Digital Echocardiography in Manned Space Flight: Remote Diagnosis and Quantitative Analysis

Principal Investigator: James D. Thomas, M.D.

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Specific Aim #1: Develop the infrastructure for digital acquisition, storage, and transmission -- both terrestrial and by satellite -- of echocardiograms.

Co-Investigators: Neil L. Greenberg, PhD, Mario J. Garcia, MD

Project #1A: Evaluation of the Human Research Facility Ultrasound with the ISS Video System

As part of our ongoing collaboration with JSC engineering and flight surgeon personnel, we were involved in the design and analysis of a test of Real-time transmission of ultrasound data from the International Space Station utilizing the ISS communications simulator at Johnson Space Center. On August 4, 2000, the video base-band signal processor of the electronic system test laboratory was utilized to digitize the video output from the ATL HDI-5000 ultrasound system and simulate the transmission of this to ground-based personnel via the orbiter communication adapter TCP/IP backbone. This test evaluated the impact of reducing transmission rate on image quality, both as individual fields are dropped as well as reduced bit resolution of the image. Images were tested at rates from 60 fields/sec down to as low as 1.875 fields/sec. The following conclusions have been reached through collaborative evaluation of investigators in Cleveland and at Johnson Space Center, particularly Shannon Melton and Ashot Sargsyan, MD, both of Wyle Laboratories. For cardiac ultrasound, optimal results were obtained at field rates of 80 or above, although rates as low as 15/sec still provided much useful information. For the abdominal examinations, lower frame-rates could be tolerated, although rates of at least 15/sec were necessary to provide meaningful, Real-time guidance to the acquisition. For strictly diagnostic purposes, however, frame-rates below 7.5 fields/sec could be tolerated for nonmoving structures. The conclusion of this was that if such a implementation can be secured aboard the ISS, then ground guidance of ultrasonic acquisition should be possible in the event of a medical contingency involving crews that do not have expert training in ultrasound. The full test of this hypothesis, however, remains to be fully validated.

Project #1B: Launch of the HDI-5000 Ultrasound System Aboard Human Research Facility Rack 1 to the International Space Station

As part of our ongoing work with JSC engineering personnel, we have successfully upgraded the flight unit to software level 10.1 which will allow acquisition of Doppler tissue imaging as well as output of digital DICOM loops. In addition, we have worked closely to demonstrate the digital acquisition capabilities of commercial software programs that will be applicable for the HRF workstation for capturing digital images from the ultrasound system. Currently, the ultrasound system is undergoing Rack integration at Kennedy Space Center and is slated for launch on Flight 5A.1 in February 2001. Initial testing is slated to begin on the second increment beginning in April 2001, with research projects funded through NRA HEDS 99-03 for study of cardiac atrophy in space.

Project #1C: Consultation with NASA Personnel Regarding Ultrasound in Exploration Class Missions

On July 25 and 26, Dr. Thomas attended a meeting at Johnson Space Center regarding the use of ultrasound aboard exploration class missions to the moon and Mars. In a presentation to the assembled experts on diagnostic and therapeutic ultrasound, the plans for the International Space Station were reviewed as well as current clinical applications of echocardiography and cardiology were presented.

Project #2: Digital Echocardiography at the Cleveland Clinic

The goal of this project is to develop the infrastructure within the Cardiovascular Imaging Center of the Cleveland Clinic Foundation to review and analyze digital echocardiographic data whether collected in the primary echocardiographic laboratory, the outpatient laboratory in the Crile Building, the intra-operative environment, or from satellite locations such as the CCF facilities in Strongsville, Independence, and Beachwood, Ohio. Digital data acquisition has been made possible with recent acquisitions and upgrades of the laboratory's current echocardiographs (which include 7 ATL HDI5000s, 10 Acuson Sequoias, 1 Acuson Cyprus, 5 Agilent Sonos 5500s, and 3 GE/Vingmed Vivid FiVe). DICOM image storage is currently feasible with the ATL, Acuson, Agilent, and GE/Vingmed systems and we are also working to achieve these capabilities with machines from Toshiba and Aloka. Network transfer from these acquisition devices is possible for all but ATL, however this capability is expected soon. Digital echocardiographic data storage and retrieval is possible using the ProSolv Echo Management System from Problem Solving Concepts (Carmel, IN). DICOM studies can be transferred from DICOM compliant echocardiographs to a server running ProSolv Echo Server (v4.0.0.13) and ProSolv DICOM Server software. We are currently using a PowerEdge 4400 server (Dell Computer Corp., Round Rock, TX) with 1 GB RAM and 500 GB of local RAID storage. Current network transfers are on a restricted VLAN (subnet 62) within the Cleveland Clinic Campus. Network drops are available in each of the clinical echocardiographic exam rooms. These drops are connected to a Catalyst 5509 network switch (Cisco Systems, San Jose, CA) and are currently configured to support 10BT transfers. Average echocardiographic exams contain approximately 30 loops and 10 still images (2D plus spectral Doppler). Generally, each loop is a series of frames from a single cardiac cycle, although the definition can be expanded to multiple cycles if clinically required, i.e. atrial fibrillation. The server and the five primary review workstations are also connected to this switch at 100BT. The ProSolv review software (Echo Viewer v4.0.0.13) is installed on a variety of workstations with at least 512 MB of RAM. Queries can be made from these workstations and data transferred to the server. Transfer time from the echocardiograph to the server is device specific due to the storage architecture of the machine and the compression settings selected. The Sequoia (Acuson, Mountain View, CA) stores data to an internal hard disk in a JPEG compressed DICOM format. The user has the ability to configure the degree of compression for loops (low, medium, high). Transfer to the server can be initiated with a single key press at the conclusion of the study or data can be streamed out a clip at a time during the study. The Sonos 5500 (Agilent Technologies, Andover, MA) also stores data to an internal hard disk, but not in a DICOM format. Their Integrated Digital Interface (IDI) option is required for DICOM connectivity. Data transfer to the server is automatically initiated when the study has ended. The user has the ability to configure the type and degree of compression for loops and stills (compression: none, RLE, JPEG; degree of compression controlled by a quality factor 0-100). The HDI-5000 (ATL Ultrasound, Bothell, WA) with the Digital Video Streaming package also stores DICOM data to an internal hard disk, but currently JPEG compressed images can only be copied to optical media for sneaker-net transfer. The GE/Vingmed Vivid FiVe offers a DICOM mode in which polar scanline data is transferred for each clip from the scanner to the EchoPac environment where DICOM files are created (including scan conversion and compression). These files are transferred from EchoPac to the server at the conclusion of the study. The user has the ability to configure the type and degree of compression for loops and stills (compression: none, RLE, JPEG; degree of compression controlled by a quality factor 0-100) as well as their physical size (full, half, quad). Average study transfer times are shown below in **Table 1**. Study retrieval times from the server (including decompression) are approximately 1 MB/s. Long-term storage is currently feasible using a PowderHorn tape library (StorageTek, Louisville, Colorado). The library will hold up to 6,000 20GB cartridges. An archive utility from Problem Solving Concepts performs a scheduled backup of daily studies to the tape archive. This can currently be performed using the standard file transfer protocol (FTP) or through a network file system (NFS) connection. The utility also automatically removes studies from local storage that have been previously archived. Average access time to retrieve a study from the deep archive (StorageTek tape archive) is 2 minutes 20 seconds although the range for access is between 1.5 and 4.5 minutes. The mean transfer rate (including tape mounting and data transfer) is 0.40 MB/s. Over 11,000 echocardiographic studies during the past six months have been transferred through a network switch. We currently store and archive approximately 120 studies per day. Average study size is ~42 MB and the daily volume is greater than 5 GB of data per day. We have also recently demonstrated the feasibility of applying digital echocardiography to core lab projects. Our research lab (core lab) serves as a centralized site for standardized review of echocardiographic images for many large multi-center studies. Traditionally, these echocardiographic studies are sent on conventional super-VHS videotape (which has already suffered some degree of image degradation secondary to the tape duplication process) using overnight express mail. Each step in this process is time consuming and expensive. We have recently validated the process of using Internet technology to transfer digital echo images, without any loss of image quality, to our center. We have shown this process, in addition to preserving image quality, to be much more cost and time efficient – factors particularly important when critical patient care decisions need to be made.[1]

Echocardiograph	Transfer Rate (MB/s)
Acuson Sequoia	0.40
Agilent (HP) Sonos 5500	0.10
ATL HDI-5000	0.15
GE/Vingmed System FiVe	0.06

Table 1: Transfer characteristics from various echo machines

Project #3: Acquisition of Echocardiogram by Novice Operators

Once ISS assembly is complete, it is anticipated that dedicated science acquisitions from the ultrasound system will be performed by highly trained crewmembers. In the interim, however, astronauts involved in the assembly stage of the ISS will have only very basic training in the operation of the HDI-5000, and reassurances must be given that they will have sufficient ability to perform contingency examinations in the case of a medical emergency. To test the hypothesis that novice operators can perform diagnostic ultrasound studies, we have undertaken a clinical trial at The Cleveland Clinic at the request of Dennis Grounds, Manger for the Human Research Facility. In this study, five employees of The Cleveland Clinic Foundation without prior training in ultrasound examination have received four hours of focused training before attempting examinations with the HDI-5000. All operators performed exams on normal subjects and patients with defined pathology. For the normal subjects, images acquired included the apical four-chamber cardiac image for left ventricular size and function by 2-D imaging, presence and magnitude of mitral regurgitation by color Doppler, and mitral flow propagation by color M-mode Doppler. For general ultrasound imaging, they obtained a right upper quadrant image for gallbladder visualization and wall thickness assessment, right flank imaging for kidney size (**Figure 1**) and presence of hydronephrosis, color Doppler guided pulsed Doppler assessment of the right femoral artery, and short axis images of the right femoral and popliteal veins obtained with and without compression by the transducer. The patients recruited included ones with mitral regurgitation, left ventricular dysfunction, gallstones, renal or bladder calculi, and deep venous thrombosis. Although complete analysis is still ongoing, preliminary analysis demonstrates excellent capability for general imaging by these novice operators, with acceptable image acquisition using cardiac ultrasound but only when guided in real-time by an expert sonographer. Echocardiographic images were digitally stored from each patient by both the novice operator as well as the experienced sonographer. The following views were analyzed (**Table 2**) by the experienced sonographer: 2D apical chamber views, pulsed tissue Doppler velocities from the lateral mitral annulus, pulsed and color M-mode Doppler of left ventricular filling, and pulsed Doppler velocities through the LVOT. No significant differences in LV volumes, flow propagation velocities, and tissue Doppler velocities were observed. In a recently formed collaboration with MetroHealth Medical Center LifeFlight (the busiest civilian medical helicopter transport organization east of the Mississippi river), we have started preliminary training and utilization of echocardiography during the transport of critically ill cardiac and trauma patients. This application has extremely broad implications in not only simulating the adverse conditions that may be encountered aboard the ISS/Space shuttle but also may have a major role in the emergent assessment of potentially life threatening injuries sustained during military encounters (particularly in remote regions not served by major medical centers).

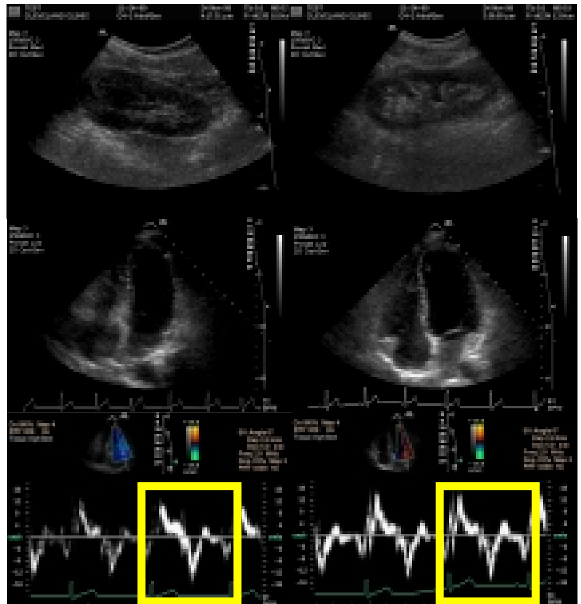

Figure 1: Comparison of novice (left) and expert views (right) of the kidney (top), left ventricle (middle), and mitral annular velocities (bottom) [note: box indicates one cardiac cycle]

Measurement	Novice Image	Expert Image
LV ESV (mL)	33.7 ± 7.5	34.3 ± 2.1
$LVOT_{VTI}$ (cm)	17.5 ± 2.1	16.5 ± 2.0
E' (cm/s)	14.8 ± 2.1	13.4 ± 2.6
v_p (cm/s)	46.7 ± 8.7	47.0 ± 6.6

Table 2: Quantification of echocardiographic variables from images obtained by novices and experts

Specific Aim #2: Test existing and novel digital compression algorithms for their impact on clinical interpretation and quantitative content.

