimates of the prevalence of heart sounds stratified by decade and subject group. Figure 3 shows the prevalence of S_3, S_4, and both S_3 and S_4, stratified by age. In the multinomial logistic regression model (Table III), increasing age was associated with decreased odds of an S_3 being detected (odds ratio [OR], 0.96; 95% CI, 0.95–0.96) but increased odds of an S_4 being detected (OR, 1.04; 95% CI, 1.03–1.05). There was no influence of

Table I. Characteristics of Subjects in the Study

	Asymptomatic Adults N=269	Ambulatory Seniors N=474	College Students N=152	Outpatients N=418	Other N=16	Total N=1329
Women (n [%])	185 (68.8)	324 (68.4)	72 (47.4)	191 (45.7)	14 (87.5)	786 (59.1)
Men (n [%])	84 (31.2)	150 (31.6)	80 (52.6)	227 (54.3)	2 (12.5)	543 (40.9)
Age (yr) (median [range])	48 (30–59)	74 (60–94)	21 (18–29)	66 (21–94)	27 (22–29)	63 (18–94)
Age (yr) distribution (n [%])						
<30	4 (1.5)	–	152 (100.0)	4 (1.0)	16 (100)	176 (13.2)
31–40	77 (28.6)	–	–	13 (3.1)	–	90 (6.8)
41–50	72 (26.8)	–	–	50 (12.0)	–	122 (9.2)
51–60	116 (43.1)	13 (2.7)	–	98 (23.4)	–	227 (17.1)
61–70	–	140 (29.5)	–	81 (19.4)	–	221 (16.6)
71–80	–	221 (46.6)	–	113 (27.0)	–	334 (25.1)
>80	–	100 (21.1)	–	59 (14.1)	–	159 (12.0)

Table II. Prevalence of S_3 and S_4, Stratified by Patient Group and Decade of Age

Age (yr)	Abnormal Heart Sounds (n [%])			
Asymptomatic Adults	None	S_3	Both	S_4
<30	3 (75.0)	0 (0.0)	1 (25.0)	0 (0.0)
31–40	62 (80.5)	10 (13.0)	4 (5.2)	1 (1.3)
41–50	51 (70.8)	9 (12.5)	3 (4.2)	9 (12.5)
51–60	89 (76.7)	7 (6.0)	3 (2.6)	17 (14.7)
Total	205 (76.2)	26 (9.7)	11 (4.1)	27 (10.0)
Ambulatory Seniors				
51–60	11 (84.6)	1 (7.7)	0 (0.0)	1 (7.7)
61–70	109 (77.9)	4 (2.9)	3 (2.1)	24 (17.1)
71–80	165 (74.7)	6 (2.7)	9 (4.1)	41 (18.6)
>80	69 (69.0)	4 (4.0)	1 (1.0)	26 (26.0)
Total	354 (74.7)	15 (3.2)	13 (2.7)	92 (19.4)
College Students				
<30 (Total)	84 (55.3)	59 (38.8)	5 (3.3)	4 (2.6)
Outpatients				
<30	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)
31–40	12 (92.3)	1 (7.7)	0 (0.0)	0 (0.0)
41–50	41 (82.0)	5 (10.0)	2 (4.0)	2 (4.0)
51–60	67 (68.4)	5 (5.1)	8 (8.2)	18 (18.4)
61–70	58 (71.6)	5 (6.2)	2 (2.5)	16 (19.8)
71–80	76 (67.3)	6 (5.3)	3 (2.7)	28 (24.8)
>80	31 (52.5)	5 (8.5)	3 (5.1)	20 (33.9)
<30 to >80	287 (68.7)	29 (6.9)	18 (4.3)	84 (20.1)
Other				
<30	12 (75.0)	4 (25.0)	0 (0.0)	0 (0.0)

age on the prevalence of a combined S_3 and S_4 (OR, 1.00; 95% CI, 0.98–1.01).

Figure 4 shows prevalence of the heart sounds separately for men and women. The model showed that women were less likely than men to have a detectable combined S_3 and S_4. There was no measurable influence of gender on the presence of an S_4. Table III shows the relationship between ECG findings and the presence of an S_3 or S_4. The univariable multinomial regression showed no significant relationships between ECG findings and heart sounds. ECG findings have not been included in the multivariable model.

third and fourth heart sounds

Table III. Multinomial Logistic Regression Models Showing the Relationship Between Abnormal Heart Sounds, Age, Gender, and Electrocardiographic (ECG) Findings

