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(71) Applicant *(for all designated States except US)*: **THE BOARD OF GOVERNORS FOR HIGHER EDUCATION** [US/US]; STATE OF RHODE ISLAND AND PROVIDENCE, PLANTATIONS, 301 Promenade Street, Providence, Rhode Island 02908 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SUN, Ying** [US/US]; 210 Table Rock Road, Wakefield, Rhode Island 02879 (US). **VETTER, Frederick** [US/US]; 188 Briarwood Drive, South Kingston, Rhode Island 02879 (US). **DONG, Rumei** [CN/US]; 1900 Kingstown Road, Apartment D424, Kingston, Rhode Island 02881 (US). **SALVATORE, Chiaramida** [US/US]; 49 Society Street, Charleston, South Carolina (US).

(74) Agents: **POWERS, Arlene** et al.; GAUTHIER & CONNORS LLP, 225 Franklin Street, Suite 2300, Boston, Massachusetts 02110 (US).

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(54) **Title:** INTEGRATE FINITE ELEMENT AND CIRCULATORY MODEL FOR PREDICTING HEMODYNAMIC EFFECTS OF LEFT VENTRICULAR IMPAIRMENT, RESYNCHRONIZATION AND REMODELING

(57) **Abstract:** A computational model which integrates a complex circulatory model and a finite element to determine the dynamics of a left ventricle continuously over consecutive cardiac cycles. The model includes determining a LV pressure (piv) using a circulatory model, using a finite element model piv as input and determining a LV volume (viv), computing a LV elastance according to: eiv = piv / vlv, driving the circulatory model with the ejv ; and returning to determining a LV pressure and starting the next iteration, wherein the steps continue at a sufficient time resolution for a desired number of entire cardiac cycles. The dynamic Young's modulus functions are assigned to individual finite elements, resulting in a time-varying left ventricular elastance that drives the circulatory model.

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INTEGRATE FINITE ELEMENT AND CIRCULATORY MODEL FOR PREDICTING HEMODYNAMIC EFFECTS OF LEFT VENTRICULAR IMPAIRMENT, RESYNCHRONIZATION AND REMODELING

PRIORITY INFORMATION

The present application is a continuation application of Provisional Patent Application 60/645,807 filed with the United States Patent and Trademark Office on January 21, 2005.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a computational model capable of relating the left ventricular regional myocardial contraction to hemodynamics. The fields of use include cardiovascular and pharmaceutical research, computer assisted instruction in cardiovascular physiology, and planning for cardiac surgery and treatment procedures such as the ventricular restoration surgery Cohn LH. Chen FY, Cohn LH. The surgical treatment of heart failure. A new frontier: nontransplant surgical alternatives in heart failure. Cardiology Review 10(6): 326-33, 2002. and the cardiac resynchronization therapy Adamson PB, Abraham WT. Cardiac resynchronization therapy for advanced heart failure. Current Treatment Options Cardiovascular Medicine 5(4): 301-309, 2003.

2. Description of the Prior Art

Finite element models are used to stimulate behaviors of complex systems. There are many different models for a variety of different systems which are well known to those skilled in the art. Typically the systems are subdivided into interconnected elements that represent sections in the material react in such a way that they influence the reaction of their adjacent sections. The finite element model simulates this behavior by solving differential equations for each of the elements that represents a relatively small section in the material.

For the study of the mechanics of the myocardium of the left ventricle, several models based on finite element methods have been used in the past. Bovendeerd PHM, Arts T, Delhaas T, Huyghe JM, van Campen DH, Reneman RS. American Journal of Physiology 270: H398-H410, 1996 used a finite element model accounting for the thick-walled ventricular geometry to simulate the ischemic left ventricle during a complete cardiac cycle. Their model significantly over estimated (by about double) the loss of stroke work. Ratcliffe MB, Hong J, Salahieh A, Ruch S, Wallace AW. The effect of ventricular volume reduction surgery in the dilated, poorly contractile left ventricle: a simple finite element analysis. Journal of Thoracic Cardiovascular Surgery 116(4): 566-77, 1998 used a finite element analysis for the effect of ventricular volume reduction surgery. Their model predicted the left ventricular dynamics at end of systole and end of diastole, not for the entire cardiac cycle. Guccione JM, Moonly SM, Moustakidis P, Costa KD, Moulton MJ, Ratcliffe MB, and Pasque MK. Mechanism underlying mechanical dysfunction in the border zone of left ventricular aneurysm: A finite element model study. Annals of Thoracic Surgery 71: 654-662, 2001 used a finite element model to characterize the mechanics of the border zone region of left ventricular aneurysm. Their model representation was also limited to the end-systolic and end-diastolic time instances. All the aforementioned models were focused on the left ventricle only and did not include a comprehensive representation of the circulatory system.

Sun Y, Beshara M., Lucariello RJ, Chiaramida SA. A comprehensive model for right-left heart interaction under the influence of pericardium and baroreflex. American Journal of Physiology 272: H1499-H1515, 1997 developed a comprehensive analog electrical model to characterize the hemodynamics during heart failure and the right-left heart interaction under the influence of pericardium and baroreflex. While the analog circulatory model was capable of generating realistic and physiological pressure and flow waveforms at various parts of the cardiovascular system, it did not have a three-dimensional description of the left ventricular walls. Therefore, this model was incapable of relating regional impairment of left ventricular

myocardium to its global effect on the hemodynamics of the entire cardiovascular system.

SUMMARY OF THE INVENTION

The combination of a finite element model of the left ventricular walls with a complex circulatory model so that one can predict the hemodynamic outcome of a regional left ventricular impairment.