Co-Investigators: Neil L. Greenberg, PhD, Mario J. Garcia, MD

Project #1: Collaboration with Medical Operations Personnel on the Project, "Validation of Technologies and Operations Concepts for Exploration Class Medical Operations Using the Haughton Mars Project (HMP) Testbed on Devon Island"

In collaboration with Drs. Jeffery Jones, Scott Simmons, Doug Hamilton, and other NASA engineers and flight surgeons, we participated in a blinded review of echocardiographic data contained at the Devon Island site, where a research base was established this summer as part of the ongoing Haughton Mars Project. These echocardiograms were obtained with a SonoHeart portable ultrasound device and were digitized using a field-hardened PC and stored in MPEG2 format. The individual files were then relayed via the TDRSS geosynchronous satellite system down to Johnson Space Center and then routed to The Cleveland Clinic for our review. This examination demonstrated excellent image quality, particularly for the abdominal structures, with adequate image quality on the cardiac structures, particularly after some coaching regarding image orientation. Although by design, there was at least a forty-minute delay built in to this transmission to mimic the worse case scenario of a communication from Mars, we felt that diagnostic data were obtained, even though Real-time guidance was not possible. Also as part of this examination, five pathological cases from The Cleveland Clinic were selected by Dr. Mario Garcia and forwarded to the Haughton Mars Project for retransmission along with the normal echoes. These were then interpreted by Dr. Thomas, who successfully identified all key pathological features on these examinations, even after retransmission. Overall impression was that this examination was considered quite promising for future use of portable ultrasound systems in exploration class missions.

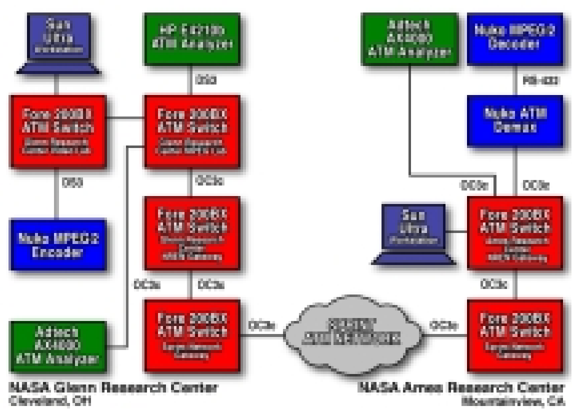

Figure 2: Echocardiographic data across NREN test configuration

Project #2: Transmission of Echocardiographic data across NREN (in collaboration with NASA Lewis and Ames)

(8/28/97) Live ultrasound transmitted at 2-5 Mbps via ATM using MPEG compression with varying cell loss and cell error ratios:

For this demonstration, a sonographer and cardiologist were present at the NASA Lewis facility in Cleveland, performing an echocardiographic study and playing it over the NASA Research and Education Network (NREN), using ATM protocol and MPEG-2 encoding (**Figures 2 and 3**). At

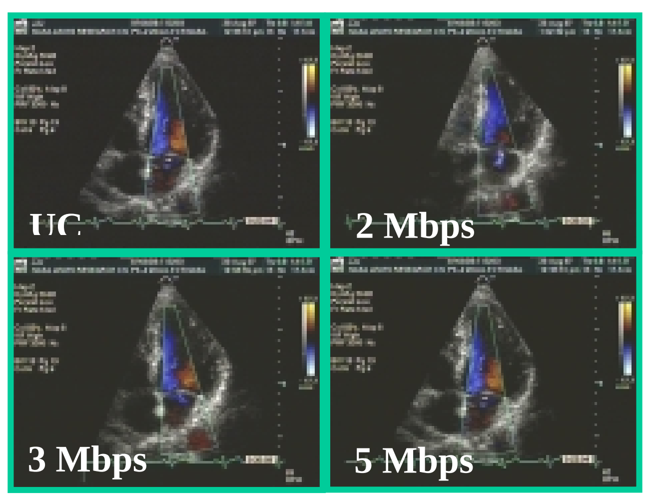

Figure 3: Echocardiographic images transmitted real-time using varying compression ratios. (UC: Uncompressed)

cell loss and cell error ratios of 10^{-5}, performance was nominal, with image quality far superior to videotape. When cell loss and cell error ratios rose to 10^{-3}, the system froze, but this represents an extreme degree of the network noise (**Table 3**). Using a two-way audio link, Dr. Thomas in California was able to guide the acquisition of the echocardiogram in Cleveland, a model for future guidance of acquisition aboard the International Space Station.

Cell Error Rate (CER)	Transmission rate (Mbps)			
	5	4	3	2
0	1	1	1	2
$1x10^{-9}$	1	1	1	2
$1x10^{-7}$	1	1	1	2
$1x10^{-5}$	2	2	1	2
$1x10^{-3}$	3	3	3	3

Table 3: Impact of transmission rate and cell error rate (CER) on image quality: 1, optimal; 2, usable; 3, marginal; 4, unusable

<u>(9/14/97) Demonstration at NREN Conference (Ames) of live echo transmission from Lewis:</u>

Dr. Thomas delivered a plenary address to this conference on echocardiographic transmission across the Next Generation Internet and then supervised the echocardiographic demonstration. This was very well received, and was voted the best demonstration of the conference.

<u>(3/11/98) Demonstration of NREN transmission of an echocardiogram to the Netamorphosis conference in Washington D.C.:</u>[2]

This demonstration was featured in the opening gala event for the conference, with attendance by members of the presidential advisory panel for the Next Generation Internet and several members of Congress, including Senators Bill Frist, Jay Rockefeller, and Bob Kerrey.

Project #3: Virtual Hospital Project

In collaboration with Dr. Muriel Ross and the NASA Ames Research Center (ARC) Center for Bioinformatics, a virtual hospital demonstration has been performed between NASA Ames, Stanford University, Salinas Community Hospital, and the Navajo Indian Reservation, and the Cleveland Clinic showing feasibility for high bandwidth (50-622 Mbps) telemedicine between remote clinics and tertiary care hospitals. Among the planned activities is real-time transmission of three-dimensional echocardiograms acquired at the Cleveland Clinic and rendered in the Biocomputation Laboratory at Ames. The "Virtual Collaborative Clinic" application combines highly sophisticated medical imaging with high-performance, high-speed networking. Doctors can receive and rotate 3-D high-resolution 24-bit color stereo medical images, working online from their desktops. They can collaborate in near real-time with remote colleagues for consultation, diagnosis and treatment planning. Using a "CyberScalpel," doctors can also "cut" into images and move "bone" around for surgical simulation. The 3-D images are constructed from serial sectional images of tissues and organs obtained from electron microscopy, CT, or MR1 scans.

High-performance networks, including the NASA Research and Education Network (NREN), the National Science Foundation's Very High Performance Backbone Network Service (vBNS), Abilene, and the California Research and Educati6n Network (CaIREN2) connect participating Virtual Collaborative Clinic sites with the application server at ARC. Sites include Stanford University, the University of California at Santa Cruz Winas Valley Memorial Hospital, NASA Glenn Research Center (GRQ/Cleveland Clinic Foundation in Ohio), and the Northern Navajo Nation Medical Center in Shiprock, New Mexico, which is connected to the Virtual Collaborative Clinic via satellite from GRC. The application server is a high-end Silicon Graphics Onyx2 located at NASA ARC. Real-time collaboration is enabled by bi-directional network connections. During the collaborative session any participant, whether local or remote, may rotate the image to view it from different perspectives; participants at the other sites will see the same display. Distribution of the 3-D Virtual Collaborative Clinic images among widely dispersed sites requires high-performance networking. Major technological challenges include providing data transmission to multiple sites, minimizing latency, synchronizing the displays of large 3-D image data sets at the end sites, and accommodating satellite/terrestrial networks on disparate platforms. Both QoS and advanced multicast technologies are critical for successful prototyping of this application. Future research will focus on refining the use of these technologies to enhance application performance.

The Virtual Collaborative Clinic will "bring the clinic to the patient" via high performance networks, thus enabling rural and underserved communities to share in the benefits of advanced medical technology. Physicians and scientists will use multimedia in a distributed network to plan and practice delicate operations in virtual space. Digital libraries of virtual patients will allow doctors to share information about rare procedures and provide a powerful teaching tool for future generations of physicians. Remote hospitals will be able to access the knowledge, skills and techniques of larger institutions. The ultimate long-term goal is to extend the Virtual Collaborative Clinic technology into space to service future astronauts on the Space Station and beyond.

Initial demonstration of the Virtual Collaborative Clinic occurred on May 4, 1999, uniting the Cleveland Clinic, Stanford, Salivas, and Shiprock in consultation on cases involving coronary artery disease, congenital ventricular septal defect, and craniofacial deformation.

Project #4: Echocardiographic Image Compression

In collaboration with Rush-Presbyterian Medical Center in Chicago, a study has been performed demonstrating the clinical capability of MPEG recorded echocardiograms.[3] We have continued to investigate the use of MPEG compression and its effect on quantitative measures.[4] Six reviewers performed blinded measurements from still frame images selected from 20 echocardiographic studies simultaneously acquired in s-VHS and MPEG-1 format. Measurements were obtainable in 1401 of 1486 (95%) MPEG-1 variables vs. 1356 of 1486 (91%) sVHS variables ($p < 0.001$). There was excellent agreement between MPEG-1 and sVHS 2-dimensional linear ($r = 0.97$, MPEG-1 = 0.95sVHS + 1.1 mm, $p < 0.001$, $\Delta = 9 \pm 10\%$), 2-dimensional area measurements ($r = 0.89$), color jet areas ($r = 0.87$, $p < 0.001$) and Doppler velocities ($r = 0.92$, $p < 0.001$). Interobserver variability was similar for both sVHS and MPEG-1 readings. Our results indicate that quantitative off-line measurements from MPEG-1 digitized echo studies are feasible and comparable to those obtained from sVHS.

Xiyi Hang (OSU BME graduate student) is investigating the use of wavelet compression of echocardiographic data. We have investigated the application of the wavelet transform to 2D sequences of image data derived from digital subtraction of consecutive frames. Images were divided into primary (P) and delta (Δ) frames, with the image content of each Δ frame defined as the difference from the previous P frame. The ratio of P:Δ frames and the percentage of wavelet coefficients retained have been investigated. SNR and CR were computed for P:Δ ratios. A strategy that exploits the spatiotemporal redundancy of echocardiographic data may be utilized to maximize CR while preserving data for clinical interpretation. A wavelet compression algorithm utilizing difference image data (1P:4Δ) results in a CR of nearly 100:1 and an improved SNR (P: 36.5±0.05, Δ: 32.4±0.13 dB) compared with JPEG (31.96±0.10 dB, CR=20:1). More recently this approach has been extended using a 3-dimension wavelet transform for the compression of echocardiographic sequences.[5,6]

Specific Aim #3: Validate new quantitative approaches (Color Doppler M-mode echocardiography and Doppler Tissue Imaging [DTI]) to assess cardiovascular mechanics in microgravity.

Co-Investigators: Mario J. Garcia, MD, Neil L. Greenberg, PhD

The overall purpose of this work is to investigate new quantitative methodology for the assessment of left ventricular systolic and diastolic function. While this work is aimed directly at validating new echocardiographic methods for use aboard the International Space Station, all of this work is highly relevant to cardiology diagnostic methods on earth, both as pertains to patient care and in improving our understanding of cardiac pathophysiology. With our large team of engineers and clinical researchers, we have made significant progress in both basic and applied aspects of this work. Simultaneous acquisition of Hemodynamic and Doppler data has been obtained in over 50 patients in the OR and catheterization laboratory.