		S_3		Both		S_4	
Univariable Models	N	OR	95% CI	OR	95% CI	OR	95% CI
Age		0.955	0.946–0.964	0.996	0.981–1.011	1.037	1.026–1.048
Women vs. men		0.757	0.525–1.090	0.398	0.218–0.727	0.920	0.677–1.250
ECG findings*							
Acute myocardial infarction	8		**		**		
Prior myocardial infarction	174	0.641	0.324–1.269	0.686	0.227–2.076	3.008	0.704–12.858
Ischemia	32	0.342	0.045–2.591	3.016	0.822–11.072	1.166	0.730–1.862
Left ventricular hypertrophy	46	0.778	0.229–2.648	2.288	0.634–8.264	1.367	0.536–3.487
Abnormal	331	0.996	0.618–1.605	1.418	0.695–2.893	1.902	0.910–3.974
Borderline	220	1.893	1.188–3.016	0.752	0.273–2.076	1.093	0.739–1.616
Multivariable Model						1.057	0.667–1.675
Age		0.955	0.946–0.965	0.997	0.982–1.012	1.037	1.026–1.048
Women vs. men		0.851	0.579–1.251	0.400	0.219–0.732	0.877	0.641–1.200

*normal ECG is the reference category in all cases; **no findings of acute myocardial infarction among patients with an S_3 or both an S_3 and S_4

Discussion

Our results suggest that an S_3 is common in the asymptomatic individual younger than 40, with its presence decreasing in the decades of life thereafter. This underlying prevalence (approximately 10%) has implications in the management of those patients with a suspected acute coronary syndrome. The American College of Cardiology/American Heart Association guidelines recommend that patients with unstable angina and a concurrent auscultated S_3 be classified in the group at highest risk for adverse outcomes and considered candidates for an early invasive strategy.[18] Accurate knowledge of the true underlying frequency of the S_3 may impact these recommendations. Consequently, the implications of our findings require further corroboration with clinical outcomes.

The low prevalence of S_3 in asymptomatic subjects over the age of 50 strengthens previous findings that a detectable S_3 in older subjects may be highly specific for cardiac pathology, although the age above which an S_3 is predictive of LV dysfunction may be slightly higher than 40 years, as previously reported.[5–7]

In contrast to the S_3, detection of an S_4 was quite uncommon in subjects younger than 50 (under 10%), with increasing prevalence thereafter.

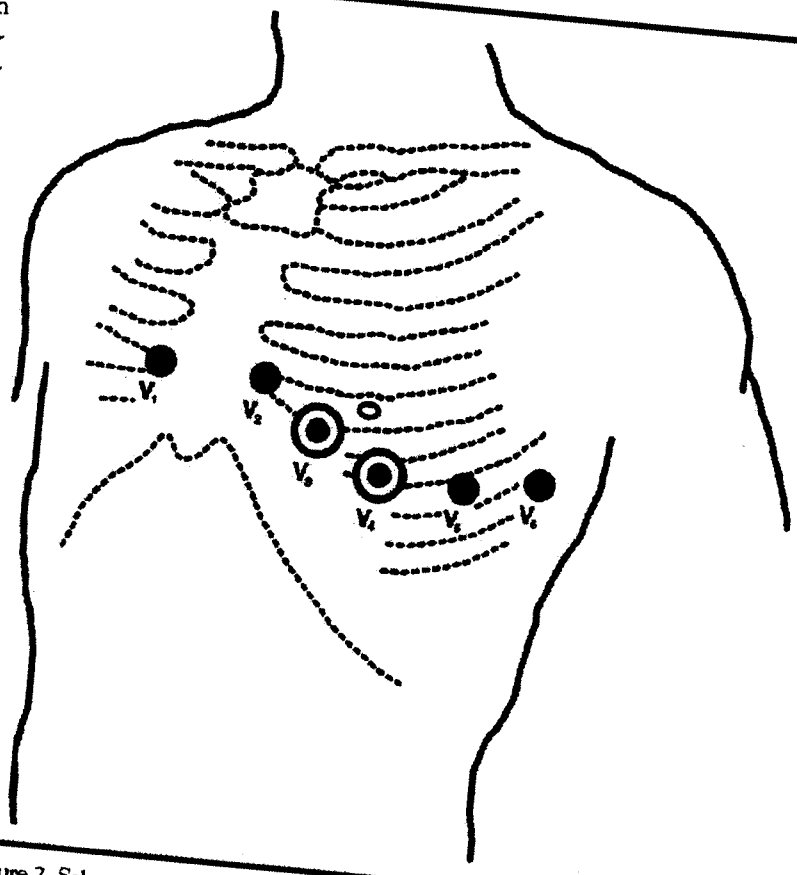

Figure 2. Schematic of the placement of the chest leads with acoustical leads in the V_3 and V_4 positions

