Feasibility of Echocardiographic Particle Image Velocimetry for evaluation of cardiac left ventricular filling function

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ABSTRACT

Heart disease is one of the primary causes of morbidity and mortality for the adult population over the age of 65. Furthermore, ailments such as hypertension can affect as many as 50% of the adult population over the age of 45. If left untreated, these ailments eventually precipitate the onset of diastolic dysfunction and heart failure. Diastolic dysfunction is the alteration or impairment of performance in either the left or right ventricle of the heart. Although there has been a marked increase in study of this disease, there is still an apparent difficulty to diagnose patients. Flow visualization techniques have been commonly employed to study the development of these diseases as they relate to the filling process of the ventricles. One method, Echo Particle Image Velocimetry (Echo-PIV) is a relatively new method for cardiac flow chamber visualization, with the potential to provide physicians with a cost-effective and safe method for obtaining high temporal resolution recordings for extending knowledge on the filling processes in cardiac chamber flow.

This work presents a new approach to extending the capabilities of Echo-PIV for more accurate measurement of cardiac flows for patients with poor quality recordings. Currently, much of the literature notes that temporal resolution and poor acoustic windows results in exclusion from study. These recordings are more representative of the contrast-enhancement studies used by physicians to better identify chamber walls. When applying standard PIV cross-correlation techniques, measurements tend to fail due to image noise and artifacts. By implementing a Moving Ensemble (MWE) with Product of Correlation (PoC) processing scheme, measurement accuracy, reliability, and robustness can be obtained for measurement in left ventricular filling assessment.

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1 Introduction

1.1 Motivation

Cardiovascular disease (CVD) and heart failure (HF) are the predominant health concerns facing older patients [1, 2]. When assessing performance of the left ventricle (LV) these diseases present severe symptoms recognizable via altered pacing tissue morphology [3, 4]. Physicians often rely on ultrasound imaging such as Pulse Wave (PW) Doppler and B-mode imaging to quantify basic blood flow alterations, changes in LV morphology, and tissue elasticity [5-7].

When symptoms alter LV physiology, the flow patterns through the chamber are also changed, due to the LV working as the "primary pump" moving blood through the body. Using flow visualization techniques such as color Doppler and MR imaging can investigate the underlying physical mechanisms in order to improve understanding of the impact flow changes have on cardiac function and vice versa [8-10]. Full chamber flow assessment remains impractical with these methods due to computational demand, cost of procedure, and low frame rates [11-13]. Development of Echo Particle Image Velocimetry (Echo-PIV), an emerging cardiac flow visualization technique, addresses these deficiencies, providing a new but relatively under-utilized visualization tool. .

Echo-PIV employs PIV image processing algorithms on contrast-enhancement B-mode ultrasound images to estimate blood velocity through the cardiovascular system. Use in LV chamber flow allows for visualization and quantification of the hydrodynamic flow properties through each of the cardiac cycle phases. This method can provide insight for improved understanding of the LV chamber filling and ejection mechanisms, with the potential for better diagnosis and treatment in cardiac disease.

This paper looks in to the developments in cardiac flow visualization as it relates to the improved ability determine LV filling properties. A description of the cardiac cycle mechanisms in LV function is described to provide an outline of the potential properties that can be observed and quantified. Other cardiac flow visualization tools are briefly described to indicate the current developments used in LV flow assessment. Echo-PIV from development to use in LV flow

establishes the difference and benefits that this method can provide over other approaches. Limitations still present in Echo-PIV are analyzed for potential points for further contribution.

1.2   Description of Left Ventricle Flow

The cardiac cycle consists of several different phases, generalized primarily to diastole, isovolumic contraction (IC), systole and isovolumic relaxation (IVR). In the left ventricle (LV) each of these phases are characterized by either a volume-change or pressure-change, as shown in Figure 1.1. Isovolumic phases (Figure 1.1, a & c) are states where volume of the LV remains constant, but chamber pressure changes due to tissue (myocyte) deformation.   Diastole is characterized by rapid volume expansion of the LV (Figure 1.1,b) as blood fills the chamber, with a slight pressure rise as the chamber reaches full expansion.   During systole rapid volume contraction of the LV (Figure 1.1,d) results in a pressure rise that works to eject blood in to the circulatory system.
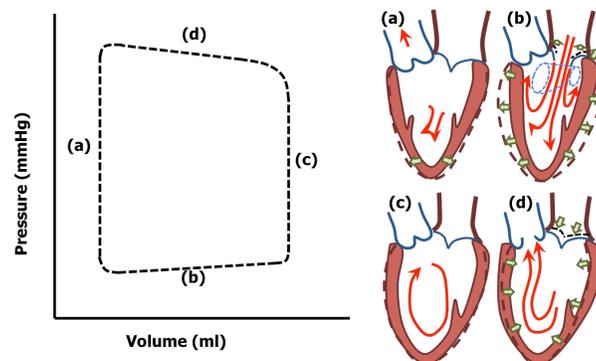
Figure 1.1: Description of the LV Flow Loop. The LV chamber undergoes phase changes that can be described interms of pressure and volume changes (Left). During isovolume phases (a & c) there is no flow from the volume, but pressures change due to tissue deformation. Diastole (b) is a state of volume expansion as blood rapidly fills the chamber. Systole (d) is a state of volume contraction as blood enters the circulatory system.

From the onset of cardiac impairment, the compliance, relaxation, and contraction of the LV chamber becomes altered. These alterations affect the volume-changing cardiac phases, related to either blood volume filling or ejection. Establishing a basic understating of the mechanics of blood flow for healthy persons during each of the cardiac phases will present the necessity of cardiac flow visualization for understanding the disease process.

Initiation of diastolic filling is prompted by the pressure difference existing between the left atrium (LA) and the LV chambers, following the LV pressure change after IVR. This pressure

difference opens the mitral valve (MV), and suction causes the blood to move from the LA to the LV [14]. As blood enters the LV a fluid jet forms from the MV to the apex [15, 16]. Blood along the exterior of the entering jet is subject to viscous shear, causing the formation of a vortex ring at the MV leaflet tips in the LV chamber. The vortex ring assists in pushing blood further into the ventricle, ensuring the fluid jet remains moving toward the chamber apex. The vortex ring eventually pinches off and the anterior portion of the vortex travels into the ventricle, creating an apical vortex formation thought to preserve kinetic energy to assist in proper redirection of blood during systole.

Once the LV has reached 90% of its total volume expansion and the pressure gradient has come to equilibrium, there is a momentary closure of the MV. A secondary, short period of filling is motivated by contraction of the LA in order to increase the pressure in the LV, for proper MV closure. After these two states are complete, the blood-filled LV begins IC, rapidly increasing pressure for systolic onset.

Systolic ejection of blood flow from the LV is characterized by flow traveling from the apex through LV outflow track (LVOT) and aortic value and into the aorta. The apical vortex formation during diastole eventually attenuates, and the flow continues along the LVOT as LV contraction occurs. Gradually a pressure difference forms between the aorta and LV, causing the aortic valve to close and ending systole.

Cardiac imaging modalities can be effective in observing the flow of blood, development of rotating flow structures, and change in volume that occur during these flow states. Through post-processing algorithms, quantification of measurements related to the vortex flow structures and relative pressures can be determined with patient specificity for use in diagnosis and developing further understanding of disease states.

1.3   Cardiac Flow Visualization: Emerging Methods

Flow visualization of the LV using Echocardiography and MR imaging techniques was first explored starting in the 1980s [12]; however, non-invasive quantitative evaluation was not introduced until the past decade. Today, methods of Color M-mode (CMM), 2D Color Doppler, and MR imaging are commonly used in research and clinical application for disease prognosis and treatment. Other, less commonly used methods such as X-ray tomography (CT) have also

been evaluated, but acquisition costs and potential harm to patients have limited any research to basic analysis. [17]

1.3.1 Color M-mode Doppler Echocardiography

Color M-mode (CMM) Doppler ultrasound is the most common modality for viewing cardiac chamber flow. As blood flows across the MV toward the Apex CMM scans measure the phase shift in reflected blood signals, recorded as axial velocities. Since the scan is not memory-intensive, high spatial and temporal resolutions can be obtained. Early studies utilizing CMM scans defined the metric of propagation velocity of the LV diastolic filling wave, providing a means of statistically separating healthy patients from diseased patients [8, 18, 19]. New metrics provide more robust and clinically significant disease separation by utilizing flow events such as identifying the Apex deceleration point. [20]
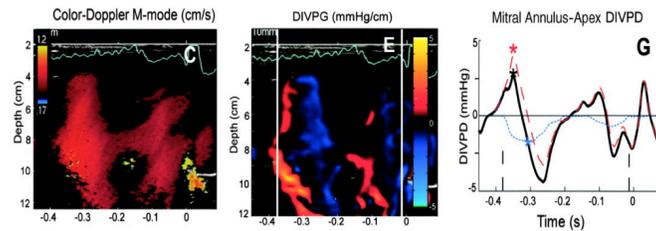
Figure 1.2: CMM scan contours (Left) provide a spatiotemporal map of blood velocity during diastolic filling of the ventricle. These velocities can be used to calculate the pressure gradient field (Middle) that motivates diastolic filling. This field can be integrated further to determine the relative pressure and obtain the pressure gradient (IVPG) that motivates proper filling of the ventricle. [9][1]

The most essential use for CMM scans is the non-invasive determination of relative pressures in the chamber during filling and ejection. This capability makes use of high temporal and spatial resolutions in providing physiologically accurate intraventricular pressure measurements (Figure 1.2) that allow for investigation of the gradients that motivate early LV filling [21, 22]. Yotti et al successfully implemented this calculation in two different disease evaluation studies [9, 23]. Their research, among others, has indicated that CMM-derived IVPG and relative pressures

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[1] Reproduced from R. Yotti et al. A Non-invasive Method for Assessing Impaired Diastolic Suction in Patients with Dilated Cardiomyopathy. Circulation (2005); 112(19): 2921-2929. Used with permission of Wolters Kluwer Health, 2014.

obtained in non-invasive measurements matched pressure-catheter readings at a nearly perfect 1-to-1 ratio with no bias error. [22, 23]

Although easy to obtain and process, CMM scans only provide a limited amount of information on flow behavior. Structure formations, such as the MV vortex ring and apical vortex, and their transport properties are not observable with this method.

