RICE UNIVERSITY

Motion Corrected Treadmill Nuclear Angiography

by

Liang Sun

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

Doctor of Philosophy

APPROVED, THESIS COMMITTEE:

John W. Clark, Jr., PhD, Professor, Chair
Electrical & Computer Engineering

Joseph Cavallaro, PhD, Professor
Electrical & Computer Engineering

Fathi H. Ghorbel, PhD, Associate Professor
Mechanical Engineering

Jeffrey L. Lacy, PhD, President
Proportional Technologies, Inc.

HOUSTON, TEXAS

APRIL, 2003
Abstract

First-pass radionuclide angiography (RNA) of the human heart is performed during peak treadmill exercise using a Multiwire Gamma Camera (MWGC) and an intravenous injection of ultra-short-lived radionuclide Tantalum-178. The study focuses on left ventricular function during treadmill exercise and the use of this technique in patients with coronary artery disease (CAD) is significant compared with other methods such as echocardiography. However, patient motion and resulting image blurring during treadmill exercise can significantly degrade resolution and introduce serious image distortion. To help eliminate the effects of patient motion, we have adopted an electromagnetic motion tracking system that can monitor the movement of patient’s left ventricle (LV), based on the real-time six-dimensional position and orientation of a sensor attached to the patient’s back, and the location of LV in the patient’s chest contour. This system implements a motion correction algorithm which significantly reduces the effects of motion artifact incurred in treadmill exercise RNA.

The motion correction algorithm is evaluated using dynamic phantom simulations, where an external radioactive marker is attached to a volunteer, who exercises at several different Bruce levels on treadmill. Correction accuracy is assessed by calculating the root mean square (RMS) error of the locations of the maximum activity pixel (centroid) in corrected and uncorrected images. These initial test results using a dynamic phantom show that the motion artifacts can be removed. The algorithm was also evaluated on patients undergoing treadmill exercise RNA. In evaluating clinical data, one must be careful to select the correct lung background beat, and find the proper LV beats to form
representative cycle, which yields reliable LV ejection fraction (EF) values. Motion-corrected images are superior with regard to the determination of ventricular wall motion and the calculation of regional ejection fraction images. In the uncorrected images, these are severely distorted and may result in an improper diagnosis.

The success of motion-corrected treadmill research points to a revolutionary new approach to stress imaging, which can potentially benefit millions of patients entering the health care system with chest pain symptoms by improving the accuracy of diagnosis, as well as, the cost-effectiveness of front-line methods of detecting cardiac dysfunction.

Key Words:

Radionuclide Angiography, First-pass Imaging, Motion Correction,

Treadmill Exercise
Acknowledgments

The completion of this dissertation could not have been fulfilled without the supports from Dr. Jeffrey Lacy, President of Proportional Technologies, Inc., and my academic advisor Dr. John Clark. Dr. Lacy patiently provided the vision, encouragement and advise on every aspect of the project for me to proceed through the doctoral research. I wish to thank Dr. Clark for his continuous guidance and helpful suggestions.

Special thanks to two professors in my thesis committee, Dr. Fathi Ghorbel and Dr. Joseph Cavallaro, for their commitments to stay with me through this process.

Many other people have provided invaluable assistance along the way. My sincere thanks to Mr. Christopher Martin and Mr. Dayang Dai for their help on system electronics and structure mechanics. Very special thanks to Dr. Athanasios Athanasiades for his participation in phantom studies. Many thanks to Mr. Henry Wallace, Dr. Robert Austin and Mr. Scott Thompson for their assistance on camera refurbishing and mechanical structure assembly. I was also blessed with many enthusiastic and caring colleagues: Myrna Edrada, Nisha Nayak, Avery Stephens, Jason Simmons, Troy Tuttle, Lu Bu, Nader Shehad, and Manan Atit in PTI. I am grateful to Dr. Jack Heo and Dr. Deval Mehta for performing clinical studies at UAB.

I would express the depth of my gratitude towards my parents Yuyu Sun and Shuzhen Hu and my dear wife Yao Wang. Thanks for their understanding, encouragement, and loving.

God promises us we are never alone on our journey of life. I held onto that promise as I journeyed through the doctoral experience. To Him, I give complete credit for completion of this process.
Table of Contents

1. Introduction..................................................................................................................1
   1.1 First Pass Radionuclide Angiocardiography.........................................................2
   1.2 Treadmill Stress Test............................................................................................5
   1.3 Previous Work of Motion Correction in Treadmill RNA.................................7
   1.4 Contributions of This Work in Clinical Exercise RNA.................................9
   1.5 Thesis Overview...................................................................................................12

2. Imaging System for Treadmill RNA.........................................................................14
   2.1 Overview...............................................................................................................15
   2.2 Multiwire Gamma Camera....................................................................................16
   2.3 High-Speed Digital Readout Electronics..............................................................22
   2.4 Motion Tracking Systems......................................................................................27
      2.4.1 Human Movement Tracking Technology......................................................27
      2.4.2 Evaluations of Motion Tracking Systems......................................................29
      2.4.3 Field Distortion and Interference.................................................................35
   2.5 Synchronization of Image and Position Acquisition........................................38

3. Motion Correction: Algorithms and Phantom Studies...........................................44
   3.1 Experimental Setup of Motion Correction............................................................45
   3.2 Motion Correction Algorithms............................................................................46
   3.3 Phantom Studies Results......................................................................................51
   3.4 Determination of LV Center Location................................................................55

4. Clinical Studies.........................................................................................................64
   4.1 Prognostic Value of Exercise RNA EF.................................................................65
4.2 Radionuclide Image Data Analysis..............................................................66
  4.2.1 End-diastole Frames Identification......................................................67
  4.2.2 Bolus Assessment.................................................................................69
  4.2.3 LV/RV Regions of Interest.................................................................70
  4.2.4 Background Subtraction and Editing Beats.........................................72
  4.2.5 End Diastole/Systole Regions.............................................................73
  4.2.6 Time Activity Curve and Ejection Fraction.........................................74
4.3 Significance of Motion Correction in Exercise RNA Analysis..................75
  4.3.1 Activity in LV: Corrected vs. Uncorrected.........................................77
  4.3.2 LV Representative Cycle: Corrected vs. Uncorrected.........................80
  4.3.3 Wall Motion and Regional EF Image: Corrected vs. Uncorrected.........82
4.4 Validation of Motion Correction by Referenced Resting RNA..................85
5. Discussion and Conclusion......................................................................90

Reference.........................................................................................................96

Appendix A: Flow chart diagram of image analysis software.......................100
List of Figures

1. Block diagram of treadmill RNA imaging and motion correction system .................. 15
2. Longitudinal diagram of MWGC detector ................................................................ 17
3. Point Spread Function measured at distance = 0 mm ........................................... 20
4. FWHM plotted against distance to AM-241 point source ....................................... 21
5. Schematic block diagram of high-speed digital image electronic readout unit ............ 23
6. Functional block diagram of PC I/O interface board .............................................. 26
7. Experimental setup for motion tracking evaluation .................................................. 31
8. Distortions of reconstructed errors in x, y and z coordinates ................................... 32
9. Experimental setup for metallic distortion evaluation ............................................. 35
10. Translational and rotational distortions at r = 35" .................................................. 36
11. Sequential timing diagram of position readout ..................................................... 40
12. Experimental setup of treadmill RNA studies with motion correction ................... 45
13. Multiwire camera conversion factor, measured based on 64 x 64 images ................ 50
14. Phantom studies setup for motion correction evaluations .................................... 51
15. Centroid position fluctuations in RNA point source images and RMSE .................. 52
16. Centroid position fluctuations in RNA at Bruce Level V ....................................... 54
17. Transmission scan images of 167 patients ............................................................ 57
18. Linear relationship between LV location and chest dimension ............................... 59
19. Histograms of linear prediction errors of LV depth and lateral position .................. 60
20. Effects of erroneous estimation of the LV location ................................................ 62
21. Sequential end-diastolic images during a study ..................................................... 68
22. Bolus evaluation .................................................................................................... 70
23. Drawing ROI in example study file.........................................................71
24. Activity histogram in example analysis................................................72
25. Left ventricular borders at end-diastole and end-systole....................73
26. Time activity curve and flow curve of LV representative cycle............75
27. Image analysis for motion-corrected treadmill RNA...........................77
28. Image analysis for uncorrected treadmill RNA....................................79
29. Images of LV representative cycle......................................................81
30. Left ventricular wall motion images...................................................82
31. Left ventricular regional ejection fraction images............................83
32. Regional EF values along LV long axis profile..................................84
33. Left ventricular volume determined from resting and corrected exercise RNA.....86
34. Left ventricular volume determined from resting and uncorrected exercise RNA...87
List of Tables

1. Physical characteristics and imaging performance of MWGC..............................17
2. Representative cathodes and anode signals and event position determination........25
3. Product specifications of two motion tracking systems.........................................30
4. Reconstruction RMSE for two motion tracking systems.........................................33
5. Translational and rotational distortions at different h with fixed r = 35”.................37
6. Errors in motion correction due to wrong estimation of LV center transverse plane...63
7. Ventricular volume response to upright exercise....................................................88
Glossary

Blood Pool Imaging
Blood pool imaging is a procedure in which the blood is labeled with a radionuclide tracer. Images can be produced in rapid sequence during first transit following bolus injection (first pass radionuclide angiography) or by gated imaging over several minutes. Such imaging enables evaluation of cardiac mechanical function by allowing visualization of the heart walls in action.

Bruce Protocol
Called the "Father of Exercise Cardiology," Robert A. Bruce is the developer of the standardized treadmill test for diagnosing and evaluating heart and lung diseases. The Bruce Protocol, as it has come to be known, is used by physicians the world over to test cardiovascular function. Specifically, different Bruce stages (levels) corresponding to treadmill speed (in mph) and inclination (in % grade) are listed below.

<table>
<thead>
<tr>
<th>Stage (Level)</th>
<th>mph</th>
<th>% grade</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7</td>
<td>10%</td>
<td>3 minutes</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>12%</td>
<td>3 minutes</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
<td>14%</td>
<td>3 minutes</td>
</tr>
<tr>
<td>4</td>
<td>4.2</td>
<td>16%</td>
<td>3 minutes</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>18%</td>
<td>3 minutes</td>
</tr>
<tr>
<td>6</td>
<td>5.5</td>
<td>20%</td>
<td>3 minutes</td>
</tr>
</tbody>
</table>

Coronary Artery Disease (CAD)
Coronary artery disease is the process in which the coronary arteries (arteries of the heart muscle) become narrowed or completely occluded. CAD can lead to a myocardial infarction (heart attack), in which portions of the heart muscle die, or myocardial ischemia (reduced blood flow), which may result in irreversible damage to the heart.
Gamma Rays, Gamma Emissions and Gamma Camera
Gamma rays are high-energy electromagnetic radiation emissions. They can penetrate materials like air and human tissue, more readily than x-rays, making them an ideal tool for examining the body's organs. A gamma camera is used to detect gamma emissions after a patient has been injected with a radioactive tracer. During the decay of the tracer, gamma rays are emitted. The camera detects the emitted gamma rays, and the position in the body from which gamma rays are emitted is recorded. Thus, an image of the distribution of the tracer in the body is obtained.

Left Ventricle (LV)
The left ventricle is one of four chambers in the heart. The left ventricle is the strongest chamber; it pumps oxygenated blood through the aorta to the active body.

Radionuclide Angiography (RNA)
Researchers use an imaging test called radionuclide angiography (RNA) to assess the heart's pumping capability by measurement of ejection fraction (EF) and cardiac wall motion. Inadequate blood flow in the coronary arteries, prior damage to the heart muscle, or heart failure are some of the conditions that can produce impaired function. A radioactive tracer is injected to label the blood, allowing clinicians to view the working heart by imaging its blood pool. In first pass RNA, which is the technique used with the multiwire gamma camera, the radioactive agent is injected rapidly into a vein in the arm as a bolus and images are collected only during the first transit of the bolus through the cardiopulmonary system.
Chapter 1

Introduction
1.1 First Pass Radionuclide Angiocardiography

Radionuclide angiocardiography (RNA) is a nuclear cardiology technique wherein blood is labeled by injection of a radioactive substance and imaged with a higher speed nuclear camera. The injected radionuclide is a tracer substance that is assumed to be distributed in direct proportion to the blood volume of any heart chamber, hence changes in radioactivity during the cardiac cycle are equivalent to volume changes in that chamber. The RNA technique has been used to measure cardiac function at rest, and during exercise, in hundreds of thousands of patients. Radionuclide measurement of ventricular function during exercise provides the opportunity to detect effects of exercise-induced ischemia on myocardial function, and it is one of the most useful independent sources of prognostic information for identifying patients likely to benefit from interventional therapy. The simplicity and low cost of such measurements also make them well-suited to be among the most important procedures to be performed in the evaluation of patients for stable chronic coronary artery disease (CAD) by providing a more rigorous and reproducible measurements of ventricular ejection function.

The sensitivity of exercise RNA for detection of CAD is greater than that of exercise electrocardiography (Borer et al., 1979; Gibbons et al., 1991). The increased sensitivity implies that mechanical manifestations of ischemia precede electrical manifestations. Recent findings (Lee et al., 1990) suggest that exercise ejection fraction (EF) is the most significant predictor of cardiovascular (CV) death among all noninvasive clinical variables (including the derived clinical indexes) and all invasive catheterization variables that they had previously determined in a large angiographic population to be
prognostically important. Consequently, abnormal exercise RNA findings may help to identify patients at increased risk, for whom invasive evaluation is indicated. Exercise RNA also improves outcome estimates that are based on information from clinical evaluation and cardiac catheterization. It may also help clarify the potential benefit of coronary revascularization, and assist in the selection of patients for revascularization procedures.

First-pass radionuclide angiocardiography (FP-RNA) is a technique whereby a bolus of a suitable radionuclide is injected into the venous circulation, and movements of the radionuclide are observed from the venous system into the right atrium, right ventricle, pulmonary artery, lungs, left atrium, left ventricle, and aorta. Images are acquired only during the initial transit of the radionuclide bolus through the heart, and once the tracer clears the left ventricle on its first pass, the acquisition is complete. As such, the acquisition time is very short, 15 to 20 seconds at rest and 5 to 15 seconds during exercise. By determining the change in radioactivity over time (i.e., by generating time-activity curves), it is possible to derive ejection fraction measurements from both the right and the left ventricles. It is also possible to measure ventricular and pulmonary blood volumes and to assess regional ventricular wall motion. The radionuclides typically used for first-pass studies include technetium 99m-labeled DTPA (diethylamine triamine pentacetic acid) and technetium 99m-labeled pertechnetate. Recently, ultrashort-lived radionuclides such as Tantalum-178 (half-life of 9 minutes) have been employed to reduce patient radiation dose significantly. First-pass studies have the advantage of short study acquisition time, the ability to eliminate within limits the effects of premature beats
during acquisition, and the ability to image the left and right ventricles with temporal separation avoiding interference of one with the other. Also background from other stationary sources the liner is substantially reduced.

