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**CENTRAL CIRCULATORY HEMODYNAMICS AS A
FUNCTION OF GRAVITATIONAL STRESS**

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Most current knowledge regarding the central hemodynamic functions in man are known for the supine posture, data having been obtained during acute cardiac catheterization procedures. Very detailed descriptions of ventricular and vascular function and their coupling have been published for this posture. Unfortunately, similar sophisticated analyses from invasive data for the upright posture in man are lacking due to the unusual conditions required for study. Tilt studies in the clinical cardiac catheterization laboratory are generally reserved for electrophysiologic studies as opposed to hi-fidelity hemodynamic recordings. Limited animal studies are available which have evaluated some aspect of ventricular/vascular function for the upright posture.

The effects of gravity upon cardiovascular performance still remains to be more precisely elucidated. Certainly, gravitational stresses at extremes of human tolerance are even less well described. Man has ventured into such hostile environments as those imposing as much as 9-10 times the force of gravity on his system to other environments in which he experiences the virtual absence of gravity. To make

recommendations regarding the health and safety operational envelopes for these environments, an understanding of how these alterations in gravitational stress effect cardiovascular function and its integration with other systems becomes more critical. Investigations must, of necessity, begin with gaining insight into the "normal" physiologic response, then advance to understanding responses to mild degrees of pathophysiology.

This study focuses on an evaluation of the central hemodynamics in a nonhuman primate model to variations in gravitational states. The baboon, phylogenetically close to man was chosen as the human surrogate. The study environments selected are head-down and head-up tilt in the physiology laboratory, centrifugation to test hypergravic stress, and parabolic flights to test transient acute responses to microgravity.

Therefore, the objectives of the present study are:

- 1) Develop the chronically instrumented conscious baboon model for hemodynamic studies,
- 2) Evaluate baroreflex function, contractility, pulsatile and steady ventricular loading characteristics, and the ventricular/vascular coupling phenomenon during postural tilt changes,
- 3) Evaluate ventricular/vascular function during centrifugation (acceleration stress),
- 4) Evaluate ventricular/vascular performance during transient microgravity induced by parabolic flight,
- 5) Compare acceleration responses pre- and post- 48 hour

head-down tilt with and without fluid loading and anti-G trousers.

This project is still in its early phases. To date, we have developed the chronically instrumented baboon model. We have also begun collecting data and performing the required analyses into ventricular/vascular function. This report will summarize the surgical technique and the hardware R&D required. Additionally, some examples of data analysis will be presented. Finally, some comments on future plans and directions will be presented.

MODEL DEVELOPMENT

The previous year has been utilized to develop the implanted animal model. Prior to surgical transducer implantation the selected baboons are acclimatized to a vest or jacket and a confinement chair used for the studies. Acceptance of these devices is prerequisite for surgical implantation. Echocardiography and radionuclide angiography noninvasive studies are also performed. Finally, a pre-surgery complete right and left heart catheterization supine and 70° head-up tilt, each with aortography is performed.

All surgical subjects undergo food and water restriction for 14 hours preoperatively. Preoperative medications include ketamine HCL (10 mg/kg im) and atropine sulfate (0.04 mg/kg iv). Maintenance anesthesia is provided by fentanyl citrate (50 mcg/kg iv) and supplemented by isoflurane

administered via a cuffed endotracheal tube connected to a volume controlled ventilator.

The surgical approach is via a left intercostal thoracotomy at the 4th intercostal space. A linear incision along the long axis of the pericardium is made, followed by placement of sutures to cradle the heart away from the mediastinum. Aortic instrumentation consists of an electromagnetic flow probe placed at the root of the ascending aorta, and a Konigsberg pressure transducer placed immediately distal to the margin of the flow probe. Another flow probe is placed around the descending aorta distal to the divergence of the brachiocephalic and subclavian arteries. Atrial instrumentation consists of a kinkless catheter tubing placed in the right atrial appendage and the body of the left atrium. Left ventricular instrumentation is comprised of a Konigsberg pressure transducer placed in the apex of the left ventricle, endocardial ultrasound crystal pairs positioned in 3 axes: anterior to posterior, free wall to septum, and base to apex. Epicardial crystals have been used for several baboons, and an additional crystal pair is positioned to measure LV free wall thickness in this situation. Additional instrumentation is limited to placement of a heavy-duty silastic occluder cuff encircling the inferior vena cava immediately posterior to the right atrium.

Intraoperative medications consist of bretylium tosylate (2-5 mg/kg/min iv) diluted to 2 mg/ml with 5% Dextrose in sterile water, lidocaine HCL, and procainamide HCL. After placement of all instrumentation, the wire leads and fluid catheters are

tunneled subcutaneously to exit the skin in the interscapular region of the back, where they are secured with mattress sutures of monofilament nylon. The percutaneous wire and catheter implants are positioned so their velour wrapping is at the level of the skin, to provide a scaffold for fibroblastic ingrowth. A thoracostomy tube is positioned at the 8th intercostal space for drainage, and serial aspirations are made for 24 hours.

Postoperative care consists of intensive care monitoring until the baboons can sit up without assistance. Analgesia is provided by oxymorphone HCL (0.1 mg/kg im) or buprenorphine HCL (0.02 mg/kg im) for a period of at least 72 hours. Baboons are closely monitored for caloric intake, and are liberally supplemented with fresh fruit on a daily basis. Antibiotic therapy with cephapirin sodium (10 mg/kg im) or gentamycin (4 mg/kg im) is usually implemented due to the 3-4 hour length of the surgical procedure. The baboons are fitted with a nylon vest which contains a pocket at the interscapular lead exit site for protecting the transducer wires.

Wound healing is monitored closely at 48 hour intervals. Initial care immediately after surgery consists of using hydrogen peroxide on the exteriorized velour to remove fibrin and cellular material. Peroxide is never used for direct wound treatment. After this initial cleansing, the velour is dried with gauze and povidone iodine solution (0.1%) is placed on the velour at the percutaneous exit site. Wound care thereafter is minimal, consisting of cleaning the velour when sebaceous secretions adherent. If lead sites become erythematous or an exudate is

apparent around the velour, the exit sites are gently cleansed with normal saline and a Q-tip swab, followed by lavage with 0.1% povidone iodine or 0.1% chlorhexidene solutions, and topical placement of povidone iodine ointment for residual antimicrobial activity.

Fluid lines are flushed at 48-72 hour intervals with heparinized saline, and serial blood cell counts are performed as a monitor of clinical status. Fluid lines are then filled with heparin after the flushing procedure. When recovery is complete, chair training resumes. A repeat right and left heart catheterization is performed to calibrate transducer elements.