1.3.2   2D Doppler Echocardiography

Ultrasound Doppler offers a 2D velocity measurement modality, allowing physicians to observe the full LV axial velocity field. Echodynamography or Vector Flow Mapping (VFM) provide a two approaches for processing scan axial velocities to obtain radial velocities for improved visualization and the ability to quantify vortex properties. The first uses contour level properties and separation of the axial velocity flow field into rotational and irrotational flow to estimate radial velocity. [24] The other approach utilizes speckle tracking echocardiograph (STE) wall displacement and the fluid conservation equations to estimate radial velocity, as shown in Figure 1.3 [25]. Both methods have been able to closely match *in vitro* model and simulation flow estimates (Figure 1.3, Right). [24-28]
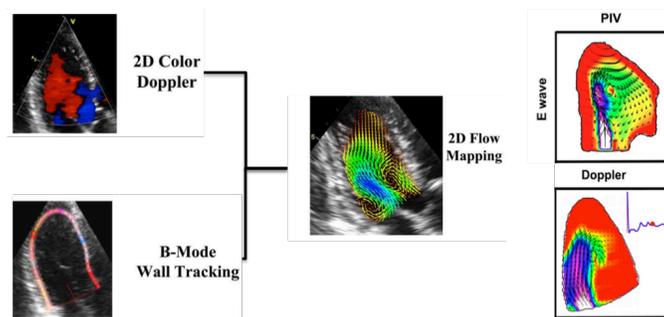
Figure 1.3: Example of VFM through the approach by D. Garcia (2010). Axial velocity components of the flow are provide by the Color Doppler scan. Radial velocities are determined by using the continuity equation with tissue motion from STE used as boundary conditions. VFM is shown to produce comparable measurements to other methods. [25][2]

Unlike CMM, 2D Doppler temporal resolution is limited, reduced to approximately 20 frames per second. This limitation makes assessment of short-lived phases (i.e. IC and IVR) difficult,

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[2] D. Garcia et al, Two-Dimensional Intraventricular Flow mapping by Digital Processing Conventional Color-Doppler Echocardiography Images, IEEE Transactions on Medical Imaging, October 2010. Used with permission of IEEE, 2014.

and calculation of properties such as relative pressure impractical. Velocity fields are also very noisy, requiring substantial smoothing to resolve an appropriate flow field representation, reducing peak velocity measurements and make obtaining physically accurate vortex properties improbable.

1.3.3 Magnetic Resonance Imaging (MRI)

Phase contrast (pc) MR imaging (pc-MRI), was first used in the late 1980s, to visualize flow in phantom models [29]. In 1995, pc-MRI was implemented for LV visualization using clinical scan data. [30] Quantitative evaluation for LV flow properties during diastole and systole were not performed until 2002, when Ebbers et al used the method to calculate relative pressure fields of a healthy patient for a cine loop 4D scan. [10] The resolved pressure matched clinical behaviors, but severely underestimated peak pressure values, due largely to significantly low frame rates, as shown in Figure 1.4. Since this initial work in pc-MRI a number of new studies have been published which more accurately estimate peak relative pressures and IVPG, and employ this method for determination of LV chamber fluid transport properties. [15, 31] MRI offers some of the highest spatial resolution of existing clinical scans, but cost of operation, need for computationally demanding reconstruction, and low frame rates make this method impractical for large clinical cohort studies.
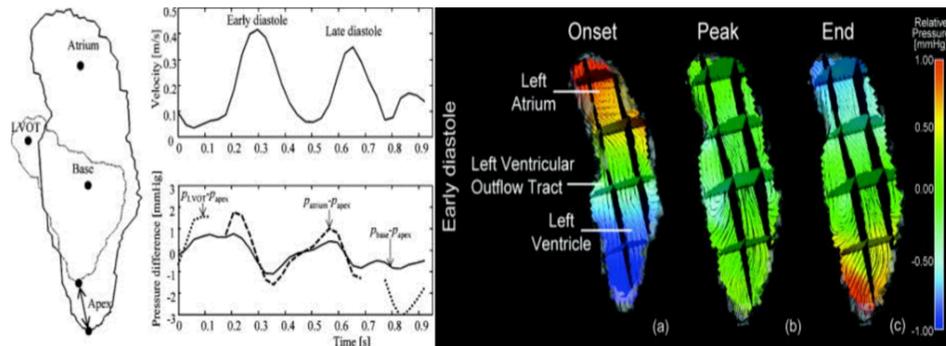
Figure 1.4: Mapping of relative pressure from pc-MRI velocity fields. Relative pressure fields during diastolic filling (Right) depict the expected behavior that occurs when blood flow enters the expanding LV volume. The IVPG agrees well with CMM results. [10]³

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³ T. Ebbers et al. Noninvasive Measurement of Time-varying Three-dimensional Relative Pressure Fields within the Human Heart. Journal of Biomechanical Engineering (2002); 124(1): 288-293. Used with permission of ASME, 2014.

1.4 Echo Particle Image Velocimetry

1.4.1 Development of Echo-PIV

Digital Particle Image Velocimetry (DPIV) is a well-established and developed tool for application in experimental fluid dynamics [32]. Laboratory DPIV experiments employ micron-sized flow tracing particles that are illuminated by a pulsed laser sheet and imaged with digital cameras. Image series are evaluated for particle image pattern correlation to estimate frame-to-frame displacement [33].

Echo Particle Image Velocimetry (Echo-PIV) is an emerging field of cardiac flow visualization, which uses ultrasound imaging and particle image velocimetry (PIV) principles to measure blood flow displacements. Echo-PIV utilizes B-mode imaging for recording patient data. This imaging modality is analogous to the illuminating pulsed laser sheet and high-speed cameras used in laboratory PIV experiments. Ultrasound contrast agents, the flow tracing particles in this application, are protein or lipid-encapsulated, acoustically opaque, bio-inert gas bubbles [34]. After recording is complete the image frame series must be processed on another machine using PIV correlation algorithms to obtain velocity measurements.

Echo-PIV offers a flow visualization method that overcomes many of the deficiencies of other approaches. B-mode recordings provide spatial resolutions that match 2D Doppler and MR imaging with frame rates comparable to CMM recordings [13]. By using PIV algorithms, Echo-PIV provides both components of the velocity field, eliminating the need for high smoothing and in-field assumptions that limit 2D Doppler. Echo-PIV has the potential to provide physiologically accurate velocity measurements with suitable temporal and spatial resolution, enabling observation of short-lived cardiac stages such as IC and smaller *in vivo* flow structures such as the MV vortex ring. Extensive laboratory modeling and numerical simulation studies have validated the feasibility and reliability of Echo-PIV while suggesting optimal guidelines for imaging and seeding [35-38].

1.4.2 Echo-PIV in LV Chamber Assessment

Implementation of Echo-PIV for LV chamber flow visualization has developed gradually, with publication of less than a dozen research papers focused on clinical application in the past 5 years. Sengupta et al presented the first investigation that utilized Echo-PIV for LV chamber flow visualization in 2007, assessing the flow nature that occurs during isovolumic phases of

adolescent pigs using very high frame rates (~200 Hz). [39] Results validated their hypothesis that isovolumic phases, considered hemostatic, were actually states that allow for proper flow redirection.

Following Sengupta's influential work clinical studies of LV flow utilizing Echo-PIV have developed analytical methods for determining chamber hydrodynamics in both healthy control groups and groups with a variety of cardiac diseases. A majority of current Echo-PIV publications analyze the dynamics and geometries of the apical vortex, detailing common findings for geometric properties across their healthy patient control groups. These measurements have been critical to the understanding of healthy LV properties. All studies indicate that patient vortex regions occupy over 50% of the LV length, are positioned deeper in the ventricle and are more elliptical (SI greater than 2). [16, 40, 41] All disease states show significantly lower values for each of these measurements.

Quantification of vortex strength (VS), a measurement of hydrodynamic circulation, can signify indicate the regions where vortices form and has been investigated for its use as a marker of LV mechanical performance [15, 42]. To date, one clinical study using Echo-PIV has investigated VS to assess LV performance after LV impairment. Expanding Sengupta's work, Abe et al indicates a statistically significant change in VS values between early diastole and IC for healthy individuals [42]. Diseased patients with systolic impairment do not exhibit a value change in VS between the two stages.

Abe's research did implement a simplified approach for vortex identification, corrupting the accuracy of the total vortex area quantified. This strategy may also lead to inaccurate VS values, since the vorticity of the entire image is used to obtain measurements. Additionally, the control patient group included LVDD-diagnosed patients possibly change the statistics. By having intermixed LVDD grades in the control, HFREF and HFPEF, there may be shared properties that corrupt statistics, making it difficult to use VS as a possible metric for diagnosis.

