

**Submitter :** Ms. Patricia White  
**Organization :** Inovise Medical, Inc.  
**Category :** Device Industry

**Date:** 09/29/2006

**Issue Areas/Comments**

**Packaged Services**

**Packaged Services**

Please see multiple attached files.

CMS-1506-P-195-Attach-1.PDF

CMS-1506-P-195-Attach-10.PDF

CMS-1506-P-195-Attach-2.PDF

CMS-1506-P-195-Attach-3.PDF

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Correlated Audioelectric Cardiology

September 29, 2006

**Via FedEx and Electronic Submission to: <http://www.cms.hhs.gov/eRulemaking>**

Mark B. McClellan, M.D., Ph.D.  
Administrator, Centers for Medicare & Medicaid Services  
U.S. Department of Health and Human Services  
Attn: CMS-1506-P  
Mail Stop C4-26-05  
7500 Security Boulevard  
Baltimore, Maryland 21244

**Re: Medicare Program; The Hospital Outpatient Prospective Payment System and CY 2007 Payment Rates; CY 2007 Update to the Ambulatory Surgical Center Covered Procedures List; the Ambulatory Surgical Center Payment System and CY 2008 Payment Rates; Medicare Administrative Contractors; and Reporting Hospital Quality Data for FY 2008 Inpatient Prospective Payment System Annual Payment Update Program --HCAHPS\* Survey, SCIP, and Mortality; Proposed Rule  
CMS-1506-P  
Comments on Packaged Services—0069T “Acoustic heart sound recording and computer analysis”**

Dear Dr. McClellan:

On behalf of Inovise Medical, Inc. we are pleased to submit comments on the above-captioned Proposed Rule for the 2007 Hospital Outpatient Prospective Payment System (the “Proposed Rule”). Inovise Medical, Inc., is a medical device company in Portland, Oregon, that is committed to the development of innovative relatively low cost diagnostic products. Inovise is the developer and manufacturer of the Audicor® System, a cardiac diagnostic device used in the diagnosis and management of patients with heart failure. The Audicor® System is used to perform acoustic heart sound recording and computer analysis, which is billed under code 0069T. We were disappointed to see that CMS is proposing to package this service under the 2007 OPPS, however, we appreciate the opportunity to respond to the concerns raised by the Centers for Medicare and Medicaid Services (CMS) in the Proposed Rule by clarifying certain facts about the device and the related procedure and by providing new information that was not available at the time the Proposed Rule was drafted. We are confident that your review of these data will support a decision to unpackage this procedure and to assign code 0069T to an Ambulatory Payment Classification group for 2007.

**I. Background on Audicor® System and Acoustic Heart Sound Recording with Computer Analysis**

The Audicor System was cleared by the U.S. Food and Drug Administration in 2003 to acquire, analyze, display and print heart sound data useful in the identification of cardiac conditions

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MIA 313906-1.075705.0011

Attach 11  
195

associated with left ventricular dysfunction. A supplemental clearance was obtained in 2005 to allow for displaying and monitoring cardiac indices, including Left Ventricular Systolic Time (LVST), QS1 and S3 strength, measures of heart pump function. LVST measures the time interval that the heart is pumping (the interval between the first and second heart sounds): a longer time correlates with better heart pump function. QS1 (also called EMAT or electromechanical activation time) measures the time from the start of the electrical signal for heart to pump (the Q wave) to the beginning of pumping (first heart sound): a shortened time period correlates with greater heart pump function. S3 strength measures the strength of the third heart sound, which is generally not heard when listening to a healthy patient's heart: a value >5 correlates with elevated left ventricular filling pressure or cardiac overload. A copy of a report showing these values is attached (Attachment A). A packet of peer-reviewed, published clinical literature on the use of acoustic heart sound recording is also attached (Attachment B); included among these papers is a symposium supplement from the journal Congestive Heart Failure, which focuses on acoustic heart sound recording and was published in July/August 2006.

The acoustic heart sound recording procedure principally is performed in the following settings: (1) in the emergency department (ED) to evaluate patients with shortness of breath to assist with the diagnosis of heart failure, (2) in the electrophysiology outpatient clinic (or physician office) to optimize settings in patients with cardiac resynchronization therapy (CRT) device implantation, (3) in the heart failure outpatient clinic (or physician office) to monitor and manage patients receiving medical or other therapies for heart failure. Currently, most utilization is in major hospital centers, and Medicare beneficiaries comprise the majority of patients who are undergoing procedures with the device.

The American College of Cardiology (ACC) sought new coding for the acoustic heart sound recording procedure in November 2003. Because the technology was new, the procedure was assigned a Category III Current Procedural Terminology (CPT) code. Although not part of the request by ACC, the CPT Editorial Panel included language to the descriptor designating the acoustic heart sound procedure as an add-on to the 12-lead electrocardiograph (ECG) procedure. The descriptor for the technical component/facility service read:

*0069T Acoustic heart sound recording and computer analysis;  
acoustic heart sound recording and computer analysis only (List separately in addition to  
codes for electrocardiography)  
(Use 0069T in conjunction with 93005)*

The initial device offerings of the Audicor® system provided a 12-lead ECG report together with the acoustic heart sound recording report and accommodated attachment of the Audicor® device to an ECG cart. The device was designed this way because it was felt that combining the acoustic heart sound recording procedure with a 12-lead ECG would improve work flow. Early in its adoption and use the acoustic heart sound recording procedure was performed primarily in patients presenting in EDs with shortness of breath. Many of these patients will also have an ECG performed to assist with diagnosis (to rule out myocardial infarction or arrhythmia as the cause of the shortness of breath).

As the use of the device has evolved to include patients in heart failure clinics being evaluated for management of heart failure and patients in electrophysiology clinics undergoing optimization of CRT devices, physician-users requested that the 12-lead ECG co-functionality of the devices be removed because it was unnecessary. Therefore, the current devices do not include a 12-lead ECG report.

It is important to understand that the acoustic heart sound recording procedure never required a 12-lead ECG for its performance—the heart sounds recording was simply an attachment to the device to improve work flow. The device does incorporate a single electrical lead (two sensors) together with the acoustic sensors, but this is simply to obtain heart timing information that is used in determining some of the cardiac indices measured by the Audicor® system. The measures reported by the Audicor® system relate to heart pump function—these are different from the electrical measures obtained by an ECG. The acoustic heart sound recording procedure is ordered and performed separately and independently from an ECG procedure. Some patients in whom acoustic heart sound recording is performed will have an ECG; others will not.

## **II. Request to Unpackage Code 0069T and 2007 Proposed Rule**

Acoustic heart sound recording under code 0069T was packaged for the 2006 OPPS. For the 2007 OPPS, Inovise requested that the procedure be paid separately as it is a distinct diagnostic test like other diagnostic tests that are paid separately under OPPS. In the Proposed Rule, CMS proposed maintaining the packaging status for this procedure “because it is closely linked to the performance of an ECG, should never be reported alone, and is estimated to require only modest hospital resources.”<sup>1</sup> We are pleased to respond to each of these concerns.

### **A. Acoustic Heart Sound Recording is Not Closely Linked to the Performance of an ECG**

As explained in Section I, above, the acoustic heart sound recording procedure is not linked to the performance of a 12-lead ECG procedure. We understand that there may have been confusion on this point due to the initial version in 2004 that added sound to a 12-lead device. The inclusion of a single electrical lead for timing purposes as part of the acoustic heart sound recording procedure does not mean that this procedure comprises a 12-lead ECG. In this regard, the acoustic heart sound recording procedure is like any other procedure which involves gating of the diagnostic information based upon the cardiac cycle, like echocardiography and nuclear cardiac imaging. (See Attachment C for copies of echocardiography images which show a single electrical lead superimposed on the ultrasound image.)

The acoustic heart sound recording procedure may be performed in patients in whom an ECG is also ordered, but in this regard, the procedure is no different from a chest-X-ray, the ECG, or a BNP (natriuretic peptide) test—all of which are paid separately.

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<sup>1</sup> 71 Fed Reg. 49506,49534 (Aug. 23, 2006).

**B. Acoustic Heart Sound Recording under Code 0069T may be Reported Alone Beginning in 2007**

The evolution of the technology away from any relationship with ECG reporting was recognized by the CPT Editorial Panel, which in response to a request from the ACC, has removed the add-on designation and reference to reporting with any ECG procedure effective January 1, 2007.

The new descriptor reads:

*0069T Acoustic heart sound recording and computer analysis; acoustic heart sound recording and computer analysis only*

Therefore, beginning January 1, 2007, it will be perfectly proper to report code 0069T without an ECG or any other procedure.

**C. Acoustic Heart Sound Recording Involves Significant Resources Relative to Other Services to which it may be Packaged**

In the Proposed Rule, CMS noted: "Using CY 2005 claims, we had only 9 single claims for CPT code 0069T, with a median line-item cost of \$1.93, consistent with its low expected cost."<sup>2</sup> The acoustic heart sound procedure is billed under a Category III code and was packaged in 2005. There was very little incentive for hospitals to bill using this code given the scrutiny payers apply to all Category III codes and the lack of any incremental payment due to the packaged status. Frankly, in 2005, Inovise was not yet mature enough in our reimbursement outreach to customers to help educate them on the importance of billing the procedure and properly reflecting the costs on claim forms for purposes of future OPPS rate-setting.

We cannot explain the \$1.93 median cost observed on the 9 single claims. Since the procedure would almost never be performed as a sole OPPS service, it is unlikely that the 9 single claims were accurately coded.

The Audicor<sup>®</sup> device acoustic sensors currently sell for \$35 for the two used during a single procedure. During 2005, the average sales price to hospitals for these sensors was \$25. In addition, hospitals pay \$7,000 to \$17,000 to purchase the equipment (console and printer) used to perform the procedure. The more expensive model offers greater functionality and includes an additional computer to do serial display of Audicor changes along with Bi-V timing changes. Considering the acoustic sensors and equipment plus costs for clinical staff to run the procedure (approximately 30 minutes for a nurse, technologist or other trained staff) and overhead, we estimate total costs of ~\$80 for the procedure. This represents a substantial cost considering the payment for an ECG tracing of \$23.60 (Proposed Rule payment for APC 0099)

**D. Acoustic Heart Sound Recording is a Distinct Cardiac Diagnostic Procedure**

In the Proposed Rule, staff also indicated: "To the extent that the acoustic heart sounding recording service may be more frequently provided in the future in association with ECGs or

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<sup>2</sup> Id.

other OPPS services as its clinical indications evolve, we expect that its cost would also be increasingly reflected in the median costs for those other services, particularly ECG procedures."<sup>3</sup> Although we would agree that it would be rare that the acoustic heart sound procedure would be reported alone in the absence of any other OPPS services, we respectfully disagree with the characterization of the acoustic heart sound recording procedure as being "associated with" other procedures.

The acoustic heart sound recording procedure may be performed with a broad range of other services depending upon the particular case in which the test is ordered. For example, in a patient presenting to the ED with shortness of breath, a chest-X-ray, ECG, a BNP test and an ED visit may be performed and billed together with the acoustic heart sound recording procedure. In a patient visiting a heart failure clinic for management of diet and medications, the acoustic heart sound recording procedure may be performed together with an outpatient clinic visit. In a patient coming to an electrophysiology clinic for optimization of CRT settings, the acoustic heart sound recording procedure may be reported together with codes to report electronic analysis of CRT devices. Therefore, there is no particular service to which the acoustic heart sound recording procedure is associated.

It also appears quite unlikely that the costs of the acoustic heart sound recording procedure would be reflected in the median costs for these other services. First, all of the other services identified above are separately paid under OPPS (or under the Clinical Laboratory Fee Schedule, in the case of BNP). Under the OPPS single-claim methodology, it is likely that most, if not all, of the claims that would include code 0069T would be dropped because these would comprise multiple separately payable line items plus a single packaged service—there would be no single procedure to which the 0069T line item could be packaged. Even if the costs for the acoustic heart sound recording procedure were retained under the single claims methodology, the costs for the acoustic heart sound recording procedure would not be expected to have a meaningful impact on the median costs because many of the other services involve millions of single claims. The acoustic heart sound recording procedure is not expected to be performed at anywhere near the frequency of these other procedures and so would not be expected to impact the median value of the cost of these other procedures.

### **III. Summary and Recommendation**

In summary, we request that the acoustic heart sound recording procedure under code 0069T be unpackaged under OPPS because (1) it is not associated with any other single service, (2) the costs are not likely to map to any particular APC, and (3) the costs are not low compared with other procedures that may be performed at the same session.

As a separately paid service, we would recommend assignment to APC 0096 "Noninvasive vascular studies" (proposed payment ~\$97) or APC 0097 "Cardiac and ambulatory blood pressure monitoring" (proposed payment ~\$63) or to a new technology APC (e.g., APC 1502 level II [\$50-\$100] with proposed payment \$75) to allow for tracking of this procedure. All 3 APCs are

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<sup>3</sup> Id.

economically consistent with the estimated costs for the procedure and the 2 clinical APCs appear reasonably coherent clinically to the acoustic heart sound recording procedure.

As noted above, the acoustic heart sound recording procedure is performed together with clinic or ED visits, chest-X-rays, ECGs, and BNP tests to assist with diagnosis and management of patients with left ventricular dysfunction. All of these other services are paid separately. We are simply asking that the same criteria be applied to the acoustic heart sound recording procedure to allow separate payment for this distinct diagnostic service.

\* \* \* \*

We appreciate your consideration of our comments. If you have any questions about our comments or the attachments, please contact our reimbursement counsel, Paul Radensky, M.D., J.D., at 305.347-6557. Thank you for your attention to this matter, which is of critical importance to Inovise.

Sincerely yours,



Patricia White  
Chief Executive Officer

Attachments

Cc: Mr. Herb Kuhn  
Carol Bazell, M.D.  
Edith Hambrick, M.D., J.D.  
Kenneth Simon, M.D. M.B.A.  
Diane Wallis, M.D., F.A.C.C., F.C.C.P., American College of Cardiology  
Denise Garris, American College of Cardiology  
Stephanie Kennan, Office of Senator Ron Wyden  
Catherine Finley, Office of Senator Gordon Smith

# **Attachment A**

CMS-1506-P

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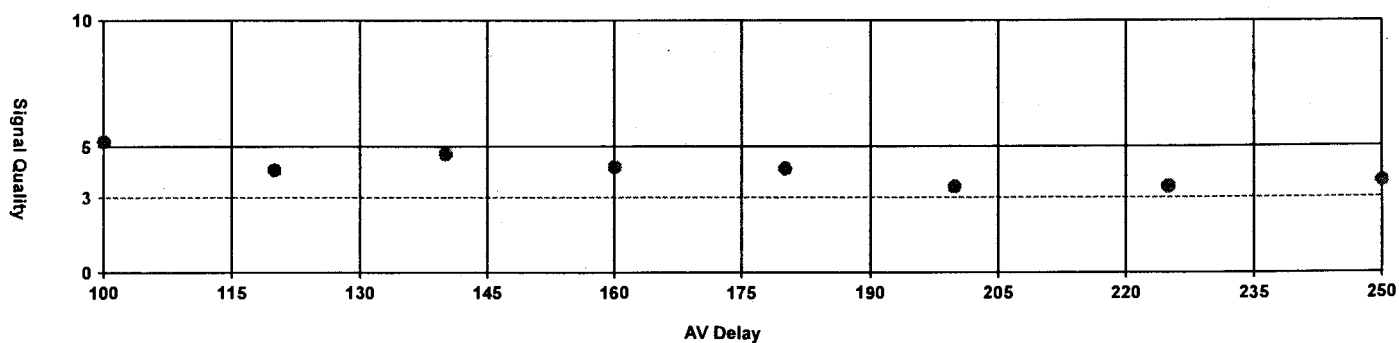
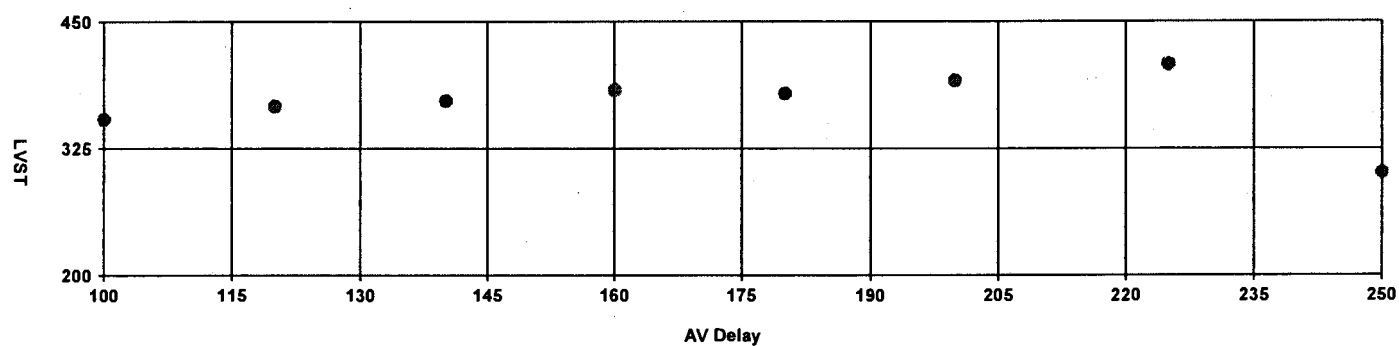
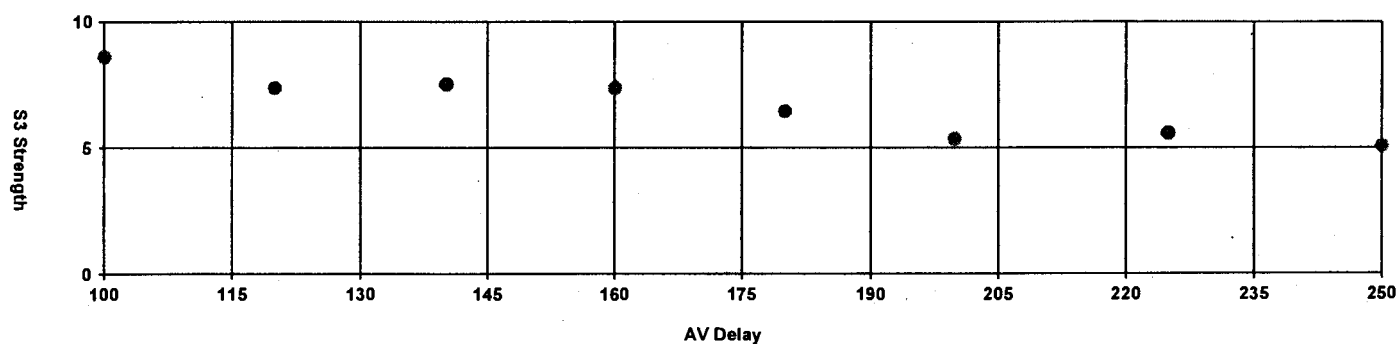
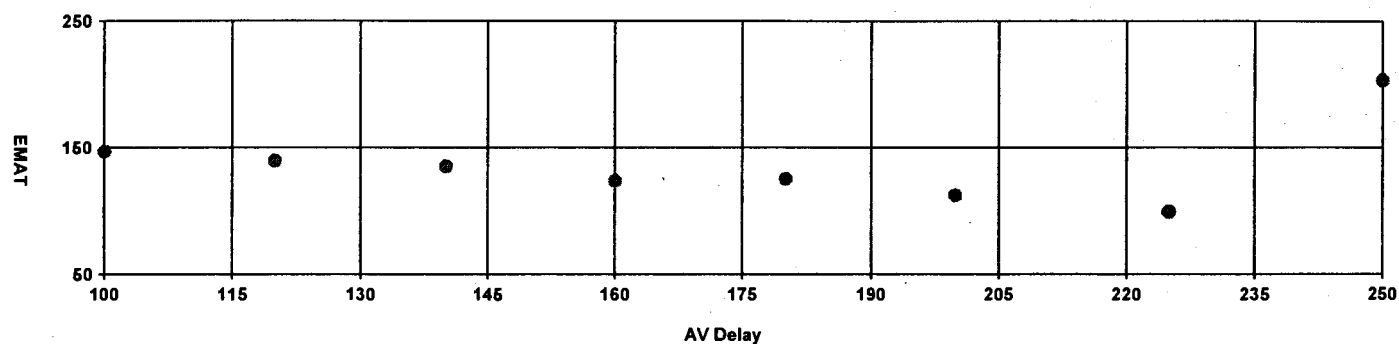
Patient ID: deb03

Gender: Male

Age: 50

Channel: Combined

Reviewed by: \_\_\_\_\_



Device ID: PP-01

Version: 1.1.16

# **Attachment B-1**

**CMS-1506-P**

**Comments on Packaged Services—0069T**  
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# Congestive Heart Failure®

july · august 2006

volume 12 · issue 4 · supplement 1

FOR SPECIALISTS AND PRIMARY CARE CLINICIANS TREATING HEART FAILURE ■

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

### review paper

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

W/ Frank Peacock, MD; Alex Harrison, MD; Alan S. Maisel, MD

### original papers

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

Sanjiv J. Shah, MD; Andrew D. Michaels, MD, MAS

#### Systolic Dysfunction: Correlation of Acoustic Cardiography With Doppler Echocardiography

Michel Zuber, MD; Peter Kipfer, MD; Christine Attenhofer Jost, MD

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

Markus Roos, MD; Stefan Toggweiler, MD; Michel Zuber, MD; Peiman Jamshidi, MD; Paul Erne, MD

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

Ayesha Hasan, MD; William T. Abraham, MD; Lori Quinn-Tate, RN, MN; Lei Brown, RDCS, RVT; Ali Amkieh, MD

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

W/ Frank Peacock, MD; Alex Harrison, MD; Donald Moffa, MD


### case reports

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

Stefan Toggweiler, MD; Michel Zuber, MD; Paul Erne, MD

#### Acoustic Cardiography in the Differential Diagnosis of Dyspnea

W/ Frank Peacock, MD

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

### review paper

- The Utility of Heart Sounds and Systolic Intervals Across the Care Continuum** 2  
W. Frank Peacock, MD; Alex Harrison, MD; Alan S. Maisel, MD

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W. Frank Peacock, MD

Sponsored by Winthrop-University Hospital and supported by an unrestricted educational grant from Inovise Medical, Inc.

