



# The Fourth Heart Sound Revisited: Assessing Cardiographics Associated with Late Diastolic Propagating Events Using High Frame Rate Echocardiography

Andrew W. McCrary<sup>1\*</sup>, Cooper Moore<sup>2\*</sup>, Sydney D. Collins<sup>1</sup>, Gregory M. Sturgeon<sup>1</sup>, Melissa Lefevre<sup>3</sup>, Olaf T. von Ramm<sup>2</sup>, Piers C.A Barker<sup>1\*</sup>

## Abstract

**Background:** Stroke is the second leading cause of death and the leading cause of adult disability worldwide. A better understanding of stroke risk factors and outcome may help guide efforts at reducing the community burden of stroke.

**Objective:** To observe the relationship of hs C-Reactive Protein level in first ever ischemic stroke.

**Methodology:** This cross-sectional descriptive study was conducted in the Department of Medicine, Sir Salimullah Medical College and Mitford Hospital during the period of 6 months to find out the relationship of hs C-Reactive Protein level in first ever ischemic stroke. For this purpose 100 patients with acute ischemic stroke were selected. All acute stroke patient were included as per inclusion and exclusion criteria. Then marker of stroke High Sensitivity CRP were done. Data were collected by using a preformed data sheet and statistical analysis was done in detailed and by using SPSS 20.

**Results:** This study shows the average age was 62.12 years. Male predominance than female. CI was the most common subtype stroke (38%). The most common risk factor were hypertension (72%), then smoking (44%), hyperlipidemia (28%) and atrial fibrillation (26%). Majority (63%) were hs CRP level >3 mg/L. It was observed that hyperlipidemia and ischemic heart disease were associated with higher CRP level.

**Conclusion:** In conclusion this study demonstrated that high CRP level is associated with stroke severity at admission and is an independent predictor of early seven-day mortality after ischemic stroke.

**Keywords:** High frame rate echocardiography; Phonocardiogram; Electrocardiogram; Fourth heart sound

## Introduction

Understanding and assessing ventricular mechanics and diastology in patients using echocardiography remains a significant clinical and research challenge. Existing echocardiographic diastolic measurements are used as a composite, with no single assessment yet able to offer comprehensive, reliable insight.<sup>1</sup> In addition, echocardiographic measures established for adults may not be directly transferrable to the pediatric population due to differences in heart rate, cardiac size, and maturational differences in myocardial cellular structure. From a physical exam standpoint, an audible fourth heart sound (S4 or “atrial gallop”) is associated with a pathologic decrease in ventricular compliance, often indicating the development of diastolic dysfunction.<sup>2</sup> While

## Affiliation:

<sup>1</sup>Department of Pediatrics, Duke University, Durham, NC

<sup>2</sup>Department of Biomedical Engineering, Duke University, Durham, NC

<sup>3</sup>Department of Cardiology, Duke University, Durham, NC

## \*Corresponding author:

Andrew W. McCrary, MD, Division of Pediatric Cardiology, DUMC Box 3090, Durham, NC 27710 USA.

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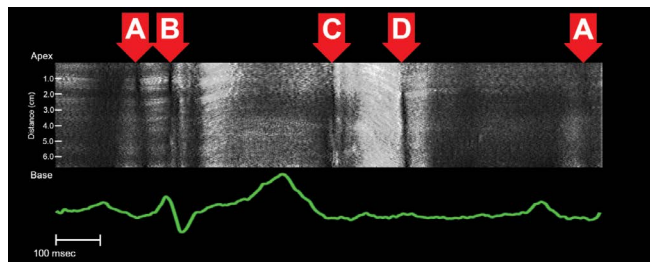
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S4 heart sounds are easily recorded by phonocardiography even in normal people, they are notoriously difficult to auscultate in pathologic states with poor observer accuracy.<sup>3,4</sup> Differences between a phonocardiographic tracing of the S4 in normal people and an audible S4 in states of left ventricular pathology are not known.