In cases where physiologically accurate velocities were not obtained, Hong et al developed a set of quantitative vortex property measurements. These measurements look at ratio of pulsatile vortex strength to average vortex strength over the entire cycle. The first parameter, relative strength, is a ratio of field vorticity strengths. The second, vortex relative strength, is a ratio for vortex-only vorticity strengths. The original work implementing these quantifiers indicated

(Figure 1.5) that healthy patients express a higher VRS measurement than disease-impaired patients. [16] The development of these measurements were motivated by the speculation Hong et al provided, which inferred that high velocity regimes are short lived, allowing flow to be characterized by accurate rotation measurements only. However, with limited computational and experimental results to validate this processing strategy, Echo-PIV using low frame rates may be resolving non-physical vortex regions. More work must be conducted to validate that this processing approach does in fact resolve what is physically occurring in LV flows.
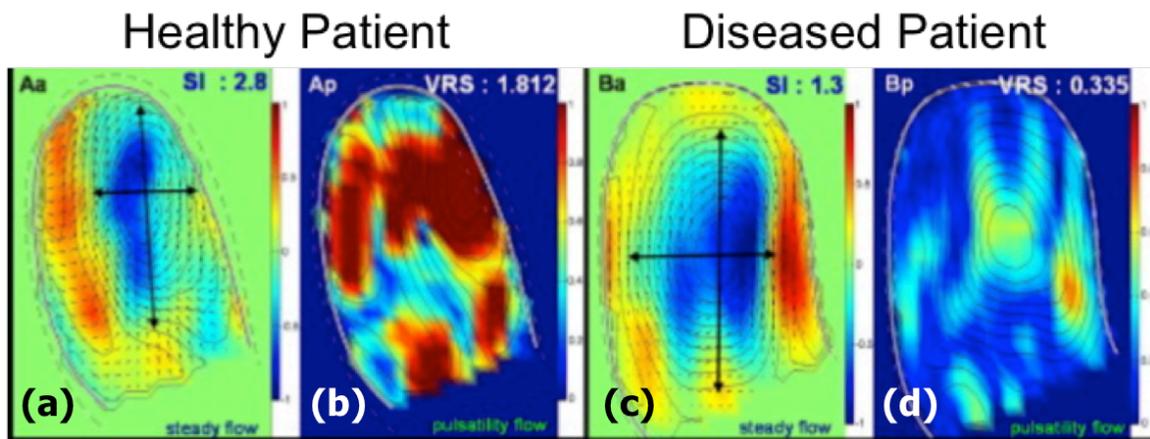
Figure 1.5: Example of findings for vortex geometry properties and Vortex Relative Strength (VRS). Vortex geometry assessment allows physicians to understand if alterations to the LV are directly reflected in flow property changes. Measurements from VRS allow physicians to examine if vortex strength is attenuated due to dissipation. Higher VRS measurements indicate higher rotation and strength. [16][4]

Ensuing research by Faludi, Lampropuolos and even Hong himself have provided starkly different VRS measurements between studies, suggesting that either processing settings or selected thresh-holding make this quantifier difficult to justify. [16, 40, 43] In the study by Faludi et al, higher VRS properties were seen in the disease-specific mitral valve replacement subjects versus the control group. The publications of Hong and Lampropuolos show an opposite effect, with diseased patients expressing a lower VRS than the healthy control patients. No hypothesis was offered for this deviation, although speculation suggests mitral valve

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[4] G. Hong et al. Characterization and quantification of vortex flow in the human left ventricle by contrast echocardiography using vector particle image velocimetry. Journal of the American College of Echocardiography – Cardiovascular Imaging (2008); 1(6): 705-717. Used with permission of Elsevier, 2014.

replacements may produce more vortex regions *in vivo*. These findings imply that a modified measurement created to "side-step" inaccurate velocity findings may be questionable for creating a statistically significant and reliable disease-separable metric.

Two studies have explored kinetic energy and dissipation as they relate to LV mechanical performance. Cimino investigated a healthy patient cohort for baseline properties, while Prinz studied the effects of diastolic impairment. Both studies hypothesized formation of the apical vortex minimizes energy loss for optimal performance in healthy patients, while Prinz further suggested that dissipation increases with disease progression, beginning with early diastolic flow alteration. [43, 44]

Cimino et al, in their examination of healthy patient LV baseline properties, additionally assessed relative pressure in conjunction with vortex dynamics. In their study, a solver based on the Pressure Poisson Equation was used, similar to the solver implemented by Ebbers et al for 4D pc-MRI LV pressure assessment. [10] Results were presented (Figure 1.6) which show qualitatively that healthy patients express the same behavior, regardless of ventricle geometry. [44] Relative pressure fields also show the expected pressure rises during diastole as a result of blood deceleration and volume filling, as seen in both pc-MRI and CMM studies.
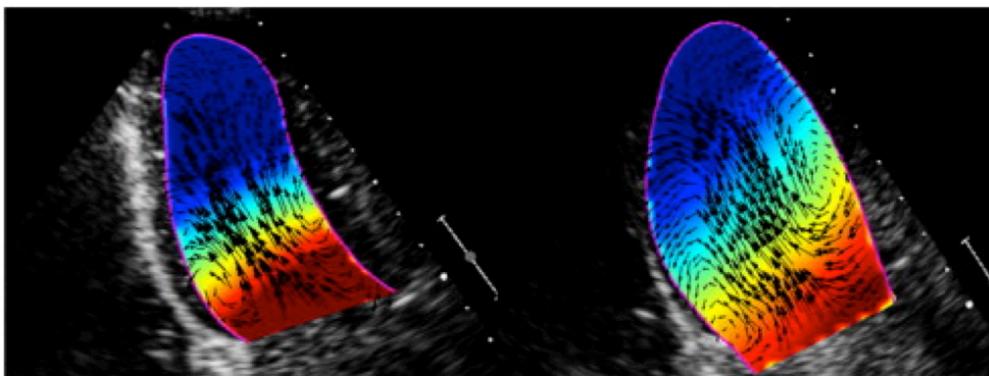
Figure 1.6: Example of relative pressure derived from healthy patients taken from the baseline study performed by Cimino et al. Relative pressure fields during early filling show that lower cavity pressures near the Apex draw blood from the LA to the LV, resulting in volume expansion. Patient properties, such as LV geometry, will not affect the flow nature as long as individuals are not diseased. [44][5]

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[5] S. Cimino et al. In vivo analysis of intraventricular fluid dynamics in healthy hearts. European Journal of Mechanics – B/Fluids (2012); 35(1): 40-46. Used with permission of Elsevier Masson SAS, 2014.

1.5   Limitations in Echo-PIV application

Even as Echo-PIV emerges as a viable tool for LV chamber flow visualization, limitations exist which impact the validity of results. The primary limitation on the effective use of Echo-PIV rises from technology capabilities. Temporal resolution for PIV processing must be optimized to allow for robust cross-correlation to resolve accurate flow measurements. In a review of cardiac flow visualization techniques Sengupta suggested that frame rate frequencies should be higher than 60 Hz, noting that if short-lived isovolumic phases are desired frame rates need to be higher than 150 Hz. [12] In Kheradvar's *in vitro* model, scans were taken at 35 Hz and after processing it was noted that peak velocities were not resolvable, and under low frame rate and spatial resolution conditions smaller flow features may not properly resolve as seen in Figure 1.7. [35]
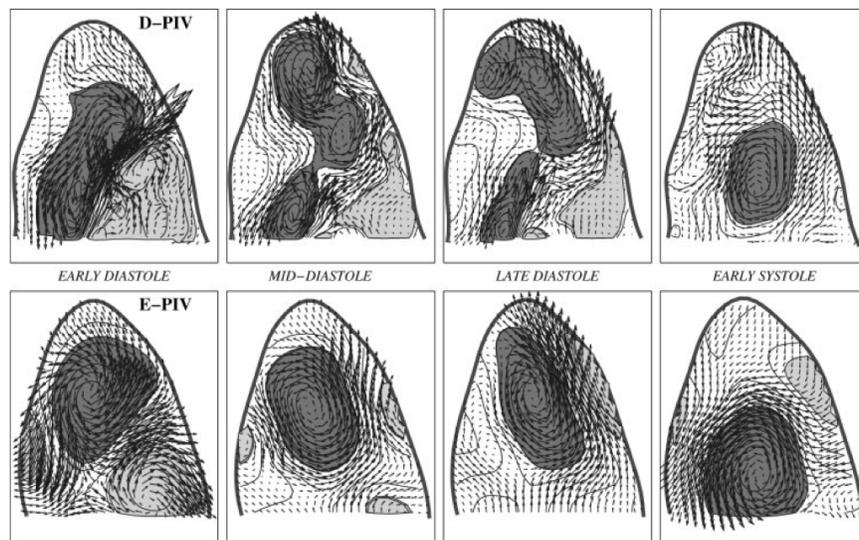
Figure 1.7: Comparison of velocity fields from *in vitro* studies performed by Kheradvar et al. Results show that Echo-PIV can resolve the behavior, but peak velocities and smaller vortex regions are not resolvable using the implemented frame rates and processing strategy. [35][6]

A majority of the clinical publications utilized scan frame rates between 60 Hz and 100 Hz, resulting in the inability to resolve peak velocities. [16, 41, 43, 45] As previously indicated the inability to resolve peak velocities prompted researchers to explore methods for quantifying vortex properties, turning the focus of Echo-PIV research toward LV vortex assessment. These

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[6] A. Kheradvar et al. Echocardiographic Particle Image Velocimetry: A Novel Technique for Quantification of Left Ventricular Blood Vorticity Pattern. Journal of the American Society of Echocardiography (2010); 23(1): 86-94. Used with permission of Elsevier, 2014.

lower frame rate studies have shown the ability to determine statistically significant alterations in vortex geometries between healthy and LV impaired patients [16], however, the ability to calculate other relevant properties may be impractical. From Cimino et al, the published analysis of relative pressure from Echo-PIV results were limited to only qualitative assessment. Prinz et al determined relative pressure from Echo-PIV as well, but in comparison to LV pressure catheter readings, plots were difficult to interpret or justify. Reported Echo-PIV pressure differences between Left Atrium and Mid LV (0.10 ± 0.05) were substantially below works reported in CMM by Yotti et al [9]. Future research pertaining to pressure measurement calculations should be made using the optimized settings employed by Abe et al. [41, 44]

Improper seeding and image adjustment limit the collection of reliable signals for robust PIV measurements. Proper imaging for LV flows requires homogenous seeding of the chamber with concentrations that do not leave the majority of the ventricle empty, while also preventing the chamber from becoming saturated with contrast. [12] Experimental models and simulation studies have attempted to provide suitable recommendations for *in vivo* Echo-PIV applications, but results indicate substantially varying and at times untranslatable values. Experimental models have suggested that 10% of the total volume concentration at injection (or introduction) should be imaged at any time instance based on geometry and flow loop volume. [38] Simulation studies of LV flow suggest that frame rates (~ 50 Hz to 200 Hz) require different bubble concentrations (~ 30 bubbles per ml to 10 bubbles per ml) to optimally resolve peak velocities. [36]

Clinical studies have generally injected bubble concentrations at 0.1 ml of agent per bolus injection. Other recommend have advocated imaging as the concentration dilutes, using the manufacturing mechanical index, and imaging using the tissue harmonic setting of B-mode imaging. [12] As clinical use of Echo-PIV moves forward, limitations should be addressed and suggestions should be optimized to obtain the highest quality scans for either vortex assessment or resolution of accurate velocity measurements.