Echocardiography is another modality that can be used to assess regional wall motion and global ventricular function of the heart. Comparatively speaking, radionuclide imaging techniques are superior in the following aspects: (a). The measurement of ejection fraction by radionuclide techniques depends on the measurement of changes in radioactivity within the left or right ventricle during the cardiac cycle, which is virtually independent of the shape of the ventricle or the distance between the heart and the detector. It is totally objective and well validated. The echocardiographic measurement of ejection fraction, on the other hand, is a geometric measurement of a few operator chosen ventricular cross-sectional images, such limited and subjectively chosen cross sections are assumed to represent the global performance of the ventricle. Furthermore, the quality and reliability of echocardiographic images varies inversely with the distance between the heart and the ultrasonic transducer so that sub-optimal studies are frequently performed in obese patients. As a result of these shortcomings, echocardiography delivers only a qualitative assessment of ventricular function. (b). When applied to the detection of ischemia during exercise, radionuclide methods can reliably and accurately evaluate peak exercise function. However, echocardiographic acquisition is often performed after the subject has stopped exercising on the treadmill. It has been well documented with radionuclide imaging techniques that there are rapid changes in ventricular volumes, ejection fraction, and regional wall motion immediately after
cessation of exercise. Consequently, there are no data available to suggest that echocardiography can be used to accurately measure the exercise ejection fraction, which is the single most powerful prognostic measurement in patients with coronary artery disease.

1.2 Treadmill Stress Test

The diagnostic and prognostic value of exercise first-pass RNA has been discussed in the last section. Today, the bicycle ergometer and the treadmill are the most commonly used devices for dynamic exercise testing. The bicycle ergometer is usually cheaper, takes up less space, and makes less noise. Upper body or chest motion is usually reduced, but care must be taken so that isometric exercise is not performed by the arms. The work load administered by the simple bicycle ergometers is not well calibrated and is dependent on pedaling speed. It is too easy for a patient to slow pedaling speed during exercise testing and decrease the administered workload. Although bicycling is a dynamic exercise, most individuals perform more work on a treadmill because a greater muscle mass is involved and most subjects are more familiar with walking than cycling, especially in the United States.

In most studies comparing exercise levels achieved using upright cycle ergometry or treadmill exercise, maximal heart rate values have been demonstrated to be roughly similar, whereas maximal oxygen uptake has been shown to be 6 - 25% greater during treadmill exercise (Myers et al., 1991). The treadmill offers several important advantages over the bicycle ergometer for exercise stress testing: (a) the wide range of treadmill
speed and slope affords greater flexibility in test design and administration; (b) maximal exertion on the treadmill is less often limited by fatigue, weakness or discomfort of the quadriceps muscles than with bicycle exercise; and (c) treadmill exercise results in a more uniform stress than bicycle exercise as reflected by comparable \( O_2 \) requirements per unit body weight at similar workloads for all subjects, regardless of their state of health or physical fitness (Naughton et al., 1988). Individuals are therefore more likely to reach aerobic capacity and peak-predicted heart rate with treadmill exercise (Potts et al, 1991).

Sullivan and co-workers (1984) studied 14 male patients with exercise test-induced angina and ST-segment depression with treadmill testing on three consecutive days to evaluate the reproducibility of certain treadmill variables. Measured oxygen uptake displayed very good reproducibility at peak exercise, the onset of angina, and the gas exchange anaerobic threshold. The heart rate and ST-segment displacement, the onset of angina, and the anaerobic-threshold gas exchange were found to be reproducible at peak exercise. Noninvasive estimates of myocardial \( O_2 \) demand and ischemia were also reproducibly determined.

When treadmill testing was first introduced into clinical practice, practitioners adopted protocols used by major researchers, for example, Bruce and his co-workers (1971). Stuart and Ellestad (1980) surveyed 1375 exercise laboratories in North America and reported that of those performing treadmill testing, 65.5% use the Bruce protocol for routine clinical testing. This protocol uses relatively large and unequal 2 to 3 MET
(metabolic equivalent) increments in work every 3 minutes. In our clinical studies, we also adopt Bruce protocol for treadmill testing.

During dynamic treadmill RNA, motion artifact is unavoidably introduced by motion of the entire body or by structures within the thorax. In two-dimensional (2D) radionuclide imaging, these artifacts present themselves predominantly as blurring or ghost repetitions of the moving structures along corresponding directions. Motion artifact prevention techniques used in medical imaging (e.g., MRI, SPECT) generally fall into three major categories: (a) techniques that prevent or restrict the motion of the patients during image acquisition; (b) methods that monitor position or track motion; and (c) methods that employ signal processing techniques to restore the image, incorporating information that is embedded in the image data. Due to the nature of treadmill exercise, the patient’s motion should not be tightly restricted, and hence the first technique is not applicable. The last technique is a post-processing method, which may be useful in restoring images corrupted by slight motion (and which are immune to motion prevention techniques). This latter technique is not appropriate for significant motions related to treadmill working or running. Hence, we focus attention on the motion tracking methodologies in the following section.

1.3 Previous Work of Motion Correction in Treadmill RNA

Techniques for motion correction during exercise FP-RNA have been pursued over the last decade. The Dual-isotope method is commonly-used by researchers to correct substantial chest motion during treadmill exercise. In this method, an external
radioactive marker (\(^{241}\)Am or \(^{125}\)I) is applied to the patient's sternum as a reference position (Groch et al., 1985; Foster et al., 1995). \(^{241}\)Am has a photopeak of 54 keV (or 30 keV for \(^{125}\)I) that is separable from the 140 keV peak of the \(^{99m}\)Tc, which is a combined function/perfusion radiopharmaceutical for the evaluation of myocardial perfusion in patients with suspected or known heart disease. During data acquisition, two simultaneous data sets are recorded, one for each photopeak. The principal photopeaks of the two isotopes are then separated. The location of the \(^{241}\)Am (or \(^{125}\)I) point can be tracked throughout the study. The \(^{99m}\)Tc raw image data are subsequently reregistered on a frame-by-frame basis according to the magnitude and direction of the motion marker in each frame.

The dual-isotope method has obvious drawback. Since the spatial location of the image data frame is repositioned only by moving the centroid location of the external point source two-dimensionally, the dual-isotope method is limited to plane movement corrections and inherently assumes that the patient is rotationally fixed about both horizontal and vertical spatial axes (an unrealistic assumption for a patient moving excessively at high treadmill exercise rates). An illustration given by Lacy (2000) clearly shows that with use of such 2-dimensional correction technique, the motion of subject is just partially corrected. The errors of motion correction are twice more than those of motion correction when the rotational data is incorporated.

To overcome the drawback of the dual-isotope method, Yano et al. (1995) developed a motion correction algorithm without an external point source (the single-isotope method),
wherein the uncorrected LV motion images are displayed for placement of a large region of interest (ROI) over the left ventricle (LV) and ascending aorta (AA). A time-activity curve for the ROI is then generated. The portion representing the LV phase (from end-diastole to end-systole) is selected by denoting a beginning and ending cardiac cycle. The centroid of this ROI is determined in each frame. The spatial location of the image data is repositioned by moving the centroid location for the composite image data frame over the LV phase (Acharya and Grenier, 1989). Although the single-isotope method yields similar motion-corrected results compared to traditional dual-isotope method, in both moving phantom and clinical studies, it is obvious that such achievements are obtained with sacrifice of a large reference region of the AA during image acquisition. For high-resolution cardiac RNA studies which focus on the LV region, inclusion of the unrelated region occupies a large amount of the image buffer, and significantly lowers the LV image resolution.

1.4 Contributions of This Work in Clinical Exercise RNA

As described in 1.1 and 1.2, patient’s ventricular ejection fraction derived from exercise RNA study is found to be the most significant predictor of cardiovascular event among all noninvasive and invasive clinical variables, and for exercise methodology adopted clinically, treadmill exercise has significant advantages over bicycle ergometer for stress testing. However, first-pass radionuclide angiographic analysis to quantify patient’s ventricular ejection fraction that had been done before were largely from resting study (Nichols, et al., 1994; Williams, et al., 1998), a few from bicycle ergometer study (Gibbons, et al., 1982), and only several from treadmill exercise study (Groch, 1985;
Yano, et al., 1995). The limitations of motion correction methods adopted in reported treadmill exercise studies were discussed in 1.3. Basically, all these correction methods - either the dual-isotope method by referencing to the location of external source, or single-isotope method by referencing to the location of ascending aorta, did not solve the problem fundamentally. The straightforward solution to eliminate the motion artifacts in left ventricle (LV) image during rigorous treadmill exercise is to track the translational and rotational 6-D movement of the LV itself during the image acquisition, and re-register the image file frame by frame from the tracking information, rather than following the moving locations of external source or other remote structure on the border of the LV chamber only in 2-D on the acquired image data.

Motion tracking technology was primitive about 10-20 years ago, when researchers had to rely on acquired cardiac nuclear images themselves to tell the movement of the screened target organ. More recently, new motion tracking (or motion encoding) technology has been well developed, as arisen from the motion picture animation industry. It gives full possibility to track the position of target organ in real time during nuclear imaging process, and directly corrects the movement of target organ in acquired images from the recorded position information. For example in clinical brain SPECT imaging, Fulton et al. (1999) adopted a mechanical six degree-of-freedom (DOF) tracker to accurately measure head movements during the study. When queried, the tracker reports the current position and orientation of the end effector in tracker coordinates. There are six parameters, three for reporting 3D position and three for pitch, yaw and roll. With information provided by the head tracking system and fully 3D reconstruction, the
accuracy of brain SPECT images can be considerably improved when significant head
motion occurs. Similarly, head motion due to a sneeze, cough, sudden awakening, or
response to pain during long-time PET scanning is widely regarded as a source of image
degradation and resolution loss. To solve this problem, Lopresti et al. (1999) utilized an
optical position-sensitive detector capable of simultaneously providing highly accurate,
high-frequency measurements of the position and orientation of the patient’s head during
scanning. This motion tracking device permits either retrospective or real-time re-
projection of lines-of-response (LOR) in PET imaging, and demonstrates exceptional
performance in terms of accuracy and stability. Such electro-optical tracking methods for
correcting motion artifacts is a much needed development, to fully realize the potential of
high-resolution PET imaging.

Unfortunately, so far there is no published literature on elimination of motion artifacts of
patient’s LV RNA images acquired during treadmill exercise, based on tracker
information to quantitatively measure heart movement during a study, as the
aforementioned methodologies addressed in SPECT and PET imaging studies. This is
partly due to technical factors. For example, the sampling rate of a recently developed
gamma camera is higher than that of SPECT or PET system (at least 40 Hz, i.e., 40
scintigraphic frames per second), whereas the highest position sampling frequency of the
aforementioned optical tracking system is 20 Hz. In addition, the relatively large size of
the position sensor and the complicated design of the tracking system, can limit the
rigorous movement of patient at peak exercise.
In this thesis, we will develop an RNA imaging system, with the latest development in human movement tracking technology, to accurately report the position of patient’s LV during treadmill first pass RNA study. The sampling rate of motion tracking system will be as high as 120 Hz, synchronized with the same high imaging sampling rate of the adopted gamma camera. With the information provided by the heart tracking system, the movement of patient’s LV due to treadmill exercise during RNA image acquisition can be restored in each acquired image frame. All image frames with restoration or compensation of the LV movement will form the corrected RNA image file during treadmill stress test, and will be analyzed using standard first-pass RNA image analysis software. The completion of this project will signify the first research work done to quantitatively locate the position of patient’s LV by an external tracker simultaneously with the treadmill RNA image acquisition, and motion artifacts in LV RNA images will be eliminated by physically tracking the movement of the LV itself.

1.5 Thesis Overview

Imaging system for treadmill RNA with motion tracking technology will be discussed in chapter 2. Functional components of the system include multiwire gamma camera, high-speed digital image readout electronics, and motion tracking system. Different kinds of motion trackers are evaluated and the one with minimum position determination error is selected. The selected motion tracker is also tested with field distortion and interference error, and the synchronization of image and position data acquisition is investigated. Chapter 3 will discuss motion correction algorithms and their applications in point source phantom studies. Movement of point source in phantom study RNA images will be
corrected directly from the 6-D position report from the tracker. The determination of LV center location from patient's chest contour information is discussed, as the study extends from tracking point source movement in phantom study to tracking LV movement in clinical study. Chapter 4 will use pre-developed standard software specifically designed for human cardiac first-pass RNA study to do comparative image analysis on raw and motion corrected RNA images acquired during patient's treadmill exercise. Quantitative diagnostic results obtained from the image analysis, such as LV regional ejection function and LV end-diastolic volume changes, yield significant results of tracking and correction of LV movement during treadmill RNA acquisition. Chapter 5 will discuss and conclude our novel development of motion-corrected treadmill RNA.
Chapter 2

Imaging System for Treadmill RNA
2.1 Overview

We develop a treadmill radionuclide angiocardiography (RNA) imaging system that includes a multiwire gamma camera (MWGC), high-speed digital read-out electronics, a motion tracking system, and back-end PC control and image processing.

Figure 1. Block diagram of treadmill RNA imaging and motion correction system.

A block diagram of the treadmill RNA system is shown in figure 1. The MWGC employs a pressurized xenon wire chamber detector, that has a high count rate capability and excellent image quality. A high-speed digital logic hardware interface (designed and manufactured by Proportional Technologies, Inc.) provides fast delay-line signal readout from the MWGC, with a maximum image formation rate of 160 frames per second. An external frame synchronization signal is sent to the position tracking system, for simultaneous acquisition of sensor coordinates from a sensor positioned on the back of the subject. Image and position data are fed into a Pentium IV 1.5 GHz PC, through the
data BUS and RS-232 serial port, respectively. Images are then processed to eliminate motion artifact frame by frame using the acquired 6-dimensional position information.

Each component in the imaging system is discussed in detail in the next several sections, particularly the performance evaluation of the motion tracking systems, and the synchronization of position recordings and image frames. The clinical safety issue of the entire system is discussed in the last section of this chapter. The motion correction algorithm and other software aspects of the system are discussed in considerable detail in chapter 3.

2.2 Multiwire Gamma Camera

Conventional gamma cameras utilize sodium iodide (NaI) crystals for detection of radiation. There are two distinct types of cameras available: single crystal and multicrystal cameras. In single crystal devices, count rate is limited by pulse pileup to about 150,000 count per second (cps) (Lewellen and Murano, 1981). This limitation in count rate hinders adequate cardiac first-pass imaging. Single crystal cameras also have large intrinsic image nonuniformities and require correction circuitry and frequent surveillance for drift (Abrahamson et al., 1981). Multicrystal gamma cameras (MCGC) possess improved count-rate capability, but have relatively poorer spatial resolution (1 cm), which is imposed by the size of their individual crystal elements (Heyda et al., 1984). To minimize these limitations, Lacy et al. (1974, 1984) developed a camera that employs a multiwire proportional detector rather than a NaI crystal. The inherent imaging characteristics of the multiwire gamma camera (MWGC) include spatial resolution,
count-rate performance, and image uniformity. Here, the MWGC is superior to both single and multicrystal NaI devices.

<table>
<thead>
<tr>
<th>MWGC Physical Characteristics and Imaging Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive area</td>
</tr>
<tr>
<td>Sensitive depth</td>
</tr>
<tr>
<td>Gas mixture</td>
</tr>
<tr>
<td>Gas pressure</td>
</tr>
<tr>
<td>Spatial resolution</td>
</tr>
<tr>
<td>Energy resolution</td>
</tr>
<tr>
<td>Maximum count rate</td>
</tr>
<tr>
<td>Total camera weight</td>
</tr>
<tr>
<td>External dimensions</td>
</tr>
</tbody>
</table>

Table 1. Physical characteristics and imaging performance of MWGC.