Project #1: Color M-Mode Assessment of Left Ventricular Diastolic Function

Color Doppler M-mode echocardiography has been utilized to determine the influence of ventricular relaxation and preload on diastolic flow propagation and estimate both transmitral and intraventricular pressure differences using the Euler equation. This modality provides a spatiotemporal description of ventricular filling that preserves the temporal resolution of pulsed Doppler and provides an additional spatial distribution of velocities along an ultrasound scanline. Simultaneous acquisitions of color M-mode velocity distributions and diastolic filling pressures, using multisensor micromanometer catheters (Millar, Houston, TX), allow for an instantaneous analysis of the pressure-velocity relationship (**Figure 4A**).[7] The Euler equation describes the spatial pressure distribution (δp/δs) along an inflow streamline and can be solved using the spatiotemporal velocity distribution and differentiation with respect to space and time (**Figure 4B**). In contrast to standard Doppler indices, we have shown that the early diastolic flow propagation velocity (v_p) is a relatively preload independent index of LV filling.[8] In both canines and humans, we found strong relationships between ventricular relaxation (τ)

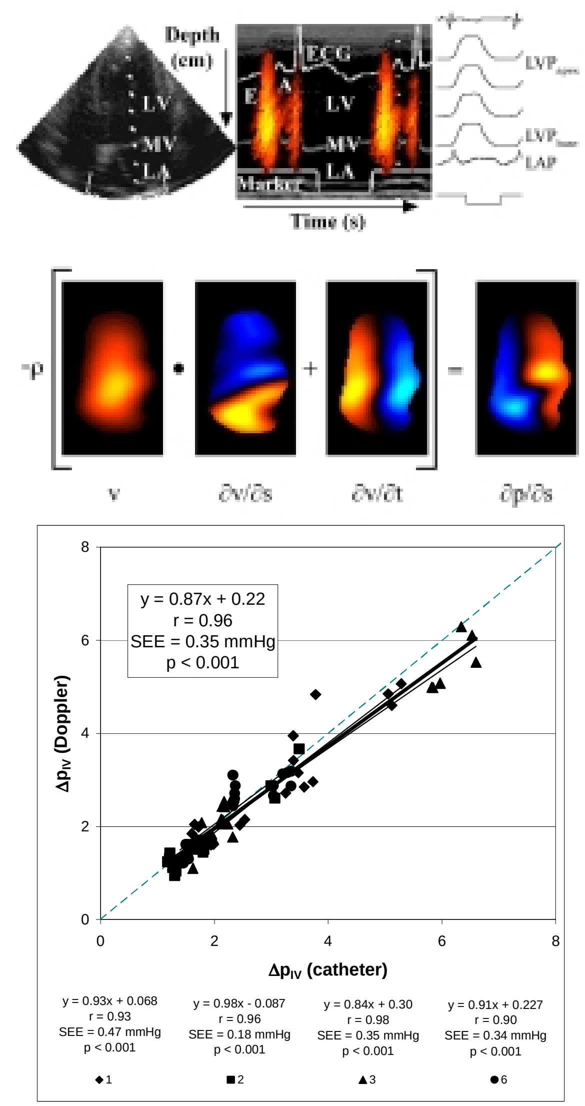

Figure 4: (A) Color M-mode of left ventricular filling with simultaneous hemodynamics; (B) Graphic solution to the Euler equation to estimate pressure differences; (C) Noninvasive assessment of intraventricular pressure differences: Comparison with direct measurements

and v_p (r=-0.78, p<0.001). We have also shown that transmitral[9,10] (ΔP_{MV}) and intraventricular[11] ($\Delta P_{IV;}$ **Figure 4C**) pressure differences can be estimated noninvasively in both canines and humans using the Euler equation.[12] We have also validated the application of a simplified version of the Euler equation to estimating these pressure gradient which represents a technique that may be easier to adapted to clinical use initially due to it's simplicity and need for less sophisticated analysis tools.[13] Noninvasive approaches for diastolic assessment have been limited due to the lack of velocity information, difficulty and subjectivity of measurements, and because extracted parameters are only *indirectly* related to diastolic function. Color M-mode echocardiography provides a spatiotemporal description of ventricular filling that preserves the temporal resolution of pulsed Doppler and provides an additional spatial distribution of velocities along an ultrasound scanline.

Our research efforts have focused on three aspects of ventricular filling: (1) determining the influence of LV relaxation and preload on the color M-mode flow propagation velocity [v_p], (2) estimating transmitral and intraventricular pressure differences using the Euler equation, and (3) interpreting the relationship between regional LV relaxation and the intraventricular pressure gradient. Simultaneous acquisitions of color M-mode velocity distributions and diastolic filling pressures allow for an instantaneous analysis of the pressure-velocity relationship. Spatiotemporal velocity distributions are processed from digital echocardiographic image files and left atrial and ventricular pressure waveforms are recorded using Millar multisensor micromanometer catheters.

Preload was varied in animal investigations using caval balloon occlusions and in patients with a low flow cardiopulmonary bypass condition. As expected, LA pressure decreased significantly during the low flow state as compared to baseline and τ remained relatively constant (67.9±25.0 vs. 60.7±15.6 ms, p=0.21). While the peak E-wave velocity decreased significantly during the low flow state (70±16 vs. 52±24 cm/s, p<0.03), v_p extracted using eigenvector analysis or isovelocity contouring was not significantly altered (33.1±10.1 vs. 28.3±11.9 cm/s, p=0.16). In both canines and humans, we found strong relationships between τ and v_p (r=-0.78, p<0.001).

The Euler equation describes the spatial pressure distribution ($\delta p/\delta s$) along an inflow streamline. Data obtained during intraoperative studies shows that the Euler equation allowed accurate estimation of ΔP_{MV} (y=0.95x+0.24, r=0.96, ε=0.08±0.54 mmHg) as compared to the simplified Bernoulli equation (y=0.31x+0.69, r=0.72, ε=-1.70±1.39 mmHg). Intraventricular pressure differences (Δp_{IV}) represented 71.1±12.6% of the total pressure difference (2.58±0.66 mmHg) from the atrium to the left ventricular apex in a series of animal experiments. The error between invasive and noninvasive estimates of Δp_{IV} was 0.03±0.29 mmHg. We have also examined the relationship between the pressure distribution and regional relaxation (τ at the LV apex and base).

In contrast to standard Doppler indices, we have shown that Color M-mode flow propagation velocity (v_p) is a relatively preload independent index of LV filling. We have also shown that transmitral (ΔP_{MV}) and intraventricular (ΔP_{IV}) pressure differences can be estimated noninvasively in both canines and humans using the Euler equation, demonstrating the importance of inertial contributions.

Project #2: Assessment of Ventricular Function using Doppler Tissue Imaging

Doppler tissue imaging (DTI) is another new methodology available for the assessment of cardiac function. In contrast to regular Doppler imaging, Doppler tissue imaging records the velocity of myocardial motion rather than blood flow.

To investigate the preload (in)dependence of DTI, we have obtained data from both patients and animals. We evaluated data from 30 patients with renal failure immediately before and after dialysis. These results demonstrated significant changes in the transmitral filling indices, but little or no change in the DTI systolic and diastolic velocities. We have also investigated the influence of preload under varying inotropic-lusitropic conditions in an animal model. In these experiments we used vena cava balloon occlusions under different conditions (baseline, esmolol, dobutamine) and measured diastolic early filling velocity (E') in the septal region of the mitral annulus and evaluated these data with the corresponding end-diastolic pressures (EDP) and volumes (EDV). Least squares linear regression analysis was performed to determine the relationship between changes in E' and changes in preload. Similarly, these E'/EDP and E'/EDV slopes where analyzed as a function of the time constant of ventricular relaxation (tau). Following caval occlusion, under baseline conditions, E' decreased with both EDV (range: 0.001 to 0.234 cm/sec/ml average: 0.080±0.085 cm/sec/ml) and EDP (range: -0.045 to 0.619 cm/sec/mmHg, average: 0.202±0.274 cm/sec/ml). Similar changes were observed during dobutamine (E'/EDV: range: 0.04 to 0.30 cm/sec/ml, average: 0.11±0.08 cm/sec/ml; E'/EDP: range: 0.04±1.21 cm/sec/mmHg, average: 0.43±0.33 cm/sec/mmHg) and esmolol (E'/EDV: range: 0.01 to 0.06, average: 0.04±0.017; E'/EDP: range: -0.05 to 0.25, average: 0.09±0.09) infusions. Overall, dE'/dEDP and dE'/dEDV decreased with increasing tau ($y = -0.011x+0.9$, $r=0.71$ and $y = -0.0023x+0.21$, $r=0.61$ respectively). Early diastolic myocardial tissue velocities are preload dependent, but this dependency is inversely related to ventricular relaxation.[14]

Strain Rate Imaging is a new modality derived from tissue color Doppler imaging. Strain rate can be estimated as the spatial derivative of velocities (dv/dt) obtained by tissue Doppler echocardiography (TDE). Such data demonstrate the thickening between any two points in the heart and holds out the promise of a translation-independent method of assessing wall motion. At the Cleveland Clinic Cardiovascular Imaging Center, we have been evaluating two different systems for strain rate imaging. Utilizing the GE/Vingmed ultrasound system, we have analyzed polar (scan line) data to evaluate the utility of strain rate imaging in coronary artery disease. We noted significantly lower myocardial strain in areas of the infarction than in normal territory.[15] To extend the utility of strain rate imaging to raster-based output maps, we have developed software within the LabVIEW environment to calculate the spatial derivative of velocity. This has been applied to investigate patients with hypertrophic cardiomyopathy and has demonstrated dramatically lower strain rates at the base of the heart with compensatory hypercontraction at the apex of the heart.[16,17,18]

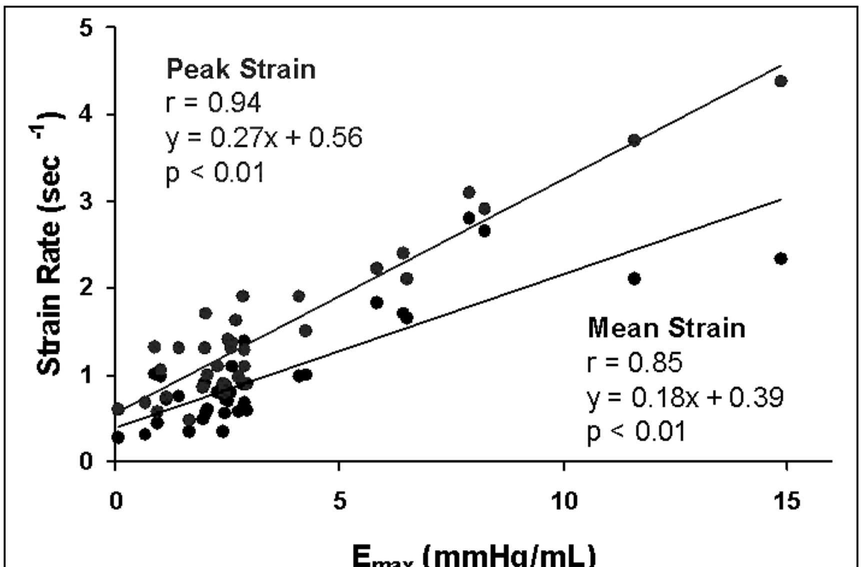

Figure 5: Relationship between strain rate and elastance

We have also investigated the relationship between myocardial systolic strain rate and LV contractility in an animal model.[19] TDE color M-mode images of the interventricular septum were recorded from the apical 4-chamber view during 5 different inotropic stages. Simultaneous LV volume and pressure were obtained with a combined conductance-high fidelity pressure catheter. Peak elastance (E_{max}) was determined as the slope of end-systolic pressure-volume relationships during caval occlusion and used as the gold standard of LV contractility. Peak systolic TDE myocardial velocities (Sm) obtained at the basal septum, peak (ε_p) and mean (ε_m) strain were compared against E_{max} by linear regression. Results indicate that TDE derived ε_p and ε_m are strong noninvasive indices of LV contractility (**Figure 5**). These indices appear to be more reliable than Sm, perhaps by eliminating translational artifact. Furthermore, we have recently demonstrated that non-invasively derived strain rate measurements may be a more sensitive marker for acute myocardial ischemia then other non-invasive echocardiographic (i.e end-diastolic volumes and ejection fraction) and even invasive indices (i.e +dp/dpmax, end-diastolic pressures, tau)[20].