1.6 Conclusion

Flow visualization techniques offer physicians and researchers a mechanism to improve understanding, diagnosis and treatment of cardiovascular diseases (CVD) and heart failure (HF) as they relate to the left ventricle (LV). Methods such as Color Doppler and MRI, which allow

for determination of hydrodynamic properties such as relative pressure changes and apical vortex characteristics, are routinely used for velocity measurements in LV chamber despite providing only limited spatial information or low frame rates which make assessment of flow interactions difficult to resolve. Echo-PIV, an emerging flow visualization tool, can overcome these limitations to further expand knowledge and understanding of cardiac flow and disease alterations.

Prospective research in Echo-PIV will need to address multiple situations and potential variants in both disease state sample imaging and healthy state sample imaging, in order to develop settings considered optimal in all situations. Multi-frame PIV processing techniques should be employed in future Echo-PIV image assessments. These techniques should reduce the impact of noise and image artifacts in robust measurement acquisition. Future work with Echo-PIV measurement results should be planned as comparison studies employing clinically accepted field processes such as PC-MRI, color M mode imaging and 2D Color Doppler, in order to validate velocity measurements are capable of accurately quantifying flow field behavior. Given the difficulty in diagnosing diseases such as LV diastolic dysfunction, it is imperative LV chamber flow properties present complete flow information to obtain quantifiable measurements in relative pressure and vortex strength. As techniques improve focus must remain on their adaptability as new measurement methods for metrics that in time may become standard diagnostic tools.

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2 Feasibility of Echocardiographic Particle Image Velocimetry for evaluation of cardiac left ventricular filling function

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2.1 Abstract

Echo-PIV has potential for investigating cardiac flows, however it has yet to reach a point of accepted clinical use due to image quality from routine recordings limiting PIV measurement accuracy. This paper presents an Echo-PIV methodology that combines a moving window ensemble (MWE) with a Product of Correlations (PoC) processing scheme that overcomes noise and recording artifact limitations. This novel processing methodology is demonstrated with a cohort of diseased subjects suffering from left ventricular filling dysfunction (LVDD) that has undergone routine contrast-enhance examination.

The method was assessed qualitatively and quantitatively to demonstrate measurement accuracy by comparison to standard PIV processing. Both processing approaches were evaluated for their ability to resolve physical quantities against corresponding patient Color M-Mode (CMM) Doppler recordings. In reliable velocity measurement analysis, only 60% of standard PIV processing measurements were reliable, substantially lower than the MWE methods, which were determined 90% reliable. Direct comparison of Echo-PIV and CMM recording temporal peak velocities by correlation indicated that MWE with PoC produced a marked improvement in agreement (0.79 ± 0.10) over standard PIV processing (0.66 ± 0.12).

2.2 Introduction

Heart disease is one of the predominant causes of morbidity and mortality worldwide [1]. Non-invasive imaging modalities such as echocardiography and magnetic resonance imaging (MRI) provide physicians with the proper tools for diagnosis and treatment. Image recordings can facilitate viewing and measurement of cardiac chamber geometries, blood flow, and tissue motion [2-4]. Development of post-processing techniques for recordings can potentially determine crucial clinical measurements that are used routinely for diagnostic purposes [4-7].

Cardiac chamber flow visualization using non-invasive imaging has grown during the past decade, largely due to technological advancement [8]. Color Doppler Echocardiography and MRI techniques for chamber flow visualization were first presented in the early 1980s [9], but lack of computational capabilities delayed the development of reliable post-processing techniques until the last decade.

Color Doppler Echocardiography resolves axial blood velocities by calculating the phase shift between transmitted and received signals. Two separate Color Doppler modalities are typically provided on ultrasound machines, Color M-Mode (CMM) Doppler and 2D Color Doppler. CMM Doppler produces a spatiotemporal color contour of velocities collected from a single scan-line [10], which have been used in the development new metrics and non-invasive measurements [4, 5, 11]. 2D Color Doppler Echocardiography records axial velocities contour of full cardiac chamber flow across the cycle, allowing for direct measurement of vortex structures and determination of radial blood velocities for more intuitive visualization [12, 13].

MRI in cardiac flow visualization is often performed using phase-contrast MRI (pc-MRI). Images obtained are velocity encoded, where the image gray-scale intensity corresponds to a specific displacement. Through post-processing non-invasive measurement of physical properties can be determined [7, 14].

Current non-invasive imaging techniques are limited in the amount of cardiac flow information provided. CMM scans a small segment of the full chamber flow, preventing visualization of flow structures, while 2D Color Doppler computational costs reduce the available frame rate [8]. MRI recordings provide low sampling rates, and computational and operational costs limit its widespread use [8, 9]...Echo Particle Image Velocimetry (Echo-PIV), a recent development in

flow visualization, provides adequate spatial resolution with high temporal resolution for improved understanding of cardiac chamber flows [8, 9].

Digital Particle Image Velocimetry (DPIV), a well-established tool in experimental fluid dynamics [15], typically employs micron-sized flow tracing particles illuminated by a pulsed laser sheet and imaged with digital cameras for evaluating particle image pattern correlation to estimate frame-to-frame displacement in an image series [16].

Echo-PIV employs ultrasound B-mode imaging, commonly used in both Speckle Tracking Echocardiography (STE) and Left Ventricle (LV) geometry measurement, for recording data. This imaging modality is analogous to the illuminating laser sheet and cameras used in DPIV experiments. Ultrasound contrast agents, the flow tracing particles in this application, are protein or lipid-encapsulated, acoustically opaque, bio-inert gas bubbles [17]. After image recordings are collected the imaging frame series must be processed on a separate machine using PIV correlation algorithms to obtain blood flow measurements.

Sengupta et al. first demonstrated the application of Echo-PIV in cardiac flows, measuring the flow of blood in the Left Atrium (LA) & Left Ventricle (LV) [18]. Experimental models and numerical simulations of LV models have since been performed to further optimize the quality of Echo-PIV clinical recordings [19, 20]. Clinical research continues to focus on heart diseases, including congestive heart failure (CHF) [21-23].

Despite increased interest in Echo-PIV, less than one third of the published studies address analysis of clinical data, demonstrating that Echo-PIV has yet to reach a level of acceptance within the medical community. Limited acceptance is largely due to poor image quality, which governs the quality of the PIV measurements. Due to safety concerns [17] contrast agents are only used in routine imaging with patients that produce low quality recordings after initial imaging (Figure 2.1, Left), leading to poor resolution of the contrast bubbles. During clinical research studies where high quality recording patients can be injected contrast agents, particle images with high contrast and signal to noise ratio can be obtained (Figure 2.1, Right). Since clinical research focuses on characterizing cardiac diseases, the majority of study-specific patients tend to generate low quality recordings. This limits Echo-PIV studies using clinical data to "optimal" cases, further inhibiting acceptance in the medical community due to sample population bias [21-23].
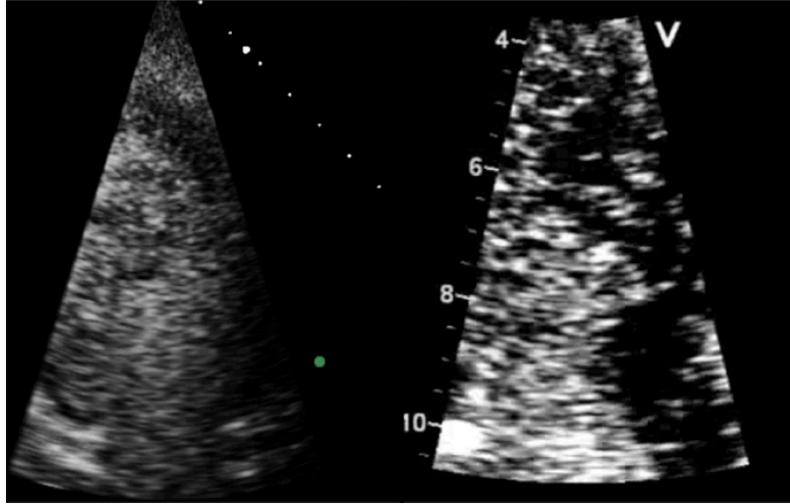
Figure 2.1: Comparison B-Mode images between scans for (Left) an average patient from clinical scans and (Right) a healthy patient who produces high resolution scans. [18][7]

Even when applying optimal parameters scan quality can still be inadequate, requiring improved processing strategies [19]. Several approaches have been designed to overcome limitations in Echo-PIV measurement quality, including *in situ* algorithms for correlation peak amplification, robust peak detection, outlier removal, and flow field reconstruction based on conservation laws [24, 25]. However, these strategies are geared toward steady flow regimes for experimental models and peripheral arterial/vascular flows [26, 27]. Ensemble correlation processing techniques in PIV offer an approach for improving signal quality and prediction accuracy by performing measurements along a time series of recordings [28, 29]. Such methods typically require a sufficient temporal record in order to reach a converged average value, limiting application to steady state flows. Cardiac flows are unsteady, preventing the ability to gather a suitable temporal record for ensemble correction processing. However, an ensemble-based method could be used on cardiac Echo-PIV recordings in order to obtain velocity measurements that are potentially more robust and accurate.

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In this work we hypothesize that implementing a short-time (3 frame) moving ensemble method can produce flow measurements with improved accuracy and robustness for Echo-PIV applications on low quality scan images.

This paper will present *in vivo* results based on the proposed Echo-PIV processing, demonstrating the importance of overcoming noise and recording limitations generated from contrast-enhanced low quality routine clinical images. A clinical patient cohort was organized to compare resulting Echo-PIV velocity measurements against CMM-derived velocity measurements. These comparisons, qualitative & quantitative, serve as preliminary evidence that Echo-PIV velocity measurements using the methodology developed herein are in agreement with clinically accepted CMM measurements.

2.3 Methodology

2.3.1 Patient Data Acquisition

Patient examinations were conducted in two sessions, separating routine imaging (including CMM Doppler) from contrast-enhancement imaging. Patient recordings were collected using iE33 ultrasound systems. Contrast-enhancement B-mode recordings for 2-chamber, 3-chamber, and 4-chamber arrangements were obtained for each patient. The sweep angle was narrowed to a region-of-interest (ROI) containing solely the LV from apex to mitral annulus. This setting increases image magnification, but extends the temporal resolution (94 fps to 178 fps, average 150 fps). All recordings contain at minimum two heartbeat cycles. Acquisition parameters and contrast agent concentration were varied in order to establish optimal settings for each subject.