A new high-frame-rate echocardiographic display technique, the Regional Motion Display (RMD), is based on difference imaging and has allowed for the unique visualization of several propagating myocardial events (PEs) in the left ventricle (LV) lateral wall throughout the cardiac cycle, including diastole.<sup>5</sup> Four discrete events associate with transient PEs, corresponding to Late Diastole, Early Systole, Late Systole, and Mid Diastole (Figure 1 arrows labeled A, B, C, and D respectively). Of particular interest is the propagation velocity of the Late Diastolic PE (LDPE) which may be an indicator of diastolic myocardial compliance and yield more prognostic data than an audible S4. This study therefore aimed to define the characteristics of a discrete and easily seen LV lateral wall late diastolic propagating event (LDPE) in healthy children and young adults and compare the timing of this event with standard clinical measurements in late diastole.



**Figure 1:** Example RMD from the Lateral Wall of the left ventricle in a 20 year old volunteer. The top of the RMD corresponds to the apical region of the wall, and the bottom of the RMD the basal region. This RMD was generated from images acquired at 1000 per second. The four PEs are indicated by the red arrows. The LDPE is labeled A, early systolic labeled B, late systolic labeled C, and mid diastolic labeled D.

## Material and Methods

### Patient Population

All participants were enrolled with informed consent under Duke Institutional Review Board Protocol 00026106. Nine healthy male participants aged 6-22 years old were recruited with a median age of 20 years. Subjects had no previous record of cardiovascular disease and had no cardiac abnormalities by standard echocardiogram or electrocardiogram. All study data for each patient were acquired within a one-hour period.

### Study Procedures and Measurements

High frame rate B Mode images were acquired using the Duke University Phased Array Ultrasound Scanner, T5.6 Apical 4-chamber views (AP4) were obtained with temporal

resolution of 587 to 1174 frames per second using a 3.5 MHz, 96 element linear array with active aperture of 21 mm by 14 mm (Volumetrics LLC, Durham, NC). High Speed B Mode images are shown simultaneously with the difference images during live scanning. An RMD was generated from these HFR images to record and measure rapidly propagating events in the myocardium.

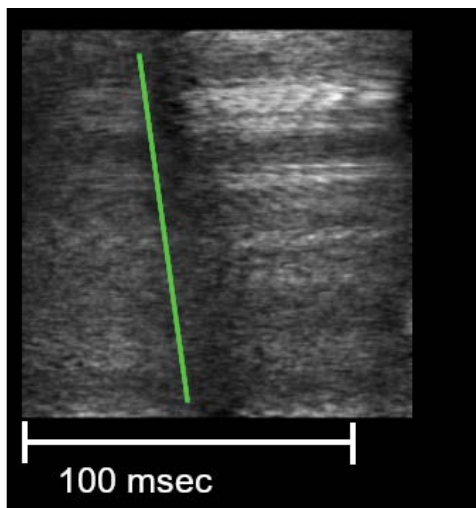
Additionally, standard clinical B Mode images, Pulsed Wave Tissue Doppler Imaging (PW-TDI), and phonocardiographic tracings were acquired using a GE Vivid E95 system/6S transducer (Boston, MA) with a synchronous electrocardiogram. Phonocardiographic data were acquired using a HP Model 21050A transducer. All events were timed with respect to the onset of the QRS complex in the synchronous electrocardiogram. The onset of the S4 was measured from the phonocardiogram as the first positive deflection after the P-wave in the synchronous electrocardiogram. For this study, timing of the peak of the a' wave and the onset of the s' wave in the PW-TDI spectrum were measured at the lateral mitral valve annulus. The synchronized RMD, PW-TDI, phonocardiographic and electrocardiographic tracings are shown in Figure 1 for a 20 year old male subject. As the data were acquired over the course of one hour, the images were scaled to normalize the R-R interval for the beat indicated by the vertical bars on the electrocardiogram. To confirm the validity of timing comparisons from all three modalities, the R-R interval was measured in each electrocardiogram. The R-R interval varied by  $\pm 40$  msec at most for each patient across all three modalities. No scaling or adjustment was applied to any temporal measurements.