The MWGC produces a signal whose duration is one-tenth that of NaI. The basic physical characteristics of the detector are summarized in Table 1, and a longitudinal section through the device is shown in figure 2. The detector consists of two drift regions (A, B) and a detection region (C), contained within an aluminum pressure vessel having a thin aluminum entrance window of spherical shape.

![MWGC DETECTOR](image)

Figure 2. Cross sectional view of the multiwire gamma camera (MWGC).
A collimator acts as "lens" to the gamma camera by projecting an image of a source distribution onto the detector by allowing only those gamma rays traveling along a path perpendicular to the camera face within a tight opening angle to reach the detector. Those gamma rays not following this path are absorbed by the collimation. A photon entering through the aluminum window interacts with the pressurized gas (xenon) in region A, and produces free electrons and positive ions proportional to discharged energy. At low anode voltages, the electrons may recombine with the ions. At a sufficiently high drift field nearly all electrons are collected, and the detector is known as an ionization chamber. At yet higher voltages the electrons can avalanche in the very high field region within a few wire dimensions of the anode, thus creating a larger amplification of the number of electrons. As the positive ions left in the wake of the avalanche drift towards the cathode, a portion of the electrons (~10%) is delivered as signal. The amplified signal is picked up as a pulse from the anode wire plane and simultaneously induced signals are produced in the two cathode sense electrode grids.

Position determination of the anode avalanche is obtained by detection of the signals induced in the two cathode grids, which are oriented orthogonally to each other. Each wire of each cathode grid is attached to a tap of a discrete delay line, and position is sensed by measurement of the delay time between occurrence of the avalanche on the anode grid and arrival of the signals at the ends of the cathode delay lines. Unlike previously reported delay-line readout systems for medical applications (Perez-Mendez et al., 1976), very high-speed delay lines (delay = 10 nsec/cm) are employed. This provides
a maximum delay-line clearance time of less than 250 nsec and a typical mean clearance
time of 150 nsec. Therefore, rate performance is substantially improved with this system.

The performance characteristics of the MWGC are tested in various ways. Intrinsic
detector resolution is determined by irradiation of the detector along a narrow line (< 1
mm width). The resolution for x-ray energy at 28 keV determined by this technique is
2.5 mm full-width half maximum (FWHM), and 5 mm full width tenth maximum
(FWTM). Image uniformity is investigated by irradiation of the uncollimated detector
with an Am-241 source at a distance of 1.5 meters. Uniformity fluctuations of at most
± 5% are present. Most of the nonuniformity is confined to very high frequency
fluctuations within a spatial scale of less than 3 mm. The event-rate performance of the
camera is investigated by irradiation of the uncollimated camera with a 40-mCi Am-241
source. The results show that the peak count rate with 30% energy window and
ambiguity rejection is 850,000 cps. This is many times that of single crystal NaI cameras
which peak at about 150,000 cps. The MWGC is also tested for the effects of gas
contamination, which shows that no discernible deterioration of resolution on Cd-109
pulse-height spectrum occurred over a 90-day period.

Lacy et al. (1988) compared first-pass left ventricular RNA performed with the MWGC
to conventional left ventricular first-pass RNA performed with a multicrystal gamma
camera (MCC). The overall left ventricular count sensitivity (count/mCi/sec/
millisteratians, or "msr") was significantly higher with the MWGC (176±132 versus
108±49, p<0.001) yielding images of higher statistics with higher resolution collimation
(31 versus 63 msr). Left ventricular ejection fraction was $0.54 \pm 0.18$ by MWGC and $0.54 \pm 0.18$ by MCC with an excellent correlation between the two techniques ($r = 0.94$).

The detection of wall motion abnormality was virtually identical with the two techniques ($4.8 \pm 1.5$ by MWGC and $4.8 \pm 1.9$ by MCC). Intra and inter-observer reproducibility by MWGC was excellent ($r = 0.99$ and 0.99, respectively). Thus, adoption of this new MWGC technology in this project provides first-pass studies of higher statistical quality and improved resolution, affording more precise assessment of left ventricular performance.

Figure 3. Point Spread Function measured at distance = 0 mm.
The resolution performance of the MWGC detector is evaluated using a 1 mCi Am-241 point source, with High Sensitivity collimator on (hole length of the collimator is 1.1 cm). The Point-Spread Function (PSF) is defined as the profile of counts along a line through centroid pixel, and the Full Width Half Maximum (FWHM) from point spread function is regarded as MWGC resolution \textit{in vivo}. Figure 3 shows the PSF measured in this way for Am-241 source on the surface of the camera (distance = 0). The resolution determined is 6.92 mm FWHM.

The point spread functions are obtained for various distances between source and collimator. The FWHMs from these point spread functions are plotted in Fig. 4. The tests with different detectors yield similar results, wherein the FWHM resolution degrades roughly linearly with the increasing source distance from the MWGC surface.

![Figure 4. FWHM plotted against distance to AM-241 point source.](image)
From the transmission scan data, in average the distance from the LV center to the surface of front chest is 3.45 inches (or equivalently, 8.76 cm). Therefore, if the patient’s front chest is as close to the MWGC surface as possible, the FWHM resolution in heart radionuclide image is about 19 mm according to figure 4.

2.3 High-Speed Digital Readout Electronics

Encoding of the position of an event is accomplished using high-speed digital circuitry. The system electronics include two major functional units: a detector signal readout unit, and a data I/O transfer unit between the front-end board and the back-end PC ISA BUS.

The electronic block diagram of detector signal readout unit is shown in figure 5. In the first stage, the typical cathode-coupled delay-line chamber configuration is indicated. As an event occurs in the avalanche region, negative charge is delivered by the anode wire, whereas image positive charges are conducted through the cathodes. Injection of the smoothly distributed cathode signals into a continuous delay line provides a very simple means of determining avalanche location along the anode wire. Since the anode signal can be read immediately, whereas the cathode readout is delayed, this injection essentially converts the spatial image distribution into a time distribution allowing avalanche position to be determined simply by appropriate timing of the arrival of the delay-line output signals. The four original time delays obtained from each of the delay lines are first filtered by a window discriminator to narrow the pulse width. Subsequently, they are digitized by high-speed Emitter-Coupled Logic (ECL) counters at 300 MHz, which are gated on by the anode signal, and gated off by the delay-line outputs.
Figure 5. Schematic block diagram of high-speed digital image electronic readout unit.

The four digital values of delay times are passed on to a high-speed processing unit that forms the digital sum of the coordinates obtained from a given delay line (X or Y respectively). This sum value is compared with a constant value equal to the total delay of the delay line X or Y. This test rejects any confused events that result from pile-up or scatter within the detector gas. Simultaneously with the sum test, the programmable
logic chip also computes a difference between the delays on each axis and adds a digital offset value. This value for each axis in terms of 8-bit words is used as the event position (zero offset is conventionally assigned at the center of the chamber). The offset difference values (8-bit cord$x and 8-bit cord$y) are passed through a formatting circuit that sets the desired frame format up to $128 \times 128$ in frame size. The formatted digital position coordinates are transferred through a first in, first out (FIFO) image memory. Within a frame interval, hundreds of thousands of events occur. The frequency (or the number) of events occurred at any particular coordinate $(x, y)$ is evaluated by reading out the corresponding address of memory, adding 1 to the content of that memory, and writing it back to the original storage address. The image frame data [BD0 ... BD7] are finally transferred to PC I/O functional unit. The digital sum, difference logic, and memory read/add/write are implemented with high-speed Lattice Semiconductor Large Scale Integration (LSI) Programmable Logic Devices (PLDs). Another key component in high-speed digital image readout unit is Motorola micro-controller HC11, which plays import role in controlling and/or reading-back of positive and negative high voltages, 3-lead ECG input signal, threshold control, external frame synchronization signal, external foot pedal signal (as starting indicator of image acquisition), etc.

Table 2 provides better understanding of cathode and anode signal waveforms and determination of event location in detector chamber, by representative drawings of corresponding analog/digital (pulse) signals and schemes for avalanche position calculation.
Table 2. Representative cathodes and anode signals and event position determination.

The PCIO interface card is ISA compatible, which uses one of the PC's I/O expansion slots. The main function for this device is to facilitate data transfer between the PC computer and the Digital Image Readout Unit and it is described in Figure 6. There are two data paths between PCIO and the Digital Image Readout Unit. The first one is the 8-bit wide parallel high-speed data path for image data, which flows from Digital Image Readout Unit to PCIO. The other is the low speed serial data path. The serial data flows in both directions. The PC and the Digital Image Readout Unit exchange non-image related data via this path. ISA-bus provides 10-bit I/O address (A0-A9), through which PC sends out commands. PAL (Programmable Array Logic) is responsible for PC ISA bus address decoding. Particularly four addresses not conflicted with other PC interruptions are selected (0x280-0x283) for data/status read and command/control write.
HDPL (High Density Programmable Logic) contains the main control logic for the whole PCIO card. Primarily it functions as: (1) serial and parallel data conversion for the serial data path; (2) communication timing control; and (3) ISA bus logic.

Figure 6. Functional block diagram of PC I/O interface board. Signal descriptions: CD (Command Data): 8-bit serialized data; RD (Read Data); DIR (DIRection of data transfer); G (Gate signal); BALE (Byte Address Latch Enable)

The Windows 2000 operating system and its ancestors are not specifically designed for real-time applications. Receiving image data at 160 frames per second requires very fast response from PC. To ease the real-time requirement on the PC software, extra buffer is added on the PCIO. A 32KB IDT7203 FIFO chip serves the data buffer function. Digital
Image Readout Unit can burst the image data at the speed of 320 KB/sec into this FIFO buffer regardless whether the PC software is receiving them or not, and the PC software can read out the image data whenever the operating system grant it necessary resource to do so. In other word, when the image data arrive at PCIO, the PC software is not required to access the PCIO while the operating system is busy servicing other high level interrupt requests like system time, hard drive access etc.

2.4 Motion Tracking Systems

2.4.1 Human Movement Tracking Technology

Human movement tracking systems can be classified in terms of sensor/transmitter location relative to human body as: (a) inside-in; (b) outside-in; and (c) inside-out systems.

Inside-in systems are those which employ sensor(s) and transmitter(s) that are both positioned on the body (e.g., a glove with piezo-resistive flex sensors). The sensors generally have small form-factors and are therefore especially suitable for tracking small body parts (e.g., finger, eye, and toe). For larger body parts, bending or flexing sensors across joints involves a transfer of joint angle to the bend angle of the strip, which significantly reduces the accuracy of the technology. Since in our application large body parts (human torso) should be tracked accurately, this technology is not appropriate.

An outside-in system employs an external sensor that senses artificial source(s) or marker(s) on the body (e.g., an electro-optical system that tracks reflective markers).
Video camera-based technologies are widely used in the family of optical tracking systems. The optical tracker with the latest technology has high accuracy of 0.014" and a maximum update rate of 60 Hz (POLARIS system, Northern Digital Inc., Waterloo, Canada). Unfortunately, the performance of such technology is dependent on the type of lens or the field of view of the camera. Video camera-based technologies are only operational in a limited workspace due to the field of view of the camera(s). If accommodation of more intensive movement range is required and the field of view of one or multiple camera(s) is increased, tracking resolution is decreased. Currently, the most advanced 60 Hz framing rate technology available in optical tracking systems provides insufficient bandwidth. Due to these limitations, optical tracking systems are eliminated from consideration in this project.

Inside-out systems employ sensor(s) on the body that sense artificial external transmitter(s) (e.g., a coil moving in an externally generated electromagnetic field), or natural external source(s) (e.g., a mechanical head tracker using a wall or ceiling as a reference or an accelerometer moving in the earth’s gravitational field). The external transmitter is able to provide 6D world-based information (i.e., joint-axial rotation can be measured). Generally, inside-out systems are the products most frequently available in human movement tracking technology. Commercial products fall into three major categories: (a) electromagnetic position/orientation trackers; (b) acoustic position/orientation trackers; and (c) mechanical position/orientation trackers. Mechanical tracking systems are ruled out since all tend to be bulky and heavy, limiting movement and workspace availability in any treadmill exercise study. Another difficult
problem related with mechanical trackers is that they may not be sufficiently robust to fit multiple users of different height, weight and gender.

2.4.2 Evaluations of Motion Tracking Systems

Our search for a suitable motion tracking system has been narrowed to electromagnetic and acoustic systems. In the area of electromagnetic systems, Polhemus Inc. (Colchester, VT) manufactures 70% of the world’s supply of these systems. These systems consist of a fixed magnetic-dipole transmitting antenna called a “transmitter”, one or several movable magnetic-dipole receiving antennae called “sensor(s)”, and associated electronics. Both the transmitter and sensor antennas consist of three mutually orthogonal loops (coils). Excitation of a loop antenna produces a field that consists of a far-field component, the intensity of which decreases with the inverse square of the distance (r) between the transmitter and sensor (i.e., \(1/r^2\)). Excitation of each loop of the transmitter antenna by a driving signal identical in frequency and phase produces a single axis transmitter dipole. Transmitter excitation is a pattern of three states, wherein excitation of the transmitter results in a sensor output that consists of a set of three linearly independent vectors, which contain information sufficient to determine the position and orientation of the sensor relative to the transmitter. Essentially nine measurements are available to solve for the six unknowns of \(x\), \(y\), \(z\) for position and azimuth (yaw), elevation (pitch), and roll for orientation.

Acoustic trackers use high-frequency sound to triangulate a source within the work area. Most recently, InterSense, Inc. (Burlington, MA) has developed an advanced sensor
called InertiaCube, which is an integrated digital “smart-sensor” module that is based on micro-electro-mechanical systems (MEMS) technology. It has gyros and accelerometers built-in, as well as solid-state magnetometers. Position tracking is performed by accelerometry with ultrasonic drift correction, not just the pure time-of-flight trilateration that is used traditionally. This results in vastly improved update rates, resolution, and immunity to ultrasonic interference.

Consequently, we evaluated aforementioned two motion tracking systems. Manufacturer specifications are listed in table 3, yielding the impression that electromagnetic-based Polhemus system performs better than acoustic-based InterSense system, with smaller translational and rotational accuracy errors, and a larger rotational coverage.

<table>
<thead>
<tr>
<th></th>
<th>Polhemus Fastrak</th>
<th>InterSense IS-600 Mark 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Translation Accuracy</td>
<td>0.03” RMS</td>
<td>0.25” RMS</td>
</tr>
<tr>
<td>Angular Accuracy</td>
<td>0.15º</td>
<td>0.25º</td>
</tr>
<tr>
<td>Translation Coverage</td>
<td>30”</td>
<td>Between 24” and 108”</td>
</tr>
<tr>
<td>Angular Coverage</td>
<td>All-attitude</td>
<td>-80º to +80º</td>
</tr>
<tr>
<td>Maximum Linear Velocity</td>
<td>Not Specified</td>
<td>15 ft / sec</td>
</tr>
<tr>
<td>Maximum Angular Velocity</td>
<td>Not Specified</td>
<td>1200º / sec</td>
</tr>
</tbody>
</table>

Table 3. Product specifications of two motion tracking systems.