The hemodynamic information desired is essential to the questions being addressed and requires rather sophisticated and extensive invasive physiologic data acquisition. The methodologies necessary to obtain certain data requires surgical implantation of transducers in the heart as well as great vessels. It is obvious that ethical and moral constraints prohibit the use of human volunteers. It is also necessary to obtain data and derive parameters of cardiovascular function that may be easily extrapolated to human physiology for these operational environments. Additionally these invasive data are necessary to provide the basis for and validation of computer model constructs for ventricular/vascular function in the microgravity environment. The evaluation baroreflex responses and describing physiologic changes with intact baroreflexes is similarly important. It is well known that quadrupeds have different cardiopulmonary and arterial baroreflex responses

compared to humans or nonhuman primates phylogenetically close to man.

INSTRUMENTATION R&D

A number of R & D efforts have been required. Several blood flow transducers were evaluated, including transit-time doppler, permanent magnet EMF and standard EMF flow probes. We determined that for the time being, standard EMF was the best probe for our studies until a custom-designed pulsed doppler flow system is constructed and tested. Additionally, we have had several custom modifications made to the Konigsberg transducers. Using totally silastic transducers we have had manufactured monofilament molded special angles to the distal portions of both the aortic and LV transducer elements. The aortic cell has a 90° bend and the LV pressure cell has a 135° angle over a 1 cm distance. The distal shank of the LV transducer was reinforced. Furthermore, silastic rings are applied to the distal portions to aid with surgical implantation stabilization. A custom-designed "kinkless" silastic tubing is used for the atrial lines. This allows placement of a small 2FR Millar catheter into the LA and LV. The leads are encased with fine velour fixed with a silastic glue. This innovation has prevented the infectious complications post-op. Specialized jackets have been designed to keep the transducer leads secure and take the pressure off exit sites.

Two other R&D products relate to centrifugation. A special designed "G" chair for the animal arm of the centrifuge has been manufactured and tested. We are also having a computer

controlled signal conditioner/biotelemetry system unit designed and assembled by NASA ARC. This unit will interface with our transducer elements and allow us to collect data remotely from the centrifuge arm. The unit may be used for study of other environments with difficult accessibility.

DATA ANALYSIS:

Data are passed through antialiasing filters (corner frequency of 100 Hz, 30 Db/octave roll-off) and digitized offline at a sample rate of 500 Hz using a Concurrent Computer (Model SLS-6300, real-time Unix 5.0) and LabWorkbench commercial software. Signals are then post-processed using both custom-designed and commercial (DaDisp, DSP Corporation) software.

Five consecutive beats are averaged for LV and Ao pressures and ascending aortic flow (ASC FLOW). Averaged beats are used to measure basic pressure and flow parameters. The first derivative of LV pressure are taken and the peak positive & peak negative values averaged for 10 beats are then determined. Average pressure and flow for simultaneous beats are submitted to Fourier analysis. Harmonics of pressure are divided by corresponding harmonics for flow to derive the aortic input impedance, and the phase angles of flow are subtracted from corresponding phase angles of pressure. The fifth to the fifteenth harmonic values are averaged to determine the characteristic impedance, Z_c (See Figs 1,2).

These same averaged beats of pressure and flow are also submitted to a 3-element Windkessel analog model of the

circulation. This model uses a Marquardt fitting algorithm to fit a calculated flow from input pressure to a measured flow. With an optimal fit, the model returns estimates for Z_c , peripheral resistance (R_p), and systemic arterial compliance (C), see Figs 3,4. These values are then compared to conventional calculations of these variables using a linear regression analysis, Figs 5-8.

A hydraulic occluder cuff is used to decrease pressures transiently. Simultaneous LV pressure and volume are submitted to a time-varying elastance model to determine the end-systolic pressure volume relationship (ESPVR). At least 7 beats and a minimum fall in systolic pressure of 10% of baseline are required for analysis. Any runs with ectopic beats are discarded. The ESPVR is fitted with a linear regression and the slope taken as the estimate of ventricular elastance, an index of contractile function, Figs 9,10. The volume intercept, V_o , is determined as well.

RESULTS

Fourteen baboons have been enrolled in some phase of model development. There has been 1 surgical death in the eldest cull animal and there have been 2 post-op hemorrhages. The hemorrhages were due to a transit-time doppler probe in one case and the aortic transducer (pressure cell) in another. Since incorporating silastic rings on the implanted transducers and using silastic electromagnetic flow probes these problems have not been seen. One animal suffered sudden death, presumed

arrhythmic. One fluid line became nonfunctional prior to use of silastic rings.

The head-down tilt studies will be conducted with the primates under sedation to alleviate anxiety. Initial trials with low dose midazolam (Versed) infusion have been performed. Unlike humans, the baboon is more resistant to the sedative pharmacological effects of this new agent such that intermittent Ketamine injections are required. Future studies will incorporate Ketamine infusion at a lower dose level.

Initial supine and tilt data are under analysis. A combination of commercially available signal analysis software (DaDisp, DSP Corporation) and custom programmed software are used to analyze data.

Some very preliminary results suggest that the pulsatile load of the baboon is not significantly changed as a function of posture changes, in contrast to peripheral resistance which increases. We previously found compliance decreased with the upright tilt under sedation. In six of the baboons' data thus analyzed the compliance values tended to be unchanged but were quite variable.

In a comparison of model vs. conventional calculations of parameters of LV loading we found that these were well correlated for both supine and head-up tilt conditions. The Z_c , however, was less well correlated with the upright posture than R_p . Compliance values tend to be overestimated by the 3-element Windkessel when compared to C determined from the RC time (τ) of aortic diastolic pressure decay.

Pre and post-ketamine studies are also under analysis. Finally, we have found in preliminary analyses that contractility by the ESPVR appears to be unchanged with 70° head-up tilt. Analyses are still in progress and in too premature status to apply statistical tools. Some examples of the types of analysis being performed are included.

CONCLUSION

We have demonstrated that we can instrument a nonhuman primate, the baboon, for sophisticated invasive hemodynamic evaluation of the cardiovascular system. We are establishing a noninvasive studies protocol such that these data may be compared with invasive findings. This year the tilt studies will be completed, as well as the centrifugation and parabolic flight tests. Data analysis is ongoing in parallel fashion. We further hope to extend development of some vascular access technology. We also expect delivery of a new cardiovascular signal conditioner/biotelemetry system for testing and evaluation. This system is scheduled to include a new custom-designed doppler probe which will provide flow velocity as well as vessel dimension.