Project #3: Estimation of Left Ventricular Operating Stiffness from Doppler Early Filling Deceleration Time

A shortened early transmitral filling deceleration time (E_{DT}) has been qualitatively associated with increased filling pressure and reduced survival in patients with cardiac disease and increased left ventricular operating stiffness (K_{LV}). An equation relating K_{LV} quantitatively to E_{DT}, has previously been proposed and validated in a canine model. To determine whether E_{DT} might be used to quantitatively estimate K_{LV} in humans, we studied 18 patients undergoing open-heart surgery during several varying hemodynamic conditions.[21] Transesophageal echocardiographic (TEE) 2-D volumes and Doppler flows were combined with high fidelity LA and LV pressures to determine LA operating stiffness (K_{LA}) and K_{LV}. From digitized Doppler recordings, E_{DT} was measured and compared against changes in LV and LA volumes and pressures during diastole. A shorter E_{DT} (180 ± 39 ms) was associated with higher LV end-diastolic pressure ($r = -0.56$, $p = 0.004$) and net atrio-ventricular stiffness ($r = -0.55$, $p = 0.006$) but had its strongest association with K_{LV} ($r = -0.81$, $p<0.001$). Based on the previous analytical equation, K_{LV} was predicted from E_{DT} as $K_{pred} = (0.07/E_{DT})^2$. For 50 hemodynamic stages in these 18 patients, $K_{LV} = 1.01K_{pred} – 0.02$, $r = 0.86$, $p < 0.001$, ΔK ($K_{pred} - K_{LV}$) = 0.02 ± 0.06 mmHg/ml (**Figure 6**). These results indicate that in adults with cardiac disease, E_{DT} provides an accurate estimate of LV operating stiffness and support its application as a practical non-invasive index in the evaluation of diastolic function.

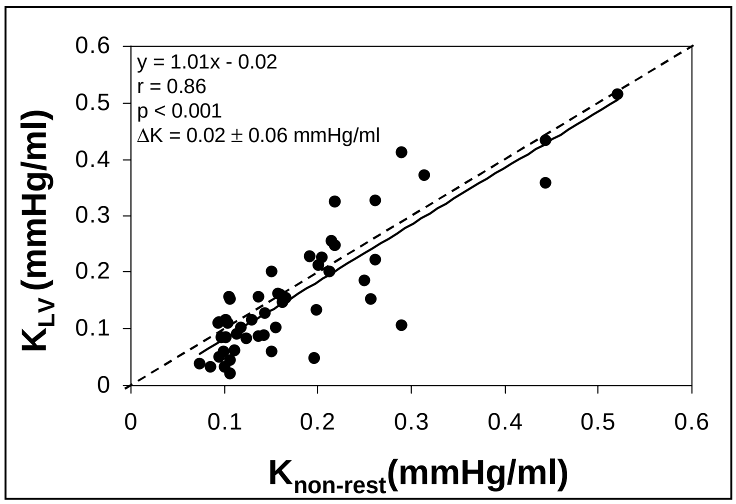

Figure 6: Assessment of LV operating stiffness

Project #4: Characterization of Pulmonary Venous Inertance

As part of our overall theme of defining the fundamental physical components governing fluid dynamics within the heart, we have endeavored to determine the inertial component of pulmonary venous flow, so as to better interpret clinical recordings of flow in those veins. This work has demonstrated that pulmonary venous flow is primarily governed by inertial forces with relatively little convection or viscous effects.[22]

Project #5: Bed-Rest Studies

We have begun collaborating with investigators from the National Space Biomedical Research Institute to validate the use of the above load independent indices of cardiac function in manned space flight. Our initial collaboration involves a series of bed rest studies at the Brigham Hospital in Boston, MA. Subjects undergo 14 days of 4° head-down bedrest with three subsequent days of study during recovery. Among the investigations that we are directing are the acquisition of exercise echocardiographic data pre and post bed rest, acquisition of DTI mitral annular velocity pre and post bed rest and acquisition of color M-mode flow propagation. In addition, left ventricular volumes and cardiac output are measured as is brachial reactivity is assessed for possible changes intravascular tone. A total of five patients have been studied to date, with a total of 12 anticipated over the next year.

Another collaboration involves work with Dr. Benjamin Levine at the University of Texas-Southwestern in Dallas. Dr. Levine has conducted numerous bed rest and flight-based experiments, and we are beginning to analyze color M-mode data from the bed rest studies being conducted in Dallas. This work is directed at determining whether there is a functional consequence to the atrophy that appears to occur during prolonged space flight and bed rest. To further this investigation, in collaboration with Dr. Levine (Institute for Exercise and Environmental Medicine, Dallas, TX), a revised grant application for Space Life Sciences has been submitted in response to NRA 99-HEDS-03. The title of the project is Cardiac Atrophy During and after Long Duration Spaceflight: Functional Consequences for Orthostatic Intolerance and Risk of Cardiac Arrhythmias.

Further collaboration with Dr. Ben Levine, utilizing the results of bed-rest experiments, has validated the application of combined echocardiographic indices for the assessment of left ventricular filling pressures in healthy volunteers (**Figure 7**).[23] While we have previously validated these indices in acutely ill patients with known heart disease,[24] validation of these techniques for the assessment of this important index of left ventricular function in otherwise healthy individuals can be of significant important in the non-invasive (and remote) assessment of crew health and response to manned spaceflight.

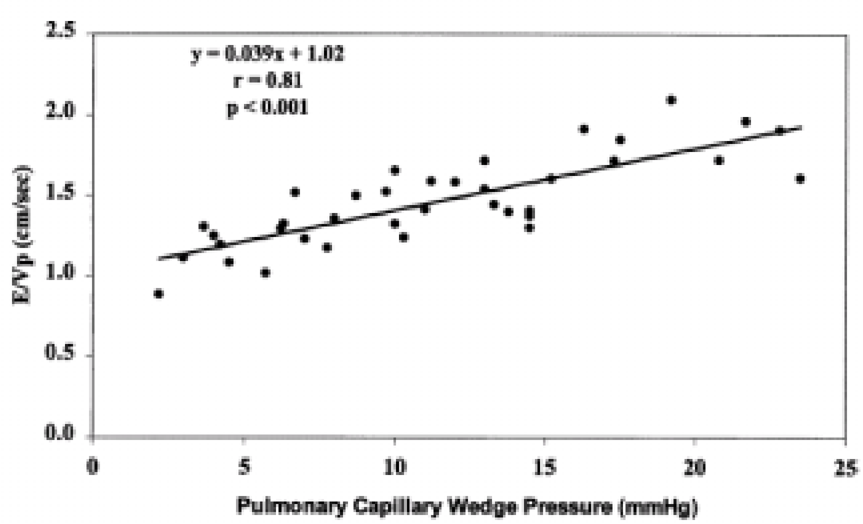

Figure 7: Relationship between echo indices of LV filling and wedge pressure

Specific Aim #4: Refine the acquisition, segmentation, display and analysis of three-dimensional echocardiograms.

Co-Investigator: Takahiro Shiota, MD

The general purpose of this work is to investigate the impact of a real-time 3-dimensional ultrasound imaging system for evaluating human cardiovascular physiology and pathology. The entire work is aimed directly at validating a new real-time 3D echocardiographic method that may be used aboard the International Space Station in the future. Real-time 3D ultrasound system has several unique advantages over currently available 2D ultrasound imaging systems; First, the imaging of the entire heart in 3D space is very fast (3 seconds) and does not require special training or expertise. Second, heart chamber size, volume and myocardial mass, can be determined without any geometrical assumptions. Considering the effect of microgravity on heart chamber mass, this capability cannot be emphasized too much. In addition, once the 3D images of the heart are acquired digitally in the Space Station, the same 3D data set can be transferred digitally from the Space Center to clinical imaging centers such as the Cleveland Clinic, where analysis of the imaged heart an be performed. The original 3D ultrasound system was large and heavy. However, the weight has been reduced from 800 to 600 lbs over the past year without losing any quality of the system. In this new lighter system, the ability to obtain blood flow velocity in 3D space, which we call color Doppler 3D flow mapping, has been added. Blood velocity information in 3D space have provided more comprehensive understanding of human cardiovascular phenomena, including intraventricular and left ventricular outflow tract blood flow velocity patterns. Such new 3D blood flow information may shed light on the change in blood flow distribution under the microgravity. With our team of engineers and clinical researchers, we have made significant progress in both basic and applied aspects of this particular specific aim.

<u>Human Studies</u>: A total of 813 patients with a variety of cardiac diseases have been examined by real-time 3-dimensional echocardiography (Volumetrics Medical Imaging, Durham, NC) at the Cleveland Clinic since September 1997. In almost all the patients who underwent real-time 3D studies, left ventricular (LV) absolute volumes, end-diastolic and end-systolic LV volumes, were determined without any geometrical assumptions. Also stroke volumes and ejection fractions were determined.

Project #1: Validation with MRI: We validated the 3D ultrasound method for determining absolute LV volumes using magnetic resonance imaging (MRI) in patients with cardiomyopathy.[25] A total of 34 patients were evaluated with the real-time 3D method in the operating room (n = 15) and in the echocardiographic laboratory (n = 19). Thirteen of 28 patients with cardiomyopathy and 6 other subjects with normal LV function were evaluated by both real-time 3D echocardiography and MRI for obtaining LV volumes and ejection fractions for comparison. There were close relations and agreements for LV volumes ($r = 0.98$, $p < 0.0001$, mean difference = -15 ± 81 ml) and ejection fractions ($r = 0.97$, $p < 0.0001$, mean difference = 0.001 ± 0.04) between the real-time 3D method and MRI when 3 cardiomyopathy cases with marked LV dilatation (LV end-diastolic volume > 450 ml by MRI) were excluded. In these 3 patients, 3D echocardiography significantly underestimated the LV volumes due to difficulties with imaging the entire LV in a 60° x 60° pyramidal volume. Thus, real-time 3D echocardiography is feasible in patients with cardiomyopathy and may provide a faster and lower cost alternative to MRI for evaluating cardiac function in patients.

Project #2: Structure and motion of the mitral annulus: In other human studies, we have assessed mitral valvular abnormalities, which have complex geometry. In this study, new computer software was developed to obtain segmentation of the mitral annulus using commercially available 3D echocardiographic review software (EchoTech). This new software has been utilized to extract 2D planes rotated about the central axis of the left ventricle. Annular hinge points on each of 9 2D planes (separated by 20 degrees) throughout the cardiac cycle are extracted and mitral annular area, annular excursion, and nonplanarity of the annulus can be quantified. In a group of patients who previously had mitral valve repair surgery, we found that mitral valve geometry 5 years after the surgical repair has been maintained with the assistance of an annuloplasty Cosgrove ring. This study was published in the Annuls of Thoracic Surgery in 2000.[26]

Project #3: Evaluation of outflow obstruction in hypertrophic cardiomyopathy: In addition, blood flow obstruction in the left ventricular outflow tract in patients with hypertrophic obstructive cardiomyopathy has been assessed by real-time 3DE. The new 3DE has provided superior capability for assessing morphological and hemodynamic abnormalities encountered in those patients as compared to conventional 2D ultrasound methods.[27] This figure demonstrates a 1/x relationship between LVOT velocity and LVOT area.

Project #4: Volumetric changes with simulated microgravity: We also studied cardiac function using a tilting bed system, mimicking microgravity in 10 normal subjects employing real-time 3DE. Stroke work of the left ventricle is different under microgravity conditions as compared to normal gravity conditions. Other hemodynamic indices such as ejection fraction and LV volume are also investigated under both conditions. This study was presented in November at the 73rd meeting of the American Heart Association in Atlanta.[28]

<u>Animal Experiments</u>: Through collaboration with Dr. Michael Jones in the Laboratory of Animal Surgery and Medicine at the National Institutes of Health we have conducted several series of animal investigations to address the accuracy of LV volume measurements and flow quantification using real-time 3D echocardiography.