This invention is directed to a computation model capable of relating the left ventricular regional myocardial contraction to hemodynamics. The model includes methods of integrating a finite element model of the left ventricle (LV) into an analog electrical model of the cardiovascular system. The resulting model is computationally efficient such that simulation of cardiovascular dynamics over several cardiac cycles can be obtain in a reasonable time frame. The computational model includes the use of time-varying Young's modulus of individual finite elements to define the global LV elastance over a cardiac cycle, the definition of infarct zone by reduced Young's modulus, the use of two or more 2D LV wall profiles to interpolate the 3D LV geometry, the interaction between the finite element model and the circulatory model via the LV elastance at every integration times step, the prediction of the hemodynamic effects of action potential propagation in the myocardium, and the use of the model to assess outcomes of LV infraction, cardiac, resynchronization therapy using biventricular pacing, and LV remodeling surgery. The model provides the basis for developing a commercial simulation software system that can be used by pharmaceutical and medical device industries, researches in cardiovascular dynamics, clinicians for diagnosis of congestive heart failure, educators and students for cardiovascular physiology.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other features of the present invention will now be described in greater detail

with reference to the accompanying drawings, wherein:

Figure 1 is a schematic diagram of the system showing the interaction between a finite element model of the left ventricle and an analog electrical model of the entire cardiovascular system;

Figure 2 is a graph of time-varying Young's modulus for normal and infarct elements;

Figure 3 is a scheme to interpolate 3D LV geometry by use of normal 2D profile and an infarct 2D profile;

Figure 4 is of hemodynamic waveforms generated by the model for normal and 18% infarction;

Figure 5 are graphs of the model results versus clinical data; and

Figure 6 is a graph demonstrating the ability of the model to represent the transient phase of the model predicted LV volume over several cardiac cycles.

DETAILED DESCRIPTION OF THE INVENTION

This invention integrates a complex circulatory model and a finite element dynamically and efficiently. It is presently the only available computational model that can relate LV regional myocardial contraction to the hemodynamic consequences for both transient and steady states of the cardiovascular dynamics. The 3-dimensional mesh generated by two 2-dimensional finite element calculations significantly decreases the computation time. Traditional 3D finite element LV models usually take days to compute and require supercomputers or clustered processors. With the algorithm, it is possible to run many cardiac cycles continuously to reveal the transient phase within a relative short time. The circulatory model is also much more comprehensive than the 3-element Windkessel model used in this type of models in the past. It includes the functions of four cardiac chambers, cardiac valves,

pulmonary circulation, systemic arterial bed, and venous return. The model is physiological by generating realistic hemodynamic waveforms in response to changes of various physiological and/or pathophysiological variables. No other model is capable to represent these mechanisms in such a comprehensive way.

There are many advantages of the system including the use of time-varying Young's moduli of individual finite elements to define the global LV elastance over a cardiac cycle; the definition of infarct zone by reduced Young's modulus, the use of two or more 2D LV wall profiles to interpolate the 3D LV geometry, the interaction between the finite element model and the circulatory model via the LV elastance at every integration time step, the prediction of the hemodynamic effects of action potential propagation in the myocardium, and the use of the model to assess outcomes of LV infarction, cardiac resynchronization therapy using biventricular pacing, and ventricular restoration surgery.

The model provides a platform to describe normal and abnormal left ventricles, and predicts the hemodynamic consequences of a specific infarct zone. The model has several application areas including cardiovascular research, computer assisted instruction, pharmaceutical research, planning and assessment of LV remodeling surgery, optimization of cardiac resynchronization therapy by biventricular pacing, and relating medical imaging data (MRI, SPECT, echo) to diagnosis of congestive heart failure.

The model differs from present technology in that there is an integration of the finite element LV model and the circulatory model. This should bring the computation models out of pure research and find many applications in cardiology, cardiac surgery, medical device and pharmaceutical industry.

Thus, the model is a more sophisticated circulatory model and the representation of normal and infarct LV geometry. The computation efficiency is another advantage, allowing the integrated model to run on a general propose PC with a reasonable computation time. Additional improvement in computation can be obtained by use of a high-performance

computer or a cluster of processors.

Figure 1 is a schematic of the model in accordance with the invention. The simulation system is based on two models that are tightly coupled together. The finite element model of the left ventricle uses the LV pressure as the input and determines the LV volume at each and every time step. The LV elastance, defined by the instantaneous pressure/volume ratio, drives the analog electrical model that determines the pressures and flows at various parts of the cardiovascular system. The response of the circulatory model defines the LV pressures of the next time step, thus propagating the numerical integration forward in time.

The contraction of the finite element LV model is controlled by the time-varying Young's modulus assigned to each finite element. Figure 2 shows the typical Young modulus curves over a cardiac cycle assigned to the normal elements (dotted) and the infarct elements (solid). The contraction of normal myocardium is associated with the increase of the Young's modulus during systole. By contrast, the infarct myocardium has a significantly reduced Young's modulus during systole.

Although it is possible to use a true 3D finite element LV model, the resulting computation time would be enormous. The current interest is the global LV elastance, not the details of regional wall motion. It is sufficient to use two or more 2D LV wall profiles to interpolate the 3D LV geometry. As shown by the short axis view in Fig. 3, the infarct profile is assigned to sector θ_2. The two sectors θ_1 are transitional from the infarct profile to the normal profile. The endocardial border of this sector is interpolated with the square root of the sinusoidal function. The normal sector is assumed to be axis symmetrical.