Table 2-1: Patient B-mode Imaging Frame Rates

Patient	1	2	3	4	5	6	7	8
# Scans	1	1	3	1	2	1	2	2
Scan Sampling Rate (fps)	148	156	146	94	98	156	166	178

Patient Cohort

The patient cohort was provided by the Center for Cardiology at Wake Forest University Baptist Medical Center in accordance with IRB 08-057 approved protocols. Only patients needing contrast-enhancement during routine examination were included in this study . Exclusion criterion was imposed on individual scans with very low seeding, due to concentration or improper imaging. Selected subjects suffered from or showed signs of suffering from heart failure, however the progression stage was not considered. In total 8 patients from the clinical study were selected, with general information presented in Table 2-2. Additional patient information is provided in Table 2-3.

Table 2-2: Cohort Clinical Information Breakdown

Clinical Procedure	Gender (Total/Female)	Age (Yrs) (Average, Min/Max)	E/A	B-mode scans (Total)
Color M-mode	5/3	58.8 (32/74)	1.19	13

E/A: Ratio of peak early (E) diastolic filling velocity to peak atrial contraction (A) filling velocity

Table 2-3: Additional Individual Scan Information

Patient	1	2	3	4	5	6	7	8
# Scans	1	1	3	1	2	1	2	2
Peak E Velocity (cm/s)	66.9	100.9	49.1	55.6	88.2	93.7	53.7	55.0
Peak A Velocity (cm/s)	40.0	54.8	76.1	70.6	38.3	Fused	67.3	86.0

E: Early diastolic filling, *A*: Atrial contraction filling

2.3.2   Color M-mode Processing

CMM recordings were stored in a 256-bit color image format, requiring interpolation to transform velocity measurements from the color scale domain to the velocity domain. This was accomplished using a combined velocity-interpolation and de-aliasing algorithm developed by the AEThER Lab at Virginia Tech and the Center for Cardiology at Wake Forest University Baptist Medical Center [11]. Lab technicians typically adjust the aliasing boundaries for improved visualization of the filling contours, shown in Figure 2.2, requiring the additional de-aliasing step. Velocity regions were segmented to preserve only the diastolic inflow region for comparison to Echo-PIV results.
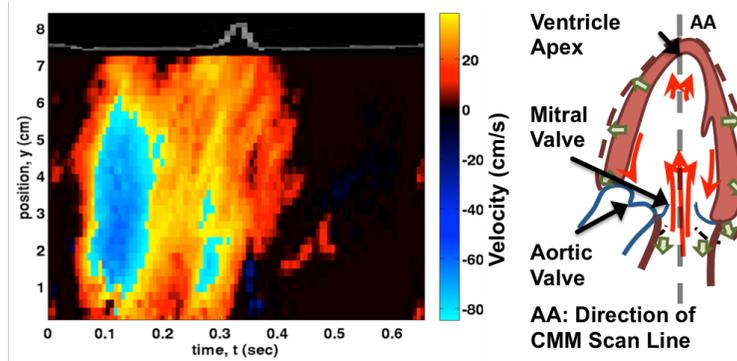
Figure 2.2: Examples of Color M-mode Echocardiography (Left), a spatiotemporal contour measure of blood velocity in the LV. Scan was taken from Mitral Valve to Apex, as shown in the example illustration (Right).

Following transformation and segmentation of patient recordings, velocity contours were down-sampled to match the resolution of the EchoPIV patient scans to allow for direct comparison of velocity measurements between recording methods. Down-sampling was performed in MATLAB using a two-dimensional bi-cubic scheme.

2.3.3   Particle Image Velocimetry

Particle Image Velocimetry (PIV) is a correlation-based technique that estimates the average displacement of a flow field between two sequential image pairs [16]. The standard cross-correlation (SCC) technique in PIV computes the cross-correlation between an image pair after Fast-Fourier transformation (FFT). This processing strategy was designed for images obtained from laser-illuminated particle-seeded flow fields. These images, under proper seeding, illumination, and exposure, produce bright particles with dark backgrounds.

Under optimal ultrasound system settings and seeding, contrast-enhanced B-mode images taken for PIV processing purposes can produce a similar appearance. However, recording robust images are difficult since contrast agents used in routine scans are only reserved for patients that produce low quality images after initial image [17]. Resulting PIV estimates typically contain erroneous velocity estimates, obtained from correlation plane displacement signals with low SNR.

2.3.3.1   Moving Window Ensemble Correlation

Ensemble-average correlation (Figure 2.3) was originally developed for μPIV as a means to increase signal-to-noise ratio (SNR) of correlation plane estimates on images containing high

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background noise and out-of-focus particles [28, 29]. This correlation technique is typically reserved for steady state or time-averaged flows with little temporal velocity variation. Frame-to-frame correlation planes from a large frame series are averaged together, producing an average correlation velocity estimate expressed mathematically below.

$$\overline{R}(s) = \sum_{i=1}^{N} R_i(s)$$

Equation 1

In this equation, the values at each position s on the individual correlation planes R_i are summed together to obtain the average correlation plane estimate, $\overline{R}$. The ensemble-average correlation technique may also reduce the influence of image artifacts and out-of-plane motion on cross-correlation estimates.

Using the traditional ensemble correlation to perform cardiac Echo-PIV assessment is not suitable given the periodic and unsteady nature of cardiac flows. Moving window ensemble (MWE) correlation scheme (Figure 2.3) offers an alternative approach by using a short-time ensemble series to resolve accurate velocity measurements from noisy data that cannot produce clear, robust instantaneous measures [30]. If the time series is sufficiently short, little change in displacement between frames will be present, providing an instantaneous velocity measurement.
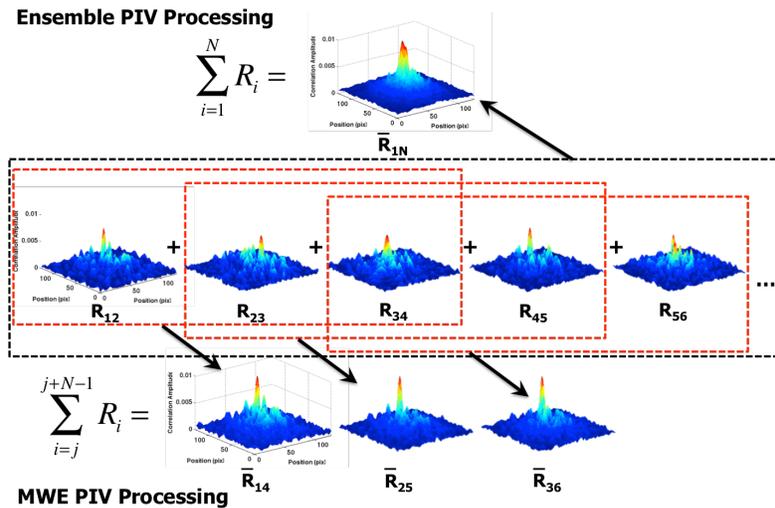
Figure 2.3: Comparison of traditional Ensemble PIV procedure to MWE PIV. In Ensemble processing, a large series of frames are used to obtain a mean or steady flow measurement. MWE employs a short series to obtain near instantaneous peak velocity measurements while reducing inplane variation.

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2.3.3.2 *Ensemble based on Sum of Correlation*

Ensemble averaging and MWE schemes employ an arithmetic mean, where all terms in the data set are summed and scaled to find a suitable average [28-30]. This method, herein referred to as Sum of Correlation (SoC), is described mathematically below.

$$\overline{R}(s) = \sum_{i=j}^{j+N-1} R(s)$$

Equation 2

Formulation of the SoC differs slightly from Ensemble-Averaging; in this case, j refers to the starting correlation for the MWE. The SoC method is dependent on the condition that all correlation planes have a common statistical mode near a constant displacement. Limitations in method accuracy arise from erroneous correlated noise, which impacts convergence. If random noise correlates at a common mode with high amplitude over the short-series, this peak could dominate the true displacement, causing SoC method-based MWE to fail. This can be overcome by increasing the number of frames used in the image series, as shown in Figure 2.4. However, if the series becomes too large, displacement between frames may change, preventing the ability to obtain a time-accurate measurement. Thus, there is a need for faster convergence to the true solution with the shortest possible frame series applicable to ensure robust measurement.
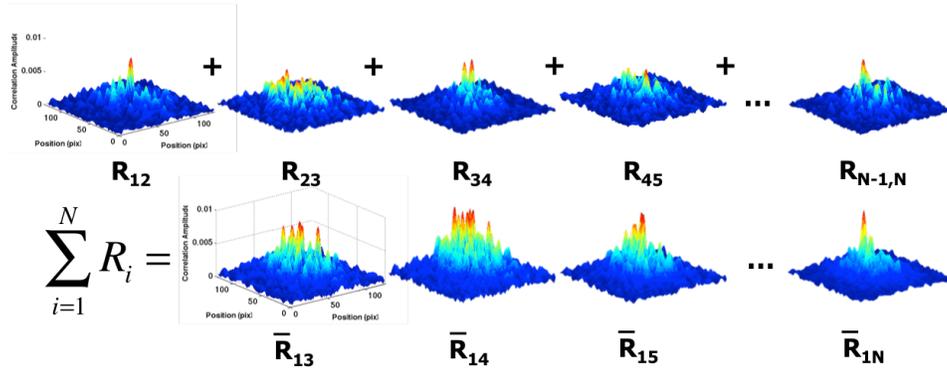
Figure 2.4: Sample of ensemble correlation from a high velocity component flow that converges slowly. The true displacement exists in all planes, but erroneous noise is present which hinders proper convergence. In order to obtain a "reliable" measurement, *n* number of planes are needed.

2.3.3.3 *Ensemble based on Product of Correlation*

Instead of an arithmetic mean, the use of a geometric mean as an alternative approach to data averaging MWE correlation can potentially yield improved robustness over SoC. In this scheme correlation planes are multiplied together, allowing only consistently high-level correlation values to exist within the correlation plane.

Hart (2000) developed an error correction technique that utilized multiplication of correlation planes on instantaneous velocity measurements [31]. This processing scheme can increase SNR by removing non-overlapping random correlation noise. However, for Echo-PIV, where the spatial resolution is limited and the flow tracer size is large, did not provide acceptable results (data not shown).