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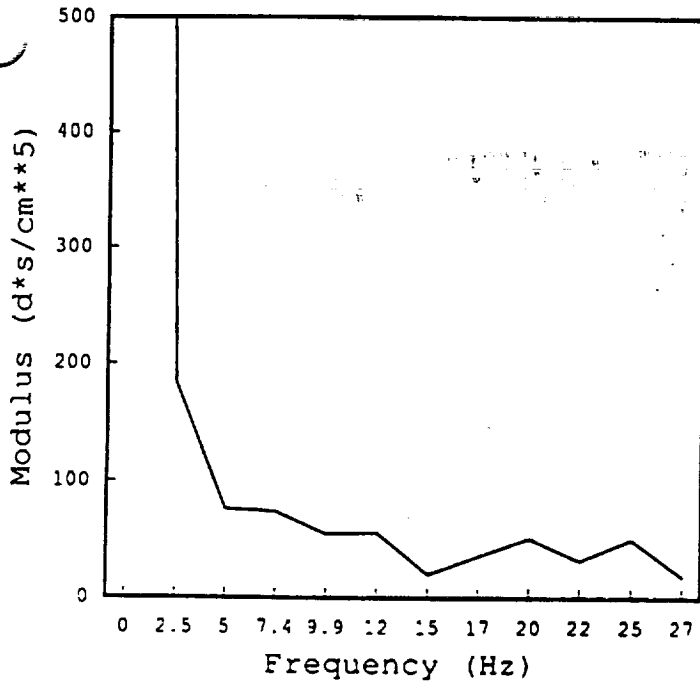
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A108 Aortic Input Impedance

SUPINE



A108 Aortic Input Impedance

UPRIGHT

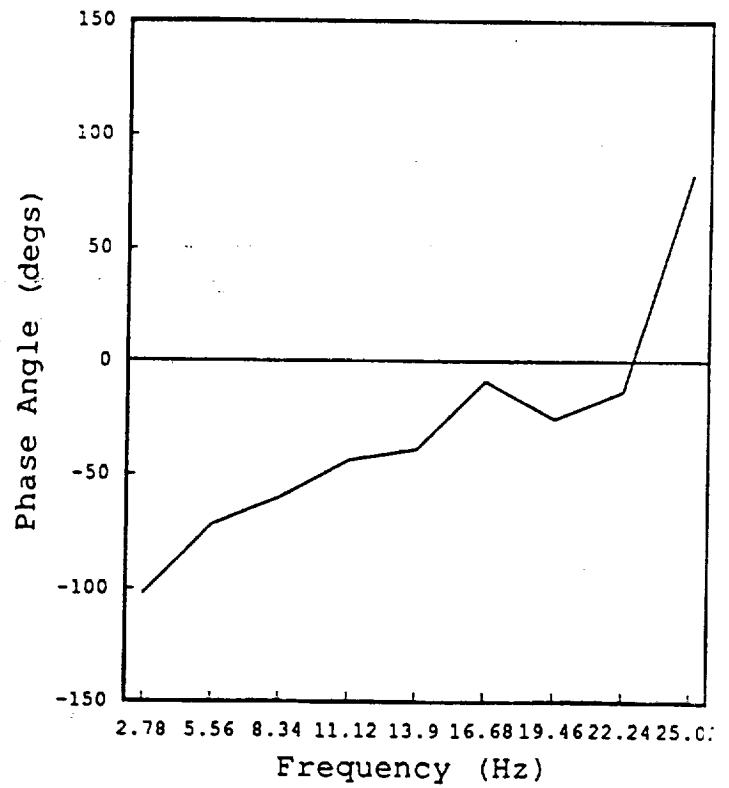
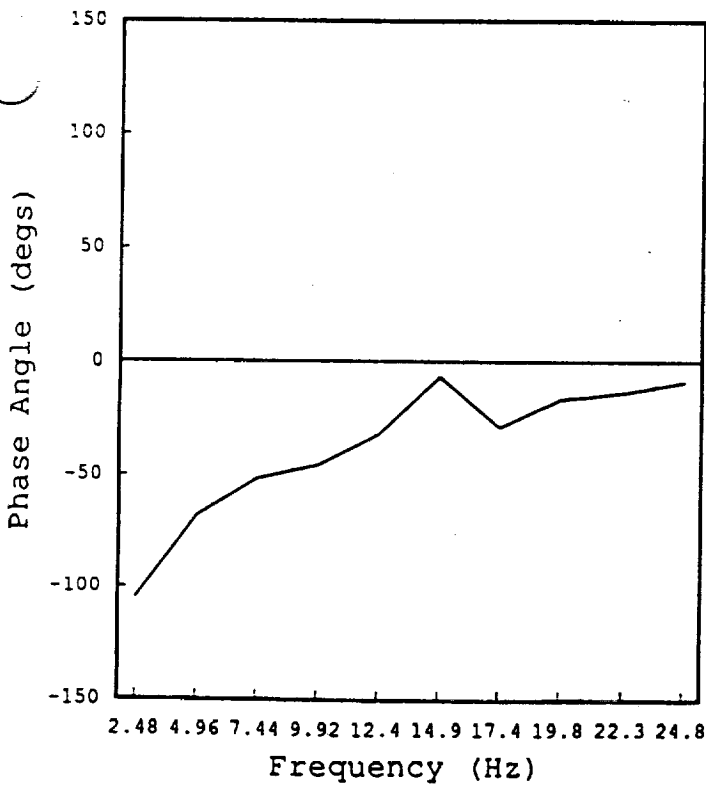
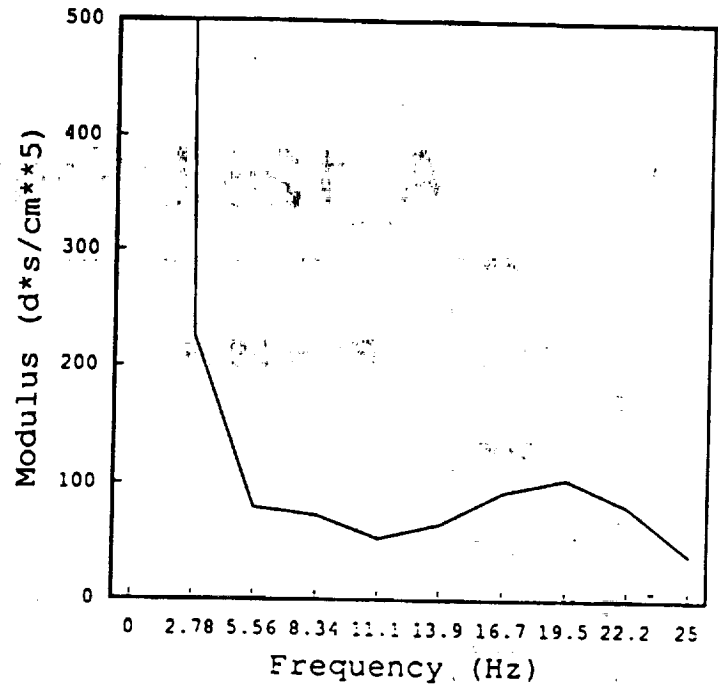