The tight coupling between the finite element model and the circulatory model is advantageous in a sense that the finite element LV model constantly receives feedback from the circulatory system. This feedback allows the LV model to be an integrated part of the overall cardiovascular system, thereby making it behaves in a more physiological way. For examples, the LV may contract differently under the condition of high systemic arterial

resistance (hypertension) or an insufficient mitral valve (mitral regurgitation). The interaction between the finite element model and the circulatory model at each and every time step is shown below:

1. The circulatory model determines the LV pressure (p_{lv}).
2. The finite element model uses p_{lv} as input and determines the LV volume (v_{lv})
3. The LV elastance is computed according to: $e_{lv} = p_{lv} / v_{lv}$.
4. The new e_{lv} is used to drive the circulatory model.
5. Go to step 1 and start the next iteration.

Figure 4 shows the hemodynamic waveforms generated by the cardiovascular system for the normal case and a case of 18% LV infarction. Whereas in Figure 5 the model predicted the effects of LV infarct size on the ejection fraction (EF) and LV end-systolic and end-diastolic volumes. The solid lines are linear regression lines fitted to the model results. The dotted lines are linear regressions lines fitting to patient data reported by Sciagra R, Imperiale A, Antoniucci D, Parodi G, Comis G, Pupi A. Relationship of infarct size and severity versus left ventricular ejection fraction and volumes obtained by 99mTc-sestamibi gated single-photon emission computed tomography in patients treated with primary percutaneous coronary intervention. European J Nuclear Medicine & Molecular Imaging 31: 969-974, 2004. In the case of the EF (top) the model result matched the clinical data almost exactly. In the case of LV volumes, the clinical data were normalized to the body surface area, which the model did not represent. Nevertheless the slopes of the regression lines matched very well. Thus, this simulation study supported the validity of the model. The model is not only capable of characterizing the contractility and preload relations but also quantitatively accurate in predicting the hemodynamic effects of varying the LV infarct size.

The model predicted the transient phase of the LV volume in response to the introduction of a 20% infarction at time = 0. The model usually takes 15 to 25 cardiac cycles

to reach a steady state. Currently the computation time is about 30 minutes for a cardiac cycles on a 3 GHz PC. The simulation shown here contains 18 cardiac cycles. Thus, it took 9 hours to complete. This example also demonstrates the importance of having a computation-efficient model.

The immediate applications of the integrated model are in the area of research in cardiovascular dynamics and computed-assisted instruction of cardiovascular physiology.

Future applications include the ventricular restoration surgery Cohn LH. Chen FY, Cohn LH. The surgical treatment of heart failure. A new frontier: nontransplant surgical alternatives in heart failure. Cardiology Review 10(6): 326-33, 2002. As an alternative to heart transplant, ventricular restoration surgery removes the infract myocardium and pulls the viable muscles together. The goals of this surgery are to return the LV a more normal shape and to make LV more efficient. Certain procedures of ventricular restoration surgery have recently received FDA approvals. So far in the present recommended ventricular restoration surgery, the Dor procedure, the borders between the infarction and viable contracting myocardium is determined by visual inspection and palpation identification during the surgery. The myocardium within the borders is removed. This procedure needs a very experienced team. The model offers a method to predict the hemodynamic results of regional infarction before and after the restoration surgery, thus to assist in determining the appropriate amount of infarct myocardium to be removed.

Additionally the model can be used to predict the hemodynamic effects of action potential propagation in the myocardium. The hemodynamic waveforms in Fig. 4 were generated by the model under the assumption that all finite elements began to contract at the same time. The model is also capable of relating the various patterns of action potential propagation to their hemodynamic consequences. This can be achieved in the model by delaying the Young's modulus curve for each element according to the arrival time of the action potential wave. Such simulation will contribute to the understanding of certain clinical

procedures such as cardiac resynchronization therapy (CRT). The CRT has recently been approved by the FDA as a procedure to treat congestive heart failure Adamson PB, Abraham WT. Cardiac resynchronization therapy for advanced heart failure. Current Treatment Options Cardiovascular Medicine 5(4): 301-309, 2003. The CRT uses biventricular pacing via a catheter placed near the apex of the right ventricle and another one placed near the base of the left ventricle via the great cardiac vein. The mechanism for improved LV function observed in patients are not well understood. The proposed model should be able to study the underlying mechanisms and help optimizing the instrumental parameters of the CRT device.

This invention integrates a complex circulatory model and a finite element dynamically and efficiently. It can relate LV regional myocardial contraction to the hemodynamic consequences. The 3-dimensional geometry generated by two 2-dimensional finite element calculations significantly decreases the computation time. Traditional 3D finite element LV models usually take days to compute and require supercomputers or cluster processors. With the algorithm, it is possible to run many cardiac cycles continuously to reveal the transient phase within a relative short time (Fig. 6). The circulatory model is also much more comprehensive than the 3-element Windkessel model used in this type of models in the past. It includes the functions of four cardiac chambers, cardiac valves, pulmonary circulation, systemic arterial bed, and venous return. The model is physiological as demonstrated by the bottom panel of Fig. 5, where the preload (LV end-diastolic volume) increases in response to the infarction. No other model is capable to represent such mechanisms.

There are many advantages of the invention over the prior systems. These include the use of time-varying Young's modulus of individual finite elements to define the global LV elastance over a cardiac cycle, the definition of infarct zone by reduced Young's modulus, the use of two or more 2D LV wall profiles to interpolate the 3D LV geometry, the interaction between the finite element model and the circulatory model via the LV elastance at every integration time step, the prediction of the hemodynamic effects of action potential propagation

in the myocardium, and the use of the model to assess outcomes of LV infarction, cardiac resynchronization therapy using biventricular pacing, and ventricular restoration surgery.

