FEASIBILITY STUDY OF NONINVASIVE VENOUS PRESSURE MEASUREMENT

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FOREWORD

This report presents the results of a four month investigation by Biosystems, Inc. into the feasibility of noninvasive venous pressure measurement, which was performed under contract NAS W-1559. Valuable technical guidance was provided by Dr. Fred B. Benjamin and Dr. Sherman P. Vinograd of N.A.S.A. Headquarters, and Dr. George Armstrong of the N.A.S.A. Manned Spacecraft Center.

The purpose of the program was to determine the feasibility of potential techniques for measurements on the venous system in space, which would not violate the integument. Of the many methods evaluated artificially and experimentally, three were selected as prime candidates for early development: superficial vein pressure chamber occlusion, limb venous occlusion plethysmography and digital plethysmography. Preliminary tests were performed in order to evaluate these techniques. Additionally, P-A delay and A wave obliteration were found in need of further research.

The authors gratefully acknowledge the important contributions of Dr. I. F. S. Mackay (U. of Puerto Rico Medical School) and Dr. Carl Kupfer (U. of Washington Medical School) on experimental studies, Drs. Lawrence Stark and James Dow (U. of Illinois at Chicago Circle) on measurement techniques and Mr. Joel Newman on program management. Acknowledgement is also given to the 109 experts in the field who responded to our questionnaire and stimulated activity along several new paths in our investigation.

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I INTRODUCTION

Venous pressure is generally determined by estimating the height above the heart at which the veins in the arm collapse or where the venous pulse in the jugular vein can no longer be seen. In surgery or when more accurate measurements of peripheral or central venous pressure are required, a catheter is inserted into a superficial vein or threaded back to the heart. Pressure transducers or manometers on the catheter indicate the venous pressure. Obviously none of these techniques are suitable for measurement of an astronaut's venous pressure in space. The purpose of this study was to determine the feasibility of modifying existing techniques or developing new methods for noninvasive venous pressure measurement under weightless conditions. Our investigations led to nine types of measurements which were considered seriously as potential noninvasive venous pressure measurement systems. Three methods were chosen as having the highest likelihood of success for development as a usable venous pressure measurement technique for space applications in the near future. These three techniques are the superficial pressure chamber occlusion method, limb venous occlusion plethysmography and digital plethysmography. Experimental verification and preliminary designs are presented for each of these three methods. We conclude that one or more should be developed as space hardware.

The importance of measurements of parameters of the venous system during prolonged weightlessness cannot be underestimated at this time. The role of the venous system and active venous tone in reducing blood pooling in the lower part of the body during positive ($+G_z$)acceleration has been thoroughly explored, and led to the development of a variety of G protection devices. The increase of venous pressure in the head during negative acceleration ($-G_z$) and the associated discomfort, red out, and petechiae have received somewhat less study. The effect of weightlessness on the venous system, however, has only begun to be investigated. Related experiments involving prolonged water immersion and especially prolonged bed rest have shown significant cardiac deconditioning, reduction in venous tone, loss of fluid volume, and a significantly reduced ability to withstand normal or elevated accelerations. The limited experience on cardiovascular effects of prolonged weightlessness in the Mercury and Gemini programs has indeed led one to suspect deconditioning in the venous system as evidenced by post-flight response on tilt table tests. To extrapolate very far on the basis of these non-controlled experiments would be unwise at this time, and it is clear that for predictive medical reasons as well as research, on-board measurements of the important parameters of the venous system should be included on space missions in the near future.

The next question involves which parameters of the venous system should be measured. It is clear that venous pressure, whether peripheral or central, although of some interest, will not by itself be sufficient to predict very much about the state of the venous system or the ability of the astronaut to withstand acceleration stresses. It also seems doubtful that venous pressure measurements alone will be sufficient to determine the efficacy of any of the cardiac conditioning devices proposed. Venous volume, venous blood flow and especially the distensibility and tone of the veins are certainly very important parameters which should be measured. For this reason we have weighed quite heavily the physiological significance of many of the proposed measurement techniques. We place more emphasis on those techniques which, by themselves or in conjunction with other measurements, could yield information about both venous distensibility and venous pressure.

Our method of approach in investigating techniques which might lead to noninvasive venous pressure measurements was to start with a fundamental examination of the physical variables involved in the venous system in any segment (excluding overall cardiac control) and then do an exhaustive tabulation of the parameters which could be measured and the techniques available for measuring them. The starting point for this is the simplified block diagram representing the relevant hemodynamic aspects of the venous system in any segment (i.e. limb, digit, thorax). In Figure 1-1 the pressure-flow-volume relations depend upon a number of independent variables, only some of which are measurable. In Figure 1-2, superimposed on the same basic structure, are the more important variables which might be measured in order to indicate the state of the venous system in general, and venous pressure in particular. One might, for example, measure the pressure of the venous blood at a point in the system by an inferential measurement of some property of this blood which changes with pressure, such as density, speed of sound, or color. Another class of noninvasive venous pressure measures are null-balance measurements. A common implementation of the null method of measurement is to introduce a known balancing pressure which is just sufficient to overcome all or some of the effects of the unknown venous pressure, as reflected by changes in flow, distension, etc.

One more parameter which could be monitored to indicate the state of the

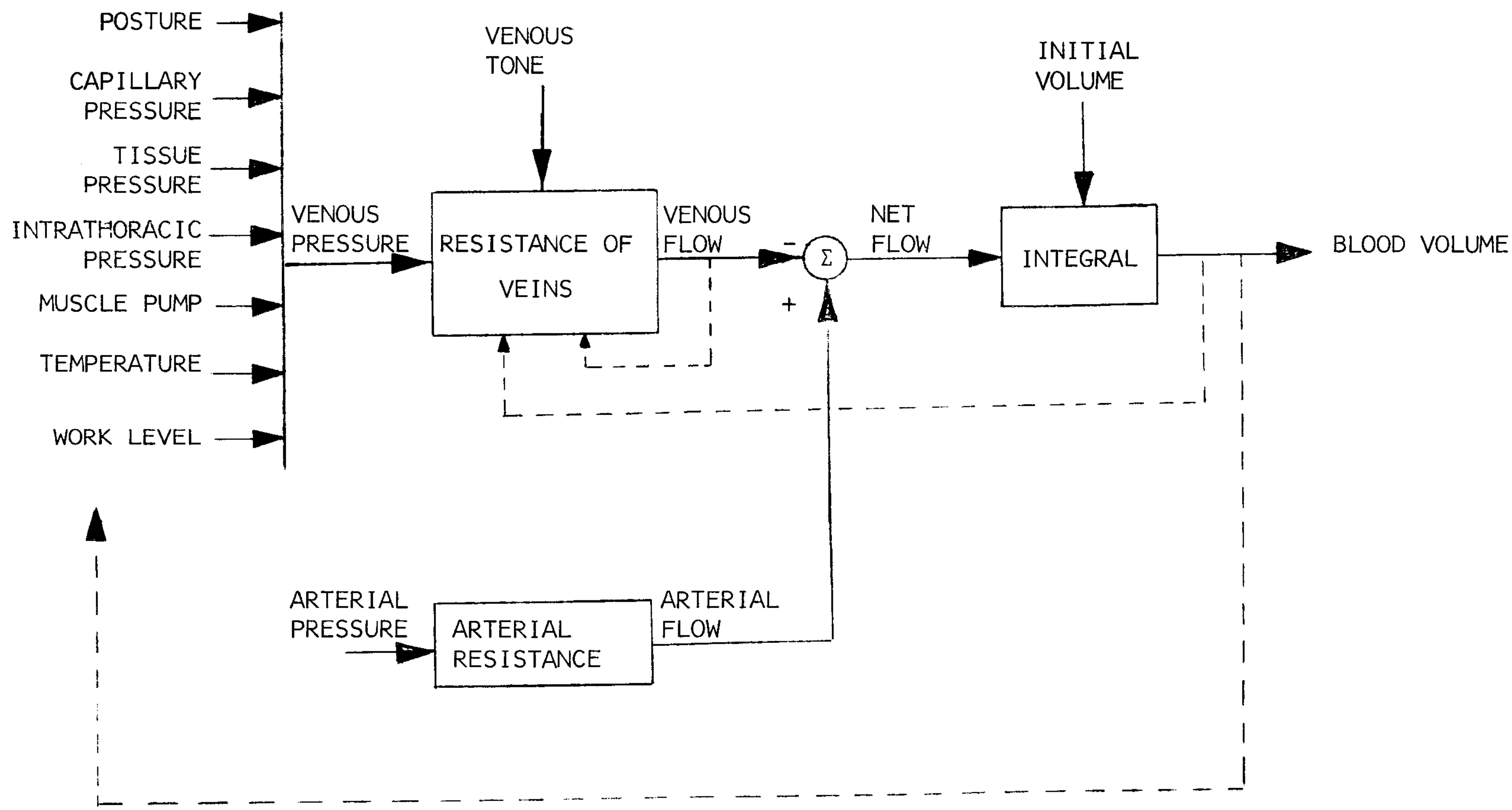


FIGURE 1-1 SIMPLIFIED VENOUS SEGMENT BLOCK DIAGRAM

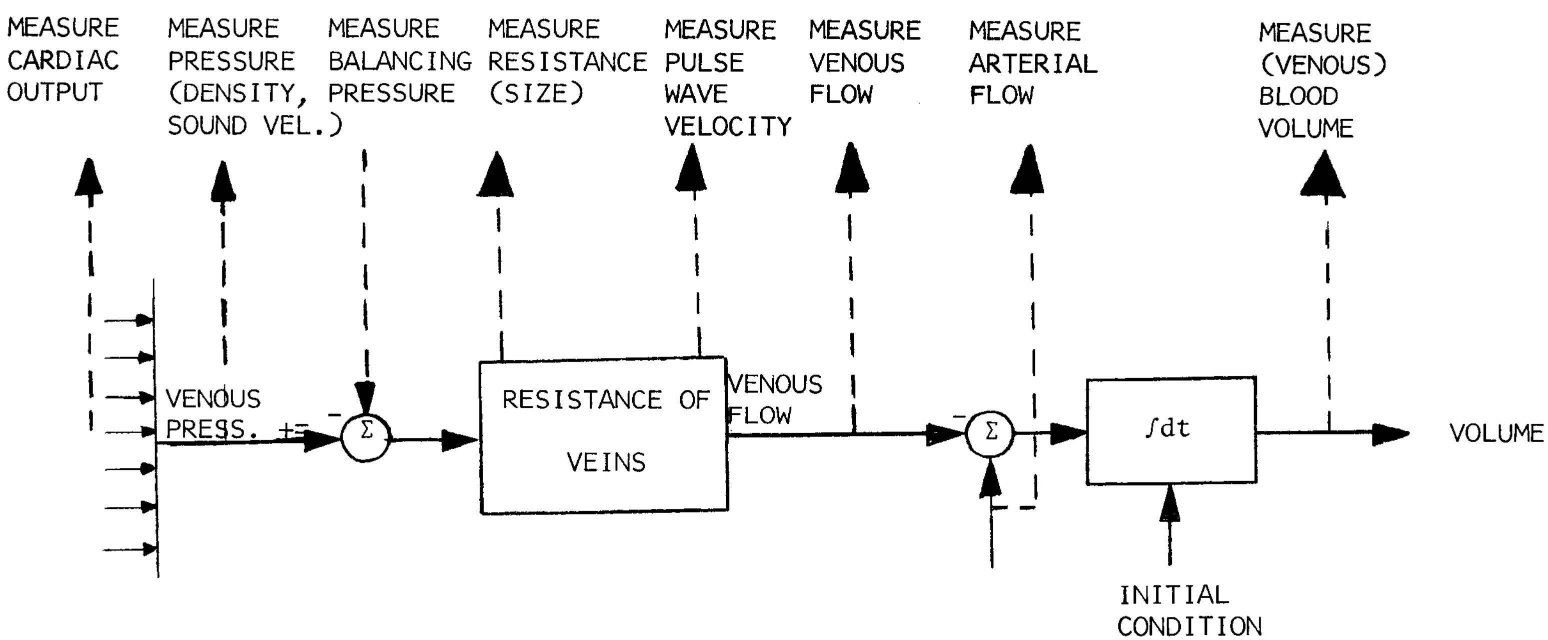


FIGURE 1-2 <u>SITES FOR VENOUS SYSTEM MEASUREMENTS</u>

venous system is the resistance of the veins in the segment under observation. This resistance might be measured indirectly by the pressure flow relationship across the segment. Changes in the resistance, as indicated by changes in the vessel shape (i.e. flattening or distension), could also be used as a measure. A known balancing pressure could be utilized to produce the shape changes. Pulse wave velocity has been called out as still another particularly interesting possible measurement related to venous tone and distensibility.

Noninvasive measurement of venous flow is important both in its own right and as an inferential indication of venous pressure. Measurement of arterial flow into a segment (or strictly speaking, the difference between entering and exiting arterial flow) is of course an important cardiovascular parameter. Of perhaps greater relevance in this discussion, however, is the observation that net arterial flow minus the rate of change of blood volume equals the net venous flow through a segment. Finally, the net segmental flow can be integrated to yield the change of blood volume in some portion of the body.

The measurement sites called out are all potentially valuable for study of the physiological status of the venous system under both weightless conditions and when exposed to controlled stress. The type of instrumentation which can be applied to these measurements is summarized in Table 1-1. By careful consideration of the information which could be gained by combinations of the measurements referred to in Table 1-1 and without particular regard to the state of development or verification of the techniques, a preliminary list of noninvasive venous pressure measurement concepts was arrived at. Nine of these techniques are summarized in Section 2 of this report. They were considered for application not only in a resting measurement in weightlessness,

Variable to be Measured	Volume	Flow	Pulse Wave Velocity (Artificial or Natural Pulse)	Measure Vessel Resistance or Size	Produce (and Measure) Balancing Pressure	Measure Pressure Via Density or Sound Velocity	Measure Cardiac Output
Noninvasive Techniques	Water Plethysmograph	Ultrasonic (Doppler)	Capacitance Microphones	Optical - Flattening	Cuff	Ultrasonic Probes	Impedance Collar
	Air Plethysmograph	Thermal	Crystal Microphones	Direct Observation	Pressure Chamber	Thermograph	Thermal
	Impedance Plethysmograph		Phlebomanometers	Ultrasonic	Manometer		Ballistocardiogram
	Photoplethysmograph			Thermograph	Electromagnetic Force Generator		Pulse Area Estimate
	Capacitance Cage			IR Photograph	Fluid Pressure		
	Mercury Strain Gauge			Distensibility (V/ P)	Flack Test		

TABLE 1-1 INSTRUMENTATION FOR TECHNIQUES FOR POSSIBLE APPLICATION IN NONINVASIVE VENOUS MEASUREMENTS

but also to indicate the venous response to different stresses such as Valsalva maneuvers, lower body negative pressure, exercise, occlusion cuffs or centrifuging. The nine techniques discussed are:

a. Venous Occlusion Plethysmography

b. Pulse Wave Velocity

c. Pressure Chamber Occlusion

d. Ocular Method

e. PA Delay

f. Standing Wave Resonance

g. Peripheral A Wave Obliteration

h. Venous Runoff Rate

i. Thermography

Section 3 of this report examines the physiological significance of venous pressure measurements, discussing the relationship among pressure, capacity, distensibility and volume in the venous system. In this section the problem of interpretation of venous pressure measurements and the importance of the sites where these measurements are taken are treated. The expected alteration of the venous state under weightless conditions is also discussed. Section 4 treats in detail the three specific techniques recommended for further consideration on the basis of their physiological significance, experimental verification and promise of early development into space hardware. These three techniques, (venous occlusion plethysmography, the pressure chamber occlusion method and digital plethysmography) are subsequently evaluated in terms of performance criteria in the merit weighing and conclusions of Section 6. The decision as to which, if any, of these techniques should be further developed ultimately depends upon the relative importance which NASA feels should be assigned to each of the factors discussed in this section.

In addition, the use of pulse wave velocity measurements presents some intriguing possibilities which would require considerably more research to fully exploit. Because of the intricacies of these methods a separate section is included in this report. Appendix A is devoted to a special study by Dr. E. O. Attinger evaluating pulse wave velocity as a noninvasive measure of central venous pressure. His report examines the factors which determine the wave velocity, the techniques for measuring and recording this velocity, and the physiological significance of PWV measurements. Its conclusion does not support the immediate use of PWV alone as an indication of venous pressure.

Significant experimentation was conducted by Biosystems to determine the feasibility of a number of suggested techniques. These experiments (seven in all) are written up in Appendix B. Of these, the experiments involving the pressure chamber method (B.1), air plethysmograph venous occlusion(B.2), pulse wave velocity (B.4), PA delay (B.3) and A wave obliteration (B.6) were particularly valuable in evaluating the techniques in terms of accuracy, feasibility and ease of performance and calibration. Appendix C of this report is an annotated bibliography divided into six sections, summarizing the most important points in the literature and annotating the 109 most relevant articles. Appendix D is a total bibliography of 208 articles relating to noninvasive pressure measurement, gathered from a reading list of over 600 articles and cross indexed to the annotated bibliography. Appendix E summarizes the results of our questionnaire mailing. The responses were quite helpful, and the cooperation was very encouraging. Of the 226 forms sent out 109 were filled out and returned. Appendix F lists the most important personal visits and contacts which were made in the course of this program. We are extremely grateful to all of the many experts who assisted us in determining the feasibility of—

the various noninvasive venous pressure measurement techniques described herein.

II DESCRIPTION OF POTENTIAL NONINVASIVE SENSORS OF VENOUS PRESSURE

This section briefly reviews nine of the techniques which received serious consideration in this program. Each section points out the principle of the technique, the instrumentation involved and the feasibility of the measurement and the state of development. Venous occlusion plethysmography (including digital and limb and encompassing venous runoff) and the pressure chamber method are considered in greater detail under specific techniques. Pulse wave velocity is treated extensively in Appendix A.

2.1 Venous Occlusion Plethysmography

Plethysmography is measurement of change in volume. A noninvasive measurement of venous pressure can be made using plethysmography and a venous occluding cuff. The occluding cuff is placed proximal to the plethysmograph and the cuff pressure increased while the segment volume is recorded. When the cuff pressure causes the pressure outside the veins to equal the venous pressure inside the veins, venous outflow stops while arterial inflow continues and the limb volume increases. That first increase in volume (over the pulsatile variation) signals that cuff pressure has caused some of the veins to collapse. The first veins to collapse would be those near the surface and as more pressure were applied deeper veins would also be collapsed. The pressure in all the veins is probably less than the pressure in the cuff due to the force needed to overcome tissue pressure and skin resistance. The disparity is lessened by raising the cuff pressure slowly and allowing an equilibrium to be established. Because of the difference in cuff and actual venous pressure, a calibration constant would have to be applied to the results of studies using this method if true venous pressure were to be obtained. That adjustment is similar to the acknowledged difference in cuff and intraarterial pressure measurements in which case the higher pressure figures for the recorded non-invasive measurement with a sphygmomanometer tend to be linearly related to the invasive measurement with a needle or catheter.

The change in volume of a limb at a given occluding cuff pressure indicates the distensibility of the veins in that limb. If the cuff pressure is increased in a continuous fashion or in steps, the corresponding change in volume can be plotted. The slope of the volume versus pressure curve indicates the venous tone, and the reciprocal (change in volume/change in pressure) is the venous compliance or the venous distensibility. If the occlusion cuff pressure is suddenly raised to diastolic arterial pressure all of the venous outflow will be obstructed. Volume increase can then be measured as a function of time and represents the arterial inflow into the limb. Therefore, venous occlusion plethysmography can readily be used to measure venous pressure, venous tone and arterial inflow.

The venous volume measured will depend on the position of the plethysmograph. Digital hand or foot volume measurements measure mostly skin venous volume change. When the forearm or calf is included in the plethysmograph both skin and muscle venous changes are measured. If only a segment of a limb such as a calf or forearm is included, mostly muscle venous volume is detected. That difference can be of practical importance since the innervation of skin veins is much more extensive than muscle veins. The region to be measured would depend on the information desired. When only a segment is measured it can be isolated by distal arterial occlusion. For forearm plethysmography one cuff is placed about the wrist and inflated to a pressure above the arterial systolic blood pressure. That cuff stops the hand circulation and isolates the forearm. Such an arterial occlusion generally induces vascular reflexes which abate in 60-90 seconds. A proximal cuff can then be inflated to stop venous outflow and the resulting volume change measured. The use of the isolated segment technique is necessary to obtain accurate arterial inflows but less important in the measurement of venous pressure and venous distensibility.

The measurement of venous tone would ideally be done by measuring the volume change from the collapsed through the distended state of the veins. The state of distension of the major peripheral veins under prolonged weightlessness is unknown and must be checked. If the veins are normally distended, then inflation of the proximal cuff could only further increase the cross-sectional area. For this reason venous distensibility and venous tone measurements might be limited to the upper portion of the sigmoid shaped venous distensibility curve.

In weightlessness with the hydrostatic drops eliminated it might be possible to estimate the central venous pressure accurately from the large vein peripheral venous pressure. The two should differ only by a small and probably constant pressure equal to the slight pressure gradient from the extremities into the chest cavity.

Venous occlusion plethysmography is a promising method for measuring venous pressure since it can yield more than just venous pressure information.

An automatic system could be developed to program the measurement of venous pressure along with venous tone and arterial inflow. If arterial pressure were also measured this type of an instrument could record the cardiovascular parameters of physiologic interest; arterial pressure, arterial inflow, venous pressure and venous tone.

2.1.1 Occluding Cuff

The cuff for creating the venous occlusion should have the following characteristics: 1. It should be flacid enough to cause no venous stasis when in the noninflated state and to conform to the surface of the segment to be measured when inflated. 2. It should be wide enough to insure an even distribution of the occluding pressure over the veins. Cuffs 6 to 14 cm wide have been used on the thigh and arm with larger cuffs necessary in the thigh region. 3. The pressure in or under the occluding cuff should be measured accurately. 4. The cuff pressure rate of change should be adjustable over a wide range, about 0.25 mm Hg/sec to 120 mm Hg/sec. An air inflated cuff would best meet these requirements. A gas system would also avoid the problem as regards possible rupture and leakage of a liquid system into the space craft under zero gravity conditions. Both open and closed loop pressure filling programs could be considered for the cuff inflation.

The occluding cuff is put as close to the plethysmograph as is practical. If the cuff is too close to the plethysmograph it will squeeze blood into it causing a "cuff artifact". That is a deflection on the volume curve that would appear to be due to inflow of arterial blood but is actually due to backflow of venous blood from beneath the cuff. The artifact can be measured if the arterial inflow is stopped and the occluding cuff inflated. If the artifact is regular and of the same volume each time it can be subtracted with each curve. If it is slow and irregular the occlusion cuff must be moved. The cuff artifact is of more importance in blood inflow measurements and is not a serious problem with venous pressure measurements where there is still venous flow. In that case the inflation rate is slow and the blood squeezed can also go into deeper channels and flow centrally.

If the occluding cuff is too far from the plethysmograph the sensitivity of the system will be reduced because of the time delay between venous occlusion pressure and measured change in volume. This fact is especially important in doing digital plethysmography where the occluding cuff must be on the finger not on the wrist.

Only a short occluding time is needed to measure arterial inflow; if the occlusion time is too prolonged the limb will undergo reflex vasomotor changes. In the forearm or calf only a few beats are needed to calculate flow and in the digits one or two cardiac beats will suffice. If the occlusion is not total, as would be the case with venous pressure and tone measurements, it can be more prolonged without endangering the measurements by invoking reflex changes.

2.1.2 Methods of Measuring Volume Change

The final selection of a method to sense the change in limb volume would depend on the information needed. If absolute values for venous tone and blood inflow measurements are desired then the direct methods of volume measurement would be indicated. If only venous pressure is to be measured, relative changes in volume could be used for the end point detector. The more commonly used techniques for volume detection are : water displacement plethysmography, capacitance plethysmography, impedance plethysmography, photoplethysmography, thermal flow measurements and Doppler shift techniques. The latter two do not measure volume change but are included since they sense changes in blood flow and blood velocity and might be considered to sense the end point in an occlusion venous pressure measurement.

The choice among the several available ways of sensing the change in venous volume in a limb or digit can be made on the basis of the instrumentation itself, since each method has been shown to correlate with some or all of the others. With the exception of the calorimetric technique, the sensors and circuits used in the other methods (volume, strain gage, impedance and photoplethysmography) do not differ widely in their complexity or reliability (given modern electronic components) and each is in current use in medical research.

The key to the choice, then, must be found in the reliability and repeatability of the measurement, not of the equipment. For man in space, the prevailing assumption is that he is healthy when he departs and that any degradation in his well-being is a consequence of his extraterrestrial environment. With this in mind, the problem of on-site calibration of the sensor of venous engorgement becomes a major one, and the critical question to be asked is revealed: Can the sensor be repeatably placed on the body such that relative changes in its output are validly interperable as an index of venous condition? The following sections detail the various methods of plethysmographic measurements.

a. Water Displacement Plethysmography

The limb or segment is placed in a container filled with water. Any change in the volume of the limb will be reflected in a change or displacement of the water. The expected changes in volume of a limb on inflation of a venous occlusion cuff are of the order of 5% of the original volume, which sets the range over which the plethysmograph must operate. The limb may be exposed directly to the water but more often is enclosed in a sleeve within the plethysmograph. The temperature of the water is generally controlled and monitored since it has such a large effect on vascular tone. The change in water volume can be detected by a flow meter or from the change in air volume in a chimney connected to the plethysmograph. An electrical volume transducer could detect either water or air displacement. Air movement above the plethysmograph has been measured using optical recorders, bellows, spirometers, and differential pressures. Generally when this technique is used to measure blood flow, a known pressure in the range of 20 mm Hg is applied to the limb to collapse the veins. If this technique were used in space where the veins would be under some pressure above zero the pressure or the plethysmograph itself would become an occluding cuff and the pressure where the first volume change occured would be invalid. The volume displaced is calibrated by injecting a known amount of water into the plethysmograph and noting the resulting deflection on the recording apparatus. This method offers the advantage of being the standard in the field and the most commonly used technique with much supporting experimental data. Water displacement gives the absolute measurement of volume and, being incompressible is less susceptable to drift due to temperature variation. It suffers from the inconvenience of a liquid system especially as regards use in space where the added weight and bulk would be a detriment. Its high thermal conductivity and capacity would render it less useful for measuring limb volume changes unless it were regulated to skin temperature. Otherwise the temperature of the plethysmograph would in itself alter the blood flow.

b. Air Displacement Plethysmography

Many of the disadvantages of the water displacement method can be overcome by substituting air or other gases. An air filled bag made of very pliable membrane is wrapped about the segment to be measured and the outer shell of nondistensible material wrapped around that. Thus, if the segment increases in volume the air in the bag is displaced. Because air is compressible, it is necessary to maintain a finite pressure in the bag and that pressure is also applied to the segment to be measured. As long as the pressure does not cause the pressure in the tissues outside the vein to exceed the pressure inside the vein it will not interfere with the measurement of venous pressure. The volume of air displaced can be measured by the methods mentioned above. If a large volume reservoir is connected to the cuff, the change of pressure in the system can be used to measure the volume. Such a design would require no more than 3 mm Hg change in pressure for the total volume measurement. For example, at 1/3 atmosphere cabin pressure with forearm flows of upwards of 30 cc/100ml tissue/min, this method would require 25 liters of air in the system. The air displacement method has one disadvantage which it shares with the water displacement method. Both place a cuff on the area and impede the normal evaporation of sweat. It also has the problem of thermal drift in the baseline which is inherent in a system using a compressible medium. That drift could be compensated for by balancing the measurement of volume with a constant volume system connected to the back of the transducer so any temperature change effect was automatically cancelled. The air displacement method does have the advantage of measuring absolute values and of using onboard gasses which would reduce weight and bulk. Changes in cabin pressure would have to be compensated for by measurement of gage pressure in cuff and plethysmograph.

c. Strain Gauge Measurement

The measurement of girth gives an indirect measure of volume. For a section of a limb which is considered to be a cylinder with a fixed length, the volume is equal to twice the percentage change in circumference for small changes in circumference. The changes in circumferences found in these measurements are of the order of one to two percent. A common form of the strain gauge is the mercury-in-rubber type which is constructed of small bore silicone rubber tubing filled with mercury and fitted with copper plugs in either end. Stretching the tubing will change the resistance between the two plugs. That resistance change measured by a bridge can be related to the percentage change in the length of the tubing, which in turn is related to the volume of the segment under the gauge. The gauge can be calibrated on the limb just prior to use by stretching it a known percentage of its length and noting the resulting resistance change. Thermal effects on resistance can be cancelled by utilizing a compensating gauge not subjected to the strain. The strain gauge method usually indicates blood inflows which are lower than those measured with water or air displacement plethysmography. Strain gauge methods are not as accurate on a digit or hand or foot as they are on a calf or forearm (92). The strain gauge method does offer the advantages of being light weight and relatively non-restricting. This method would probably be the method of choice for measuring venous pressure but would be second to air displacement plethysmography for measuring venous tone since the latter gives absolute values.

d. Capacitance Plethysmography

If a metal screen is placed loosely around a limb, the screen to skin capacitance can be measured. The skin acts as the ground and the screen acts as the active electrode or charged plate. A second shielding screen is placed around the charged one and is also grounded. With venous occlusion the limb volume increases and the distance between the skin and the fixed screen decreases, causing the capacitance across the air gap to change. The change is typically detected by the change in phase or frequency of an oscillator. Calibration is accomplished by placing a balloon under the screen and inflating it to several known volumes. Only relative values for volume change are measured. The main advantage of this method is that only a small area of skin is covered, that is the area under the grounding electrode.

e. Impedance Plethysmography

The tissues in a limb can be treated as a conductor with resistance properties. Thus, electrical impedance can be measured using AC excitation and related to the volume of the conductor. Since the distance between the two recording electrodes is known, impedance change can be related to volume variation. The simultaneous variation of resistive and reactive impedances causes a problem. As noted in the annotated bibliography this whole concept for measurement of blood flow has recently been challenged (Section B.1 Limb Occlusion Plethysmography). This method has been used more often to measure relative changes in digital blood flow.

f. Photoplethysmography

Changes in the flow of blood through a section of a limb can be detected by measuring the transmission of light through that section. If the sensitivity of the detector is broad the instrument would measure blood in both the oxygenated and reduced forms. Such a technique gives a good pulse measurement but is limited to relative volume measurements. The measurements are limited to digits and sections of skin in other areas of a limb. The results are also quite dependent on instrument placement which if not done carefully can cause large variation from recording to recording in the same person.

g. Thermal Flow Measurements

The thermal conductance of a section of a limb will vary with the amount of blood in it. Therefore, if a constant source of heat were placed a known distance along a limb from a temperature sensor, the variation in thermal conductance could be measured and changes in blood flow inferred. The measurement is relative, not absolute. The main disadvantage is that the heat source may cause changes in the blood flow. Sensor placement is also critical.

h. Doppler Shift Method

If ultrasonic waves are transmitted up and down stream in a moving column of blood there will be a difference in the frequency of the returning sound caused by the fluid velocity. That frequency shift can be used to measure the velocity of a column of blood in the limb. Without knowledge of the varying vessel diameter, however, the relation between velocity and volumetric flow is unknown.

2.2 Artificial Pulse Wave Velocity in Superficial Vein

Determination of propagation speed of a pulse in a fluid filled elastic tube has been suggested as an indirect measure of the fluid pressure, as well as the elastic properties of the tube. Pulse wave velocity is determined primarily by vessel radius, wall thickness and elastic modulus of the wall, all of which are pressure dependent. Considerable experimental evidence on this subject has been gathered for the arterial pulse, and recently reviewed by Attinger (17). Much of the arterial work performed at reduced pressures can be extrapolated to the venous system but only with great caution. The venous pressure method would probably utilize an external artificial pulse created by brief mechanical compression or decompression of a prominent superficial vein on a limb. Two pressure transducers mounted over this vein and a known distance apart would record the time required for the pressure pulse to cover the intervening distance. The wave velocity (1-10m/sec) is then compared with a standard function or prior calibration to determine venous pressure.