## REVIEW PAPER

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

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

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

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

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

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

W. Frank Peacock, MD;<sup>1</sup> Alex Harrison, MD;<sup>2</sup> Alan S. Maisel, MD<sup>3</sup>

From the Department of Emergency Medicine, Cleveland Clinic, Cleveland, OH;<sup>1</sup> the Division of Cardiology, Department of Medicine, University of California, Irvine Medical Center, Orange, CA;<sup>2</sup> and the Department of Medicine, Veterans Affairs San Diego Healthcare System and University of California, San Diego, San Diego, CA<sup>3</sup>

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

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

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

## Heart Sounds and Systolic Time Intervals

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

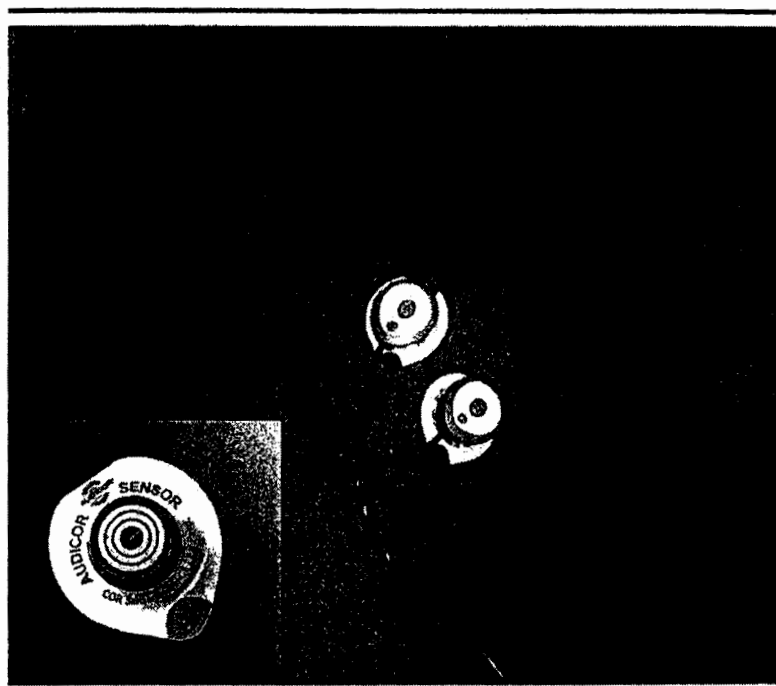


Figure 1. Placement of the AUDICOR sensors (Inovise Medical, Inc., Portland, OR)

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

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

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

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

**Table.** Definitions of Diastolic Time Intervals

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

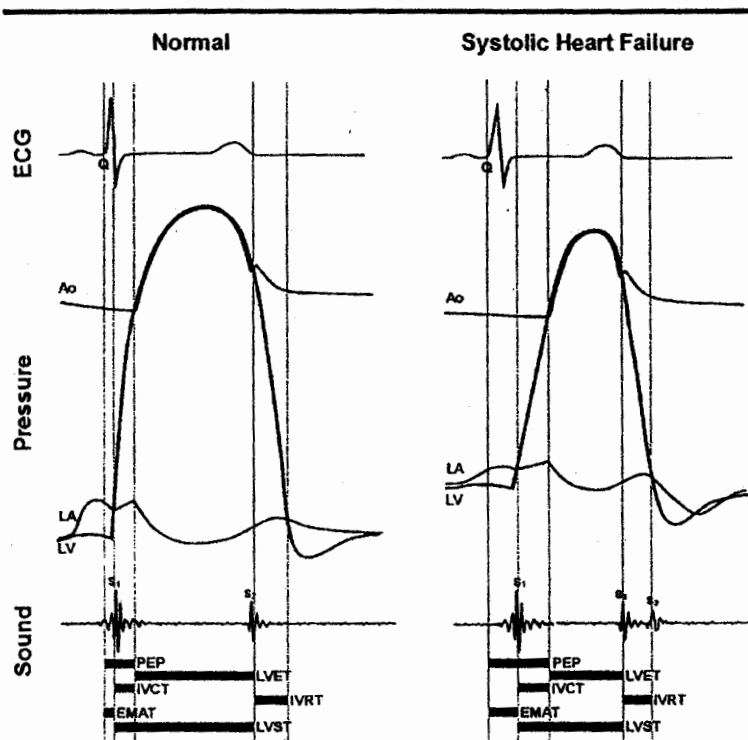


Figure 2. Heart sounds and systolic time interval data provided by the AUDICOR device (Inovise Medical, Inc., Portland, OR). (Pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR data.) ECG=electrocardiogram; Ao=aorta; LA=left atrium; LV=left ventricle; PEP=pre-ejection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

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

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

for prompt clinical use. Acoustic cardiography can provide objective measurements of heart sounds as well as valuable information about systolic time intervals that have proven useful in a variety of clinical settings (Figure 2, Table). A detailed investigation and discussion of the hemodynamic correlates of the  $S_1$  and systolic time interval follows in this supplement.<sup>33</sup>

### Acoustic Cardiography and Its Correlation to Gold Standards

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

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

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

### Clinical Applications of Acoustic Cardiography

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

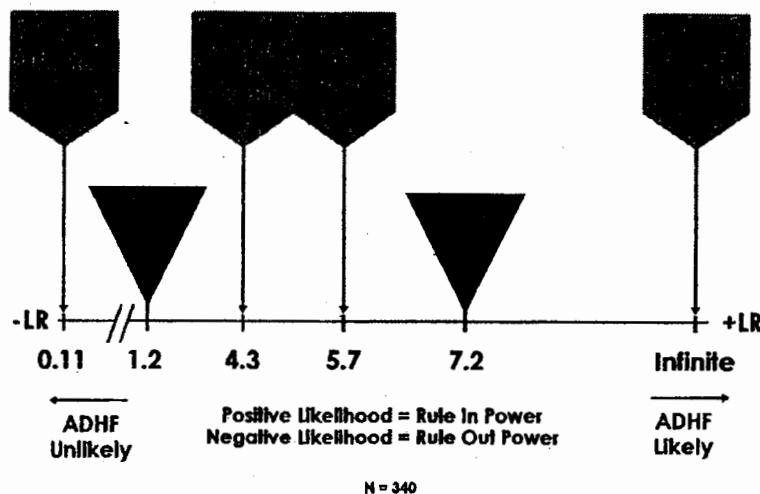


Figure 3. Synergy between acoustic cardiography-detected  $S_3$  and B-type natriuretic peptide (BNP) (pg/mL). ADHF=acute decompensated heart failure; LR=likelihood ratio

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

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

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

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

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



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

**Inpatient Hospital Setting.** The appearance, disappearance, or change in the  $S_3$  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.<sup>42</sup> The baseline data obtained in the ED may then be utilized to assist in determining therapeutic efficacy throughout a patient's hospital stay. As well, while few data currently exist for diagnosing ADHF that occurs as a secondary event during a hospitalization, one could speculate that having a baseline or BNP and acoustic cardiogram on admission could significantly aide in this diagnosis. Should an elevation in BNP occur and/or an  $S_3$  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.<sup>13</sup> This is in stark contrast to the randomized controlled clinical trials that led to the approval of CRT devices for treating HF. All of these trials implemented optimization strategies.<sup>7-11</sup>

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

regurgitant flow (indicating the onset of ventricular contraction).<sup>42</sup> Acoustic cardiography can optimize the settings of the CRT device by creating the shortest electromechanical activation time, defined as the time from the onset of the QRS complex (ventricular depolarization), to the  $S_1$ , 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.<sup>33</sup> 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<sup>43</sup> and case studies demonstrating the applicability of this technique in CRT optimization.

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

## Summary and Conclusions

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

## REFERENCES

- Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol*. 2005;46:e1-e82.
- Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-167.
- Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med*. 1992;327:685-691.
- Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med*. 2001;134:550-560.
- Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-717.
- Bordy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;252:225-237.
- Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol*. 2002;39:194-201.
- Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. *Circulation*. 2003;108:2596-2603.
- Auricchio A, Abraham WT. Cardiac resynchronization therapy: current state of the art: cost versus benefit. *Circulation*. 2004;109:300-309.
- Leclercq C, Hare JM. Ventricular resynchronization: current state of the art. *Circulation*. 2004;109:296-299.
- Jarcho JA. Resynchronizing ventricular contraction in heart failure. *N Engl J Med*. 2005;352:1594-1597.
- Meluzin J, Novak M, Mullerova J, et al. A fast and simple echocardiographic method of determination of the optimal atrioventricular delay in patients after biventricular stimulation. *Pacing Clin Electrophysiol*. 2004;27:58-64.
- Leon AR. Cardiac resynchronization therapy devices: patient management and follow-up strategies. *Rev Cardiovasc Med*. 2003;4(suppl 2):S38-S46.
- Potain C. Les bruits de galop. *Sem Med*. 1900;20:175.
- Sokolow M. *Clinical Cardiology*. 5th ed. Norwalk, CT: Appleton & Lange; 1990.
- Joshi N. The third heart sound. *South Med J*. 1999;92:756-761.
- Abrams J. Current concepts of the genesis of heart sounds. II. Third and fourth sounds. *JAMA*. 1978;239:2790-2791.
- Arevalo F, Meyer EC, Maccanone DM, et al. Hemodynamic correlates of the third heart sound. *Am J Physiol*. 1964;207:319-324.
- Stefadouras MA, Little RC. The cause and clinical significance of diastolic heart sounds. *Arch Intern Med*. 1980;140:537-541.
- Patel R, Bushnell DL, Sobolka PA. Implications of an audible third heart sound in evaluating cardiac function. *West J Med*. 1993;158:606-609.
- Rihal CS, Davis KB, Kennedy JW, et al. The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. *Am J Cardiol*. 1995;75:220-223.
- Drazner MH, Rame JE, Stevenson LW, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med*. 2001;345:574-581.
- Drazner MH, Rame JE, Dries DL. Third heart sound and elevated jugular venous pressure as markers of the subsequent development of heart failure in patients with asymptomatic left ventricular dysfunction. *Am J Med*. 2003;114:431-437.
- Ishmail AA, Wing S, Ferguson J, et al. Interobserver agreement by auscultation in the presence of a third heart sound in patients with congestive heart failure. *Chest*. 1987;91:870-873.
- Lok CE, Morgan CD, Ranganathan N. The accuracy and interobserver agreement in detecting the 'gallop sounds' by cardiac auscultation. *Chest*. 1998;114:1283-1288.
- Jauhar S. The demise of the physical exam. *N Engl J Med*. 2006;354:548-551.
- Ozawa Y, Smith D, Craig E. Origin of the third heart sound, II. Studies in human subjects. *Circulation*. 1983;67:399-404.
- Glover DD, Murrah RL, Olsen CO, et al. Mechanical correlates of the third heart sound. *J Am Coll Cardiol*. 1992;19:450-457.
- Kono T, Rosman H, Alam M, et al. Hemodynamic correlates of the third heart sound during the evolution of chronic heart failure. *J Am Coll Cardiol*. 1993;21:419-423.
- Manson AL, Nudelman SP, Hagley MT, et al. Relationship of the third heart sound to trans-mitral flow velocity deceleration. *Circulation*. 1995;92:388-394.
- Friedman SA, Davison ET. The phonocardiographic assessment of myocardial function in the aged. *Am Heart J*. 1969;78:752-756.
- Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation*. 1968;37:149-159.
- Shah SJ, Michaels AD. Hemodynamic correlates of the third heart sound and systolic time intervals. *Congest Heart Fail*. 2006;12(4 suppl 1):8-13.
- Moyers B, Shapiro M, Marcus GM, et al. The performance of phonoelectrocardiographic left ventricular systolic time intervals and B-type natriuretic peptide levels in the diagnosis of left ventricular dysfunction. *Ann Noninvasive Electrocardiol*. In press.
- Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA*. 2005;293:2238-2244.
- Zuber M, Kipler P, Attenhofer Jost C. Systolic dysfunction: correlation of acoustic cardiography with Doppler echocardiography. *Congest Heart Fail*. 2006;12(4 suppl 1):14-18.
- Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA*. 1989;261:884-888.
- Collins SP, Lindsell CJ, Peacock WF, et al. The combined utility of an S<sub>3</sub> heart sound and BNP levels in emergency department patients with dyspnea. *J Card Fail*. 2006;12:286-292.
- Peacock WF, Harrison A, Molit D. Clinical and economic benefits of using AUDICOR S<sub>3</sub> detection for diagnosis and treatment of acute decompensated heart failure. *Congest Heart Fail*. 2006;12(4 suppl 1):32-36.
- Acute Decompensated Heart Failure National Registry (ADHERE) database. Available at: <http://www.adhereregistry.com>. Accessed May 14, 2006.
- Peacock WF, Emerman CL, Costanzo MR, et al. Early initiation of intravenous therapy improves heart failure outcomes: an analysis from the ADHERE registry database. *Ann Emerg Med*. 2003;42:S26.
- Collins SP, Lindsell CJ, Peacock WF IV, et al. The effect of treatment on the presence of abnormal heart sounds in emergency department patients with heart failure. *Am J Emerg Med*. 2006;24:25-32.
- Hasan A, Abraham W, Quinn-Tate L, et al. Optimization of cardiac resynchronization devices using acoustic cardiography: a comparison to echocardiography. *Congest Heart Fail*. 2006;12(4 suppl 1):25-31.

## 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*

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

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

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

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

### Methodology and Definitions

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

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

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

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

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

inexpensive system (AUDICOR, Inovise Medical, Inc., Portland, OR). This acoustic cardiograph records, stores, displays, and interprets simultaneous digital ECG and heart sound data, using unique dual-purpose sensors that acquire both electrical and acoustic data from the V<sub>1</sub> and V<sub>4</sub> positions. The AUDICOR system's computerized algorithm uses wavelet-based signal processing techniques combined with a hidden Markov model to identify normal and abnormal heart sounds, and it determines the timing of heart sounds in the cardiac cycle by comparing the sounds to the onset of the P wave and QRS complexes in the simultaneously recorded ECG. The algorithm was developed using files annotated by phonocardiography experts, and it has been clinically validated using Doppler echocardiography and invasive hemodynamic data from patients with a variety of cardiac abnormalities. The AUDICOR system produces a variety of measurements, including the presence and strength of heart sounds (such as the S<sub>3</sub>) and the duration of STIs.

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

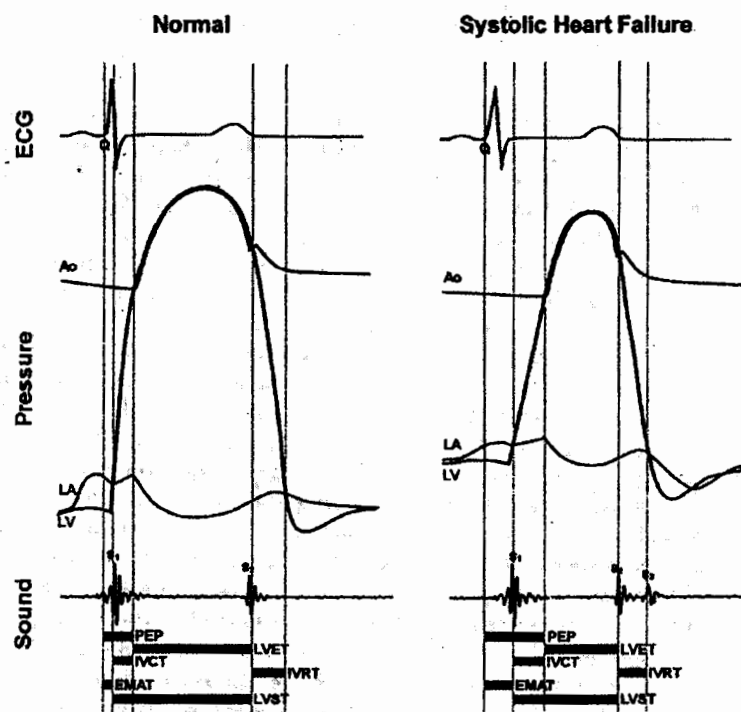


Figure 1. Illustration of systolic time intervals in relation to the cardiac cycle depicted via electrocardiographic (ECG) and pressure waveforms (pressure waveforms are displayed here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data.). Traditional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

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

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

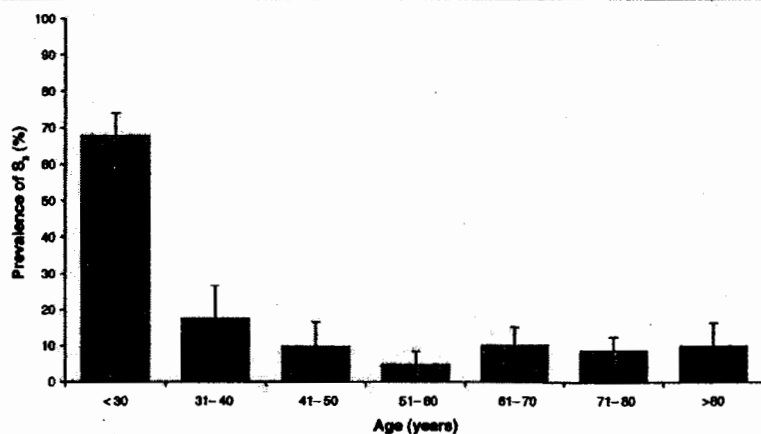


Figure 2. Prevalence of the  $S_3$  by age in asymptomatic individuals. Prevalence of the  $S_3$  decreases markedly in subjects older than 30 years. Adapted with permission from *Congest Heart Fail.* 2005;11:242-247.<sup>16</sup>

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.<sup>15</sup> It is the PEP/LVET ratio that has been most used to diagnose LV dysfunction.<sup>10,15</sup>

Of note, the STIs measured by the AUDICOR system are different from those conventionally measured. The AUDICOR system measures the  $Q-S_1$ ,  $Q-S_2$ , 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.<sup>16</sup> determined the prevalence of the  $S_3$  (Figure 2). Using these same record-

ings, the normal ranges of STIs using the AUDICOR system were calculated. The study sample comprised 1194 individuals (age,  $57.8 \pm 20.3$  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,<sup>17-21</sup> valvular heart disease,<sup>22,23</sup> acute myocardial infarction,<sup>24</sup> and in the perioperative period.<sup>25</sup> Phonocardiography has traditionally been the gold standard for detection of the  $S_3$ , 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 cardiovascular system, resulting in the  $S_3$ .<sup>24,26-28</sup> An increase in mitral inflow in early diastole, followed by a rapid cessation of that inflow, appears to be the

ideal setting in which the pathologic  $S_3$  becomes audible.<sup>26</sup> These hemodynamic conditions increase the deceleration rate of early mitral inflow, a finding that has been associated with the  $S_3$ .<sup>29-31</sup>

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.<sup>32</sup>

In the same cohort of 90 patients, we hypothesized that tissue Doppler imaging would provide insight into the physiology of the pathologic  $S_3$ . 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.<sup>33,34</sup> Since  $E/E'$  takes into account the volume and pressure of mitral inflow ( $E$ ) as well as stiffness of the myocardium ( $E'$ ), we hypothesized that the  $E/E'$  ratio would be independently associated with the  $S_3$ .

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  $S_3$  ( $p=0.009$ ).<sup>35</sup> 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.

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

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

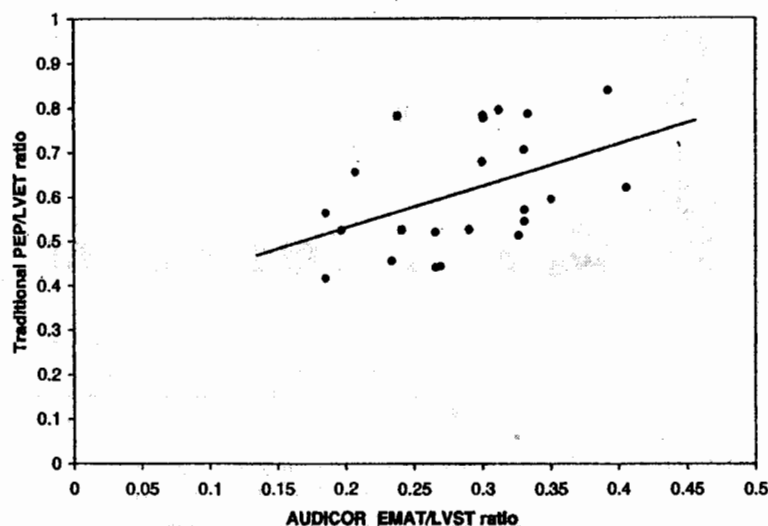


Figure 3. Scatterplot of traditional systolic time intervals (STIs) (pre-ejection period [PEP]/left ventricular ejection time [LVET]) and AUDICOR (Inovise Medical, Inc., Portland, OR) STIs (electromechanical activation time [EMAT]/left ventricular systolic time [LVST]). The AUDICOR and traditional STI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

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

In a study of 81 patients undergoing cardiac catheterization and echocardiography, we used the AUDICOR system to study the relationship between STIs and parameters of LV dysfunction. EMAT ( $r=-0.51$ ;  $p<0.0001$ ), EMAT/LVST ( $r=-0.41$ ;  $p=0.0001$ ), and Q-S<sub>2</sub> ( $r=-0.39$ ;  $p=0.0003$ ), correlated with LVEF, but not LV filling pressure. Since STIs, as measured by the AUDICOR system, appear to be more closely related to LVEF, and the  $S_3$  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.<sup>44</sup> described a noninvasive method for determining LV end-systolic elastance, a measurement that has traditionally required cumbersome invasive measurement with a conductance catheter and occlusion of the inferior vena cava. The noninvasive measurement described by Chen and colleagues requires echocardiographic, sphygmomanometric, and STI data,



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

The addition of AUDICOR-derived data such as the  $S_3$  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.<sup>45</sup> Thus, the AUDICOR system could potentially be used to improve the emergency diagnosis of heart failure.

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

help optimize CRT is another potential use of the system.

## Conclusions

Bedside diagnosis remains a vital tool in the diagnosis and treatment of heart failure. The AUDICOR system provides a simple, inexpensive, and quantitative method to determine the presence of the  $S_3$  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.