The model provides a platform to describe normal and abnormal left ventricles, and predicts the hemodynamic consequences of a specific infarct zone. The model has several application areas including cardiovascular research, computer assisted instruction, pharmaceutical research, planning and assessment of LV remodeling surgery, optimization of cardiac resynchronization therapy by biventricular pacing, and relating medical imaging data (MRI, SPECT, echo) to diagnosis of congestive heart failure.

The integration of the finite element LV model and the circulatory model should prove to be an important break-through in transitional research. This should bring the computation models out of pure research and find many applications in cardiology, cardiac surgery, medical device and pharmaceutical industry.

The model includes a more sophisticated circulatory model and the representation of normal and infarct LV geometry. The computation efficiency is another advantage, allowing the integrated model to run on a general propose PC with a reasonable computation time. Additional improvement in computation can be obtained by use of a high-performance computer or a cluster of processors.

The software system has been completely implemented in a C++ program for Windows by use of a public domain development system (wxWindow).

Although the present invention has been shown and described with respect to several preferred embodiments thereof, various changes, omissions and additions to the form and detail thereof, may be made therein, without departing from the spirit and scope of the invention.

What is claimed is:

Claims

1. A computational model which integrates a complex circulatory model and a finite element to determine the dynamics of a left ventricle continuously over consecutive cardiac cycles.

2. The computational model of claim 1 which includes the following steps of interaction between the finite element model and the circulatory model at each time step:

determining a LV pressure (p_{lv}) using a circulatory model;

using a finite element model p_{lv} as input and determining a LV volume (v_{lv});

computing a LV elastance according to: $e_{lv} = p_{lv} / v_{lv}$;

driving the circulatory model with the e_{lv} ; and

returning to determining a LV pressure and starting the next iteration, wherein the steps continue at a sufficient time resolution for a desired number of entire cardiac cycles.

3. The computational model of claim 1 wherein dynamic Young's modulus functions are assigned to individual finite elements, resulting in a time-varying left ventricular elastance that drives the circulatory model.

4. The computational model of claim 1 wherein three-dimensional left ventricular parameters are determined for two or more two-dimensional finite element profiles of the left ventricular walls to achieve computational efficiency.

5. The computational model of claim 1 wherein an analytical function, such as the square root of a sinusoidal function, to interpolate laterally between a normal wall profile and an infarct wall profile.

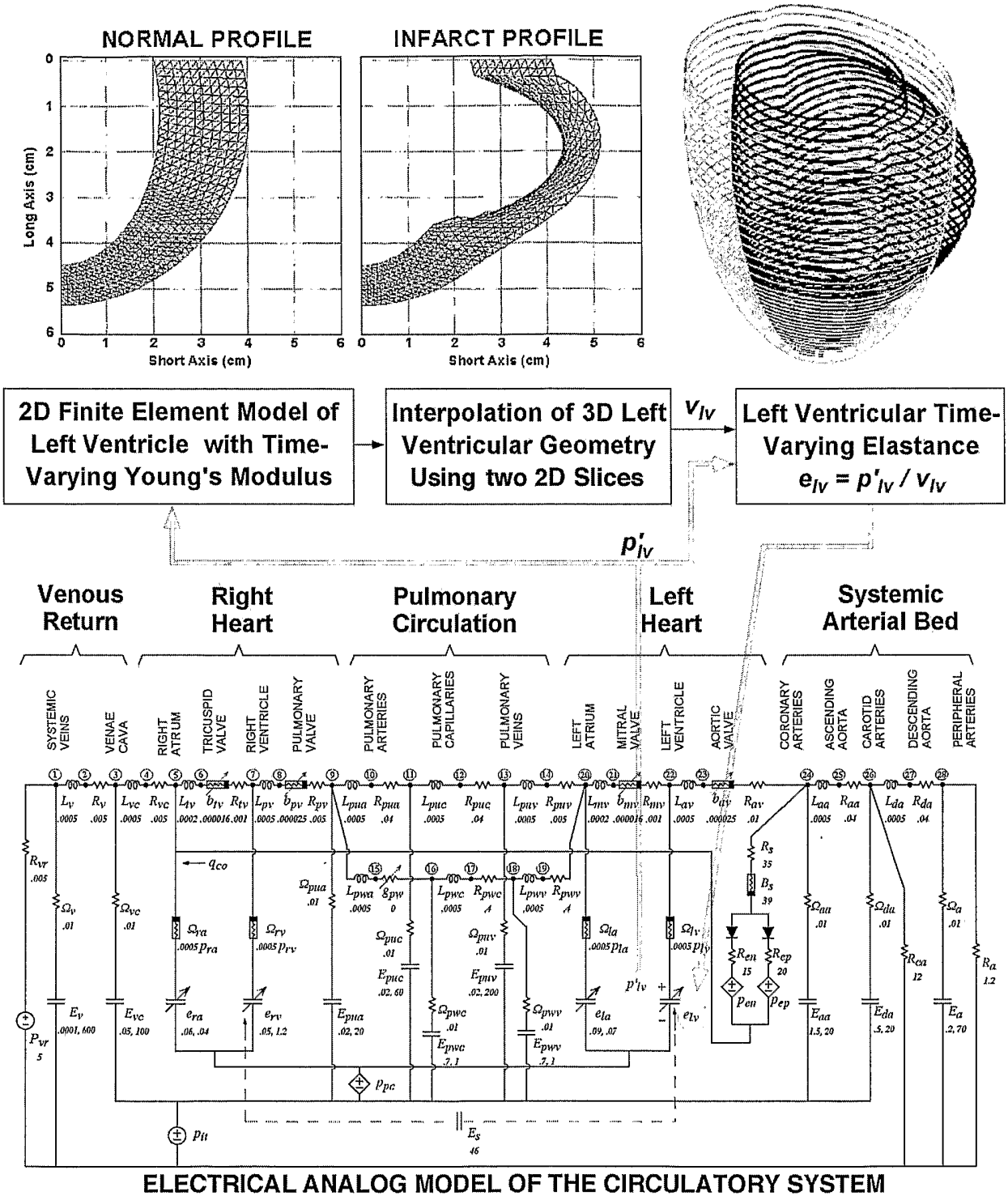
6. The computational model of claim 1 wherein the analog circulatory model can be extended to include additional cardiovascular compartments and physiological control mechanisms.