Our experimental evaluations of these motion tracking systems were designed as follows:

1. A motor-controlled rigid wooden rod was built to generate repetitive rotations around its center point.

2. The rotational speed of rod can be increased/decreased by adjusting the motor speed from level 1 (slowest) to level 10 (fastest).
3. The maximum linear speed of the moving rod reaches 38"/sec or 96.5cm/sec at motor speed level 5, which corresponds to the maximum speed of a subject’s movement during running at Bruce level V on the treadmill (derived from the analysis of the previously-recorded clinical data).

4. Two Polhemus system sensors, or two InertialCubes with SoniDiscs of the IS-600 system are firmly attached to both ends of the rigid rod shown in figure 7, so that the relative position between the sensors is fixed. (Note that sensor #1 coordinate and transmitter coordinate could be completely different).

![Figure 7. Experimental setup for motion tracking evaluation.](image)

A motion correction algorithm is developed (details in Chapter 3) to calculate the fixed location of sensor #2 in sensor #1 coordinates \((x, y, z)\) in terms of the directly-recorded absolute 6 degree-of-freedom (6-DOF) position data of the two sensors in the transmitter coordinate \((X, Y, Z)\). The two different motion tracking systems were tested under the same setup configurations of sensor locations and movement speeds. The fluctuations of three translational positions of sensor #2 in sensor #1 coordinate frame are shown in figure 8 (only results at motor level 5 are shown), along with quantitative root mean square (RMS) reconstruction errors corresponding to each translational direction.
Figure 8. Distortions of reconstructed errors in x, y and z coordinates.
<table>
<thead>
<tr>
<th>RMSE</th>
<th>Polhemus Fastrak II</th>
<th>InterSense IS-600 Mark 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X)</td>
<td>Motor Level 1</td>
<td>0.0193&quot; (0.049cm)</td>
</tr>
<tr>
<td></td>
<td>Motor Level 3</td>
<td>0.0232&quot; (0.059cm)</td>
</tr>
<tr>
<td></td>
<td>Motor Level 5</td>
<td>0.0196&quot; (0.050cm)</td>
</tr>
<tr>
<td>(Y)</td>
<td>Motor Level 1</td>
<td>0.0562&quot; (0.143cm)</td>
</tr>
<tr>
<td></td>
<td>Motor Level 3</td>
<td>0.0444&quot; (0.113cm)</td>
</tr>
<tr>
<td></td>
<td>Motor Level 5</td>
<td>0.0430&quot; (0.109cm)</td>
</tr>
<tr>
<td>(Z)</td>
<td>Motor Level 1</td>
<td>0.1037&quot; (0.263cm)</td>
</tr>
<tr>
<td></td>
<td>Motor Level 3</td>
<td>0.1051&quot; (0.267cm)</td>
</tr>
<tr>
<td></td>
<td>Motor Level 5</td>
<td>0.1107&quot; (0.281cm)</td>
</tr>
</tbody>
</table>

Table 4. Reconstruction RMS errors of location of sensor #2 in sensor #1 coordinate for two motion tracking systems.

Table 4 shows a more straightforward demonstration of the evaluation. From the table information, the following conclusions can be made:

- The RMS errors for the reconstructed relative x, y and z positions of sensor #2 in sensor #1 coordinate do not depend on the moving speed for both systems.
- The RMS errors for the reconstructed relative x, y and z positions of sensor #2 in sensor #1 coordinate of InterSense system are approximately 4-5 times larger than those of Polhemus system.

The experimental evaluations of the performances of two motion tracking systems are consistent with Manufacture’s specifications, in which the translation accuracy of IS-600 system is 8 times worse than that of Fastrak (0.25" vs. 0.03") and the angular accuracy of
IS-500 system is 1.6 times worse than that of Fastrak (0.25° vs. 0.15°). Our evaluations of the combined translation and angular accuracy show that the 6-degree accuracy of IS-600 is approximately 4.5 times worse than that of Fastrak. We further conclude that the Fastrak performs much better in meeting the required position accuracy, which will be addressed briefly below.

The normal RNA image format adopted in our studies has resolution of $32 \times 32$ pixels and the size of imaging area is $25cm \times 25cm$ or $9.84'' \times 9.84''$. According to Nyquist theorem (Gonzalez and Woods, 2002), a band-limited image function $f(x,y)$ can be recovered completely from sample whose separation is

$$
\begin{cases}
\Delta x \leq \frac{W_u}{2} \\
\Delta y \leq \frac{W_v}{2}
\end{cases}
$$

where $W_u$ and $W_v$ represent the widths in the image horizontal ($u$) and vertical ($v$) directions, respectively, of the smallest rectangle that completely encloses the region $R$. Therefore,

$$
\Delta x, \Delta y \leq \frac{1}{2} \times \frac{25}{32} = 0.3906 \text{ cm} = 0.1538 \text{ inch}
$$

(2.1)

and error fluctuations in position determination should be within the range of $\Delta x$ or $\Delta y$ (i.e., $\leq 0.39 \text{ cm}$ or $0.15''$). The maximum error of Polhemus tracking system shown in table 4 is $0.11''$, hence it will keep the original image information and properties. The maximum error of InterSense tracking system is $0.58''$, which is well beyond the Nyquist sample range and will result in image aliasing (Gonzalez and Woods, 2002). Because it involves under-sampling, aliasing manifests itself through high-frequency components masquerading as low-frequency ones. In images, it appears as low-frequency patterns scattered throughout the image.
2.4.3 Field Distortion and Interference

Although the electromagnetic (EM) Polhemus motion tracking system has been selected for our study purpose, it should be recognized that conductive or ferrous metals can distort the projected EM field. The presence of other active electronic devices may also result in field distortion via interference, producing inaccurate position readings from the tracking system. In our imaging system setup, the MWGC detector has an aluminum cover. Although the sensor is worn on subject’s back during actual experiment, wherein its separation distance from the aluminum camera cover is at least the width of subject’s chest, the effects of metallic environment on EM sensor reading still needs careful evaluation.

The testing setup used is shown in figure 9. The position of the sensor in the transmitter coordinate frame is kept the same by rigid connection, the distance between the sensor and the MWGC detector \((h)\) varies from 6.0” to 16.0” with incremental step of 1.0”. Three sets of tests were done at transmitter/sensor separation distances of \(r = 15”\), 25” and 35”, respectively.

Figure 9. Experimental setup for metallic distortion evaluation.
For each set in the test, the relative distance between the transmitter and the receiver ($r$) is kept the same, whereas the distance between the receiver and the MWGC detector ($h$) was varied from 6.0” to 16.0” in incremental steps of 1.0”. Since the detector head represents a large metal object, it can affect the accuracy of motion tracking system, since that system relies on EM measurements.

\[ h = \text{distance from sensor to collimator (inch)} \]

\[ d = \text{deviation (inch)} \]

\[ \text{Polhemus Test 3 (r = 35.0")} \]

Figure 10. Translational and rotational distortions at $r = 35”$

Figure 10 shows translational and rotational distortions of sensor position readings at $r = 35”$. These results represent the “worst” case since accuracy of sensor position readouts diminishes with transmitter/sensor separation due to the fact that the magnetic field generated by the transmitter falls off with the square of the distance.

Qualitatively, the relationship among $r$, $h$ and deviation is:

- At fixed $r$, deviation increases with decreasing $h$ (when the sensor moves closer to the detector).
- At fixed $h$, deviation increases with increasing $r$ (when the sensor moves further away from the transmitter).
• In actual experimental situations, $r$ should be sufficiently large to allow free movement of the subject, and $h$ should be small enough to allow accurate image recordings of the MWGC.

<table>
<thead>
<tr>
<th>$h$</th>
<th>$\Delta x$ (inch)</th>
<th>$\Delta y$ (inch)</th>
<th>$\Delta z$ (inch)</th>
<th>$\text{Yaw}$ (degree)</th>
<th>$\text{Pitch}$ (degree)</th>
<th>$\text{Roll}$ (degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0.02215</td>
<td>0.02018</td>
<td>0.012104</td>
<td>0.173</td>
<td>0.1079</td>
<td>0.0413</td>
</tr>
<tr>
<td>14</td>
<td>0.04447</td>
<td>0.04288</td>
<td>0.016522</td>
<td>0.269</td>
<td>0.142</td>
<td>0.0711</td>
</tr>
<tr>
<td>13</td>
<td>0.07365</td>
<td>0.08115</td>
<td>0.022743</td>
<td>0.451</td>
<td>0.2387</td>
<td>0.1135</td>
</tr>
<tr>
<td>12</td>
<td>0.10992</td>
<td>0.12304</td>
<td>0.035207</td>
<td>0.721</td>
<td>0.4009</td>
<td>0.1812</td>
</tr>
<tr>
<td>11</td>
<td>0.1566</td>
<td>0.1811</td>
<td>0.05751</td>
<td>1.088</td>
<td>0.6408</td>
<td>0.2973</td>
</tr>
<tr>
<td>10</td>
<td>0.22861</td>
<td>0.25516</td>
<td>0.091893</td>
<td>1.57</td>
<td>0.915</td>
<td>0.4643</td>
</tr>
<tr>
<td>9</td>
<td>0.32111</td>
<td>0.35113</td>
<td>0.148256</td>
<td>2.273</td>
<td>1.3486</td>
<td>0.7211</td>
</tr>
<tr>
<td>8</td>
<td>0.48062</td>
<td>0.48037</td>
<td>0.248545</td>
<td>3.32</td>
<td>1.9227</td>
<td>1.146</td>
</tr>
<tr>
<td>7</td>
<td>0.74266</td>
<td>0.64578</td>
<td>0.439322</td>
<td>4.787</td>
<td>2.6086</td>
<td>1.8972</td>
</tr>
<tr>
<td>6</td>
<td>1.17445</td>
<td>0.83778</td>
<td>0.784936</td>
<td>6.717</td>
<td>3.2471</td>
<td>3.1829</td>
</tr>
</tbody>
</table>

Table 5. Translational and rotational distortions at different $h$ with fixed $r = 35''$.

Table 5 shows actual readouts of sensor position as it moves closer to the camera surface at $r = 35''$. Both translational and rotational distortions are within the Nyquist range of 0.15'' (equation 2.1) for values of $h$ as small as 11'', which in most cases corresponds to the minimum chest width of the subject. This evaluation supports the feasibility of using the EM Polhemus tracking system for our study.
2.5 Synchronization of Image and Position Acquisition

Synchronization of sensor's 6-DOF position record to the current RNA image frame is one of the most crucial aspects involved in image motion correction. As discussed in the whole system diagram (figure 1), a position record is acquired by the motion tracking system upon receipt of an external frame synchronization signal (FSS), which is generated by the HC11 micro-controller within the digital image readout electronic unit, simultaneously with the formation of a current RNA image frame. Therefore, we study the actual latency period measured from the start of the external sync signal transmission to the first indication of a response from the Polhemus motion tracking system.

ANSI/IEEE Standard 100-1977 defines the latency period as “the time elapsing between the application of a stimulus and the first indication of a response”. This definition however, does not mention the time required to transmit the response. Therefore, in our consideration of synchronization in position and image data acquisition, we need to examine both aspects: the “Sync-to-Output Latent Period” and the “ASCII Output Record Transmit Period”.

Sync-to-Output Latent Period

The latent period of the Polhemus FASTRAK system consists of three component processing periods: (a) the time required to sample the magnetic fields \( t_1 \); (b) the time to solve for the receiver coordinates \( t_2 \); and (c) the time to make the solutions available for output \( t_3 \) (Jones, 2000).
Application of an external synchronization pulse initiates magnetic field sampling, a period that lasts about 3.5 ms.

\[ t_1 = 3.5 \, ms \]  \hspace{1cm} (2.2)

The samples are then solved for receiver coordinates, a period that requires another 2 ms.

\[ t_2 = 2.0 \, ms \]  \hspace{1cm} (2.3)

The solution is then placed in an output buffer and is made ready for transmission over the interface in use, a period that is assumed to be very fast.

\[ t_3 = 0.0 \, ms \]  \hspace{1cm} (2.4)

The total “Sync-to-Output” latent period is the sum of (2.2), (2.3) and (2.4):

\[ T_1 = t_1 + t_2 + t_3 = 5.5 \, ms \]  \hspace{1cm} (2.5)

Note that \( T_1 \) is independent of update rate.

**ASCII Output Record Transmit Period**

The factory default ASCII output record \( x - y - z - \alpha - \beta - \gamma \) is composed of 47 bytes (3 status bytes, 6 data words each 7 bytes long, and a CR LR terminator). If the system is set at 57.6 kBaud (maximum Baud-rate with error-free RS232 transmission), the time required to transmit 47 bytes ASCII data is:

\[ T_2 = \frac{47 \, \text{bytes} \times 8 \, \text{bits/byte}}{57.6 \, \text{bits/ms}} = 6.528 \, ms \]  \hspace{1cm} (2.6)

Therefore, the full period from the beginning of the external Sync to tracker 6-DOF position readout is:

\[ T = T_1 + T_2 = 5.5 + 6.528 = 12.028 \, ms \]  \hspace{1cm} (2.7)
The maximum sampling rate of external Sync signal applied to the Polhemus system is 120 Hz (i.e., a period of 8.33 ms). At such a sampling rate, it is clear that the 6-DOF position readouts would not have enough time to complete, according to equation (2.7). To analyze this problem, we assume that the three consequent position recordings can be represented as follows:

Record 1 of ExtSync1: \( X_1 \ Y_1 \ Z_1 \ \alpha_1 \ \beta_1 \ \gamma_1 \)
Record 2 of ExtSync2: \( X_2 \ Y_2 \ Z_2 \ \alpha_2 \ \beta_2 \ \gamma_2 \)
Record 3 of ExtSync3: \( X_3 \ Y_3 \ Z_3 \ \alpha_3 \ \beta_3 \ \gamma_3 \)

The sequence of the formation of position record and readout in first three image external sync periods is shown in figure 11.
From the sequential timing diagram of the Polhemus position record formation and corresponding readout (figure 11), the lack of synchronization between the position report and the external sync signal can easily be seen. The detailed timing sequence is explained as follows:

1. With reception of the 1st external sync signal, the Polhemus system starts to generate first 6-DOF position record of the tracker, which takes 5.5 msec \((T_1\text{ in equation 2.5})\). Although the PC keeps reading data from the RS-232 port which is interfaced with the Polhemus, there is no data readout during this 5.5 msec period, since the Polhemus is not ready to put the data in an output buffer.

2. By the end of the Polhemus Record Generation phase (i.e., the falling phase of Rec. Gen. Signal), the PC starts the effective read period, during which \(x - y - z - \alpha - \beta - \gamma\) data are reported sequentially. However, while the effective reading process is proceeding, the 2nd external sync signal arrives.

3. Since the PC reports the position record every external sync period, the first 6-DOF position report is incomplete and results in a partial readout of the buffer. The PC spends approximately \(2.83/6.5=44\%\) of its total effective reading time in the 1st external sync period, thereafter only X1, Y1 (or, X1, Y1 and Z1) are read out.

4. From the beginning of the 2nd external sync pulse, the Polhemus starts to form the second record of tracker position, which again takes 5.5 msec. Simultaneously, the PC spends the first 3.67 msec of this period trying to read out the remaining 6-DOF position data related to the record #1 in the buffer \((Z1, \alpha 1, \beta 1\text{ and } \gamma 1)\). This read period ends before the complete formation of record #2 by Polhemus. Hence
there is an idle PC read period, since there is nothing in the buffer although the PC
sattempts to read something.