### Regional Motion Display (RMD)

RMD is a new method for visualizing vibrational events in myocardial walls that are based on high speed images acquired at rates of 250 per second and above. The technique has been previously described in detail by our group.<sup>5</sup> RMD is sensitive to motion and vibrations in two and three dimensions and is angle independent. The RMD generation proceeds with outlining a cardiac wall as the Region of Interest (ROI), generally from the apex to base at end-diastole of one or more stored cardiac cycle image sequences. Image pixels in sequential high speed frames within the ROI are then subtracted and the resultant brightness values stored. This subtraction emphasizes temporal changes at each pixel of the ROI. These subtracted values are then integrated across the width of the ROI, i.e. the wall thickness, at each unique position along the length (Apex to Base) of the ROI. The resultant set of averaged values along the ROI constitutes one RMD sample. This process continues for all pairs of sequential difference images throughout the stored cardiac cycle. The final display, the RMD, is thus a record of brightness value changes within the ROI from Apex to Base sampled at the frame rate displayed sequentially sample by sample in time correspondence with the original images

throughout one or more cardiac cycles. To state more simply: the RMD displays changes in brightness which are related to positional and velocity changes of each point along the selected cardiac wall (ROI) at each instance of the cardiac cycle. The RMD shows unique propagating events which are easily seen as discrete lines during the cardiac cycle.

Propagating events were seen in the RMD of all participants as sloped dark bands amid bright targets. The most prominent, the Last Diastolic Propagating Event (LDPE), is indicated by the arrow labeled A in Figure 1. For this study, the onset time of the LDPE was measured with respect to the onset of the QRS complex by recording the time of the transition from bright to dark at the apical side of the RMD. Velocity of the LDPE was measured by fitting a line to the leading edge of the PE, as indicated in Figure 2. The leading edge of the LDPE is defined as the transition from bright to dark in the RMD.



**Figure 2:** Enlarged RMD for the measurement of the LDPE velocity. The LDPE is characterized by a bright region with a dark band that propagates through the center. The leading edge, i.e. the transition from bright to dark, is detected, and the slope of the resultant line yields the velocity of the PE.

## Results

Participant ages ranged from 6 to 22 years. A LDPE was seen in all subjects in the study. The measurements from all subjects are shown in Table 1. The average onset of the LDPE was  $26.9 \pm 16.9$  msec prior to the onset of the QRS complex. In all subjects, the LDPE traveled from apex to base with an average velocity of  $3.0 \pm 1.9$  m/sec. There is a trend for increasing LDPE velocity with younger age ( $R^2 = 0.569$ ,  $p = 0.02$ ).

## Discussion

In this pilot study of normal children and young adults, we assessed the cardiographics associated with an easily visualized LDPE by high frame rate echocardiography. Given that the timing of the LDPE in this cohort was contemporaneous with

the phonocardiogram S4, we hypothesize that this advanced imaging technique in fact visualizes the S4 heart sound propagating in the LV lateral wall. The variation in the wave velocity and its positive correlation with age is intriguing, and further study is needed to determine this parameter's role in assessing diastology. Reliably visualizing the S4 opens a range of research directions from basic physiology to understanding the characteristics of a pathologic, audible S4 heart sound – thus a non-invasive measurement of diastolic function.

RMD, Tissue Doppler Imaging, and Phonocardiography each measure independent signals and events in the heart, with the cascade of late diastolic events being the focus of this study. As the RMD is a 2D imaging based approach, it provides information in 2 spatial dimensions and time. In distinction, Tissue Doppler imaging derives its signal from the small one-dimensional positional changes in sequentially received echoes and provides an estimate of local tissue velocity at a single location in the heart in the direction of the transmitted ultrasound pulse. In the phonocardiograph, the signal is the longitudinal mechanical wave that is generated by blood motion in the heart. This signal is transmitted through the chest wall and measured by a microphone on the body surface. Phonocardiography is most sensitive to sounds that are generated in the direction of the microphone, e.g. apical placement of the microphone will be the most sensitive to the sound generated by blood entering the left ventricle.

Since S4 is thought to be linked to variations in ventricular stiffness on auscultation, characterizing and quantifying this event may be an opportunity to more precisely assess ventricular diastolic function. The consistency of this event across the study participants suggests that the data reported in this study may be characteristic of “normal” healthy children and young adults. This study was limited by a small sample size of volunteers, and only investigated healthy subjects. Additional testing in both normal and pathologic cases is needed to establish true definitions of “normal” and “abnormal” for this phenomenon. The variation in the wave velocity and its positive correlation with age is intriguing and may represent maturational differences in myocardial compliance; further study is needed to determine this parameter's role in assessing diastology. RMD also holds the potential to move beyond the LV lateral wall to other segments of the heart and even provides an opportunity to explore mechanical coupling of the right and left ventricular myocardium.