7. The computational model of claim 1 wherein the finite element model can be extended to

cardiac chambers other than the left ventricle.

8. The use of the computational model of claim 1 to determine the theoretically optimal amount of infarct mass to be removed in the ventricular restoration surgery by predicting the hemodynamic consequence of removing a certain amount of infarction from an impaired left ventricle.

9. The use of the computational model of claim 1 to determine hemodynamic effects of the propagation of action potentials in myocardium.



ELECTRICAL ANALOG MODEL OF THE CIRCULATORY SYSTEM

FIG. 1

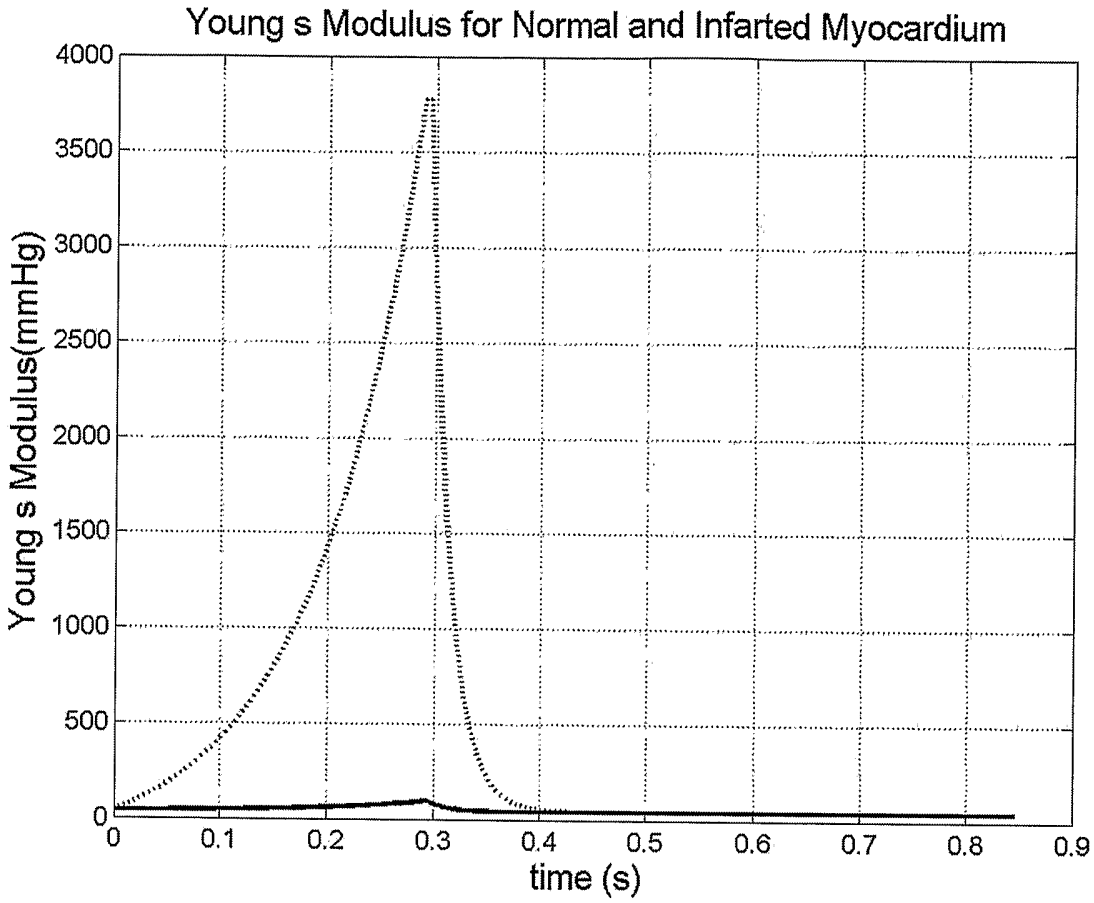

Young s Modulus for Normal and Infarted Myocardium
Young s Modulus(mmHg)
4000
3500
3000
2500
2000
1500
1000
500
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
time (s)