An S_4 detected by auscultation has long been considered indicative of ventricular dysfunction.[19,20] Previous studies have demonstrated the presence of an S_4 during episodes of angina, in patients with coronary artery disease,

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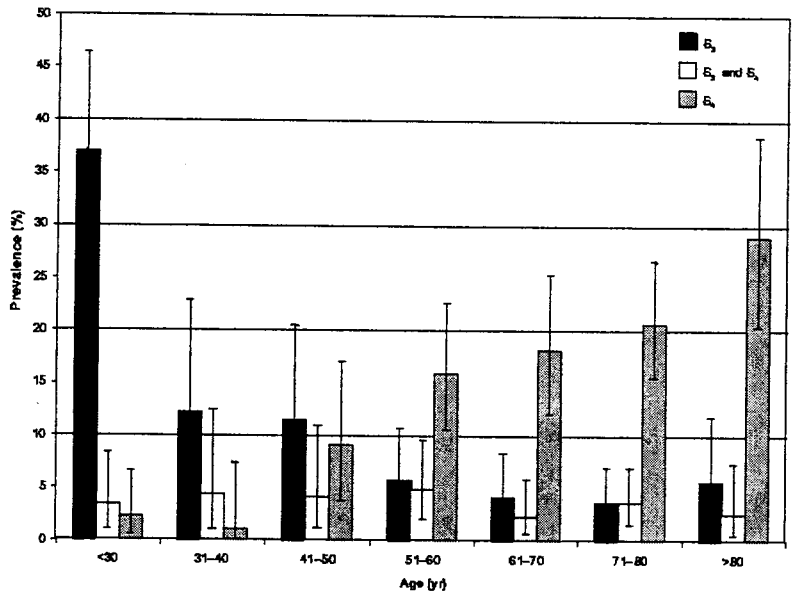


Figure 3. Prevalence of S_3 and S_4 heart sounds stratified by age. Subjects with a finding of S_3 and S_4 are not included in those with findings of S_3 or S_4 only; findings are mutually exclusive. Error bars represent 95% confidence intervals.

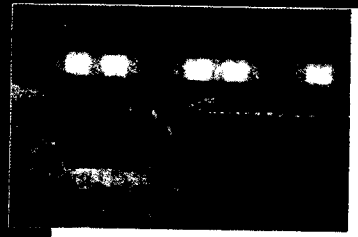
and during ischemic stress tests.[16,21,22] Several studies in the early and mid-1970s questioned the validity of this belief. Spodick and Quarry,[12] examining 250 consecutive ambulatory subjects in the Framingham Heart Study, found a phonocardiographic S_4 to be present in 73.1% of healthy patients and 74.3% of patients with CV disease. In a subsequent study of 100 patients of whom half were healthy and half had hypertension, these investigators found a similar 70% prevalence of S_4 in healthy subjects as well as those with hypertension.[15] Eriksen and Rasmussen[11] detected an S_4 using phonocardiography in over 50% of 1714 healthy middle-aged men. Other studies have reported a similar prevalence of S_4 in healthy individuals, although they are limited by a small total enrollment and referral bias.[10,13,14]

At the center of the S_4 controversy may be the difference between an auscultated vs. a phonocardiographically detected S_4. Previous studies on diagnostic and prognostic significance have traditionally focused on an S_4 detected by auscultation.[19,20] With the advent of new technology being incorporated into the bedside ECG, it is necessary to determine the diagnostic and prognostic significance of a phonocardiographic S_4 that may not have been evident on auscultation.

Technology available in the 1970s, when studies suggested a high prevalence of S_4 in healthy individuals, may have inaccurately detected S_4. The low frequency range sound of the S_4 (10–50 Hz)[23,24] overlaps the frequencies of the S_1 (30–150 Hz), making it difficult to differentiate from a split S_1. Our more modern phonocardiographic technique showed a prevalence more consistent with auscultation—Aronow and colleagues[16] found an S_4 to be present at rest in 14% of healthy subjects (n=100) and 43% of subjects with angina (n=100). While the studies discussed here indicate there may be an S_4 present in a subset of asymptomatic patients, it is uncertain whether this is pathologic. Future studies addressing the diagnostic and prognostic significance of a phonocardiographically detected S_4 are fundamental to resolving these discrepant findings.