Project #1: Aortic regurgitation - quantification and functional significance: In one of these collaborative works, we investigated the accuracy of 3D LV volume measurements in animals with aortic regurgitation (AR) along with 2D automated digital analysis of blood flow (ACM) employing electromagnetic flow probes and meters (EM) as a reference method. In 8 sheep, a total of 26 hemodynamic states were obtained pharmacologically 14 weeks after the aortic valve non-coronary ($n = 4$) or right coronary ($n = 4$) leaflet was incised to produce AR. Reference standard LV stroke volume (SV) and AR volume were determined using EM. Simultaneous epicardial real-time 3DE studies were performed to obtain LV end-diastolic volumes (LVEDV), end-systolic volumes (LVESV) and LVSV by subtracting LVESV from LVEDV. Simultaneous ACM was performed to obtain LVSV and transmitral flows; AR volume was calculated by subtracting transmitral flow volume from LVSV. An excellent relationship was found between LVSV derived from EM and those from the real-time 3DE ($r = 0.93$, $p < 0.001$, mean difference (3D - EM) = - 1.0 ± 9.8 ml). A good relationship between LVSV and AR volumes derived from EM and those by ACM was found ($r = 0.88$, $p < 0.001$). A good relationship between LVSV derived from real-time 3DE and that from ACM was observed ($r = 0.73$, $p < 0.01$, mean difference = 2.5 ± 7.9 ml). Thus, the combination of ACM and real-time 3DE for quantifying LV volumes, LVSV and AR volumes was validated by the chronic animal study.[29] In one of the animal studies, we aimed to determine the quantitative interrelationships of aortic regurgitant volume (RV), stroke volume (SV), and stroke work (SW), using the possible best method for each measurement. For 26 hemodynamic conditions in 6 sheep with surgically created chronic aortic regurgitation, the EM method was utilized to obtain RV. A conductance catheter was placed in the LV for estimating SW from the LV pressure-volume loops. Real-time, 3DE was used to image LV and a newly developed computer-assisted 3D system (EchoTech, Lafayette, CO) was applied to determine LV end-diastolic (EDV) and end-systolic (ESV) volumes. SV was calculated as (EDV-ESV). RV by EM ranged from 7 to 32 ml/beat (mean 22±8). LVSV derived 4DE ranged from 27 to 63 ml/beat (mean 45±9). There was a significant linear relationship between RV derived by EM and SV obtained by 3DE ($r = 0.83$, $p < 0.01$). An even closer relationship was found between RV and SW obtained by the conductance catheter system ($r = 0.87$, $p < 0.001$). In conclusion, LV stroke volume and, more importantly, stroke work increased proportionally with the amount of aortic regurgitant volume quantitatively, reflecting the additional energy consumption required by volume overload in aortic regurgitation.[30,31]

Project #2: Flow Quantification using real-time 3D color Doppler: In another animal study, we aimed to determine the two dimensional spatial velocity profile and to quantify the flow rate in the LVOT by using real-time 3D color Doppler, which became available during this period. A total of twelve different hemodynamic conditions were created in 4 sheep. Real-time 3D color Doppler data from the LVOT were obtained using an apical view. From the 3D volumetric data, the short axis, cross-sectional color images (c-plane) of the LVOT at peak systole were derived and digitally transferred to a PC. Care was taken to select the brightest and the largest peak systolic color image from multiple cardiac beats stored in the image memory buffer for the off-line analysis. By using custom software, color-encoded velocity information was decoded into digital velocity data points to visualize and analyze the spatial velocity distribution. The peak flow rate was also calculated by the spatial integration of these data. An electromagnetic (EM) flow probe was utilized to obtain reference LVOT flow rates. In the LVOT, non-uniform, markedly skewed profiles with higher velocities adjacent to the septum were consistently observed. Peak systolic LVOT flow rates by EM ranged from 63 to 163 ml/s (mean 115 ± 29). Peak flow rates by 3D color ranged from 36 to 144 ml/s (mean 83 ± 27). There was a reasonably good linear relationship between EM and 3D peak flow rates ($r = 0.80$, $y = 0.74x - 2.5$, $p<0.01$), but with an underestimation (mean difference = -28 ± 14%), probably primarily due to low temporal resolution of 6 - 9 volumes per second. In conclusion, using the c-plane, real-time color 3D imaged the spatial velocity distributions in the LVOT. Estimation of the peak blood flow rate was possible, demonstrating the utility of this new method for better understanding blood flow phenomena and its quantification.[32]

Project #3: LA Volume Quantification and Non-invasive Assessment of LA Function: Since the left atrium (LA) exhibits a complex geometry (body asymmetry and presence of left appendage), real-time 3DE (RT3DE) should be advantageous for measuring LA volume over 2DE. Therefore, we aimed to establish the accuracy of LA volume measurements by RT3DE compared to MRI. RT3DE was used for LA volume measurement in 7 patients, using 7 parallel planes from the apical-4 chamber view. The smallest and the largest LA volumes, including the appendage were measured at the onset of the QRS and at the end of the T wave, respectively. The largest and the smallest LA volumes measured by MRI were 120±41ml and 81±36 ml, respectively. The largest and the smallest LA volumes measured by RT3DE were 109±38ml and 62±35 ml, respectively. There was an excellent correlation between the RT3DE LA volumes and MRI LA volumes (y=0.95x-11, r=0.93, p<0.05, SEE =15.6ml). Bland and Altman analysis showed good agreement between MRI-obtained LA volumes and those obtained by RT3DE. RT3DE significantly underestimated LA volumes obtained by MRI by 16±17% (p<0.05). In conclusion, LA volumes can be accurately estimated by RT3DE though with some underestimation relative to MRI.[33]

Project #4: Quantification of LV Mass: Conventional echo methods for determining left ventricular mass (LVM) require geometric assumptions. It is hypothesized that real-time 3D echo (RT3DE) can reliably determine LVM without geometric assumptions. The aim of this study was to validate the use of RT3DE for determining LVM and to compare with conventional 2DE methods in normals and chronic animal models with myocardial infarction (MI) or aortic regurgitation (AR). In 24 sheep (7 normal, 7 chronic AR and 10 chronic MI) RT3DE was used to acquire the entire LV with and without contrast enhancement. We also calculated LVM by M-mode echo using the D^3 formula and by 2DE using the Simpson's rule. Postmortem measured LVM was used as a reference standard. Interobserver variability of LVM by RT3DE was calculated as SD of the difference between two operators measurements expressed as a % of the average value. LVM by 2DE, M-mode, RT3DE and autopsy weight were 85±25 g, 138±52 g, 99±30 g and 108±32 g, respectively. Overestimation of LVM by M-mode (y = 1.50x - 25, r = 0.92) was found, especially for chronic MI (fig.A). A stronger correlation existed between LVM and RT3DE mass without contrast (y = 0.89x + 2.6, r = 0.97) (fig.B) as compared to 2DE (y = 0.70x + 9, r = 0.89). However LV volume with contrast enhancement overestimated LV volume without contrast (mean difference 11±5 ml) resulting further underestimation of LVM by contrast enhancement. Interobserver variability of LVM by RT3DE was 4.6 %. RT3DE without contrast provided an excellent technique to determine LVM as compared to conventional 2D and M-mode methods.[34]

***In Vitro* Experiments**: We have investigated basic instrumental studies, aiming to understand mechanical and physiological advantages and limitations of real-time 3DE method. In one of these studies, we aimed to test 3DE for evaluating LV volumes with modeled aneurysm. Normal and aneurysmal geometric balloon models created and volume measurements using software from Volumetrics and EchoTech (short-axis LV slice and long-axis LV rotational methods) were employed. The lack of a suitable noninvasive method for assessing left ventricular (LV) volume and function has been a major deficiency of two-dimensional (2D) echocardiography for geometrically asymmetrical hearts. Results indicate that the real-time 3D system provided excellent estimation of strictly quantified reference balloon LV volumes with aneurysms.[35]

In another in vitro study, we studied the resolution of RT3DE system, which may affect the accuracy of LV volume calculations. RT3DE with a 2.5 MHz matrix phased array scanner was used to acquire images of 15 different balloons. The actual volume was measured by a graduated cylinder, and ranged from 68 to 266 ml. For each phantom, we measured two volumes by tracing the inner and outer boundary of 9 short-axis parallel slices. The thickness of the balloon was also measured in different locations to assess axial and lateral resolution. We also studied the images of 3 rubber cylinders. Although actual thickness of the balloon was less than 0.3 mm, the axial thickness of the balloon measured 2.0±0.4 mm and the lateral thickness was 6.0±1.0 mm. Volume measured from the inner contour of the balloon was slightly smaller than the actual volume (-11%), while the volume measured by tracing outside the balloon overestimated actual volume by 51% (Figure). The measured thickness of the cylinders versus the real thickness were 3.9 vs 1.7 mm, 4.5 vs 2.3 mm and 6.4 vs 3 mm respectively. In conclusions, actual LV volume was slightly underestimated by RT3DE when the inside of the cavity was measured but this was much more accurate then tracing the outer margin. This may be explained by the limited resolution of the current RT3DE. Higher frequency transducers such as those of 3.5 MHz and 5 MHz will be required to overcome this limitation.

SUMMARY/FUTURE DIRECTIONS:

In follow-on to the foundations laid in this grant (NCC9-60), we have submitted three grants to NASA funding agencies, which have received favorable reviews. Although pending final budgetary approval, we anticipate to participate in the following projects.

In response to HEDS-99-03, we submitted a grant entitled: "**Diagnostic Ultrasonography in Flight: Technical and Training Aspects**." It is essential that NASA personnel and the crew have confidence in the ability of the ultrasound system to deliver diagnostic information in the event of a medical contingency on orbit. In pursuit of this critical goal, this proposal focuses directly on the issue of crew training and guidance of ultrasound acquisition using ground-based experts viewing Real-time transmitted ultrasound images from the ISS. If successfully implemented, this work should enable accurate diagnosis of cardiac, abdominal, retroperitoneal, and vascular emergencies occurring in space. It also will be an important proving ground for future, more dedicated research acquisitions.

Looking even farther into the future, we see a great need for further work in three-dimensional echocardiography, especially with regard to automated registration and interpretation. We have demonstrated the superior localizing capabilities of real-time three-dimensional echocardiography, but currently this device is impractical for space use. However, within the next ten years, it is anticipated that this technology will be smaller than the currently planned HDI-5000, thus allowing its use both on orbit and in deep space. To this end, we prepared a submission to the Smart Medical Care System aspect of the National Space Biomedical Research Institute, entitled "**Diagnostic 3D Echocardiography: Development Of Novel Compression, Segmentation And Registration Techniques For Manned Space Flight Application**." This would expand our analysis of three-dimensional ultrasound to allow automated registration with previously acquired MRI and CT datasets in hopes of detecting changes as they occur in space. There will also be important compression aspects to this work as a four-dimensional echocardiographic dataset may be compressible considerably with minimal loss of diagnostic content.

In response to NSBRI 00-01 we submitted a grant entitled "**Echocardiographic Assessment Of Cardiovascular Adaptation And Countermeasures In Microgravity**" to address the orthostatic intolerance and reduced exercise capacity. Hypovolemia, cardiac atrophy, and autonomic dysfunction have each been hypothesized to contribute to this post-flight debility, but their relative importance is unclear. Furthermore, it is unknown whether actual abnormalities within the myocardium develop with long-term space flight. Therefore, reliable portable noninvasive methods will be needed in order to detect and quantify these changes. Our central hypothesis is that microgravity affects cardiovascular function not only through changes in chamber volume and mass but also through changes in myocardial properties. A definitive test of this hypothesis is at least several years away when dedicated life science missions are possible aboard the ISS. However, within the scope of this grant, we propose several specific aims that will be critical to the ultimate comprehensive study of the cardiovascular system in space.
Specific Aims:
1) Assessment of the effect of chronic volume and pressure unloading on ventricular myocardial properties using a sophisticated chronic bovine model of ventricular unloading induced through the use of a left ventricular assist device (LVAD).