Fig. 1

A_126 UPRIGHT IMPEDANCE

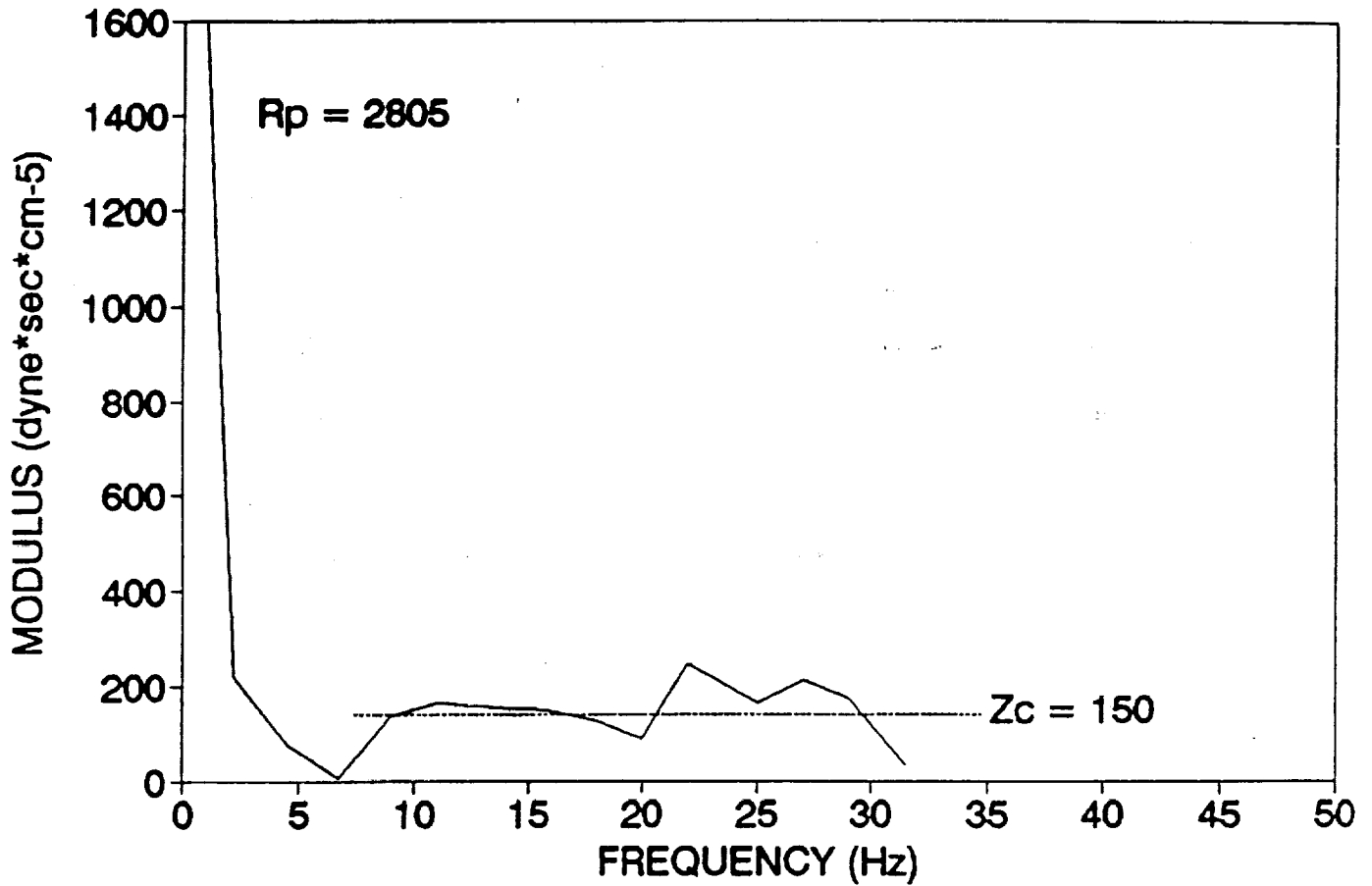
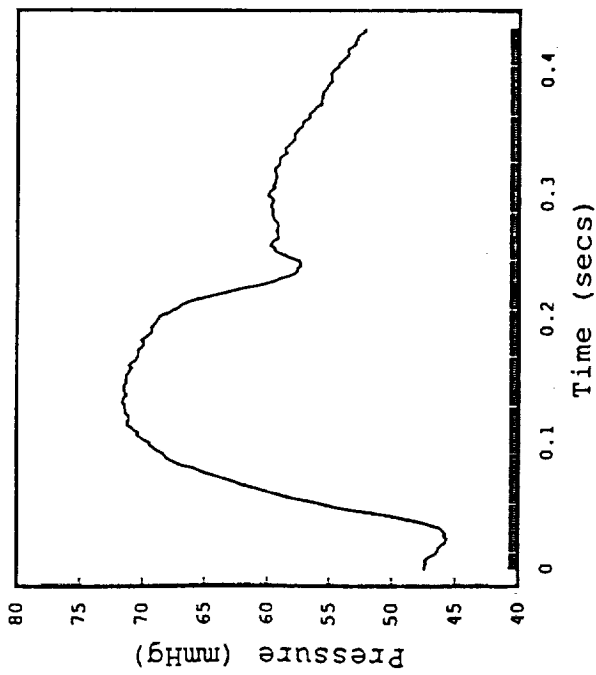