A good evaluation of this technique using conventional equipment under laboratory conditions was performed by Mackay et al on veins at elevated pressures with encouraging results (136). An experiment performed for us by Dr. Attinger measuring PWV in excised veins shows a monotonic increase in velocity with pressure over the range 0-30cmH_2O (Appendix B.4).

The instrumentation required for the measurement consists of two sensitive light weight pressure transducers, a low displacement electrically controlled mechanical stimulator, and a timing and gating circuit to measure the time interval of approximately 10msec. Disadvantages of the technique include its dependence on venous tone as well as pressure and the necessity for locating a prominent superficial vein. Its utility in measurements on partially collapsed veins at low intravascular pressure is questionable.

Because of the great complexity of the interpretation of PWV for arteries as well as veins we have gone into the theoretical and practical aspects of the subject in some depth. Appendix A of this report, prepared by Dr. E. O. Attinger, treats the theoretical ramifications of PWV, physiological significance, and methods of measurement of PWV. His conclusion is negative as far as its immediate application to venous pressure measurement. However, in conjunction with an independent measure of venous pressure in a superficial vein (such as by the pressure chamber technique) the measurement of PWV might yield a useful indication of venous distensibility and tone. (See discussion of P-A delay, Section 2.3).

2.3 P-A Delay Interval

2.3.1 Theory

We have indicated in Section 2.2 that the technique of pulse wave velocity measurement for indirect determination of peripheral venous pressure shows relatively little promise at normal pressure levels since the wave velocity is slow and the pressure pulse (whether natural or artificial) is quickly damped out. In trying to determine noninvasively the venous pressure, tone or state of distention of large veins in the thorax, however, we have been led to serious consideration of a technique which depends upon the speed of transmission of the naturally occurring venous pulse. The origin of this venous pulse is in the atrial contraction portion of the cardiac cycle. According to Brecher and Galletti (213) "During atrial systole (approximately end of P wave of electrocardiogram) the atrial volume decreases precipitously. The rate at which the atrial volume decreases and the ventricular volume simultaneously increases speaks in favor of a negligible back flow of atrial blood into the veins during atrial systole." In fact, recent studies (184) have shown that the pulsatile component of venous flow is significant in the central thoracic veins (up to 70% of average flow) and varies with respiration. This atrial contraction produces a pressure pulsation which travels back along the vena cava and major veins and can be detected at the jugular vein and in the antecubital region. Since the speed of transmission of a pressure pulse in a visco-elastic vessel depends upon the transvessel pressure and the wall characteristics, measurement of this transmission speed for the great veins holds out some hope of inferring central venous pressure or state of constriction of the major veins (See detailed discussion on pulse wave velocity in Appendix A)

The simplified wave equation describing the propogation of a disturbance along an ideal undamped visco-elastic tube is given by:

$$\frac{\partial^2 P}{\partial t^2} = \frac{EA}{2r\rho} \frac{\partial^2 P}{\partial Z^2} \tag{2.1}$$

and the propagation speed of the pulse wave is given by:

$$V = \left[\frac{EA}{2\,r\rho}\right]^{\frac{1}{2}} \tag{2.2}$$

Where E is the modulus of elasticity of the tube, A is the wall thickness, r is the tube radius and ρ is the fluid density (97). If the modulus of volume elasticity

$$K = \frac{\frac{dp}{dv}}{V} \tag{2.3}$$

is used instead of the one dimensional modulus of elasticity the wave propagation velocity given by:

$$V = \left[\frac{K}{\rho}\right]^{\frac{1}{2}} \tag{2.4}$$

Including the effects of damping in the tube not only makes the wave form decay as it travels along the tube, but also slightly slows its transmission speed for a lightly damped system. It is readily appreciated that for the case of veins the volume modulus of elasticity is very far from constant, varying strongly as a function of "radius" of the vein and consequently pressure of the blood as well as the extravascular pressure. In discussing the collapsible nature of veins, Alexander (2) points out the theoretically distinct phases of "filling, during which the geometry of the vessel wall is restored to the cylindrical shape without increasing in circumference" and elastic distention of the vein segment through its increase in "circumference and length" (2). Pressure volume curves for venous segments show a filling phase in which the volume increases greatly and almost linearly with small increases in pressure leading to a very low volume modulus of elasticity and low expected pulse wave velocity. At higher pressures there appears an elastic region, in which the incremental changes in volume with increases in pressure become lower and lower until the vein appears almost rigid and does not expand under further increases in pressure. In this elastic region the volume modulus of elasticity is continually increasing and would lead to predicted increases in pulse wave velocity for pressures exceeding approximately 5 to 10 mm Hg. In fact, such increases of pulse wave velocity with venous pressure in this region have been observed for excised veins in our experiments described in Appendix B.4. The second observation of considerable interest in this regard is the fact that the pressure volume curve for veins even at very low pressures is very strongly affected by the state of constriction or dilation of the vein. A constricted vein will show a high modulus of elasticity even at very low pressures where the dilated vein is in the "filling" phase and theoretically should lead to a high pulse wave velocity even at low pressure. This latter observation leads to the possibility that pulse wave velocity can be used as an estimate of central venous tone provided that central venous pressure can be determined independently. Thus, two possibilities remain for interpretation of pulse wave velocity in the central venous system. The first is as an indication of central venous pressure, provided that the venous tone can be controlled or assumed relatively constant. The second possibility is as a measurement of the state of constriction of the major veins, provided that venous pressure can be estimated by some other means. Some quantitative support for the effect of changes in venous pressure on pulse wave velocity are afforded by Mackay and Aster. In Mackay's experiments on artificially induced pulses in a peripheral vein in which the venous pressure was raised through an occluding cuff. The nearly linear relationship between pulse wave velocity and pressure is shown clearly (138).

2.3.2 Major Problems to be Explored

The method using the P-A delay is frought with difficulties of an instrumentation nature and, perhaps more serious, the unknown physiological significance of this interval. However, since the other techniques considered offer relatively little promise of learning much about central venous tone or pressure, except insofar as these are reflected in the periphery during weightlessness, the P-A delay should be given serious future consideration. The results of our preliminary experiments on measuring P-A delay in individuals at various tilt angles show that the P-A interval does appear to decrease with increasing central venous pressure, which is in the direction predicted by the theory. (See experimental results in Appendix B.3). Little quantitative information about the actual magnitude of pulse wave velocity in the superior vena cava or its agreement with theory can be given at this time, especially as we have not measured the electromechanical delay.

Among the problems associated with use of the P-A delay are the following: The transmission of the venous pulse from the right atrium to the jugular can only be accomplished when there is no obstruction in the path or when all the veins are at least partially distended. Under normal 1 G conditions with the subject erect, this is not the case, as portions of the vessels are collapsed at least during part of the respiratory cycle. Since our experiment showed a detectable A wave at the jugular for the subject horizontal, it may be hoped that this same condition would exist under weightlessness. Secondly, as expected we observed significant variation of the P-A delay with inspiration and expiration, presumably because of the changes in the intrathoracic pressure and the consequent central venous pressure and vein distention. This mechanism clearly must be further explored, and in particular an interesting possibility is the use of controlled breathing as a regulated test input to determine the affect on the P-A interval and its correlation with intravenous pressure or tone. Another problem involves the discrimination and interpretation of the A wave when recorded peripherally, since it often appears in measurements as merely a shoulder on the C wave. Thus, peak measurements are difficult to determine unless some techniques for removing the arterial component is included. Possibilities for this include measurement at two points close together on the vein, or independent measurement on the arterial pulse pressure to subtract it from the venous recording. Either of these represent further instrumentation complications. Similarly, the observed modification of the pulse wave shape with pressure or tone presents a problem, and it may well be that the most significant interval is achieved by measurements from the peak of the P wave to peak of the A wave. A possible solution to this problem is the use of a cross correlation scheme between the P wave and the venous pulse pressure wave in a narrow window of time (50-150msec). The peak of the cross correlation might represent a better estimate of the P-A delay. Even more basic problems are associated with the nature of atrial systole, and its variation with pressure. Mackay points out that the timing of the peak pressure pulse generated by the atrium varies with the filling pressure of the heart (136).

2.3.3 Instrumentation

The instrumentation required for measurement and analysis of the P-A interval requires judicious use of currently available components. As demonstrated in the experiments in Appendix B.3 the P wave is easily picked up with standard EKG leads, and as long as the jugular is not collapsed, the A wave is easily measured by a technique such as the pressure balloon used by Mackay. We feel that more reliable pulse pressure measurements which may be more easily obtained might result if, instead of the pressure chamber, a light low impedence displacement transducer such as a pizeoelectric or capacitance microphone could be used. Crystal microphones of the types used by Weltman et al (201) for arterial pulse wave velocity yield satisfactory pulse pressure waveforms, but are limited by their high sensitivity to movement artifacts.

The determination of the P-A interval automatically requires the development of a set of peak detecting gated trigger circuits or the use of cross correlation as mentioned. Although the techniques are well known, their application requires considerable development effort. Finally, if it is found that the important physiological variable is pulse wave velocity, and not simply the P-A interval, then some technique must be found for measuring the electromechanical delay. If it is assumed that this delay is constant, it need only be measured once. A preflight measurement in which simultaneous electrocardiograms and phonocardiograms are taken is a possibility. Automatic detection of the atrial contractions as picked up by the phonocardiogram is by no means a trivial task. Despite the large number of instrumentation and physiological questions, the P-A delay technique remains an intriguing possibility.

2.4 Standing Wave Resonance

The production of standing pressure waves, which can occur in a solid, liquid, or gas, is a common phenomenon. The production of a standing wave depends on the possibility of wave motion being transmitted in the medium in one direction and its being reflected back in the opposite direction in such a way that the nodes of the waves traveling in the two directions coincide and the antinodes of the waves augment. This resonance phenomenon forms an amplification for pressure stimulation at the natural frequency. Furthermore, the measured quality is frequency rather than velocity of pulse wave as in other PWV applications.

The frequency of a standing wave in a fluid filled tube is a function only of the length of the tube and the wave velocity in the medium. For tubes which have the characteristics of veins, the wave velocity depends upon the tension in the wall of the tube, and hence on the pressure in the tube. With several simplifying assumptions, the relationship between the fundamental resonant frequency and the physical characteristics of a superficial vein are given by:

$$f = \frac{1}{4l}\sqrt{\frac{Eh}{2\rho r}} \qquad (2.5)$$

where:

f is the fundamental resonant frequency

l is the length of the vein segment (with a pressure source at one end and occluded at the other)

E is the tangential modulus of elasticity

h is the wall thickness (assumed small relative to r)

ρ is the density of the blood

r is the mean radius of the vessel; the vein will be elliptical, but this equation will yield sufficiently accurate values for eccentricities of 0.6 or less (See Figure B-10, Appendix B).

This equation predicts for a transmural pressure of 10 cm H_2O, a 0.5 meter length of segment and an eccentricity of zero (circular cross-section), that the fundamental resonant frequency would be one cycle per second. However, on the basis of empirical data taken from excised segments, 2.5 cycles per second is a more likely value. (See Figure B-9, Appendix B). The odd harmonics of the standing wave will also resonate, so that utilizing a pressure pickup to detect frequencies to 12.5 c.p.s. would be desirable.

On the basis of data which have been accumulated on the characteristics of isolated veins, it may be possible to establish a standing wave in a venous segment and correlate the frequency of the resonant wave with the transmural pressure. However, the problem has not been sufficiently studied <u>in vivo</u> where the vein is surrounded by normal connective tissue. Whether a standing wave can be created depends partly on the rate at which the wave is damped and, thereby, lost. Although the arterial system has been studied from this point of view, it is possible that the venous system is so severly damped by surrounding tissue that it would be difficult to establish a venous standing wave over a significant length of vessel. Even in attempts to detect artificially induced pulses in arteries (whose walls are more suitable for the propagation of such waves), it has been found that at low transmural pressures the transmission characteristics are poor and attenuation is evident over a 30 cm segment (125).

In addition to the problem of attenuation, which would affect the feasibility of this scheme, there are several other significant factors which bear upon its validity in eliciting useful data about the venous system.

Although the wall thickness, radius and elastic modulus are dependent upon the venous pressure, they are also affected by venous tone and by any longitudinal stress imposed on the vein. Thus a change in tone, for example, could be mimicked in its effect upon the resonant frequency by a change in pressure or body position. The complexity of this relationship and the shallowness of our understanding of it create doubt that an "index of venous performance" can be obtained by this method, much less any specific quantified parameter.

The ambiguous shape of the cross-section of the vein segment studied also clouds any measure based upon a standing-wave procedure. Even in weightlessness, it is likely that the effects of respiration, atrial activity and posture will cause local volume changes in the central venous system. These changes are characterized by the non-uniformity of the cross-section, often to the point of collapse - a condition which would prohibit the setting up of resonance.

In the use of artificially induced pressure waves within the vasculature, the detectors appear to be unaffected by transmissions through adjacent tissue. Despite this hopeful observation, it should be noted that any tissue overlying the vessel at the point to which the inducer is applied may well modify the wave shape induced. The rheological nature of the vessel walls makes them responsive to wave shape in that their elastic modulus varies with frequency. Thus a suddenly applied disturbance directly impinging on the vein wall will result in a higher velocity of propogation, within the vessel, than will one that is more cushioned by the overlying tissue. It is, therefore, doubtful that the placement of the pulse inducer can be sufficiently constant, both with respect to the superficial vein and to the adjacent tissue, to allow a practical embodiment of this method.

While theoretical considerations suggest that venous pressure might be estimated noninvasively by measurement of the frequency of an artificially created standing wave in a venous segment, it is a method of dubious practicality. Although extensive investigation of the subject has not been carried out, the rather pessimistic conclusions of Section 2.2 apply even more strongly to this technique.

2.5 Superficial Vein Pressure Chamber Balance

As mentioned earlier, it is a well known clinical observation that the central venous pressure may be estimated by observing the height above the right heart level at which venous pulsations occur in the external jugular vein or by observing the height of a limb at which venous collapse occurs (1).

The estimation is based on the fact that a column of blood in a gravity field will exhibit a pressure drop which closely approximates the height above some arbitrary reference level as long as the vessel is not collapsed between the point of reference and the point of observation (103). The larger and more superficial the vein, the more easily the venous pulsation or the venous collapse can be observed.

The distinct nature of the phenomenon of venous collapse is best understood by considering the distensibility characteristics of isolated veins, described by Ryder (169). Examination of Ryder's venous distensibility curves reveals that for every vessel there is a zone along the curve where the rate of volume change of the vessel is large for a corresponding small change in transluminal pressure. This zone is invariably where the pressure across the vessel wall is near zero. In this zone the distensibility curve is least affected by changes in venous tone. Furthermore, an endpoint of venous pressure measurement, if taken in this zone, is sharp and distinct.

No such clinical observation is likely, however, under weightless conditions. Under such circumstances, the peripheral venous system will probably always be filled at rest, regardless of the relative position of the heart (178). By application of external pressure to a vessel through the skin, however, the transluminal pressure may be reduced to zero for any chosen vessel segment. By this maneuver, the vessel being studied may be "moved" along its distensibility curve to the steep zone near zero. The appearance of venous collapse indicates that the endpoint has been reached and the external pressure required to reach the balance point is equated to venous pressure.

Such a technique may be used to measure venous pressure noninvasively under weightless conditions. Its limitations are theoretically no greater than those for the clinical technique described by Adams (1) as long as a highly distensible membrane is chosen for the application of pressure. Several authors have previously described the use of this technique to measure venous pressure.

A simple pressure chamber was described over sixty years ago by von Recklinghausen (189) and shortly thereafter by Hooker (104). Hooker's instrument consisted of a glass chamber which was cemented to the skin with collodion over the vessel to be measured. Pressure was applied directly to the skin over the vessel via air or water. Goldmann (83), Linnér (130), and Brubaker (39) have described methods for measuring the pressure in much smaller veins of the conjunctiva and episclera in which the pressure is transmitted to the vessel via a thin, transparent membrane. In their experiments, the restrictions on membrane characteristics were very severe because of the small size of the vessels being measured. For larger vessels, however, thicker and less distensible membranes would be satisfactory.

In an effort to eliminate the artifact introduced by vessel occlusion, Okino (157) attempted to work out a noninvasive method of applying partial flattening of collapsible tubes by strain transducers connected in various manners. He was unable to obtain consistently linear correlations with intraliminal pressures. He did not, however, study a system in which a pressure chamber of the desirable characteristics, such as that of Hooker, is used for the measurement.

A simple pressure chamber has been constructed and tested by Biosystems.

These preliminary tests have produced repeatable, consistent readings over a range of 5 to 85 cm water pressure. The average deviation from simultaneous invasive measurement was 2.1 cm water and the standard deviation was 2.5 cm water. The pressure chamber gave a linear response over the range tested, and the correction for skin compression was small. The experiment is presented as Appendix B.1 of this report. At low pressure values a casual test of the Durham tonometer, used as a pressure chamber, produced good correlation with the above described pressure chamber constructed by Biosystems. In the higher ranges, however, it under estimated the venous pressure probably because of the small area of the sensing tip (5 mm) (30).

The pressure chamber method is applicable to large, superficial veins which are filled. The jugular vein or the veins of the antecubital space are satisfactory in lean individuals. In the course of our initial experimental evaluation the procedure for using the pressure chamber has been found to be simple, rapid, easy to perform and reliable.

2.6 Ocular Method

The relationship between intraocular pressure and episcleral venous pressure of the human eye has been studied by noninvasive methods (83, 84). This relationship is given by the formula:

$$P_i - P_e = R \times F \qquad (2.6)$$

where P_i is the intraocular pressure, P_e is the episcleral venous pressure just outside the sclera, R is the resistance against which aqueous humor flows out of the eye, and F is the rate of outflow of aqueous humor from the eye. Rewriting this equation to express episcleral venous pressure, P_e, yields:

$$P_e = P_i - (R \times F). \tag{2.7}$$

It is evident from equation 2.7 that if intraocular pressure, resistance to outflow, and outflow rate were known or measured by noninvasive techniques, a peripheral venous pressure could easily be calculated.

Intraocular pressure, P_i, has been extensively measured in humans by noninvasive techniques, termed "tonometry" (174,85,142). The methods of Schiötz, Goldmann, or Mackay are simple, quick, and easily adaptable to conditions of space flight. These three methods, however, require topical anesthesia. A fourth method, described by Durham (58), may be carried out without anesthesia.

The resistance to outflow of aqueous humor from the eye, R, may be obtained by a noninvasive method known as "tonography" (89,128,153). Tonography consists of increasing the intraocular pressure by application of a known constant force for four minutes and measuring the resulting decrease in volume of the eye. The change in volume is calculated from the pressure data using standardized calibration curves worked out for human eyes by Friedenwald (74). Utilizing pressure data from tonography and Friedenwald's nomogram of scleral rigidity one is able to calculate the resistance to outflow of the eye, R. The procedure ordinarily is performed using topical anesthesia, but could be modified to be done without anesthesia by using the Durham tonometer.

The final factor in equation 2.7, the outflow rate from the eye, F, has been measured in humans by Goldmann (84) and by Grant (89). Outflow has a value of approximately 2.3 microliters per minute. It is assumed that the outflow rate of a given eye is fairly constant, except for changes which are related to the diurnal variation in intraocular pressure, the peak of which may be estimated by the water drinking test (150). The exact cause of the diurnal variation, however, is not well understood (186,55,56). If preflight determinations of diurnal variation in intraocular pressure suggested that F were relatively constant, measurement of P_i and R by tonometry and tonography in flight would yield values of a peripheral venous pressure, P_e.

On the one hand, this method has already been used to estimate the effect of drugs on the episcleral venous pressure (24). On the other hand, the relationship between the pressure in the episcleral veins and other veins of the body has not been extensively studied. In an experiment we performed to measure this relation in monkeys, we showed that under special circumstances, variations in the pressure of veins near the eye closely parallel variations in pressures in the jugular system. (See experimental write up in Appendix B.5), This relationship may be disrupted, however, by variations in arterial pressure, and probably by other factors as well (40). There is certain evidence that in the human the episcleral venous pressure may not be as greatly influenced by body position as is the pressure in larger peripheral veins (77). Measurement of the episcleral venous pressure by this technique, therefore, would have to be considered a peripheral technique for small vessels, and consequently of less general physiological significance.

In summary, tonometry and tonography may be combined to measure a peripheral venous pressure near the eye by noninvasive techniques. Currently available instruments could be modified to make it possible for this determination to be carried out without topical anesthesia, but not without some loss of accuracy.

2.7 Peripheral A Wave Detection

It has been observed by Mackay and others that one of the problems of venous pressure measurement using venous occlusion plethysmography is that the most superficial vein is first occluded by increasing cuff pressures, and that deeper veins are gradually occluded as the pressure in the cuff increases. Therefore, volume increase in the distal segment resulting from venous occlusion occurs gradually rather than sharply. The precision of the estimation of venous pressure is thereby compromised.

The problem of vessel depth can be circumvented by utilization of a detection system which is sensitive exclusively to phenomena in superficial veins. One such system is described at length as the pressure chamber method in Section 4.2. Another detection system may be based on the presence of pressure waves which are propagated along the venous system as a result of cardiac activity.

One such wave, the A wave, is generated by the contraction of the right atrium of the heart and is propagated along the great veins (See Section 2.5 for further explanation). Whether the A wave of the right atrium reaches the antecubital veins of the arm or not is somewhat a matter of dispute. Mackay, however, has identified a venous pressure wave which may be detected at the antecubital space and has, for lack of a more appropriate term, called it the "peripheral A wave". This wave, at normal cardiac rates, occurs approximately 0.2 seconds following the P wave of the electrocardiogram (See Appendix B.3). It is observed only when the venous system between the heart and the point of detection is partly filled -- not when any portion of it is collapsed. The fact that the peripheral A wave disappears when a venous segment between the point of detection and the heart is collapsed provides a method for measuring the venous pressure of the superficial veins of the periphery. A small fluid filled balloon connected to a low volume displacement pressure transducer is placed over the antecubital space. A venous occlusion pressure cuff is placed proximally to the volume sensor and gradually inflated until the peripheral A wave disappears. At this point, the pressure in the cuff has just occluded the superficial veins of the arm. The pressure in the occluding cuff at the endpoint may be easily converted into venous pressure by comparison to a previously determined series of direct pressure measurements.

The method described above is simple and has been carried out on a preliminary basis by Biosystems (See Appendix B.6). Unfortunately, however, the technique is not described in the literature, and there are no other supportive data. The accuracy of the technique, therefore, remains unknown and must be established by clinical experimentation. The simplicity of the detection system and the utilization of a naturally occurring pressure wave make it a method which is worthy of investigation. Furthermore, it can be combined with venous occlusion plethysmography to derive other parameters of the venous system such as venous tone and blood flow.

2.8 Central Venous Pressure Determination by Measurement of Venous Runoff Rate

As described in Section 2.1, venous occlusion plethysmography is a method of obtaining several parameters of the arterial and the venous circulatory systems by measurement of the change in volume of a segment which occurs when venous outflow from the segment has been obliterated. Most writers have dealt solely with the increasing portion of the volume curve which follows venous occlusion. Few have considered the decreasing portion of the volume curve following cuff release. This section deals with the use of venous runoff plethysmography as a method of estimating central venous pressure.

If the veins draining a limb are temporarily occluded, the volume of the limb distal to the occlusion will gradually increase, principally because of the increase in volume of small and large veins of the limb. The limb volume will reach a new steady state at an elevated venous pressure. If the occluding cuff is suddenly released, the volume of the limb will decrease until its original steady state volume has been reached at normal venous pressure. The following derivation is intended to show that it is theoretically possible to calculate venous pressure by studying the curve of limb volume decrease following cuff release.

At steady state, with the occluding cuff inflated, blood flow into the arm equals blood flow from the arm, or,

$$Q_a = Q_v \qquad (2.8)$$

where Q_a equals the arterial inflow into the limb and Q_v equals the venous return from the limb. The resistance of the venous system under the cuff will be given by the relation

$$R = (P - p)/Q_v \qquad (2.9)$$

where R is the venous resistance under the cuff, P is the venous pressure immediately distal to the cuff, and p is the venous pressure immediately proximal to the cuff. At any given time following cuff release, the rate of change of volume of the distal limb, dV/dt, will be given by

$$-dV/dt = Q_v(t) - Q_a(t) \qquad (2.10)$$

It has been shown by Mackay that immediately following cuff release, Q_v is very large compared to Q_a, so Equation 2.10 can be simplified to:

$$-dV/dt = Q_v \quad \text{(venous flow)} \tag{2.11}$$

Substitution of Equation 2.9 into Equation 2.11 gives

$$-dV/dt = (P(t) - p(t))/R(t) \tag{2.12}$$

for any time t. Since changes in proximal pressure (p) will be small compared to changes in P with time, Equation 2.12 may be rewritten

$$-dV/dt = (P(t) - p)/R(t) \tag{2.13}$$

Rearrangement of Equation 2.13, solving for p, gives

$$p = P(t) + dV/dt \times R(t) \tag{2.14}$$

If an appropriate value for P(o) has been chosen at $t = 0^-$ (prior to cuff release), it is reasonable to assume that R will rapidly change from a high value (when the cuff is inflated) to its normal low value (after the cuff is released) so that at time, t_1 a short time following cuff release, $P(t_1)$ will not differ greatly from P(o). The difference between $P(t_1)$ and P(o) is accounted for by setting

$$P(t_1) = K'P(o) \tag{2.15}$$

Furthermore, the pressure in the occluding cuff may not be identical to P(o) but may differ from it by a precalibrated bias and sensitivity, such that

$$P(o) = K''P_{cuff} + P_{bias} \tag{2.16}$$

Substituting Equations 2.15 and 2.16 in 2.14 yields

$$p(t_1) = K'''P_{cuff} + K'\, P_{bias} + \left.\frac{RdV}{dt}\right|_{t=t_1} \tag{2.17}$$

where R is the normal low value of resistance and t_1 is shortly after cuff release. Equation 2.17 shows that it is possible to obtain a value of venous pressure by examining the rate of volume decrease at a specific time, t_1, following the release of a venous occluding cuff from a limb which is in steady state, provided K'', and R have been previously determined from calibration experiments. If a constant cuff pressure is used, K and K'' may be combined into a single correction factor, K'''.

It is obvious that an analysis of the volume decrease function of the distal segment must not violate the assumptions of the previous derivation. The method necessarily depends on the possibility that the resistance, R can return to its normal value sufficiently rapidly, and that the distal venous pressure at time, t_1, will remain near its value at time 0. The possibility is increased by utilizing a narrow occluding cuff and by choosing an occlusive cuff pressure which is not far above normal venous pressure. It is encouraging that a similar problem, the so-called "cuff artifact" which arises in digital venous occlusion plethysmography, has been overcome by appropriate instrument design (See Section 4.2).

A determination of central venous pressure may be carried out in the following manner. A volume detector, such as one of those described in Section 2.1, is placed on the arm or forearm. Two identical venous occlusion cuffs of special design are placed around the arm as near the shoulder as possible. Both cuffs are inflated to a preselected level, for example, 20 mm Hg, where they remain until the volume of the distal segment has increased to a new level and is steady. Then the distal cuff is quickly released. The time required for the veins under the distal cuff to fill is noted as a rapid decrease in volume. This time is taken as t_1. The volume is allowed to reach its original steady state once more, while the proximal cuff is still inflated. The second cuff is then released. At t_1 seconds following the cuff release, the rate of change in volume of the plethysmograph is noted. This is

$$\left.\frac{dV}{dt}\right|_{t=t_1} \tag{2.18}$$

The values of P_{cuff}, dV/dt, K, K" and R are substituted into equation 2.17 which is then solved for p, the venous pressure proximal to the occluding cuff.

It is probably necessary that the values for K and R be determined with invasive methods in the same individual in which the determination will later be done for most accurate results. Furthermore, if the occluding cuffs are placed as near the chest as possible, and the venous resistance between them and the intrathoracic veins is low, as it is likely to be under weightless conditions, the value of p obtained will be a close measure of central venous pressure.

In order to test the validity of this method, a substantial number of central venous cannulations would have to be performed under a variety of conditions in order to establish the limitations of the proposed technique. The methods of volume detection, however, have been well developed and used extensively in other techniques and are described in Section 4.1.

It is interesting to note that the analysis of the volume decay curve of venous runoff from a limb after cuff release has not been studied from this point of view by previous investigators. Greater attention has been given to the phase of volume increase of venous occlusion plethysmography.

2.9 Thermography

The use of thermography (or infrared photography) to determine noninvasively the diameter of major superficial veins was investigated. It was hoped the states of the venous system, as reflected in changing vein size and venous volume distribution might be apparent from photographs indicating changed warm regions containing blood. Wave lengths in the region of 1 to 1.2 microns have been suggested (168). Unfortunately, the resolution in state-of-the-art thermography does not permit quantitative information to be derived on individual veins. Furthermore, because of the non-circular geometry of veins, a single two dimensional view would not be sufficient for volume determination even if the resolution were improved. An alternative use of thermography to detail the total blood flow in a limb or other section by noting its average temperature may have some application to venous measurements. No experimental data is currently available to support this approach. As a practical matter, the size, weight and reliability of current thermography equipment makes it unsuitable for space applications.

III PHYSIOLOGICAL SIGNIFICANCE OF MEASUREMENTS

Approximately 70% of the blood volume is contained in the post-capillary capacitance vessels which thus act as a circulatory reservoir. This system adjusts the venous return under conditions of stress, maintains adequate ventricular filling pressures, and is a major determinant of cardiac output. In studying the dynamics of this network, difficulties are encountered which are not important factors when investigating the pre-capillary resistance vessels. The low pressures intrinsic to the system are greatly influenced by hydrostatic effects which must be taken into account. The pressure gradients which assure central flow make it hazardous to predict central events from peripheral information unless the circumstances of measurement are well controlled. Though the actual gradients may be small, (a mean pressure drop of 1.8 cm H_2O has been demonstrated from a distended antecubital vein to the central veins) their value relative to true central pressure is large. In a distensible system since small pressure changes may reflect significant variations in flow these changes must be accurately determined. The phenomenon of collapse, to be discussed below, makes local pressure measurement of little significance in evaluating venous tone, and also serves to increase peripheral pressure gradients.

3.1 Venous Return

Factors which facilitate venous return can be discussed under the following headings:

Muscular Pump. The veins in the periphery are equipped with valves which translate extraluminal forces into central flow. On quiet standing, the venous pressure in the feet is equal to the weight of a column of blood to the height of the hydrostatic indifference point just below the right atrium. With muscular effort, this pressure is greatly reduced as central flow increases.

Respiratory Pump. Inspiration decreases intrathoracic pressure and results in emptying of extrathoracic vessels. Since the veins are collapsable, only a finite increase in flow can be produced before collapes makes further enhancement impossible. Only the cranial and vertebral veins are held open and thus can sustain negative pressures.

Ventricular Suction. Contraction of the ventricles results in downward displacement of the atrio-ventricular junction. This increases atrial capacity causing a drop in atrial pressure and an increase in vena caval flow.

Active Venoconstriction. Variations in venous tone are mediated by the adrenergic fibers of the sympathetic nervous system. There is no active venodilation, and in a comfortable environment little if any resting venous tone. It appears that the venous system acts uniformly and is not influenced by local factors which effect the resistance vessels. The receptors which activate the sympathetic outflow to the veins are not well known, but it is no longer thought that the reflex response invariably parallels that of the resistance vessels.