FIG. 2

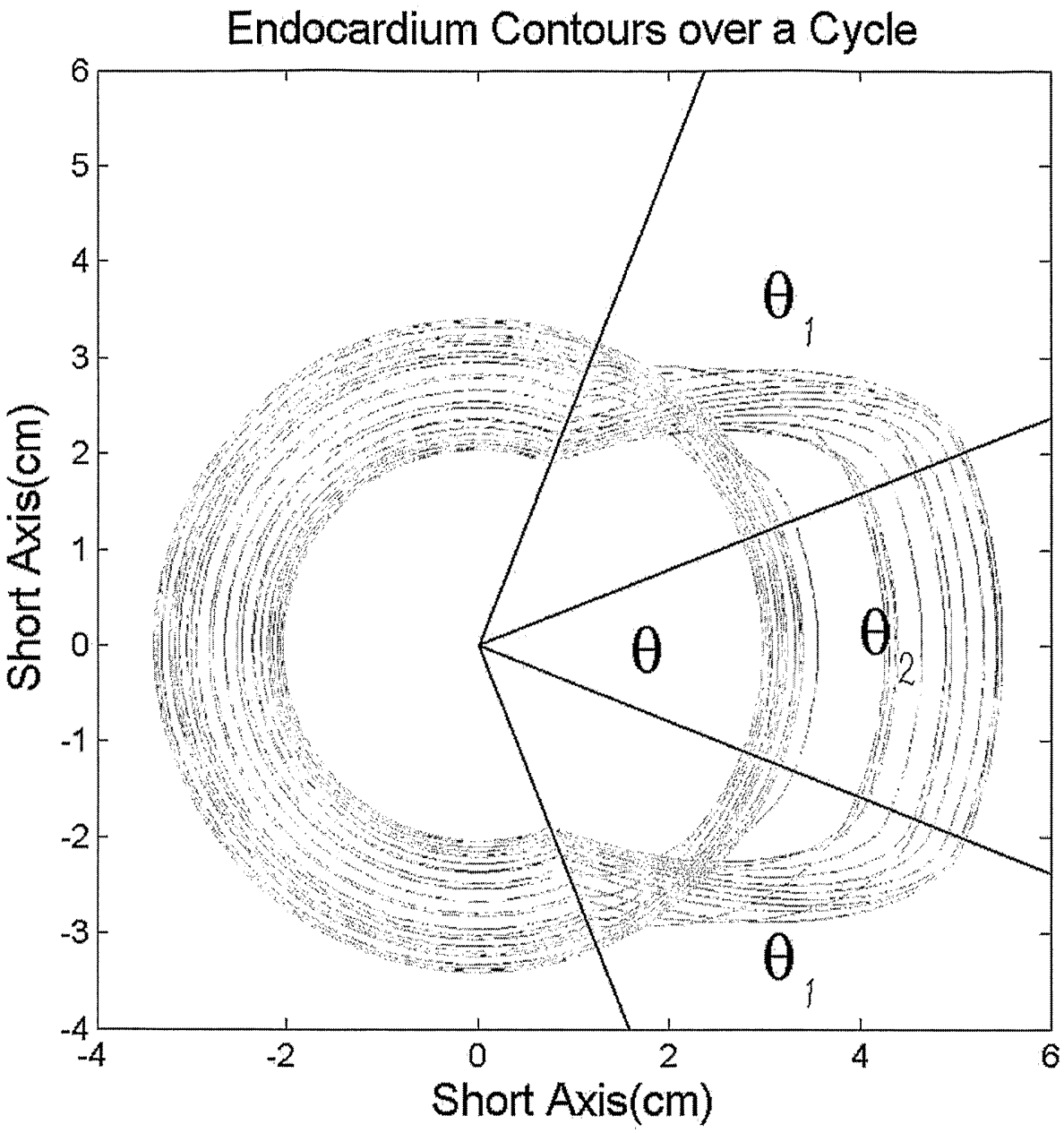

Endocardium Contours over a Cycle
Short Axis(cm)
Short Axis(cm)
θ1
θ
θ2
θ1
6
5
4
3
2
1
0
-1
-2
-3
-4
-4
-2
0
2
4
6