5. At the end point of record #2 formation, the PC begins its 2nd effective read
period, which extends into the 3rd external sync signal period. Again, the PC can
not finish reading out all the position data related to record #2, and only gets a
part out (X2 and Y2) by the end of the 2nd external sync pulse. Therefore, the
position record reported by the PC during the 2nd external sync is (Z1,
\( \alpha_1, \beta_1 \) and \( \gamma_1 \), X2, Y2).

6. The remaining actual data corresponding to record #2 is delayed and reported in
the external 3rd sync pulse period. Similarly, the PC just catches the first two
readouts of the record #3 before the advent of the 4th sync pulse.

Experimentally, the above characterized non-synchronized position records captured by
the PC have been tested. The testing software is simple, namely at each external sync
loop, write all the readouts from the RS-232 buffer and the external sync index number to
a temporary file. A representative result is as follows:

\[
\text{ExtSync 1: } X1 \quad Y1 \quad Z1 \quad | \quad \text{ExtSync 2: } \alpha_1 \quad \beta_1 \quad \gamma_1 \\
X2 \quad Y2 \quad Z2 \quad | \quad \text{ExtSync 3: } \alpha_2 \quad \beta_2 \quad \gamma_2 \\
X3 \quad Y3 \quad Z3 \quad | \quad \text{ExtSync 4: } \alpha_3 \quad \beta_3 \quad \gamma_3
\]

For example, in the period of ExtSync2, the PC reports the tracker current positions on X,
Y and Z (X2, Y2 and Z2) and the previous positions on \( \alpha, \beta \) and \( \gamma \) (\( \alpha_1, \beta_1 \) and \( \gamma_1 \)). If we
wish to correct the motion artifact in image #2, related to the ExtSync2, three
translational position data (X2, Y2 and Z2) of the current record and three rotational
position data of the following record (\( \alpha_2, \beta_2 \) and \( \gamma_2 \)) should be used. In this way, one
can achieve the desired synchronization of the position record with the external sync signal.

It should be noted that if the sampling frequency of the external sync is equal or less than 80 Hz (i.e., period of external sync is $\geq 12.5$ msec), the position record adjustment for the synchronized reporting is not be needed, since $12.5$ msec > $T$ in equation (2.7) and the Polhemus/PC system has sufficient time within the external sync period to form and transmit the position data.
Chapter 3

Motion Correction:

Algorithms and Phantom Studies
3.1 Experimental Setup of Motion Correction

The experimental setup of treadmill RNA imaging studies with motion correction is shown in figure 12. The subject wears a back-support harness, where the mobile Polhemus sensor is attached, and the transmitter is mounted on a swing arm extended from the MWGC structure frame (connection is not shown in the figure), and acts as global reference coordinate.

Figure 12. Experimental setup of treadmill RNA studies with motion correction.

In clinical studies, the back sensor tracks the movement of human heart via two sources of positioning information: real-time back sensor position (in transmitter coordinates) and heart position (in back sensor coordinates). The second source information has a relatively fixed value if there is no movement of heart within the human torso. The rigid
connection assumption is adopted throughout all our studies. An estimate of the center of the left ventricle in human chest contour is determined from clinical transmission scan data (discussed in detail later in this chapter). The addition of a point source in front of subject’s chest is used only for the phantom evaluation of motion correction hardware and algorithms. In the experimental setup used in such phantom studies, the back sensor tracks the movement of the point source from two sources of information: the real-time position of the back sensor in global transmitter coordinates, and fixed point source displacement in back sensor coordinates.

3.2 Motion Correction Algorithms

A 3D coordinate transformation includes terms for the position (translation) and orientation (rotation) of the transformed object. To express translation and rotation in the same manner, homogeneous matrices are used. For a 3D translation, homogeneous matrices have a supplementary dimension. The $3 \times 3$ rotational matrix is extended by adding a fourth column and a row of zeroes with the exception of the last element, which is assigned a value of $1$.

The transformation $H$ corresponding to a translation by a vector $ai+bj+ck$ is
\[ H = \text{Trans}(a, b, c) = \begin{bmatrix} 1 & 0 & 0 & a \\ 0 & 1 & 0 & b \\ 0 & 0 & 1 & c \\ 0 & 0 & 0 & 1 \end{bmatrix} \]  

where \( i, j, k \) is unit vectors along \( x, y, z \) coordinate direction.

The transformations corresponding to rotations about the \( x, y \) or \( z \) axes by an angle \( \theta \) are

**Roll:**  
\[ \text{Rot}(x, \theta) = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos \theta & -\sin \theta & 0 \\ 0 & \sin \theta & \cos \theta & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]  

**Elevation or Pitch:**  
\[ \text{Rot}(y, \theta) = \begin{bmatrix} \cos \theta & 0 & \sin \theta & 0 \\ 0 & 1 & 0 & 0 \\ -\sin \theta & 0 & \cos \theta & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]  

**Azimuth or Yaw:**  
\[ \text{Rot}(z, \theta) = \begin{bmatrix} \cos \theta & -\sin \theta & 0 & 0 \\ \sin \theta & \cos \theta & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]  

The Polhemus Fastrak II system reports 6-DOF data in the following sequence: three translations, azimuth, elevation and roll degrees. Having defined an object, yaw corresponds to a rotation \( \alpha \) about the \( z \) axis, pitch corresponds to a rotation \( \beta \) about the \( y \) axis, and roll corresponds to a rotation \( \gamma \) about the \( x \) axis. When these rotations, together with the translations, are applied to the object (i.e., the \( xyz \) coordinate axes with a \( z-y-x \) rotation sequence) the transformation can be expressed as:

\[ \text{TRANS} = H \cdot \text{Rot}(z, \alpha) \cdot \text{Rot}(y, \beta) \cdot \text{Rot}(x, \gamma) \]  

(3.5)
In general, if we pre-multiply the frame transformation by a transformation representing a translation and/or rotation, then that translation and/or rotation is made with respect to the base reference coordinate frame (Eq. 3.6).

\[ \text{POS} = \text{TRANS} \cdot P \]  

(3.6)

\( P \) is the fixed position vector of heart (in clinical studies) or point source (in phantom studies) relative to the back-sensor in Sensor coordinates:

\[ P = \begin{pmatrix} Px \\ Py \\ Pz \end{pmatrix} \]  

(3.7)

\( \text{POS} \) is the calculated new position of heart or point source in global reference Transmitter coordinates, from known back sensor translational movement \( ai + bj + ck \) and rotations \( \alpha, \beta \) and \( \gamma \). Let \( \text{TRANS} \) be written in the explicit form of equation (3.5). We can therefore write a transformation \( \text{POS} \) representing the position and orientation of the heart or point source in global transmitter coordinates as:

\[ \begin{bmatrix} \cos \alpha \cos \beta & -\sin \alpha \cos \gamma + \cos \alpha \sin \beta \sin \gamma & \sin \alpha \sin \gamma + \cos \alpha \sin \beta \cos \gamma \\ \sin \alpha \cos \beta & \cos \alpha \cos \gamma + \sin \alpha \sin \beta \sin \gamma & -\cos \alpha \sin \gamma + \sin \alpha \sin \beta \cos \gamma \\ -\sin \beta & \cos \beta \sin \gamma & \cos \beta \cos \gamma \end{bmatrix} \]

\[ \begin{bmatrix} a \\ b \\ c \end{bmatrix} \]  

(3.8)

\[ \text{POS} = \begin{bmatrix} \text{POS}_x \\ \text{POS}_y \\ \text{POS}_z \end{bmatrix} = \text{TRANS} \cdot \begin{bmatrix} Px \\ Py \\ Pz \end{bmatrix} \]

\[ \begin{bmatrix} (\cos \alpha \cos \beta)Px + (-\sin \alpha \cos \gamma + \cos \alpha \sin \beta \sin \gamma)Py + (\sin \alpha \sin \gamma + \cos \alpha \sin \beta \cos \gamma)Pz + a \\ (\sin \alpha \cos \beta)Px + (\cos \alpha \cos \gamma + \sin \alpha \sin \beta \sin \gamma)Py + (-\cos \alpha \sin \gamma + \sin \alpha \sin \beta \cos \gamma)Pz + b \\ (-\sin \beta)Px + (\cos \beta \sin \gamma)Py + (\cos \beta \cos \gamma)Pz + c \end{bmatrix} \]  

(3.9)
Through equation (3.6), coordinates corresponding to the coordinate system determined by sensor on the body (a moving coordinate system) can be translated to coordinates with respect to the fixed laboratory inertial coordinate system (i.e., transmitter). Consequently, the real-time movement of heart or point source, or instantaneous changes of heart or point source position in the global transmitter coordinate frame due to body motion during treadmill exercise, can be precisely tracked in terms of real-time changes of back sensor 6-DOF position in the transmitter coordinate \((a,b,c,\alpha,\beta,\gamma)\), and fixed displacement of heart or point source in the back sensor coordinate \((Px,Py,Pz)\). In order to perform the correction, each image frame must be corrected back to some arbitrary but fixed reference point. The computed average of the position data is adopted as the reference point so that image data would be lost only from the periphery. If the position of heart or point source expressed in transmitter coordinates \((POS_{x,ref}, POS_{y,ref}, POS_{z,ref})\) is regarded as a reference, motion effects can be fully eliminated by a re-alignment of the subsequent images to the reference position by "undoing" the corresponding \((POS_{x}, POS_{y}, POS_{z})\) displacements. That is,

\[
\begin{align*}
\Delta x &= (POS_{x} - POS_{x,ref}) \times scale \\
\Delta y &= (POS_{y} - POS_{y,ref}) \times scale \\
\Delta z &= (POS_{z} - POS_{z,ref}) \times scale
\end{align*}
\] (3.10)

Note \(\Delta x, \Delta y\) and \(\Delta z\) are in the context of image coordinate, a conversion factor \(scale\) is adopted to relate displacements in global room coordinate (in the unit of inches) to those in image coordinate (in the unit of pixels). Since RNA images are 2-D, generally only changes in two directions (e.g., \(\Delta x\) and \(\Delta y\)) need to be applied to the original images to eliminate motion effects.
It is first necessary to calculate the conversion factor *scale* between pixels and linear distance in space. Experimentally static images of an Am-241 point source are acquired at different positions along the surface of the multiwire camera. The pixel containing the maximum activity (centroid) is used to represent the position of the point source. Static images are collected in $64 \times 64$ pixel format, and displacements of the maximum activity pixel are measured and recorded (in pixels) in the image coordinate. A correlation plot (linear fitting) of the measured point source position displacement and the corresponding pixel displacement of source in the image is shown in figure 13. A pixel calibration of 4.60 pixel/inch is obtained for the $64 \times 64$ pixel image. In the real-mode acquisition software, image correction is performed on a $32 \times 32$ pixel image. Therefore, the calibration factor becomes 2.30 pixel/inch or 0.91 pixel/cm.

![Graph showing the relationship between point source displacement and maximum activity pixel](image)

$y = 4.60x + 17.30$

Figure 13. Multiwire camera conversion factor, measured based on $64 \times 64$ images.

Usually the translational restoration displacements $\Delta x$ and $\Delta y$ of image motion correction are not exactly equal to an integer number of pixels. In such a case, a $2 \times 2$ neighborhood weighting image mask is applied to calculate a restored pixel value from percentages of its overlapping with the 4 neighboring original pixel values.
3.3 Phantom Studies Results

The motion tracking system and the motion correction algorithms were tested by phantom studies simulating the clinical conditions of treadmill exercise RNA, as shown in figures 12 and 14. The mobile sensor was firmly attached on a harness back support, which was worn tightly by a volunteer (figure 14a). The volunteer exercised at Bruce Levels III, IV and V (figure 14c) with an Am-241 radioactive point source securely strapped over the lower sternum and shielded so that no significant radiation exposure was received (figure 14b). Motion correction was performed using predictions of source position determined via equation (3.9), in terms of back sensor 6-DOF readouts, and the known fixed-value of point source 3-D displacement in the back sensor coordinate frame.

(A)  
(B)  
(C)  

Figure 14. Phantom studies setup for motion correction evaluations.

Movements of the point source during treadmill exercise phantom studies were corrected using equations (3.9) and (3.10). If the motion tracking worked perfectly, stationary MWGC images of the point source should be obtained. Accuracy of the correction is quantified by tracking the position of the maximum activity pixel (centroid) in uncorrected and corrected images in terms of pixel index both in horizontal and vertical
directions. The RMS errors of the centroid point positions of uncorrected and corrected images are calculated to verify the performance of the motion correction algorithms.

Bruce Level III

![Graph A](image1)

RMSE: 1.4281/0.4073

uncorrected  corrected

![Graph B](image2)

RMSE: 1.7964/0.3801

uncorrected  corrected

Bruce Level IV

![Graph C](image3)

RMSE: 1.9077/0.4248

uncorrected  corrected

![Graph D](image4)

RMSE: 2.9716/0.4516

uncorrected  corrected

Figure 15. Centroid position fluctuations in uncorrected and corrected RNA point source images and corresponding RMSE values. (A) Horizontal direction (Bruce III); (B) Vertical direction (Bruce III); (C) Horizontal direction (Bruce IV); (D) Vertical direction (Bruce IV).
Ideally the centroid pixel position in corrected image should stay same through all sequential image frame indexes (i.e., flat line as a function of frame index). Figure 15 shows the fluctuations of the centroid pixel position in horizontal and vertical image directions of uncorrected and corrected MWGC point source image sequences, from a volunteer exercising at Bruce Level III (treadmill speed at 3.4 mph, inclination at 14%) and Level IV (treadmill speed at 4.2 mph, inclination at 16%) respectively. Corresponding RMSE values are provided for quantitative comparison.

Overall the RMSEs of centroid location in corrected image coordinates are significantly smaller than those in uncorrected image coordinates. In transition from Bruce level III to level IV, the subject had to change exercise mode from walking to running, which resulted in an increased bouncing of centroid location in the uncorrected MWGC point source images. The upward/downward (vertically from 1.80 to 2.97 pixels) and leftward/rightward (horizontally from 1.43 to 1.91 pixels) motions are indicated by larger peak-peak amplitude of centroid location at Bruce level IV. The more rigorous motion at level IV also produces more frequent movement in both directions. Despite large changes in RMSEs of centroid location in uncorrected images, the centroid location RMSEs in corrected images remain almost unchanged. All values of corrected RMSEs are around 0.4 pixels in representative 32×32 image format (1 pixel = 1.10 cm), or 0.174” (0.442 cm). Recalling the motion reconstruction RMSEs intrinsic to Polhemus system tested in table 4 (maximum value of 0.111” or 0.281 cm), the measured point source MWGC centroid RMSEs are consistent with those values.
Point source phantom studies were also done at the most rigorous exercise (Bruce Level V, treadmill speed at 5.0 mph, inclination at 18%). Centroid point fluctuations and RMSEs in horizontal and vertical uncorrected/corrected image coordinates are shown in figure 16. It can be seen that the movement frequency of the subject is further increased (obviously in horizontal direction). Uncorrected and corrected horizontal/vertical centroid location RMSEs are similar to those in figure 15(c) and (d) at this treadmill running level.

Bruce Level V

![Graph showing centroid position fluctuations and corresponding RMSE values at Bruce Level V.](image)

Figure 16. Centroid position fluctuations in uncorrected and corrected RNA point source images and corresponding RMSE values at Bruce Level V. (A) Horizontal direction; (B) Vertical direction.