Exposure to cold, a deep breath, hyperventilation, and increased intrathoracic pressure, such as that induced by the valsalva maneuver, all cause reflex venoconstriction. Exercise causes local as well as general peripheral venoconstriction although there is dilation of the resistance vessels in the exercising muscle. There is only a graded and transient venoconstrictor response to pooling of blood in the extremities by tilt or suction. The regulation of arterial inflow produced by sustained constriction of resistance vessels is probably most important in adjusting the volume contained in the limbs under gravitational stress. Carotid sinus hypotension has been shown to cause only a minimal increase in venous tone despite a marked response of the resistance vessels. Shepherd (177) has suggested the unifying concept that situations which cause an increase in cardiac output and a decrease in systemic vascular resistance are associated with increased venous tone.

Because the venous system is collapsible, pressure measurements in the undistended state give information only concerning the relationship of intra- and extra- luminal forces. Venous tone cannot be assessed by pressure measurements on collapsed veins, and thus a major determinant of the dynamics of the capacitance system is overlooked. Certainly, central pressures are important in assessing cardiac performance, but peripheral pressures do not truly reflect these unless a) the veins are distended, and b)hydrostatic effects are negated by accurate placement of reference levels. If these factors are taken into account, the gradients encountered are acceptably small for determining relative changes in central pressures. If one is to understand the responsiveness of the capacitance system, however, a study of venous tone is of utmost importance.

In order to assess venous tone or distensibility, one must know pressure/volume relationships. These are most easily obtained in an isolated venous system studied plethysmographically. Since local factors do not influence venous tone, stasis does not produce artifactual changes. Using plethysmography, pressure/volume diagrams can be obtained from peripheral segments; the finger, arm, and leg have been studied in this fashion. The venous system appears to act as a unit, thus generalizations concerning venous tone can be made from local information.

3.2 Effects of Weightlessness

In the weightless state, hydrostatic effects are no longer present. The venous system should be filled in a uniform fashion, though the degree of distention will depend on the blood volume. The latter has been shown to decrease under weightless conditions secondary to diuresis induced by the redistribution of the blood volume to the thorax with resultant distention of atrial and pulmonary stretch receptors. Pressure measurements in this state will not be distorted by hydrostatic effects, but they are subject to the same limitations of interpretation as those obtained under 1 G. An accurate estimate of central venous pressure can no longer be made by distending a peripheral vein by placing it in a dependent position. One must therefore accept the accentuation of pressure gradients due to flow through semicollapsed or elliptical vessels. Peripheral measurement of pressure will therefore not be valuable except as a gross estimate of changes in central pressure during weightlessness. The more peripheral the site studied, the less reliable it will be.

Estimations of venous distensibility will be most useful. The observed orthostatic intolerance after bed rest and weightlessness is due to factors which result in increased pooling of blood in the extremities. What role the venous system plays in this deconditioning can be assessed by stressing the system during and following exposures and noting changes in observed venous tone. This can be accomplished by challenging the system with a factor known to cause venoconstriction, such as a Valsalva maneuver or a deep breath, ergometer tests, or lower body negative pressure and serially grading the response.

3.3 Summary

The capacitance system adjusts the circulating blood volume and maintains venous return. As such it influences cardiac performance. Since it is a collapsible system, pressure measurements do not give information as to venous tone, and peripheral pressures only grossly estimate central venous pressure unless the peripheral vein is distended. An estimate of true central venous pressure is, of course, important in understanding cardiac events. For determining the reflex responsiveness of the system, however, one must know distensibility. There is evidence that the venous system is unaffected by local factors and acts in concert so that generalizations from local to general peripheral responses can be made. It is felt that both pressure and tone measurements must be obtained if the function of the capacitance system is to be validly assessed.

IV. SPECIFIC TECHNIQUES AND HARDWARE IMPLEMENTATION

Three specific noninvasive venous pressure techniques have been selected as showing the greatest promise for early development to space hardware. All three involve a null pressure scheme, in which the pressure required to balance the intravascular venous pressure is determined. The end points for two of the techniques (digital and limb plethysmography) is an increase in volume associated with occlusion of some veins by a cuff. These two techniques differ in the physiological significance and type of instrumentation. The end point for the pressure chamber occlusion method is the flattening of a superficial vein.

All three of these techniques have been given preliminary tests and look very promising. This section presents design considerations for each of the three instruments, as far as they have been carried under the current study.

4.1 Forearm Venous Occlusion Plethysmography

The principles involved in venous occlusion plethysmography as a technique for the noninvasive measurement of venous pressure have been covered in Sections 2 and 6. Briefly, a proximal venous occluding cuff is gradually inflated while distal volume is monitored with a plethysmograph. The pressure in the occluding cuff when the volume first shows an increase is the venous pressure, modified by a predictable sensitivity. Air displacement and strain gauge plethysmography appear to be the most practical and reliable methods of volume measurement.

4.1.1 Occluding Cuff

The occluding cuff would be 8 cm across and long enough to wrap around the upper arm or forearm of the subject with an overlap to insure an even distribution of the pressure. The length would vary from 20 to 60 cm depending on the person and the site measured. The cuff would be made of thin rubber, 0.005" thick, and the tubing carrying air into it would have an internal diameter of 8-10 mm. The cuff could be made in two forms. In either case it would need a shell or outer covering of nondistensible material so the pressure changes would be imposed on the limb. One form would consist of a flexible cuff which would be stored flat and then wrapped about the arm or forearm when ready for use. This form would take up little space but would be at a different place on the limb for each application. The second form would be to have the occlusion cuff encased in a shell that the forearm would be put into. This shell would probably be on the forearm area only and therefore this form would not be used for occlusion at the arm. The shell would resemble a plaster cast which had been split and hinged on one side. In that manner the shell could be hinged open, the forearm placed inside and the shell closed again. Each shell would be custom fit to the subject and would have the advantage of applying the pressure cuff in the same place with each measurement. This design would also incorporate the plethysmograph in the shell, thereby insuring that the cuff and plethysmograph were the proper distance apart. The flexible covering design would be made of cloth with an appropriate fastening method. The shell would be made of hard plastic.

The cuff would be connected to a pressure regulator which could increase cuff pressure at programmed rates of from 0.25 mm Hg/sec to 120 mm Hg/sec. The latter rate would make possible the measurement of arterial inflow. If such a measurement were not required, the lower rate alone would suffice.

The pressure regulator would be programmed to increase the pressure at a given rate while the forearm volume was being measured. The air pressure would be recorded with an electrical pressure transducer zeroed at cabin pressure. Figures 4-1 and 4-2 illustrate the essential features of the venous occlusion cuff and its inflation system.

4.1.2 Air Displacement Plethysmography

The displacement of air or other gasses can be used to detect the volume change of the forearm or other limb area. A cuff of 0.005 inch rubber 5 to 7 cm wide would be placed around the area to be measured and a nondistensible material wrapped around it. If the shell design were used the plethysmograph would be incorporated into the shell along with the venous occlusion cuff (see Figure 4-2). The air displacement plethysmograph would be connected to tubing of 5 mm internal diameter which in turn would be connected to a volume detecting system. The cuff would be under a small amount of pressure. That pressure would be necessary to approximate the plethysmograph and the skin and make detection of the endpoint more apparent. The pressure in the cuff should not exceed the venous pressure and should probably be under 5 mm Hg to avoid interference with normal peripheral venous pressures expected in space. Volume changes in the plethysmograph would be detected with a high displacement pressure transducer. That could be in the form of a large air volume with a pressure transducer in the circuit, or a bellows or piston. In any case the recording system would not increase the pressure more than 2-3 mm Hg above the base line pressure necessary in the cuff for recording the first volume change. The problem of thermal drift in the volume measurement could be compensated for by balancing the pressure or volume transducer with a

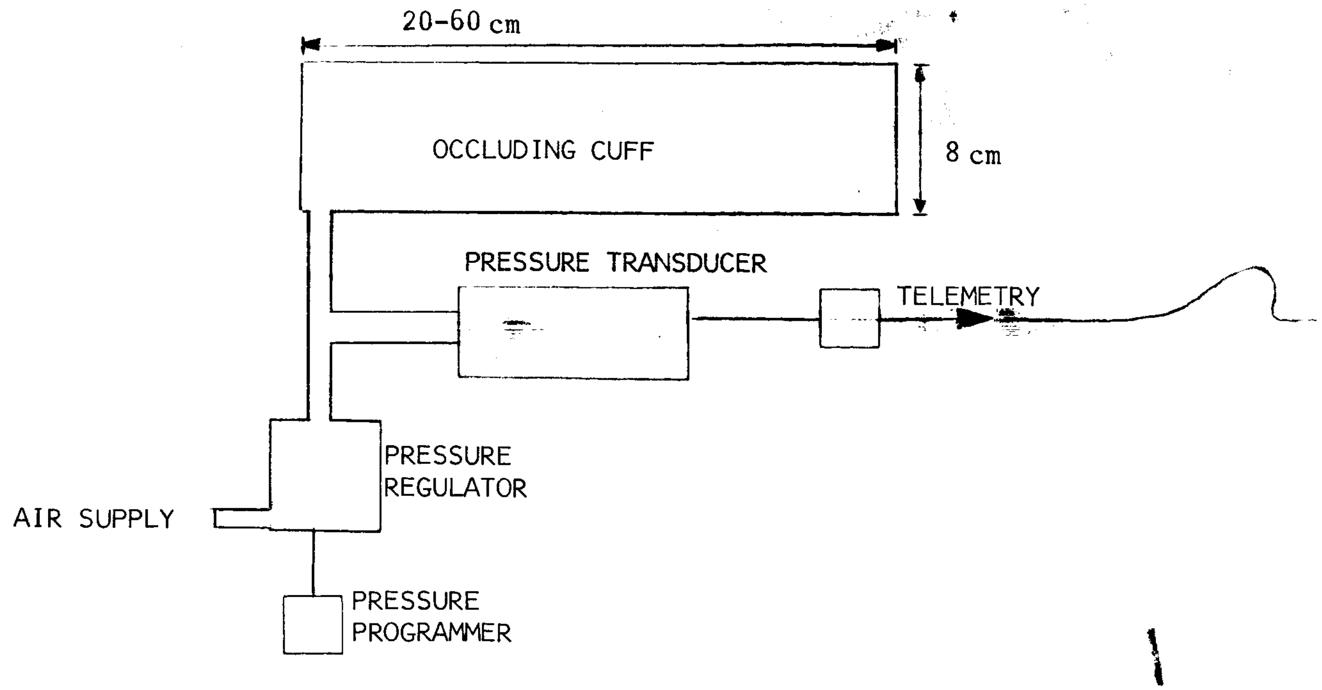


FIGURE 4-1 BLOCK DIAGRAM OF OCCLUDING CUFF AND INFLATION SYSTEM

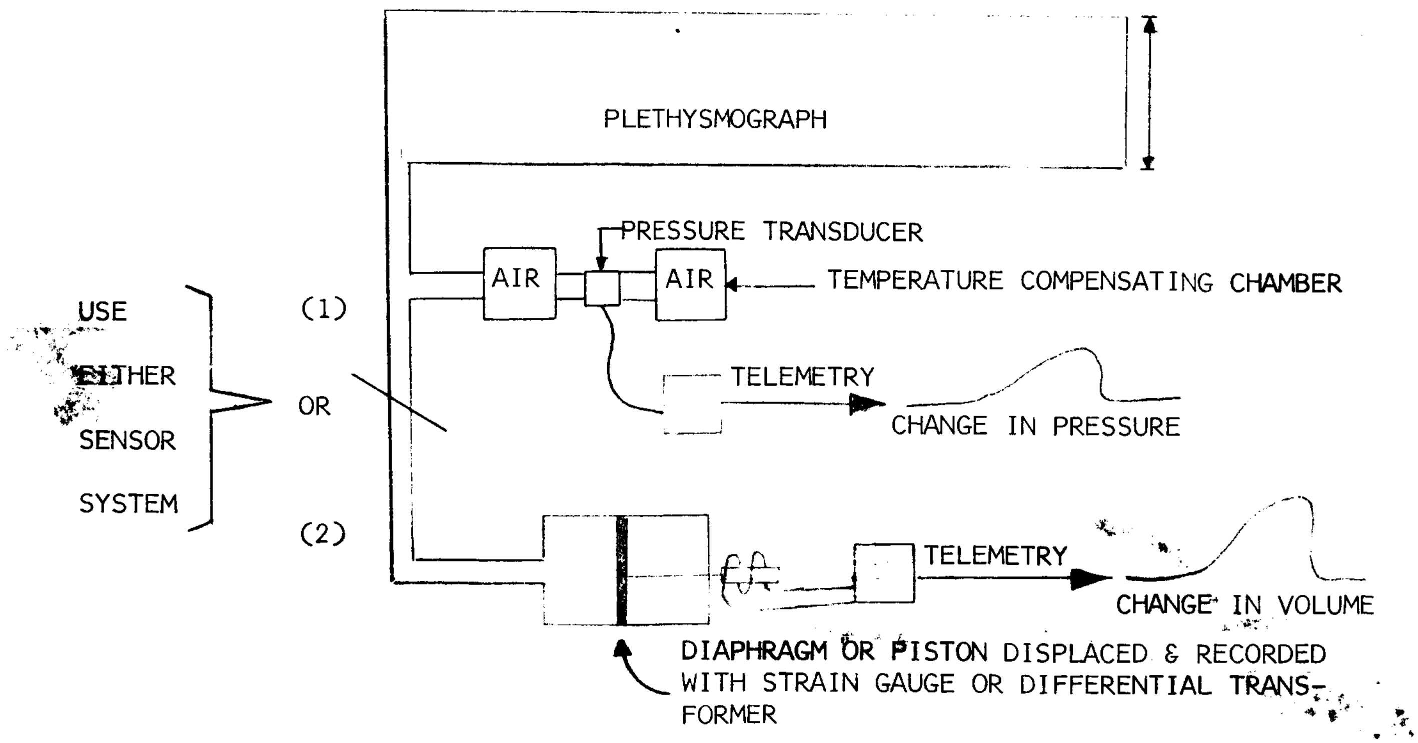


FIGURE 4-3 BLOCK DIAGRAM OF PLETHYSMOGRAPH AND READOUT EQUIPMENT

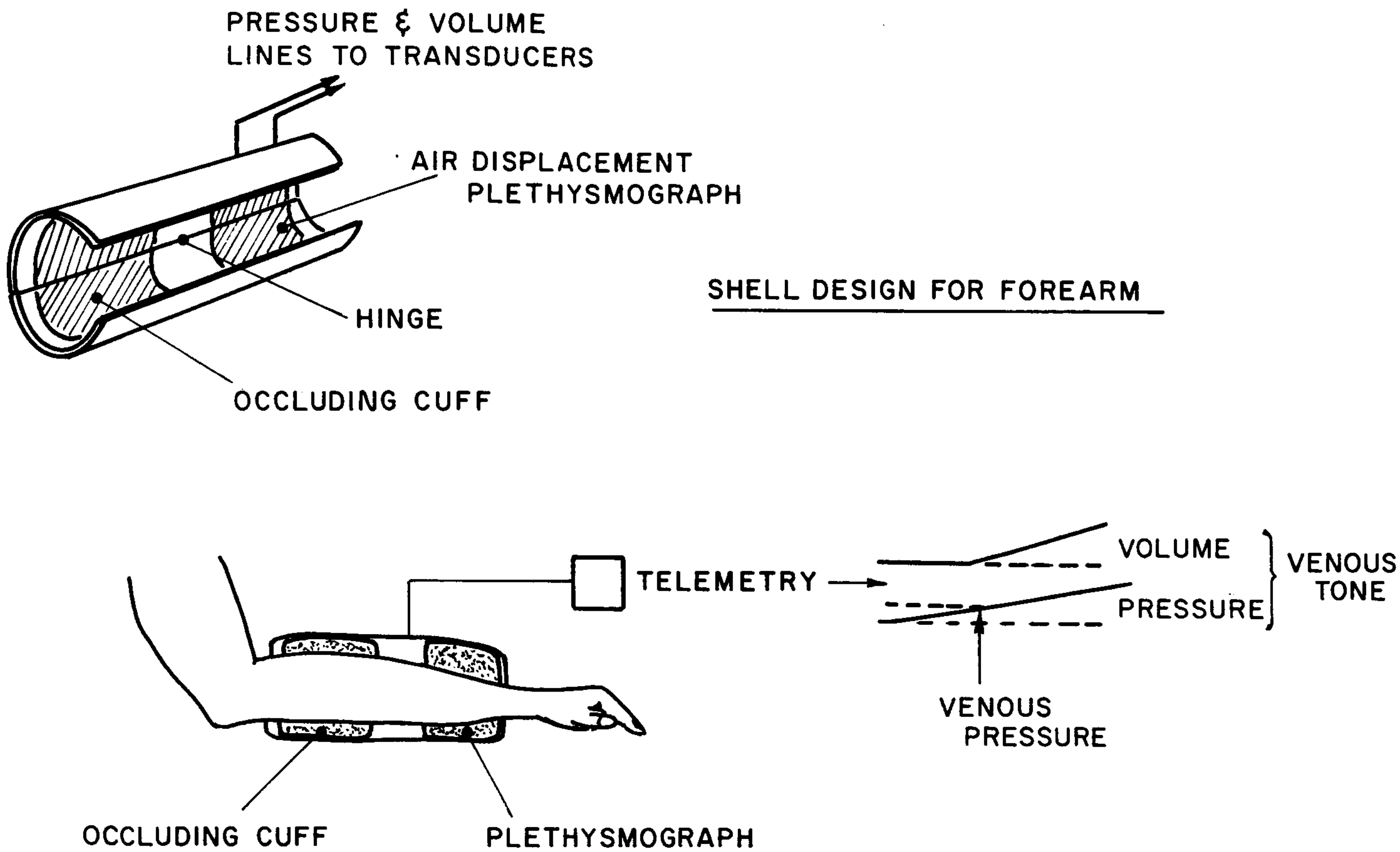


FIGURE 4-2.

PHYSICAL CONCEPT OF
VENOUS OCCLUSION PLETHSMOGRAPH.

closed volume of air so that the thermal effect would be automatically subtracted. In forearm measurements the volume shifts would range up to 10 or 15 cc's. Details of this method are shown in Figure 4-3. A simple displacement plethysmograph was built and tested as part of this program (See Appendix B.2). The measurements were not noticeably affected by occluding cuff placement above or below the elbow.

4.1.3 Strain Gauge Plethysmography

For small changes in volume the percent change in circumference is twice the percent change in volume. Circumference is measured as the change in resistance of a strain transducer fastened around a limb segment. The transducer could be a rubber tube 0.5 mm internal diameter with a wall thickness of 0.8 mm and filled with mercury or electrode paste. The base resistance would be approximately 2-4 ohms. Thermal drift in the transducer would be minimized by employing a suitable compensating element in the sensing circuitry. The instrument is placed at the midpoint of the forearm and then tightened a known percentage of its length, noting the resistance change for a calibration. For example if a one percent change in the length of a gauge caused a 0.5 ohm change in the resistance, and with venous occlusion there was a one ohm change in the resistance of the gauge then the percentage change in forearm circumference would be two percent and the change in forearm volume would be four percent. If forearm volume were one liter the corresponding change in volume would be 40 cc. See Figure 4-4 for details of this method.

Our preliminary experiments using the occluding cuff and air plethysmograph, calibrated against an invasive measure of forearm venous pressure,

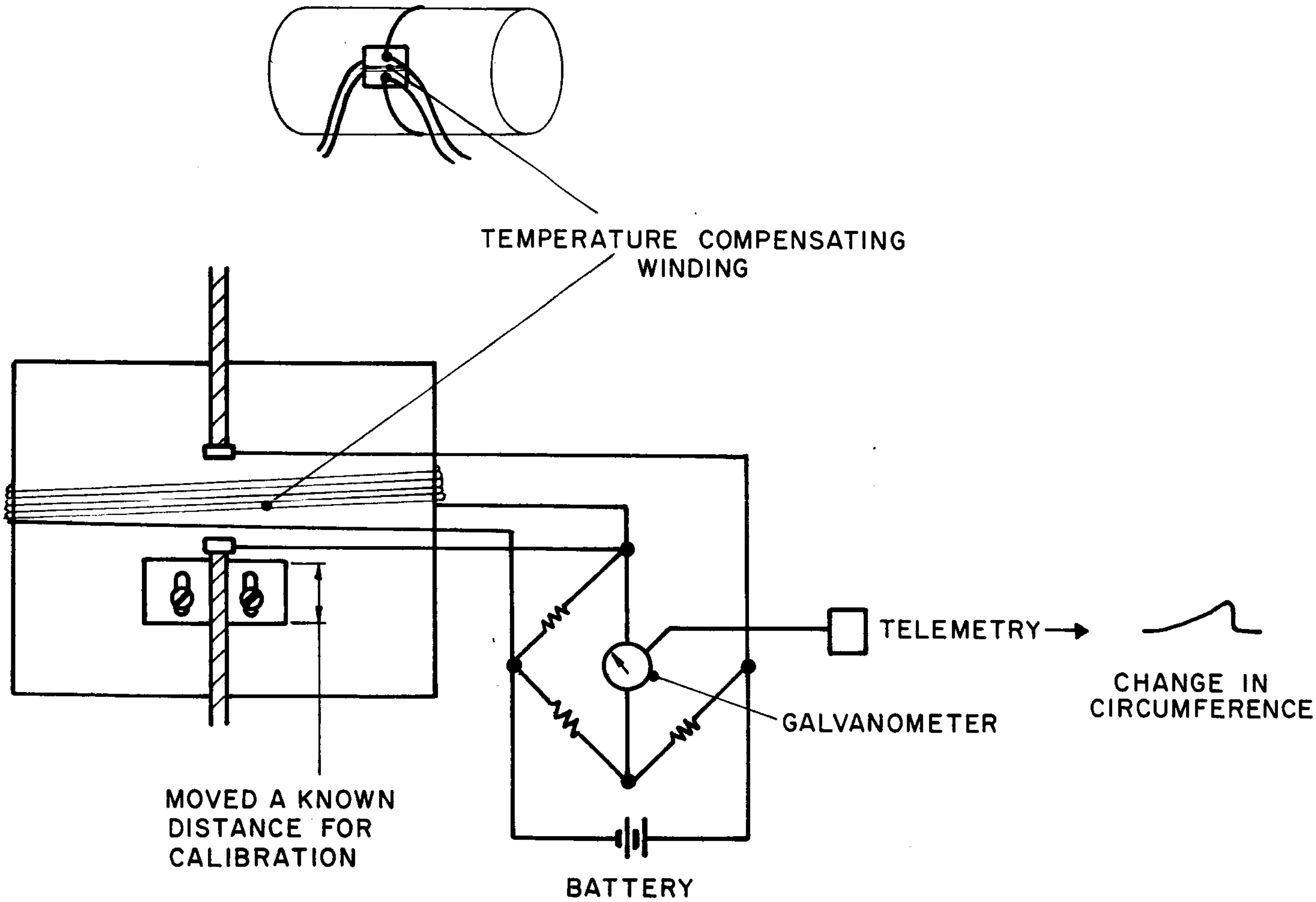


FIGURE 4-4.

FUNCTIONAL DIAGRAM OF STRAIN GAUGE PLETHYSMOGRAPH.

is reported in Appendix B.2. End point detection of recorded volume increase presents no particular problem, and the implementation seems quite feasible.

4.1.4 Summary

Limb venous occlusion plethysmography can be used to indicate limb venous pressure, venous tone and perhaps central venous state by venous runoff. The device consists of an occluding cuff with associated inflation system, a volume sensor (air or strain gauge pletheysmograph) and a readout system. Preliminary experiments indicate its applicability as a reliable, space compatible venous pressure sensor.

4.2 Superficial Vein Occluding Pressure Chamber

Noninvasive methods of measurement of the pressure in the arterial system take advantage of the fact that the pressure in the arterial system is relatively high, as compared to the pressure in the venous system, and is quite pulsatile. The pressure chamber method of noninvasive measurement of venous pressure takes advantage of two properties of the venous system.

1. The venous system is composed of numerous parallel branches, many of which are very near the surface of the skin.
2. The vessels of the venous system are much less rigid than the vessels of the arterial system.

These two properties furthermore, allow one to circumvent other properties of the venous system which seem to make its pressure difficult to measure - namely that the venous pressure is usually quite low and only weakly pulsatile. Measurements using the pressure chamber technique may be made on any large distended superficial vein. When applied to the jugular, the method indicates approximate central venous pressure in weightlessness.

The pressure chamber method is a type of null technique in which the pressure in a superficial vein is balanced against the pressure in a small chamber applied to the skin. The balancing process occurs across the wall of the vessel, the surrounding subcutaneous tissue, the skin, and the membrane which forms the contacting inner wall of the chamber (See Figure 4-5).

The physical characteristics of large, isolated veins which make such a measurement possible are shown in Figure 4-6. The distensibility curve for a single venous segment is characterized by three zones. In the first zone, a small change in volume is accompanied by a large change in pressure. The characteristics of this portion of the curve are greatly influenced by the thickness and rigidity of the collapsed wall of the vessel. The second zone is characterized by a rapid increase in the volume of the vessel for a small change in pressure. This zone is characteristically near a transmural pressure of zero. The third zone of the curve is characterized by a gradually decreasing slope as pressure and volume increase. The shape of the third zone is greatly influenced by venous tone (the tension in the smooth muscle fibers of the wall of the vessel) but the first two zones are nearly unaffected by venous tone.

The existence of zone two of the venous distensibility curve makes it possible to establish a sharp endpoint, since large changes in venous volume may be observed for small changes in pressure. This rapid change in venous volume, observed as a sudden collapse or a sudden filling of a venous segment, serves as a convenient endpoint for the pressure chamber method of venous pressure determination.

The principle is represented graphically in Figure 4-7. Here, the distensibility characteristics of a single vein are represented by a family of pressure-volume curves. Each curve represents the distensibility characteristics

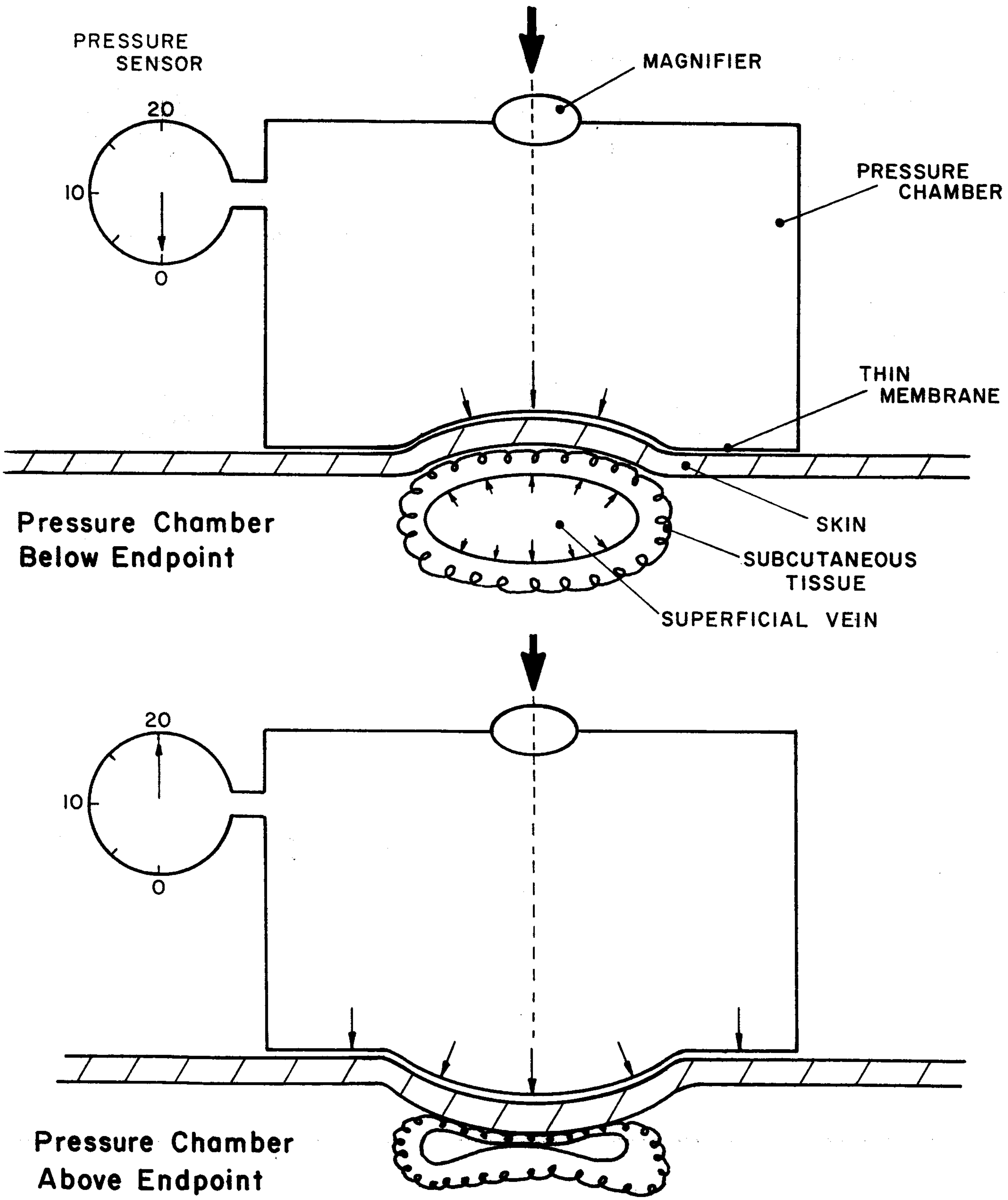


FIGURE 4-5

FUNCTIONAL DIAGRAM OF OCCLUDING PRESSURE CHAMBER.