Fig 2

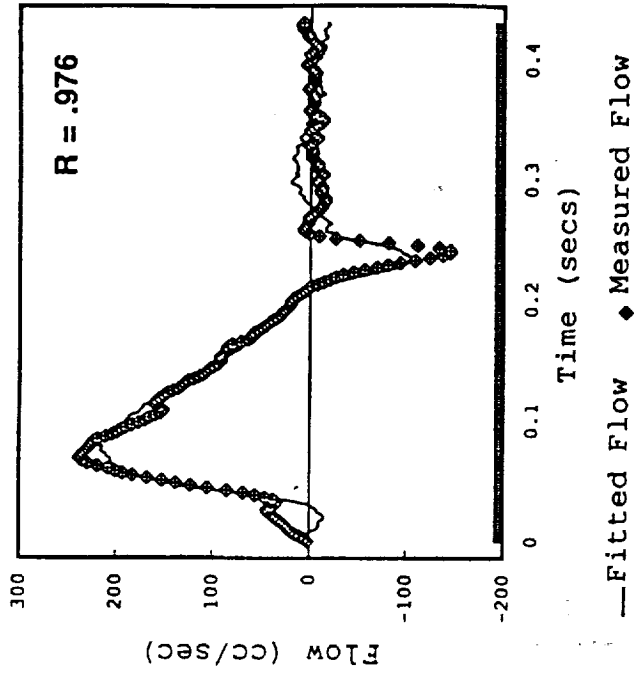
A106 Aortic Pressure - Upright

Time of Cardiac Cycle = .43 secs



A106 Flow - Upright

Time of Cardiac Cycle = .43 secs



PARAMETER

Z_c

R

C

FINAL VALUE

76.43 $d^*s^*cm^3$

2475 $d^*s^*cm^5$

1.85 cc/mmHg

COEFFICIENT VARIANCE

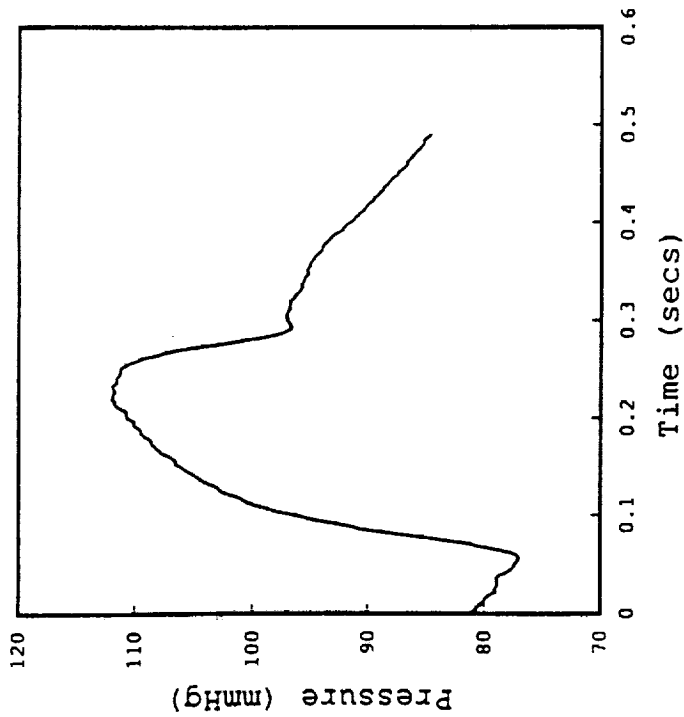
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.0440