By utilizing a multiplication scheme in a temporal ensemble, noisy, erroneous peaks may be filtered out quickly, allowing convergence of this scheme through a reduced number of frames while providing increased confidence in correct peak detection. This method, referred to herein as Product of Correlation (PoC), is described mathematically below.

$$\overline{R}(s) = \prod_{i=j}^{j+N-1} R(s)$$

Equation 3

In order to demonstrate the added robustness provided by PoC, a sample set of correlation planes are presented. In the example the instantaneous and SoC vectors are erroneous, due to poor correlation signal (SCC, Figure 2.5, Left) and high noise correlation (SoC, Figure 2.5, Middle). Using a short-time series of 3 correlation planes with the SoC processing algorithm, the true peak is present and strong, but there is an erroneous correlation peak of higher strength present in the plane. By using the PoC processing algorithm across the same 3 correlation planes (Figure 2.5, Right), the correlation plane is able to converge to the correct peak.
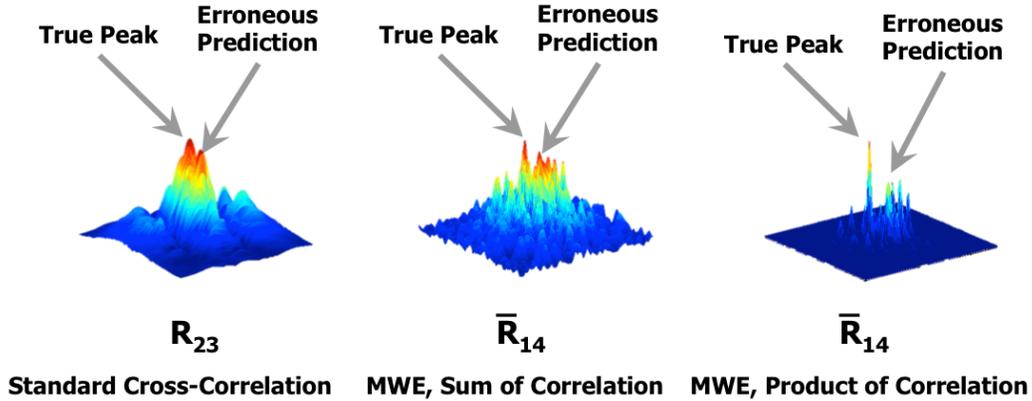
Figure 2.5: Example of correct velocity prediction by PoC against erroneous predictions from SCC and SoC at a selected velocity prediction during diastolic inflow.

Random noise using this strategy should effectively be filtered out, achieving an exponential SNR increase. This is due to the small ensemble size, which decreases the likelihood of high variability between the peak estimates, while ensuring that random noise should not have significant overlap across the correlation planes. In SoC averaging if high noise exists in one correlation plane, this could possibly lead to erroneous prediction, even if the noise is low in the remaining correlations. Averaging by PoC provides more weight to these lower noise correlations to attenuate any high noise correlations that may exists, giving the true peak a higher likelihood of being detected.

2.3.3.4 *Processing Methodology*

Baseline processing for the patient cohort B-mode imaging was carried out using Standard Cross-Correlation (SCC), the current standard for measurement in Echo-PIV. Robust Phase Correlation (RPC) processing, a method of optimized energy phase filtering used to improve correlation, was conducted to assess the impact of additive noise removal on velocity predictions [32-34]. The proposed ensemble methods, using RPC filtering, were also used on the patient cohort image data. All processing was performed through the use of a customized version of PRANA PIV suite developed by the AEThER Lab at Virginia Tech [35].

Cases were processed using a three-pass, continuous window deformation correlation scheme on a grid resolution of 8 x 8 pixels [36]. Physical window sizes were 128 x 128 pixels with effective resolution of 48 x 48 pixels using a Gaussian apodization function [33]. These

parameters were based on physical pixel width and height of the ROI and the theoretical peak velocity that can be observed within the LV. Application of the RPC method requires knowledge of the flow tracer diameter, established as an average size of 7 pixels. Ensemble sizes for both SoC and PoC methods were restricted to 3 correlation planes, in order to avoid underestimation effects introduced by the averaging.

2.3.4 Post-processing

2.3.4.1 Valid Measurement Probability

Information from the correlation planes was assessed to quantify improvements from proposed strategies through measurement quality. Confidence of correct peak displacement can be estimated through the Peak-to-Peak ratio (PPR) by dividing the primary correlation peak height by the secondary correlation peak height [37]. Although there is not a direct link between the peak ratio and error for any given measurement, correlations with low PPR are more likely to have failed or have high errors. Keane and Adrian showed that any PIV measurement with a PPR less than 1.2 has a high likelihood of being a false correlation while Hain and Kähler suggested that PPR above 2.0 could be assumed correct [37, 38]. Charonko and Vlachos demonstrated that for standard PIV processing and RPC correlation there is a direct correspondence between peak ratio and uncertainty of a given measurement [39].

2.3.4.2 Flow Field and Pseudo CMM Comparisons

Velocity and vorticity fields for a representative heart cycle were compared qualitatively for the different processing methods, in order to ensure that the measured velocities are physically consistent. Vorticity calculations were carried out using a second-order, central finite differencing scheme.

Velocity measurements from Echo-PIV results were sampled along a scan-line axis from MV to Apex to produce pseudo-CMM contours, mirroring the scan-line contour obtained during CMM recording. A qualitative comparison was conducted; pseudo-CMM contour for each processing type for a single beat were compared side-by-side to the patient CMM scan after it had been segmented, interpolated and resampled as described in the Color M-mode Processing Section.

Patient pseudo-CMM contours for each patient were also assessed quantitatively against their respective resampled CMM map in order to verify that velocity predictions for Echo-PIV matched the values that would be measured during CMM examination. Peak velocity values at each time instant during diastole were sampled from both the CMM and Echo-PIV pseudo-CMM, generating a velocity histogram. Correlation coefficients between recording methods were determined to provide a quantifiable measurement for the agreement between velocities and flow behavior resolved between Echo-PIV and CMM recordings.

2.4 Results

2.4.1 PIV Confidence Measurements

Quantification of the percentage of reliable vectors using the PPR demonstrates the benefit of using a short time series ensemble. Prior to comparison, the PPR values for the ensemble techniques must be scaled accordingly. Measured values from SoC were divided by a factor of 3 (based on arithmetic mean) while the PoC values were normalized by the cube root (based on geometric mean).

Results from the cumulative density function (CDF) of PPR statistics (Figure 2.6) indicate that approximately 20% of all SCC values (solid red) are between 1 and 1.2. This means 20% of all measurements have a high probability of being erroneous. By contrast, the remaining methods contain less than 10% of all measurements with PPR values within this range. Furthermore, if a PPR of 2 is used as the minimum threshold for valid detection [38], only 43.29% of SCC measurements can be considered as reliable, a sharp contrast to approximately 90% of valid measurements produced using the ensemble methods.
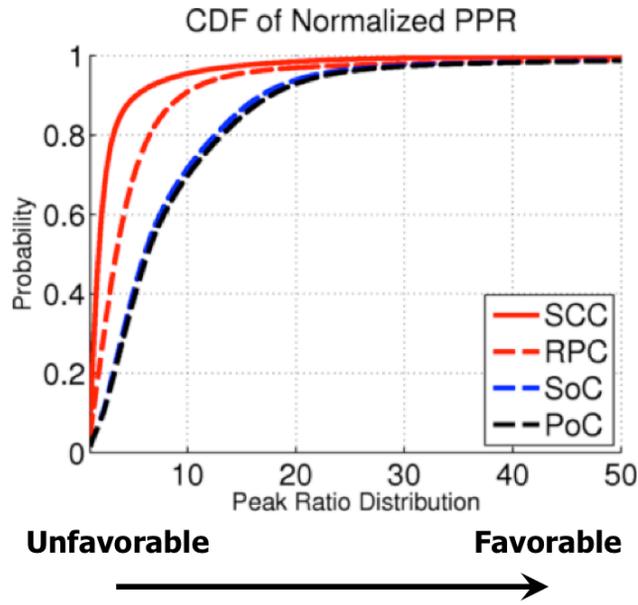
Figure 2.6: Cumulative Density Functions (CDFs) of Peak-to-Peak ratio (PPR) for each processing method. Curves up and to the left indicate lower average PPR and thus potentially less reliable correlation data.

Table 2-4: Peak-to-Peak Ratio Statistics for processing methods.

Process	Probability under PPR of 1.2 (x 100)	Probability over PPR of 2 (x 100)
SCC	18.48	43.29
RPC	9.41	70.55
SoC	2.51	89.77
PoC	2.46	90.43

2.4.2 Analysis of Early Filling Flow

The early filling stage of diastole following the opening of the mitral valve (MV) but prior to the formation of the apical vortex structure involves a high velocity slug of fluid entering the LV volume. [40, 41] Peak filling velocities are normally observed during this period as part of a fluid jet moving from across the MV toward the apex, along with a vortex ring forming beginning at the MV tips. [14, 21, 42] Figure 2.7 shows representative results during early filling from a single patient (Patient 1, Table 2-3) for all four processing methods.

Several observations from the time-series flow field show the performance from each processing method. The first time-step (Time t) depicts the initial penetration of the inflow jet into the LV.

Each processing method captures the expected flow, where the bulk of the jet flow at the base of the frame is moving upward in one direction with two continuous regions of shear forming along the jet exterior. At the second time-step (Time t+1Δt), the resolved flow field from SCC processing captures a reversal in flow, suggesting blood flow is moving from the LV back in to the Left atrium. This behavior disagrees with normal physiological expectations, suggesting that SCC has failed to properly resolve the flow properly..