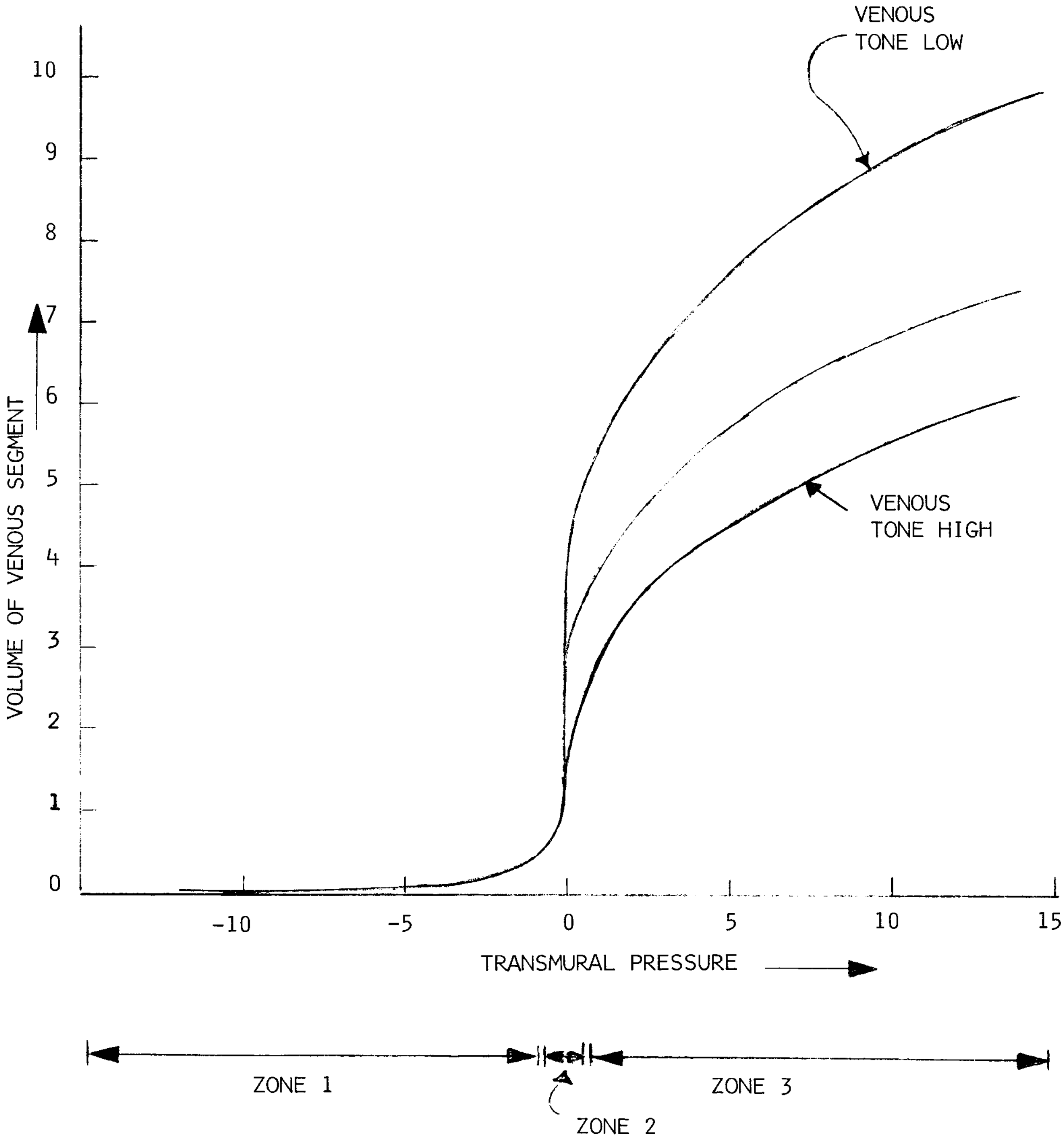


FIGURE 4-6 PRESSURE-VOLUME RELATIONSHIP OF LARGE ISOLATED VEINS

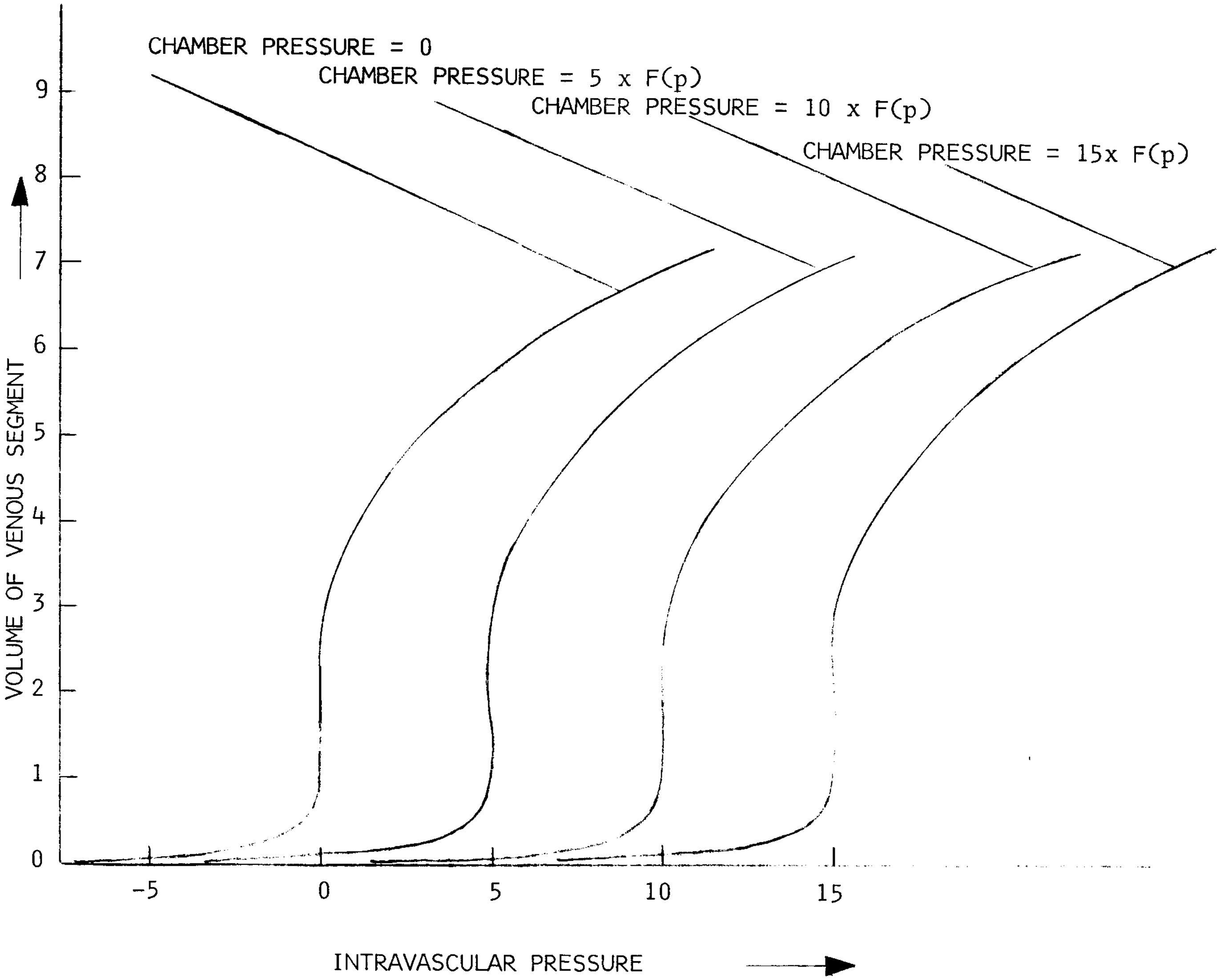


FIGURE 4-7 DISTENSIBILITY CHARACTERISTICS OF A TYPICAL VEIN

of a venous segment for a corresponding pressure applied to its surface by an opposing pressure chamber. It can be seen that for any given intravascular pressure greater than zero, there is a corresponding chamber pressure such that the transmural pressure corresponds to zone 2 of its distensibility curve, thereby, defining the endpoint.

The relationship between the chamber pressure and the venous pressure at the endpoint described above is called the chamber sensitivity.

$$F(p) = \text{Pressure in chamber/Pressure in vein} \tag{4.1}$$

We have demonstrated experimentally that this sensitivity for large, superficial vessels of the arm and for properly selected chamber membranes is nearly constant and equal to one in the range from 5 to 85 cm water pressure. (See Appendix B.1). The endpoint described above is advantageous because of its simplicity of detection and the constancy of the chamber sensitivity.

The endpoint may be detected by at least three methods. The simplest is direct observation through the chamber of sudden collapse of the venous segment, aided by tangential illumination. A second method is measurement of a sudden change in the radius of curvature of the membrane over the venous segment by optical means. A third method is detection of a sudden change in the position of the center of the venous segment (of the chamber membrane) relative to the edges of the segment by mechanical means.

4.2.1 Pressure Chamber

The dimensions of a pressure chamber and the characteristics of its membrane depend on the dimensions of the vessel to be measured. The instrument concept described in the following section is designed to be used for veins which measure approximately 3 mm to 15 mm in their greatest elliptical diameter. The instrument consists of three components: The chamber and its membrane, the pressure sensor, and the endpoint detector. Each of these three components will be discussed separately.

The chamber and the membrane are the most important components of the instrument. They must conform to rigid specifications if the instrument is to perform satisfactorily. The dimensions of the membrane depend on the size of the vessel to be measured. The chamber should be approximately three times the diameter of the largest vein to be measured. Therefore, for an instrument to measure veins of 3 mm to 12 mm in diameter, a 36 mm diameter membrane would be used. The height of the chamber, however, is not critical. The membrane itself must be highly distensible. Graphite lubricated sheets of Silastic 372 Medical Elastomer .001 inch thick have been found to have the desired properties. Similiar membranes prepared from latex rubber are equally satisfactory.

The pressure sensor may be of many types which are available. A self contained instrument would simply utilize a diaphragm or Bourdon tube operated dial which could be read directly by the operator. If recording or transmission of data were desired, the pressure sensor would consist of any low displacement pressure transducer contained in the pressure chamber. The range of the pressure sensor should be approximately 0 to 50 mm Hg with resolution of approximately 1% FS.

4.2.2 Endpoint Determination

The type of endpoint detector chosen is somewhat arbitrary. Its design should meet the specific demands on the instrument. The simplest type of endpoint detection would be direct observation of venous collapse (See Figure 4-8). The observation of the vessel would be facilitated by

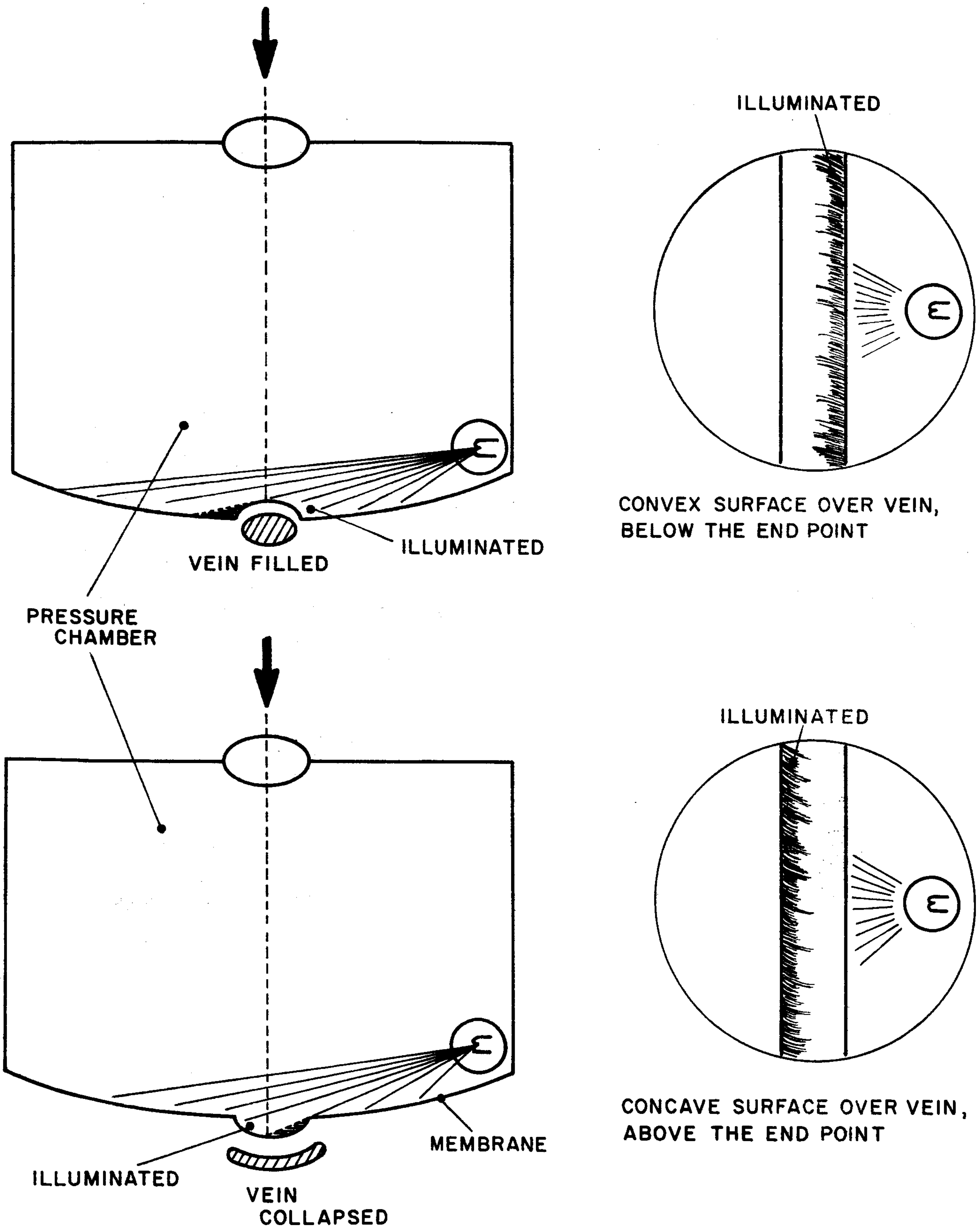


FIGURE 4-8

SIMPLEST TECHNIQUE FOR "END POINT" DETECTION USING PRESSURE CHAMBER.

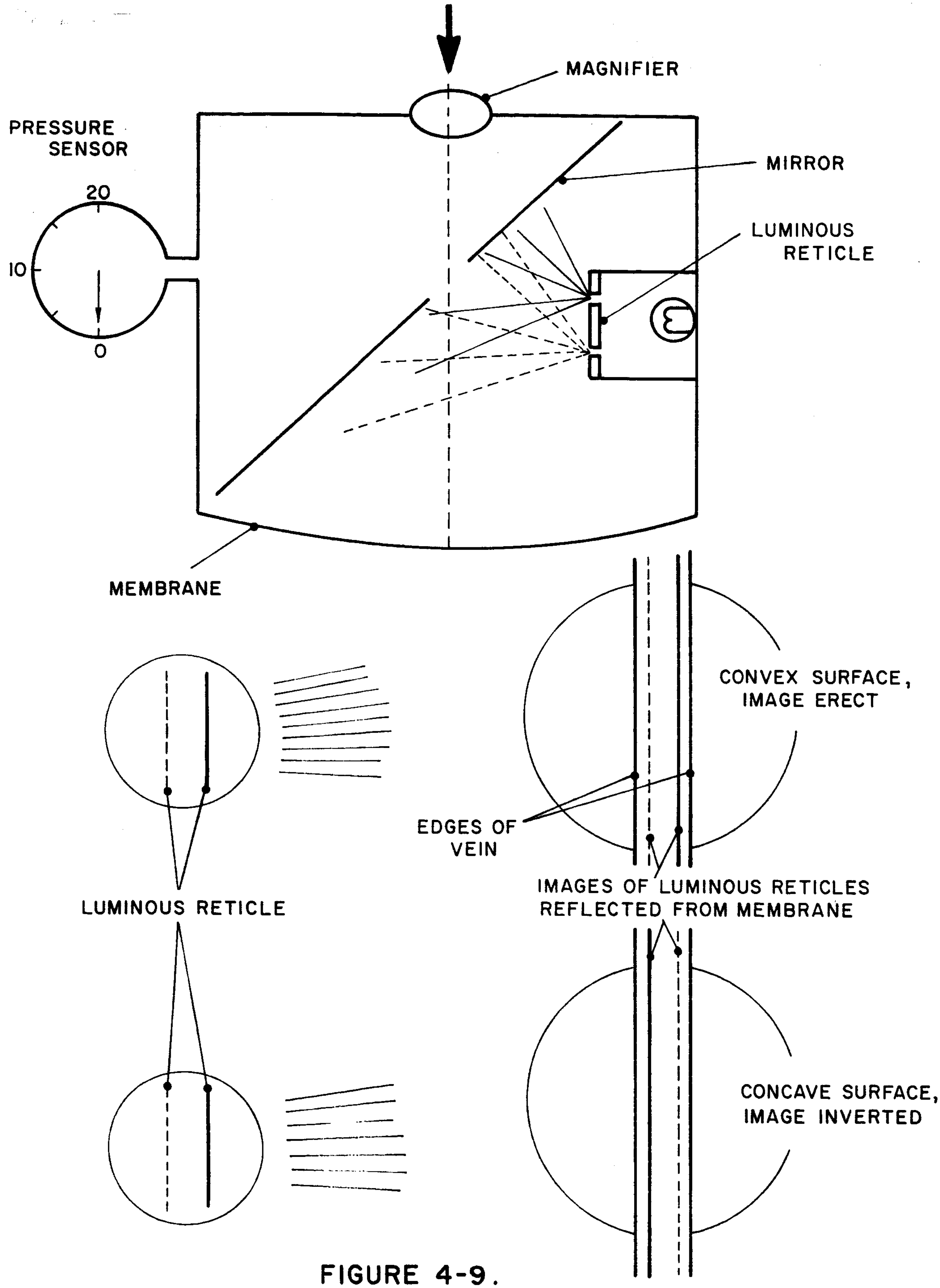


FIGURE 4-9.

INVERTING IMAGE METHOD OF DETECTING CHAMBER "END POINT".

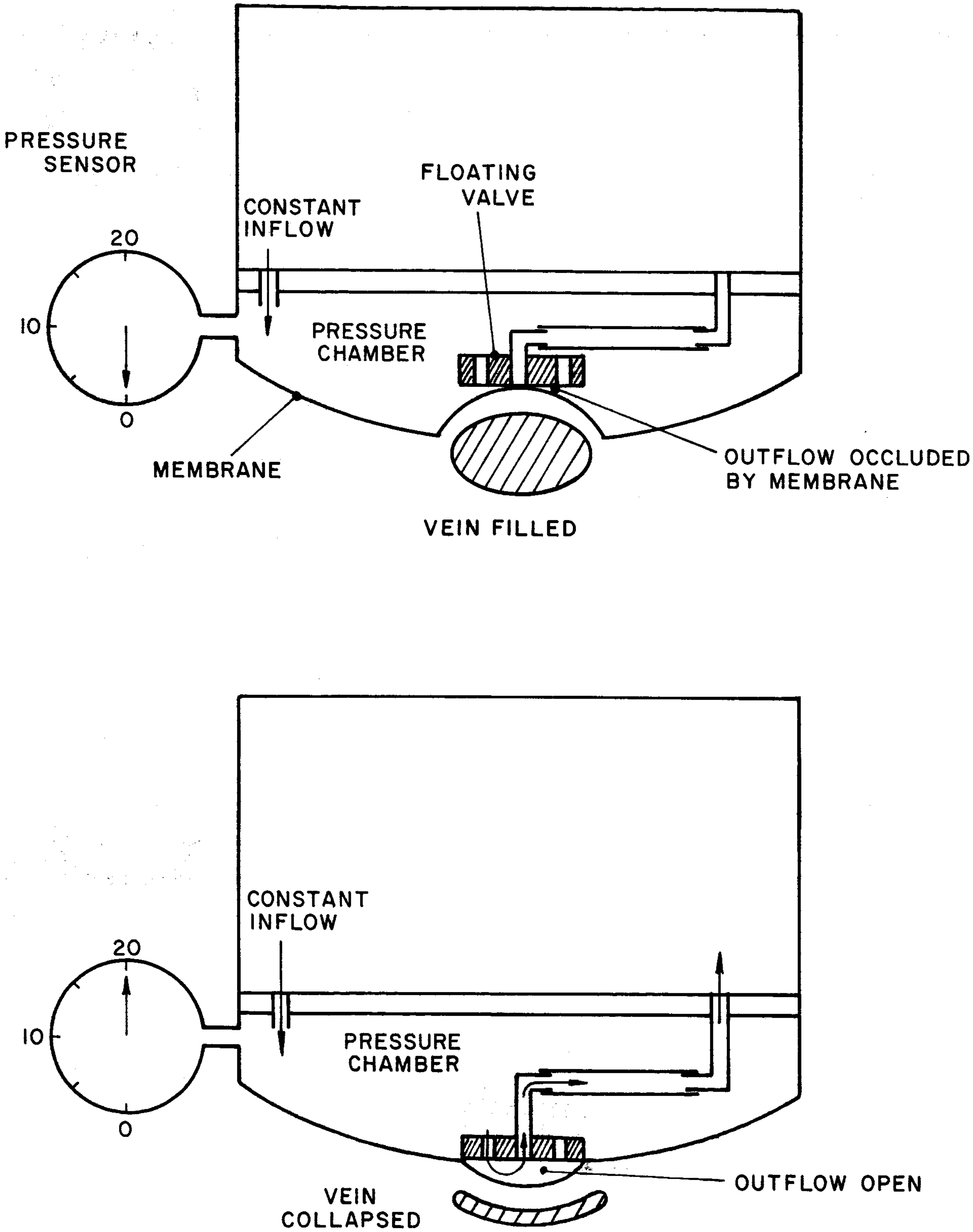


FIGURE 4-10.

MECHANICAL "END POINT" DETECTION IN PRESSURE CHAMBER.

the addition of a low power magnifier and tangential illumination.

A second type of visual endpoint would be equally satisfactory. A reflective membrane would be used allowing the vessel wall to actaas a cylindrical mirror. When the vein presented a convex surface, the membrane would reflect an eredt image. When the vein presented a concave surface, the membrane would reflact an inverted image. The endpoint would be read as the point at which the erect image suddenly became inverted (See Figure 4-9).

For continuous recording, a mechanical endpoint detector might be used along with feedback control of chamber pressure. A simple type of feedback controlling detector would use the membrane itself as a value to regulate chamber pressure (See Figure 4-10). A footplate, slightly larger in diameter than the largest vein to be measured, would house the exit aperture and allow it to "float" with the membrane. At chamber pressures below the endpoint, the membrane would occlude the exit aperture allowing chamber pressure to rise. Above the endpoint, the exit valve would open. Proper choice of continuous inflow rate into the chamber would allow an equilibrium to be established. Such an endpoint detector would allow the instrument to be used for continuous automatic recording of venous pressure subject only to limitations on the effect of the contact pressure on the skin. Accurate placement of such an instrument over the center of the vessel would be critical, however.

A fourth type of endpoint detector would use a principle similiar to the one used in the Durham tonometer (58). Fluid would be infused into the chamber at a constant rate, causing a steady increase in chamber pressure. Prior to venous collapse, the rise in pressure would be smooth, At the point of collapse, a notch in the pressure curve would be seen, which represents the chamber pressure at the endpoint (See Fig. 4-11). If this type of endpoint detection were chosen, smaller diameter membranes would be preferrable in order to make the endpoint larger and easier to detect.

4.2.3 Summary

A simple method of noninvasive measurement of the venous blood pressure which takes advantage of the innate characteristics of the venous system is described. The instrument consists of a pressure chamber with a thin, elastic membrane, a pressure sensor, and an endpoint detector. A variety of types of endpoint detector may be used, depending on whether the instrument is intended to be used by a trained operator who is able to recognize the endpoint, whether it is intended to be used as a self-recording instrument, or whether it is intended to be used as a continuous monitor of venous pressure. Experimentation with a preliminary design of the instrument shows that it is simple to operate, gives results rapidly, is painless, and gives reasonably accurate values of venous pressure.

The results of noninvasive venous pressure measurements utilizing an experimental pressure chanber have been summarized in Appendix B.1. A large needle was inserted into a superficial vein of the forearm of a human subject and the intravenous pressure continuously monitored with a low displacement pressure transducer. Simultaneous readings were taken of the pressure of the same vein using a pressure chamber, taking direct visualization of venous collapse as the endpoint. Pressure in the vein was varied by inflating and deflating a standard blood pressure cuff placed around the arm. Seventy-six readings were taken at venous pressures between 5 and 85 cm water. The data are plotted in Figure B-1. It can be seen that the standard

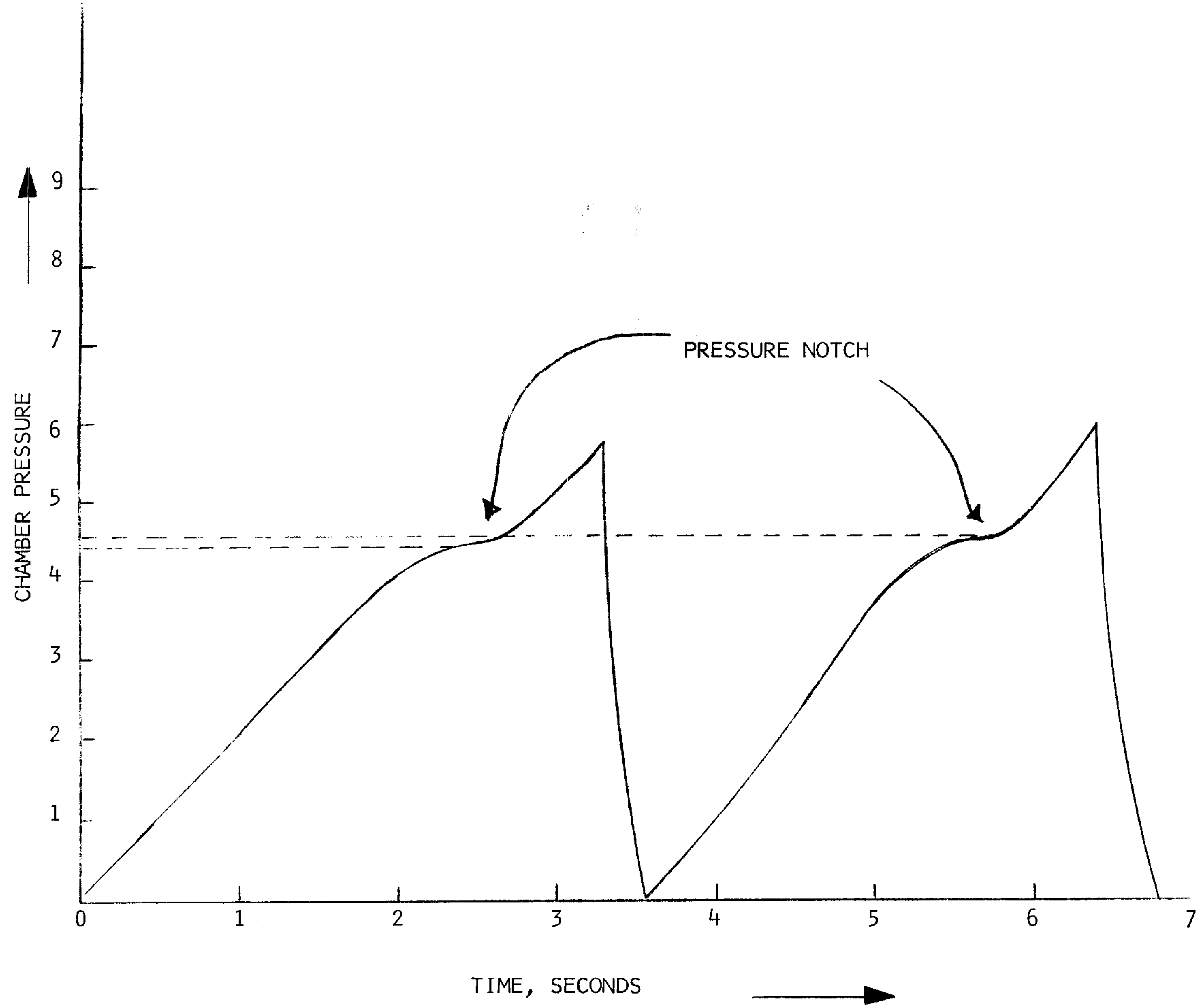
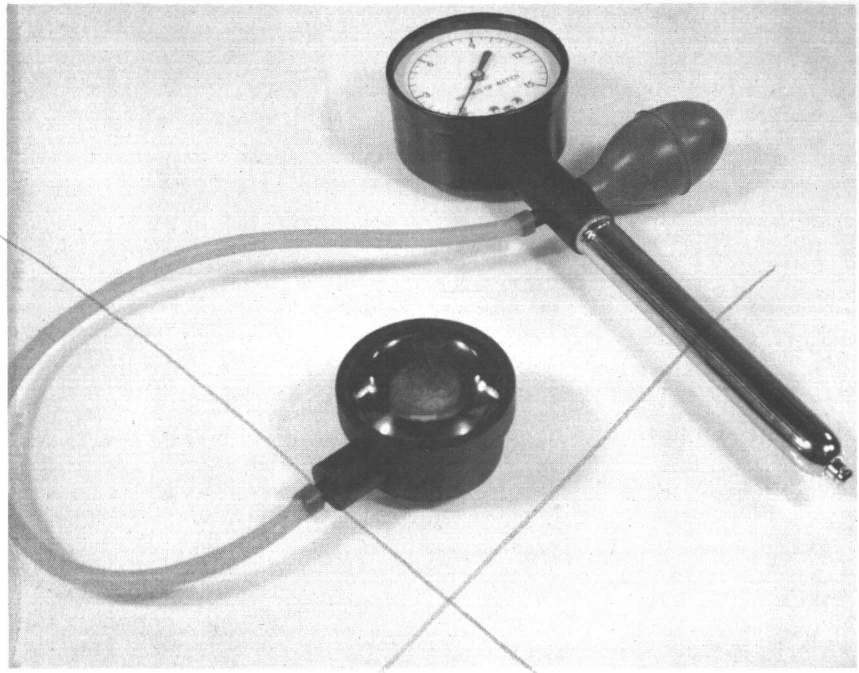


FIGURE 4-11 PRESSURE vs TIME RELATIONSHIP FOR THE DURHAM TONOMETER



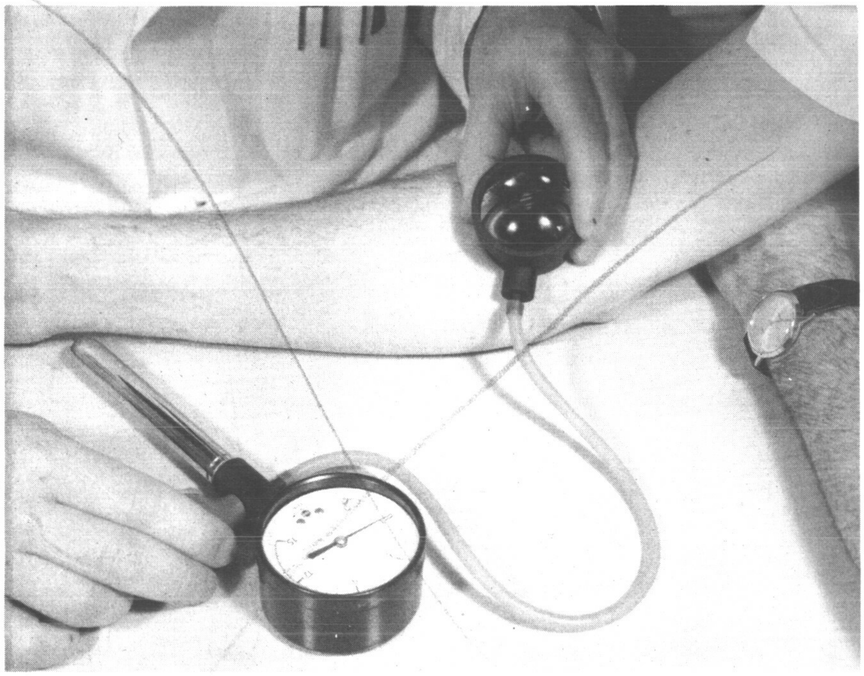


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FIGURE 4.12 EXPERIMENTAL OCCLUDING PRESSURE CHAMBER

FIGURE 4.12 EXPERIMENTAL OCCLUDING PRESSURE CHAMBER deviation of the noninvasive method from the invasive method was only 2.5 cm water.

4.3 Digital Plethysmography

Digital venous occlusion plethysmography is considered as a separate important measurement technique which differs from limb plethysmography in several important details. Because of the distant site, digital plethysmography measures higher venous pressures (more peripheral) than in the limb, and reflects more heavily venous pressure in skin than surrounding muscle. Its site makes it less meaningful physiologically in terms of variations in central venous pressure, although good correlations have been shown in some instances. When used to determine both arterial and venous flow, as by Burch, (42,43) the technique can be easy to use and yield useful data. It is extremely rapid to apply (several heart beats) and requires minimal inconvenience to the subject. As the occluding pressure is slowly raised to venous occlusion pressure, the measured volume changes abruptly from a beat-by-beat pulsation to a steady increase. An example of such a recording is shown in Figure 4- 3 , from Brown, Giddon and Dean (34).

The instrumentation, as for limb venous occlusion plethysmography, requires a pressure controlled cuff, a plethysmograph, and programming and data reduction equipment. It differs primarily in the selection of an appropriate plethysmograph.

The first step in evaluating the several methods for measuring finger volume is to examine the factors, other than venous, which affect their response (convenience, size, weight and such matters are covered in Section V).

To the extent that somatic changes in the astronaut's condition can be predicted, the non-venous factors (artifacts can be reduced. That technique which is least affected by the remaining factors is the one of choice.