## REFERENCES

- 1 Rame JE, Dries DL, Drazner MH. The prognostic value of the physical examination in patients with chronic heart failure. *Congest Heart Fail.* 2003;9:170–175, 178.
- 2 Zimetbaum PJ, Josephson ME. Use of the electrocardiogram in acute myocardial infarction. *N Engl J Med.* 2003;348:933–940.
- 3 Jessup M, Brozena S. Heart failure. *N Engl J Med.* 2003;348:2007–2018.
- 4 McMurray JJ, Pfeffer MA. Heart failure. *Lancet.* 2005;365:1877–1889.
- 5 Selig MB. Stethoscopic and phonocardiographic devices: historical and future perspectives. *Am Heart J.* 1993;126:262–268.
- 6 Pierre-Carl Potain (1825–1901) cardiovascular physician. *JAMA.* 1966;196:1086.
- 7 Leatham A. *Auscultation of the Heart and Phonocardiography.* 2nd ed. Edinburgh, Scotland: Churchill Livingstone; 1975.
- 8 Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation.* 1968;37:149–159.
- 9 Weissler AM, Harris WS, Schoenfeld CD. Bedside techniques for the evaluation of ventricular function in man. *Am J Cardiol.* 1969;23:577–583.
- 10 Lewis RP, Rittgers SE, Froester WF, et al. A critical review of the systolic time intervals. *Circulation.* 1977;56:146–158.
- 11 Silverman ME. Aubrey Leatham: twentieth century pioneer in auscultation. *Clin Cardiol.* 1999;22:155–157.
- 12 Jauhar S. The demise of the physical exam. *N Engl J Med.* 2006;354:548–551.
- 13 Mangione S, Nieman LZ. Cardiac auscultatory skills of internal medicine and family practice trainees. A comparison of diagnostic proficiency. *JAMA.* 1997;278:717–722.
- 14 Sokolow M. Physical examination. In: Sokolow M, McIlroy MB, eds. *Clinical Cardiology.* 5th ed. Norwalk, CT: Appleton & Lange; 1990.
- 15 Craig E. Heart sounds: phonocardiography; carotid, apex, and jugular venous pulse tracings; and systolic time intervals. In: Braunwald E, ed. *Heart Disease.* 2nd ed. Philadelphia, PA: WB Saunders Co; 1984:40–67.
- 16 Collins SP, Arand P, Lindsell CJ, et al. Prevalence of the third and fourth heart sound in asymptomatic adults. *Congest Heart Fail.* 2005;11:242–247.
- 17 Drazner MH, Rame JE, Dries DL. Third heart sound and elevated jugular venous pressure as markers of the subsequent development of heart failure in patients with asymptomatic left ventricular dysfunction. *Am J Med.* 2003;114:431–437.
- 18 Drazner MH, Rame JE, Stevenson LW, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med.* 2001;345:574–581.
- 19 Perloff JK. Importance of elevated jugular venous pressure and a third heart sound in asymptomatic left ventricular dysfunction. *Am J Med.* 2003;114:499–500.
- 20 Umverferth DV, Magorien RD, Moeschberger ML, et al. Factors influencing the one-year mortality of dilated cardiomyopathy. *Am J Cardiol.* 1984;54:147–152.
- 21 Glover DR, Litter WA. Factors influencing survival and mode of death in severe chronic ischaemic cardiac failure. *Br Heart J.* 1987;57:125–132.
- 22 Folland ED, Kriegel BJ, Henderson WG, et al. Implications of third heart sounds in patients with valvular heart disease. The Veterans Affairs Cooperative Study on Valvular Heart Disease. *N Engl J Med.* 1992;327:458–462.
- 23 Abdulla AM, Frank MJ, Erdin RA Jr, et al. Clinical significance and hemodynamic correlates of the third heart sound gallop in aortic regurgitation. A guide to optimal timing of cardiac catheterization. *Circulation.* 1981;64:464–471.
- 24 Joshi N. The third heart sound. *South Med J.* 1999;92:756–761.
- 25 Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in non-cardiac surgical procedures. *N Engl J Med.* 1977;297:845–850.
- 26 Mehra NJ, Khan IA. Third heart sound: genesis and clinical importance. *Int J Cardiol.* 2004;97:183–186.
- 27 Braunwald E, Perloff JK. Physical examination of the heart and circulation. In: Braunwald E, ed. *Braunwald's Heart Disease.* 7th ed. New York, NY: Elsevier; 2005:817–818.
- 28 Manson AL, Nudelman SP, Hagley MT, et al. Relationship of the third heart sound to transmitral flow velocity deceleration. *Circulation.* 1995;92:388–394.
- 29 Van de Werf F, Boel A, Geboers J, et al. Diastolic properties of the left ventricle in normal adults and in patients with third heart sounds. *Circulation.* 1984;69:1070–1078.
- 30 Van de Werf F, Geboers J, Kesteloot H, et al. The mechanism of disappearance of the physiologic third heart sound with age. *Circulation.* 1986;73:877–884.
- 31 Pozzoli M, Febo O, Tramarin R, et al. Pulsed Doppler evaluation of left ventricular filling in subjects with pathologic and physiologic third heart sound. *Eur Heart J.* 1990;11:500–508.
- 32 Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA.* 2005;293:2238–2244.
- 33 Dokainish H. Tissue Doppler imaging in the evaluation of left ventricular diastolic function. *Curr Opin Cardiol.* 2004;19:437–441.
- 34 Ho CY, Solomon SD. A clinician's guide to tissue Doppler imaging. *Circulation.* 2006;113:e396–e398.
- 35 Shah SJ, Marcus GM, Gerber IL, et al. Physiology of the third heart sound: novel insights from tissue Doppler imaging and invasive left ventricular hemodynamics [abstract]. *J Am Soc Echocardiogr.* 2006;19:582.
- 36 Garrard CL Jr, Weissler AM, Dodge HT. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation.* 1970;42:455–462.
- 37 Stack RS, Sohn YH, Weissler AM. Accuracy of systolic time intervals in detecting abnormal left ventricular performance in coronary artery disease. *Am J Cardiol.* 1981;47:603–609.
- 38 Hamosh P, Cohn JN, Engelman K, et al. Systolic time intervals and left ventricular function in acute myocardial infarction. *Circulation.*

- 1972;45:375-381.
- 39 Lewis RP, Boudoulas H, Welch TG, et al. Usefulness of systolic time intervals in coronary artery disease. *Am J Cardiol*. 1976;37:787-796.
- 40 Leier CV, Magorien RD, Boudoulas H, et al. The effect of vasodilator therapy on systolic and diastolic time intervals in congestive heart failure. *Chest*. 1982;81:723-729.
- 41 Lewis RP, Boudoulas H, Leier CV, et al. Usefulness of the systolic time intervals in cardiovascular clinical cardiology. *Trans Am Clin Climatol Assoc*. 1981;93:108-120.
- 42 Wanderman KL, Goldberg MJ, Stock RS, et al. Left ventricular performance in mitral regurgitation assessed with systolic time intervals and echocardiography. *Am J Cardiol*. 1976;38:831-835.
- 43 Cheng HM, Chuang SY, Hsu PF, et al. Systolic time intervals revisited: correlations with N-terminal pro-brain natriuretic peptide in a community population. *Heart Vessels*. 2005;20:256-263.
- 44 Chen CH, Fetica B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol*. 2001;38:2028-2034.
- 45 Michaels A, Marcus G, Jordan M, et al. Audioelectric parameters are superior to BNP for detecting hemodynamic evidence of heart failure [abstract]. *J Am Coll Cardiol*. 2006;47(suppl A):67A.
- 46 Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853.
- 47 Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539-1549.
- 48 Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140-2150.
- 49 Doshi RN. Optimizing resynchronization therapy: can we increase the number of true responders? *J Cardiovasc Electrophysiol*. 2005;16(suppl 1):S48-S51.
- 50 Baker C, Love CJ, Moeschberger ML, et al. Time intervals of cardiac resynchronization therapy in heart failure. *Am J Cardiol*. 2004;94:1192-1196.



## ORIGINAL PAPER

## Systolic Dysfunction: Correlation of Acoustic Cardiography With Doppler Echocardiography

*For detection of left ventricular (LV) systolic dysfunction in the outpatient setting, simultaneous electrocardiographic and heart sound data have been shown to be helpful. In 161 patients with suspected or known cardiac disease, echocardiography and acoustic cardiography were performed. Acoustic cardiographic parameters correlated to echocardiography included: presence or absence of  $S_3$ , electromechanical activation time (EMAT), LV systolic time (LVST), and EMAT/LVST. LV ejection fraction was  $\geq 50\%$  in 82 patients ( $S_3$  present in 9.8%) and  $< 50\%$  in 79 patients ( $S_3$  present in 30.4%; the  $< 50\%$  group also had a greater EMAT, EMAT/LVST, and lower mean LVST [ $p < 0.05$ ]). Patients with an  $S_3$  had a lower ejection fraction, larger mean left atrial and LV dimensions, and an increased proportion of diastolic dysfunction. Acoustic cardiography allows reliable detection of the  $S_3$ , which correlates with echocardiographic evidence of impaired LV function, and the EMAT/LVST ratio reflects reduced ejection fraction, providing an affordable, accessible means to assess LV dysfunction in the outpatient setting. (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.<sup>1</sup> Consequently, a reliable, convenient, and cost-effective method to detect impaired LV function is desirable. To address this problem, physicians have widely adopted other tests for heart failure, such as the measurement of B-type natriuretic peptide (BNP). However, the inverse relationship between sensitivity and specificity for heart failure across the commonly encountered range values of BNP has limited the diagnostic value of this test.<sup>2</sup> To provide a more suitable diagnostic method, Inovise Medical, Inc. (Portland, OR)

has developed the AUDICOR system. This is a system that records, stores, displays, and algorithmically interprets simultaneous digital electrocardiographic (ECG) and sound (i.e., acoustic cardiographic) data, including the  $S_3$ , by using proprietary, dual-purpose sensors placed in the  $V_3$  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.<sup>3</sup> Since the system records acoustic cardiographic data throughout the entire cardiac cycle, it permits the measurement of systolic time intervals (STIs) as diagnostic parameters in addition to the  $S_3$ .

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

### Methods

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## Results

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

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

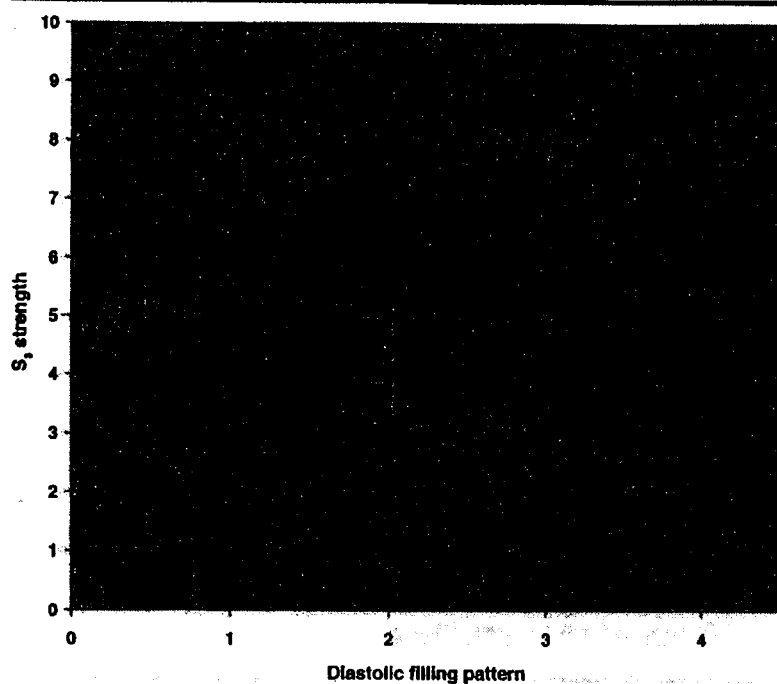


Figure 1.  $S_3$  strength vs. diastolic filling pattern in patients with left ventricular ejection fraction  $<50\%$ . 1=normal filling; 2=delayed relaxation; 3=pseudonormal pattern; 4=restrictive pattern

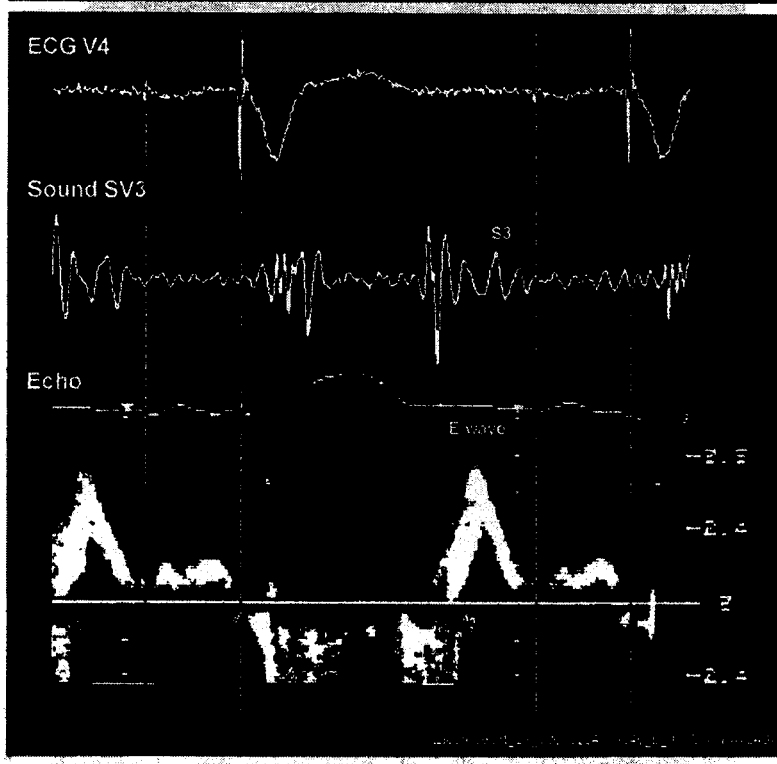


Figure 2. Temporal relationship between the  $S_3$  and a prominent E wave

(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 <sub>3</sub> present (%)	40	9.3*	80	100.0*
Electromechanical activation time (EMAT) (ms)	96±26	100±19	98±13	114±24
LV systolic time (LVST) (ms)	351±35	348±36	343±35	326±22
EMAT/LVST	0.28±0.09	0.29±0.06	0.29±0.05	0.35±0.07

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

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

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

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

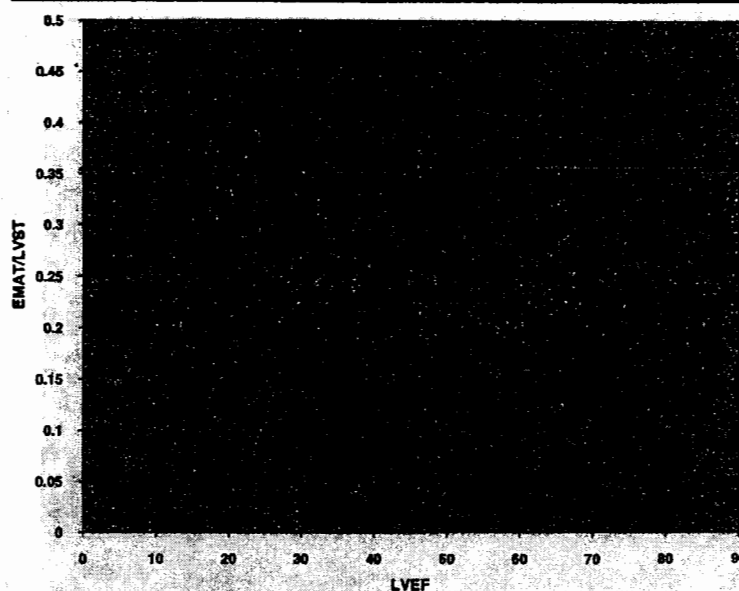


Figure 3. Electromechanical activation time (EMAT)/left ventricular systolic time (LVST) vs. left ventricular ejection fraction (LVEF) (%)

## 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.<sup>5</sup> Abnormal diastolic heart sounds, especially the S<sub>3</sub>, have long been associated with hemodynamic abnormalities that underlie heart failure.<sup>3,6,7</sup>

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

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

**Systolic Time Intervals.** Consequently, it would be desirable to have parameters for detecting ventricular dysfunction in addition to the  $S_3$ . A possible set of diagnostic parameters that can fulfill this role are STIs. Traditionally, STIs required the recordings of the ECG, phonocardiogram, and the carotid pulse tracing. The resultant diagnostic parameters included electromechanical systole (Q onset to  $S_3$ ), 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.<sup>8,9</sup> However, the ratio of PEP/LVET has been shown to be less sensitive to heart rate. Normal ranges have been established for the STIs, and values outside the normal range have been correlated with LV dysfunction (cardiac output, stroke volume, LV end-diastolic pressure).<sup>10-12</sup> LVET was shown to be highly correlated with PEP/LVET and useful in diagnosing heart failure.<sup>8,11</sup> As a result of LVSD, the LVET shortens and the PEP lengthens, primarily due to a diminished rate of LV pressure rise during isovolumetric contraction.<sup>13</sup>

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

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

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

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

## Conclusions

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

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

## REFERENCES

- 1 American Heart Association. *Heart Disease and Stroke Statistics—2005 Update*. Dallas, TX: American Heart Association; 2005.
- 2 Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647-654.
- 3 Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA*. 2004;293:2238-2244.
- 4 Ommen SR, Nishimuro RA. A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography: update 2003. *Heart*. 2003;89(suppl III):iii18-iii23.
- 5 Baker C, Love CJ, Moeschberger ML, et al. Time intervals of cardiac resynchronization therapy in heart failure. *Am J Cardiol*. 2004;94:1192-1196.
- 6 Drazner MH, Rame JE, Stevenson LW, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med*. 2001;345:574-581.
- 7 Lok CE, Morgan CD, Ranganathan N. The accuracy and interobserver agreement in detecting the 'gallop sounds' by cardiac auscultation. *Chest*. 1998;114:1283-1288.
- 8 Lewis RP, Rittgers SE, Froester WF, et al. A critical review of the systolic time intervals. *Circulation*. 1977;56:146-158.
- 9 Weissler AM, Harris WS, Schoenfeld CD. Bedside techniques for the evaluation of ventricular function in man. *Am J Cardiol*. 1969;23:577-583.
- 10 Stack RS, Sohn YH, Weissler AM. Accuracy of systolic time intervals in detecting abnormal left ventricular performance in coronary artery disease. *Am J Cardiol*. 1981;47:603-609.
- 11 Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation*. 1968;37:149-159.
- 12 Garrard CL, Weissler AM, Dodge HT. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation*. 1970;42:455-462.
- 13 Braunwald E. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA: WB Saunders Co; 1980:56.

## 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

**D**espite 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 be modified in any way. To benefit as many patients as possible, the methods of evaluation of hemodynamic function should be safe, reliable, widely available, and cost-effective.

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

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

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

### Methods

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

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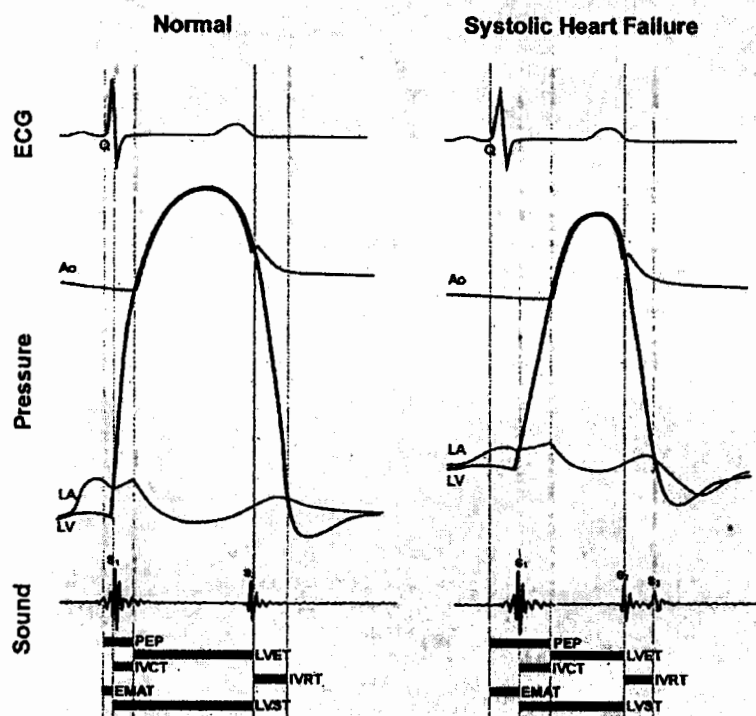
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**Table.** Demographic, Hemodynamic, and Acoustic Cardiographic Characteristics of the Patients With Left Ventricular (LV) Systolic Dysfunction (n=17)

Age (yr)	60±10
Heart rate (bpm)	81±20
Left bundle branch block (%)	5.9
QRS duration (ms)	130±40
LV ejection fraction (%)	32±11
LV end-diastolic pressure (mm Hg)	17±8
LV dP/dt <sub>max</sub> (mm Hg/sec)	1348±468
S <sub>1</sub> present (%)	41.2
Electromechanical activation time (EMAT) (ms)	93±25
LV systolic time (LVST) (ms)	329±31
EMAT/LVST	0.28±0.07

Data are presented as mean ± SD except where indicated otherwise.  
dP/dt<sub>max</sub>=maximum contractility



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

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

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

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

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

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

## Results

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

Figure 2 shows data from the pre-left ventriculogram tracings and reveals that in patients with LVSD and in whom the %LVST is <45%, there is a strong linear relationship between LVEDP and S<sub>1</sub> strength. However, in the patients whose %LVST is >45%,



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

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

Figure 4 shows that in patients with LVSD, values of EMAT >100 milliseconds are associated with LV  $dp/dt_{max}$  <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  $\geq 70$  bpm, the LVDT at each heart rate tends to be shorter in patients with LVSD vs. without LVSD.