FIG. 3

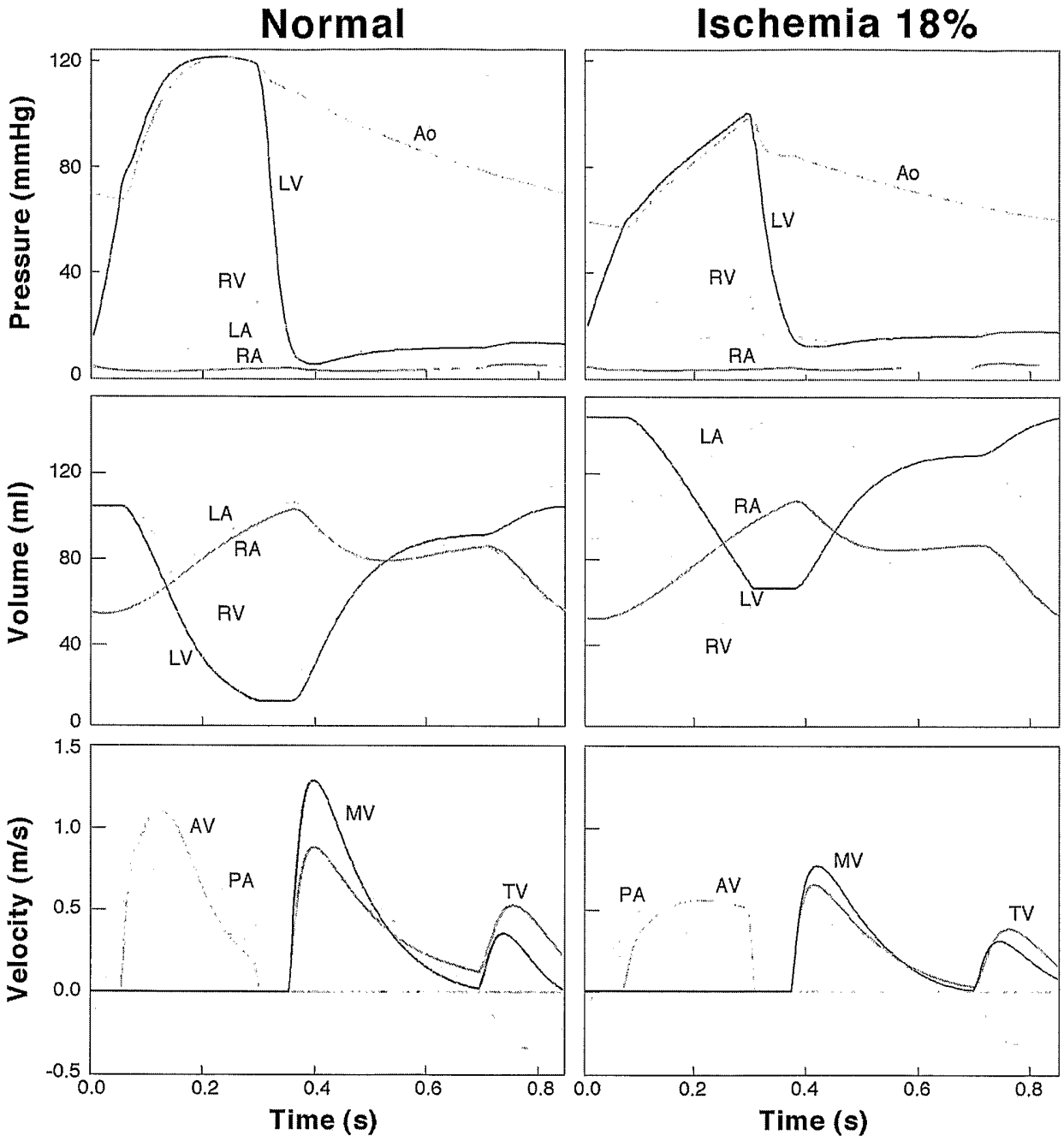
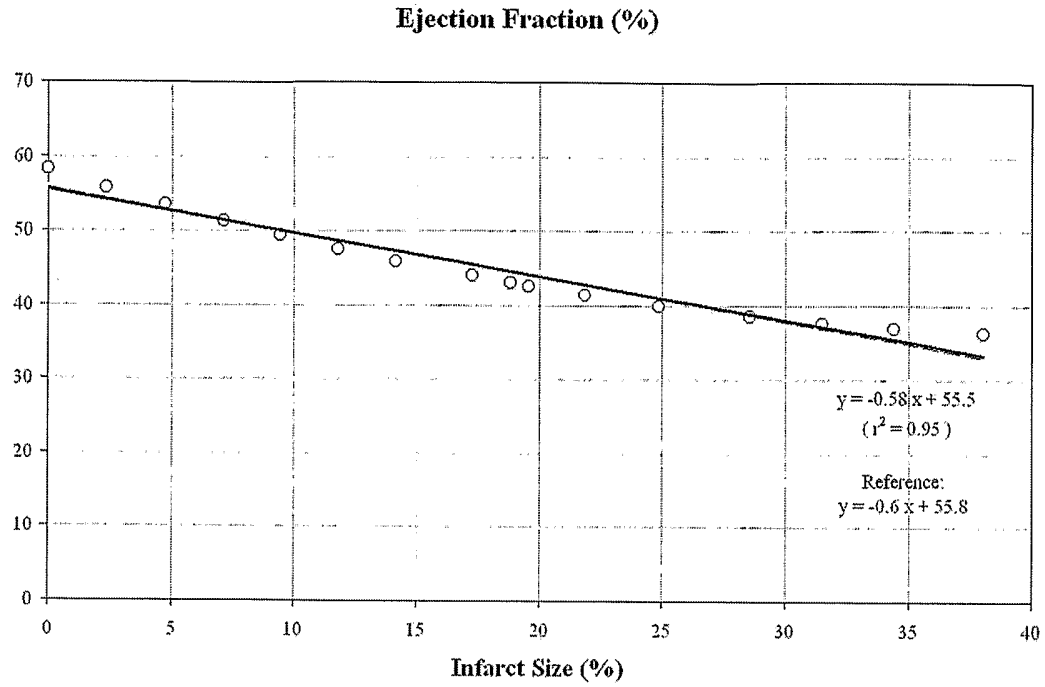

Normal
Ischemia 18%
Pressure (mmHg)
120
80
40
0
Ao
LV
RV
LA
RA
Volume (ml)
120
80
40
0
LA
RA
RV
LV
Velocity (m/s)
1.5
1.0
0.5
0.0
-0.5
AV
PA
MV
TV
0.0
0.2
0.4
0.6
0.8
Time (s)

FIG. 4


Ejection Fraction (%)
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Infarct Size (%)
y = -0.58 x + 55.5
(r² = 0.95)
Reference:
y = -0.6 x + 55.8