Detection of either the S_3 or S_4 did not seem to be related to ECG findings in our subjects. Patients with borderline ECG results did demonstrate increased odds of having a detectable S_3, but in the absence of a relationship between definite ECG findings and heart sounds, it might be concluded that the significant result may be spurious. If a true result, the clinical implications are somewhat unclear. Further, the automated interpretation of the ECG may not be sufficiently accurate to determine relationships between heart sounds and ECG findings. For example, the eight patients with automated readings of acute MI were visually over-read by a board-certified cardiologist. Two of the ECGs had paced rhythms that the algorithm missed, resulting in a misclassification. One patient was in atrial flutter and the algorithm did not apply the confounder adjustment, resulting in a misclassification as probable acute ST-segment elevation. One subject had ST depression that was confirmed by visual over-read. Three subjects had borderline ST-segment elevation that was confirmed visually. One subject had ST elevation that was confirmed by visual over-read.

Our intent was to determine the prevalence of an S_3 and S_4 in asymptomatic subjects. Our cohort reported no acute complaints but did not undergo further workup to determine the presence of occult cardiac disease. Other medical conditions, such as hypertension, have been identified as producing S_4 in otherwise asymptomatic individuals, and there may have been hypertensive subjects in our cohort, resulting in an overestimate of the prevalence of S_4. Exclusion of hypertension would be expected to exaggerate our finding that S_4 may not be as common as previously considered. The short sampling timeframe may also limit our findings; the majority of patients had only 10 seconds of data sampled, and measurements were made only once. Repeat measurements or longer samples may result in an increased prevalence, as a greater opportunity is provided to detect a quiet or intermittent S_3 or S_4. The automated ECG reading was algorithmically generated and not based on manual interpretation. While this ensures consistency across readings, subtle changes or atypical findings may have been missed.



By Jeffrey Lindsey, PhD, EMT-P

Heart Sounds

Do you hear what I see?

I remember learning about heart sounds in paramedic class 20 years ago. Back then, I probably couldn't tell you much about their value, because it was one of those skills you learned but never make practical application of in the field. Actually, up until seeing this innovative device, the Audicor System, I probably still couldn't talk about heart sounds with any certainty of their value in the prehospital setting. If you're nodding your head thinking the same thing, read on.

The Audicor System is an exciting technological breakthrough. Inovise Medical Inc. integrated a special "language and interpretation" of heart sounds into the system, which was designed with female patients (who often don't present with "normal" symptoms during cardiac events) in mind.

Audicor improves the detection of acute cardiac conditions by analyzing S3 and S4 heart sounds. The device is a small computerized unit, similar to a typical EMS ECG monitor. The unit allows the user to view the rhythm and also input patient information for record-keeping. You apply your ECG electrodes for a 12-lead tracing as you normally would, with the exception of the V3 and V4 electrodes, which are replaced with a special electrode (see photos below) that has an audio sensing device, like a microphone. The sensor detects S3 and S4 heart sounds and transmits the sound to the monitor, which displays the results in a waveform readout.

The comprehensive printout it provides quite frankly "wowed" me (see Figure 1, p. 106). It resembles a 12-lead printout but with some other great information. At the bottom of the printout, the S3 and S4 heart sounds are displayed similar to an ECG tracing or graph. At the top right, a cross-section of the heart illustrates the estimated area at risk and the size/location of the infarct. The upper left corner has patient information and pertinent findings regarding the ECG and heart sounds.

When detecting an S3 heart sound, the provider must consider decompensating heart failure and left ventricular dysfunction. With an S4 heart sound, a provider must consider acute ischemia and reduced ventricular compliance. An entire article could be devoted to heart sounds, but here, I touch only on the basics. Regarding S3 and S4 heart sounds:

- An S3 or S4 sound on a patient who otherwise has a normal ECG or an ECG with non-specific ST-T wave changes should raise a red flag. Bring such sounds to the attention of hospital staff so they'll know to search for a cause;
- In patients presenting with shortness of breath, an S3 is strongly indicative of left ventricular dysfunction and congestive heart failure, which may or may not be accompanied by rales;
- In a patient presenting with a history of chest pain or weakness, the presence of an S3 sound suggests left ventricular dysfunction secondary to coronary artery disease and high-risk ACS;
- If an S4 heart sound is found and the patient has no evidence of left ventricular hypertrophy (LVH) or chronic, poorly controlled hypertension, the finding suggests ventricular ischemia and stiffening of the ventricular wall; and
- If an S4 heart sound is found in a patient with ECG evidence of LVH or the patient has a long history of poorly controlled hypertension, the finding is indicative of chronic afterload effects on the heart.

I was impressed by how simply this device works and even more impressed by the price; the unit is approximately one-third the cost of a current EMS ECG monitor. However, don't get impulsive

PHOTOS: JEFFREY LINDSEY

To use the Audicor, apply your 12-lead electrodes in the usual manner, replacing leads V3 and V4 with the system's special sensors.