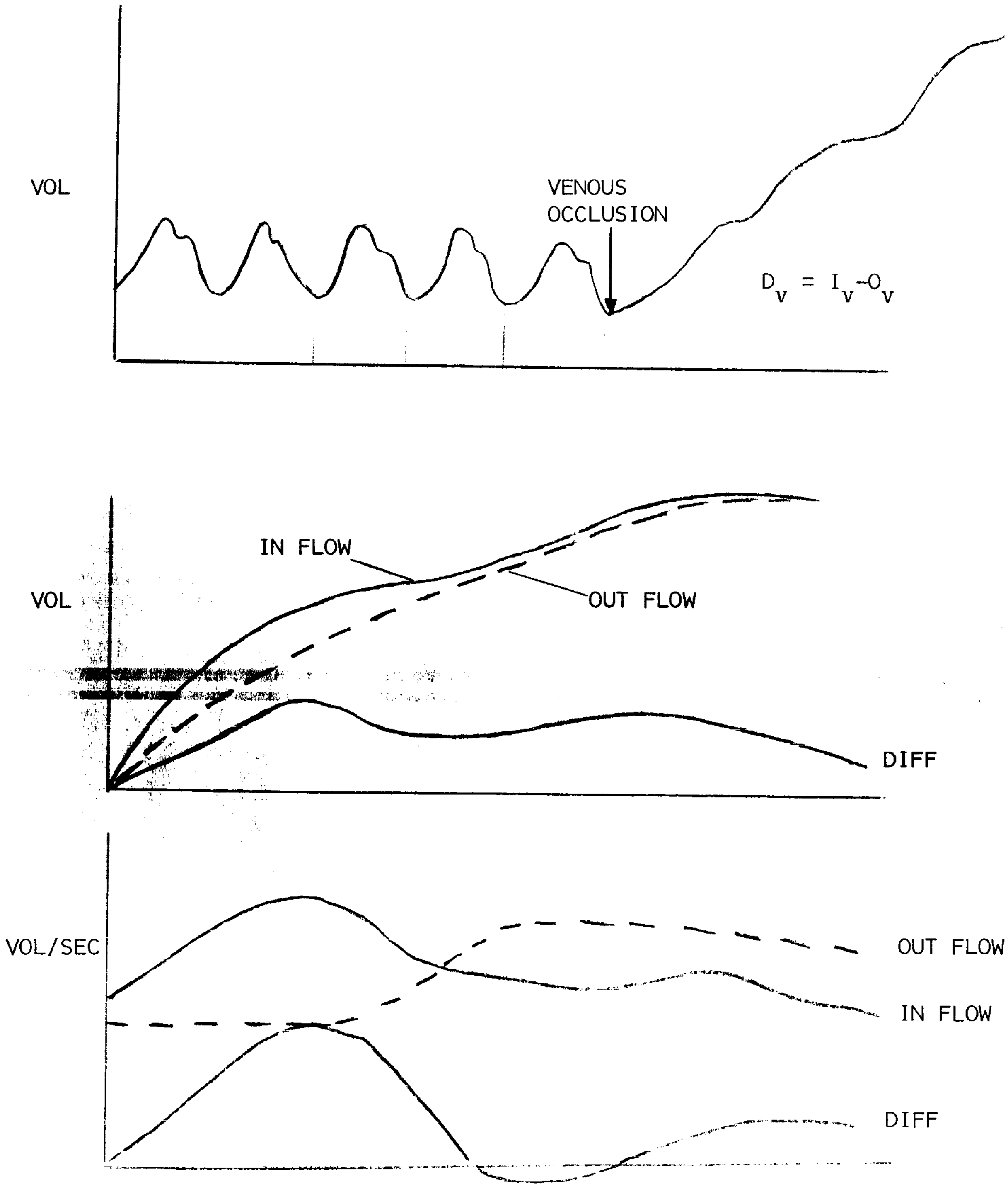

FIGURE 4-13 DIGITAL VOLUME AND FLOW vs TIME FOR INCREASING CUFF PRESSURE

[from C. C. Brown (34)]

Five techniques were examined; air volume, water volume, strain gauge, impedance and photoplethysmography. The calorimetric technique was omitted because of the extra complexity of a chamber filled with a temperature controlled liquid. The photoplethysmograph appears to offer the best chance of satisfactory performance. However, it is definitely a relative measure and is subject to several sources of error. The remaining portion of this section will be devoted to itemizing the sources of these errors and to a proposed design which holds promise of minimizing them in a space borne application.

4.3.1 Photoplethysmograph

The type of illuminator and the type housing and spectral response of the photo-sensor including mounting and spectra (response) have been studied extensively for photoplethysmography. Most investigators, however, have not been specifically interested in events on the venous side of the circulation, but have encountered venous engorgement nonetheless. Briefly, the factors which influence the design of these photo-sensor components are:

a. The relative response of the system to oxygenated and reduced hemoglobin
b. The sensitivity of the system to hematocrit
c. The sensitivity of the system to hemolysis
d. The high frequency response of the system as it may affect the accurate rendering of arterial events.
e. The low frequency response of the system as it affects the accurate rendering of slow or steady-state engorgement of the vessels (principally veins)
f. Temperature sensitivity
g. Dependence of the response upon prior responses
h. Linearity of output with changes in blood volume

i. The effect and extent of local heating of the skin by the illumination

j. The spontaneous signals arising in the photosensor and its ancillary circuits (noise and drift)

k. The response of the sensor to changes in position, relative to the skin, of it and the illuminator

l. The effect of contact pressure on the skin by the sensor and/or the illuminator

m. The effect of stray light.

Also to be considered, of course, is the ease of application of the device as it affects the repeatability and hence the validity of the data.

Consideration of these factors by various investigators over the last thirty years has resulted in a group of designs which obviate many but not all of the problems. In the laboratory, it is not expected that changes will occur in hematocrit or that the subject's blood will show significant hemolysis; these factors, therefore, have been given only minor considerations in extant designs. The effects of such changes in the blood as they are "seen" by photoplethysmography are predictable, however, and so can be taken into account. For long-term, space-borne use of photoplethsmography, the major problem involves the method of affixing a light-photosensor assembly to the subject with a reproducible contact pressure and location. One of many possible arrangements to achieve these criteria is given below.

4.3.2 Digital Occluding Cuff

In venous occlusion plethysmography, the venous pressure and tone are derived from the extent of the volume change induced by the controlled inflation of a proximal pressure cuff. Since digital photoplethysmography has been used so little in venous occlusion techniques, the design criteria which apply to the cuff and its pressure control device are less clear than those of the sensor assembly. Among the cuff-pressure control design considerations are the following:

a. The effect of cuff wall stiffness on the predictability of the induced venous pressure.

b. The coincidence of cuff inflation with events in the cardiac cycle

c. The "cuff artifact": the extent to which the inflation of the cuff causes distal movement of venous blood and thereby obscures the natural response of the venous parameters.

d. The optimal inflation or deflation rate of cuff pressure

e. The dependence of the technique on the site of the cuff.

f. The effect of temperature on cuff pressure

g. The effect of ambient atmospheric pressure on cuff pressure and its control

Once again, the matters of convenience and reproducibility must be considered in cuff design.

4.3.3 Instrument Design

A finger photoplethysmograph system which takes into account the criteria listed above is depicted in Figure 4-14. The system components have been chosen to be compatible with the size, power and weight restrictions imposed by space flight. The duration of the measurement need be no longer than one minute and might be as brief as 10 seconds.

The limitations on its use are few. It requires the insertion of a bare finger, without any constricting garment on the arm. It requires that a plug be inserted to accomodate differing finger-lengths. It uses a source of gas pressure of about 15 psi above the ambient. The arm and hand should

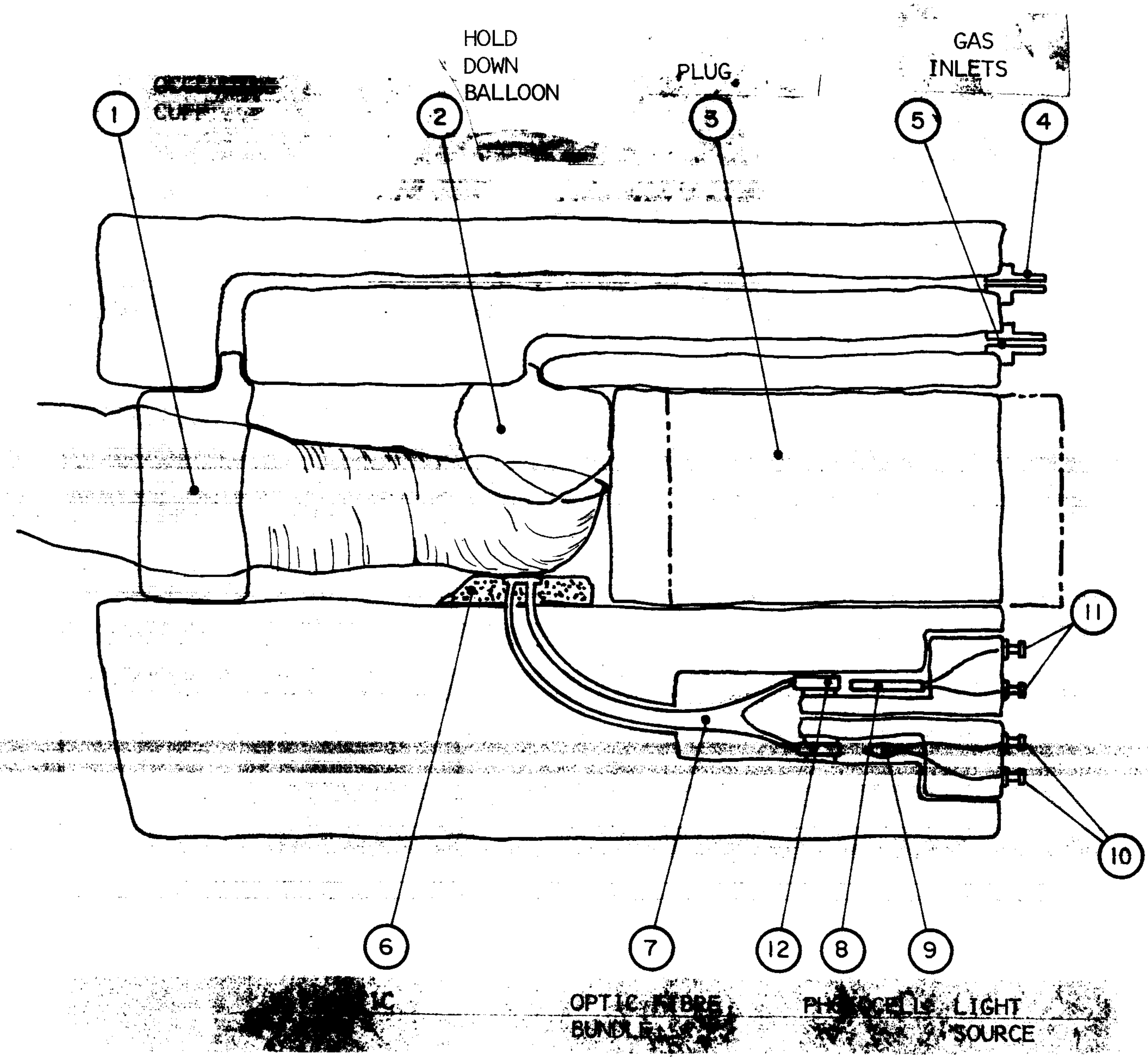

FIGURE 4-14.

FUNCTIONAL DIAGRAM OF DIGITAL PLETHYSMOGRAPH.

be held reasonably still during the measurement.

In Figure 4-14 are shown:

1. The occluding cuff. Silicone rubber of 0.002" thickness would be satisfactory.

2. A hold-down "balloon". Also of rubber but not so thin as the occluding cuff. This would be inflated to a maximum of 10 mm Hg gauge pressure during plethysmography, but could be inflated to pressures higher than systolic in order to render the finger tip bloodless; this would allow detection of skin color and texture changes. One investigator has inadvertently shown that the occluding cuff may not be required at all (54). In the course of ascertaining the effects of contact pressure between his sensor and the finger, he showed that the blood volume pulse waveform obtained with separate venous occlusion could be replicated by control of the contact pressure. Whether a similar relationship will hold true for venous engorgement has yet to be determined.

3. A plug to accomodate different finger lengths so that the same portion of the fingertip is viewed at each use.

4. Gas inlet for the occluding cuff.

5. Gas inlet for the hold-down balloon.

6. Plastic pad to insure that the tip of the optic fiber [7] is always the same distance from the skin.

7. The optic fiber bundle. Approximately 150 twenty-micron fibers will give a suitable tip diameter of 0.5 mm. Half of the fibers will go to the light source [9] and half to the photocell [8]. It is included mainly to keep heat from the finger.

8. The photocell. CdS or CdSe photoconductive cells have been most used. However, one of the newer Silicon photodiodes will give faster response, greater temperature stability and sufficient sensitivity at the desired wavelengths.

9. The light source. A large variety of rugged, long-life miniature lamps are available. Not more than 10 milliwatts input power is needed.

10. Light source terminals. The power for the lamp should be well-regulated D.C., highly filtered.

11. Photocell terminals. The photocell would be used in a bridge circuit which is followed by a D.C. amplifier having provision for switching to capacitive coupling. Its upper frequency half-power point should be 30.hz. The bridge must be powered by a well-regulated and ripple-free supply. Both the amplifier and the power supply can be made from encapsulated operational amplifiers, each having a volume of less than one cubic inch.

12. One of three places at which optical filters can be placed. The others are: between the light source and the optic fiber and between the optic fibre and the finger. The choice of wavelength is not certain. While most users employ 8,050 Å, they do so in order to minimize the difference between oxygenated and reduced blood, thus exhibiting their indifference to venous events. A large difference in the extinction coefficient of arterial and venous blood is shown, *in vitro*, at 6,500 Å, yet records (198) from a fingertip at that wavelength show pulsations. In this device, since the effects of relative motion will be minimized, even shorter wavelengths may be useable in order to discriminate against

arterial changes.

The occluding cuff is to be slowly inflated so that at the earliest plethysmographic change its pressure will be indicative of the venous pressure and so that subsequent changes will give an index of venous tone. A simple way of obtaining a sufficiently linear increase of pressure within the cuff is diagrammed in Figure 4-15.

P_s represents a supply of gas. Its pressure and flow are discussed below. R represents a pressure regulator which provides a constant (gauge) output pressure (P_A) relative to A, the ambient atmospheric pressure. O denotes an orifice, the resistance of which reduces yields a pressure drop to P_B. V is a valve which directs the flow of gas alternatively to the atmosphere or to a chamber of volume S. C is the cuff, connected permanently to S. V' is a valve which allows the pressure of S and C quickly to equilibrate with A. G is a gauge to monitor the pressure of volumes S and C.

The scheme depends upon the observation that, for any gas, if the ratio $\frac{P_A + A}{P_B + A}$ is greater than a critical constant, the flow through the orifice will be independent of P_B. The value of the critical constant depends upon the molecular weight, viscosity and specific heats of the gas; for air, N_2 and O_2 its value is about 1.7 . Table 4-2, below, gives the computed pressure P_A (psig) to achieve this condition for two values of P_B and two values of A.

TABLE 4-2

	P_B \ A (psi)	15	5
psig	0	10.5	0.35
	6	20.7	10.55

Conditions for Constant Flow

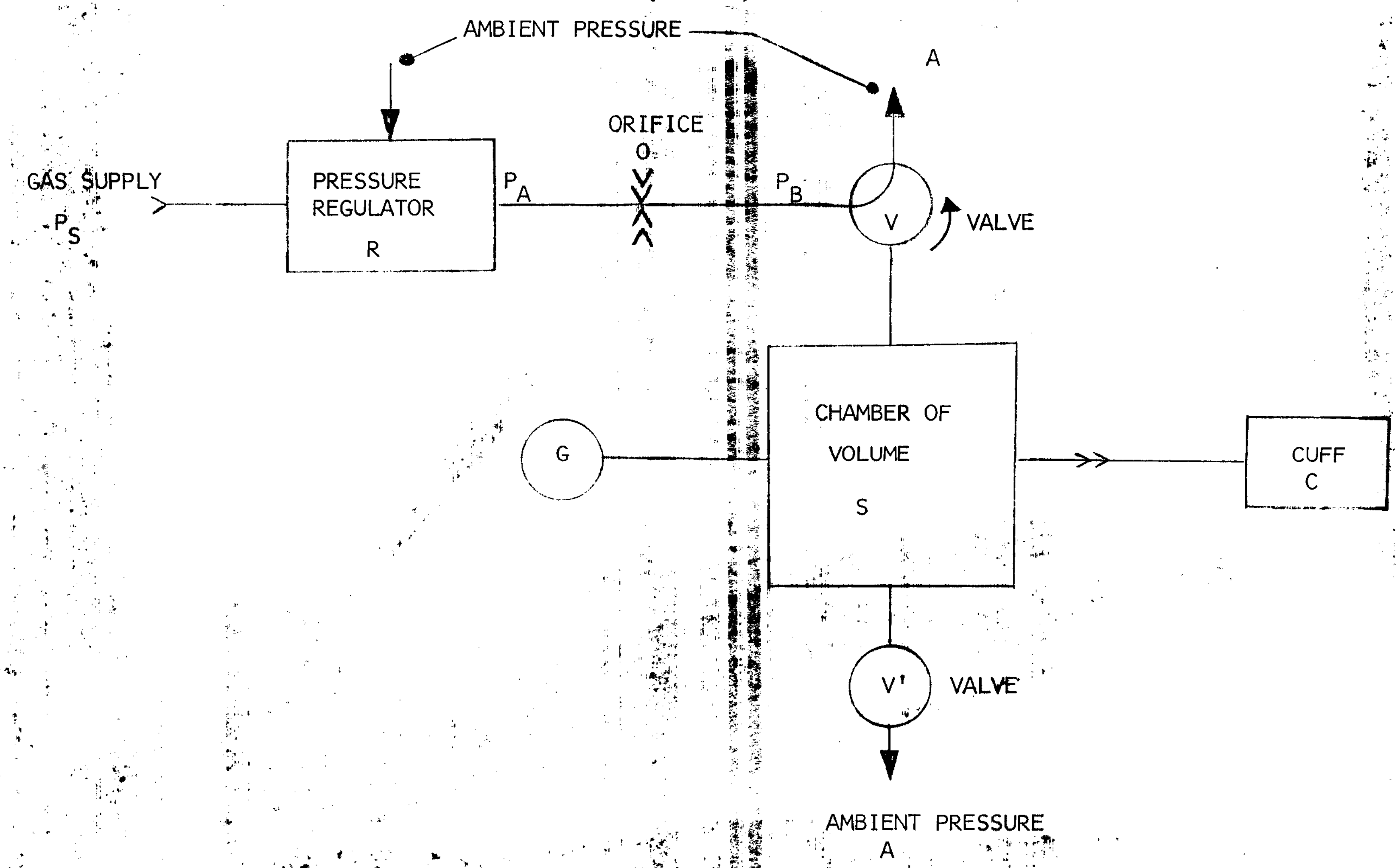

FIGURE 4-15 SCHEMATIC OF INFLATION SYSTEM FOR DIGITAL PLETHYSMOGRAPH

The supply pressure, P_S, should be at least 15 psi higher than P_B in order that R give good regulation; the higher, the better.

Now if the constant flow of gas is assured by having a sufficiently high P_A, and if the flow is directed into the volume S + C, the chamber and cuff pressure will begin to rise. Although the pressure rise will be exponential, for any desired duration it can be made to approximate a straight line, as closely as one wishes, by controlling the orifice, O, and the volume S. The volume of the cuff (about 2.5 ml as shown) should be much smaller than S.

In making the measurement, the sequence of events is:

a. Adjust the plug to the correct position.

b. Have valve V-V' such that the flow of gas is to the atmosphere and S is vented (normal position).

c. Insert finger.

d. Apply pre-set pressure to hold-down balloon.

e. Relax the finger.

f. Put V-V' in its alternate position (actuated).

g. Record the photocell output and the pressure indicated by gauge G for the next 10 to 30 seconds.

   (In a well-calibrated system, it will not be necessary to record the pressure; it will be sufficient to know at what instant the valve was actuated).

h. When the volume first starts to increase (discounting small pulsations arising from arterial sources), as indicated by a change in the photocell output, the pressure in S is proportional to the venous pressure in the finger.

i. At any time, return valve V (but not V') to its normal position. The photocell output will then indicate the venous filling corresponding to the pressure retained in S and C. Several such pressure-volume values give a measure of venous distensibility.

The calibration factors or curves which apply to this system and which must be determined empirically in order to obtain quantitative data are:

1. The relationship between occluding cuff pressure and the venous pressure induced by the occlusion.
2. The relationship between the photocell output and the venous pressure induced by various occluding pressures.
3. (Optional and controllable) The relationship between the pressure measured by G and the time elapsed since valve V actuation.

The first two of these can be readily combined for relative measures of both venous pressure and tone. If, on a person of "normal" venous state, the relationship between occluding pressure and photocell output is determined, then either a rise or fall in venous pressure or a change in distensibility of the veins can be detected and quantified on an arbitrary scale.

4.3.4 Summary

Digital plethysmography measures venous pressure in a finger rapidly and with little subject inconvenience. It has been used extensively for blood flow measurements. This section presents a preliminary design for a space compatible instrument comprising a ring occluding cuff, a pressure programmer, and a small photoplethysmograph.

V MERIT WEIGHING AND CONCLUSIONS

Of the large number of possible noninvasive techniques considered, some of which are summarized in Section 2, three stand out as the most likely candidates for rapid further development to the state of practical instrumentation for use in space. These techniques all share the following atributes:

1. The physiological significance of the measurement is well understood.
2. The technique has been verified experimentally by Biosystems, or has been tested and clearly documented elsewhere.
3. The hardware required to realize the measurements for space is within the state-of-the-art.

The three techniques so chosen are the ones which are discussed in detail in Section 4, namely limb venous occlusion plethysmography, the occlusive pressure chamber method and digital plethysmography. In the merit weighing ranking given below these techniques are ranked relative to each other and also, where possible, relative to some arbitrary reference level of requirement or restraint. A final ranking of the desirability of further development of each of these methods requires not only their relative standing according to each of the factors in the merit weighing model, but also an evaluation of the relative importance or weight attached to poor performance on physiological significance as opposed to instrument volume, or comparisons of subject inconvenience with accuracy and power. These decisions can only be made in the context of the overall mission objective and constraints. These relative weights are best assigned by NASA.

5.1 Merit Weighing

The following tabulation (Table 5-1) summarizes the merit weighing process and the resultant conclusions.

MERIT WEIGHING OF NONINVASIVE VENOUS MEASUREMENT TECHNIQUE - TABLE 5-1

FACTOR	VENOUS OCCLUSION PLETH.	DIGITAL OCC. PLETH.	PRESSURE CHAMBER	REMARKS
I. Physiological Factors				
1.1 Significance 1: Not significant. 3: Significant, but not the most important. 5: Precisely what is wanted.	5	3	4	Pressure chamber can give pressure close to central if applied to jugular. Rating based on single antecubital vein.
1.2 Extent of Experimental Verification 1: Never tried. 3: Tried in one careful set of expts. not repeated. 5: A large body of data and literature exists.	5	5	3.5	Pressure chamber has been tested by Biosystems with excellent comparison to invasive pressure.
1.3 Interference With Normal Venous Flow (Percentage of Total Venous Flow Occluded)	2	4	4	

FACTOR	VENOUS OCCLUSION PLETH.	DIGITAL OCC. PLETH.	PRESSURE CHAMBER	REMARKS
1.3 Continued 1: < 30% 2: < 10% 3: < 5% 4: < 1% 5: < .1%				
II. Accuracy and Repeatability 1: $\sigma <$ 50% FS 2: $\sigma <$ 30% FS 3: $\sigma <$ 20% FS 4: $\sigma <$ 10% FS 5: $\sigma <$ 5% FS	4	3	5	Estimates based on current instrumentation - improvement expected.
III. Simplicity of Use				
3.1 Subject Inconvenience 1: Painful or unpleasant. 2: Requires full attention. 3: Requires cooperation - immobilizing. 4: Subject aware of test - non interfering. 5: Subject unaware of test.	2	4	3	
3.2 Time Required 1: t < 20 man minutes 2: t < 10 man minutes	2	3	4	Includes time to set up and calibrate.

FACTOR	VENOUS OCCLUSION PLETH.	DIGITAL OCC. PLETH.	PRESSURE CHAMBER	REMARKS
3.2 Continued 3: t < 5 man-minutes 4: t < 1 man-minute				
3.3 Training in Method 1: t < 5 man days 2: t < 3 man days 3: t < 2 man days 4: t < 1 man day 5: t < 1/2 man day	4	4	3-4	Longer training for pressure chamber based on manual endpoint detection.
IV. Effects of Space Environment on Accuracy				
4.1 Effect of Weightlessness 5: No effect on measure	5	5	5	Methods work best under weightlessness. Greater correspondence of peripheral to central pressure.
4.2 Effects of Increased G's 1: Measure cannot be taken. 2: Questionable validity. 3: Requires compensation. 4: Slight effect. 5: No effect.	3	2	4	
4.3 Effect of Ambient Temperature and Humidity 1: Measure cannot be taken.	4	4.5	4	Assuming within detectable limits.

FACTOR	VENOUS OCCLUSION PLETH.	DIGITAL OCC. PLETH.	PRESSURE CHAMBER	REMARKS
4.3 Continued				
2: Questionable validity. 3: Requires compensation. 4: Slight effect. 5: No effect.				
4.4 Effects of Ambient Pressure	3	4.5	3	Compensation is not difficult.
1: Measure cannot be taken. 2: Questionable validity. 3: Requires compensation. 4: Slight effect 5: No effect.				
V. Physical Specifications				
5.1 Weight	2	3	5	
1: < 10 lbs 2: < 5 lbs 3: < 2 lbs 4: < 1 lb 5: < 1/2 lb				
5.2 Volume	2	3	5	
1: < 1000 cu. in. 2: < 300 cu. in. 3: < 100 cu. in.				

FACTOR	VENOUS OCCLUSION PLETH.	DIGITAL OCC. PLETH.	PRESSURE CHAMBER	REMARKS
5.2 Continued				
4: < 50 cu. in. 5: < 20 cu. in.				
5.3 Power	3	3	5	
1: < 20 w 2: ≵ 10 w 3: < 5 w 4: < 2 w 5: < 1 w				
VI. Data Presentation	5	5	5	
1: Requires skilled observer. 3: Suitable for telemetering with corrections. 5: Can be manually or automatically transmitted with no further processing.				

5.2 Conclusions

All three of the techniques evaluated have been tested and shown to work satisfactorily for measuring venous pressure. The limb venous occlusion method indicates venous pressure in vessels not too far from the heart, and also provides a measurement of venous distensibility which may be of equal or greater physiological significance. Further study is required to determine its usefulness in conjunction with venous runoff rates for determination of central venous pressure. Its implementation will be the largest and most complex of the techniques suggested, and like the pressure chamber method, it will be subject to drift due to changes in cabin pressure or temperature unless these are compensated for in the instrument. The pressure chamber method will employ some new and novel techniques. The basic principle, however, has been verified as long as 60 years ago. It will be light and simple to use, but may require some astronaut training for determination of the end point correctly. As described in Section 4.2, several promising techniques are available for simplifying the task of reading the end point for the pressure chamber method by visual observation. It would not be too difficult to devise an automatic end point sensor to eliminate the factor of skill or uncertainty in taking the reading. The measurement of pressure by the chamber method, over a superficial vein in a limb or the jugular, might be augmented in the future with a pulse wave velocity technique, combining the two to yield venous tone as well as venous pressure. Digital plethysmography has been used for some time as an indication of arterial blood flow and venous pressure, and might be adapted to physiological measurements in space without a great deal of modification in principle. However, its major disadvantage is in the site in which the measurements are taken, being so far from the central venous system as to have perhaps less physiological significance than other techniques.

Experiments using all three techniques yield very encouraging results. A program has been prepared outlining the further development of these instruments, including breadboard models of two types and a space-compatible engineering model of the one deemed most suitable for ultimate application.

Additionally, two of our methods show substantial promise based on our experiments. These, however, require considerable research and development on both their physiological significance and the instrumentation necessary for use as automatic monitoring systems. Of the two, the P-A delay method is perhaps the most attractive in the long run, as it holds promise of indicating noninvasively the state of central venous tone. The A wave obliteration technique also requires further research on the nature of the transmission of the natural venous wave.

APPENDIX A

PULSE WAVE VELOCITY AS A NONINVASIVE MEASURE OF CENTRAL VENOUS PRESSURE

by E. O. Attinger

A.1 Factors Which Determine the Wave Velocity

A.1.1 General Theory

The velocity with which a pressure wave travels in the vascular system depends upon the physical properties of the vessel walls and the characteristics of blood flow.

The pertinent equations for the motion of blood through a vascular segment and the associated motions of the vessel wall are usually derived by means of hydrodynamic theory and the theory of elasticity, both of which belong to the domain of continuum mechanics. The principles of continuum mechanics are formulated in two kinds of equations: field equations and constitutive equations. The field equations express the general principles of balance of mass, balance of momentum, balance of energy, etc., and are valid for all types of continua. The particular materials of which these media consist are defined by constitutive equations. It is in the latter domain where the major approximations are made and where differences between theoretical and experimental results arise (209,210).

In the vascular system we are dealing with nonsteady flow in a system of distensible tubes. The primary forces which determine the motion of the vessel wall are the pressure difference between the inside and the outside of the vessel (transmural pressure) and the viscous drag of the fluid. The ratio between stress and the resulting deformation of the wall is called the elastic modulus E:

$$E = \frac{\text{stress}}{\text{strain}} \quad \frac{S}{\Delta x/x_o}$$

where $\Delta x/x_o$ is the relative change in one dimension, say, length. In a visco-elastic material the stress strain relations are frequency dependent. Furthermore, in the vascular system the value of E depends upon the absolute value of x_o, because the behavior of the vessel wall is nonlinear.

Since the vessel wall is three dimensional, the wall material is characterized by three elastic moduli, one relating pressure to change in radius Δr (tangential modulus E_t), one relating pressure to change in length Δz (longitudinal modulus E_z), and one relating pressure to change in wall thickness Δh (radial modulus E_r). Suppose there is only a stress in the z direction S_z, which produces a strain ε_{zz}

$$\varepsilon_{zz} = \Delta z/z_o = k_{zz}S_z = S_z/E_z$$

If three orthogonal stresses (S_z, S_r, and S_t) are present, the strain resulting from a given stress cannot be independent of the other two stresses.

$$\varepsilon_{zz} = \varepsilon_{zz_o} - \varepsilon'_{zz} - \varepsilon''_{zz} = k_{zz}S_z - k_{zr}S_r - k_{zt}S_t \qquad (A.1)$$

where k_{ij} relates the stress S_j to the strain e_{ii}. Hence the increase in vessel length due to a stress in the z direction is reduced because the tangential and radial stresses which are present produce strains in the tangential and radial directions with a corresponding contraction in the longitudinal direction. The absolute value of the ratio strain in the i direction due to a stress in the j direction over the strain in the j direction due to the stress in the j direction is called the Poisson ratio σ_{ij}.

For a closed, untethered cylindrical tube with a transmural pressure, P, the stresses in the three directions are:

$$
\begin{array}{lll}
\text{radial stress} & S_r = -P & \\
\text{tangential stress (Hoop stress)} & S_t = Pr/h & \quad (A.2) \\
\text{long. stress} & S_z = Pr/2h &
\end{array}
$$

where r and h are the mean radius and wall thickness of the vessel at the pressure P.