2) Validation of non-invasive Doppler echocardiographic indices for the assessment of left ventricular contractility and relaxation including color M-mode Doppler derived diastolic intraventricular pressure gradients (IVPG) and tissue Doppler derived myocardial systolic and diastolic strain rates (ε'_s, ε'_d).
3) Validation of Doppler derived exercise cardiac output and contractile reserve and their potential utility for the *early detection* of myocardial dysfunction during prolonged space flight.
Additional deliverables to NSBRI include (a) the development and distribution of stand-alone software and algorithms for implementing the quantitative analysis of Doppler echocardiographic data so they may be applied to ultrasound data obtained from remote sources and (b) the establishment of an Echocardiographic Core Facility for the NSBRI and NASA research and clinical community, capable of applying standard and novel analysis techniques in a rigorous fashion to echocardiographic data obtained from selected ground-based experimental models, pre- and post-flight examinations, and eventually from in-flight acquisitions.
If successfully implemented, these Aims will allow the cardiovascular sequellae of space flight to be studied much more rigorously, while providing consistent, objective echocardiographic interpretation to the entire NASA community.

Also, in continuing our close collaboration with Dr. Ben Levine from the University of Texas Southwestern in pursuit of space physiology questions, we submitted a grant entitled "**Cardiac Atrophy And Diastolic Dysfunction During And After Long Duration Spaceflight: Functional Consequences For Orthostatic Intolerance And Risk Of Cardiac Arrhythmias**." We have proposed both bedrest and flight studies analyzing the impact of cardiac atrophy in space and the changes that occur in cardiovascular mechanics as diagnosed by Doppler tissue imaging and color M-mode flow propagation. The intensive work that we have performed in the operating room and the animal laboratory will be invaluable in applying data acquired in space to this important question.

References:

1. Firstenberg MS, Greenberg NL, Garcia MJ, Morehead AJ, Cardon LA, Klein AL, Thomas JD. Internet-based transfer of cardiac ultrasound images. *J Telemedicine and Telecare*, 2000;6(3):168-171**.**
2. Main ML, Foltz D, Firstenberg MS, Babinsky E, Bailey D, Frantz B, Pleva D, Baldizzi M, Meyers DP, Jones K, Spence MC, Freeman K, Morehead A, Thomas JD. Real-Time Transmission of Full Motion Echocardiography over a High Speed Data Network: Impact of Data Rate and Network Quality of Service. *J Am Society Echo*, 2000;13(8):764-770.
3. Soble JS, Yurow G, Brar R, Stamos T, Neumann A, Garcia M, Stoddard MF, Cherian PK, Bhamb B, Thomas JD. Comparison of MPEG digital video with super VHS tape for diagnostic echocardiographic readings. *J Am Soc Echocardiogr* 1998; 11:819-825
4. Garcia MJ, Thomas JD, Greenberg NL, Sandelski J, Herrera C, Mudd C, Wicks J, Spencer K, Alex Neumann A, Sankpal B, Soble J. Comparison Of MPEG-1 Digital Video With S-VHS Tape For Quantitative Echocardiographic Measurements. *J Am Soc Echocardiogr*, accepted.
5. Hang X, Greenberg NL, Thomas JD. Compression of Echocardiographic Data using the Wavelet Packet Transform. IEEE Computer Society, Los Alamitos, CA; Computers in Cardiology, 1998; pp. 329-331.
6. Hang X, Greenberg NL, Garcia MJ. Compression of high frame rate echocardiographic sequences using 3D-wavelet transform. *Circulation* 1999; 100(18)I-571.
7. Thomas JD, Garcia MJ, Greenberg NL. Application of color Doppler M-mode echocardiography in the assessment of ventricular diastolic function: potential for quantitative analysis*.* *Heart Vessels* 1997 (Suppl 12):135-137.
8. Garcia MJ, Smedira NG, Greenberg NL, Main M, Firstenberg MS, Odabashian J, Thomas JD. Color M-Mode Doppler Flow Propagation Velocity is a Preload Insensitive Index of Left Ventricular Relaxation: Animal and Human Validation. *J Am Coll Cardiol* 2000; 35(1):201-208.
9. Greenberg NL. Vandervoort PM, Thomas JD. Estimation of instantaneous diastolic transmitral pressure difference from color Doppler M-mode echocardiography*.* *Am J Physiol* 271*(Heart Circ Physiol* 40*)* H1267-H1276, 1996.
10. Firstenberg MS, Vandervoort PM, Greenberg NL, Smedira NG, McCarthy PM, Garcia MJ, Thomas JD. Noninvasive Estimation of Transmitral Pressure Drop Across the Normal Mitral Valve in Humans: Importance of Convective and Inertial Forces During Left Ventricular Filling. *J Am Coll Cardiol* 2000; 36(6): 1942-1949.
11. Greenberg NL, Vandervoort PM, Firstenberg MS, Garcia MJ, Thomas JD. Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. *Am J Physiol*, accepted.
12. Nakatani S, Firstenberg MS, Greenberg NL, Vandervoort PM, Smedira NG, McCarthy PM, Thomas JD. Determination of Mitral Inertance in Humans: A Critical Factor in Estimating Transvalvular Pressure Difference From Flow Velocity. *Am J Physiol*, accepted.
13. Firstenberg MS, Greenberg NL, Garcia MJ, Prior DL, Smedira NG, Thomas JD. Semi-automated Analysis of Color M-mode Echocardiographic Images for Determining Transmitral Pressure Gradients Using a Simplified Euler Equation. *Computers in Cardiology IEEE 1999.* 1999;26:181-184.
14. Firstenberg MS, Greenberg NL, Main ML, Drinko JK, Odabashian JA, Thomas JD, Garcia MJ. Determinants of Diastolic Myocardial Tissue Doppler Velocities: Influence of Relaxation and Preload. *J Appl Physiol* 2001;90: 299-307.
15. Pasquet A, Armstrong GP, Greenberg NL, Marwick TH. Regional myocardial strain: A quantitative color Doppler measure for stress echocardiography. *Circulation* 1998;98(17):I-83.
16. Castro PL, Greenberg NL, Firstenberg MS, Drinko J, Lever HM, Garcia MJ, Thomas JD. Abnormal Strain Throughout the Base of the Left Ventricle in Hypertrophic Cardiomyopathy. *J Am Coll Cardiol* 2000; 35(2):423A.
17. Castro P, Greenberg NL, Garcia MJ, Thomas JD. Accuracy of strain rate measurements using tissue Doppler echocardiography. *J Am Society Echo* 1999;12(5):398.
18. Castro PL, Greenberg NL, Meurs KM, Lehmkuhl LB, Agler D, Abdalla I, Lever HM, Thomas JD, Garcia MJ. *In Vitro* and *In Vivo* Validation of Doppler Derived Segmental Myocardial Strain Rate in Feline and Human Hypertrophic Cardiomyopathy. (Submitted)
19. Greenberg NL, Garcia MJ, Firstenberg MS, Castro PL, Main M, Travaglini A, Odabashian JA, Drinko JK, Rodriguez L, Thomas JD. Doppler Derived Myocardial Systolic Strain Rate is a Strong Index of LV Contractility. (Submitted to Circulation)
20. Firstenberg MS, Greenberg NL, Smedira NG, Castro PL, Thomas JD, Garcia MJ. The Effects of Acute Coronary Occlusion on Non-Invasive Echocardiographically Derived Systolic and Diastolic Myocardial Strain Rates. Current Surgery 2000;57:466-472.

21. Garcia MJ, Firstenberg MS, Greenberg NL, Smedira NG, Rodriguez L, Prior DL, Thomas JD. Estimation of left ventricular operating stiffness from Doppler early filling deceleration time: A human validation study. *Am J Physiol* 2001; 280(2): H554-.
22. Firstenberg MS, Greenberg NL, Smedira NG, Prior DL, Scalia GM, Thomas JD, Garcia MJ. Doppler echo evaluation of pulmonary venous-left atrial pressure gradients: human and numerical model studies. *Am J Physiol* 2000;279 H594-H600.
23. Firstenberg MS, Levine BD, Garcia MJ, Greenberg NL, Cardon L, Morehead AJ, Zuckerman J, Thomas JD. Relationship of echocardiographic indices to pulmonary capillary wedge pressure in healthy volunteers. *J Am Coll Cardiol* 2000; 36(5): 1664-1669.
24. Garcia MJ, Ares MA, Asher C, Rodriguez L, Vandervoort P, Thomas JD. An Index of Early Left Ventricular Filling that Combined with Pulsed Doppler Peak E Velocity May Estimate Capillary Wedge Pressure. *J Am Coll Cardiol* 1997; 29:448-54.
25. Shiota T, McCarthy PM, White RD, Qin JX, Greenberg NL, Flamm SD, Wong J, Thomas JD. Initial clinical experience of real-time 3-Dimensional echo in patients with ischemic and idiopathic dilated cardiomyopathy. *Am J Cardiol* 1999;84:1068-1073.
26. Gillinov MA, Cosgrove DM, Shiota T, Qin J, Tsujino H, Stewart WJ, Thomas JD, Porqueddu M, Blackstone EH. The Cosgrove-Edward annuloplasty system preserves mitral annular flexibility and function at 5 years**.** *Annuls of Thoracic Surgery* 2000, 69:717-21.
27. Qin JX, Shiota T, Lever HM, Rubin, DN, Bauer F, Tsujino H, Drinko JK, Agler DA, Thomas JD. Left ventricular outflow tract area measured by real-time 3D echocardiography in hypertrophic cardiomyopathy with systolic mitral valvular anterior motion. (Submitted)
28 Qin JX, Travaglini A, Marwaha VR, Xu Y, Firstenberg MS, Rodriguez LL. Change in the left ventricular stroke work during tilt test detected by real-time 3-dimensional echocardiography. Circulation 1999; 99: I-357
29. Shiota T, Jones M, Tsujino H, Qin JX, Zetts AD, Greenberg NL, Cardon LA, Panza JA, Thomas JD. Real-time 3D Echocardiography and Semi-automated Digital Color Doppler for Quantifying Absolute Left Ventricular Volumes, Stroke Volumes and Regurgitant Volumes in Aortic Regurgitation: A Chronic Animal and Clinical Study (Submitted).
30. Shiota T, Jones M, Agler DA, McDonald RW, Marcella CP, Qin JX, Zetts AD, Greenberg NL, Cardon LA, Sun JP, Sahn DJ, Thomas JD. New Echocardiographic Windows for Quantitative Determination of Aortic Regurgitation Volume Using the Color Doppler Flow Convergence and Vena Contracta. *Am J Cardiol* 1999; 83:1064-1068.
31. Shiota T, Michael Jones M, Tsujino H, Huskey KD, BA, Qin JX, Travaglini A, Zetts AD, Greenberg NL, Cardon LA, Panza JA, Thomas JD. Real-time 3D Echocardiography for Evaluating Left Ventricular Stroke Work in Aortic Regurgitation: A Chronic Animal Study. (Submitted)
32. Tsujino H, Jones M, Shiota T, Qin JX, Cardon LA, Morehead AJ, Travaglini A, Bauer F, Zetts AD, Greenberg NL, Panza JA, Thomas JD. Estimation of the Spatial Mean and Peak Flow Velocities Using Real-time 3D Color Doppler Echocardiography. IEEE Computer Society, Los Alamitos, CA; *Computers in Cardiology,* 1999; pp. 173-176.
33. Bauer F, Shiota T, White RD, Qin JX, Travaglini A, Tsujino H, Thomas JD. Left Atrial Volume Measurement by Real-Time 3D Echocardiography. *J Am Coll Cardiol* 2000; 35:437A.
34. Agnese Travaglini, MS, Michael Jones, MD, Takahiro Shiota, MD, PhD, Jian Xin Qin, MD, Fabrice Bauer, MD, Hiroyuki Tsujino, MS, Lisa A Cardon, Annitta J Morehead, Neil L Greenberg, PhD, Julio A Panza, MD, Arthur D Zetts, James D Thomas, MD. Measurement of Left Ventricular Mass using Real-time 3D and 2D Echocardiography in a Chronic Animal Model. *J Am Coll Cardiol* 1999; 35(2):468A
35. Qin JX, Jones M, Shiota T, Greenberg NL, Tsujina H, Firstenberg M, Gupta PC, Zetts AD, Xu Y, Sun JP, Cardon LA, Odabashian JA, Flamm SC, White RD, Thomas JD. Validation of real-time three-dimensional echocardiography for quantifying left ventricular volumes in the presence of a left ventricular aneurysm: *In vitro and in vivo* studies. *J Am Coll Cardiol 2000; 36:900-907.*

ADDITIONAL REFERENCES:

Chandra S, Thomas JD. Digital storage and analysis of color Doppler echocardiograms. *Echocardiography* 1997; 14: 91-102.