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

## Discussion

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

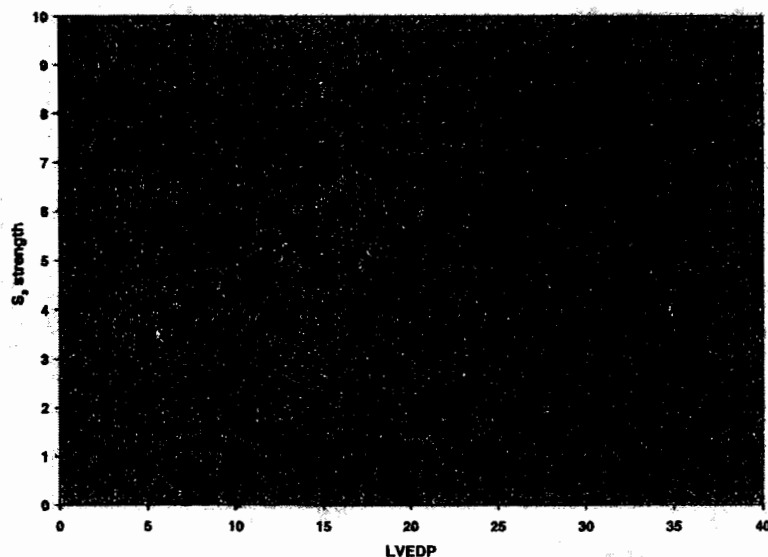


Figure 2.  $S_3$  strength vs. left ventricular end-diastolic pressure (LVEDP) in the patients with left ventricular systolic dysfunction; pre-ventriculogram recordings. Filled circles=left ventricular systolic time (LVST) <45% of R-R interval ( $R=0.982$ ;  $p<0.0001$ ); empty circles=LVST >45% of R-R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

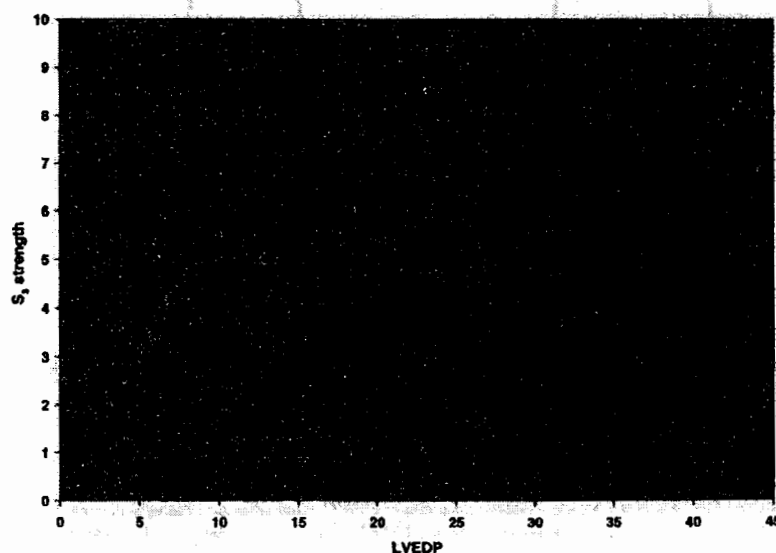


Figure 3.  $S_3$  strength vs. left ventricular end-diastolic pressure (LVEDP) in the patients with left ventricular systolic dysfunction and left ventricular systolic time <45% of R-R interval. Filled circles=pre-ventriculogram ( $R=0.982$ ;  $p<0.0001$ ); empty circles=post-ventriculogram ( $R=0.956$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

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

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

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



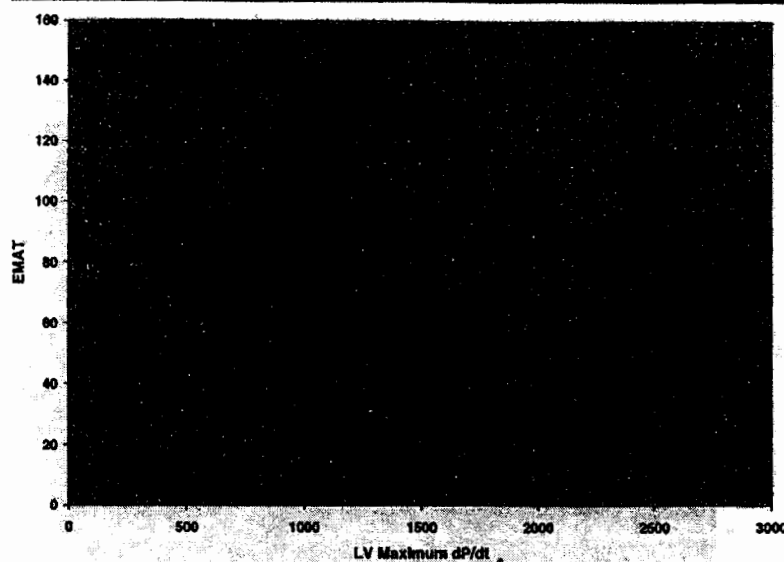


Figure 4. Relationship of electromechanical activation time (EMAT) to left ventricular (LV) maximum contractility (dP/dt) in the patients with left ventricular systolic dysfunction ( $R=-0.961$ ;  $p=0.063$ )



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

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

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

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

As shown in Figure 4, the decreased force of LV contraction revealed by a low dP/dt<sub>max</sub> 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<sub>max</sub> is especially relevant because it is highly sensitive to abnormalities of contractility.<sup>3</sup> Since dP/dt<sub>max</sub> 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<sub>max</sub> is very sensitive to changes in preload, especially if contractility is increased.<sup>3</sup> Measuring dP/dt<sub>max</sub> is most useful for evaluating directional changes in contractility during interventions in which acute changes in preload can be assessed.

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

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

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

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

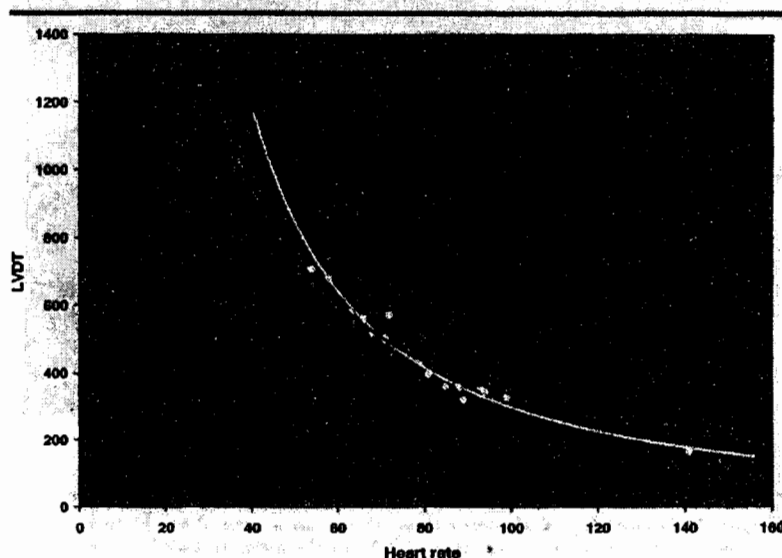


Figure 6. Left ventricular diastolic time vs. heart rate in patients without vs. with left ventricular systolic dysfunction, defined as ejection fraction (EF) <50%. Black=EF ≥50% ( $R=-0.952$ ;  $p<0.0001$ ); white=EF <50% ( $R=-0.985$ ;  $p<0.0001$ )

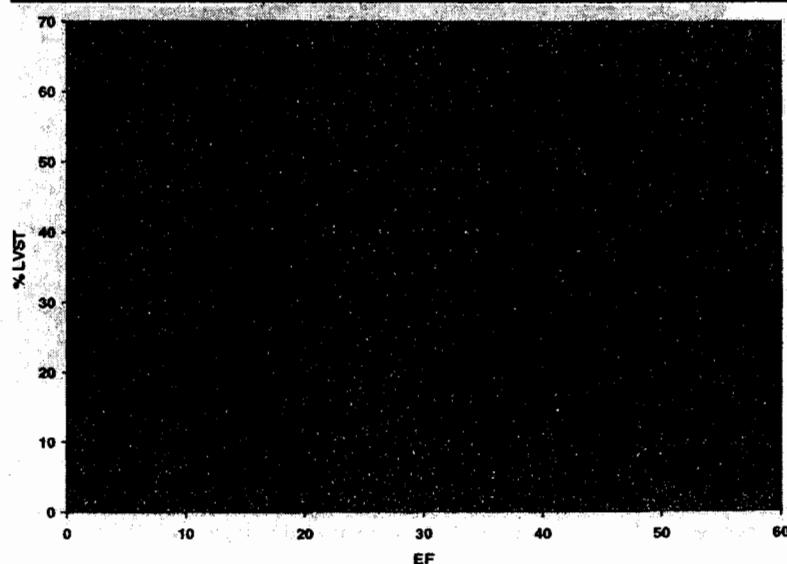


Figure 7. Relationship between left ventricular systolic time as a percentage of the R-R interval (%LVST) and ejection fraction (EF) in patients with left ventricular systolic dysfunction, by heart rate subgroups. Filled circles=heart rate ≤75 bpm; empty circles=heart rate >75 bpm

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

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

# **Attachment B-1**

**CMS-1506-P**

**Comments on Packaged Services—0069T  
“Acoustic heart sound recording and computer analysis”**

**September 29, 2006**

**Inovise Medical, Inc.  
10565 SW Nimbus Avenue, Suite 100  
Portland, Oregon 97223-4311  
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radionuclide studies can be used to confirm the presence of LVSD, their high cost and limited availability make them unsuitable for widespread use as screening tests.<sup>11</sup> Also, although the echocardiogram has been used to help optimize pacemaker settings following implantation of the CRT device, its use in this context is cumbersome, time-consuming, and highly dependent on the skill of the operator. As shown by their ease of use and their quantitative

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

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

## Conclusions

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

## REFERENCES

- 1 Shah SJ, Michaels AD. Hemodynamic correlates of the third heart sound and systolic time intervals. *Congest Heart Fail.* 2006;12(4 suppl 1):8-13.
- 2 Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA.* 2005;293:2238-2244.
- 3 Little WC. The left ventricular  $dp/dt_{max}$  and diastolic volume relation in closed-chest dogs. *Circ Res.* 1985;56:808-815.
- 4 Meiler SE, Boudoulas H, Unverferth DV, et al. Diastolic time in congestive heart failure. *Am Heart J.* 1987;114:1192-1198.
- 5 Baker C, Love CJ, Moeschberger ML, et al. Time intervals of cardiac resynchronization therapy in heart failure. *Am J Cardiol.* 2004;94:1192-1196.
- 6 Weissler AM, Harris WS, Schoenfeld CD. Bedside techniques for the evaluation of ventricular function in man. *Am J Cardiol.* 1969;23:577-583.
- 7 Stack RS, Sohn YH, Weissler AM. Accuracy of systolic time intervals in detecting abnormal left ventricular performance in coronary artery disease. *Am J Cardiol.* 1981;47:603-609.
- 8 Garrard CL, Weissler AM, Dodge HT. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation.* 1970;42:455-462.
- 9 Lewis RP, Rittogers SE, Froester WF, et al. A critical review of the systolic time intervals. *Circulation.* 1977;56:146-158.
- 10 Weissler AM, Harris HS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation.* 1968;37:149-159.
- 11 American Heart Association. *Heart Disease and Stroke Statistics—2005 Update.* Dallas, TX: American Heart Association; 2005.

## 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  $\pm$  SD of  $17 \pm 16$  milliseconds and gave a correlation coefficient of  $r=0.90$  ( $p<0.001$ ). In 17 of the 22 cases (77.3%), the difference between echocardiographic and acoustic cardiogram CRT optimization results was  $\leq 20$  milliseconds. Furthermore, the echocardiographic 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.<sup>1,2</sup>

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

is acoustic cardiography. One approach to acoustic cardiography (AUDICOR, Inovise Medical, Inc., Portland, OR) records, stores, displays, and algorithmically interprets simultaneous electrocardiographic (ECG) and acoustic data. These data are collected using proprietary ECG/sound sensors placed in the standard precordial  $V_1$  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):

- $S_1$  strength: a measurement of the overall acoustic energy of the  $S_1$

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

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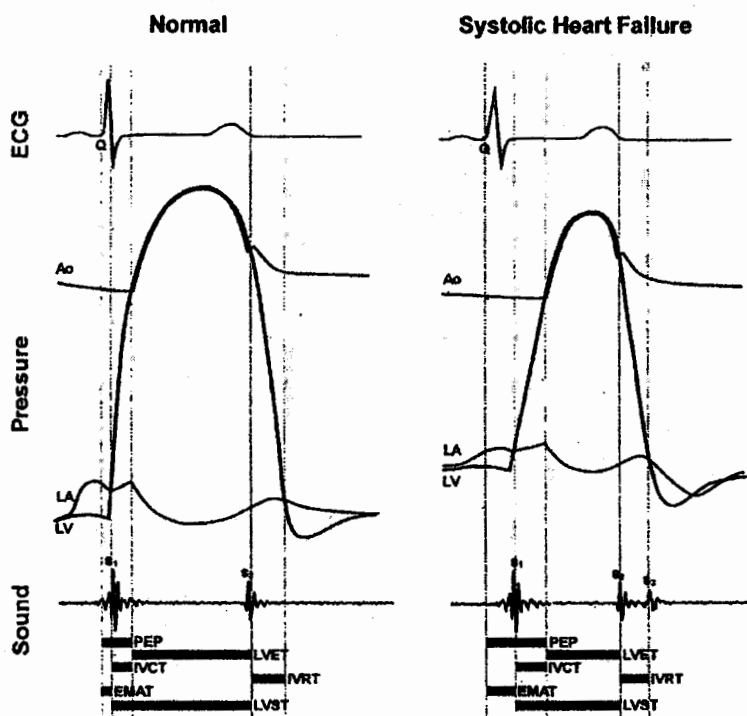


Figure 1. Relationship of traditional systolic time intervals to acoustic cardiographic systolic parameters (normal vs. systolic heart failure). (Pressure waveforms are provided here for convenience of reference and are not part of the AUDICOR [Inovise Medical, Inc., Portland, OR] data.) ECG=electrocardiogram;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

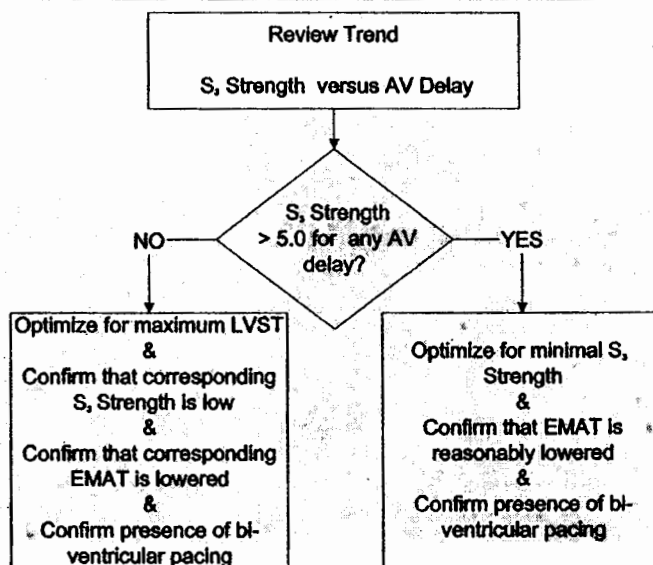


Figure 2. Flow chart used to determine the best atrioventricular (AV) delay during cardiac resynchronization therapy optimization using acoustic cardiography. LVST=left ventricular systolic time; EMAT=electromechanical activation time

hemodynamic abnormalities known to be associated with heart failure.<sup>3,4</sup> In particular, the comparison of acoustic cardiography parameters with relevant hemodynamic parameters obtained during left heart catheterization studies have shown that: 1)  $S_1$  strength correlates well with the absolute value of the LV end-diastolic pressure (LVEDP); 2) a prolonged EMAT is associated with reduced LV maximum contractility; and 3) reduced LVST values correlate to reduced LV ejection fraction (LVEF) in patients with systolic dysfunction.<sup>5</sup>

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

## Methods

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

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

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

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

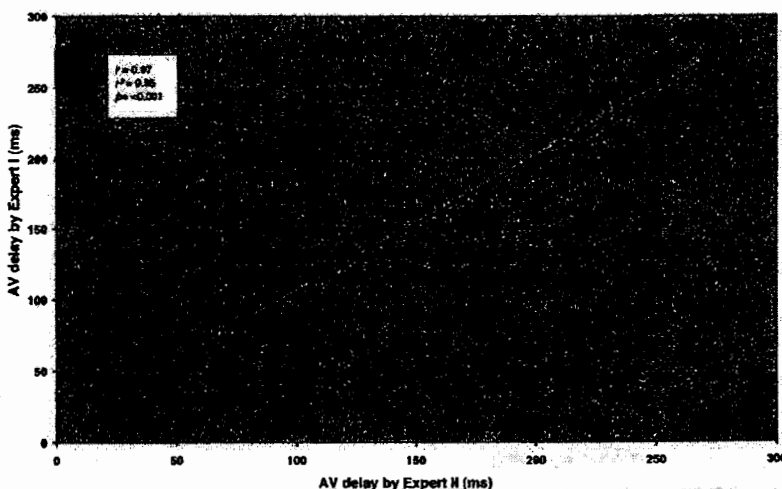
**Doppler Echocardiography.** The echocardiographic studies were performed with a Hewlett Packard (Palo Alto, CA) 4500 Ultrasound system in Doppler transmitral flow mode. For the echocardiographically guided AV optimization, patients were placed in the left lateral position. The selection of the appropriate 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

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

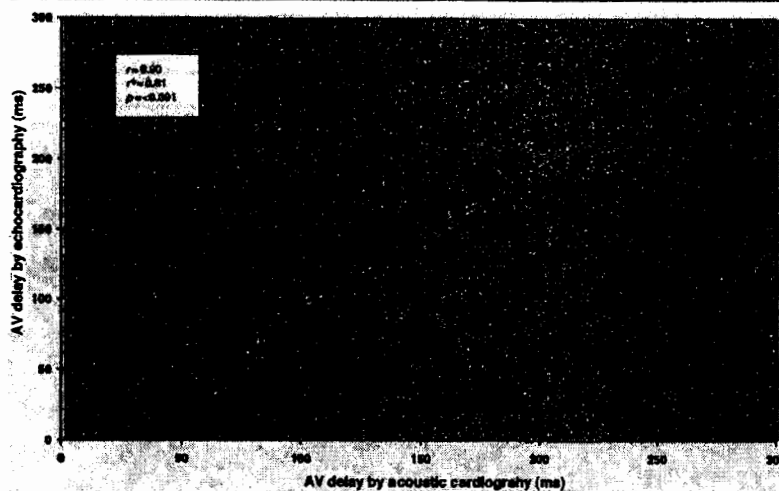
SUBJECT No.	DOPPLER ECHO	$\Delta$ (ECHO, ACOUSTIC)	ACOUSTIC CARDIOGRAPHY		
			CONSENSUS	EXPERT I	EXPERT II
1	130	30	160	160	160
2	60	20	80	80	80
3	225	0	225	225	250
4	100	0	100	100	100
5	150	10	160	160	160
6	210	20	230	230	230
7	160	0	160	160	160
8	140	10	150	150	150
9	190	30	220	190	220
10	280	70	210	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 $\pm$ SD	168 $\pm$ 53	17 $\pm$ 16	175 $\pm$ 50	175 $\pm$ 50	177 $\pm$ 50
$\Delta$ =difference					



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

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





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

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

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

## Results

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

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

**Comparison of AV Delays Recommended by Acoustic Cardiography and Echocardiography.** The Table shows the echocardiographically and acoustic cardiographically determined AV settings as well as the difference between both methods for each subject. For the 22 subjects included in the study, recommendations from both methods matched for 17 (77.3%) subjects within 20 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  $168 \pm 53$  milliseconds, and for the acoustic cardiography-based analysis it was  $175 \pm 50$  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.<sup>1</sup> 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.<sup>1</sup> The achieved increase in preload leads to two positive effects: 1) an increase in effective filling pressure, with a consequent increase in LV end-diastolic volume and increase in stroke volume via the Frank-Starling mechanism; and 2) an overall reduction in LVEDP, and thereby improvements in the LV diastolic function as reflected by changes in the E/A ratio and, potentially, a reduction in diastolic dysfunction class.<sup>7</sup> In particular, in postimplantation patients, the reduction in LVEDP is important to support the reverse remodeling process.<sup>8</sup>

It was shown in left heart catheterization studies that acoustic cardiographic parameters correlate well with relevant hemodynamic parameters that are key in the optimization of CRT devices in patients with systolic heart failure. As Roos et al.<sup>5</sup> have shown, the  $S_3$  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  $<1.0$ .<sup>5,6</sup> In particular, in the latter patients, the  $S_1$  strength might not show sufficient variation during the AV optimization, so one can obtain additional guidance for the AV optimization through systolic time intervals, namely EMAT and LVST. EMAT will increase with a reduction in LV maximum contractility, while LVST decreases with a reduction in LVEF.<sup>5,9</sup>

The relationship among EMAT, LVST, and the Doppler 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  $S_1$  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  $S_1$  strength

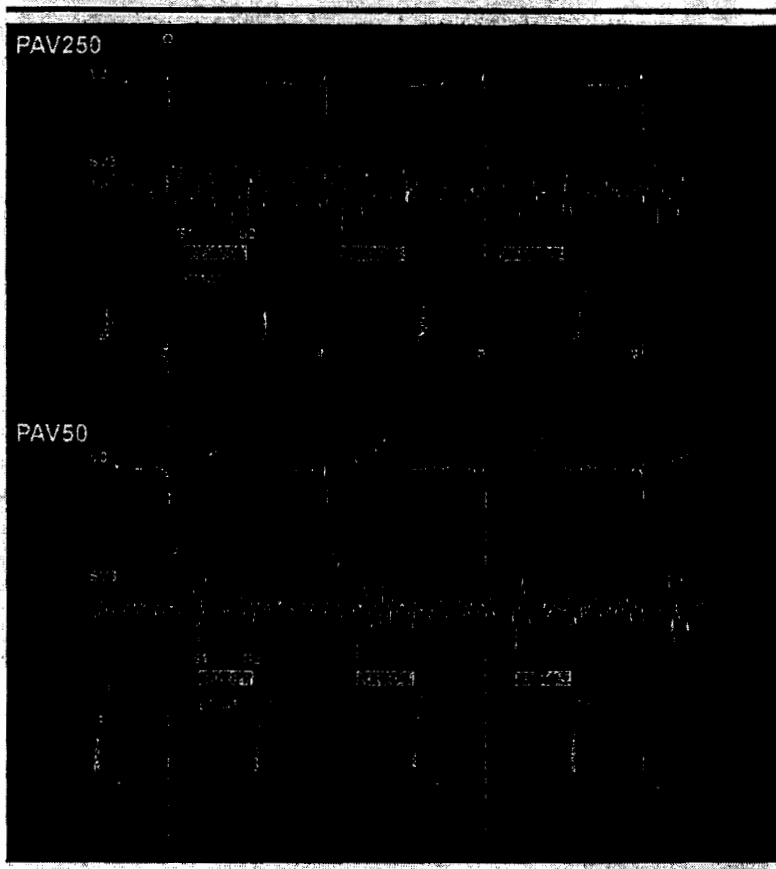


Figure 5. Illustration of electrocardiographic, AUDICOR (Inovise Medical, Inc., Portland, OR) systolic time intervals (electromechanical activation time [EMAT], left ventricular systolic time [LVST]), and echo Doppler transmitral flow pattern in a cardiac resynchronization therapy patient for short and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

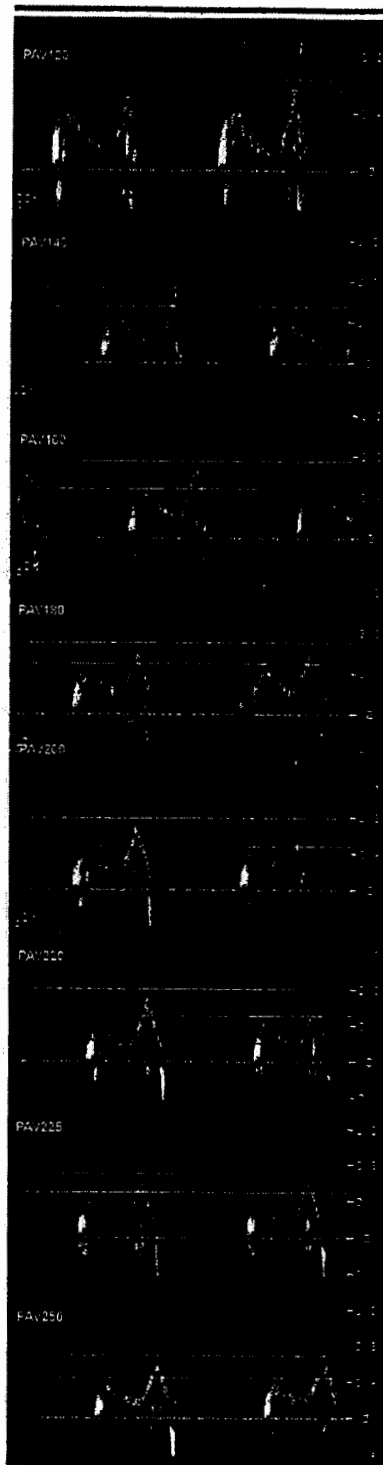


Figure 6. Echocardiographic Doppler transmitral flow pattern for all of the atrioventricular delays tested in study subject number 3