In an anisotropic material there are six Poisson ratios. Indicating a strain due to a stress in the tangential direction by a single prime, that due to a stress in the radial direction by a double prime, and that due to a stress in the longitudinal direction by a triple prime, these six ratios can be expressed as follows:

$$
\begin{array}{ll}
\sigma_{zt} = \varepsilon'_{zz}/\varepsilon_{tt} = k_{zt}E_t & \sigma_{rz} = \varepsilon'''_{rr}/\varepsilon_{zz} = k_{rz}E_z \\
\sigma_{zr} = \varepsilon''_{zz}/\varepsilon_{rr} = k_{zr}E_r & \sigma_{tz} = \varepsilon'''_{tt}/\varepsilon_{zz} = k_{tz}E_z \quad (A.3) \\
\sigma_{rt} = \varepsilon'_{rr}/\varepsilon_{tt} = k_{rt}E_t & \sigma_{tr} = \varepsilon''_{tt}/\varepsilon_{rr} = k_{tr}E_r
\end{array}
$$

and the strains (ε_{ii}) in the three directions become

$$\varepsilon_{zz} = \Delta z/z_o = k_{zz}S_z - k_{zr}S_r - k_{zt}S_t$$

$$\varepsilon_{rr} = \Delta h/h_o = k_{rr}S_t - k_{rz}S_z$$

$$\varepsilon_{tt} = \Delta r/r_o = k_{tt}S_t - k_{tr}S_r - k_{tz}S_z$$

where k_{ij} are the coefficients relating the stress in the j direction (S_j) to the strain in the i direction (ε_{ii}), and the subscript o indicates the dimension before the application of the stress; in the absence of shearing strains

$(\varepsilon_{ij})_1 k_{ij} = k_{ji}$. Assuming a thin-walled vessel and small strains ($2h/r_o \ll 1$ and neglecting second order terms), the change in volume of the vessel for a stress -P is given by:

$$\frac{\Delta V}{V_o} = \frac{Pr_o}{2h_o} \left[k_{zz} + 4\ (k_{tt} - k_{tz}) \right] \tag{A.5}$$

For an isovolumetric wall material, Equation (A.5) becomes

$$\frac{\Delta V}{V_o} = \frac{Pr_o}{2h_o} \left[2\left(\frac{1}{E_t} + \frac{1}{E_r} \right) - \frac{1}{E_z} \right] \tag{A.6}$$

and if the material is isotropic, it simplifies to

$$\frac{\Delta V}{V_o} = \frac{3Pr_o}{2h_o E} \tag{A.7}$$

and there is only one Poisson ratio with a value of 1/2.

For a thin walled, isotropic, homogeneous elastic tube with circular cross section filled with an incompressible fluid, theory predicts the following relation for the propagation of a pressure wave (Moens-Korteweg):

$$c_M^{\ 2} = \frac{E_t h}{2\rho r} \tag{A.8}$$

where c = wave velocity

E_t = elastic modulus of the wall substance in the tangential direction

h = wall thickness

r = mean radius

ρ = density of fluid

Because of the deformation of the tube due to the application of pressure, the strains in all three directions of the coordinate system (r,Θ,z) have to be considered and the elastic modulus in the tangential direction E_t becomes:

$$E_t = (1 - \sigma^2) \frac{\Delta p}{\Delta r} \frac{r^2}{h} \qquad (A.9)$$

where σ is the Poosson ratio

Δp is the change in pressure

Δr is the associated change in radius

Substituting (A.9) in (A.8) one obtains:

$$c_M^2 = \frac{E_t h}{2\rho r} \quad \frac{(1 - \sigma^2)\ \Delta pr}{2\rho \quad \Delta r} \qquad (A.10)$$

Hence for small deformations in a linear system of the type specified for Equation (A.8) the wave velocity depends on the elastic modulus of the wall material, the wall thickness and the tube radius. However, each of these parameters is a function of the distending pressure p. Using the theory of elasticity for thin walled elastic tubes, Bergel has modified this equation as follows:

$$c_L^2 = \frac{E_t h}{2\rho r} \cdot \frac{2 - m}{2 + m\ (m - 2)(1 - \sigma - 2\sigma^2) - 2\sigma^2} \qquad (A.11)$$

where $m = h/r$.

Because vessel walls are viscoelastic and therefore must exhibit wave dispersion, one can derive a frequency dependent expression for the complex wave velocity. Such an expression has been given by Womersley:

$$c_W^2 = (\frac{E_t\ h}{3\ \rho})\ (\frac{2r + h}{(r+h)^2})\ (1 - F_{10}) \qquad (A.12)$$

$$\text{where } 1 - F_{10} = 1 - \frac{2 . J_1 \ (\alpha j^{3/2})}{\alpha \ j^{3/2} \ J_o \ (\alpha j^{3/2})} \tag{A.12}$$

$$\alpha^2 = \frac{r^2 \ \omega}{\nu}$$

ω = angular frequency

ν = kinematic viscosity

$j^2 = -1$ and

J_o and J_1 are Bessel functions of the first kind of order zero and one respectively.

The change in the form of the pressure pulse as it travels along the vascular system has been explained by wave reflections, dispersion and non-uniform properties of the vascular wall. In the presence of frictional losses the wave equation becomes:

$$\frac{\partial^2 p}{\partial z^2} = \frac{1}{C^2}\left(\frac{\partial^2 p}{\partial t^2} + K\frac{\partial p}{\partial t}\right) \tag{A.13}$$

The friction losses result in an exponential decay of the wave as it propagates away from the source. The solution of Equation (A.13) for a sinusoidal distrubance $P_o \sin \omega t$ in the direction of the positive z-axis becomes then:

$$P\ (z,t) = P_o\ e^{-\alpha_1 z} \sin(\omega t - \beta z) \tag{A.14a}$$

or in the exponential form:

$$P\ (z,t) = P_o e^{-\gamma z} e^{j\omega t} \tag{A.14b}$$

where $\gamma = \alpha_1 + j\beta$ propagation constant

α_1 = damping constant

β = phase constant

For the case of the superposition of a downstream and an upstream traveling wave the pressure at any point is given by adding the solutions for each wave. The result is an expression of the form:

$$P\ (z,t) = P_1 e^{j\omega t\ -\ \gamma z} + P_2 e^{j\omega t\ +\ \gamma z} \qquad (A.15)$$

where $P\ e^{j\omega t}$ and $P_2 e^{j\omega t}$ represent the disturbance creating the downstream and the upstream traveling waves, respectively.

The velocity at which a simple harmonic distrubance travels is the phase velocity C_p:

$$C_p = \frac{\Delta e}{\Delta\Theta}\ \omega = \frac{\omega}{\beta} = \lambda f \qquad (A.16)$$

where Δe = distance over which the velocity is measured

$\Delta\Theta$ = difference in phase angle between the two sites of measurement

[illegible]ve length

ω = angluar frequency

In a simple elastic system the phase velocity is related to the physical properties of the system by Equations (A.10) or (A.11). Therefore, the determination of the phase velocity offers theoretically an easy experimental approach to the evaluation of the elastic properties of a blood vessel in vivo.

In contrast to the phase velocity, the group velocity C_g expresses the speed at which the compound wave and hence the energy travels:

$$C_g = \frac{d\omega}{d\beta} \qquad (A.17)$$

In general the group velocity would be expected to be close to the familiar foot-to-foot velocity of the pressure pulse. Because the pressure pulse changes its shape considerably during its travel, points of equal pressure on the rising and falling parts of the pressure pulse will have different transmission times and therefore the foot-to-foot velocity only approximates the group velocity. More complex theories for the relations between wave velocity and the properties of vascular walls have been derived by Klip, Anliker and Mirsky (119, 11-15, 151) (See Appendix C.3). However, the following assumptions were made in all these derivations either explicitly or implicitly:

i) The fluid is incompressible and newtonian.

ii) The vessel is cylindrical, uniform and infinitely long.

iii) The physical properties of the vessel wall are linear

iv) The vessel wall is thin ($h/r \ll 1$).

v) The wall material is isotropic and homogeneous.

vi) In the theories where viscoelasticity is considered it is assumed that the imaginary part of E and σ (due to viscous effects) are much smaller than the real parts.

vii) The density of the fluid and the wall material are about equal

viii) All quantities of the order $2\pi r/\lambda = \omega r/c$ are negligible (λ = wave length).

The primary problems arise with assumptions ii-vi. The geometry of the vascular bed is characterized by a complex arrangement of randomly branching tubes which are neither uniform in their properties, nor homogeneous and isotropic. Linearity may be safely assumed over the pulsatile pressure range in the arterial system but not for different mean pressures. Wall thickness, vessel radius and elastic modulus are functions of the transmural pressure. Although these functions can be approximated by exponential expressions for a given state of the vascular system, the coefficients and exponents of these expressions change as "vascular tone" changes. Damping is both pressure and frequency dependent. A comparison between theoretically predicted and experimental results is presented in the next section.

A.1.2 Experimental Data

Relatively few experiments have been reported in which theoretically derived wave velocities were compared with experimental measurements (216, 221, 165, 166, 147, 10-15, 23 and 18). While the experiments with rubber tubes have provided considerable insight into the general phenomena of wave propagation in viscoelastic, fluid filled tubes, the results are not directly transferrable to wave transmission in the vascular tree, because of the complex structure and behavior of the latter. Furthermore, the experimental techniques are much more limited and measurement errors considerably larger in animal experiments than those of model measurements. We have not been able to find any measurement of wave velocity in veins at physiological venous pressures. From the various experiments reported in the literature the following conclusions can be drawn:

a. Relation Between Wave Velocity and Elastic Modulus in Arteries

Measured values of about 8 m/sec in the femoral artery compare well with velocities predicted from the dynamic elasticity data obtained by Bergel (c 9 m/sec), but poorly with those predicted from the distensibility data reported by Patel or by Peterson (c 20 m/sec). Our own results are close to those obtained by Bergel. No satisfactory explanation for the marked differences between the above two sets of data has yet been offered (214). It is, therefore, not entirely surprising that measurements of wave velocity at various distending pressure appear to correlate rather poorly with those predicted from Equation (A.10) (219). The main factors which determine the wave velocity are E, r and h and all three parameters are pressure dependent. This dependence can be approximated by exponential functions. However, the coefficient and exponents of this relation depend not only on the "vascular tone", but also on the amount of stretch to which the vessel is subjected. This variable pressure dependence appears to be the major problem in any practical application of wave propagation theory to the vascular bed.

b. Damping

The propagation of the pressure pulse and the behavior of arterial input impedances is markedly influenced by the viscoelastic properties of the vascular wall. With presently available instrumentation it has not yet been possible to obtain accurate values for the damping coefficients in vivo, since the phase angle between the real and the imaginary component of the elastic modulus is less than 5°. However, model experiments have shown that the viscous damping of the wall is more important than the viscosity of the blood, at least as far as the input impedance is concerned. At low transmural pressure damping appears to be much larger than at higher transmural pressures. For example, venous pressure pulses (generated by the right atrium) are observed in the thoracic venae cavae, but are not measurable in the distal part of the abdominal vena cava, although the flow pulses are still present (208).

c Frequency Dependence of Wave Velocity

Both theoretically and experimentally it has been shown that several modes of wave propagation may exist in the vasculature. However, only for the lowest frequency mode (Moens-Korteweg) have the relations between experimental data and theory been explored in some detail, although it is generally assumed that impact waves (such as those produced by Landowne) correspond to one of the higher modes.

The ratio dynamic/static elastic modulus rises from 1 at $\omega = 0$ to about 1.2 for the thoracic aorta and 1.7 for the carotid artery at $\omega = 12$, and remains at about these levels at the higher frequencies corresponding to the harmonic components of the pulse wave. The change in this ratio is generally assumed to be related to the viscous properties. The latter, however, are of a peculiar character, since the modulus of the coefficient of viscosity appears to be independent of frequency for $\omega > 12$, while the phase angle continues to increase (218).

d. Wave Reflections

Measurements of phase velocity of the harmonic components of the pressure pulse are complicated by the fact that wave reflections are present in the arterial system. The measured apparent wave velocity oscillates both as a function of frequency and of location. The measurements are usually carried out over distances which correspond to 1 - 5% of the wave length of the fundamental frequency of the heart beat. McDonald and Taylor (147), therefore, argued that the wave velocity obtained from the higher frequency components more nearly reflects the "true" wave velocity because for a given path length reflection effects tend to average out better for shorter wave lengths.

Measurements of the foot-to-foot velocity are complicated by the fact that the pressure pulse changes its shape during its travel toward the periphery and that therefore corresponding points do not maintain the same relationship to the center of gravity of the pulse wave.

e. Noncircular Cross Sections

At transmural pressures of less than 5 cm H_2O, arteries and veins begin to lose their circular cross section. If no external constraints are present the cross section assumes first an elliptic shape. If stresses are applied under this condition, the major semiaxis decreases and the minor semiaxis increases as pressure increases. If the transmural pressure decreases still further the vessel collapses completely. Except for Rödenbeck (see annotated bibliography) these relations have not been theoretically investigated.

Because of low intravascular pressures in the venous system, the extravascular pressures contribute significantly to the transmural pressures in contrast to the arterial system. Hence in the thorax, transmural pressure is on the average larger than that of the contributaries of the intrathoracic veins, since the extravascular pressure is identical with intrapleural pressure. On the other hand, veins embedded in tissue are exposed to positive extravascular pressure, which is a function of muscular activity and interstitial pressure. Furthermore, the differences between transmural pressure and driving pressure become much more significant in a low pressure system. For instance, the pressure relations in the carotid artery, jugular vein, aorta and superior vena cava, for a cardiac output of 4.4 l/min can be estimated as follows: (right atrial pressure = 0)

	Carotid	Jugular	Aorta	SVC
Intravasc. press. (cm H_2O)	150	10	150	2
Extravasc. press. (cm H_2O)	5	5	- 5	-5
Transmural press. (cm H_2O)	145	5	155	7
Driving press. (cm H_2O)	150	10	150	2
Flow (cm^3/sec)	10	10	90	90
Press. assoc. with kinetic energy of mean flow (cm H_2O)	.1	.1	.4	.4

In addition, the mechanical behavior of the vessel wall is also influenced by hemodynamic events. For instance, the collapse of the large veins at the entrance to the thorax is determined in part by the pressure losses due to flow acceleration and the hemodynamic behavior in the segments distal to the collapse is determined by the physical laws associated with the vascular "waterfall".

Furthermore, the dimension of the veins are much more influenced by longitudinal strains than that of arteries. Major changes in such strains may occur during motions of the limbs and neck.

A.2 Methods

This involves an estimate of the travel time of a naturally occuring or artificially introduced disturbance between two locations according to Equations (A.16) or (A.17) or simply from $C = \frac{\Delta \ell}{\Delta t}$, which is Equation (A.12). Because pressure pulses are easier to measure, they are usually used for this purpose rather than flow pulses although theoretically the latter are just as suitable.

The requirements for measuring equipment are apparent from the following table:

C (cm/sec)	$\Delta\ell$ (cm)	f (cps)	$\Delta\Theta$ (degrees)(Eq.16)	Δt (sec)(Eq.18)
100	5	1	18	.05
		20	360	
	20	1	72	.2
		20	1,440	
500	5	1	3.6	.01
		20	72	
	20	1	14.4	.04
		20	288	
2,000	5	1	.9	.0025
		20	18	
	20	1	3.6	.01
		20	72	

From these calculations the following conclusions can be drawn:

a Phase Velocity

This requires measurement of the difference between two phase angles. Except if an artificially generated sine wave is introduced as the disturbance to be measured, the phase angles will have to be obtained by means of Fourier-analysis from the calculated coefficients of the sine and cosine components. As we have shown previously, the maximum accuracy obtainable with presently available instrumentation is in the order of 3 - 4° for Θ, i.e. 6 - 8° for $\Delta\Theta$ (Attinger et al.: Circulation Res. 19: 233, 1966) (211). This is of the same order as the expected values for low frequencies measured over short distances. For the higher frequencies of interest or for measurements over longer distances, the phase difference may be larger than 360° and it may be impossible to estimate the number of rotations of the phase vector with any confidence particularly in the presence of wave reflections (Section A.1.2.d).

b. Foot-to-Foot Velocity

Although with modern equipment the expected time intervals could be measured with great accuracy, the errors will be large in practice because of the distortion of the wave form. For instance if a volume pulse is introduced into the venous system by means of a step function the rise time will be at least .01 sec. After the pulse has travelled for a distance the rise time may have increased to .05 sec. Depending upon which points one chooses for evaluating the travel time, the error will be at least .02 sec. If the sensors are coupled to the vessel through fluid columns the frequency response is flat to at most 30 cps, which introduces additional errors. If indirect pressure measurements (for instance, by use of piezo electric crystals) are used the problems of frequency response will be largely eliminated.

A.2.2 Indirect Methods

a. Measurement of Time Delay Between a Peripheral Venous Pressure and Atrial Contraction

Although such measurements are technically easy to perform (either from ECG or phonocardiogram) the method assumes that the relationships between electrical or mechanical activity of the heart and hemodynamic events remains constant. This has been shown not to be true because of the changes in myocardinal "contractility" and cardiac dimensions under various physiological conditions (change in body position, exercise, etc.). Furthermore peripheral venous pressure pulses are not always present (see annotated bibliography) and their amplitude is small. Again the problem of choosing appropriate points of the display of the two variables for measurements arises. Hence, not only would the error in time delay measurement be considerable but on the basis of our present understanding this delay could not be related reliably to any physiologically meaningful performance characteristic of the venous system.

b. Measurement of Resonant Frequency by Generating a Standing Wave

Although at first sight this method appears attractive, the suggested analogy with an organ pipe does not apply. We know of no location within the venous system where such a standing wave could be generated without involving adjacent tissue. The generated wave length would of course depend on the relative contributions of the vein itself and that of the surrounding structures. In most instances the latter would be larger than the former.

A.3 Physiological Significance of Wave Velocity Measurements

Since 1840 serious efforts have been devoted to the concept that the arterial pulse wave velocity could be used as an index of the distensibility of the arterial wall. Although the proposed theories differ in the degree of sophistication they agree that the wave velocity depends primarily on the radius and wall thickness of the wall and the elastic modulus of the wall material. These three variables are pressure dependent and the pressure dependence varies with the state of the vascular system Experimental data show that the theoretical concept is basically sound, i.e. the arterial wave velocity increases toward the periphery. For instance, the mean radius of the aorta in ten large dogs at a distending pressure of some 140 cm H_2O was found to decrease from 1.2 cm at the root of the aorta to .27 cm in the external iliac artery. Over the same distance the elastic modulus of the arterial wall increases from about 3×10^6 to about 12×10^6 dyn cm^2. This gives an estimated wave velocity of $\approx$ 1.4 m/sec in the arch of the aorta and of $\approx$ 11 m/sec in the external iliac. The corresponding measured values are closer to 4.5 and 8 m/sec. Hence, even in the arterial system (to which practically all the work in this field has been devoted) it is not possible to predict the wall characteristics from wave velocity measurements with any degree of confidence even if the pertinent measurements of r, h and E are available. The reasons for this were discussed in some detail in Section A.1.2. Both the approximations used in the derivation of the theory and the accuracy of present measurement techniques are inadequate for this purpose. It is apparent from the general expression for the wave velocity

$$C = f\ (r,\ h,\ E,\ \sigma_{ij},\ v_t) \qquad \text{(A.19)}$$

where v_t is an index of vasomotor tone and the other symbols were defined in Section A.1.1 that until a method for measuring v_t becomes available it will not be possible to determine either C or its changes by the measurement of changes in pressure even if r, h, E and σ are known.

In the venous system the situation is even more complex because of the high damping in a low pressure system, the partial collapse of venous segments, the influence of external pressure on the cross section, and the effective physical properties of the vessel wall and the presence of numerous valves. Even if these factors are eliminated in carefully controlled in vitro experiments, the experimental values for wave velocity are nearly twice as large as those predicted from the theory (See Figures B-9 and B-10). The general pressure dependence of the observed wave velocity is similar to that predicted by theory but the quantitative relations are yet undetermined. Even if these relations were to be established experimentally, I see no a priori reason why they could be extrapolated to the system exposed to a zero g-field.

A.4 Conclusion

At the present level of our understanding of the cardiovascular system the determination of wave velocity as an index of venous pressure is not to be recommended. It would, however, be most useful if pressure and flow measurements in the cardiovascular system were to be combined with wave velocity measurements, since this might lead to better definition of cardiovascular performance characteristics.

I am doubtful of the value of venous pressure measurements as an index of the state of the venous system (see also Alexander) and would propose that the efforts in this field should also be directed toward venous flow and venous tone measurements.

APPENDIX B

EXPERIMENTAL WORK

B.1 Occlusive Pressure Chamber

Experiment: The Chamber Pressure Method Compared to Invasive Measurement

Investigators: Dr. R.F. Brubaker and Dr. D.M. Worthen

Methods: A resting human subject seated with the arm at heart level was tested. A superficial vein of the forearm was cannulated with a #20 needle through which heparinized saline solution was slowly infused. The needle was connected to a low displacement pressure transducer for continuous recording of peripheral venous pressure. A pressure chamber, constructed to the dimensions outlined in Figure B-1 was used for noninvasive pressure measurements of the same vessel. An arterial sphygmomanometer cuff was placed around the arm to control venous pressure and elevate it to any desired level. A total of 76 pressure determinations were taken with the pressure chamber between 5 and 85 cm water pressure. The noninvasive measurements were plotted against the simultaneous invasive measurements and are shown in Figure B-2. The invasive venous pressure measurement was unknown to the operator of the pressure chamber, who used direct visualization of venous collapse as the endpoint.

Results: The average deviation of the noninvasive determination from the invasive determination was 2.1 cm water. The standard deviation was 2.5 cm water. No transfer correction was applied in determining these deviations.

Conclusions: It was concluded that the pressure chamber method of noninvasive venous pressure determination was feasible and easy to carry out. Without any precalibration of the instrument, reasonably accurate values were obtained over a wide range. From the appearance of the data plotted in Figure B-2, it was concluded that the accuracy could be increased even further by precalibration.

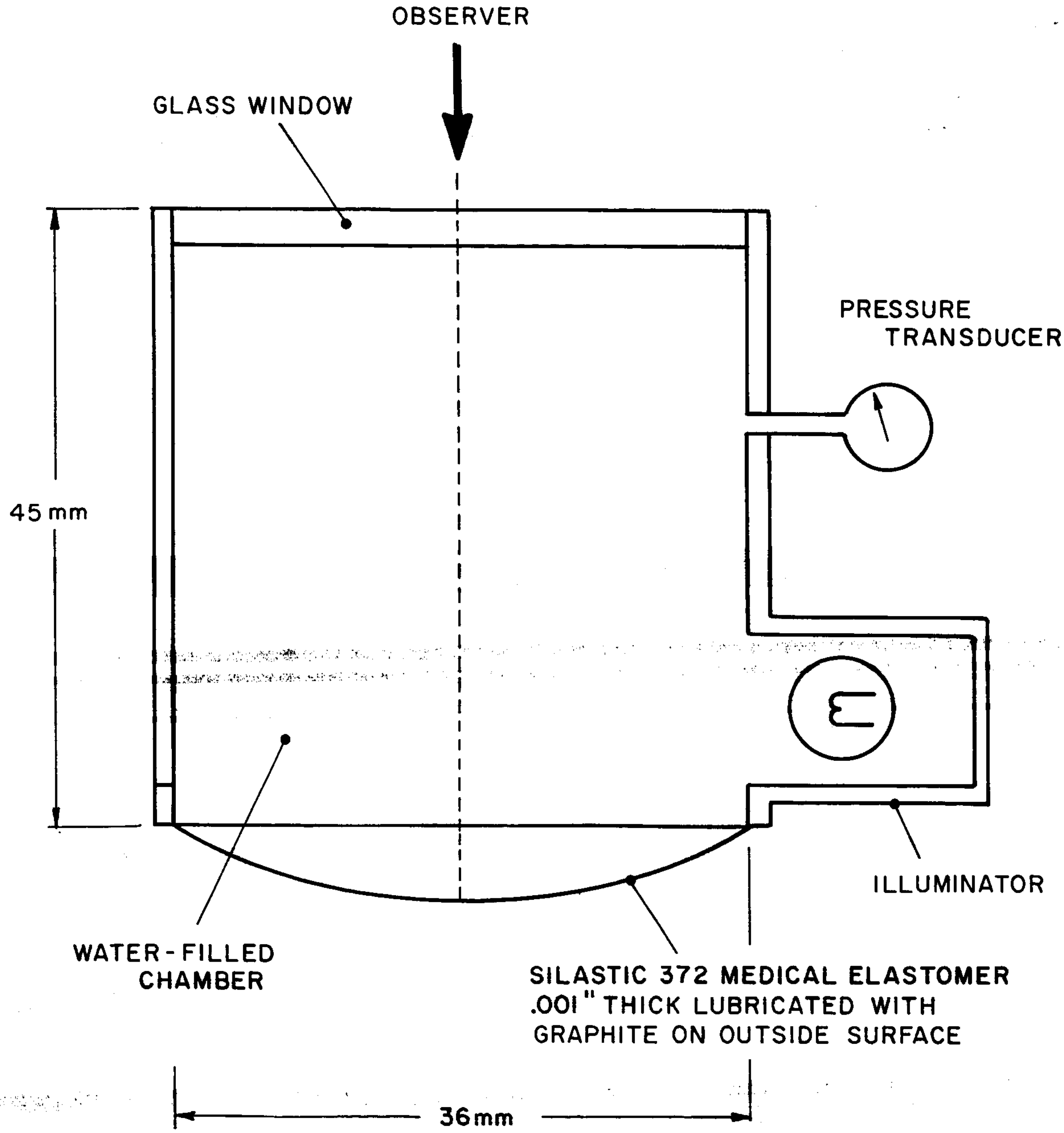

FIGURE B-1.

EXPERIMENTAL PRESSURE CHAMBER.

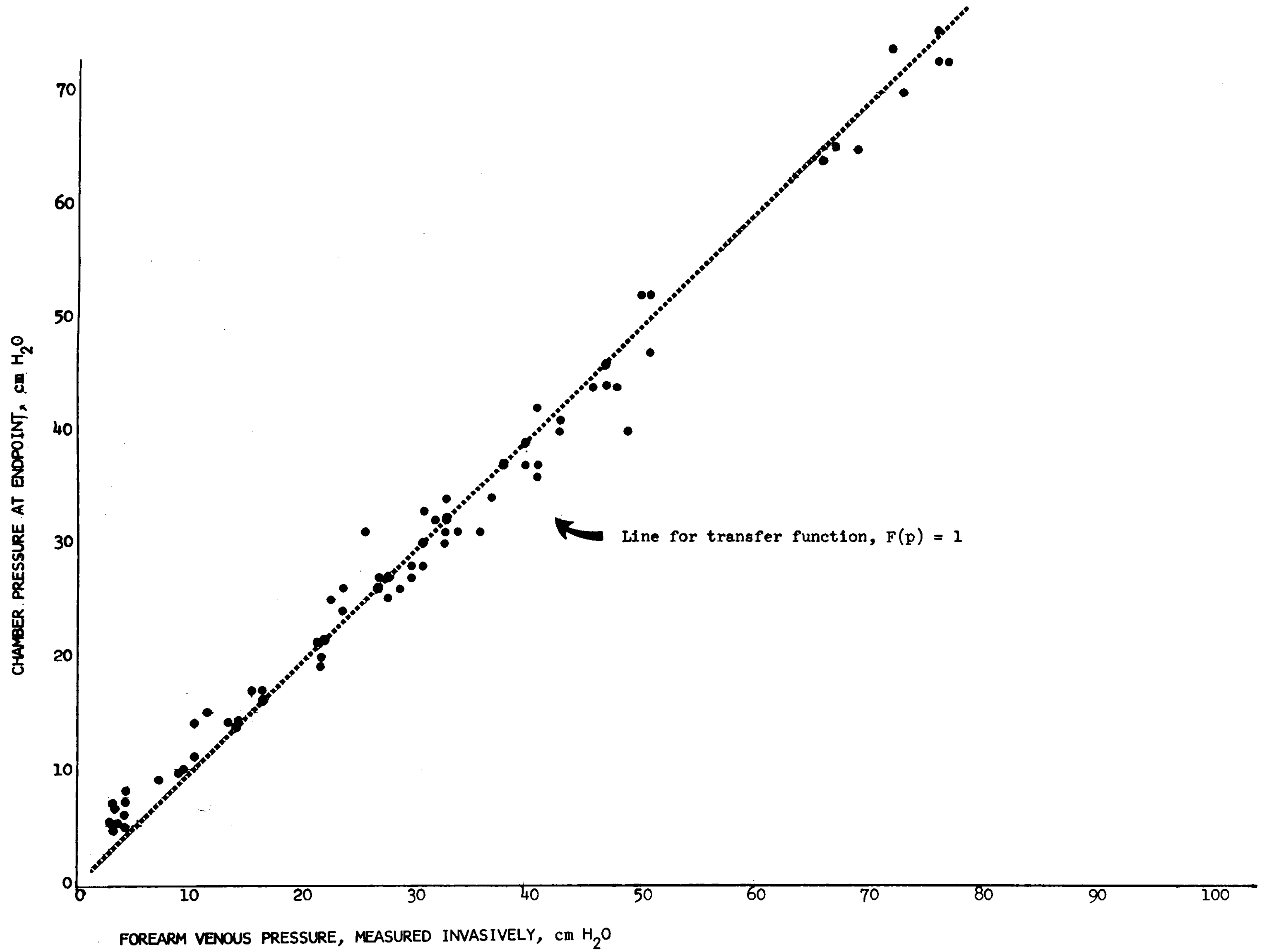

FIGURE B-2 VENOUS vs CHAMBER PRESSURE

B.2 Forearm Air Displacement Plethysmography

Experiment: The evaluation of forearm air displacement plethysmography as a detector of a change in volume for determining venous pressure and distensibility using an arm venous occluding cuff, comparison with invasive measurement of venous pressure.

Investigators: Dr. D. M. Worthen and Dr. R. F. Brubaker

Methods: A human subject was either sitting or supine with the forearm at heart level. A venous occluding cuff was placed on the arm and an air displacement cuff, 10 by 30 cm, placed about the forearm. Both cuffs were made of 0.005 inch rubber dental dam and were loosely wrapped about the limb then secured in place with a nondistensible wrapping of gauze. In one experiment a 20 gauge needle was placed in a vein located distally in the forearm and the plethysmograph placed proximal on the forearm. In the other experiment the position of the two was reversed with the monitoring needle being placed proximal and the plethysmograph distal on the forearm. The occluding cuff pressure was increased at a constant rate of 0.12 mm Hg per second while the true venous pressure was measured with the needle connected to a transducer and displayed on a Grass polygraph. Volume change in the plethysmograph was measured as the pressure change in a transducer likewise connected to a Grass polygraph. The endpoint of venous pressure was measured in retrospect as the occluding pressure at which there was a definite upswing in the volume curve. Variation in the volume of the forearm occured with cardiac and respiratory cycle and made the endpoint obvious only after it was passed. The venous distensibility was measured by noting the volume change versus the pressure change for a given period of time. The plethysmograph was calibrated by injecting known amounts of air into the cuff and noting the deflection on the recording graph.

<u>Results</u>: Figure B-3 shows a plot of the true (needle) pressures versus the pressures derived from the occlusion method. When the needle was proximal to the plethysmograph the values were consistently higher. When distal the values were quite close. It is possible that the plethysmograph acted as enough of an occlusion to elevate the venous pressure measured in the needle and compensate for the transfer function that would be obvious had a second needle been above the plethysmograph. The second experiment showed the cuff pressure to be higher than the true or recorded venous pressure which is what would be expected. Figure B-4 is a drawing of what a recording would look like. The endpoint is subtle but reproducable. The calculated values of distensibility is reasonable for a forearm.

<u>Conclusions</u>: It was apparent that the method could be used to measure venous pressure and venous distensibility. The difference in the derived and actual venous pressure is the predicted cuff sensitivity and an understanding of its exact nature would require further experimentation. As long as the endpoint were precise its absolute value would be less important than the fact that it was reproduceable. Distensibility of the veins can easily be measured with this technique.