Chandra S, Garcia MJ, Morehead A, Thomas JD. Two-dimensional Fourier filtration of acoustic quantification echocardiographic images: Improved reproducibility and accuracy of automated measurements of left ventricular performance. *J Am Soc Echocardiogr* 1997;10:310-9.

Nakatani S, Garcia MJ, Firstenberg MS, Rodriguez L, Grimm RA, Greenberg NL, McCarthy PM, Vandervoort PM, Thomas JD. Noninvasive Assessment of Left Atrial Contractility by a Combination of Transmitral and Pulmonary Venous Flow. *J Am Coll Cardiol* 1999;34(3):795-801.

Nakatani S, Thomas JD, Vandervoort PM, Zhou J, Greenberg NL, Savage RM, McCarthy PM. Left ventricular diastolic filling with an implantable ventricular assist device: Beat-to-beat variability with overall improvement. *J Am Coll Cardiol* 1997; 30: 1288-1294.

Pasquet A, Greenberg N, Brunken R, Thomas JD. Marwick TH. Effect of color coding and subtraction on the accuracy of contrast echocardiography. *International Journal of Cardiology*. 70(3):223-31, 1999.

Pu M, Vandervoort PM, Greenberg NL, Powell KA, Griffin BP, Thomas JD. Impact of wall constraint on the velocity distribution in the proximal flow convergence zone: Implications for color Doppler quantification of mitral regurgitation. *J Am Coll Cardiol* 1996; 27: 706-713.

Qin JX, Jones M, Shiota T, Greenberg NL, Cardon LA, Zetts AD, Tsujino H, Thomas JD. Comparison of Left Ventricular Stroke Volume Determination by Real-time Three-dimensional Echocardiography and Conventional Two-dimensional Echocardiography: An Animal Study During Non-ischemic and Ischemic Conditions. Computer in Cardiology 1998;25:645-648.

Qin JX, Jones M, Shiota T, Greenberg NL, Firstenberg MS, Tsujino H, Zetts AD, Sun JP, Cardon LA, Odabashian JA, Flamm SD, White RD, Panza JA, Thomas JD: New digital measurement methods for left ventricular volume using Real-time three-dimensional echocardiography: Comparison with electromagnetic flow method and magnetic resonance imaging. *Eur J Echocardiography* 2000;1:96-104.

Qin JX, Jones M, Shiota T, Travaglini A, Greenberg NL, Tsujino H, Zetts AD, Cardon LA, Odabashian JA, White RD, Thomas JD. Accuracy of left ventricular volume, ejection fraction and mass measured by real-time 3-dimensional echocardiography in the presence of aneurysm. (Submitted).

Scalia GM, Greenberg NL, McCarthy PM, Thomas JD, Vandervoort PM. Noninvasive assessment of ventricular relaxation time constant (tau) by Doppler echocardiography. *Circulation* 1997; 95: 151-155.

Sun JP, Yang XS, Qin JX, Greenberg NL, Zhou J, Vazquez CJ, Griffin BP, Stewart WJ, Thomas JD. Quantification of mitral regurgitation by automated cardiac output measurement: Experimental and clinical validation. J Am Coll Cardiol 1998;32:1074-82.

Sun JP, Stewart WJ, Pu M, Fouad FM, Christian R, Thomas JD. Automated cardiac output measurement by spatiotemporal integration of color Doppler data: In vitro and clinical validation. *Circulation* 1997; 95: 932-939.

Thomas JD, Zhou J, Greenberg NL, Bibawy G, McCarthy PM, Vandervoort PM. Physical and physiological determinants of pulmonary venous flow: Numerical analysis. *Am J Physiol (Heart Circ Physiol 41)* H2453-H2465, 1997.

Secknus MA, Marwick TH. Evolution of dobutamine echocardiography protocols and indications: Safety and side-effects in 3011 studies over five years. *J Am Coll Cardiol* 1997;29:1234-40.

Heupler S, Lauer M, Williams MJ, Shan K, Marwick TH. Increased left ventricular cavity size, not wall thickness, potentiates myocardial ischemia. Am Heart J 1997 (in press).

Marwick T, Mehta R, Arheardt K, Lauer MS. Use of exercise echocardiography for prognostic evaluation in patients with known or suspected CAD. J Am Coll Cardiol 1997;30:83-90.

Rubin DN, Ballal RS, Marwick TH. Outcomes and cost implications of a clinical- based algorithm to guide the discriminate use of stress imaging before noncardiac surgery. Am Heart J 1997;134:83-92.

Tsujino H, Shiota T, Qin JX, Greenberg NL, Flachkampf FA, Thomas JD. Assessment of the mitral annular motion using real-time 3D echocardiography: a clinical study. J Am Soc Echocardiogr. 1999;12: 402 (Abstract)

Qin JX, Shiota T, Sun JP, Odabashian JA, White RD, Flamm SD, Thomas JD. A new digital method for estimating left ventricular volume using real-time 3d echocardiography: a comparison with magnetic resonance imaging. J Am Coll Cardiol 1999; 33: 441A.

Tsujino H, Jones M, Shiota T, Huskey KD, Qin JX, Travaglini A, Zetts A, Greenberg N, Cardon LA, Panza J, Thomas JD. Left ventricular stroke work in aortic regurgitation: an animal study using conductance catheter and real-time 3D echocardiography. J Am Soc Echocardiogr. 1999;12: 370 (Abstract)

F. Bauer, T. Shiota, J.X. Qin, H. Tsujino, A. Travaglini, V. Marwaha, M. Jones, JD Thomas. Change in left atrial function during acute coronary occlusion: a pressure volume loop analysis. American Heart Association 1999, Atlanta. Circulation 1999.

F.Bauer, V. Marwaha, A. Zetts, J. Panza. Non-invasive assessment of left ventricular chamber stiffness with real-time 3D echocardiography: Comparison with an invasive method in an animal study. American Heart Association 1999, Atlanta. Circulation 1999.

Qin JX, Jones M, Shiota T, Zetts AD, Greenberg N, Cardon LA, Panza JA, Thomas JD. Accurate measurement of left ventricular stroke volumes using real-time, 3d echo during non ischemic and ischemic conditions. J Am Coll Cardiol 1999; 33: 486A.

Qin JX, Jones M, Shiota T, Morehead A, Tsujino H, Zetts AD, Greenberg NL, Cardon LA, Panza JA, Thomas JD. Real-time three-dimensional contrast echocardiography for left ventricular cavity visualization: animal and clinical studies. J Am Coll Cardiol 1999; 33: 431A.

Qin JX, Jones M, Shiota T, Tsujino H, Greenberg NL, Zetts AD, Cardon LA, Drinko JK, Panza JA, Thomas JD. Left ventricular stroke volume determined by real-time 3D echo in animals with LV aneurysms: comparisons with 2D echo and angiography. J Am Soc Echocardiogr 1999; 12(5): 362.

Qin JX, Shiota T, Lever H, Rubin D, Yalcin F, Drinko JK, Agler DA, Thomas JD. Left ventricular outflow tract area measured by real-time 3D echocardiography in hypertrophic obstructive cardiomyopathy. J Am Soc Echocardiogr 1999; 12(5):381.

Qin JX, Jones M, Shiota T, Greenberg NL, Tsujino H, Xu Y, Sun JP, Odabashian JA, White RD, Stewart WJ, Thomas JD. Geometry and motion of the mitral annulus assessed by real-time 3D echocardiography: a comparison with MRI. J Am Soc Echocardiogr 1999; 12(5): 379.

Qin JX, Jones M, Shiota T, Tsujino H, Greenberg NL, Zetts AD, Cardon LA, Panza JL, Thomas JD. Value of real-time 3D echo and semi-automated digital Doppler color flow mapping during different LV loading conditions in aortic regurgitation. J Am Soc Echocardiogr 1999; 12(5): 372.

Qin JX, McCarthy PM, Shiota T, Firstenberg MS, Smedira NG, Hoercher K, Buda T, Tsuijino H. Real time 3D echocardiographic study of left ventricular function after infarct exclusion surgery. Circulation 1999; 99: in press.

Cardon L, Firstenberg MS, Garcia MJ, Greenberg NL, Thomas JD. Effects of Preload Alterations on Tissue Doppler Diastolic Myocardial Velocities in Normal Subjects. *Euro J Echo*. 1999 (Suppl);S69 (abs).

Cardon L, Firstenberg MS, Greenberg NL, Garcia MJ, Shiota T, Qin JX, Tsujino H, Marwaha VR, Thomas JD. Real-time Three-Dimensional Assessment of Total Cardiac Volume and the Ratio of Chamber Specific Volumes. *Euro J Echo*. 1999 (Suppl);S86 (abs).

Firstenberg MS, Greenberg NL, Klein A, Drinko J, Cardon L, Volsko T, Morehead AJ, Katz WE, Thomas JD. Feasibility of All Digital Internet Transfer and Core Lab Assessment of Multi-Center Transesophageal Echocardiographic Studies. *Euro J Echo*. 1999 (Suppl);S43 (abs).

Firstenberg MS, Cardon L, Greenberg NL, Garcia MJ, Morehead AJ, Zuckerman J, Farr D, Levine BD, Thomas JD. Non-invasive Echocardiographic Estimation of Left Ventricular Filling Pressures in Normal Patients. *Euro J Echo*. 1999 (Suppl);S70 (abs).

Han P, Shiota T, Tsujino H, McCarthy PM., Qin JX, Bauer F, Travaglini A, Firstenberg M, Thomas JD. Assessment of Aortic Annular Motion in Patients With Ischemic Cardiomyopathy by Real-Time 3D Echocardiography (RT3DE) Before and After the Infarct Exclusion Procedure JACC;2000, 35, 460.

Bauer F, Jones M, Shiota T, Qin JX, Tsujino H, Travaglini A, Zetts AD, Panza JA, Thomas JD. Assessment of Left Atrial End-Systolic Pressure Volume Relationship in an Animal Model: A Real-Time 3D Echocardiographic and Hemodynamic JACC;2000;35, 471.

Qin JX, Shiota T, Lever HM., Rubin DN., Bauer F, Tsujino H, Drinko JK, Martin M, Thomas JD. Comparison of Percutaneous Transluminal SeptalStudy J Myocardial Ablation and Septal Myectomy in Hypertrophic Obstuctive Cardiomyopathy. JACC;2000,35,191.

Camarano G, Jones M, Shiota T, Ernst I,. Zetts AD, Thomas JD, Panza JA. Effect of Remodeling Following Myocardial Infarction on Left Ventricular Size and Function: A Real-Time 3-Dimensional Echocardiographic Study. JACC;2000,35,443.

Tsujino H, Shiota T, Qin JX, Bauer F, Travaglini A, Greenberg NL, Thomas JD. Estimation of the Spatial Mean and Peak Flow Velocities Using Real-time 3D (RT3D) Color Doppler Echocardiography: An In Vitro Experiment. JACC;2000,35,436.

Bauer F, Jones M, Shiota T, Qin JX, Tsujino H, Morehead AJ, Cardon LA, Travaglini A, Zetts AD, Panza JA, Thomas JD Left Atrial Contractile Function During Left Ventricular Ischemia With and Without Left Atrial Ischemia. JACC;2000,35,458.

Bauer F, Jones M, Shiota T, Qin JX, Tsujino H, Travaglini A, Zetts AD, Panza JA, Thomas JD Left Atrial Volume and Function: Relationship to Left Ventricular Function. JACC;2000,35,494.

Bauer F, Shiota T, White R, Oin JX, Travaglini A, Tsujino H, Thomas JD. Left Atrial Volume Measurement by Real-Time 3D Echocardiography. JACC;2000,35,437.

Travaglini A, Jones M, Shiota T, Qin JX, Bauer F, Tsujino H,. Cardon LA, Morehead AJ, Greenberg NL, Panza JA, Zetts AD, Thomas JD. Measurement of Left Ventricular Mass (LVM) Using Real-Time 3D and 2D Echocardiography in Chronic Animal Model. JACC;2000,35,468.