Evaluations of phantom studies in this section suggest that the Polhemus motion tracking system and motion correction algorithm constitute a very reliable way to eliminate the significant body motion during treadmill exercise RNA imaging. The RMS values of
remaining correction errors are within the range of half pixel. In digital images, each pixel is a discrete sample of the original scene. According to equation (2.1) and Nyquist theorem, the motion correction is performed at twice or more the highest spatial frequency in the scene, hence avoiding aliasing in the image after correction. In phantom studies, the movement of point source mimics the movement of heart in clinical experiments. Point source 3-D position in back sensor coordinate \((P_x, P_y, P_z)\) can be directly measured by putting another sensor right at the source location. In order to apply the system and algorithm to track the heart movement, the movable center of the left ventricle (LV) in back sensor coordinates should be accurately determined.

### 3.4 Determination of LV Center Location

Since the cardiac left ventricle (LV) is our target imaging structure in the human body, the location of LV center in back sensor coordinate frame \((P_x, P_y, P_z)\) is a very crucial parameter in motion correction algorithms. The goal of this section is to develop a general algorithm to find the position of left ventricular center from the human chest contour measurements on the transverse section plane in the middle thorax crossing the LV center. Errors arising from imprecise estimation of the depth of the LV center from the back of the torso, as well as the lateral position of LV center from left (or right) side of the torso, and the vertical cross section level of chest contour, are studied. The subsequent erroneous LV movement predictions are evaluated and the effects on motion corrected images are analyzed on representative treadmill exercises.
The location of left ventricular center in human thorax is determined from transmission scans of 167 patients (Data from Emory University, Atlanta, GA). All scans are performed on a 21 slice Posicam PET scanner (Positron Corp., Houston, TX) equipped with a rotating rod transmission source. The central slice through the LV (as determined by the operator during processing) is analyzed. Figure 17 shows central slice images for each patient profile, which includes 82 females and 85 males, with the average weight of 163 lbs. The patients are arranged from left to right, top to bottom by increasing weight from 102 to 243 lbs. The highlighted area indicates the region of the left ventricle.
Figure 17. Transmission scan images of 167 patients.
The body edge is found using a simple thresholding technique, specifically by searching from the outside into the center of each image with a $2 \times 2$ mask. The first mask with averaged pixel value greater than 50 (in 0-255 gray scale image) is the outer edge of the body. The geometric center of the ventricular outline is then calculated and the displacements of this LV center point from left, right, front and back sides of the body outline are obtained in image pixels. The information of LV center location is finally transformed into millimeters based on image spatial sampling format (1 pixel = 6.8 mm).

The location of LV center in the transverse thorax is modeled in terms of following definitions:

*Depth of the Chest* is the maximum distance from the front side of the body outline to the back side of the body outline.

*Depth of the LV Center* is the distance from the LV center to the back side of the body outline.

*Width of the Chest* is the maximum distance from the left side of the body outline to the right side of the body outline.

*Lateral Position of the LV Center* is the distance from the LV center to the left side of the body outline.

The relationship between the depth of the LV and the depth of chest, and the relationship between the lateral position of the LV and the width of chest are studied in figure 18. Both relationships can be well-characterized by linear functions, with correlation coefficients of 0.8876 and 0.6931 respectively. Accurate determination of the depth of
LV is more important compared to that of the width of the LV, since the rotational movement during treadmill exercise is about the patient’s sagittal plane and different estimates of LV depth in the transverse plane will predict different heart movements, especially in horizontal direction (will be discussed in detail later).

\[ y = 0.755x - 1.001 \]  

\[ y = 0.388x - 0.359 \]

Figure 18. Linear relationship (A) between LV depth and chest depth; and (B) LV lateral position and chest width.

The remaining errors of linear prediction of LV depth as a function of chest depth are analyzed to see if they are dependent upon the width of the chest. Similarly, the remaining errors of linear prediction of LV lateral position as a function of chest width are analyzed to see the dependencies upon the depth of the chest. Quantitative analysis shows that the linear prediction errors of LV depth (based on the chest depth information) are independent of the chest width parameter, and the linear prediction errors of LV lateral position (based on the chest width information) are independent of the chest depth.
parameter. Therefore, the depth ($D$) and lateral position ($W$) of the LV center can be simply modeled as linear function:

$$
\begin{align*}
D &= 0.755d - 1.001 \text{ (inch)} \\
W &= 0.338w - 0.359 \text{ (inch)}
\end{align*}
$$

where $d$ is the depth of the chest and $w$ is the width of the chest. Both parameters can be obtained by chest contour measurement on the patient’s torso.

![Histograms of linear prediction errors of LV depth (A) and lateral position (B). Gaussian fittings with stand deviation values are also shown.](image)

Figure 19. Histograms of linear prediction errors of LV depth (A) and lateral position (B). Gaussian fittings with standard deviation values are also shown.

Figure 19 shows histograms of linear prediction errors of the depth and lateral position of LV center locations on 167 patients’ data. A Gaussian function, or “hypothesis test”, is applied to fit the error histogram, as a basic method of exploring possible differences between estimates and actual data. The area under the Gaussian curve represents probability: 68.26% of cases will lie within 1 standard deviation of the mean, 95.44%
within 2 standard deviation, and 99.14% within 3 standard deviations. In another words, there is less than 1% chance that the linear prediction error of LV center will lie outside 3 standard deviations. Therefore, in the following studies we assume a prediction error of 3 standard deviation values on the depth and width of the LV center, to determine the extent to which heart motion correction is degraded.

To study the effects of erroneous LV center estimation on heart motion correction, we intentionally add an error to the control value of depth or lateral location of the LV center with 3 times the standard deviation listed above (i.e., 0.936 and 1.623 inch, respectively). Assuming that the control value results in ideal or freezing radionuclide images of the left ventricle, the additional fluctuations upon the changes of depth or width determination are due to the incorrect LV center estimation. Figure 20 shows remaining uncorrected motions caused by 0.936 inches or 1.623 inches overestimation on the LV center depth or width, with a typical subject's movement profile on treadmill exercise Bruce Level IV.

Quantitatively, the remaining uncorrected motion due to the erroneous estimation of LV center position can be identified by root mean square error (RMSE) of the remaining fluctuations in Figure 20. It can be seen that maximum possible RMS error of motion correction due to erroneous LV center determination is about a quarter of a pixel (0.265).
Figure 20. (A). Erroneous estimation of depth of the LV center (by 0.935 inch) resulting in erroneous motion correction in image vertical direction; (B). Erroneous estimation of depth of the LV center (by 0.935 inch) resulting in erroneous motion correction in image horizontal direction; (C). Erroneous estimation of lateral position of the LV center (by 1.623 inch) resulting in erroneous motion correction in image vertical direction; (D). Erroneous estimation of width of the LV center (by 1.623 inch) resulting in erroneous motion correction in image horizontal direction.
In the above studies, we discussed the effects of erroneous determinations of depth and lateral position of the LV center on the heart motion correction. In fact all the analyses so far are based on the assumption that the transverse plane across the LV center has been accurately identified. Therefore, the effects of erroneous determination of position of this LV center transverse plane should also be evaluated. Table 6 provides quantitative RMS errors of the remaining fluctuations on the uncorrected motion due to incorrect identification of the transverse plane, with vertical displacements from 1.0” to 3.0”. The maximum possible RMS error of motion correction due to erroneous LV center plane determination is 1/6 of a pixel (0.168).

<table>
<thead>
<tr>
<th>Error Source</th>
<th>Vertical Fluctuations in Corrected Image (Pixel)</th>
<th>Horizontal Fluctuations in Corrected Image (Pixel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erroneous LV center transverse plane estimation (±1.0&quot;)</td>
<td>0.0132</td>
<td>0.0346</td>
</tr>
<tr>
<td>Erroneous LV center transverse plane estimation (±2.0&quot;)</td>
<td>0.0217</td>
<td>0.0953</td>
</tr>
<tr>
<td>Erroneous LV center transverse plane estimation (±3.0&quot;)</td>
<td>0.0322</td>
<td>0.1680</td>
</tr>
</tbody>
</table>

Table 6. Errors in motion correction due to wrong estimation of LV center transverse plane.
Chapter 4

Clinical Studies
4.1 Prognostic Value of Exercise RNA EF

Exercise EF is the most significant predictor of cardiovascular (CV) death among all noninvasive clinical variables (including the derived clinical indexes) and all invasive catheterization variables. Lee et al. (1990) investigated the prognostic applications of RNA and its ability to stratify patients into subgroups at low and at high risk of dying or experiencing future cardiac events. A few RNA variables, including exercise EF, rest EF, exercise/rest end-diastolic LV volume, exercise wall motion abnormalities, exercise systolic blood pressure, etc., are considered in the study. Results imply that the most useful information for predicting prognosis is neither the patient’s EF before exercising nor the amount by which the EF changes during exercise. Neither the rest EF nor ΔEF alone adequately describes prognosis for medically treated patients with coronary artery disease (CAD).

In predicting future CV events in patients with CAD, exercise EF is considerably stronger than any other variables at predicting the occurrence of CV mortality and any CV event. The relation between exercise EF and the hazard (risk) of CV death was depicted as: For exercise EF of less than 0.50, the risk of death increases linearly as EF decreases, with the highest risk occurring at the lowest EFs. For exercise EF of more than 0.50, there is no gradation in CV morality. A similar relation exists for total events. For example, Cox model analysis with multiple variables (Cox, 1972) suggests that, a patient whose exercise EF is 13 points lower than that of another patient has an increased risk approximately equivalent to that conferred by having one additional major coronary artery with a 75% or greater stenosis. Considering the entire range of EF values, the
effect of exercise EF on outcome is clearly nonlinear (see figure 1 in Lee et al., 1990). Quantitatively, 46 of the 90 CV deaths and 51 of the 147 CV events occurred in the 105 patients with exercise EFs of less than 0.35. Patients with a depressed exercise EF are considerably more likely to have future cardiac events, particularly a fatal event, compared with patients whose exercise function is normal. Although two patients with equivalent exercise EFs may have a similar prognosis, it is certainly possible that the mechanism of death could be different in the patient whose EF substantially decreases with exercise compared with the patient whose EF increases from rest condition. Therapeutic approaches to reduce mortality may also be different in those patients.

4.2 Radionuclide Image Data Analysis

After the first-pass RNA is acquired and motion correction is performed on the image data, correspondingly follow-up image analysis is necessary to obtain LV (or RV) representative cycle images, time activity curve (TAC), and ejection fraction (EF). Although image acquisition and analysis are distinct steps, normally analysis is done immediately following acquisition in order that any technical deficiencies can be detected in time to repeat the study if required. Specialized software was developed for RNA image analysis, as performed in the following processing step. Detailed flow chart diagram of image analysis software is illustrated in Appendix A.
4.2.1 End-diastole Frames Identification

All end-diastole frames recorded during the study are located utilizing the digitized ECG signal recorded during image acquisition. The normal ECG is composed of a P wave, a QRS complex, and a T wave. The P wave is caused by electrical potentials generated as the atrial depolarization prior to contraction, the QRS complex is caused by potentials generated when the ventricles depolarize prior to contraction, and the T wave is caused by potentials generated as the ventricles recover from the state of depolarization. Before contraction of cardiac muscle can occur, depolarization must spread through the muscle to initiate the chemical processes of contraction. Therefore, the QRS wave occurs immediately before the beginning of contraction of the ventricles (end-diastole). The ventricles remain contracted until a few milliseconds after repolarization has occurred.

Each end-diastolic frame is identified by selection from image frame sequence corresponding to peaked R wave in the accompanied ECG recording. Proper pickup of each end-diastolic frame is crucial to calculate the accurate end-diastolic LV volume and hence results in correct estimation of LVEF index, which is defined as:

\[
\text{LVEF} = \frac{\text{LV end - diastolic volume} - \text{LV end - systolic volume}}{\text{LV end - diastolic volume}}
\] (4.1)

Each end-diastolic frame is averaged together with its two preceding and two succeeding frames. This averaged frame is then nine-point filtered and displayed on screen for the entire study.

Figure 21 shows end-diastolic (ED) frames of a representative resting-study of a patient presenting with chest pain. 32 ED frames are displayed sequentially from left to right,
from top to bottom. The first three ED frames are merely scatters from the injection line and syringe, prior to injection of the radioactive tracer. The 4\textsuperscript{th} frame shows appearance of the activity in the superior vena cava (SVC). The tracer proceeds with blood from the right atrium to the right ventricle (RV) and into the pulmonary system through the pulmonary artery, as frames #5, #6 and #7 reflect activities in right ventricle (RV) and in transition from RV to lung. After passing through pulmonary circulation, which are indicated by frames #8, #9 and #10, the tracer moves from the left atrium to the left ventricle (LV) as shown in frames #11 and #12. After the LV phase, the tracer finally moves out to the systemic circulation through the aorta (frame #16). In the first-pass studies, intensive analysis is focused on heart dynamics during the tracer's initial transit through the RV phase, lung phase and LV phase (i.e., frames #4 to #16 in this example).

![Sequential end-diastolic images during a study.](image)

Each ED frame is normalized to the maximum pixel value according to the color scale given at the right in figure 21. Thus, even though a region in one frame may be the same
color as a region in another frame, this does not mean that these regions have the same amount of activity (i.e., counts).

4.2.2 Bolus Assessment

In first-pass imaging, a rapid bolus is very important for a good study. Therefore, bolus assessment is performed immediately after beat-to-beat end-diastolic frames identification, to ascertain whether a quality bolus injection indeed takes place.

To assess bolus entry, the first end-diastolic image frame with superior vena cava (SVC) activity is selected. In this study, ED frame #4 is chosen for bolus evaluation. To create the SVC region of interest (ROI), a line representing a cross-section of the SVC is drawn in order to assess the speed of bolus entry (figure 22A). The software algorithm then constructs a histogram which shows the activity in the ROI across several heartbeats. With a good bolus, the activity should enter over a single heartbeat. A slow increase in activity which then levels off rather than a sharp peak and drop, suggests a poor bolus. Since the activity passes through the right ventricle to the lungs fairly quickly, lung activity can often show up in the latter part of the SVC histogram, especially if the patient’s heart is high in the camera’s field of view even after the motion correction.

The markers on the histogram (figure 22B) indicate end diastole. In this study the bolus is very good, which comes in just over a single heartbeat (ED frame #4).
4.2.3 LV/RV Regions of Interest

With the first-pass technique, isolation of the LV and RV entails background subtraction of the lung phase. The first clear LV frame following the lung phase, which contains apical activity, is selected (frame #12 in figure 21). The ROI is drawn based on a rough estimation of the location of the LV. It has been shown by other imaging techniques, including echocardiography and MRI, that the base of the heart, including the aortic valve plane, moves toward the apex during systole (Arts, et al., 1993; Qi, et al., 1993). In patients with a normal LVEF, the descent of the base of the heart exceeds 10 mm (Alam & Rosenhamer, 1992). Thus, it is not essential that the ROI precisely defines the left ventricle, since end diastolic ROI is likely to have substantial contamination from the end-systolic counts within the aortic root and sinuses of Valsalva. Precisely drawing the ROI would also exclude the counts in the basal portion of the ventricle at end-diastole. Both of these types of errors would result in a lowering of the EF values (Williams et al., 1997). Hence generally ROI should include more area near the base and the apex (figure 23A). Similarly, the last frame before the lung phase with right ventricular activity
(substantial activity may be starting to ascend the pulmonary artery) is selected (frame #5 in figure 21), and the ROI for the RV is drawn (figure 23B).