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

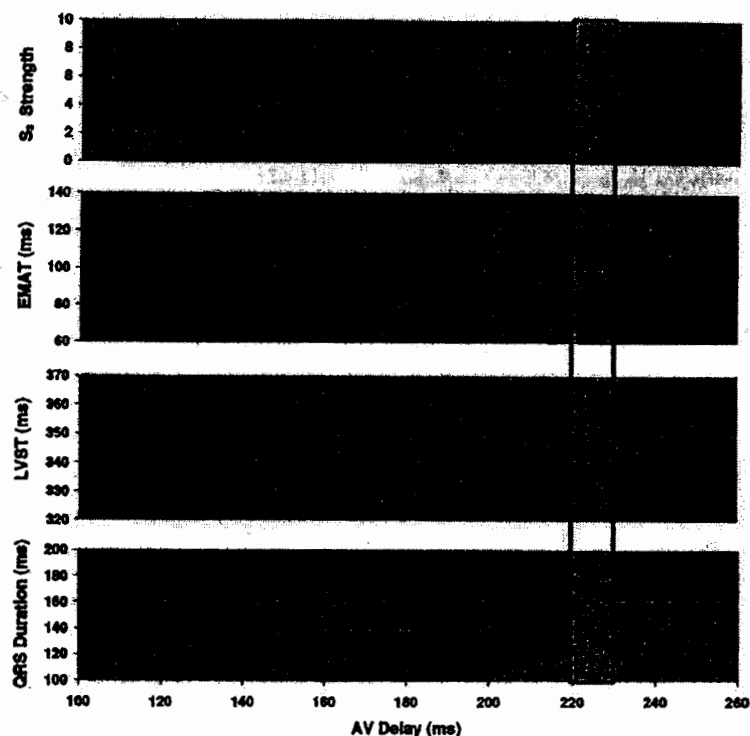


Figure 7. Trend showing the acoustic cardiogram values for all of the atrioventricular (AV) delays tested in study subject number 3. EMAT=electromechanical activation time; LVST=left ventricular systolic time

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

### Conclusions

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

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

### REFERENCES

1. Grimm R. Programming cardiac resynchronization therapy. In: Ellenbogen KA, Wilkoff BL, Kay GN, eds. *Device Therapy for Congestive Heart Failure*. Philadelphia, PA: WB Saunders Co; 2003:294-310.
2. Abraham WT, Fisher WG, Smith AL, et al., for the MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853.
3. Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA*. 2005;293:2238-2244.
4. Moyers B, Shapiro M, Marcus GM, et al. The performance of phonoelectrocardiographic left ventricular systolic time intervals and B-type natriuretic peptide levels in the diagnosis of heart failure. *Ann Noninvasive Electrocardiol*. In press.
5. Roos M, Toggweiler S, Zuber M, et al. Acoustic cardiographic parameters and their relationship to invasive hemodynamic

- measurements in patients with left ventricular systolic dysfunction. *Congest Heart Fail.* 2006;12(4 suppl 1):19-24.
- 6 Zuber M, Kipfer P, Altenhofer Jost C. Systolic dysfunction: correlation of acoustic cardiography with Doppler echocardiography. *Congest Heart Fail.* 2006;12(4 suppl 1):14-18.
- 7 Ommen SR, Nishimura RA. A clinical approach to the assessment of left ventricular function by Doppler echocardiography: update 2003. *Heart.* 2003;89(suppl III):iii18-iii23.
- 8 Ellenbogen K, Saxon L. Clinical trials of resynchronization therapy. In: Ellenbogen KA, Wilkoff BL, Kay GN, eds. *Device Therapy for Congestive Heart Failure*. Philadelphia, PA: WB Saunders Co; 2003:47-91.
- 9 Shah SJ, Michaels AD. Hemodynamic correlates of the third heart sound and systolic time intervals. *Congest Heart Fail.* 2006;12(4 suppl 1):8-13.

# **Attachment B-1**

**CMS-1506-P**

**Comments on Packaged Services—0069T**  
**“Acoustic heart sound recording and computer analysis”**

**September 29, 2006**

**Inovise Medical, Inc.**  
**10565 SW Nimbus Avenue, Suite 100**  
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- 10 Cristina Porciani M, Fantini F, Musilli N, et al. A perspective on atrioventricular delay optimization in patients with a dual chamber pacemaker. *Pacing Clin Electrophysiol*. 2004;27:333-338.
- 11 van Gelder BM, Bracke FA, Meijer A, et al. Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. *Am J Cardiol*. 2004;93:1500-1503.
- 12 Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA*. 2005;293:2238-2244.
- 13 Moyers B, Shapiro M, Marcus GM, et al. The performance of phonoelectrocardiographic left ventricular systolic time intervals and B-type natriuretic peptide levels in the diagnosis of heart failure. *Ann Noninvasive Electrocardiol*. In press.
- 14 Scharf C, Li P, Muntwyler J, et al. Rate-dependent AV delay optimization in cardiac resynchronization therapy. *Pacing Clin Electrophysiol*. 2005;28:279-284.
- 15 Roos M, Toggweiler S, Zuber M, et al. Acoustic cardiographic parameters and their relationship to invasive hemodynamic measurements in patients with left ventricular systolic dysfunction. *Congest Heart Fail*. 2006;12(4 suppl 1):19-24.
- 16 Jansen AH, Bracke F, van Dantzig JM, et al. Optimization of pulsed wave tissue Doppler to predict left ventricular reverse remodeling after cardiac resynchronization therapy. *J Am Soc Echocardiogr*. 2006;19:185-191.
- 17 Toda N, Ishikawa T, Nozawa N, et al. Doppler index and plasma level of atrial natriuretic hormone are improved by optimizing atrioventricular delay in atrioventricular block patients with implanted DDD pacemakers. *Pacing Clin Electrophysiol*. 2001;24:1660-1663.

## CASE REPORT

## Acoustic Cardiography in the Differential Diagnosis of Dyspnea

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

B-type natriuretic peptide (BNP) is often used to evaluate patients with possible HF, but its lack of specificity in commonly encountered ranges of values has limited its diagnostic usefulness.<sup>8</sup> To improve the diagnosis of acute and chronic HF, Inovise Medical, Inc. (Portland, OR) has developed the AUDICOR test. This is a system that records, stores, displays, and algorithmically interprets simultaneous digital electrocardiography (ECG) and sound. The device records both the cardiographic and acoustic data and the  $S_3$  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.<sup>9</sup>

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

**Case Description**

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

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

diffuse wheezes and right-sided basilar rales. Cardiac examination revealed a rapid, irregular heart rate and a 2/6 systolic murmur but no  $S_3$  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  $PO_2$  of 68, an  $O_2$  saturation of 92%, and a  $PCO_2$  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.

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- Abnormal Audicor finding for 40+ female
- S3 consistent with LV dysfunction
- Atrial fibrillation
- Excluding conditions detected (AFIB)

Heart rate: 35 BPM  
PR int: 9 ms  
QRS dur: 77 ms

Excluding condition(s), analysis for  
S4 detected not possible.

21-Jun-2004 12:46:54

Reviewed by: \_\_\_\_\_

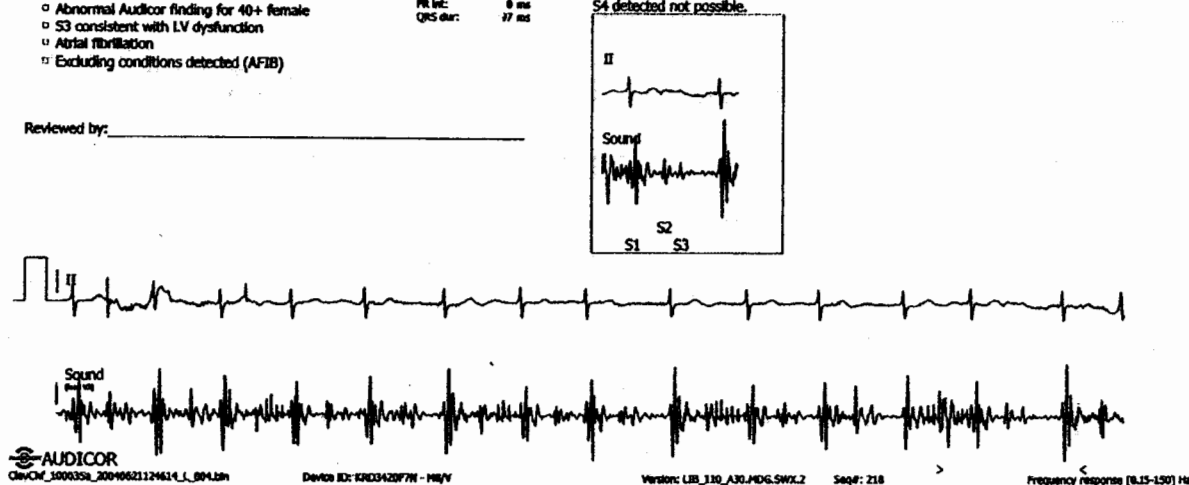


Figure. AUDICOR report showing an S<sub>3</sub>.

## 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<sub>3</sub> was not detected by auscultation, the AUDICOR test revealed that an S<sub>3</sub> was present (Figure). An S<sub>3</sub> has been shown to be highly specific for HF in the appropriate clinical context.<sup>10</sup>

Although this patient had a number of possible causes of dyspnea, the presence of an electronically detected S<sub>3</sub> makes the presence of HF very likely. For example, previous studies have shown that the electronically detected S<sub>3</sub> 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<sub>3</sub> and a BNP in the 100–500 pg/mL range).<sup>11,12</sup> The identification of HF in a patient with multiple severe illnesses is especially important, since the appropriate treatment of HF reduces patients' overall clinical burden.

## REFERENCES

- 1 American Heart Association. Heart disease and stroke statistics—2006 update. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=1928>. Accessed May 11, 2006.
- 2 Graff L, Orledge J, Radford MJ, et al. Correlation of the Agency for Health Care Policy and Research congestive heart failure admission guideline with mortality: peer review organization voluntary hospital association initiative to decrease events (PROVIDE) for congestive heart failure. *Ann Emerg Med*. 1999;34(4 pt 1):429–437.
- 3 Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol*. 2001;37:379–385.
- 4 Collins SP, Lindsell CJ, Storrow AB, et al.

- Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. *Ann Emerg Med.* 2006;47:13-18.
- 5 Pozner CN, Levine M, Shapiro N, et al. Concordance of field and emergency department assessment in the prehospital management of patients with dyspnea. *Prehosp Emerg Care.* 2003;7:440-444.
- 6 Peacock WF, Enterman CL, Costanzo MR, et al. Early initiation of intravenous therapy improves heart failure outcomes: an analysis from the ADHERE Registry Database. *Ann Emerg Med.* 2003;42:S26.
- 7 Wuerz RC, Meador SA. Effects of prehospital medications on mortality and length of stay in congestive heart failure. *Ann Emerg Med.* 1992;21:669-674.
- 8 Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med.* 2004;350:647-654.
- 9 Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA.* 2005;293:2238-2244.
- 10 Drazner MH, Rame JE, Stevenson LW, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med.* 2001;345:574-581.
- 11 Collins SP, Undsell CJ, Peacock WF, et al. Combination of BNP and automated heart sounds improves heart failure diagnostic accuracy. *Acad Emerg Med.* 2005;12(5 suppl 1):97.
- 12 Peacock WF, Harrison A, Moffa D. Clinical and economic benefits of using AUDICOR S<sub>3</sub> detection for diagnosis and treatment of acute decompensated heart failure. *Congest Heart Fail.* 2006;12(4 suppl 1):32-36.



# 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.

**ACCREDITATION STATEMENT:** Winthrop-University Hospital (WUH) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. WUH designates this Continuing Medical Education activity for a maximum of (4) credit hours in Category 1 credit towards the AMA Physicians' Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity. WUH relies upon faculty participants in its CME programs to provide educational information that is objective and as free of bias as possible. In this spirit, and in accordance with the guidelines of the program sponsor, faculty participants are expected to indicate any commercial relationship that might be perceived as a real or apparent conflict of interest.

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

**AUTHOR DISCLOSURES:** Andrew D. Michaels, MD: Inovise Medical, Inc.—Unrestricted educational grant, Research grant, Speaker's bureau; Abbott Laboratories—Research grant; Scios Inc.—Research grant. W. Frank Peacock, MD: Inovise Medical, Inc.—Research grant recipient, Advisory Board Member. William T. Abraham, MD: Amgen, Biotronik, CHF Solutions, GlaxoSmithKline, Heart Failure Society of America, Inovise Medical, Inc., National Institutes of Health, Medtronic Inc., Myogen Inc., Orgis Medical, Otsuka Maryland Research Institute, Paracor Inc., Scios Inc.—Grants/Research support; Amgen, Astra Zeneca, Boehringer Ingelheim, CHF Solutions, GlaxoSmithKline, Guidant Corp., Medtronic Inc., Merck & Co., Inc., Pfizer, ResMed, Respiromics, Scios Inc., St. Jude Medical—Consultant/Speaker's Bureau; CardioKine, CardioKinetic Inc., CHF Solutions, Department of Veterans Affairs Cooperative Studies Program, Inovise Medical, Inc., National Institutes of Health, Savacor Inc.—Advisory Board membership; Astra Zeneca, Boehringer Ingelheim, GlaxoSmithKline, Guidant Corp., Medtronic Inc., Merck & Co., Inc., Pfizer, ResMed, Respiromics, Scios Inc., St. Jude Medical—Honorarium recipient; *Congestive Heart Failure, Current Cardiology Reviews, Current Heart Failure Reports, Expert Review of Cardiovascular Therapy, Journal Watch Cardiology, Pacing and Clinical Electrophysiology (PACE), The American Heart Hospital Journal, Journal of Cardiac Failure*—Editorial Board involvement. Nothing to disclose: Donald Moffa, MD; Ayesha Hasan, MD; Ali M. Amkieh, MD; Peter Kipfer, MD; Christine Attenhofer Jost, MD, FESC; Michel Zuber, MD, FESC; Alan S. Maisel, MD; Peiman Jamshidi, MD; Stefan Toggweiler, MD; Paul Erne, MD; Markus Roos, MD; Alex Harrison, MD; Lei Brown, RDCS, RVT; Lori Quinn-Tate, RN, MN; Sanjiv J. Shah, MD.

**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 interatrial (VV) optimization of CRT devices are well established and standardized.
14. Electromechanical activation time obtained by acoustic cardiography may be useful in determining the best AV/VV settings.

## Peacock (pages 41-43)

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

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

## CME Answer Grid

- |  |  |   |   |
|--|--|---|---|
| 1. <input type="checkbox"/> T <input type="checkbox"/> F | 5. <input type="checkbox"/> T <input type="checkbox"/> F | 9. <input type="checkbox"/> T <input type="checkbox"/> F  | 13. <input type="checkbox"/> T <input type="checkbox"/> F |
| 2. <input type="checkbox"/> T <input type="checkbox"/> F | 6. <input type="checkbox"/> T <input type="checkbox"/> F | 10. <input type="checkbox"/> T <input type="checkbox"/> F | 14. <input type="checkbox"/> T <input type="checkbox"/> F |
| 3. <input type="checkbox"/> T <input type="checkbox"/> F | 7. <input type="checkbox"/> T <input type="checkbox"/> F | 11. <input type="checkbox"/> T <input type="checkbox"/> F | 15. <input type="checkbox"/> T <input type="checkbox"/> F |
| 4. <input type="checkbox"/> T <input type="checkbox"/> F | 8. <input type="checkbox"/> T <input type="checkbox"/> F | 12. <input type="checkbox"/> T <input type="checkbox"/> F | 16. <input type="checkbox"/> T <input type="checkbox"/> 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. __ |
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This activity is sponsored by Winthrop-University Hospital and is supported by an unrestricted educational grant from Inovise Medical, Inc.

## **Attachment B-2**

CMS-1506-P

Comments on Packaged Services—0069T  
“Acoustic heart sound recording and computer analysis”

September 29, 2006

Inovise Medical, Inc.  
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# The Combined Utility of an S3 Heart Sound and B-Type Natriuretic Peptide Levels in Emergency Department Patients With Dyspnea

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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.<sup>1</sup> 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.<sup>2–4</sup> 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.<sup>5</sup> 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.<sup>6–8</sup> 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%.<sup>2,9,10</sup> The addition of a second more specific test to indeterminate BNP levels could affect decision making in heart failure patients.

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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.<sup>1,11-13</sup> 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.<sup>14,15</sup> 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.<sup>16</sup>

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,<sup>17</sup> 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.<sup>17</sup> 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.<sup>16,18</sup> 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.

## 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 Kruskal-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).

## 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%

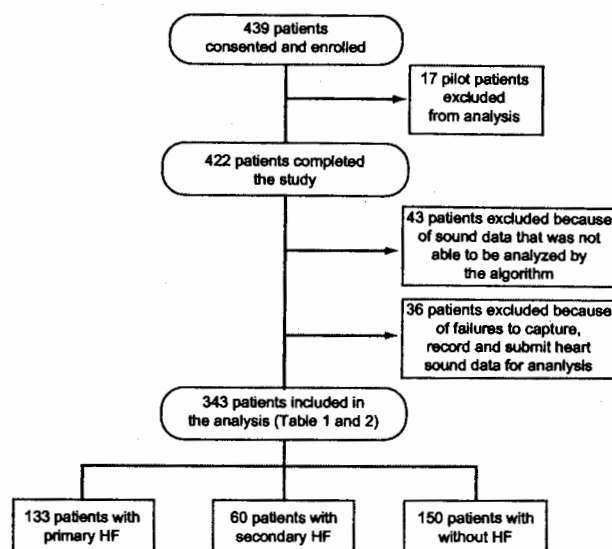


Fig. 1. Patient enrollment and data analysis.

(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	Included patients n = 343	Excluded patients n = 79	P value
Age	55 (20, 95)	68 (39-93)	69 (30-97)	61 (20-97)	61 (31-92)	.821
Race						
Caucasian	80 (53.3)	25 (41.7)	61 (45.9)	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)	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)	164 (47.8)	41 (51.9)	.534
CAD	31 (20.7)	24 (40.0)	61 (45.9)	116 (33.8)	28 (35.4)	.793
Hypertension	71 (47.3)	43 (71.7)	100 (75.2)	214 (62.4)	50 (63.3)	1.000
VHD	11 (7.3)	25 (41.7)	64 (48.1)	100 (29.2)	22 (27.8)	.891
Cardiomyopathy	3 (2.0)	17 (28.3)	45 (33.8)	65 (19.0)	22 (27.8)	.090
Prior abnormal ejection fraction*	0 (0.0)	7 (38.9)	24 (53.3)	31 (38.3)	8 (42.1)	.798
Systolic blood pressure	140 (80-220)	142 (68-215)	148 (85-257)	142 (68-257)	134 (69-219)	.030
Diastolic blood pressure	80 (39-136)	82 (37-124)	83 (39-167)	82 (37-167)	79 (47-133)	.568
Heart rate	90 (54-140)	82 (25-114)	91 (44-142)	90 (25-142)	93 (58-158)	.026
Respiration rate	20 (11-40)	20 (10-44)	22 (12-44)	20 (10-44)	20 (12-85)	.839
Oxygen saturation	98 (57-100)	96 (78-100)	96 (72-100)	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)	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)	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)	76.9 (5.4-520.8)	75.8 (6.7-384.6)	.995
Symptoms						
JVD	7 (4.7)	6 (10.0)	43 (32.6)	56 (16.5)	14 (18.7)	.613
Peripheral edema	43 (28.7)	20 (33.3)	83 (63.4)	146 (42.8)	42 (53.8)	.079
Dyspnea	118 (78.7)	51 (85.0)	128 (96.2)	297 (86.6)	68 (86.1)	.857
Orthopnea	36 (24.0)	22 (36.7)	91 (68.4)	149 (43.4)	32 (41.0)	.800
PND	20 (13.3)	16 (26.7)	52 (39.7)	88 (25.8)	27 (34.6)	.123
Congestion on x-ray	20 (13.5)	25 (42.4)	103 (77.4)	148 (43.5)	39 (49.4)	.380
BNP	48 (5-688)	94 (5-5000)	697 (5-5000)	271 (5-5000)	273 (5-4690)	.819
Auscultation						
S3	5 (3.4)	2 (3.3)	21 (16.4)	28 (8.4)	9 (12.3)	.268
S4	4 (2.7)	3 (5.0)	8 (6.3)	15 (4.5)	2 (2.8)	.748
Audiotape						
S3	9 (6.0)	5 (8.3)	45 (33.8)	59 (17.2)	0 (0.0)	—
S4	18 (12.8)	7 (13.7)	18 (17.6)	43 (14.6)	0 (0.0)	—

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

\*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 non-primary 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  $\leq 500$ ) 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

ED diagnosis	Final diagnosis	Audicor S3		Total (n = 343)
		Absent (n = 284, 83%)	Present (n = 59, 17%)	
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.



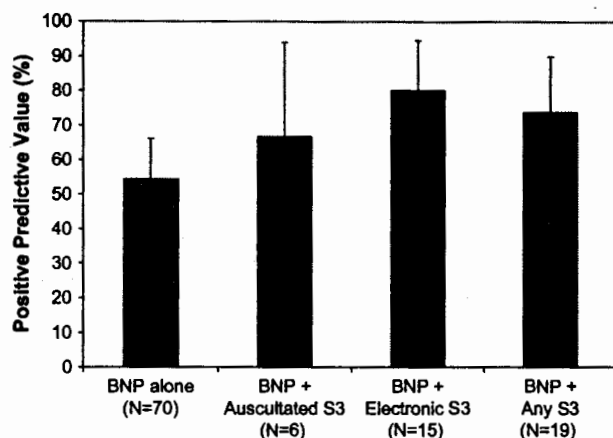


Fig. 2. Bar graph showing the positive predictive value ( $\pm 95\%$  confidence intervals) of B-type natriuretic peptide in the range 100 to 500 pg/mL with and without consideration of the presence of an S3.

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.<sup>17</sup> 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.<sup>16</sup> Further, 15% to 30% of patients older than age 50 have been shown to have electronically detected S4s.<sup>19</sup>

### 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.<sup>16</sup>

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).