Tsujino H, Jones M, Shiota T, Qin JX, Cardon LA, Morehead AJ, Zetts AD, Bauer F, Travaglini A, Greenberg NL, Panza JA, Thomas JD. Quantification of the Volumetric Flow Rate Using Real-Time 3D (RT3D) Color Doppler Echocardiography: An Animal Study. JACC;2000,35,461.

Tsujino H, Jones M, Shiota T, Qin JX,. Cardon LA, Morehead AJ, Zetts AD, Bauer F, Travaglini A, Greenberg NL, Panza JA, Thomas JD. Real-time 3D Color Doppler Echocardiography for Analysis of the Spatial Velocity Distribution in the Left Ventricular Outflow Tract. JACC;2000,335,436.

Qin JX, Jones M, Shiota T, Tsujino H, Travaglini A, Zetts AD, Cardon LA, Morehead AJ, Bauer F, Thomas JD. Real-time 3D Pulsed Wave (PW) Doppler Echocardiography for Quantification of the Left Ventricular Stroke Volume. JACC;2000,35,442.

Qin JX, Shiota T, Tsujino H, Firstenberg MS, Cardon LA, Odabashian JA, White RD, Thomas JD. Validation of Real-time 3D Echocardiography for Quantifying LV Volumes in the Presence of a LV Aneurysm: In Vitro and Clinical Studies. JACC;2000,35,186.

Agler DA, Shiota T, Tsujino H, Qin JX, Travaglini A, Bauer F, Cosgrove DM III, Stewart WJ, Thomas JD: Real-time color 3D echo Doppler improves spatial localization of mitral prolapse for flail: Operative validation. JASE 2000;13(5):430.

Bauer F, Jones M. Shiota T, Qin JX, Tsujino H. Travaglini A. Wantanabe J, Zetts AD, Thomas JD: Left ventricular outflow tract systolic acceleration for quantifying left ventricular contractility. JASE 2000;13(5):433.

Bauer F, Shiota T, Lever HM, Qin JX, Travaglini A, Tsujino H. Thomas JD: Determinants of left atrial dilatation in patients with hypertrophic cardiomyopathy. JASE 2000;13(5):467.

Bauer F, Shiota T, Qin JX, Tsujino H, Travaglini A. Thomas JD: Left atrial volume determined by real-time 3D echocardiography in patients with mitral regurgitation. JASE 2000;13(5):502.

Cardon LA, Firstenberg MS, Greenberg NL, Shiota T, Qin JX, Tsujino H, Garcia MJ, Thomas JD: Relationship between chamber specific volumes to total cardiac volume: A real-time 3D echo study. JASE 2000;13(5):440.

Firstenberg MS, Greenberg NL, Smedira NG, Prior DL, Shiota T, Qin JX, McCarthy PM, Tsujino H, Hoercher K, Buda T, Garcia MJ, Thomas JD: Effects of surgical ventricular remodeling on systolic and diastolic function: An intra-operative physiologic and real-time 3D echo study. JASE 2000;13(5):470.

Qin JX, Shiota T, McCarthy PM, Tsujino H, Bauer F, Travaglini A, Thomas JD: Improvement of LV function determined by real-time 3D echo after infarct excision with simultaneous mitral valve repair in ischemic cardiomyopathy patients with mitral regurgitation. JASE 2000;13(5):467.

Qin JX, Shiota T, Tsujino H. Agler DA, Bauer F, Travaglini A, Gillinov MA, Stewart WJ, Cosgrove DM III, Thomas JD: Transmitral inflow pattern and annulus geometry before and after mitral valve repair in patients with mitral regurgitation: A clinical real-time 3D echocardiographic study. JASE 2000;13(5):501.

Qin JX, Shiota T, Tsujino H, Greenberg NL, Odabashian JA, White RD, Stewart WJ, Thomas JD: Size and motion of mitral annulus assessed by real-time 3D echo in different cardiac diseases: Comparison with MRI. JASE 2000;13(5):490.

Travaglini A, Jones M, Shiota T, Bauer F, Tsujino H, Qin JX, Wantanabe J, Greenberg NL, Zetts AD, Thomas JD: Relationship between ejection fraction and contractility index (Emax) in chronic aortic regurgitation: Conductance catheter and real-time 3D echo study in animals. JASE 2000;13(5):501.

Travaglini A, Shiota T, Tsujino H, Bauer F, Qin JX, Greenberg NL, Thomas JD: Accuracy of the "left ventricular" volume determination using real-time 3D echocardiography: An in vitro study. JASE 2000;13(5):489.

Tsujino H, Jones M, Shiota T, Qin JX, Cardon LA, Morehead AJ, Zetts AD, Bauer F, Greenberg NL, Thomas JD: Contrast enhanced harmonic imaging of myocardial perfusion in acute and chronic myocardial infarction: An animal experiment. JASE 2000;13(5):459.

Tsujino H, Jones M, Shiota T, Qin JX, Cardon LA, Morehead AJ, Zetts AD, Bauer F, Travaglini A, Watanabe J, Greenberg NL, Thomas JD: Assessment of the geometry and dynamic motion of the mitral annulus during coronary artery occlusion: A real-time 3D echocardiographic study. JASE 2000;13(5):478.

Tsujino H, Shiota T, Qin JX, Agler DA, Bauer F, Gillinov MA, Cosgrove DM III, Stewart WJ, Thomas JD: Quantitative assessment of the mitral annular motion in mitral regurgitation: A color-encoded 2D tissue Doppler imaging study. JASE 2000;13(5):473.

Watanabe J, Jones M, Shiota T, Garcia MJ, Tsujino H, Bauer F, Qin JX, Travaglini A, Thomas JD: Color M-mode Doppler flow propagation of late diastolic velocity during preload alteration: An animal study. JASE 2000;13(5):472.

Xu T, Shiota T, Qin JX, Tsujino H. Sun JP, Bauer F, Drinko JK, Bashir M, Stewart WJ, Thomas JD: Left atrial volume and function determined by real-time 3-dimensional echocardiography in cardiac transplant recipients. JASE 2000;13(5):489.

Tsujino H, Shiota T, Qin JX, Agler DA, Bauer F, Travaglini A, Thomas JD. Quantitative Digital Color Doppler and Real-Time 3D Echocardiography for Evaluating Aortic and Mitral Regurgitation. Ultrasound in Med. & Biol. 2000; 26

Marwaha V, Shiota T, Qin JX, Bauer F, Tsujino H, Greenberg NL, Firsteinberg MS, Travagluni A, Thomas JD. Real-time Three-dimensional echocardiography for determining left ventricular size and function: comparison with conventional M-mode and two-dimensional echocardiography. JASE 2000;13(5):490.

Qin JX, Shiota T, Firsterberg MS, Sitges M, Bauer F, Travaglini A, Hoercher KJ, Buda T, Smedira NG, McCarthy PM. Efficacy of Infarct Exclusion Surgery in Patients with Severe Left Ventricular Dysfunction: A Real-Time 3d Echo Study. Circulation 2000 (in press).

Qin JX, Shiota T, Bauer F, Sato M, Wika K, Lee A, Soloviev MV, Lapyre D, Harasaki H. Hemodynamic Characteristics of a New Tri-Leaflet Mechanical Valve Prosthesis in the Mitral Position in a Calf Model: A Real-Time 3D Echocardiographic Study. Circulation 2000 (in press)

Sitges M, Shiota T, Tsujino H, Qin JX, Bauer F, Agler DA, Cardon LA, Panza JA. Real-Time Three-Dimensional Color-Doppler Evaluation of the Flow Convergence Surface for Quantification of Mitral Regurgitation. Circulation 2000 (in press)

Tsujino H, Cosgrove DM, Qin JX, Sitges M, Agler DA, Greenberg NL, Bauer F, Gillinov MA, Stewart WJ. Assessment of the Left Ventriclar Volume and Mitral Annular Function Using Real-Time 3D Echocardiography: A Clinical Follow-Up Study in Patient with Cosgrove-Edwards (CE) Annuloplasty Rings. Circulation 2000 (in press).

Firstenberg MS, Cardon L, Greenberg NL, Garcia MJ, Qin JX, Bauer F, Travaglini A, Shiota T, Thomas JD. Changes in Diastolic Intraventricular Pressure Gradients, Geometry, and Volumes with Acute Postural Changes. *Euro J Echo*. 1999 (Suppl);S68 (abs).

Cardon L, Firstenberg MS, Morehead AJ, Zuckerman JH, Farr D, Levine BD, Greenberg NL. Estimation of Left Ventricular Filling Pressures in Normal Subjects Using New Doppler Indices. *Circulation.* 1999;100(18);I-295.

Firstenberg MS, Greenberg NL, Prior DL, Smedira NG, Garcia MJ. Transmitral Pressure Gradients Can Be Assessed Using A Simplified Spatiotemporal Analysis of Color M-mode Doppler. *Circulation.* 1999;100(18);I-295.

Garcia MJ, Smedira NG, Greenberg NL, Prior DL, Firstenberg MS, Rodriguez L, Thomas JD. Quantitative Estimation of Left Ventricular Operating Stiffness from Doppler Early Filling Deceleration Time in Humans. *Circulation.* 1999;100(18);I-19

Prior DL, Greenberg NL, Firstenberg MS, Thomas JD, Garcia MJ. Manual and automated methods for orifice area quantification using the interaliasing distance from color Doppler of the proximal convergence zone: In vitro validation using pulsatile flow. *Circulation.* 1999;100(18);I-654.

Qin JX, Travaglini A, Marwaha VR, Xu Y, Firstenberg MS, Rodriguez L. Change in the Left Ventricular Stroke Work during Tilt Test Detected by Real-time 3-Dimensional Echocardiography. *Circulation.* 1999;100(18);I-357.

Qin JX, McCarthy PM, Shiota T, Firstenberg MS, Smedira NG, Hoercher K, Buda T, Tsuijini H. Real Time 3D Echocardiographic Study of Left Ventricular Function After Infarct Exclusion Surgery. *Circulation.* 1999;100(18);I-167.

Firstenberg MS, Thamilarasan M, Prior DL, Gupta R, Bashir M, Thomas JD, Klein AL. The Role of Mitral Regurgitation and Ventricular Function on Pulmonary Venous Waves in Patients with Atrial Fibrillation. *J Am Coll Cardiol* 2000:35(2);458 (Abs).

Castro PL, Greenberg NL, Firstenberg MS, Drinko J, Lever HM, Garcia MJ, Thomas JD. Abnormal strain throughout the base of the left ventricle in hypertrophic cardiomyopathy. . *J Am Coll Cardiol* 2000:35(2);423 (Abs).

Firstenberg MS, Garcia MJ, Greenberg NL, Drinko J, Odabashian J, Rodriguez L, Thomas JD. Preload and Beta-Receptor Induced Alterations in Ventricular Relaxation As Quantified by Tissue Doppler Echocardiography . *J Am Coll* 2000:35(2);495 (Abs).

Greenberg NL, Firstenberg MS, Cardon L, Garcia MJ, Thomas JD. Variation of tissue Doppler myocardial velocities due to perturbations in preload: A preserved relationship in normals. *J Am Coll Cardiol* 2000:35(2);495 (Abs).

Han P, Shiota T, Tsujino H, McCarthy PM, Qin JX, Bauer F, Travaglini A, Firstenberg MS, Thomas JD. Assessment of Aortic Annular Motion in Patients with Ischemic Cardiomyopathy by Real-time 3D Echocardiography (RT3DE) Before and After the Infarct Exclusion Procedure. *J Am Coll Cardiol* 2000:35(2);461 (Abs).

Qin JX, Shiota T, Tsujino H, Firstenberg MS, Cardon LA, Odabashian JA, White RD, Thomas JD. Validation of Real-time 3D Echocardiography for Quantifying LV Volumes in the Presence of a LV Aneurysm: In Vitro and Clinical Studies. *J Am Coll Cardiol* 2000:35(2);186 (Abs).

Chung MK, Schweikert RA, Firstenberg MS, Buda T, Natale A, Jaeger FJ, Niebauer MJ, Tchou PJ, Starling RC, Young J, Smedira N, McCarthy PM. Inducibility of Ventricular Tachycardia After Dor Procedures. *J Am Coll Cardiol* 2000:35(2);383 (Abs).