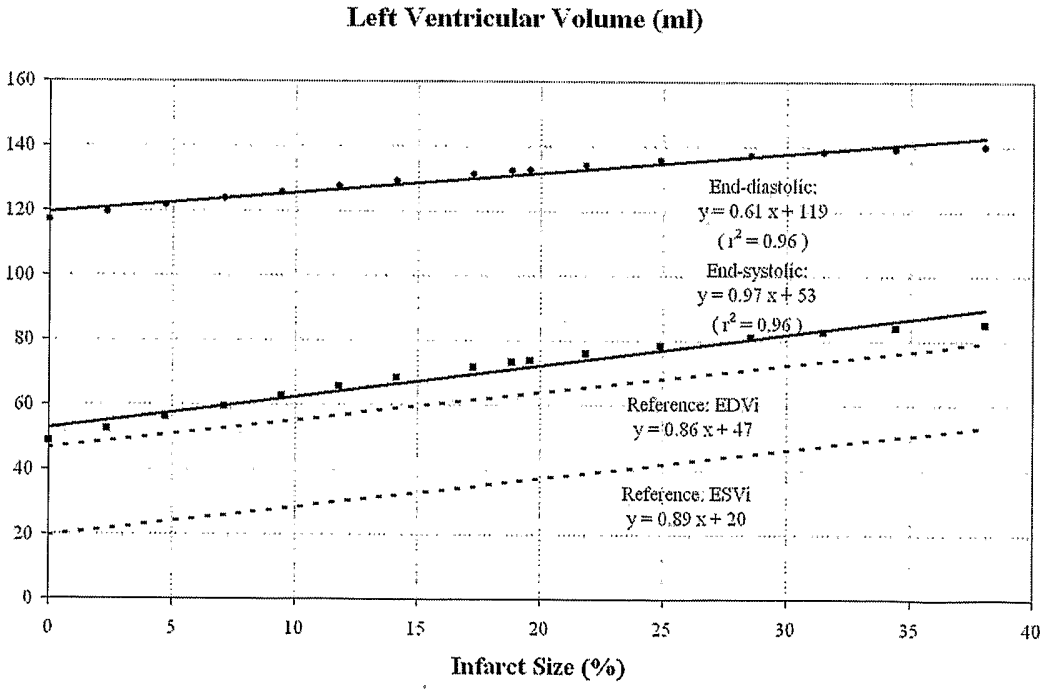

Left Ventricular Volume (ml)
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
Infarct Size (%)
End-diastolic:
y = 0.61 x + 119
(r² = 0.96)
End-systolic:
y = 0.97 x + 53
(r² = 0.96)
Reference: EDVi
y = 0.86 x + 47
Reference: ESVi
y = 0.89 x + 20

FIG. 5

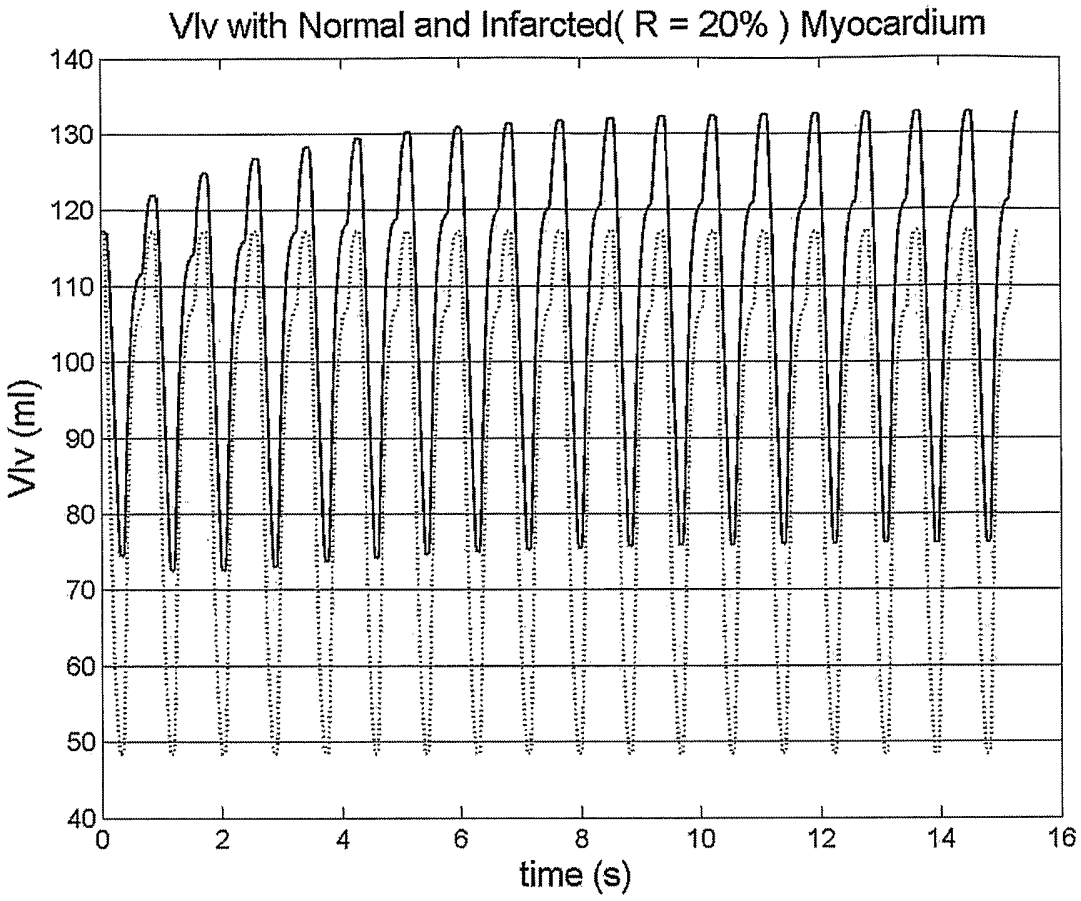

Vlv with Normal and Infarcted(R = 20%) Myocardium
Vlv (ml)
time (s)
140
130
120
110
100
90
80
70
60
50
40
0
2
4
6
8
10
12
14
16

FIG. 6