### References

1. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;261:884–8.
2. Collins S, Lindsell CJ, Storrow AB, Abraham WT. Prevalence of negative chest radiography in the emergency department patient with decompensated heart failure. *Ann Emerg Med* 2006;47:13–8.
3. Mahdyouon H, Klein R, Eyler W, Lakier JB, Chakko SC, Gheorghide M. Radiographic pulmonary congestion in end-stage congestive heart failure. *Am J Cardiol* 1989;63:625–7.
4. Kono T, Suwa M, Hanada H, Hirota Y, Kawamura K. Clinical significance of normal cardiac silhouette in dilated cardiomyopathy—evaluation based upon echocardiography and magnetic resonance imaging. *Jpn Circ J* 1992;56:359–65.
5. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–7.
6. Knudsen CW, Clopton P, Westheim A, et al. Predictors of elevated B-type natriuretic peptide concentrations in dyspneic patients without heart failure: an analysis from the breathing not properly multinational study. *Ann Emerg Med* 2005;45:573–80.
7. Maisel AS, Clopton P, Krishnaswamy P, et al. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. *Am Heart J* 2004;147:1078–84.
8. McCullough P, PG S, Aumont MC, et al. What causes elevated B-type natriuretic peptide in patients without heart failure? *J Am Coll Cardiol* 2003;41:278A.
9. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001;37:379–85.
10. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106:416–22.
11. Reddy PS. The third heart sound. *Int J Cardiol* 1985;7:213–21.
12. Sloan A. Cardiac gallop rhythm. *Medicine* 1958;37:197–215.
13. Evans W. The use of phonocardiography in clinical medicine. *Lancet* 1951;1:1083–5.
14. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997;90:335–9.
15. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA* 2005;294:1944–56.
16. Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA* 2005;293:2238–44.
17. Collins S, CJ L, Peacock WF, et al. The effect of treatment on the presence of abnormal heart sounds in emergency department patients with heart failure. *Am J Emerg Med* 2006;24:25–32.
18. Inovise Medical I, inventor Audicor-FDA 510K number K031182; 2003.
19. Collins SP, Arand P, Lindsell CJ, Peacock WF 4th, Storrow AB. Prevalence of the third and fourth heart sound in asymptomatic subjects. *Congest Heart Fail* 2006;11:242–7.

## **Attachment B-3**

CMS-1506-P

**Comments on Packaged Services—0069T  
“Acoustic heart sound recording and computer analysis”**

**September 29, 2006**

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Original Contributions

# The effect of treatment on the presence of abnormal heart sounds in emergency department patients with heart failure<sup>☆</sup>

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## Abstract

**Objective:** We sought to assess the proportion of ED patients with an electronically detected S<sub>3</sub> or S<sub>4</sub>, 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<sub>3</sub> and an S<sub>4</sub> 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<sub>3</sub> and 35.6% had an S<sub>4</sub>. For the 35 patients with HF evaluated after treatment, the proportions of both S<sub>3</sub> and S<sub>4</sub> were lower (28.6% and 8.6%, respectively;  $P \leq .0064$ ).

**Conclusions:** This study suggests the proportion of patients with an electronically detected S<sub>3</sub> in HF is more than 50%, and that its presence is affected by prior treatment with diuretics or vasodilators.

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## 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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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, in-hospital data (previous ejection fraction [EF] documented by echocardiogram, nuclear medicine scan, left and right heart catheterization, in-hospital cardiac testing and therapeutics, and hospital discharge diagnosis) and in-hospital 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 for a 4-minute period, saved to CD, and shipped to Inovise Medical for signal

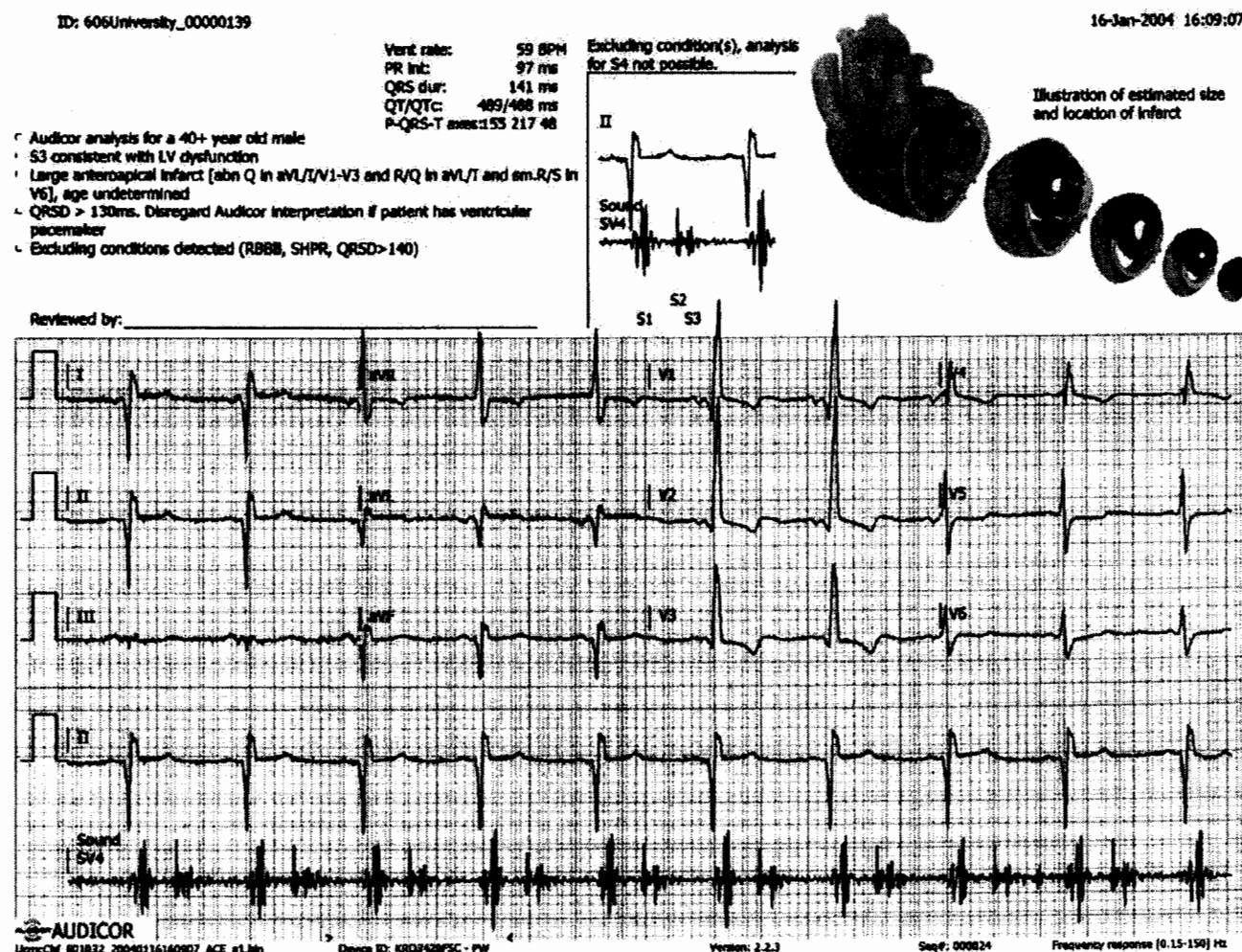


Fig. 1 Printout of the Audicor ECG. In addition to the electrical information, there is visual and typed sound information displayed.



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

	Non-HF n = 268	Secondary HF n = 43	Primary HF n = 110	All patients N = 421
<b>Demographics</b>				
Age (IQR)	58 (46-69)	71 (56-80)	71 (56-79)	61 (48-75)
Men	122 (45.5)	21 (48.8)	60 (54.5)	203 (48.2)
White	135 (50.4)	19 (44.2)	52 (47.3)	206 (48.9)
<b>Past medical history</b>				
Previous EF >40%	41 (80.4)	6 (40.0)	13 (39.4)	60 (60.6)
Previous EF <40%	10 (19.6)	9 (60.0)	20 (60.6)	39 (39.4)
History of HF	73 (27.2)	35 (81.4)	97 (88.2)	205 (48.7)
History of CAD	69 (25.7)	19 (44.2)	56 (50.9)	144 (34.2)
History of hypertension	150 (56.0)	33 (76.7)	80 (72.7)	263 (62.5)
<b>Clinical findings</b>				
Dyspnea on exertion	222 (82.8)	36 (83.7)	106 (96.4)	364 (86.5)
Jugular venous distension	22 (8.4)	12 (27.9)	36 (32.7)	70 (16.9)
Peripheral edema	94 (35.3)	26 (60.5)	68 (62.4)	188 (45.0)
<b>Diagnostic tests</b>				
No congestion on chest x-ray*	194 (73.2)	15 (34.9)	22 (20.0)	231 (55.3)
Congestion on chest x-ray	71 (26.8)	28 (65.1)	88 (80.0)	187 (44.7)
Median BNP level (pg/mL)(IQR)	66 (21-179)	485 (209-1000)	764 (459-1640)	271 (54-780)

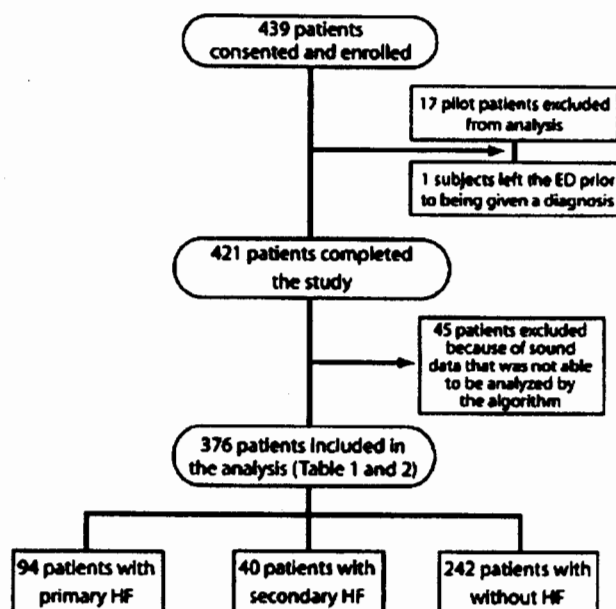
\*Columns refer to the total number and the percentage of patients unless otherwise indicated. CAD, coronary artery disease.

\*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<sub>1</sub> and S<sub>2</sub> 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<sub>4</sub> 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<sub>3</sub> or S<sub>4</sub> 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<sub>3</sub> or S<sub>4</sub> 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  $\chi^2$  tests. Analyses 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<sub>3</sub> or S<sub>4</sub>

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 ( $P = .039$ ).

**Table 2** Proportion of auscultated and electronically detected S<sub>3</sub> and S<sub>4</sub> for all patients included in the analysis and for patients stratified by hospital discharge diagnoses and prior treatment with vasodilators or diuretics

		Non-HF (n = 242)	Secondary HF (n = 40)	Primary HF (n = 94)	All (N = 376)
S <sub>3</sub>		11.2 (7.6-16.0)	25.0 (13.2-41.5)	46.8 (36.5-57.3)	21.5 (17.6-26.1)
S <sub>4</sub>		12.4 (8.6-17.4)	17.5 (7.9-33.4)	25.5 (17.3-35.8)	16.2 (12.7-20.4)
Before treatment (n = 298)	S <sub>3</sub>	11.7 (7.8-17.1)	20.6 (9.3-38.4)	57.6 (44.1-70.2)	21.8 (17.3-27.0)
	S <sub>4</sub>	10.7 (7.0-16.0)	17.6 (7.4-35.2)	35.6 (23.9-49.2)	16.4 (12.5-21.3)
After treatment (n = 78)	S <sub>3</sub>	8.1 (2.1-23.0)	50.0 (13.9-86.1)	28.6 (15.2-46.5)	20.5 (12.5-31.5)
	S <sub>4</sub>	21.6 (10.4-38.7)	16.7 (0.9-63.5)	8.6 (2.2-24.2)	15.4 (8.5-25.7)

Data are given as percentages with 95% confidence intervals.



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

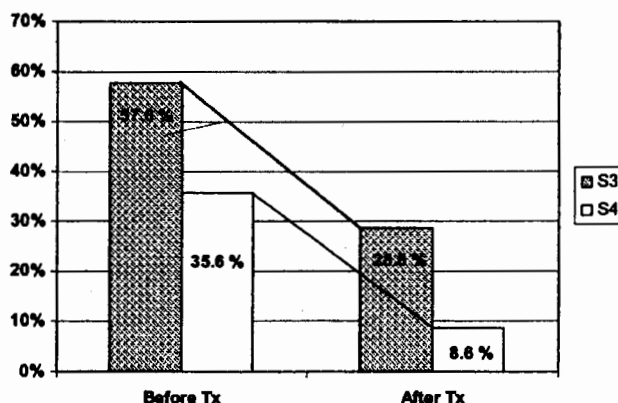


Fig. 3 Affect of treatment on proportion of patients with electronically detected heart sounds.

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.

## References

- [1] American Heart Association. Heart disease and stroke statistics—2005 update. Dallas, TX: Author; 2005.
- [2] Remes J, Miettinen H, Reunanen A, et al. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12(3):315-21.
- [3] Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989; 261(6):884-8.
- [4] Rihal CS, Davis KB, Kennedy JW, et al. The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. *Am J Cardiol* 1995;75(4):220-3.

- [5] Silver MT, Rose GA, Paul SD, et al. A clinical rule to predict preserved left ventricular ejection fraction in patients after myocardial infarction. *Ann Intern Med* 1994;121(10):750-6.
- [6] Mahdyouon H, Klein R, Eyler W, et al. Radiographic pulmonary congestion in end-stage congestive heart failure. *Am J Cardiol* 1989; 63(9):625-7.
- [7] Collins S, Lindsell CJ, Storrow AB, et al. Prevalence of negative chest radiography in the emergency department patient with decompensated heart failure. *Ann Emerg Med* [in press].
- [8] Potain C. Les bruits de galop. *Sem Med* 1900;20:175.
- [9] Sokolow M. Physical examination. *Clinical cardiology*, 5th ed. 1990.
- [10] Joshi N. The third heart sound. *South Med J* 1999;92(8):756-61.
- [11] Abrams J. Current concepts of the genesis of heart sounds. II. Third and fourth sounds. *JAMA* 1978;239(26):2790-1.
- [12] Reddy PS. The third heart sound. *Int J Cardiol* 1985;7(3):213-21.
- [13] Sloan A. Cardiac gallop rhythm. *Medicine* 1958;37:197-215.
- [14] Evans W. The use of phonocardiography in clinical medicine. *Lancet* 1951;1:1083-5.
- [15] Benchimol A, Desser KB. The fourth heart sound in patients without demonstrable heart disease. *Am Heart J* 1977;93(3):298-301.
- [16] Erikssen J, Rasmussen K. Prevalence and significance of the fourth heart sound (S<sub>4</sub>) in presumably healthy middle-aged men, with particular relation to latent coronary heart disease. *Eur J Cardiol* 1979;9(1):63-75.
- [17] Spodick D, Quarry V. Prevalence of the fourth heart sound by phonocardiography in the absence of cardiac disease. *Am Heart J* 1974;87(1):11-4.
- [18] Jordan MD, Taylor CR, Nyhuis AW, et al. Audibility of the fourth heart sound. Relationship to presence of disease and examiner experience. *Arch Intern Med* 1987;147(4):721-6.
- [19] Prakash R, Aytan N, Dhingra R, et al. Variability in the detection of a fourth heart sound-its clinical significance in elderly subjects. *Cardiology* 1974;59(1):49-56.
- [20] Swistak M, Mushlin H, Spodick DH. Comparative prevalence of the fourth heart sound in hypertensive and matched normal persons. *Am J Cardiol* 1974;33(5):614-6.
- [21] Aronow WS, Uyeyama RR, Cassidy J, et al. Resting and postexercise phonocardiogram and electrocardiogram in patients with angina pectoris and in normal subjects. *Circulation* 1971;43(2):273-7.
- [22] Collins SP, Lindsell CJ, Peacock WF, et al. Prevalence of the third and fourth heart sound in asymptomatic subjects. *Congest Heart Fail*; [in press].
- [23] Davie AP, Francis CM, Caruana L, et al. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997;90(5):335-9.
- [24] Gerber I, McKeown BH, Marcus B. Third and fourth heart sounds are highly specific markers for elevated left ventricular filling pressure and reduced ejection fraction. Toronto: Heart Failure Society of America; 2004.
- [25] Inovise Medical, Inc., Audicor-FDA 510K number K031182. 2003.
- [26] Gerber I, McKeown BH, Huddleston M. Echocardiographic, neuro-hormonal and invasively measured correlates of third and fourth heart sounds determined by audioelectric cardiography. *Journal of the American Society of Echocardiography*; 2004.
- [27] Jordan M. Third and fourth heart sounds detected by correlated audioelectric cardiography are highly specific markers for elevated left ventricular filling pressure and reduced ejection fraction. In *American College of Emergency Physicians*. 2004, San Francisco.
- [28] Andresen A, Dobkin J, Maynard C, et al. Validation of advanced ECG diagnostic software for the detection of prior myocardial infarction by using nuclear cardiac imaging. *J Electrocardiol* 2001;34(Suppl):243-8.
- [29] Wagner GS, Maynard C, Andresen A, et al. Evaluation of advanced electrocardiographic diagnostic software for detection of prior myocardial infarction. *Am J Cardiol* 2002;89(1):75-9.
- [30] Andresen A, Gasperina MD, Myers R, et al. An improved automated ECG algorithm for detecting acute and prior myocardial infarction. *J Electrocardiol* 2002;35(Suppl):105-10.
- [31] Warner RA, Ariel Y, Gasperina MD, et al. Improved electrocardiographic detection of left ventricular hypertrophy. *J Electrocardiol* 2002;35(Suppl):111-5.
- [32] Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol* 2001;37(2):379-85.
- [33] Kono T, Suwa M, Hanada H, et al. Clinical significance of normal cardiac silhouette in dilated cardiomyopathy-evaluation based upon echocardiography and magnetic resonance imaging. *Jpn Circ J* 1992;56(4):359-65.
- [34] Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347(3):161-7.
- [35] McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003;41(3):571-9.
- [36] Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. *Rev Cardiovasc Med* 2002;(3 Suppl 4):S10-7.
- [37] Drazner MH, Rame JE, Stevenson LW, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med* 2001;345(8):574-81.
- [38] Storrow A, Collins SP, Peacock WF, et al. Length of stay and charges are increased in patients with digitally detected third heart sounds. New York, NY: Society for Academic Emergency Medicine; 2005.

## **Attachment B-4**

CMS-1506-P

Comments on Packaged Services—0069T  
“Acoustic heart sound recording and computer analysis”

September 29, 2006

Inovise Medical, Inc.  
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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.*

**E**xtra 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).<sup>1</sup> 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  $S_3$ .<sup>2</sup> 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.<sup>3</sup> The atrial and ventricular "gallop" has been described in the literature dating back to the late 1800s.<sup>4</sup> 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.<sup>5,7</sup> The incidence of an  $S_4$  in acute ischemia and acute infarction approaches 100%.<sup>8</sup>

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  $S_3$  from as low as 11%<sup>9</sup> to as high as 75%,<sup>10</sup> as well as many values in between.<sup>11–16</sup> 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 two-fold: 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

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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  $V_6$ , 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

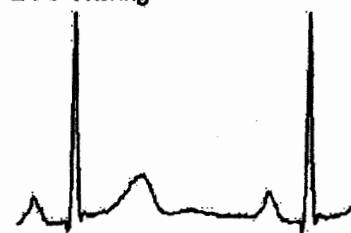
has been validated in prior studies comparing the detection of  $S_3$  and  $S_4$  to hemodynamic measurements obtained at cardiac catheterization.<sup>17</sup> Briefly, both channels ( $V_3$  and  $V_4$ ) are analyzed by the algorithm for the presence of abnormal diastolic heart sounds, using the ECG 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).

## 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

## ECG Tracing



## Sound Tracing

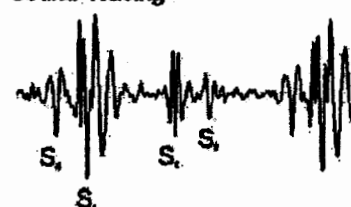


Figure 1. Location of heart sounds in the cardiac cycle. ECG=electrocardiographic

(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 [%])			
	NONE	$S_3$	BOTH	$S_4$
<b>ASYMPTOMATIC ADULTS</b>				
<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)
<b>AMBULATORY SENIORS</b>				
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)
<b>COLLEGE STUDENTS</b>				
<30 (Total)	84 (55.3)	59 (38.8)	5 (3.3)	4 (2.6)
<b>OUTPATIENTS</b>				
<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)
<b>OTHER</b>				
<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.



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

UNVARIABLE MODELS	N	S <sub>3</sub>		BOTH		S <sub>4</sub>	
		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		**		**	3.008	0.704-12.858
Prior myocardial infarction	174	0.641	0.324-1.269	0.686	0.227-2.076	1.166	0.730-1.862
Ischemia	32	0.342	0.045-2.591	3.016	0.822-11.072	1.367	0.536-3.487
Left ventricular hypertrophy	46	0.778	0.229-2.648	2.288	0.634-8.264	1.902	0.910-3.974
Abnormal	331	0.996	0.618-1.605	1.418	0.695-2.893	1.093	0.739-1.616
Borderline	220	1.893	1.188-3.016	0.752	0.273-2.076	1.057	0.667-1.675
Multivariable Model							
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<sub>3</sub> or both an S<sub>3</sub> and S<sub>4</sub>

## Discussion

Our results suggest that an S<sub>3</sub> 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<sub>3</sub> be classified in the group at highest risk for adverse outcomes and considered candidates for an early invasive strategy.<sup>18</sup> Accurate knowledge of the true underlying frequency of the S<sub>3</sub> may impact these recommendations. Consequently, the implications of our findings require further corroboration with clinical outcomes.