In the last time-step (Time t+2Δt) instantaneous results present regions of unnatural flow reversal occurring in field, suggesting processing has failed. Velocity and vorticity fields from the MWE processing depict a distinct jet feature with no development of random features in the flow, capturing the expected flow across all time-steps. From these observations it can be conclude that MWE methods produce flow fields that match the expected behavior, and offer lower random spatiotemporal variation.
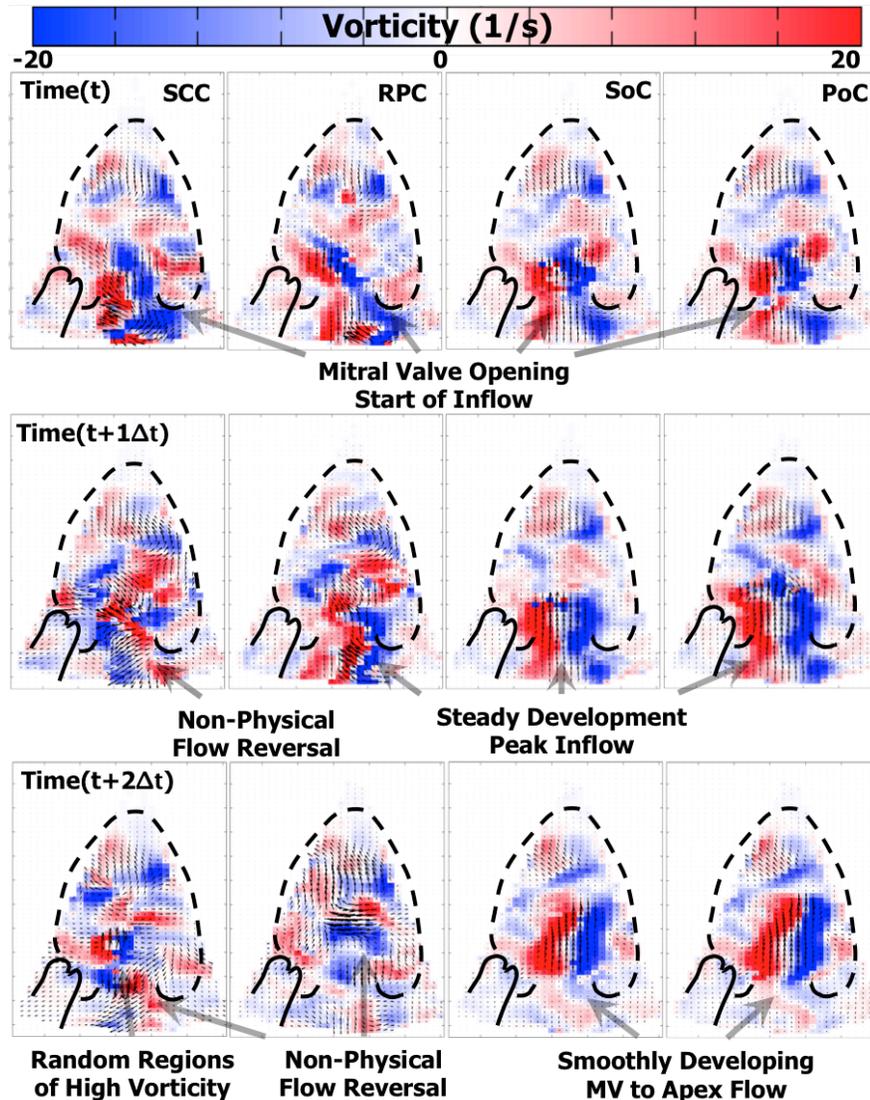
Figure 2.7: Early diastolic inflow comparison for SCC, RPC, SoC and PoC correlation strategies. During inflow, blood passes through the mitral valve, generating a region of shear, shown through the vorticity contours.

2.4.3 Analysis of Pseudo Scan-line and Comparison with CMM

Side-by-side comparisons of each Echo-PIV processing method pseudo scan-lines to CMM velocity contours are shown in Figure 2.8, in order to compare each processing method performance to a clinically established tool. In the pictured CMM velocity contour (Figure 2.8(e)) the selected patient has a dominant early filling cycle with only a slight delay to onset of late filling, possibly giving the appearance that the cycle is fused.
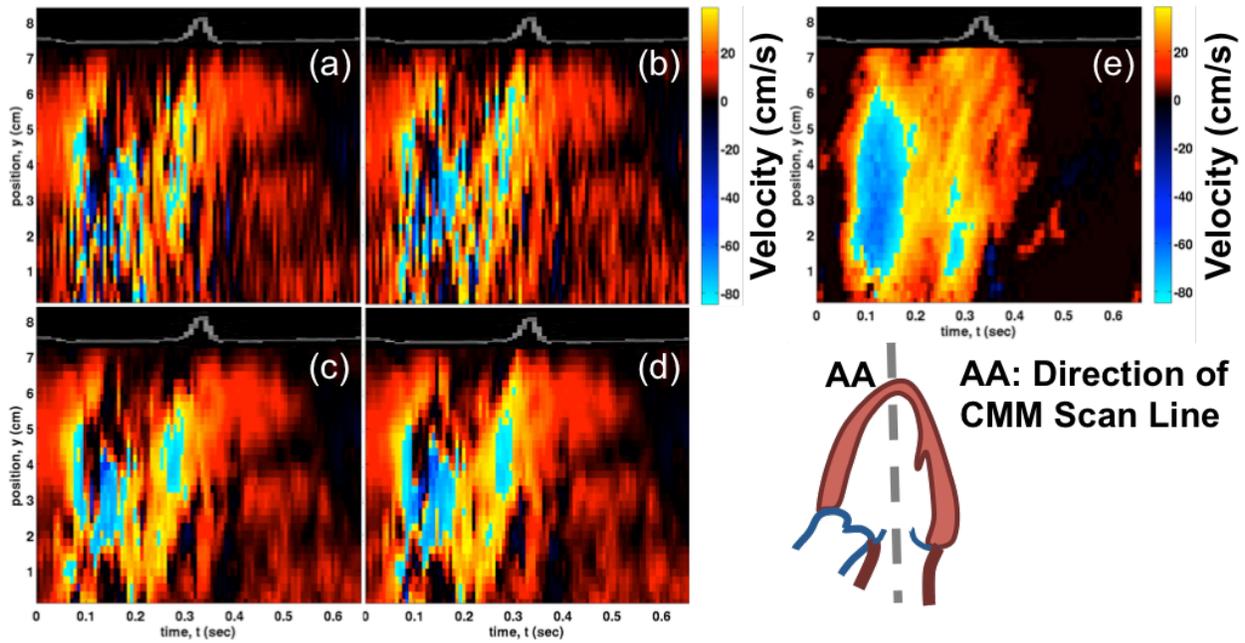
Figure 2.8: Qualitative comparison of EchoPIV to Color M-mode using a scan-line contour view. Processing strategies are for (a) SCC, (b) RPC, (c) SoC, and (d) PoC are shown side-by-side with (e) the patient clinical contour map.

Contours from instantaneous methods (SCC (a), RPC (b)) have a disordered appearance, with high noise levels and velocity gaps, barely capturing the jet inflow region (leading deep blue region, ~0.1 seconds). This inflow region, similar in both methods, is composed of near-zero velocities, indicating correlation loss and erroneous results.

Ensemble processing results more closely match the CMM contour properties, although there is still difficulty to successfully resolve the full inflow region. Correlation still appears more accurate across the later part of the early filling and more consistent measurements are produced with less fluctuation of velocity within each time step.
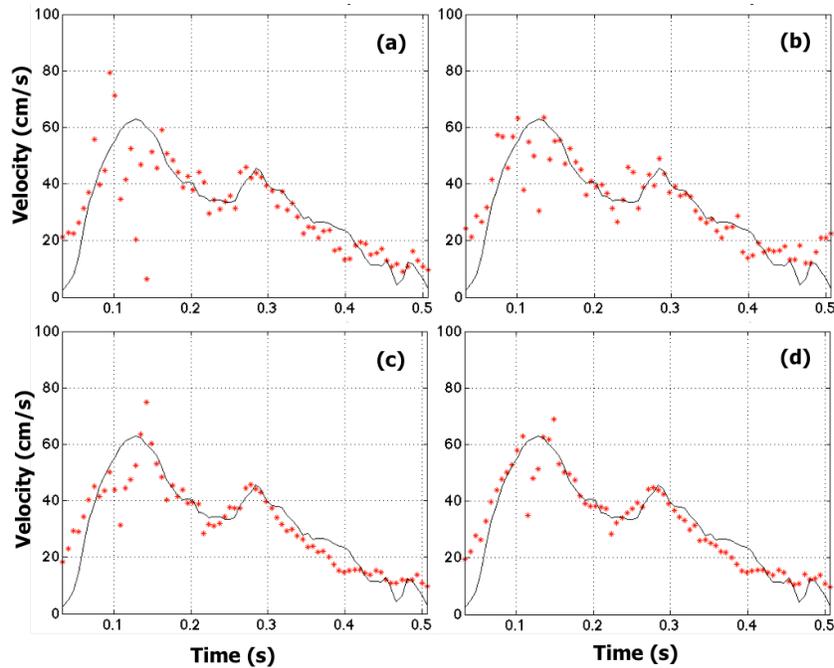
Figure 2.9: Diastolic inflow peak velocity comparison for CMM (black line) and EchoPIV (red dot). Data was sampled at each time component for peak velocity and compared for (a) SCC, (b) RPC, (c) SoC and (d) PoC

Direct comparison of peak velocity measurements between scan-line contour methods are shown in Figure 2.9, demonstrating the improvement of the proposed MWE methods. Instantaneous methods do not properly resolve peak velocities during the early filling wave, as suggested by the previous qualitative comparisons. Instantaneous SCC processing is sporadic during the early filling, but is comparable to CMM velocities during the later filling phase. Instantaneous RPC values have a higher variation, although early filling data points more consistently match the CMM data. The MWE methods each show reduced variation and very good agreement compared with CMM peak velocities.

2.4.4   Evaluation of EchoPIV Accuracy to Clinical Measurements

Quantitative assessment for the ability of Echo-PIV to accurately measure the cardiac flow was performed against the CMM velocities by calculating the correlation coefficient between the scan methods, presented in Table 2-5. For Patient 1, instantaneous processing shows a correlation coefficient of 0.81, while the MWE methods show much higher correlation (0.95). Given that scans were not taken on the same day, or at the same time, the beat-to-beat variability introduces some uncertainty.

Table 2-5: Patient Inter-method Peak Velocity Histogram Correlation

Method \ Patient	1	2	3	4	5	6	7	8	Mean (St. Dev)
SCC	0.81	0.68	0.76	0.45	0.66	0.79	0.55	0.62	0.66 (0.12)
RPC	0.87	0.38	0.76	0.72	0.69	0.87	0.58	0.65	0.69 (0.16)
SoC	0.95	0.65	0.85	0.72	0.67	0.87	0.66	0.78	0.77 (0.11)
PoC	0.95	0.72	0.85	0.77	0.69	0.90	0.68	0.79	0.79 (0.10)

Across all subjects, the standard processing method (SCC) only achieved a 0.66 average correlation coefficient. The RPC processing shows an inconsequential improvement over SCC results, and one patient appearing as a clear outlier.