Figure 23. Drawing ROI in example study file. (A). LV ROI; (B). RV ROI.

After the LV and RV ROI's are created, the computer constructs activity histogram for the LV or the RV region. Because the right ventricle wraps around the left ventricle, the LV histogram graph will have two peaks: one when the activity was concentrated in the RV and one when the activity was in the LV (figure 24A). The trough located in between the two peaks represents the lung phase. The algorithm selects all ventricular beats if their activity at end-diastole is >70% of the maximal LV activity at end-diastole. The computer then combines the selected LV beats to form a single representative cycle image sequence with back-filling algorithm, and applies a spatial (2-4-2 convolution) filter. The RV histogram graph is constructed in the same way, wherein the activity concentrated in RV ROI is more obvious and the trough representing the lung phase is also clearly seen (figure 24B).
4.2.4 Background Subtraction and Editing Beats

![Image of activity histogram and ROI selection](image)

Figure 24. Activity histogram in example analysis. (A) in LV ROI; (B) in RV ROI; (C). LV beats determination and lung background ED frame selection.

Based on the ROI's that were drawn, the computer selects an appropriate lung background beat by locating the beat with minimal activity in the LV and RV regions of interest. The end systolic frame of this beat serves as the lung background frame (figure 24C), which must be multiplied by a scale factor <1 to correct for the washout from lung to LV phase. To quantify the washout, a lung region of interest (LROI) is defined as that
region outside of the LV region in the lung background frame whose count is above 30% of the maximum extra-ventricular count. The ratio of LROI count in the end-diastolic LV frame to those in the lung background frame reflects the lung background activity remaining during the LV phase. The lung background frame is multiplied by this ratio and the resulting frame is subtracted from all of the beats/frames selected to form the final LV image.

4.2.5 End Diastole/Systole Regions

By identifying the areas of increasing activity, the computer creates an image with guide borders for the end diastolic and end systolic regions of the LV (figure 25). To aid in locating the valve plane, pixels in which activity increases from end-diastole to end-systole are flagged on the representative cycle end-diastole frame. The accurate LV region is then outlined on this frame by following the border of the flagged region in the valve plane area and along the 30% isocontour in other areas (Lacy et al., 1982).

![Figure 25](image)

(A) (B)

Figure 25. Left ventricular borders at (A) end-diastole, and (B) end-systole.
A poor bolus or a low ejection fraction can result in the appearance of descending aortic activity in the delineated LV region. This is seen as a protrusion from or extension of the inferior region of the LV. In this case, the protrusion should be cut off rather than being included in the LV region. The valvular plane midpoint and the apex point are identified, which will create an axis to be used to divide the image into 6 sectors. Regional EF’s and time-activity curves are calculated for each of these sectors.

### 4.2.6 Time Activity Curve and Ejection Fraction

The software calculates time-activity curve (TAC) and ejection fraction (EF) for the final LV image, which is a composite of the beats selected after the background has been subtracted. The final LV-TAC and the corresponding representative cycle images are scaled throughout the diastolic phase. The scaling rigorously corrects for varying activity dilution resulting from the fact that during diastole, blood with lower radionuclide activity relative to that remaining from the last systole is entering the ventricle. Each point in the diastolic phase \( (C_d) \) is corrected by

\[
C_d' = \frac{C_{\text{beg-syst}}}{C_{\text{end-diast}}} \cdot \frac{C_d - C_{\text{end-syst}}}{C_{\text{end-diast}} - C_{\text{end-syst}}} \tag{4.2}
\]

where \( C_d' \) is the scaling factor, \( C_{\text{beg-syst}} \) is counts at beginning of systole; \( C_d \) is the original counts before scaling; \( C_{\text{end-diast}} \) is counts at end-diastole and \( C_{\text{end-syst}} \) is counts at end-systole. Thus, counts at end-systole are unchanged while counts at end-diastole are scaled to equal the counts at the onset of systole. This curve is then filtered by 2-4-2 convolution.
Figure 26. Time activity curve and flow curve of LV representative cycle.

The EF is computed from the end-diastole and end-systole points in the TAC, as:

\[ EF = \frac{(\text{end diastolic counts} - \text{end systolic counts})}{\text{end diastolic counts}} \]  \hspace{1cm} (4.3)

EF value of patient’s study is 67%.

A flow curve is computed by differentiating the TAC and plotting it along with the TAC. Figure 26 shows TAC and flow curve for the representative LV cycle of the example clinical study. The activity in LV region is maximal at the beginning of the cycle (end-diastole), then drops down as LV contracts with shrinking volume until it reaches end-systole. After that, the activity increases slowly as LV refilled and returns back to the maximum activity at the beginning of the next cycle (next end-diastole).

4.3 Significance of Motion Correction in Exercise RNA Analysis

Under cardiologist supervision, patients are exercised to symptom-limited peak stress following the Bruce protocol on the treadmill. Patients are monitored using a 12-lead
EKG and blood pressure monitoring equipment. Normally venous access is obtained with an 18-gauge intercath inserted in a medial antecubital vein. At peak exercise defined as 85% of predicted heart rate or onset of symptoms, dynamic image acquisition is begun at 120 Hz sampling rate, and Ta-178 (half life = 9.3 min) is immediately injected as a tight bolus using a 30 mL saline flush. Peak exercise level is maintained during the 30 second first pass image acquisition. Vigorous treadmill exercise can result in loss of data due to patient’s lateral and vertical motion outside the camera’s field of view (FOV). Towards this end, acquisition software is embedded with algorithms for live-time graphical display of the patient’s heart position relative to the camera’s FOV during the acquisition. This feedback method ensures acquisition of high quality studies and minimizes throw-outs. Before the treadmill exercise, the patient is fitted with a snug harness tightly, on which the motion sensor is attached firmly. The location of the center of the patient’s left ventricle in sensor coordinates is estimated from the individual chest contour information as detailed in 3.4, and such frame transformation vector as defined in equation (3.7) will be adopted as that in equation (3.9) to track the real-time position of patient’s LV, corresponding to each acquired LV RNA image frame during treadmill stress study. Motions of LV in each image frame (totally about 3600 frames acquired for 30 seconds duration) can be eliminated by re-positioning it to the reference position by “undoing” the LV movements reported by the tracking system, as in equation (3.10). Motion correction in every image frame based on tracker information will be done throughout all acquired 3600 frames, and all corrected frames will be saved as corrected treadmill RNA image file. The uncorrected (raw) and corrected treadmill RNA image files for the same patient study will be analyzed by a standard image analysis software,
which will objectively evaluate and compare the quality of corrected and uncorrected treadmill RNA image data.

### 4.3.1 Activity in LV: Corrected vs. Uncorrected

Figure 27 shows ED frames of a motion-corrected treadmill RNA study (female patient, age 34, weight 270 lbs, achieved peak heart rate of 150 BPM by walking on the treadmill at Bruce level 2).

![Image Analysis for Motion-Corrected Treadmill RNA](image)

**Figure 27.** Image analysis for motion-corrected treadmill RNA. (A) Lung background ED frame and LV beats ED frames selection; (B) Activity histogram in LV ROI; (C) Activity histogram in RV ROI.
The bolus injected was very good, passing through the SVC region within two cardiac cycles (ED frames #7 and #8). LV and RV ROIs are drawn on ED frames #17 and #9 respectively. Lung background is identified as frame #10, which is determined from LV ROI activity histogram (figure 27B), where the lung ED frame activity bin is located after dropping from the initial peak representing the RV phase. In this study, the LV ROI activity histogram has a diminished second peak due to the large size of the patient. The activity of lung phase is comparable to that concentrated in LV so that the trough located in between the two peaks nearly disappears. LV beats are manually selected after the lung phase, if activity related to the corresponding ED frames is 70% of the maximal LV activity (70% threshold line is clearly indicated in figure 27B to aid selection). In this study, ED frames #13-17 are adopted to form the representative LV cycle.

Figure 28 shows comparative analysis on uncorrected treadmill RNA study (raw images). As in figure 27A, LV and RV ROIs are drawn on the same ED frames with similar contour shape. The activity histogram in LV ROI (figure 28B) gives a striking example of how significantly the image quality is degraded without motion correction. The gaps every several bins embedded in the time activity histogram (i.e., sudden drops in activity in LV ROI on one ED frame, then back to normal level on the next ED frame) are direct reflections of rhythmic movement of the patient during treadmill exercise. The reason is that the LV ROI (or RV ROI) is fixed throughout all ED frames acquired. Ideally the tracer activity profile in the region should be a smooth function with monotonic increase as the tracer accumulates or monotonic decrease as the tracer leaves. Small fluctuations
may be possible but significant changes especially deep gaps in activity profile do not occur, due to the continuous nature of unidirectional flow of the tracer with blood.

Figure 28. Image analysis for uncorrected treadmill RNA. (A). Lung background ED frame and LV beats ED frames selection; (B). Activity histogram in LV ROI; (C). Activity histogram in RV ROI.

The two deep gaps shown within the two peaks of the histogram (activity in RV and LV respectively) in figure 28B are the consequences of movement of RV and LV during image acquisition, but the corresponding ROIs are assumed to be stationary in the
analysis. Therefore the counts (i.e., activity) within the ROI vary greatly as the actual LV region in the acquired images moves out and back in the LV ROI mask set up in the analysis software. A closer observation of LV activity histogram on raw images suggests periodic occurrence of gaps in the profile (figure 28B), which is clearly resulted from periodic patient movement in both horizontal and vertical direction while walking on the treadmill. It is clear that such gaps in the time activity histogram can have performed effect in image analysis. For example, the deep trough in the second peak or LV phase will be mistakenly regarded as a pulmonary beat and the corresponding ED frame (frame #15) can be picked up as lung background frame. This is totally different and certainly wrong, compared to the lung phase selection analyzed in figure 27B. To proceed with comparative studies of corrected and uncorrected images regarding other aspects (such as LV representative cycle which will be discussed later), we manually select the same lung background frame (frame #11) and LV phase frames (frames #13-17) as the same in figure 27A.

4.3.2 LV Representative Cycle: Corrected vs. Uncorrected.

Figure 29 shows the LV representative cycle images, the corrected and uncorrected stress cycles are shown in (A) and (B) respectively. End-diastole is taken as the first frame of the representative cycle, and end-systole is defined as the frame with the minimum counts in the histogram. In both cases, 16 images are selected to form the cycle. The sequential corrected images clearly show end-diastolic activity in LV at the beginning of the cycle (figure 29A), then the activity diminishes as the LV contracts and pumps blood out to the aorta, the LV phase reaches end-systole around frame #10 with minimum activity.
Afterwards the fresh blood coming out from pulmonary circulation to refill the left ventricle, indicated by increasing activity in LV (also initiation and accumulation of activity in left atrium can be seen in figure 29A). The activity peaks at the end of the cycle, which is end-diastole and right before the starting frame of next LV cycle. Comparatively, the uncorrected images shown in figure 29B, which are obtained by processing the raw acquired images without motion correction, show serious shape and size distortions. There is discontinuity in LV blood pool at the end-diastole at the beginning of the cycle, the LV activity decreases significantly and even no activities can be seen in some frames around end-systolic phase. The LV activity restores later but obviously not enough to indicate the end-diastole of next cycle. Due to the underestimation of end-systolic activity in LV representative cycle with uncorrected images, the patient's peak exercise EF from uncorrected raw data file is overestimated (86%, compared to 83% from analysis on corrected images).

![Figure 29. Images of LV representative cycle. (A). Corrected RNA; (B). Uncorrected RNA.](image-url)
4.3.3 Wall Motion and Regional EF Image: Corrected vs. Uncorrected

Figure 30. Left ventricular wall motion images: (A). After motion-correction; (B). Before motion-correction.

Left ventricular wall motion images before and after patient’s motion correction are shown in figure 30. The corrected image (figure 30A) shows normal ventricular anatomy, whereas the uncorrected image (figure 30B) shows a very distorted and disordered shape as a result of the effects of motion blurring.

Regional ejection fraction image (REFI) is calculated on a pixel by pixel basis, and is commonly adopted to evaluate regional contractile function of ventricles. The presence of regional contraction abnormality usually results from acute myocardial infarction, though it may also occur as a consequence of ischemia during exercise stress test. In REFI, the ejection fraction at each point within the ventricular border is displayed according to the indicated normalized color scale. In this patient’s study, LV REFI from motion-corrected images (figure 31A) and that from raw uncorrected images are shown respectively. With motion correction, regional ejection fraction within the left ventricle
peaks along the inferior and superior wall, and it degrades towards the ventricular long axis. From another point of view, regional ejection fraction peaks at the apical wall, and it degrades from the apex to the mitral valve plane between the left atrium and the left ventricle. Regional ejection fraction or ventricular contraction function is continuous and in smooth transition, from boundary wall to inside, from apex to valve. The LV REF1 for uncorrected images, however, yields astonishing abnormal results. Specifically, it shows a couple of totally-isolated area of low regional ejection fraction value inside the left ventricular chamber. Such degraded regional function may mislead the physician to be more suspicious of the patient’s LAD coronary artery flow at peak exercise. The LV REF1 in figure 31B also shows some wrapped regional ejection fraction behavior around the mitral valve plane, which is never seen in conventional LV REF1 analysis and is a direct resulted of the patient’s motion during image acquisition.

(A)  
(B)

Figure 31. Left ventricular regional ejection fraction images: (A). from motion-corrected image data; (B). from uncorrected image data.
Figure 32 shows comparison of changes of regional ejection fraction values along the LV long axis, which is from the apex to mid-point of mitral valve plane in the left ventricular chamber, derived from corrected and uncorrected treadmill RNA images. From the analysis on corrected image files (figure 32A), the regional EF decreases monotonically as a continuous function from the LV apex to valve plane for all patient analysis, which corresponds normal cardiac physiology wherein the left ventricle squeezes blood from apex to aortic valve during every pumping cycle. However from the analysis on uncorrected image files (figure 32B), the regional EF fluctuates along the LV axis profile as an abnormal discontinuous function. This is because the activity moves back and forth in the uncorrected LV blood pool images, and the image analysis can hardly determine where the blood flow goes. Such regional EF curves are completely unreliable for physician to do clinical diagnosis on functionality of patient’s coronary artery.

![Corrected](image1)

![Uncorrected](image2)

Figure 32. Regional EF values along LV long axis profile. (A). Derived from corrected patient treadmill RNA; (B). Derived from uncorrected patient treadmill RNA.
4.4 Validation of Motion Correction by Referenced Resting RNA

With the availability of the MWGC and new motion correction techniques, treadmill exercise first-pass myocardial function studies can be performed routinely in patients undergoing myocardial perfusion imaging. The accuracy of the left ventricular dynamics measurement provided by the motion corrected first-pass technique needs to be assessed. Therefore, in patient study we sought to perform rest and treadmill exercise Ta-178 first-pass studies on the same patient, and then to validate the performance of motion correction by comparison with left ventricular volume images with standard resting first-pass RNA.