.0202

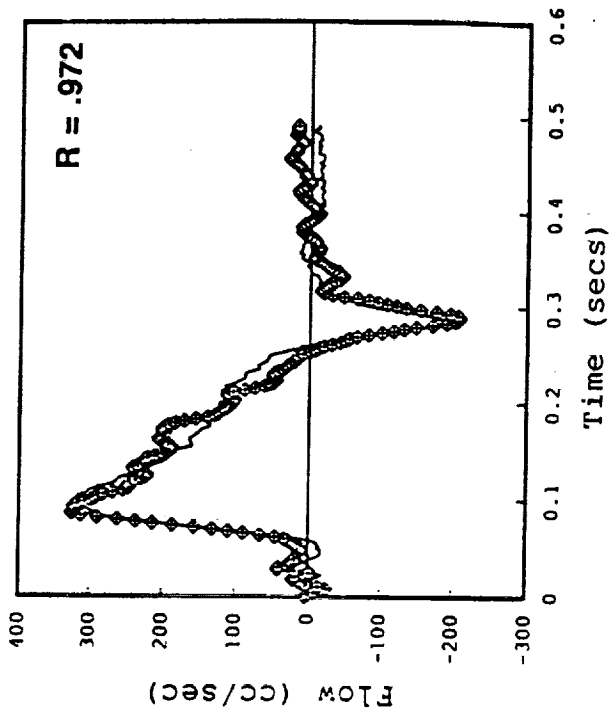
A106 Aortic Pressure - Supine

Time of Cardiac Cycle = .49 secs



A106 Flow - Supine

Time of Cardiac Cycle = .49 secs

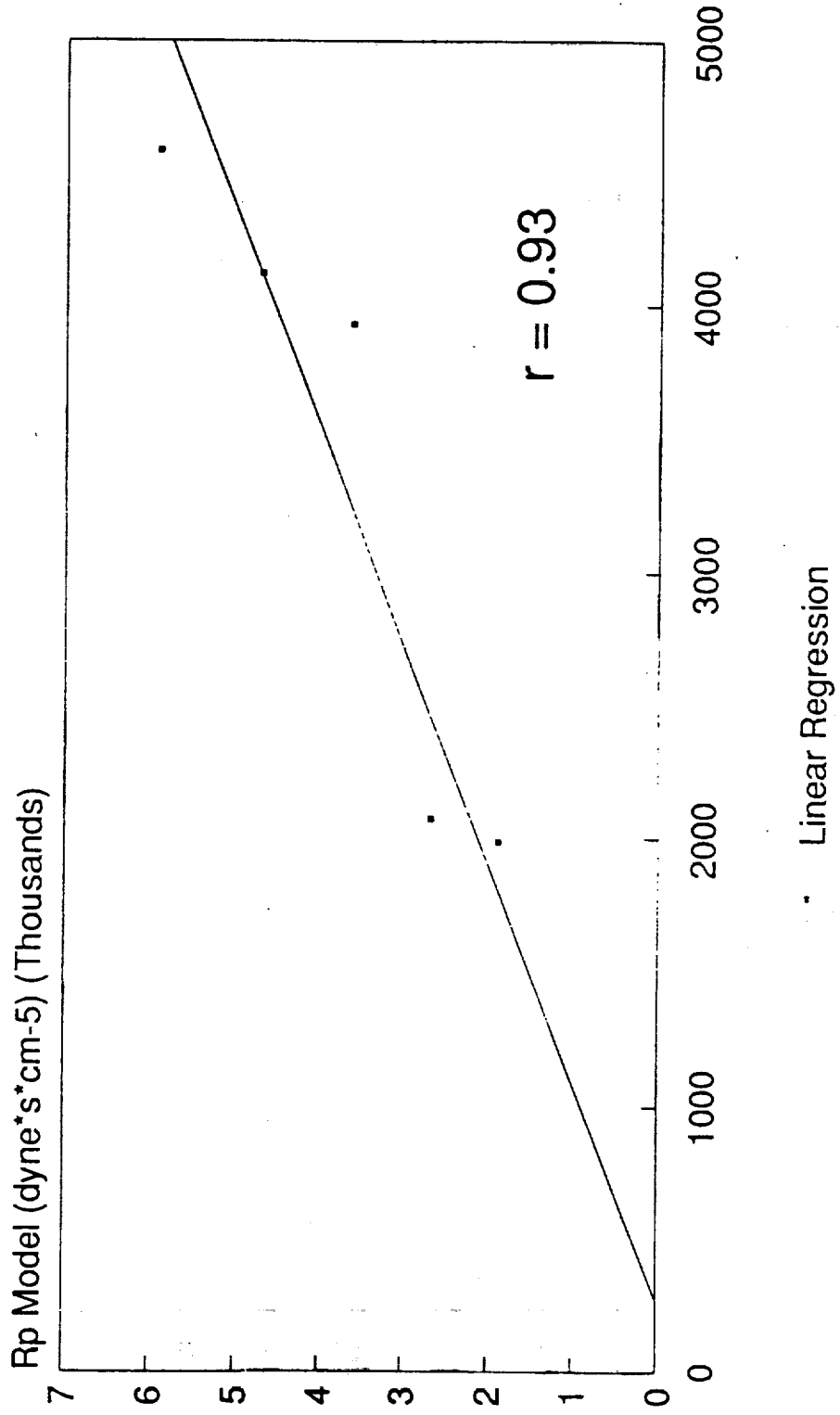


— Fitted Flow ♦ Measured Flow

| <u>PARAMETER</u> | <u>FINAL VALUE</u> | <u>COEFFICIENT VARIANCE</u> |