The MWE PoC scheme shows that the entire cohort has an improved correlation to CMM measurements. One patients measures slightly below the standard deviation range, possibly due to a small number of high variation data points between method histograms.

2.5 Conclusions

In this paper we present the application of short-time series moving ensemble PIV methods to obtain more consistent, reliable, and robust results for cardiac Echo-PIV. Qualitative fields show traditional PIV processing provides inconsistent measurements, limiting the ability to properly resolve the flow. This leads to discrepancies when comparison is made to other modalities such as CMM velocity contour recordings. The correlation PPR suggests that traditional PIV processing methods on routine clinical data can yield as many as 60% invalid measurements. In contrast, the ensemble methods result in as much as 90% valid vector probability. Echo-PIV measurement accuracy was evaluated against peak CMM contour velocities. By calculating the correlation coefficient between the two modalities the ensemble PIV methods show an increased robustness and reliability for resolving the flow compared to traditional PIV measurements. Presented results suggest that use of moving ensemble method with Product of Correlation processing has the potential of producing credible and accurate results through the entire cycle, however additional and extensive development and analysis is still required before the method is ready for routine clinical use.

2.6   References

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3 Conclusions and Future Work

This work presented a processing approach to provide clinical studies with further capabilities for patient inclusion and means for introducing the practicality of Echo-PIV in clinical use. As identified earlier, even with increased interest the medical community has yet to show signs of acceptance for use in clinical research. Most of the clinical studies employing Echo-PIV have used low frame rates and PIV processing settings that severely under-resolve velocity magnitudes, impeding on the calculation of relevant physical quantities. Furthermore, strict exclusion criterions on patient recording quality significantly reduce study cohort sizes. The methods and proposed PIV processing approaches evaluated in this work show not only the ability to obtain physically accurate measurements, but also the ability to accurately resolve the expected flow behavior. Additionally, the algorithms show the ability to reduce the level of exclusion, allowing for the processing of more patients.

There are still developments and validation that must effectively be completed going forward to substantiate the effectiveness of the proposed methods in this work. Additionally, it would be in our best interest to further expand on our understanding of seeding densities and ultrasound settings to ensure future patient cohorts provide more robust quality recordings for study. In terms of development and validation, the Product of Correlation (PoC) used in the Moving Window Ensemble (MWE) has yet to be proven effective under certain flow conditions. Early simulated image analysis failed to produce images that mirrored contrast-enhancement B-mode images. Future investigation using ultrasound image modeling software may allow use to revisit this work.

As for expanding our understanding for quality contrast-enhancement recordings, this area has only seen limited simulation and experimental investigations. The resulting suggested guidelines may not translate over as well when performing *in vivo* recording and analysis. Animal models have received limited attention in this field, but could be ideal for a method to perform tests and translate over in to *in vivo* clinical imaging.

Appendix A: IRB Approval Letters

VirginiaTech

Office of Research Compliance
Institutional Review Board
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Blacksburg, Virginia 24060
540/231-4606 Fax 540/231-0959
e-mail irb@vt.edu
Website: www.irb.vt.edu

MEMORANDUM

DATE: January 17, 2012

TO: Pavlos P. Vlachos, Kelley Stewart, John Charonko, Casandra Niebel, Brett Meyers, Robert Decarolis

FROM: Virginia Tech Institutional Review Board (FWA00000572, expires May 31, 2014)

PROTOCOL TITLE: Translational Science Team Pilot Application: Left Ventricle Filling Hydrodynamic Efficiency and Pressure Distributions as a Predictive Tool for Diagnosing Cardiac Diastolic Dysfunction

IRB NUMBER: 08-057

Effective February 13, 2012, the Virginia Tech IRB Chair, Dr. David M. Moore, approved the continuation request for the above-mentioned research protocol.

This approval provides permission to begin the human subject activities outlined in the IRB-approved protocol and supporting documents.

Plans to deviate from the approved protocol and/or supporting documents must be submitted to the IRB as an amendment request and approved by the IRB prior to the implementation of any changes, regardless of how minor, except where necessary to eliminate apparent immediate hazards to the subjects. Report promptly to the IRB any injuries or other unanticipated or adverse events involving risks or harms to human research subjects or others.

All investigators (listed above) are required to comply with the researcher requirements outlined at http://www.irb.vt.edu/pages/responsibilities.htm (please review before the commencement of your research).

PROTOCOL INFORMATION:
Approved as: **Expedited, under 45 CFR 46.110 category(ies) 5**
Protocol Approval Date: **2/13/2012 (protocol's initial approval date: 2/13/2008)**
Protocol Expiration Date: **2/12/2013**
Continuing Review Due Date*: **1/29/2013**
*Date a Continuing Review application is due to the IRB office if human subject activities covered under this protocol, including data analysis, are to continue beyond the Protocol Expiration Date.

FEDERALLY FUNDED RESEARCH REQUIREMENTS:
Per federally regulations, 45 CFR 46.103(f), the IRB is required to compare all federally funded grant proposals / work statements to the IRB protocol(s) which cover the human research activities included in the proposal / work statement before funds are released. Note that this requirement does not apply to Exempt and Interim IRB protocols, or grants for which VT is not the primary awardee.

The table on the following page indicates whether grant proposals are related to this IRB protocol, and which of the listed proposals, if any, have been compared to this IRB protocol, if required.

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VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY
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MEMORANDUM

DATE:	August 30, 2012
TO:	Pavlos P Vlachos, Kelley Christine Stewart, John James Charonko III, Casandra L Niebel, Brett A Meyers Jr, Akira Madono, Natalya Vorobtsova
FROM:	Virginia Tech Institutional Review Board (FWA00000572, expires May 31, 2014)
PROTOCOL TITLE:	Translational Science Team Pilot Application: Left Ventricle Filling Hydrodynamic Efficiency and Pressure Distributions as a Predictive Tool for Diagnosing Cardiac Diastolic Dysfunction
IRB NUMBER:	08-057

Effective August 30, 2012, the Virginia Tech Institution Review Board (IRB) Chair, David M Moore, approved the Amendment request for the above-mentioned research protocol.

This approval provides permission to begin the human subject activities outlined in the IRB-approved protocol and supporting documents.

Plans to deviate from the approved protocol and/or supporting documents must be submitted to the IRB as an amendment request and approved by the IRB prior to the implementation of any changes, regardless of how minor, except where necessary to eliminate apparent immediate hazards to the subjects. Report within 5 business days to the IRB any injuries or other unanticipated or adverse events involving risks or harms to human research subjects or others.

All investigators (listed above) are required to comply with the researcher requirements outlined at:

http://www.irb.vt.edu/pages/responsibilities.htm

(Please review responsibilities before the commencement of your research.)

PROTOCOL INFORMATION:

Approved As:	**Expedited, under 45 CFR 46.110 category(ies) 5**
Protocol Approval Date:	**February 13, 2012**
Protocol Expiration Date:	**February 12, 2013**
Continuing Review Due Date*:	**January 29, 2013**

*Date a Continuing Review application is due to the IRB office if human subject activities covered under this protocol, including data analysis, are to continue beyond the Protocol Expiration Date.

FEDERALLY FUNDED RESEARCH REQUIREMENTS:

Per federal regulations, 45 CFR 46.103(f), the IRB is required to compare all federally funded grant proposals/work statements to the IRB protocol(s) which cover the human research activities included in the proposal / work statement before funds are released. Note that this requirement does not apply to Exempt and Interim IRB protocols, or grants for which VT is not the primary awardee.

The table on the following page indicates whether grant proposals are related to this IRB protocol, and which of the listed proposals, if any, have been compared to this IRB protocol, if required.

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VirginiaTech

MEMORANDUM

DATE: January 15, 2014

TO: Pavlos P Vlachos, Kelley Christine Stewart, John James Charonko III, Casandra L Niebel, Brett A Meyers Jr, Akira Madono, Natalya Vorobtsova

FROM: Virginia Tech Institutional Review Board (FWA00000572, expires April 25, 2018)

PROTOCOL TITLE: Translational Science Team Pilot Application: Left Ventricle Filling Hydrodynamic Efficiency and Pressure Distributions as a Predictive Tool for Diagnosing Cardiac Diastolic Dysfunction

IRB NUMBER: 08-057

Effective January 15, 2014, the Virginia Tech Institution Review Board (IRB) Chair, David M Moore, approved the Continuing Review request for the above-mentioned research protocol.

This approval provides permission to begin the human subject activities outlined in the IRB-approved protocol and supporting documents.

Plans to deviate from the approved protocol and/or supporting documents must be submitted to the IRB as an amendment request and approved by the IRB prior to the implementation of any changes, regardless of how minor, except where necessary to eliminate apparent immediate hazards to the subjects. Report within 5 business days to the IRB any injuries or other unanticipated or adverse events involving risks or harms to human research subjects or others.

All investigators (listed above) are required to comply with the researcher requirements outlined at:

http://www.irb.vt.edu/pages/responsibilities.htm

(Please review responsibilities before the commencement of your research.)

PROTOCOL INFORMATION:

Approved As:	**Expedited, under 45 CFR 46.110 category(ies) 5**
Protocol Approval Date:	**February 13, 2014**
Protocol Expiration Date:	**February 12, 2015**
Continuing Review Due Date*:	**January 29, 2015**

*Date a Continuing Review application is due to the IRB office if human subject activities covered under this protocol, including data analysis, are to continue beyond the Protocol Expiration Date.

FEDERALLY FUNDED RESEARCH REQUIREMENTS:

Per federal regulations, 45 CFR 46.103(f), the IRB is required to compare all federally funded grant proposals/work statements to the IRB protocol(s) which cover the human research activities included in the proposal / work statement before funds are released. Note that this requirement does not apply to Exempt and Interim IRB protocols, or grants for which VT is not the primary awardee.

The table on the following page indicates whether grant proposals are related to this IRB protocol, and which of the listed proposals, if any, have been compared to this IRB protocol, if required.

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