At the beginning of study while in the static standing position the patients are positioned against the MWGC in the anterior view. A bolus intravenous injection of 1.5 mL Ta-178 (15-35 mCi) is made and images are acquired at 120 scintigraphic frames per second for 30 seconds. The resting study is followed by a 30-minute delay to permit decay of the radioisotope. After 30-minute, the patients undergo exercise treadmill testing according to the standard Bruce protocol. Upon reaching peak exercise (within patient capabilities), first-pass image acquisition begins, and the second 1.5 mL dose of Ta-178 (15-35 mCi) is injected as a rapid bolus. Stress images are acquired at the same frame rate of 120 frames/sec for 30 seconds. Motion correction is applied after the stress images are acquired.

In normal subjects, the response from upright rest to upright exercise in RNA study does not change much in end-diastolic volume. Iskandrian (1986) and Plotnick (1986)
respectively reported 6% and 4% moderate increase in LV ED volume during upright exercise. As exercise progresses to a higher intensity, end-diastolic volume keeps stable or declines a little somewhat, and stroke volume is maintained by a progressively decreasing end-systolic volume. For example, Slutsky and associates (1979) reported that end-diastolic volume remained unchanged in patients with coronary artery disease whether they developed angina, while Renlund (1987) reported moderate 3% decrease in LV ED volume. Therefore clinical investigations suggest that similar LV end-diastolic volume response should be found in motion-corrected treadmill stress study (possibly ±10% changed volume) compared to that in rest study on the same subject.

Figure 33. Left ventricular volume determined from resting and corrected exercise studies for a patient.
The LV images for a patient, who received both resting study and treadmill stress study are shown in figure 33. The end-diastolic LV volume compared from resting to motion-corrected exercise study is very similar. Regional ejection fraction images are also shown. In this patient, resting apical function is normal as indicated by high ejection fraction values. However at peak exercise, significantly degraded regional ejection fraction function is seen along the inferior wall indicating possibly compromised right coronary artery flow.

![Image](image_url)

Figure 34. Left ventricular volume determined from resting and uncorrected exercise studies for a patient.
Figure 34 shows left ventricular volume determined from uncorrected exercise images, compared to that from rest images. The LV volume without motion correction is much bigger with shape distortions, produced by motion artifact. The corresponding regional ejection fraction image shows strongly reduced function in the inferior wall of LV, which is very likely a result of motion artifact.

<table>
<thead>
<tr>
<th></th>
<th>Percent changes of LV EDV</th>
<th>Percent changes of LV EDV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>From upright rest to treadmill exercise derived from</td>
<td>From upright rest to treadmill exercise derived from</td>
</tr>
<tr>
<td></td>
<td>Corrected RNA</td>
<td>Uncorrected RNA</td>
</tr>
<tr>
<td>Patient #2</td>
<td>+8.4%</td>
<td>+53.9%</td>
</tr>
<tr>
<td>Patient #3</td>
<td>+4.2%</td>
<td>+58.7%</td>
</tr>
<tr>
<td>Patient #4</td>
<td>-6.6%</td>
<td>+36.1%</td>
</tr>
</tbody>
</table>

Table 7. Ventricular volume response to upright exercise using corrected or uncorrected treadmill radionuclide angiography technique.

Table 7 quantitatively shows left ventricular end-diastolic volume response to exercise in terms of percentage changes, based on image analysis of corrected and uncorrected treadmill RNA image data. It can be seen that differences in end-diastolic LV volume determined from initial resting study and repeat treadmill exercise study with motion correction are small and within ±10% range as widely reported by previous clinical research work. However, the same parameters derived from comparison between resting image data file and raw uncorrected treadmill RNA image data file are significantly increased, which demonstrate up to 50% increase of LV volume responses from upright rest to upright exercise. Such big LV volume changes are never reported from previous
research work, whether based on normal subjects or patients, giving an impossible diagnostic outcome for physiological function of an either normal or pathological ventricular chamber. This is because the back-and-forth activity movement in uncorrected raw treadmill RNA images from one frame to the other, which is consequently generated by patient’s movement during exercise, smears the activity especially at the periphery of the LV chamber, during the combination, averaging and formation of LV representative cycle from several LV beats in the early phase of image analysis. The edge detection algorithm tends to overestimate the scope of end-diastolic LV border, resulting in much increased LV volume changes.
Chapter 5

Discussion and Conclusion
We have adapted a form of radionuclide angiography (RNA) used to quantify ventricular functions in patients presenting with chest pain. In this method, blood is imaged by detecting the radioactivity of a tracer injected as a bolus into a vein and followed during its initial passage (first-pass) through the patient’s heart. First-pass RNA has some distinct advantages, including (a) the acquisition of data in only 30 seconds; (b) right ventricular function with less overlap of activity in other chambers (Williams et al., 1990); (c) a proven robust measurement of stress ventricular function at true peak exercise; and (d) the presence of a wealth of prognostic information available for management of patients with ischemic heart disease based on stratification by first-pass RNA exercise LV EFs (Lee, et al., 1990; Jones et al., 1991). Since exercise perfusion scans are most commonly obtained for evaluating patients with coronary artery disease (CAD), exercise ventricular function with first-pass RNA can provide more information for the diagnosis and severity of CAD. The treadmill is commonly used for exercise electrocardiography and myocardial perfusion imaging in the US. Treadmill exercise, however, is not routinely applied to stress RNA because of excessive patient motion.

To correct for patient motion during treadmill exercise, we implement an electromagnetic motion encoding system to treadmill RNA studies (Sun et al, 2001). A sensor is firmly attached on the back of the patient, reporting 6 degree-of-freedom position real-time data during rigorous exercise. The movement of patient’s left ventricle can be tracked accurately based on moving sensor position and the LV location in the back sensor coordinate. A full 6 degree-of-freedom motion correction algorithm has been developed and validated in moving phantom tests as well as in treadmill exercise.
phantom studies in the laboratory (Sun et al., 2002). The combined system has been applied to clinical treadmill stress tests, which considerably improves the accuracy of patient’s ventricular function analysis.

Compared to the traditional motion correction method by placing an external radionuclide point source on the patient’s chest wall as a marker of ventricular position (for example, Groch, et al., 1985), our motion tracking system demonstrates the superiority for a number of reasons. First, the external-source method is limited to two-dimensional corrections and inherently assumes that the patient is rotationally fixed about both horizontal and vertical spatial axes, which is an unrealistic assumption for a patient moving at maximum treadmill exercise rates. Second, in order to achieve better image resolution, the patient is generally asked to get close to the collimator surface of the camera, and the patient’s chest is sometimes pushed against the collimator surface during vigorous treadmill exercise. In this case, the external point source may be jammed against the collimator and may not accurately track the motion of patient’s chest. Third, the external point source may be out of the camera’s field of view during treadmill exercise, resulting in loss of tracking information in image analysis. Furthermore, use of long-lived radioactive positioning sources in clinical setting also carries significant safety drawbacks, as well as requiring additional preparation time for attaching it on the chest wall.

Yano et al. (1995) proposed a motion correction method by a center of mass approach. A large region of interest (ROI) is placed over the left ventricle and ascending aorta to
determine the centroid of the RNA image. The spatial location of the image data frame is then repositioned by moving the centroid location for the composite image data frame over the LV phase. Their clinical studies of such correction method claim that less fluctuations in time-activity curve of the LV phase, as well as up and down motion of the patient is partially corrected. However, such correction scheme has not undergone thorough validation. Only LVEF measurements are validated with this method. Even in this validation study, there is an illustration that the approach may contribute to the underestimation of exercise LVEF (Friedman, et al., 1994). Other parameters that can be derived from the first-pass exercise studies such as regional left ventricular wall motion, left ventricular volumes, diastolic function, and right ventricular function are not assessed.

The motion tracking system selected by us has been verified to yield minimum spatial reconstruction error (2.81 mm) under the test simulating patient’s running on treadmill at Bruce level V. Since the error is far less than RNA image spatial resolution (7.8 mm) or gamma camera’s FWHM resolution in left ventricular imaging (19 mm), the system is suitable to be implemented into a motion correction algorithm for the frame-by-frame repositioning of acquired first-pass image data. The motion tracking system also adds the advantage of being able to determine the chest contour of each individual patient and determine the location of patient’s left ventricle, based on the formula derived from transmission scan data. The position measurements of the patient are synchronized with RNA image acquisition, which are updated at a frequency of 120 Hz (8.33 ms/measurement), which provides satisfactory temporal resolution for the integration analysis of blood pool radionuclide images. The performance of motion tracking system
and motion correction algorithms are intensively evaluated in the lab phantom studies, wherein the subjects exercise on the treadmill with a point source attached on the sternum, simulating the LV movement. Motion correction significantly decreases the fluctuation errors by 400% to 500%.

A substantially modified version of the multiwire camera (MWGC) system with motion tracking technology has been designed and produced which facilitates convenient imaging of treadmill exercising patients. Clinical studies have been conducted, and stress images are analyzed by temporal smoothing, LV beat selection, lung background modification, creation of LV representative cycle and LVEF calculation. Motion correction has demonstrated its important role in identifying lung background beats, selecting beats related to LV phase, wall motion analysis, and regional ejection fraction image presentation. Without motion correction, dramatic artifacts of moving blood pool structures fundamentally degrade the quality of image analysis, and can yield serious and particularly dangerous clinical results to the physician.

Clinical studies of motion-corrected treadmill RNA are being conducted in Division of Nuclear Medicine, University of Alabama Birmingham Medical Center. Approximately 100-150 patient studies will be performed in the next 6 months. The future work to be done in clinical trials is the agreement between the test result acquired from a blinded reading of the rest and peak exercise ejection fraction and wall motion and that of a blinded reading of the stress Single-Photon Emission Computed Tomography (SPECT) study. This comparison will be made on the basis of (1) a Kappa statistic using results of
testing expressed on a fine point categorical scale (normal, probably normal, equivocal, probably abnormal and abnormal); (2) a correlation analysis using the results expressed as a continuous variable (ejection fraction and wall motion score versus total defect size and reversibility measured by quantitative software); and (3) binary agreement (normal versus abnormal) of the overall first-pass versus SPECT study. The hypothesis to be tested is that the agreement between a rest-stress first pass radionuclide angiogram using this technology and conventional stress SPECT, both isolated and after adjusting for underlying clinical risk, is sufficiently great that the former can identify patients that will be determined to be low risk by the latter and, thus, serve as a low cost screening test to better identify patients who are appropriate candidates for stress SPECT.

The secondary but very important aspect of future work is to assess the independent diagnostic and prognostic value of motion-corrected stress imaging as well as its added (incremental) value over other modalities such as SPECT. This added prognostic value will be assessed in the low-, intermediate-, and high-risk groups. Analyses on additional information regarding the presence of anatomically significant coronary artery disease (>50% stenosis in patients undergoing catheterization after stress testing), adverse patient outcomes occurred within 6 months after study (cardiac death, myocardial infarction, clinical worsening) and subsequent resource utilization, will be performed using multivariable modeling method.
Reference:


Lacy JL (2000). Motion Corrected Treadmill Nuclear Angiography. *NIH Proposal Phase II*


Appendix A

Flow Chart Diagram of Image Analysis Software

The image analysis software was developed in late 80s/ early 90s employed algorithms that sequentially perform the following: identification of end-diastolic frames, temporal smoothing, creation of preliminary LV and RV regions of interest, background modification, and creation of final LV representative cycle from which end-diastolic and end-systolic LV regions of interest are assigned semiautomatically. LV time activity curve is generated and LVEF is calculated automatically.

The analysis software was designed to be compatible with that came with the commercial first-pass multicrystal camera imaging system (Baird System-77, Bedford, MA) and other standard cardiac RNA image analysis software.

Motion artifacts in treadmill RNA images are eliminated from tracked LV position information right after the acquisition. The motion corrected RNA image file will be analyzed by this standard image analysis software to get diagnostic results of subject’s cardiac function.

- Start of Motion Correction

Correct the movement of patient’s LV based on tracker reported information and patient’s chest contour information, re-register the treadmill RNA image frame by frame, as discussed in detail in this dissertation.
Start of image analysis

RNA image archive file registration

EKG R wave automatic labeling and end-diastolic frames selection

Display first 32 end-diastolic frames. Each frame is averaged with 2 preceding and 2 succeeding frames.

Draw SVC region. Generate bolus activity histogram.

Draw LV ROI, RV ROI on corresponding end-diastolic frames respectively (LV beat and RV beat are also identified).

Background beat = the beat with minimal activity in the pre-defined LV and RV ROI (some beat between RV beat and LV beat).

Background frame = the end systolic frame (average of a few frames around end systolic point) of background beat serves as the background frame.

Corresponding FORTRAN programs and subroutines:

'MKGAT2' reads in the EKG and finds the R-wave peaks. 'MKGAT3' plots EKG, labels R-waves, identifies end-diastolic frame numbers, and computes R-R intervals.

'FPASS0'----

'blows': provides dynamic blow up of frame on RAMTEK. (sequential cinematics display, slow down the speed, etc.)

'drroi': general routine for ROI drawing.

'wvec': plots vectors on histograms.

'lvselect': determines background beat # and particular LV or RV beats chosen for analysis (to form representative cycle).

'decor': performs activity decay correction of Ta-178.

ILVRV=1: LV analysis
ILVRV=2: RV analysis
Computer automatically selects the dominant LV beat. Other LV beat periods are included if their activity at end-diastole is >70% of the maximal LV activity of dominant beat at end-diastole. Average the selected LV beats to form a single representative or composite cycle LV image sequence.

Subtract background frame from all frames.

Display normalized background frame.
Display end-diastolic frame.
Display normalized (end-diastolic frame – background frame).

LV/RV/SVC region and full frame activity histograms (for ALL end-diastolic frames).

Determine the ED and ES regions of the LV representative cycle with guide borders.

Enter the valve plane point and the ventricular long axis points, for drawing 6-sector image and regional EF and TAC later.

'FPAS0'----
Determines ED frame numbers of selected LV beats, forms representative LV cycle with mean R-R interval of selected beats, and finds end-systole frame number in the representative cycle.

'SPAS0'----
Selects frames in the background beat to get averaged background frame.

'SPAS00'----
Does the left lung background subtraction.
Displays normalized background and background-subtracted LV ED frame.
Draws the activity histograms for different regions.

'SPAS1'----
Draws LV ED, ES region using mask as guide.
Calculates parameters such as volume index from valve plane information.
Generate TAC throughout all frames within the single representative LV cycle. (No dilution correction applied)

Calculate EF value (without dilution correction) based on activity counts in ED and ES regions of LV representative cycle.

\[ EF = \frac{ED \text{ activity} - ES \text{ activity}}{ED \text{ region activity}} \]

Dilution correction on activity counts throughout the diastolic phase of LV representative cycle*.

Cinematic display of representative LV cycle and regional TAC/flow analysis.

Save all the analysis into *lv or *rv file for future review.

End

'FPASS1'----
Calls 'FPASS3' (which calls 'PLTTAC') to plot TAC and flow curve (non dilution corrected).
Finds LV ED frame count, calculates heart rate, EF, peak ejection rate, time to peak ejection rate, peak filling rate, and time to peak filling rate.

'FPASS1'----
Performs dilution correction. Calculates dilution corrected TAC values for each frame of representative cycle.

'FPASS2'----
Cinematic display of representative LV cycle.

'FPASS4'----
Calculates apex and centroid for global and 6-sector LV region.

'FPASS5'----
Computes TAC and flow for global and 6-sector LV region.

'FPOUT1'----
Includes 'FPOUT1-5' to finish the analysis outputs.