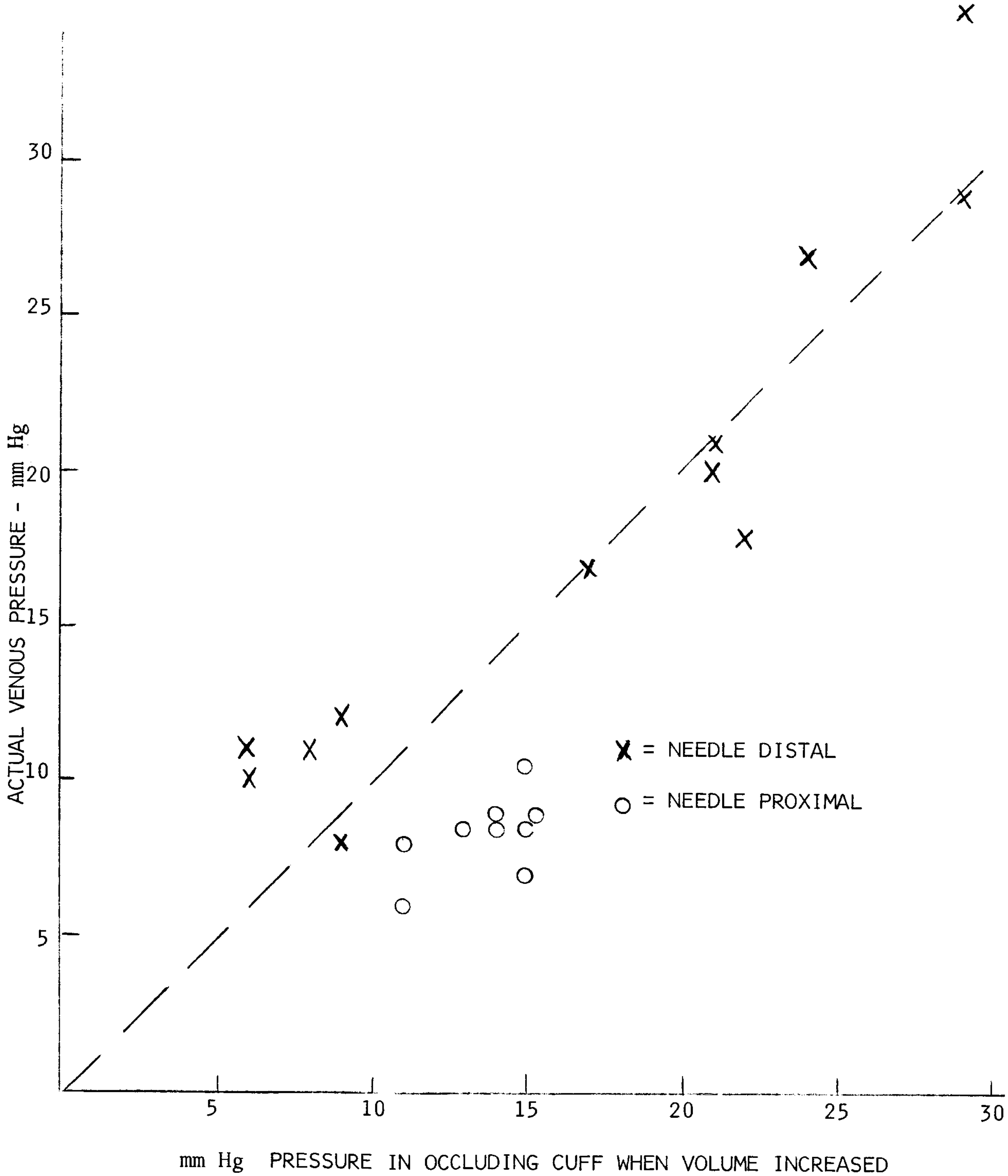

FIGURE B-3 VENOUS vs OCCLUDING PRESSURE

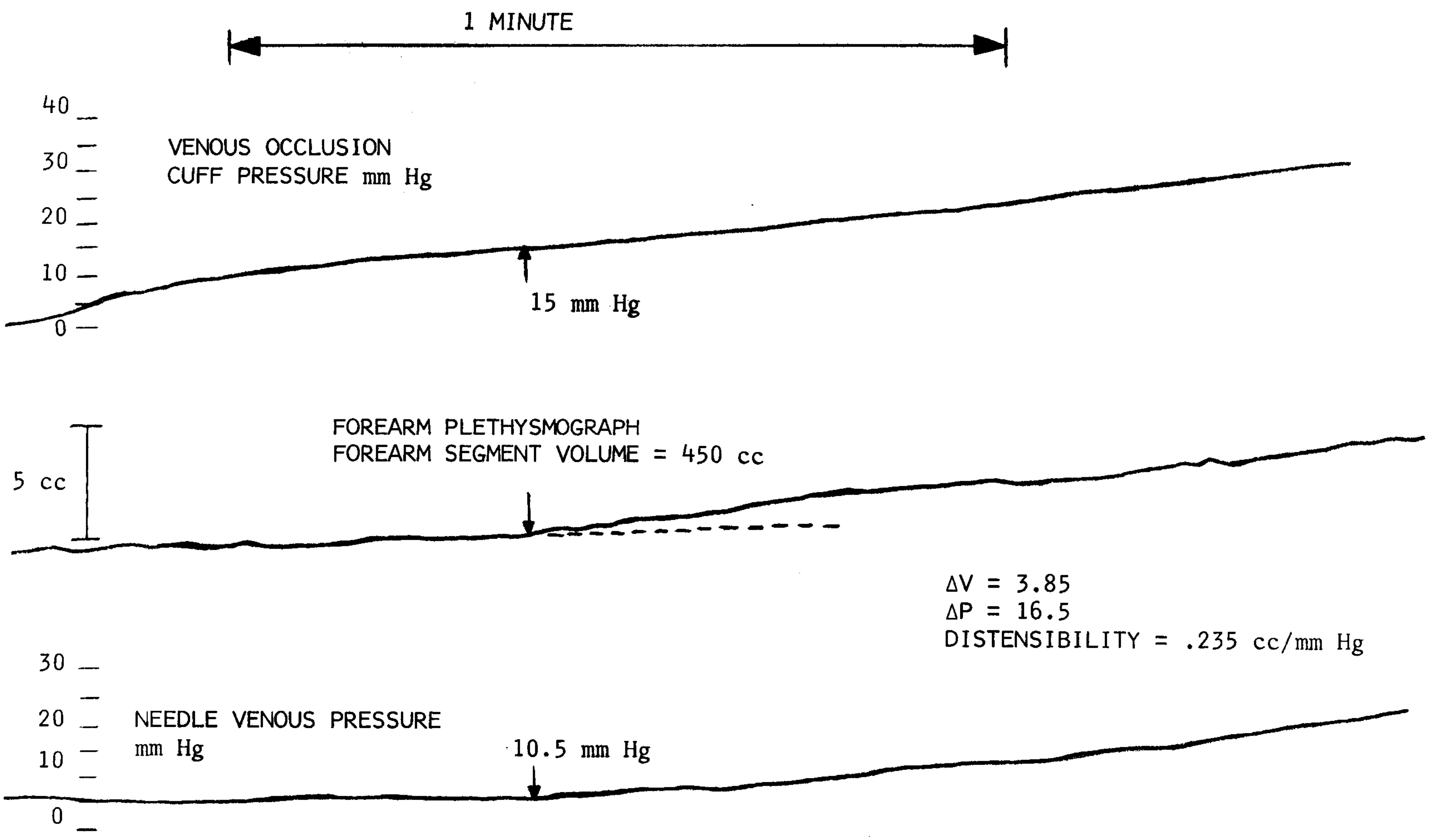

FIGURE B-4 SYNTHESIZED RECORDING OF A VENOUS OCCLUSION PLETHYSMOGRAPH

B.3 P-A Interval

Experiment: Since we were unable to discover any data on the PA interval or its possible variations with venous pressure or venous tone a series of preliminary experiments were performed to determine first of all whether this interval could be measured and what if any significance it might have.

Investigator : Dr. I.F.S. MacKay

Method: Two subjects were tested on an examining table tilted at various angles with respect to the horizontal in order to vary the venous pressure to levels above that at the static indifference point. Simultaneous records were taken of the electrocardiogram and the complex pulse pressure waves at the jugular and anticubital site. In addition, for one subject the inspiration time was recorded. The pulse pressures were measured with the balloon type pressure chamber described in Section B.6. In addition, the antecubital pressure was estimated by the cuff pressure required to obliterate the A wave as described in B.6.

Results: A typical recording is shown in Figure B-5a. Notice the clear appearance of the A, C & V waves in the jugular pulse. The greater variation of the A waves appearance in the antecubital site is typical, and led to our consideration primarily of the delay between the EKG - P wave and the A wave measured at the jugular site. (In general, the A wave at the anticubital site occurred approx. 75 m sec. after that at the jugular site).

The interval from the peak of the P wave to the peak of the A wave was measured and plotted on a beat-by-beat basis in Figure B-6 . Notice that the interval varies from 90 to 142 msec, with a mean value of approx. 115 msec, but that cyclical variation with respiration is quite regular and accounts for most

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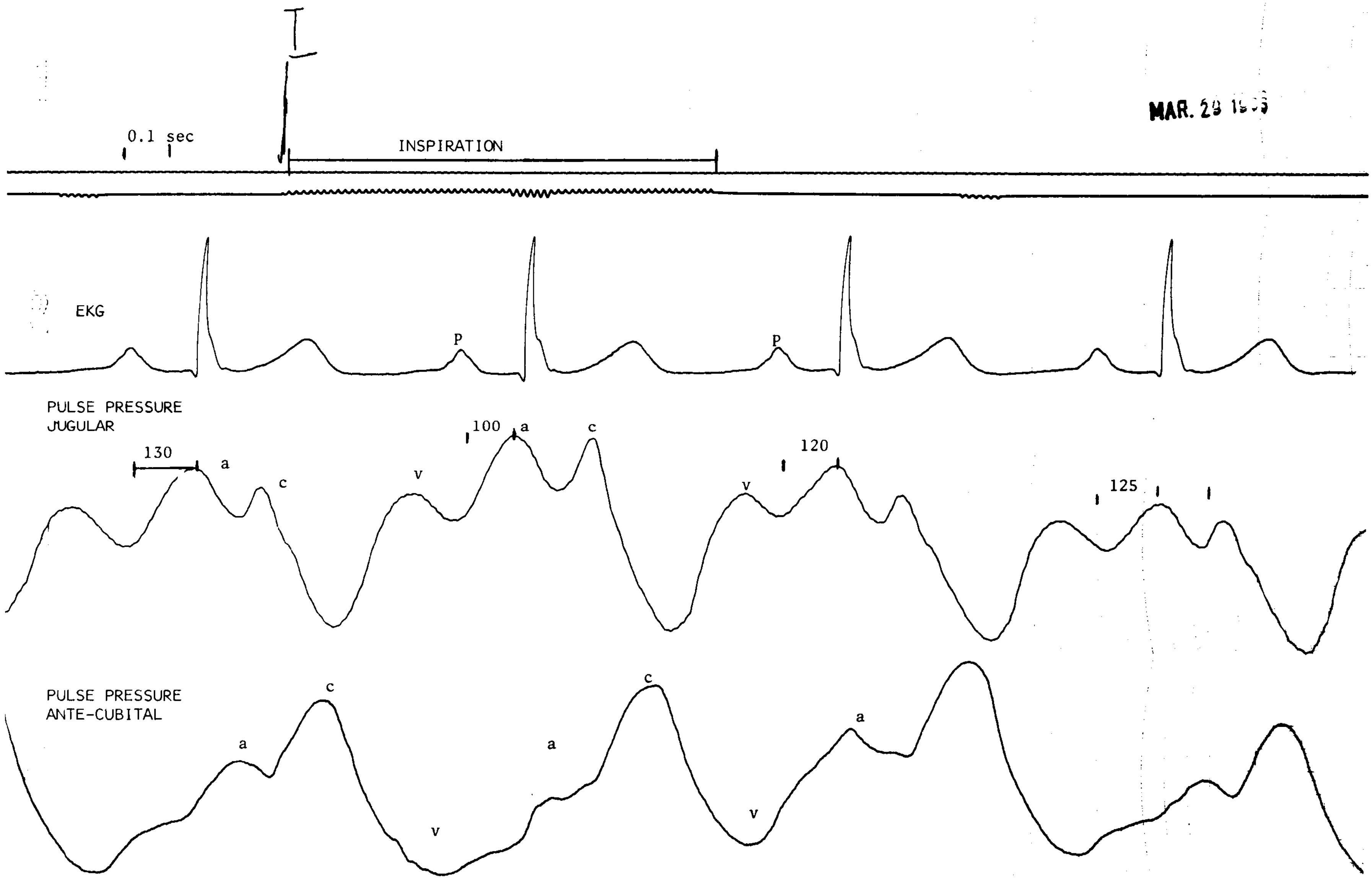

FIGURE B-5A EKG AND PULSE PRESSURE RECORDING SHOWING P-A DELAY

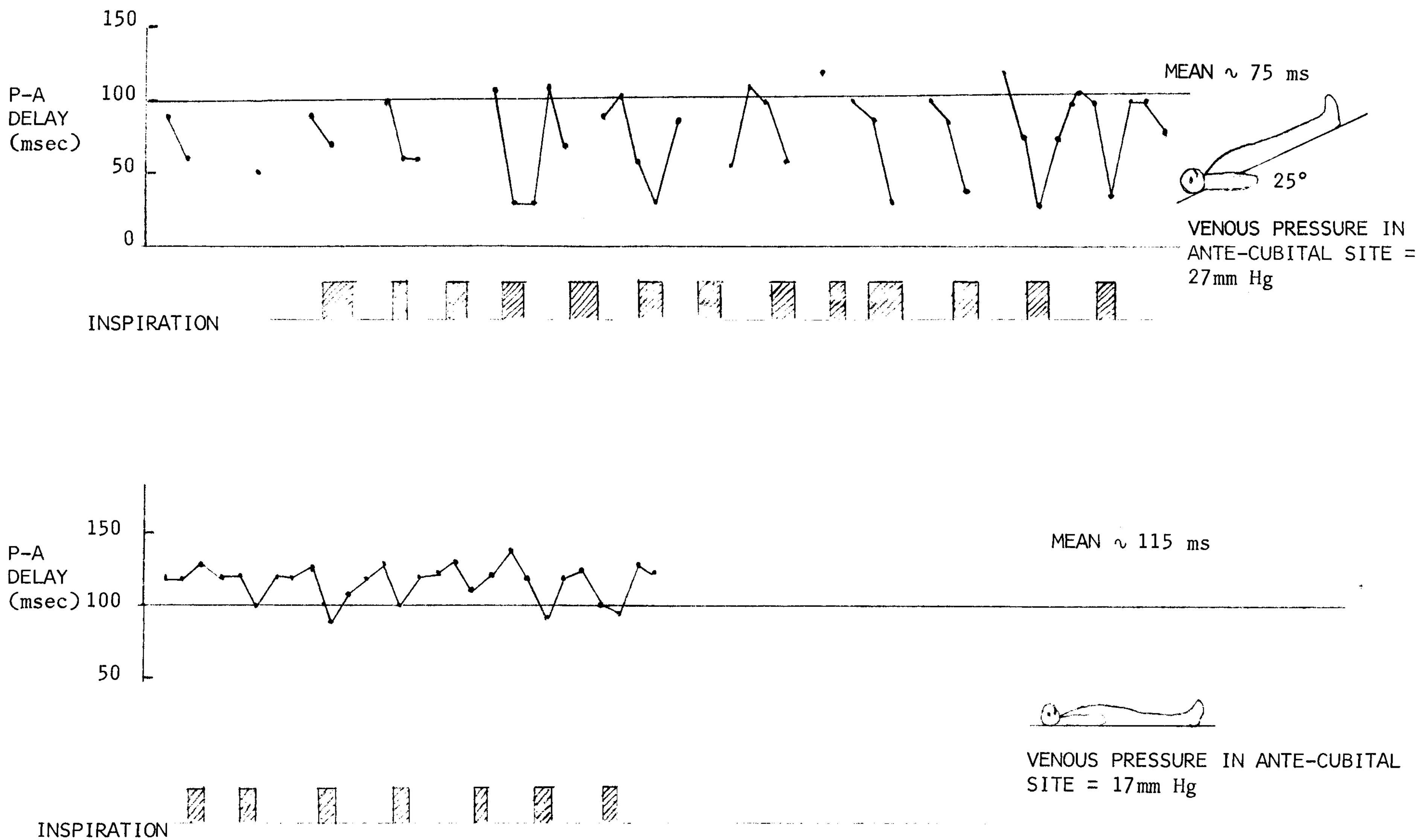

FIGURE B-6 EXPERIMENTAL P-A DELAY

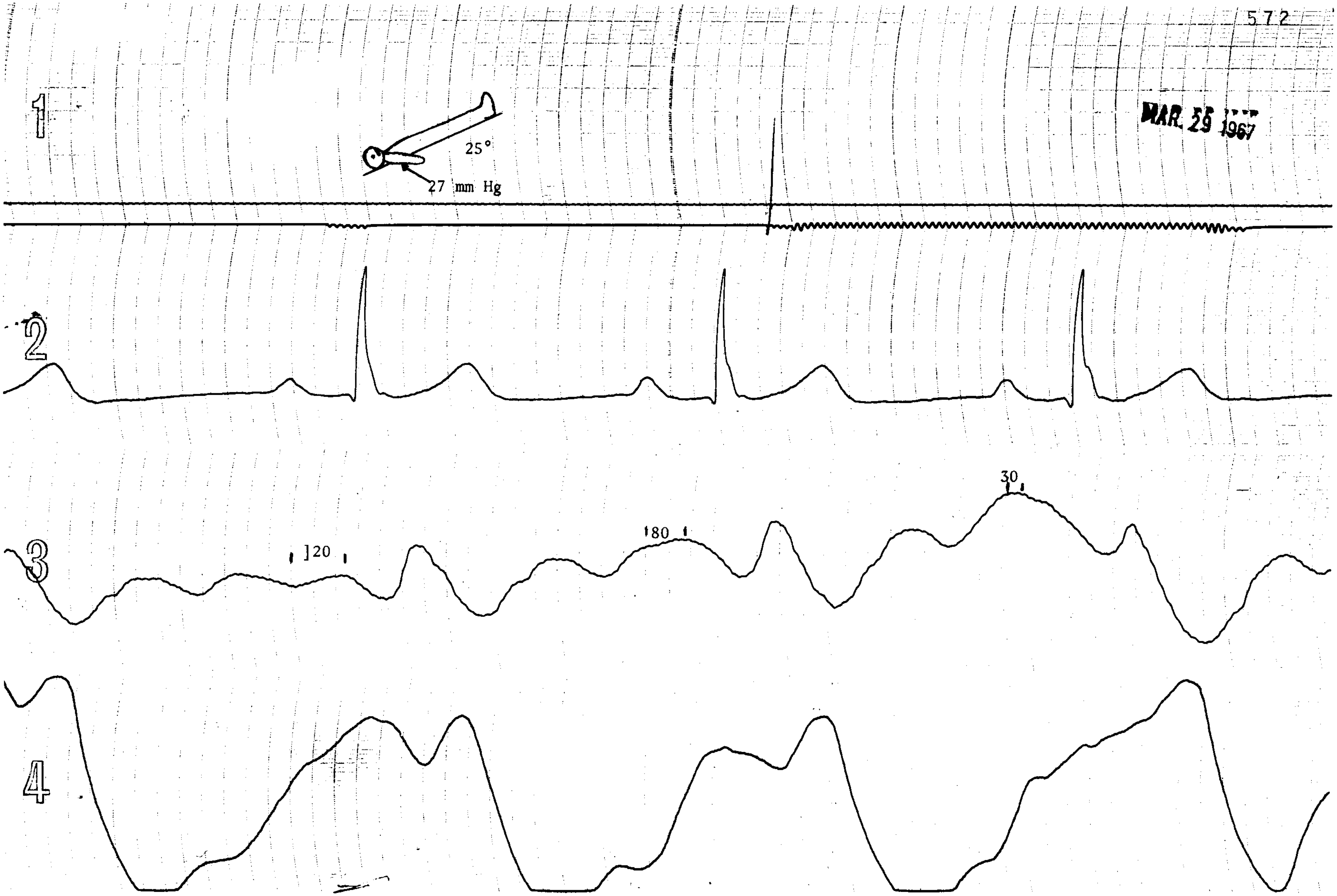

FIGURE B-5B EKG AND PULSE PRESSURE RECORDING SHOWING P-A DELAY of the P-A interval variation. As seen in the figure, for this subject horizontal, the P-A interval drops by approx. 30 msecs during inspiration.

When the same subject was tilted head down by an angle of 25°, increasing his estimated antecubital venous pressures from 17 to 27 mm Hg, the shape of the jugular pulse change and, significantly enough, the P-A interval was seen to decrease on the average. A typical respiratory cycle is shown in Figure B-5b. For some beats the A wave was difficult to detect, perhaps due to its merging with the H wave, and for these beats, generally following the end of inspiration no data was reduced. Nevertheless, the marked decrease in average P-A interval (75 msec) and the increased cyclical variation with inspiration is clearly shown in the upper part of Figure B-6.

In another experiment, (in which a subject was tilted horizontal and head down by 8°, 16° and 24°.) EKG, jugular pressure and antecubital pressure were again measured, although inspiration times were not recorded. From the brief recordings (3 beats per tilt angle). P-A delays were calculated from the EKG to the jugular pulse recording, and plotted as a function of tilt angle in B-7. In addition, the venous pressure in the antecubital region as measured by the cuff pressure for A wave obliteration is also plotted, and it is seen that with increasing head down tilt angles the venous pressure increases and the P-A delay decreases. Replotting this data as P-A delay verses venous pressure in Figure B-8 indeed shows the decrease in interval with pressure for this single preliminary experiment.

Discussion: These preliminary experiments were designed primarily to see whether or not the P-A interval could be measured and bears any relationship to venous pressure. It is clear from these early experiments that it can be measured and at least in so far as our tests show it does, as expected, decrease with increasing venous pressure. It is also clear that a good part of the observed beat to beat

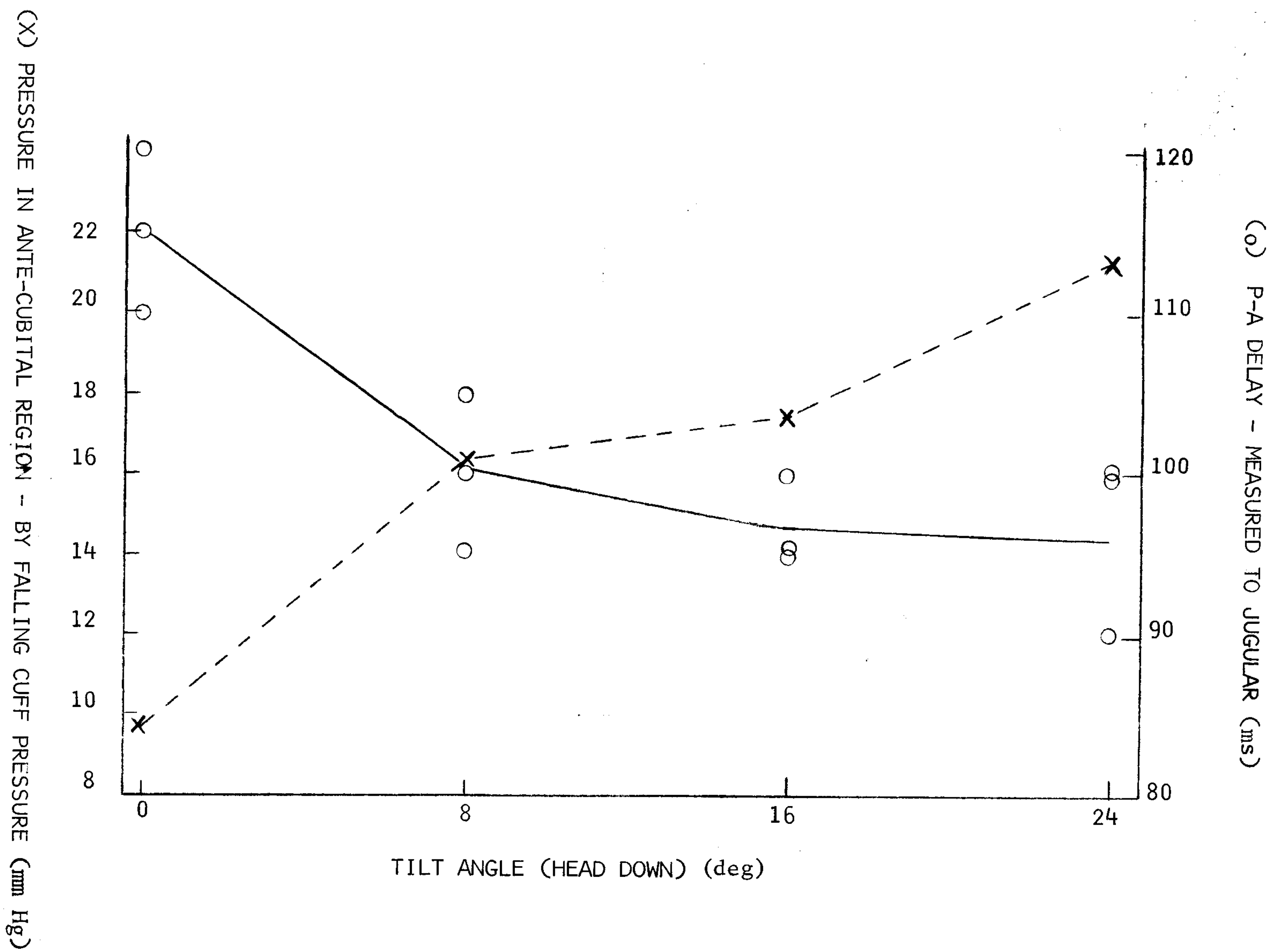

FIGURE B-7 VARIATION IN P-A DELAY AND VENOUS PRESSURE (CUFF) WITH TILT ANGLE

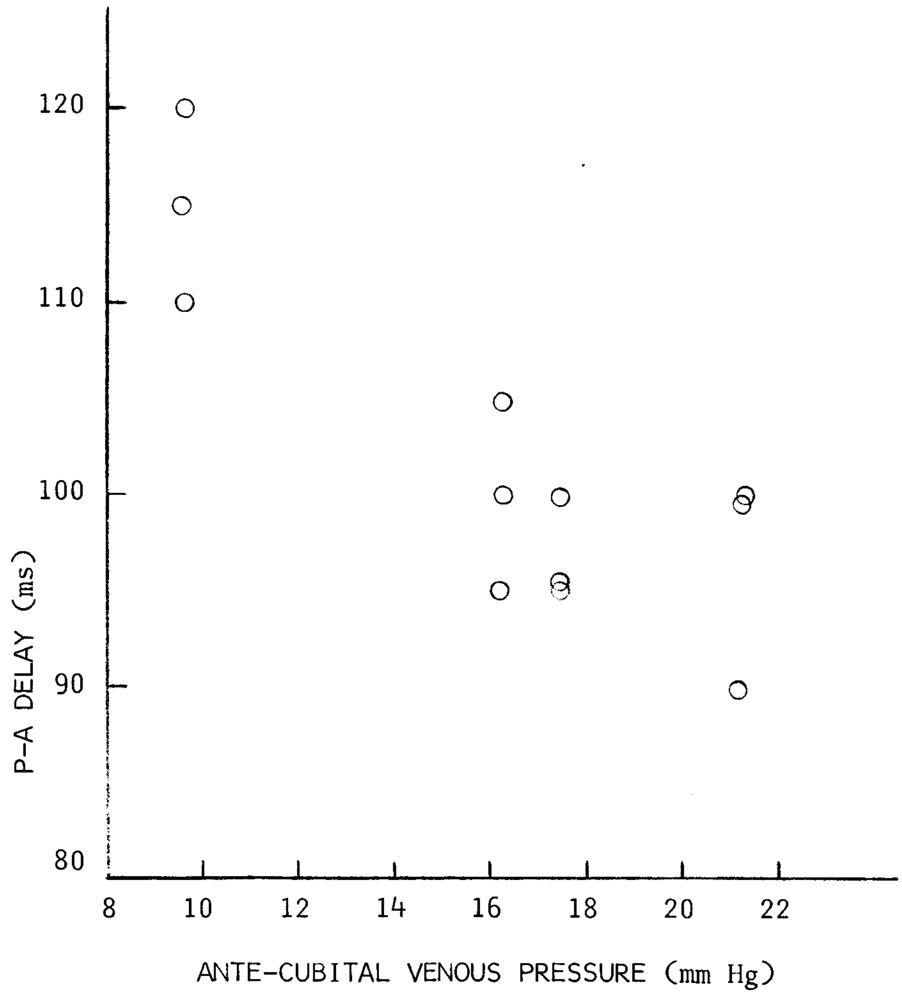

FIGURE B-8 <u>VARIATION IN P-A INTERVAL WITH ANTE-CUBITAL PRESSURE (CUFF)</u>

variation in this interval can be attributed to the changes associated with the respiratory cycle. Further research is required to establish the validity of this method as well as its true explanation in terms of pulse wave velocity. Calculated pulse wave velocity, not taking into account the 30-40 msec electro-mechanical delay between the P wave and the atrial contraction, yields PWV of the order of 5 meters/sec, which is considered quite high for any part of the venous system. In addition certain practical problems are involved with automatic monitoring of P-A interval. These include: controlling for time in the respiratory cycle, measuring the time occurance of the A wave and detecting it automatically, and use of peak detectors or cross correlators to determine the P-A interval. These problems must be solved if this technique is ever to be a useful practical monitoring method.

B.4 Venous Wave Velocity

Experiment: Venous Wave Velocity at Low Distending Pressure.

Investigator: Dr. E. O. Attinger

Method: A pressure pulse was produced by sudden injection of 0.5 ml in excised venous segments of 10 cm length, and pressure was continuously monitored at both ends by means of Statham P 23 Db pressure transducers. These experiments were carried out at various distending pressures as illustrated in Figures B-9 and B-10. Particular care was taken to maintain a uniform cross section over the measuring distance.

Results: Figure B-9 shows the pressure dependence of the velocity for the experimental data as well as for the values calculated (Equation (A.11) in Appendix A). Values for radius and wall thickness were obtained at each pressure level and E calculated for the respective pressure range, using the results of Equation (A.9) in Appendix A.

It will be seen that the experimental values are nearly twice as large as those predicted from the theory (See Appendix A, Equation A.11). Figure B-10 shows the changes in wave velocity, perimeter and cross sectional shape as a function of pressure for the low pressure range. Note that over this pressure range the wave velocity changes linearly with pressure, but that the relationship becomes exponential at higher pressure ranges. These relationships are likely to be different in intact veins, where the shape of the cross section varies with distance (partial collapse), "venous tone" changes and where valves are present.

MEASURED WAVE VOLOCITY (m/sec), PERIMETER (cm) AND RATIO OF THE MAJOR AND MINOR SEMIAXIS (a/b) AS A FUNCTION OF DISTENDING PRESSURE (cm H_2O) IN THE LOW PRESSURE RANGE.