The low prevalence of S<sub>3</sub> in asymptomatic subjects over the age of 50 strengthens previous findings that a detectable S<sub>3</sub> in older subjects may be highly specific for cardiac pathology, although the age above which an S<sub>3</sub> is predictive of LV dysfunction may be slightly higher than 40 years, as previously reported.<sup>5-7</sup>

In contrast to the S<sub>3</sub> detection of an S<sub>4</sub> was quite uncommon in subjects younger than 50 (under 10%), with increasing prevalence thereafter

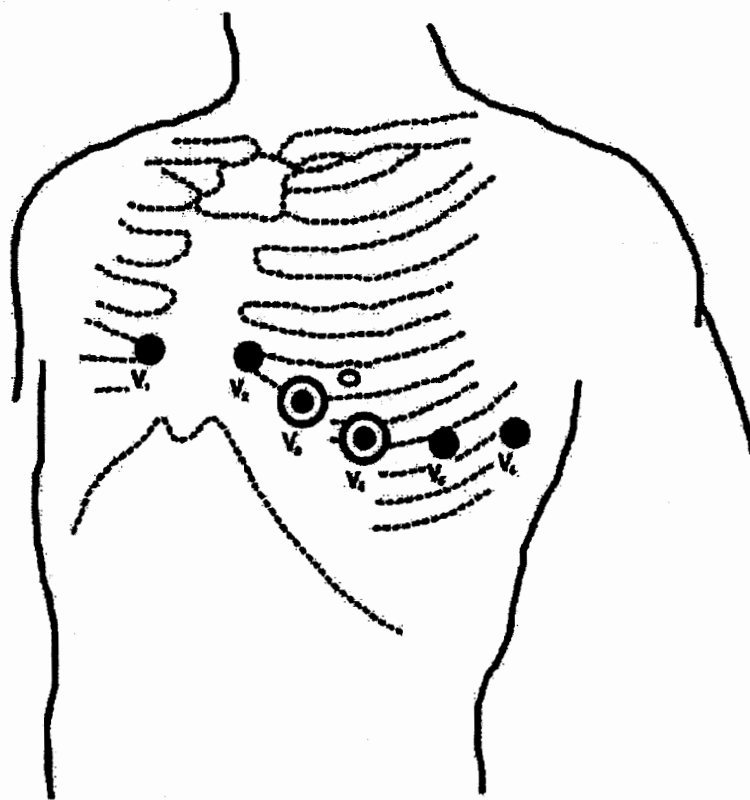


Figure 2. Schematic of the placement of the chest leads with acoustical leads in the V<sub>1</sub> and V<sub>4</sub> positions

An S<sub>4</sub> detected by auscultation has long been considered indicative of ventricular dysfunction.<sup>19,20</sup> Previous stud-

ies have demonstrated the presence of an S<sub>4</sub> during episodes of angina, in patients with coronary artery disease,



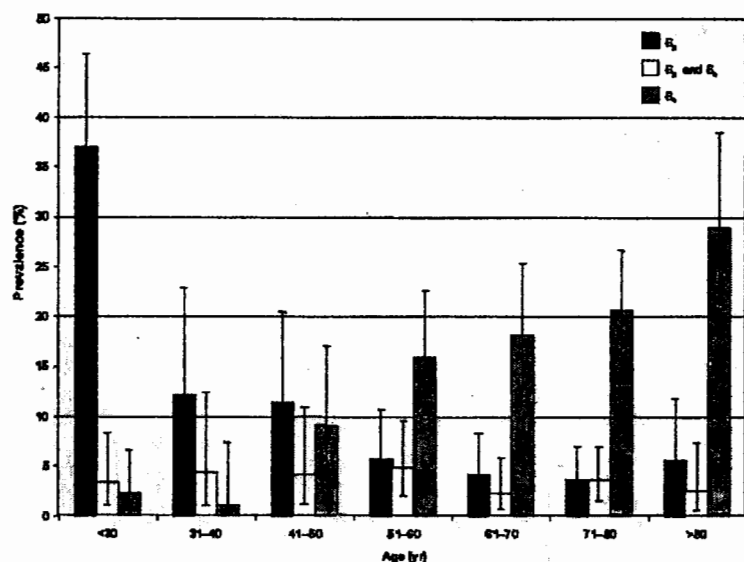


Figure 3. Prevalence of  $S_3$  and  $S_4$  heart sounds stratified by age. Subjects with a finding of  $S_3$  and  $S_4$  are not included in those with findings of  $S_3$  or  $S_4$  only; findings are mutually exclusive. Error bars represent 95% confidence intervals.

and during ischemic stress tests.<sup>16,21,22</sup> Several studies in the early and mid-1970s questioned the validity of this belief. Spodick and Quarry,<sup>12</sup> 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.<sup>15</sup> Enksson and Rasmussen<sup>11</sup> 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.<sup>10,13,14</sup>

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.<sup>19,20</sup> 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)<sup>23,24</sup> 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<sup>16</sup> 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.

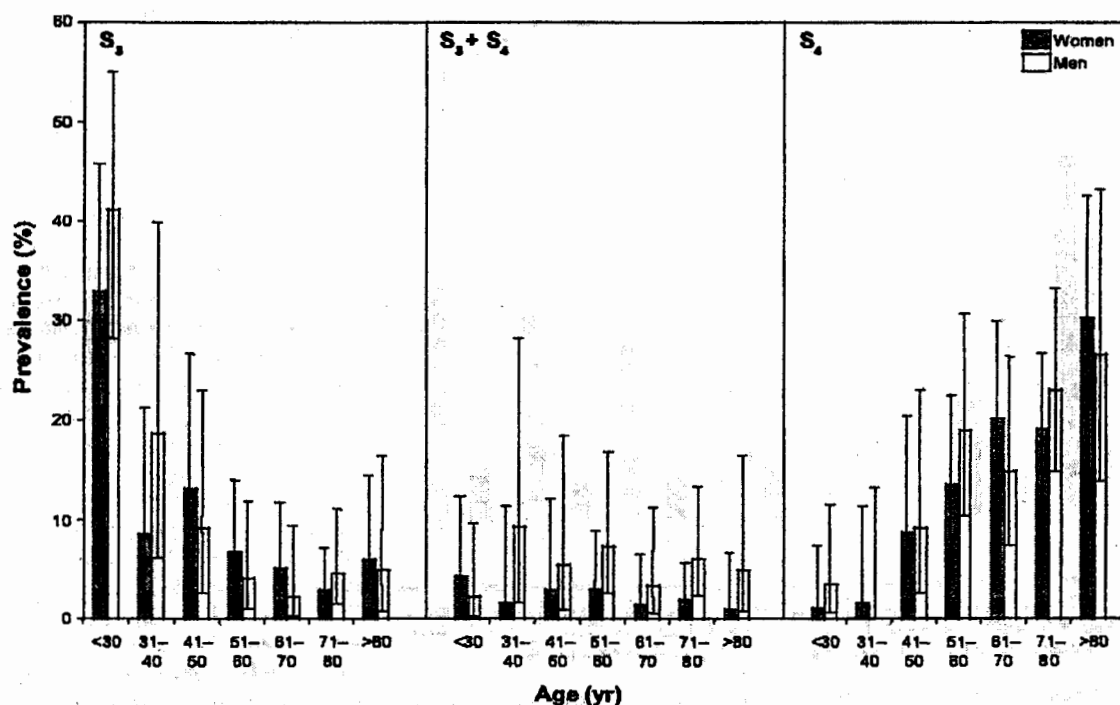


Figure 4. Prevalence of heart sounds stratified by gender and age category. Subjects with a finding of S<sub>1</sub> and S<sub>2</sub> are not included in those with findings of S<sub>1</sub> or S<sub>2</sub> only; findings are mutually exclusive. Error bars represent 95% confidence intervals.

## Conclusions

Our study suggests that the prevalence of an S<sub>3</sub> is increased earlier in life, while an S<sub>4</sub> in asymptomatic individuals is much

more common in the later decades in life. The prevalence of an S<sub>3</sub> in younger individuals is consistent with previous studies. However, the prevalence of S<sub>4</sub>

may be less common than previous phonocardiographic studies suggest, and its detection, even in the elderly, should perhaps not be ignored.

## REFERENCES

- Sokolow M. Physical examination. In: *Clinical Cardiology*. 5th ed. Norwalk, CT: Appleton & Lange; 1990.
- Joshii N. The third heart sound. *South Med J*. 1999;92(8):756-761.
- Abrams J. Current concepts of the genesis of heart sounds. II. Third and fourth sounds. *JAMA*. 1978;239(26):2790-2791.
- Potain C. Du bruit de galop. *Gaz D Hop*. 1880;53:529-531.
- Reddy PS. The third heart sound. *Int J Cardiol*. 1985;7(3):213-221.
- Sloan A. Cardiac gallop rhythm. *Medicine (Baltimore)*. 1958;37:197-215.
- Evans W. The use of phonocardiography in clinical medicine. *Lancet*. 1951;1:1083-1085.
- Perloff JK. *Physical Examination of the Heart and Circulation*. 2nd ed. Philadelphia, PA: WB Saunders Co; 1997.
- Bethell HJ, Nixon PG. Atrial gallop in coronary heart disease without overt infarction. *Br Heart J*. 1974;36(7):682-686.
- Benchimol A, Desser KB. The fourth heart sound in patients without demonstrable heart disease. *Am Heart J*. 1977;93(3):298-301.
- Eniksen J, Rasmussen K. Prevalence and significance of the fourth heart sound (S<sub>4</sub>) in presumably healthy middle-aged men, with particular relation to latent coronary heart disease. *Eur J Cardiol*. 1979;9(1):63-75.
- Spodick DH, Quarry VM. Prevalence of the fourth heart sound by phonocardiography in the absence of cardiac disease. *Am Heart J*. 1974;87(1):11-14.
- Jordan MD, Taylor CR, Nyhuts AW, et al. Audibility of the fourth heart sound. Relationship to presence of disease and examiner experience. *Arch Intern Med*. 1987;147(4):721-726.
- Prakash R, Aytan N, Dtingra R, et al. Variability in the detection of a fourth heart sound—its clinical significance in elderly subjects. *Cardiology*. 1974;59(1):49-56.
- Swiatok M, Mushlin H, Spodick DH. Comparative prevalence of the fourth heart sound in hypertensive and matched normal persons. *Am J Cardiol*. 1974;33(5):614-616.
- Aronow WS, Uyeyama RR, Cassidy J, et al. Resting and postexercise phonocardiogram and electrocardiogram in patients with angina pectoris and in normal subjects. *Circulation*. 1971;43(2):273-277.
- Marcus GM, Gerber IL, McKeown BH, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA*. 2005;293:2238-2244.
- Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation*. 2002;106(14):1893-1900.
- Fowler NO, Adolph RJ. Fourth sound gallop or split first sound? *Am J Cardiol*. 1972;30(4):441-444.
- Grayzel J. Gallop rhythm of the heart. I. Atrial gallop, ventricular gallop and systolic sounds. *Am J Med*. 1960;28:578-592.
- Perez GL, Luteada AA. When does a fourth sound become an atrial gallop? *Angiology*. 1976;27(5):300-310.
- Thompson PL. Physical examination in ischaemic heart disease. *Med J Aust*. 1976;1(14):492-495.
- Tavel ME. *Clinical Phonocardiography and External Pulse Recording*. 3rd ed. Chicago, IL: Year Book Medical Publishers; 1978.
- Wartak J. *Phonocardiography*. Hagerstown, MD: Harper & Row Publishers, Inc.; 1972.

## **Attachment B-5**

CMS-1506-P

Comments on Packaged Services—0069T  
“Acoustic heart sound recording and computer analysis”

September 29, 2006

Inovise Medical, Inc.  
10565 SW Nimbus Avenue, Suite 100  
Portland, Oregon 97223-4311  
p: 503.431.3800  
f: 503.431.3801  
w: [www.audicor.com](http://www.audicor.com)

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.

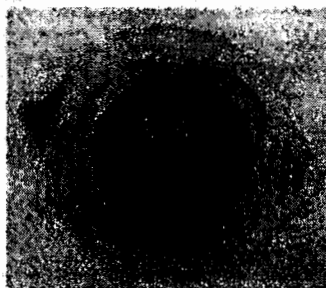
The comprehensive printout it provides quite frankly "wowed" me (see Figure 1, p. 106). It resembles a 12-lead printout but with some other great information. At the bottom of the printout, the S3 and S4 heart sounds are displayed similar to an ECG tracing or graph. At the top right, a cross-section 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 dysfunc-

tion. 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 after-load 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



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

## HANDS ON! GEAR, GADGETS & GREAT IDEAS

and immediately trade in your current unit for this one.

The Audicor has limitations. Its main function is ECG monitoring and interpretation and does not include defibrillation, pacing or other features we've grown accustomed to.

In November 2003, the device was cleared by the FDA. In April 2004, Collier County (Fla.) EMS became the first EMS system to use it in pre-hospital care. Robert B. Tober, MD, EMS medical director for Collier County, notes:

- The Audicor works better with the ambulance stopped, to reduce road noise, but the engine can remain on;
- The device functions better with air-conditioning off or on low; and
- Artifact (i.e., interference) occurs in some situations, and engineers are working on a second-generation electrode.

Tober sums up Collier's experience by saying that the Audicor

promises to provide a reliable heads-up that all is *not* always well in a patient with an otherwise normal ECG. It appears to not only deliver more sensitive interpretive algorithms in abnormal ECGs, but also deliver early warning signs that otherwise would be missed.

For additional information, contact Inovise Medical Inc. at 877/466-8473, or visit [www.inovise.com](http://www.inovise.com).



*Jeffrey Lindsey, PhD, EMT-P, is operations chief for Estero (Fla.) Fire Rescue. He holds a doctorate in instructional technology and has more than 20 years' experience in EMS, fire and rescue. He is also a senior partner with International Consulting and Training Specialists. Contact him via e-mail at [jlindsey1@aol.com](mailto:jlindsey1@aol.com).*

### Visually Zero in on Medical & WMD Conditions

VisualDx, a powerful software program from Logical Images Inc. with more than 8,700 medical photographs, allows emergency personnel to search by a patient's symptoms and view diagnostic images with the most relevance to the patient.

VisualDx covers almost all areas of visually diagnosable medicine, including illness and injury caused by weapons of mass destruction, such as

bioterrorism agents (category A, B and C agents as designated by the Centers for Disease Control and Prevention), chemical agents and radiation injuries.

The program's photographs are drawn from a collection of more than a million professionally photographed medical images obtained from prominent universities and private collections throughout the world. Logical Images updates the content and capabilities of the software regularly.

As the saying goes, "a picture is worth a thousand words," and in a randomized, controlled university study, VisualDx was shown to increase diagnostic accuracy 100% among primary care and emergency physicians (in comparison with using textbooks and medical atlases) after only five minutes of training.

Because it's just as important to determine if a patient's condition is *not* caused by a terrorist agent as it is to determine if it is, VisualDx serves as a valuable assessment and diagnostic tool for EMS. It's the only diagnostic and training tool that includes terrorism preparedness information as part of the differential for daily use in diagnosing common conditions.

"False positive diagnoses cost the health-care system money and cause unnecessary public concern," says Art Papier, MD, chief scientific officer of Logical Images. "And false negative diagnoses may be life-threatening. With VisualDx, every first responder is an alert first responder. Early detection is key."

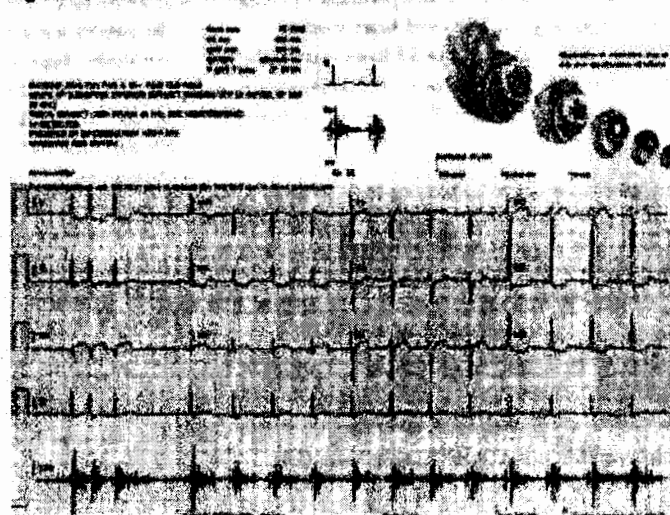
The VisualDx support system is currently used by bioterrorism preparedness regional resource centers, hospital emergency departments, U.S. Army medical command hospital facilities and public health departments throughout the United States, including major implementations in New York City, Washington, D.C., and throughout the states of Mississippi and New York.

VisualDx can be licensed to a communications center and installed on laptop computers for use in vehicles or on scene. It can also be accessed over the Internet.

The compact, easy-to-use Audicor System is moving pre-hospital care to the next level.



Figure 1: Audicor Printout



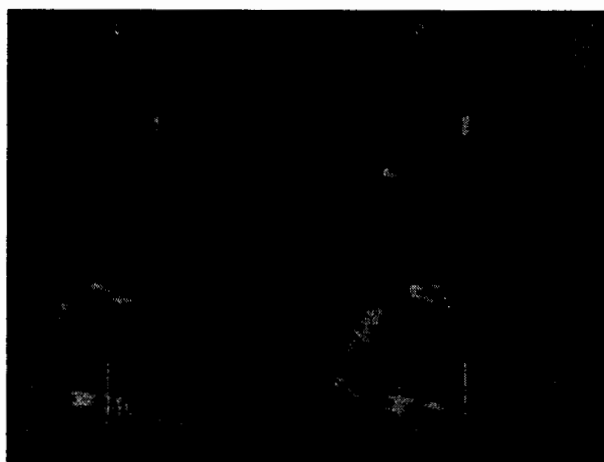
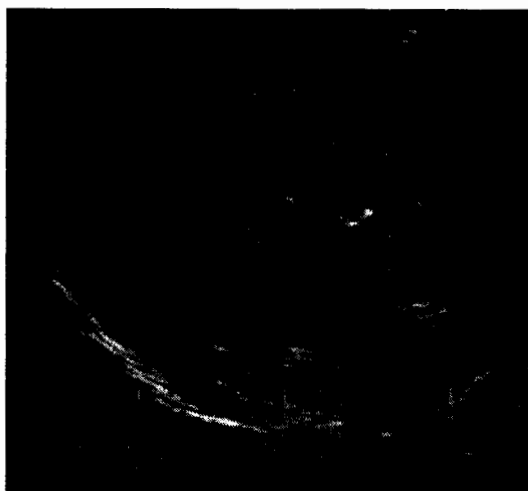
# **Attachment C**

**CMS-1506-P**

**Comments on Packaged Services—0069T  
“Acoustic heart sound recording and computer analysis”**

**September 29, 2006**

**Inovise Medical, Inc.  
10565 SW Nimbus Avenue, Suite 100  
Portland, Oregon 97223-4311  
p: 503.431.3800  
f: 503.431.3801  
w: [www.audicor.com](http://www.audicor.com)**



**Submitter :** Dr. Jorge Cassir  
**Organization :** AtlantiCare Regional Medical Center  
**Category :** Radiologist

**Date:** 09/29/2006

**Issue Areas/Comments**

**OPPS: Brachytherapy**

**OPPS: Brachytherapy**

e-Brachytherapy is a new therapy which is far safer for both patients and professional staff from the radiation safety stand point. And it should be re-imbursed, at a minimum, at the same level as the regular radioisotopes commonly used in B/chytx.



**Submitter :** Dr. Craig DeWeese

**Date:** 09/30/2006

**Organization :** Norton Hospital

**Category :** Physician

**Issue Areas/Comments**

**GENERAL**

GENERAL

See Attachment

CMS-1506-P-197-Attach-1.DOC

September 29, 2006

Office of the Administrator  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mail Stop C4-26-05  
7500 Security Boulevard  
Baltimore, MD 21244-1850

Attention: CMS-1506-P; Medicare Program; Hospital Outpatient Prospective Payment System and CY 2007 Payment Rates

Dear Administrator:

Thank you for allowing me the opportunity to provide comment on the Centers for Medicare and Medicaid Services proposed rule, published in the Federal Register on August 23, 2006. This letter is written to share my concern regarding the proposed RVU reduction for CPT19296 and CPT 19297, when performed in the hospital, and the reassignment of these codes from the New Technology to the Clinical payment rate.

CMS implemented breast brachytherapy CPT codes 19296 and 19297 on January 1, 2005 and assigned these codes to New Technology APCs 1524 and 1523 respectively. CMS proposes to reassign these codes from New Technology APCs to clinical APCs in 2007. The CMS proposed APC assignment for CPT Codes 19296 and 19297 would result in significant decreases in 2007 payment. The table below illustrates the reductions, ranging from -22.8% to -37.0%. Should CMS finalize the proposed APC assignments, it will limit our ability to offer this breast cancer treatment option to Medicare eligible women since the cost of the device surpasses the proposed payment rate.

HCCPS Code	2006 APC	2006 Payment	2007 Proposed APC	2007 Proposed Payment	Payment Change 2006-2007	Percent Change 2006-2007
19296 Breast interstitial radiation treatment, delayed	1524	\$3,250	30	\$2,508.17	(\$741.83)	-22.8%
19297 Breast interstitial radiation treatment, immediate	1523	\$2,750	29	\$1,732.69	(\$1,017.31)	-37.0%

CMS should maintain 19296 and 19297 in the New Tech APCs 1524 and 1523 respectively so that it may collect claims data through calendar year 2006 and reevaluate reassignment to a more appropriate APC for 2008. Breast brachytherapy CPT codes 19296 and 19297 are classified as device-dependent procedures since they are reliant on the use of a high cost device that is bundled into the procedure payment. APC 648 Breast Reconstruction with Prosthesis includes other similar procedures to those of 19296 and 19297. The similarities not only are clinical but also in the cost of the device. Should CMS discontinue the assignment of 19296 and 19297 in new tech APCs, an alternative request is for both CPT codes to be reclassified to APC 648.

I recommend that breast brachytherapy codes 19296 and 19297 remain in their current New Technology APCs (1524 and 1523 respectively) for 2007 to allow the opportunity to collect additional claims data. Alternatively, I recommend that CPT codes 19296 and 19297 be assigned to clinical APC 648 Breast Reconstruction with Prosthesis. To appropriately capture all procedures in APC 648, it is also recommended that CMS revise the group title from Breast Reconstruction with Prosthesis to Level IV Breast Surgery.

Sincerely,

*R. Craig DeWeese, MD*

R. Craig DeWeese, MD  
Norton Hospital  
Louisville, KY

cc. Representative Ann Northup, Appropriations Labor-HHS Subcommittee  
Carol Bazell, MD, MPH, Director, Division Outpatient Services  
Helen Pass, MD, FACS, President, American Society of Breast Surgeons  
Mark A. Malangoni, MD, FACS, Chair, American College of Surgeons

**Submitter :** Miss. Jugna Shah

**Date:** 10/01/2006

**Organization :** Alliance of Dedicated Cancer Centers

**Category :** Health Care Provider/Association

**Issue Areas/Comments**

**OPPS: Drug Administration**

OPPS: Drug Administration

Please see the attached files.

CMS-1506-P-198-Attach-1.DOC

IT 10.11.06  
198

**The Alliance of Dedicated Cancer Centers:**

**Arthur G. James Cancer Hospital and Richard J. Solove Research Institute  
City of Hope National Medical Center  
Dana-Farber Cancer Institute  
Fox Chase Cancer Center  
H. Lee Moffitt Cancer Center and Research Institute  
M.D. Anderson Cancer Center  
Memorial Sloan-Kettering Cancer Center  
Roswell Park Cancer Institute  
Seattle Cancer Care Alliance  
Sylvester Comprehensive Cancer Center**

**October 1, 2006**

**By Electronic Delivery**

Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
Room 445-G Hubert H. Humphrey Building  
200 Independence Avenue, S.W.  
Washington, D.C. 20201

**Re: File Code CMS-1506-P: Medicare Program; Proposed Changes to the  
Hospital Outpatient Prospective Payment System and Calendar Year 2007  
Payment Rates; Proposed Rule**

Dear CMS Administrator:

On behalf of the Alliance of Dedicated Cancer Centers (the "Centers"), an alliance of ten nationally recognized institutions focusing exclusively on the care of cancer patients, I am writing to comment on the Proposed Rule that would revise the Medicare prospective payment system for hospital outpatient services, as published in the *Federal Register* on August 23, 2006 (71 Fed. Reg. 49,506) (the "Proposed Rule"). The Cancer Centers, individually listed above, appreciate the opportunity to submit our comments on the topic of drug administration. This letter is the first of several comments that the Centers will be submitting on the Proposed Rule.