|------------------|----------------------------|-----------------------------|
| Z _c | 43.21 d's*cm ⁻⁵ | .0312 |
| R | 2668 d's*cm ⁻⁵ | .0387 |
| C | 1.83 cc/mmHg | .0176 |

Fig 4

Supine Rp Comparison (Model vs. Calculated)



Upright Rp Comparison (Model vs. Calculated)

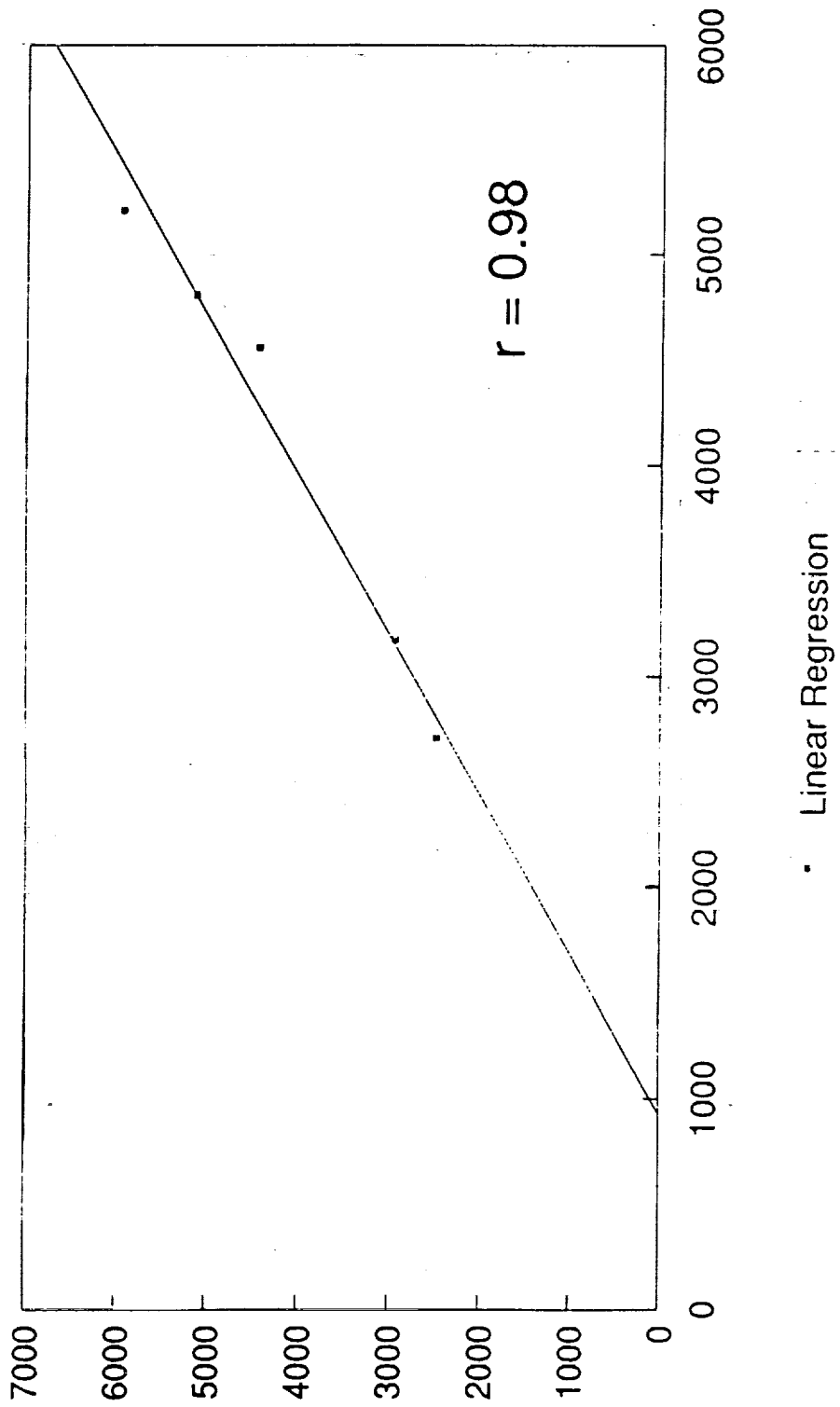
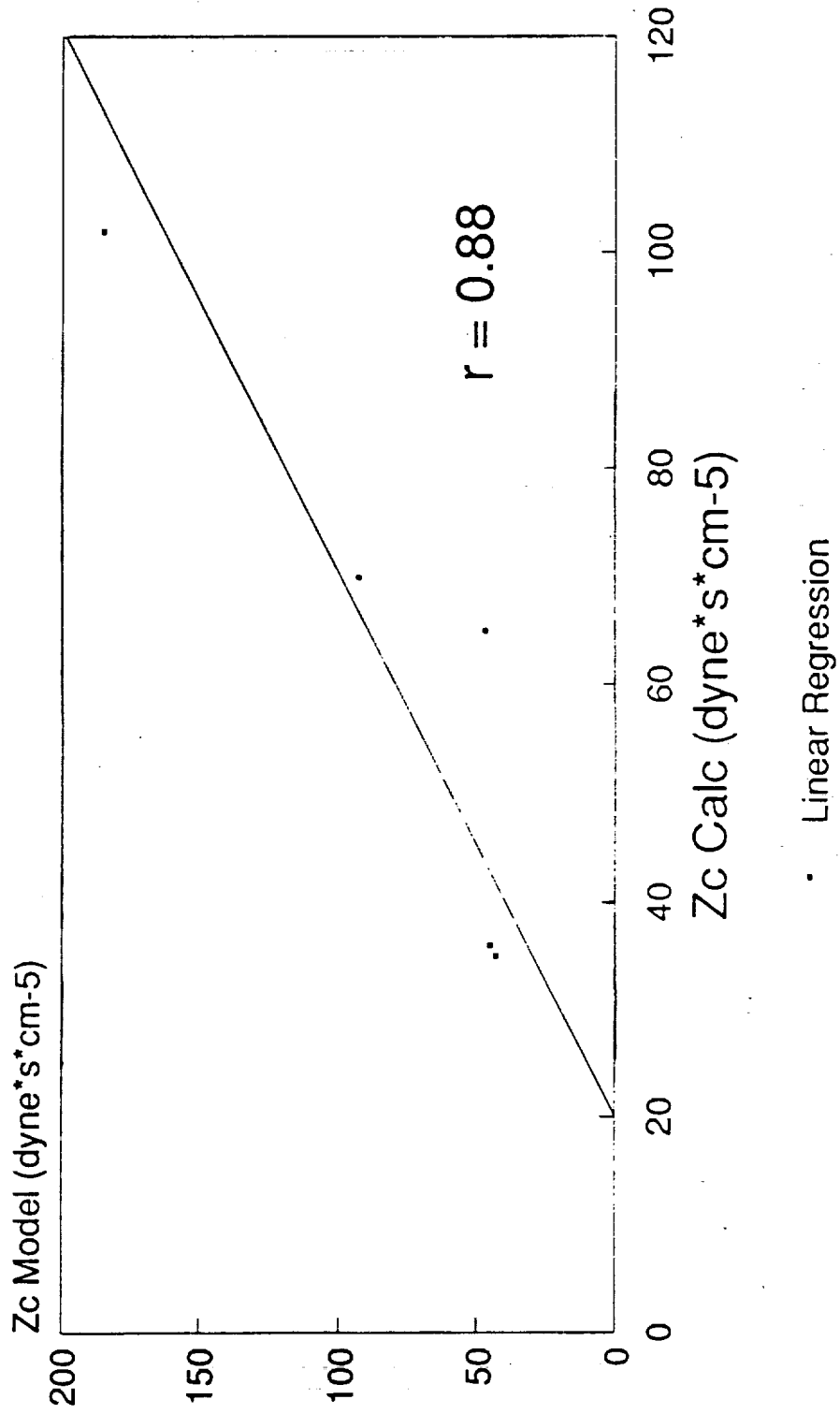