## Conclusions

This study extends the applicability of the RMD method to pediatric subjects and young adults. The RMD of the LDPE discrete line indicator was observed in all subjects propagating from apex to base at measureable velocities. The RMD characterizes a late diastolic wave propagating in the LV lateral wall myocardium, well correlated to S4 by this

| Age<br>(years) | Heart<br>Rate<br>(bpm) | Frame rate<br>(frames/sec) | ECG                           | Lateral annulus<br>PW-TDI |                           | PCG                       | RMD                         |                             |
|----------------|------------------------|----------------------------|-------------------------------|---------------------------|---------------------------|---------------------------|-----------------------------|-----------------------------|
|                |                        |                            | onset of<br>P wave<br>(msec)* | onset of<br>a'<br>(msec)* | onset of<br>s'<br>(msec)* | onset of<br>S4<br>(msec)* | onset of<br>LDPE<br>(msec)* | LDPE<br>Velocity<br>(m/sec) |
| 6              | 72                     | 867                        | -150                          | -80                       | 80                        | -50                       | -41                         | 1.03                        |
| 9              | 83                     | 867                        | -160                          | -80                       | 60                        | -50                       | -44                         | 1.15                        |
| 13             | 66                     | 709                        | -120                          | -70                       | 70                        | -30                       | -17                         | 0.68                        |
| 22             | 80                     | 587                        | -140                          | -80                       | 80                        | -40                       | -40                         | 3.55                        |
| 21             | 65                     | 587                        | -180                          | -130                      | 70                        | -50                       | -51                         | 3.65                        |
| 21             | 66                     | 1174                       | -170                          | -90                       | 80                        | -20                       | -12                         | 3.16                        |
| 20             | 58                     | 587                        | -160                          | -60                       | 80                        | -20                       | -16                         | 3.87                        |
| 19             | 50                     | 587                        | -160                          | -80                       | 70                        | -20                       | -16                         | 2.71                        |
| 21             | 77                     | 587                        | -140                          | -70                       | 70                        | -20                       | -5                          | 6.89                        |

\*Measurement from the QRS onset.

bpm - beats per minute; ECG - electrocardiogram; PW-TDI - pulse wave Tissue Doppler Imaging; PCG - phonocardiogram; RMD - Regional Motion Display

**Table 1:** Individual Participant Demographics and Measurements.

study. Further definition of normal and abnormal variations of this S4 wave and other RMD lines may lead to a new approach to the assessment of myocardial wall mechanics and provide novel insights into diastology.

### Conflicts of Interest

O.T.v.R. is the Chief Technology Officer of Volumetrics Medical Systems. The remaining authors declare no competing interests.

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### Informed Consent / Ethics Statement:

Informed consent was obtained from all participants involved in the study and approved by the Duke University Institutional Review Board (Protocol 00026106).

### Data Availability Statement

All relevant data is contained within the article.

### References

1. Nguyen MB, Dragulescu A, Chaturvedi R, et al. Understanding complex interactions in pediatric diastolic function assessment. *Journal of the American Society of Echocardiography* 35 (2022): 868-877.
2. Tavel ME, Clinical Phonocardiography and External Pulse Recording. Fourth Edition, 1985. Year Book Medical Publishers, Inc. Chicago.
3. Rectra EH, Khan AH, Pigott VM, Spodick DH. Audibility of the fourth heart sound: a prospective, blind auscultatory and polygraphic investigation. *JAMA* 221 (1972): 36-41.
4. Tavel ME. The fourth heart sound-a premature requiem? *Circulation* 49 (1974): 4-6.
5. Moore C, McCrary AW, LeFevre M. Ultrasound Visualization and Recording of Transient Myocardial Vibrations. *Ultrasound in Medicine & Biology* 49 (2023): 1431-1440.
6. Moore C, Castellucci J, Andersen MV, Lefevre M, Arges K, et al. Live high-frame-rate echocardiography. *IEEE transactions on ultrasonics, ferroelectrics, and frequency control*. 62 (2015): 1779-1787.



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