## **OPPS: Drug Administration**

For the past four years, the Centers have strongly supported improving drug administration coding and payment policy under OPPS. We are pleased that CMS has proposed a number of changes for drug administration services for 2007, including proposals to expand the number of drug administration APC groups; moving away from per-visit payment to per-service payment; and providing for separate payment for additional hours of infusion therapy. The Centers anticipate continued refinements for drug administration coding, billing, and reimbursement under OPPS. The Centers' comments on drug administration for 2007 fall into three main areas: coding, payment, and other issues for 2007. We address each of these separately below.

### **Coding Policy**

The Centers are concerned with CMS' proposal to continue requiring providers to report a combination of HCPCS C-codes and CPT codes to report drug administration services in 2007. This is how all providers report drug administration services to Medicare. However, our other payers require the full set of 2006 drug administration CPT codes to be reported. This has resulted in a situation where hospitals must report one way to Medicare (HCPCS C-codes and CPT codes) and a different way to non-Medicare payers (CPT codes), resulting in an enormous administrative and operational burden.

Because more drug administration CPT codes exist than HCPCS C-codes, and because providers are required to charge all payers the same, providers were forced to learn how to code and bill all of the CPT drug administration codes this year. We trained

our charging staff, updated internal systems and processes, and revised our encounter forms to reflect the full range of 2006 drug administration CPT codes. This was necessary because, even though all of the CPT codes were not required for Medicare, they were required by our other payers. The result is that the Centers and most other providers are currently using the full set of CPT codes to charge non-Medicare payers for drug administration services at the point of care, and converting the CPT codes into C-codes for Medicare billing on the back-end, through edits in the billing system or by conducting manual reviews. It is worth noting that several of the Centers created bill edits in their bill scrubbers but found them to be unreliable and ultimately decided to have specialized and dedicated coding staff review each record manually before submitting claims to Medicare. Having dedicated FTEs reviewing records and monitoring the coding and billing process is extremely resource intensive and operationally burdensome. Nevertheless, we have been forced to “make it work” through significant training and education efforts, internal edits, and manual review.

As CMS is aware, the Centers were never in favor of implementing the new 2006 drug administration CPT codes, since those fundamentally differ from the 2005 drug administration CPT codes (which the Centers strongly supported). We maintain our earlier position: that the 2006 drug administration CPT codes are not applicable in the hospital setting and should not be the final system of codes used to report drug administration services under OPPS in the future. Our position is based on the fact that the CPT codes were created by physicians, for physician use; in fact, the CPT Editorial Panel now seems to recognize that the codes are not optimal for the hospital setting and has indicated a willingness to revise them.

Since the Centers, like many other providers are already required to report the full range of CPT codes to non-Medicare payers, and a partial set to CMS, a move to the full use of drug administration CPT codes will streamline the administrative process. This will enable providers to charge all payers in the same manner. We are prepared to use the full set of drug administration CPT codes in 2007. However, we urge CMS to view this as an interim solution only. It is essential that CMS address the fact that the drug administration CPT codes need further revision for hospital use. The Centers urge CMS to work with the AHA and the CPT Editorial Panel to make the necessary revisions so that, by 2008, the CPT codes for drug administration will be appropriately applicable and easy to use in the hospital setting.

The Centers are concerned about both the long-term applicability of the new CPT codes and descriptions, as well as the narrative guidance included in the CPT book. As noted, the codes were created for, and by, physicians for use in the private office setting without regard to the educational, operational, and financial impact of hospital setting implementation. The CPT Editorial Panel did not have hospital use in mind when it made significant changes to the drug administration codes and descriptions, since hospitals were still reporting Q-codes at that time and Medicare had not yet decided to require CPT codes. A combination of bad timing, lack of communication, and poor coordination between CMS and the CPT Editorial Panel has resulted in the burdensome requirement that hospitals must report new codes for drug administration services in part to CMS, and in full to many other payers. Nonetheless, the Centers continue to support the use of CPT codes from 2005 and previous years instead of the old Q-codes, as CPT coding allows for greater differentiation among infusion and injection services.



For this reason – despite opposing the current CPT codes and drug administration descriptions – the Centers believe that CMS’ movement to the full use of CPT codes would reduce much of our current operational burden related to charging different payers with different code sets. It may also create the necessary impetus for CMS to work with the AHA and the CPT Editorial Panel to revise the current CPT codes and descriptors to ensure their applicability in the hospital setting. The Centers therefore urge CMS to move to full implementation of CPT codes for reporting drug administration services under OPPS for 2007. We also urge CMS to immediately begin working with the AHA and the CPT Editorial Panel to revise the codes and descriptions for drug administration services to ensure that they are equally applicable in both the physician and hospital settings. The Centers would be pleased to provide CMS with recommendations on how to revise existing CPT code descriptions to make them appropriate and usable in the hospital setting.

#### APC Payment Groupings and Payment Policy

The Centers applaud CMS for using 2005 provider claims data to create six new drug administration APCs, and for proposing to allow separate payment for each additional hour of infusion therapy. The Centers also support CMS’ proposal to pay for drug administration services on a per-service basis similar to other APC services (instead of the per-visit payment which has been the case for drug administration services since OPPS’ inception). We encourage CMS to make this proposal final for 2007. As a result of this proposed change, we expect that the OCE/PRICER logic will be revised so that claims are processed appropriately regardless of whether the CPT and C-code coding methodology is retained or if full use of CPT drug administration codes is implemented.

At a minimum, this means allowing the OCE/PRICER to generate multiple APC payments when multiple units of the same code are reported, or when multiple APCs are generated as a result of the full use of CPT codes.

The Centers have carefully reviewed CMS' Preamble Table 30.2 and agree with the new APC payment structure. However, we are concerned about the placement of several codes into APC groups.. First, the Centers agree with CMS' proposed assignment of C8952 into the Level III Drug Administration APC and expect that, if CMS moves to the full use of CPT drug administration codes for 2007, the analogous CPT code, 90774 (therapeutic, prophylactic or diagnostic injection, IV push, single or initial substance/drug), would be assigned to this same level. We question where CMS will place CPT 90775 (therapeutic, prophylactic or diagnostic injection, each additional sequential intravenous push of a new substance/drug), since it does not have an analogous HCPCS C-code. The Centers believe this code should also be placed in the Level III Drug Administration APC since the same facility resources are required whether a single injection or multiple injections of the same or a different drug are given. If the resources required are the same, the reimbursement should be the same as well.

Second, the Centers are concerned about the APC assignment and associated payment rates for the following three chemotherapy administration codes:

- 96440 (Chemotherapy administration, pleural cavity requiring and including thoracentesis);
- 96445 (Chemotherapy administration, peritoneal cavity requiring and including peritoneocentesis);

- 96450 (Chemotherapy administration into CNS requiring and including spinal puncture).

These chemotherapy administration services are far more invasive (e.g., they require catheters inserted into body cavities) and require more facility resources than the other drug administration services assigned to the same APCs. CMS proposes to place CPT codes 96440 and 96445 in a Level IV Drug Administration APC (APC 439), with a proposed payment rate of \$97.50; and CPT code 96450 in a Level VI Drug Administration APC (APC 441), with a proposed payment rate of \$154.31.<sup>1</sup> The payment rates for these services are exceptionally low. For CPT codes 96440 and 96445 (drug administration plus the associated procedure as described in the code descriptors above), the payment rate is even lower than the APC payment rate for the procedure alone. For CPT code 96450, the payment rate is only slightly higher than the code for the procedure itself. Table 1 below clearly shows the APCs and associated payment rates for the three stand-alone surgical procedures and the three chemotherapy administration services, which include the surgical procedure as part of the service.

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<sup>1</sup> 71 Fed. Reg. 49,506, 49,754-49,848 (Aug. 23, 2006) (Addendum B).

**TABLE 1<sup>2</sup>**

<b>CPT/ HCPCS</b>	<b>Short CPT Description</b>	<b>APC</b>	<b>APC Payment</b>
32000	Drainage of chest	0070	224.20
49080	Puncture, peritoneal cavity	0070	224.20
62270	Spinal fluid tap, diagnostic	0204	138.43
96440	Chemotherapy, intracavitary	0439	97.50
96445	Chemotherapy, intracavitary	0439	97.50
96450	Chemotherapy, into CNS	0441	154.31

The proposed APC payment rate for CPT codes 32000 for drainage of the chest (thoracentesis) and for 49080 for puncture, peritoneal cavity (peritoneocentesis) is significantly higher than the APC payment rate for the two chemotherapy administration codes which include these procedures as part of the overall service. It is only logical that the surgical procedure provided along with chemotherapy administration should result in a higher APC payment than either service rendered alone -- yet this is not the case. Although CPT code 96450 -- which includes both chemotherapy administration and the lumbar puncture procedure (CPT 62270) -- has a slightly higher APC payment rate than CPT code 62270 when provided on its own, this increase is not sufficient to cover the extra costs associated with providing two services instead of one.

Therefore, the Centers urge CMS to move procedure codes 96440, 96445, and 96450 out of the proposed APC groups to which they are currently assigned. CMS should either create a new APC group with a significantly higher payment rate, or simply instruct providers to report both the surgical procedure code and the drug administration

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<sup>2</sup> Id.

procedure code as separate line items. CMS will need to turn off the hospital Correct Coding Initiative (CCI) edits related to these code pairs so the OCE/PRICER can generate a separate APC payment for each separately billed service.

Finally, as stated above, we believe it will be easier for hospitals to report the full set of CPT codes to all payers, including Medicare, in 2007. As such, we have provided the following cross-walk from CPT codes to APC groupings for CMS to use in 2007. It should be noted that our mapping is quite similar to the information that CMS provided to the APC Advisory Panel at its March 2006 meeting.

**TABLE 2**

2007 APC	Drug Administration APC Level	SI	Proposed CY 2007 APC Median	CPT/HC PCS Code	Description	Notes
0436	LEVEL I	S	\$10.71	90472	Immunization admin, each add	
				90473	Immune admin oral/nasal	
				90474	Immune admin oral/nasal addl	
				90779	Ther/prop/diag inj/inf proc	
				95115	Immunotherapy, one injection	
				96549	Chemotherapy, unspecified	
0437	Level II	S	\$25.49	90772	Ther/proph/diag inj, sc/im	
				90471	Immunization admin	
				95117	Immunotherapy injections	
				95144	Antigen therapy services	
				95145	Antigen therapy services	
				95146	Antigen therapy services	
				95147	Antigen therapy services	
				95148	Antigen therapy services	
				95149	Antigen therapy services	
				95165	Antigen therapy services	
				95170	Antigen therapy services	
				G0008	Admin influenza virus vac	
				G0009	Admin pneumococcal vaccine	
0438	Level III	S	\$48.99	90773	Ther/proph/diag inj, ia	
				90774	Ther/proph/diag inj, iv push, single or intial substance/drug	
				90775	Ther/proph/diag inj, iv push, each additional sequential intravenous push of a new substance/drug	
				90761	Intravenous infusion for therapy/diagnosis; each additional hour	
				90766	Intravenous infusion for therapy/diagnosis/prophylaxis; each additional hour, up to 8 hours	
				96401	Chemo, anti-neopl, sq/im	
				96402	Chemo hormon antineopl sq/im	
				96405	Chemo intralesional, up to 7	
				96406	Chemo intralesional over 7	
				96542	Chemotherapy injection	
				96411	Chemotherapy administration; intravenous push technique, each additional substance/drug	
0439	Level IV	S	\$97.84	96409	Chemotherapy administration; intravenous push technique, single or initial substance/drug	
				96420	Chemo, ia, push technique	
				96415	Chemotherapy administration, intravenous; infusion technique; each additional hour up to 8 hours	
				96423	Chemotherapy administration, intra-arterial; infusion technique; each additional hour up to 8 hours	
				90767	Intravenous infusion, for therapy/diagnosis/prophylaxis; additional sequential infusion, up to 1 hour	
				96440	Chemotherapy, intracavitary	Move to new APC or allow payment for this code + the procedure code
				96445	Chemotherapy, intracavitary	Move to new APC or allow payment for this code + the procedure code
0440	Level V	S	\$112.94	90760	Intravenous infusion, hydration; initial up to 1 hour	
				90765	Intravenous infusion, for therapy/diagnosis/prophylaxis; initial, up to 1 hour	
				96417	Chemotherapy administration, intravenous; infusion technique; each additional sequential infusion, up to 1 hour	
				96521	Refill/maint, portable pump	
				96522	Refill/maint pump/resvr syst	
0441	Level VI	S	\$154.86	96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug	
				96416	Chemo prolong infuse w/pump	
				96422	Chemo ia infusion up to 1 hr	
				96425	Chemotherapy, infusion method	
				96450	Chemotherapy, into CNS	Move to new APC or allow payment for this code + the procedure code
				C8957	Intravenous infusion for therapy/diagnosis; initiation of prolonged infusion (more than 8 hours), requiring use of portable or implantable pump	Keep as C-code
Packaged		N/A	N/A	90768	Intravenous infusion, for therapy/diagnosis/prophylaxis; concurrent infusion (report only once per encounter)	

### Additional Drug Administration Issues

CPT codes are not intuitive for hospital use, as noted above. For this reason, the Centers and other providers have asked the CPT Editorial Panel and the AHA for information, examples, and clear guidance on applying concepts such as initial, sequential, and concurrent services. Guidance has not been forthcoming to date, however. Therefore, we urge CMS to release detailed guidance on these and other drug administration issues that have been the subject of much debate this year.

A second issue stems from the fact that, for 2006, CMS recognized that it was unnecessary to include time (hours) in the code descriptors for the add-on infusion codes (C8951 and C8955), which allowed providers to report one line item for the first hour of infusion and a second line item for the additional hours with no maximum unit of service limit. However, the analogous drug administration CPT codes do have an upper limit of “up to eight additional hours,” which means that additional line items of the add-on codes would have to be reported for infusions greater than nine hours and 31 minutes. If CMS moves to the full use of CPT codes for drug administration in 2007, it should allow hospitals to “ignore” the limit of 8 additional hours in the description of the add-on infusion codes. This will enable hospitals to report these services as they report them today, and in a manner that does not create additional administrative burdens for hospital billing systems.

A third issue CMS will need to address if it moves to the full use of CPT codes for drug administration in 2007 is how providers should report the “initiation of prolonged infusion (more than 8 hours) for therapy or diagnosis requiring the use of a portable or implantable pump.” For 2006, CMS released a new HCPCS Level II code (C8957) to report this service, but no equivalent CPT code currently exists. The Centers

agree with CMS' decision to create this code, as it allows providers to report prolonged non-chemotherapy infusions. If CMS moves forward with the full use of CPT codes for drug administration in 2007, we suggest that it continue to allow providers to report C8957. We do not believe this will be problematic in reporting to other payers, since there is no existing CPT code for this service.

Finally, if CMS does not move forward with the full use of CPT codes (choosing to retain a combination of HCPCS C-codes and CPT codes for reporting drug administration services), it must provide clear guidance on how hospitals should report hydration and a therapeutic infusion when provided during the same visit (but not concurrently). There is currently only one code (C8950) to report both services. An example of this situation is as follows: a patient presents to the hospital and receives an hour of medically necessary hydration, followed by an hour of an antibiotic infusion. Both infusions are separate and distinct and both are given for an hour, yet Medicare has only one code to report both services. Because CMS has always employed per-visit payment for drug administration services, this has not been an issue, as Medicare has to date only ever paid for the first hour of an infusion service. With per-service payment proposed for drug administration services in 2007, the Centers expect to receive payment for the actual services they provide. In the example above, the Centers would expect to receive two APC payments: one for the first hour of hydration, and one for the first hour of the antibiotic infusion.

CMS must clarify how it expects providers to report the above scenario. For example, CMS might allow two units of the first hour code (C8950) to be reported without any modifier and have the OCE generate two APC payments. Alternatively,



CMS might require two separate line items of C8950, one with modifier –59. It should be noted that, in the physician office setting, this scenario currently results in two separate payments through the use of different codes for hydration and for therapeutic infusion. CMS should allow the same payment result in the hospital setting even if it chooses to stay with a combination of CPT and HCPCS C-code reporting in 2007.

The Centers also urge CMS to review its policy of not allowing separate payment for multiple IV push injections of the same drug. Prior to 2006, providers reported IV push injections using CPT code 90784, which did not include any descriptor language limiting reporting based on whether the same drug or a new drug was pushed. Hospitals billed and received payment for each separately identifiable IV push reported, regardless of the drug. This is significant, as hospitals often push the same drug multiple times during a single patient visit and the facility resources, including nursing time, are no different whether the same drug or a different drug is provided to the patient. When hospitals administer an IV push injection of a packaged drug, providers lose reimbursement for both the IV push injection service and the drug, which we believe is grossly inappropriate. The Centers recommend that CMS revisit its policy on this issue and allow separate payment of multiple IV pushes regardless of whether the same or different drug is pushed.

\* \* \* \*

Thank you for your willingness to consider our views. We hope that CMS will address the concerns described above and make the necessary adjustments to OPPS to ensure equitable reimbursement for state-of-the-art cancer care. If you have any questions or require additional information, please contact the Cancer Centers' technical consultant on OPPS matters, Ms. Jugna Shah, at (215) 888-6037.

Sincerely,

James S. Quirk  
Executive Director  
Alliance of Dedicated Cancer Centers

**Submitter :** Dr. Shouwen Wang

**Date:** 10/01/2006

**Organization :** Arizona Kidney Disease and Hypertension Center

**Category :** Physician

**Issue Areas/Comments**

**GENERAL**

**GENERAL**

I support the position as outlined by the American Society of Diagnostic and Interventional Nephrology (ASDIN).

**Submitter :**

**Date: 10/02/2006**

**Organization :**

**Category : Physician**

**Issue Areas/Comments**

**OPPS: Brachytherapy**

OPPS: Brachytherapy

Joe Jenerette, III, MD  
Professor and Chairman  
Dept of Radiation Oncology  
Medical University of South Carolina

CMS-1506-P-200-Attach-1.DOC

Attach 15  
200

# MUSC

## RADIATION ONCOLOGY SERVICES

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Joseph M. Jenrette, III, M.D.  
*Professor and Chairman*

September 25, 2006

Office of the Administrator  
Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
Mail Stop C4-26-05  
7500 Security Boulevard  
Baltimore, MD 21244-1850

Attention: CMS-1506-P; Medicare Program; Hospital Outpatient Prospective Payment System  
and CY 2007 Payment Rates;

Dear CMS Administrator:

As a board certified Radiation Oncologist on staff at the Medical University of South Carolina (MUSC), I am very concerned about the 2007 CMS HOPPS proposed rule # CMS-1506-P and the impact these new rates will have on breast conservation surgery and brachytherapy irradiation treatments. My concerns lie in the proposed re-assignment of CPT codes 19296 and 19297 to new APCs and the proposed new payment methodology for brachytherapy sources in 2007.

I appreciate the opportunity to provide comments and truly believe CMS should continue with CPT codes 19296 and 19297 being assigned to New Technology APCs 1524 and 1523 respectively. The CMS proposed reassignment of these codes from New Technology APCs to clinical APCs in 2007 would result in considerable decreases in 2007 payment. The table below illustrates the reductions, ranging from -22.8% to -37.0%.

HCCPS Code	2006 APC	2006 Payment	2007 Proposed APC	2007 Proposed Payment	Payment Change 2006-2007	Percent Change 2006-2007
19296 Breast interstitial radiation treatment, delayed	1524	\$3,250	30	\$2,508.17	(\$741.83)	-22.8%
19297 Breast interstitial radiation treatment, immediate	1523	\$2,750	29	\$1,732.69	(\$1,017.31)	-37.0%

If CMS passes the proposed APC assignments, the cost of the device will surpass the proposed payment rate. This will severely limit our ability to offer this breast cancer treatment option to Medicare eligible women.

CMS should maintain 19296 and 19297 in the New Tech APCs 1524 and 1523 respectively so that it may collect claims data through calendar year 2006 and reevaluate reassignment to a more appropriate APC for 2008. These CPT codes are device-dependent and the APC assigned, must cover the cost of the device. Of note: the cost of the brachytherapy device is the same when implanted at time of lumpectomy or during a separate procedure.

In relation to the proposed new payment methodology for brachytherapy sources, our hospital purchases the radiation source that is used in breast conservation treatment and bills C1717 for the HDR Iridium 192. I must inform you that it is very necessary for CMS to continue with the cost to charge ratio payment methodology in order to continue providing breast conservation treatment to your Medicare patients. Our hospital must be able to cover the costs of the radiation source; if not, we will not be able to continue to provide this less invasive, highly-effective cancer treatment to your Medicare beneficiaries.

I recommend that breast brachytherapy codes 19296 and 19297 remain in their current New Technology APCs (1524 and 1523 respectively) for 2007 to allow the opportunity to collect additional claims data. And further recommend that CMS continue current payment methodology for all brachytherapy sources at hospital charges adjusted to cost calendar years 2007 and 2008.

I respectfully request that CMS heed my recommendations. I would like to continue servicing your Medicare beneficiaries.

Regards,



Joseph M. Jenrette, III, MD  
Professor and Chairman  
Department of Radiation Oncology

cc: Senator Mike Enzi, Chair, Senate Health, Education, Labor and Pensions Committee  
Senator Dianne Feinstein, Co-Chair, Senate Cancer Committee  
Senator Sam Brownback, Co-Chair, Senate Cancer Committee  
Senator Thad Cochran, Chairman, Senate Appropriations Committee  
Representative Michael Bilirakis, Energy and Commerce Health Subcommittee  
Representative Ginny Brown-Waite, Co-Chair, Congressional Caucus for Women's Issues  
Representative Katherine Harris, Member House Cancer Caucus  
Representative Ileana Ros-Lehtinen, Vice Chair, Congressional Caucus for Women's Issues  
Carol M. Bazell, M.D., M.P.H., Director, Division of Outpatient Care  
Carolyn Muller, Deputy Director, Division of Practitioner Services

James Rubenstein, MD, Chairman, American College of Radiation Oncology

Prabhakar Tripuraneni, MD, Chair, American Society of Therapeutic Radiation Oncology

W. Robert Lee, MD, President, American Brachytherapy Society