Fig. 6

Supine Zc Comparison (Model vs Calculated)



Upright Zc Comparison (Model vs Calculated)

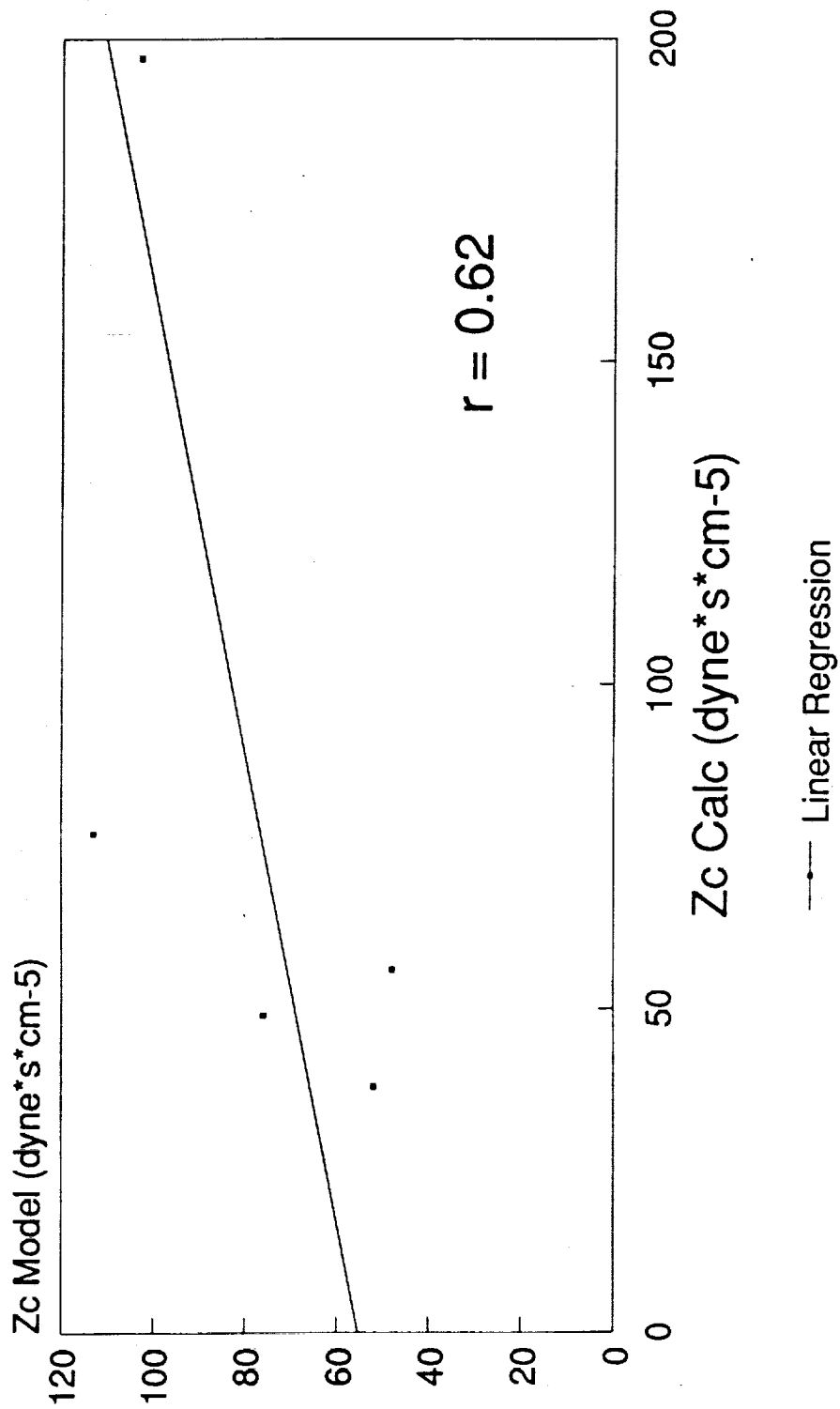


Fig. 8

A_126 SUPINE ESPVR

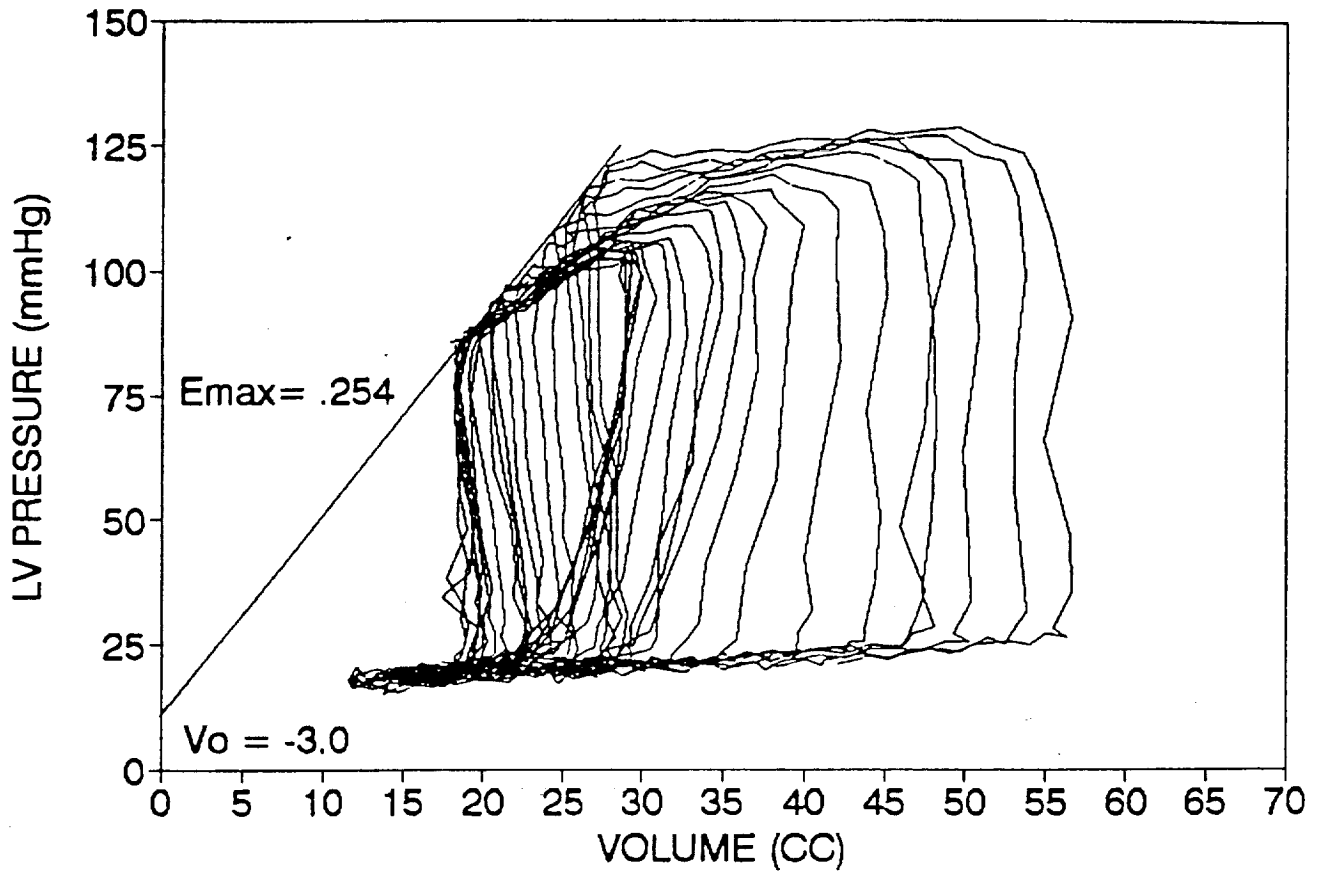


Fig. 9

A_126 ESPVR - UPRIGHT

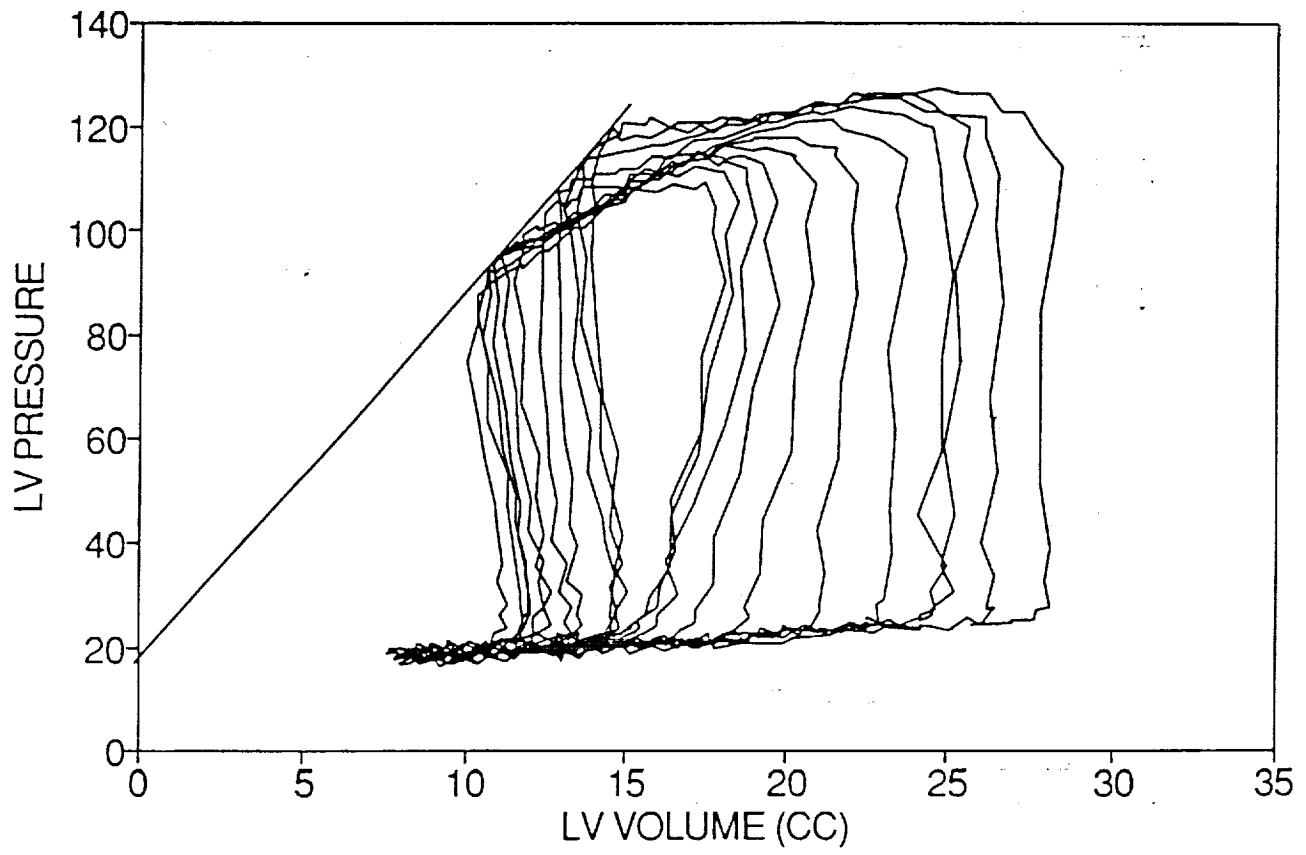


Fig . 10