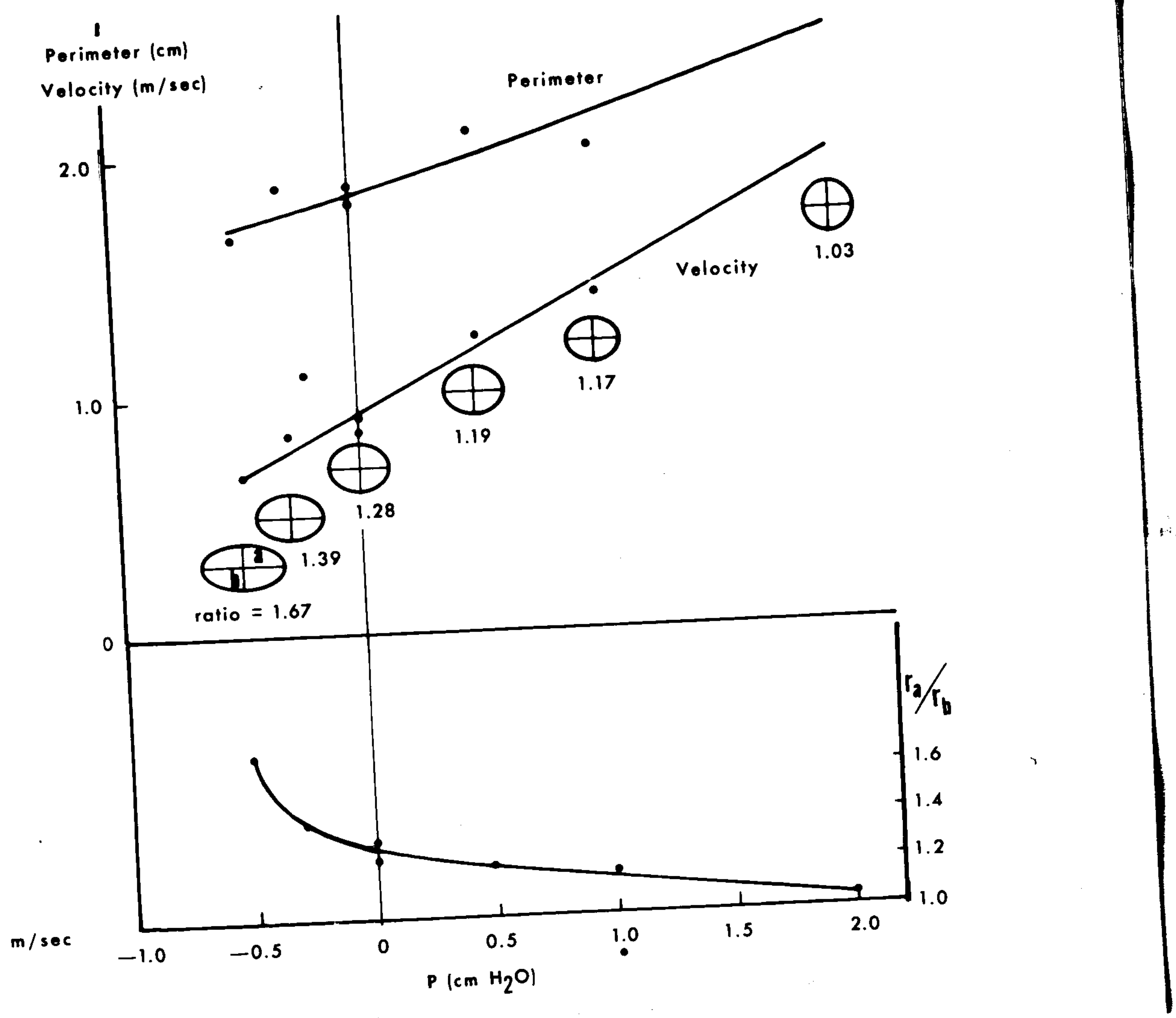

FIGURE B-9 WAVE VELOCITY AND GEOMETRY vs PRESSURE IN AN EXCISED VEIN

WAVE VELOCITY (m/sec) vs TRANSMURAL PRESSURE (cm H_2O):
CALCULATED AND EXPERIMENTAL VALUES

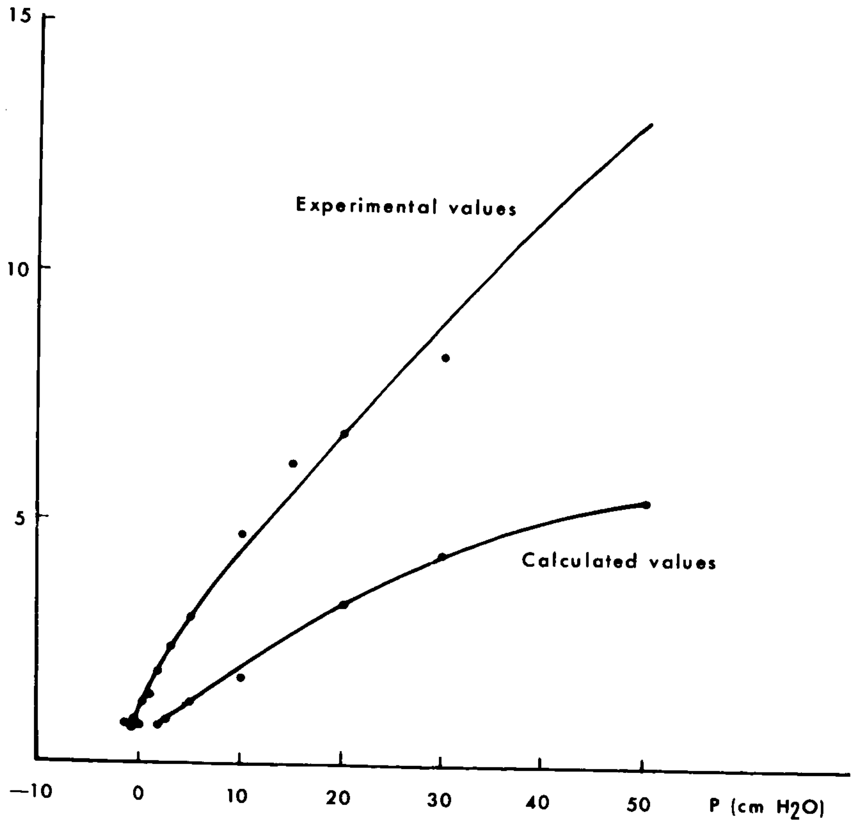

FIGURE B-10 <u>WAVE VELOCITY vs PRESSURE IN AN EXCISED VEIN</u>

B.5 Relationship Between Episcleral and Central Venous Pressure

Experiment: Determination of Relation Between Episcleral Venous Pressure and Central Venous Pressure in Monkeys.

Investigator: Dr. C. Kupfer

Methods: Rhesus monkeys of two to three kilograms weight were anethetized with 60 mg pentobarbital per kilogram body weight and artifically breathed on a respirator following endotracheal incubation. The monkey was heparinized with 1000 units per kilogram body weight and the facial artery, jugular vein (approximately 3 cm above the right atrium) and an episcleral vein on the same side as the jugular vein were canulated. In addition, the anterior chamber was also canulated and the intraocular pressure monitored. A sphygmomanometer cuff was placed around the chest of the monkey and inflated from zero to 30 mm of mercury. In this fashion, an increase in intrathoracic pressure would decrease venous return and produce an increase in central venous pressure. Recording both jugular vein and episcleral venous pressure as the two dependent variables would then permit a correlation between these two pressures. Each experiment took approximately two hours and consisted of a stepwise increase in intrathoracic pressure with appropriate time (approximately 5-10 minutes) for the venous pressure to stabilize at each new steady state. The pressures were recorded using a Grass polygraph. Measurements were made on seven monkeys.

Results: Figure B-11 presents the data on five experiments in which systemic arterial pressure as measured in the facial artery remained constant during the course of the experiment. There is a direct linear relationship between jugular and episcleral venous pressure in the ranges of pressures recorded. Although,

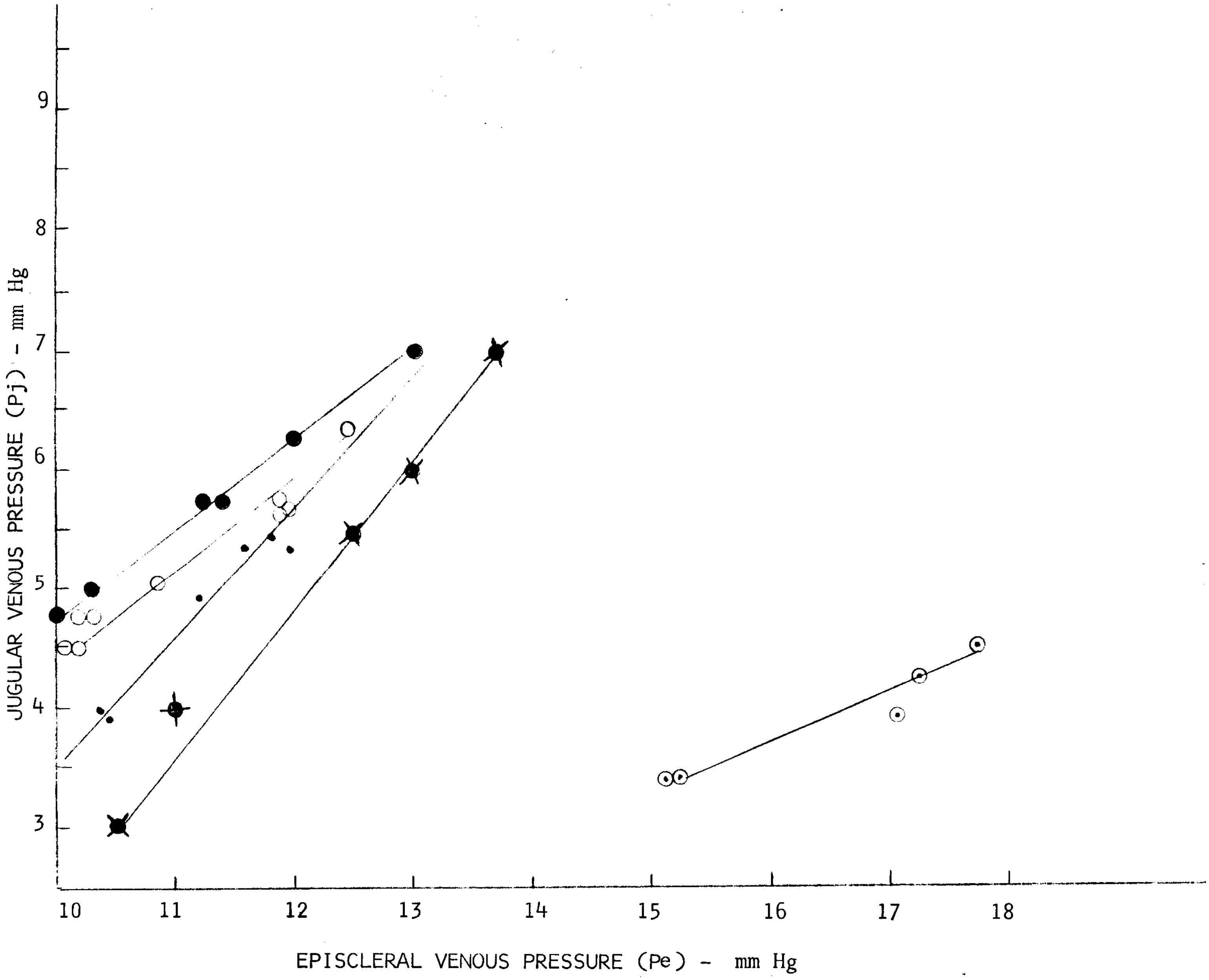

FIGURE B-11 JUGULAR AND EPISCLERAL VENOUS PRESSURE WITH CONSTANT ARTERIAL PRESSURE intraocular pressure also increased with an increasing episcleral venous pressure, it appeared that a new steady state of intraocular pressure often took from 20-30 minutes to be established and, therefore, the amount increase was too erratic in the shorter periods used in the experiments to await stabilization of venous pressure measurements. Of interest is Figure B-12 in which two experiments are plotted. In these two cases arterial pressure began to fall as intrathoracic pressure was increased. It is now noted that the rise in episcleral venous pressure is accompanied by a progressive fall in jugular venous pressure.

Discussion: In the presence of a constant arterial pressure both jugular and episcleral venous pressure increase with an increase in intrathoracic pressure. The two are related to each other in a linear fashion. This would permit the use of episcleral venous pressure as a general indicator of jugular venous pressure in the presence of constant arterial pressure. However, if arterial pressure falls, this is accompanied by a decrease in jugular venous pressure despite the fact that episcleral venous pressure still rises as a result of the increased intrathoracic pressure. Under these circumstances episcleral venous pressure is no longer a good indicator of central jugular venous pressure.

Conclusions: The purpose of these experiments was to test the feasibility of using the episcleral venous pressure determination as an indication of changes in central venous pressure. Episcleral venous pressure would be a valuable measurement because the episcleral veins are readily accessible and a non-invasive technique has been developed. It is apparent that venous pressure is affected by many factors one of which is systemic arterial pressure as indicated in these series of experiments. Consequently, unless arterial pressure is constantly monitered and found to be unchanged, episcleral venous pressure cannot be considered a good index of central venous pressure.

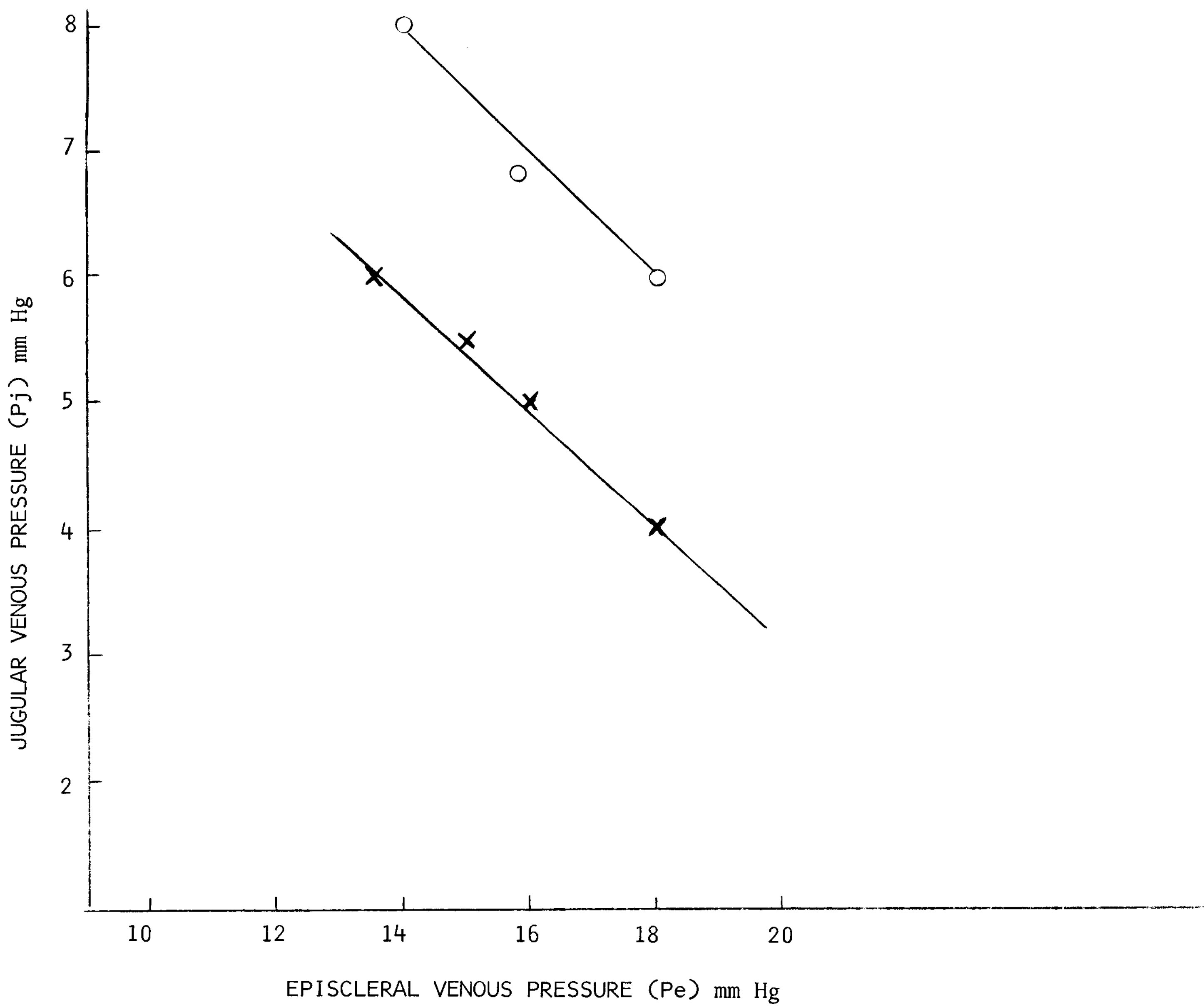

FIGURE B-12 JUGULAR AND EPISCLERAL VENOUS PRESSURE WITH FALLING ARTERIAL PRESSURE

B.6 Peripheral A Wave Obliteration

Experiment: Detection of Peripheral A Wave in the Antecubital Space and its Obliteration by a Venous Occluding Cuff.

Investigator: Dr. I.F.S. Mackay

Methods: A resting human subject supine at Trendelenburg position of 21 degrees was tested. Augmented, inverted lead III of the electrocardiogram was recorded. A volume sensor consisting of a small fluid filled balloon connected to a low volume displacement pressure transducer was placed over the antecubital space. A specially designed plastic venous occluding pressure cuff was placed around the arm. The occluding cuff was inflated slowly and deflated slowly and its effect on the contour of the peripheral A wave at the antecubital space noted.

Results: A distinct wave, the peak of which occurred 0.2 seconds after the peak of the P wave of the electrocardiogram, was easily detected. (See Figure B-13). The wave was noted to disappear with cuff pressures rising above expected venous pressure and to reappear with falling cuff pressures below expected venous pressures.

Conclusions: It was concluded that peripheral A wave detection was feasible with existing equipment and that it might be combined with superficial venous occlusion to determine venous pressure noninvasively.

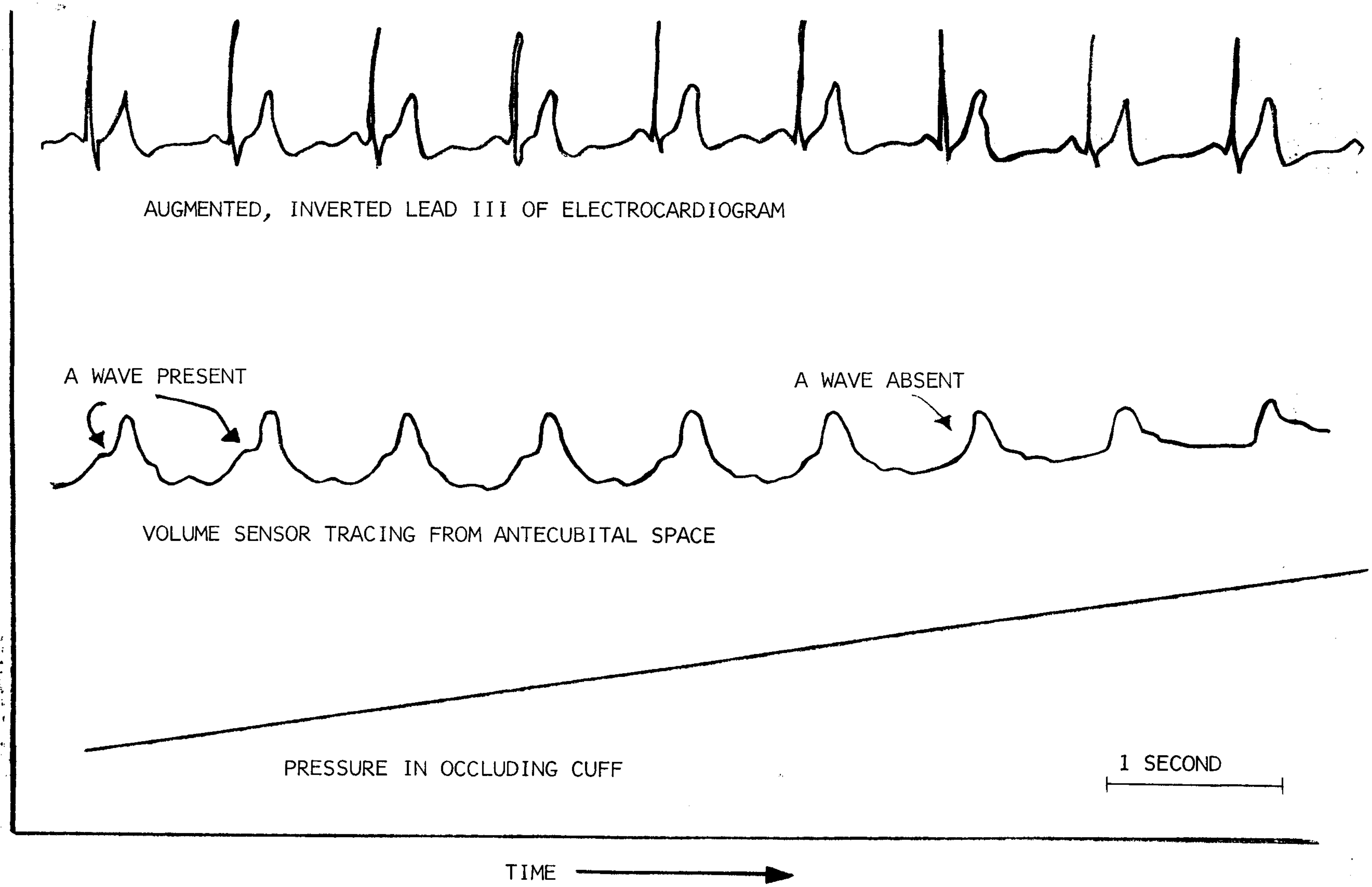

FIGURE B-13 EKG ANTECUBITAL PRESSURE AND OCCLUDING CUFF PRESSURE vs TIME

B.7 Volume Pulse Modification with an Occluding Cuff

Experiment: Noninvasive Estimation of Venous Pressure of the Forearm Using Forearm Volume Pulse and Arm Occluding Cuff.

Investigator: Dr. I.F.S. Mackay

Methods: A human subject was placed on a tilt table and an arm placed horizontal. A standard blood pressure cuff was placed on the arm and volume pulse recorder placed on the forearm. The tilt table was then placed in the following positions: 24° head down, 5° head down and 6° head up. The pressure in the arm cuff was increased at a constant rate and the forearm volume pulse recorded. The endpoint was taken as the point where the declining limb of the pulse became flat.

Results: As the cuff pressure increased the volume of the forearm began to rise and with each beat the declining limb of the volume pulse became more horizontal. The pressure in the arm cuff at which the volume pulse decline became flat is given below.

24° head down	14.0 mm Hg
5° " "	9.7 " "
6° " up	3.5 " "

The recordings from which these values were obtained are presented in Figure B-14.

Conclusions: This method gives a good endpoint for venous pressure.. It is probably the maximal venous pressure beneath the occluding cuff and differs from the true pressure by a skin factor which would have to be determined experimentally. As the occluding pressure is increased it first occludes the superficial veins and

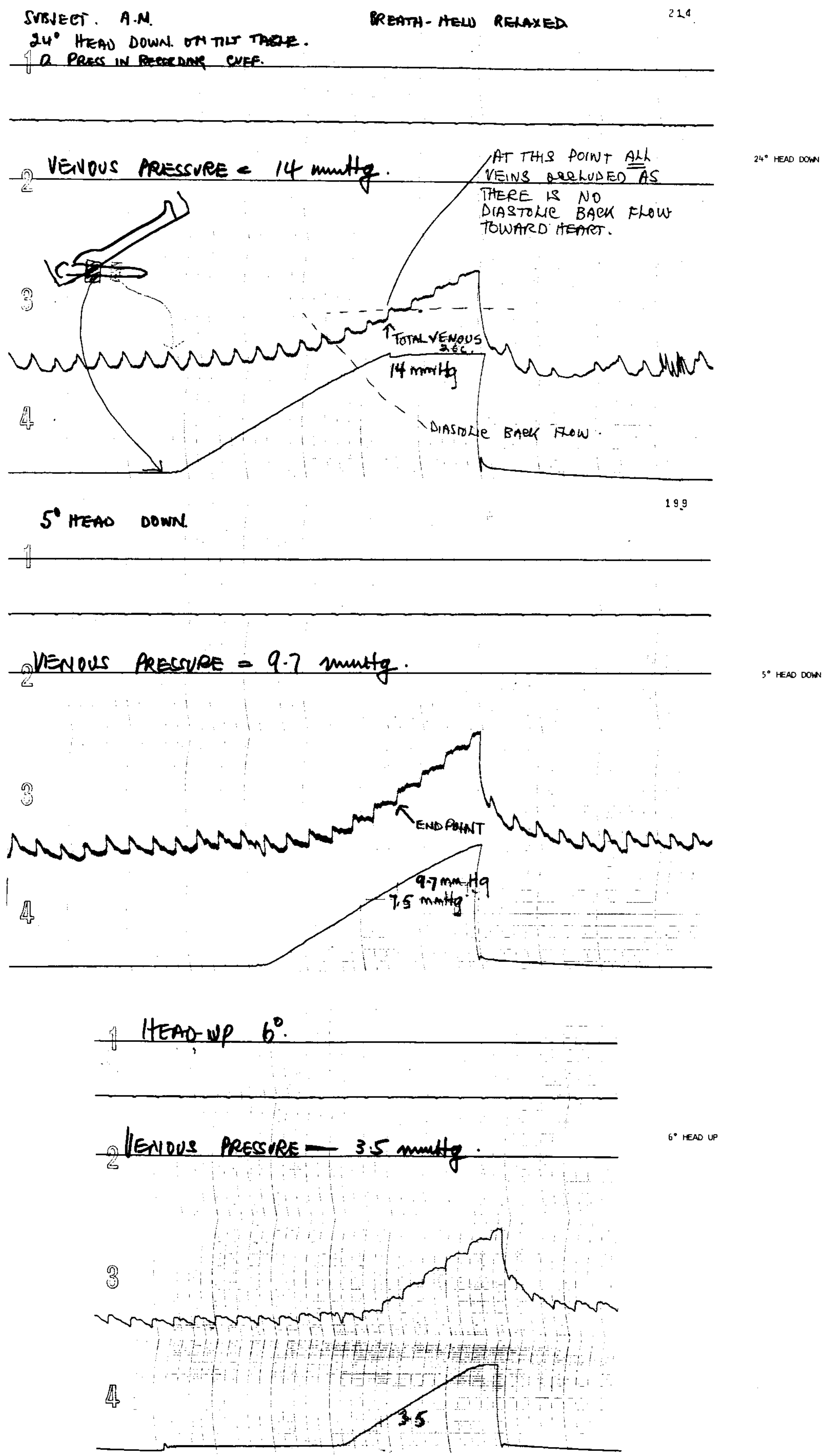

FIGURE B-14 VOLUME PULSE MODIFICATION WITH AN OCCLUDING CUFF the volume begins to increase. As the pressure increases, more and deeper veins are collapsed until the pulse looses the declining portion of its curve. At that point the volume increases due to the distention of all the veins. If future experiments showed this endpoint to be more reproducible than the first volume change, it would be a useful alternative to offer venous occlusion plethysmography.

APPENDIX C

ANNOTATED BIBLIOGRAPHY - NONINVASIVE VENOUS PRESSURE MEASUREMENT

This annotated bibliography reviews the most important articles covered in our literature survey dealing with noninvasive techniques for venous pressure measurement. It is heavily slanted towards the references relevant to the most promising techniques we have found, and therefore, does not include excessive discussions of articles on the various blind alleys which inevitably occur in a search for new techniques. The annotated bibliography is augmented by the total bibliography of Appendix D, which includes many articles which are clearly related to the study and which will be of interest to workers delving further into this area, but which either overlap other articles or were not considered sufficiently important to include in an annotated bibliography of a useful size. These articles were culled from an original reading list of over 600 articles.

In addition to a conventional library literature search and the use of general indexing (Index Medicus, Engineering Index, etc.) and specialized indexing (Aerospace Medicine Abstracts, Journal of Aerospace Medicine, etc.), we were greatly aided by two computer-generated literature searches. One of these, entitled "Noninvasive Techniques for Measuring Venous Pressure and Blood Flow Velocity" which was compiled by Dr. R. Gurd of Indiana University and containing 231 listings, was provided to us by Dr. William Z. Leavitt of the NASA Electronics Research Center. The second, a computerized literature survey to our specifications, was compiled by MEDLARS, a service of the National Library of Medicine. This latter listed 300 articles, many of which proved to be quite valuable. In addition, many of the older important references were brought to our attention by the prompt and overwhelming response to our questionnaire, and also in the course of conversations and visits with recognized investigators in the area.

The first five topics for the annotated bibliography correspond to five of the measurement techniques given serious consideration in our study. These are limb venous occlusion plethysmography, digital venous occlusion plethysmography, superficial vein pressure chamber, pulse wave velocity, and intraocular pressure (tonography). The final section on venous dynamics refers to the physiological questions of what can be measured, what its significance is, and what stresses can be applied to the system rather than the techniques for making these measurements. All of the annotated articles are included in the total bibliography of Appendix D.

C.1 Limb Venous Occlusion Plethysmography

When the return of venous blood from a limb is obstructed by occlusion, the limb increases in volume (2, 67). This volume change can be measured with a plethysmograph and the rate of volume used as a measure of blood flow into the limb. If the occluding pressure is gradually increased, the pressure at which the volume first shows a net increase is a measure of the effective venous pressure (207). If the occluding pressure is further raised, the ratio of change in pressure for a change in volume indicates the venous tone (36, 176). Thus, venous occlusion plethysmography can be used to measure venous pressure, venous tone and blood inflow.

The plethysmographic method used would depend on the information required. If venous pressure alone were needed, a simple cuff with any method for detecting volume change could be used. If skin venous pressure was to be measured, a hand or finger volume measurement would be required. If muscle venous pressure was needed, a forearm or calf measurement would be indicated. On the other hand, if the goal included measurement of venous tone, a fairly accurate volume method would be needed to derive the necessary absolute volume and pressure measurements. The plethysmographic methods are both direct and absolute and are also indirect and relative (109). The direct methods are water and air displacement plethysmography and the indirect ones include strain gauge, impedance, capacitance, photo, and thermal plethysmography as well as Doppler shift techniques.

Water displacement plethysmography is a standard method for measuring volume change with venous occlusion (94). The segment to be measured is placed inside a water filled container or sleeve and volume changes measured by the volume of water displaced. The advantage of the technique is that it measures absolute volume changes using a noncompressible medium. Its disadvantages include water pressure on the segment under gravity conditions and the imposition of a constant temperature about the segment.

Air displacement plethysmography uses air rather than water as the displaced medium. The method overcomes the pressure disadvantage of the water method and allows the limb temperature to vary. The main disadvantage is the effect of temperature on a compressible medium which causes a thermal drift in the baseline (105, 133, 205).

Strain gauge plethysmography measures the variation in girth. The percentage change of girth is equal to one half the percentage change in volume for small changes (202, 51). A rubber tube is filled with mercury and when it is stretched, its electrical resistance changes. When the tube is wrapped around a limb segment, the change measures the limb circumference. Changes in the baseline with temperature variation are cancelled electrically. The main advantage is the method's simplicity. The disadvantages are its need for calibration each time it is used and the fact it gives a relative value for volume change.

Impedance plethysmography depends on a limb segment acting as a resistance for an alternating current. The volume of such a conductor is calculated from knowledge of its conductance (G), specific resistivity (ρ) and length (1) by the relation Volume = $\rho G1^2$ (155). The basic assumptions of this method have recently been criticized (100). This method gives relative values and requires calibration each time it is used.

Capacitance plethysmography uses the skin of a limb segment and a fixed wire screen cage about the limb segment as the plates of a condenser (106). As the skin moves toward the fixed screen, the capacitance change modifies the frequency of an oscillator circuit. The system can be calibrated with a balloon between the screen and skin. This technique involves skin contact only over the small area where the grounding skin electrode is placed but lacks absolute volume measurement and requires calibration before each use.

Photoplethysmography measures the change in skin transmission by measuring the amount of light transmitted through a digit or across a segment of skin on a limb. The opacity of the skin varies with the flow of blood through it. The resulting pulse pattern gives a relative change in blood volume beneath the sensor. Light source and sensor placement are critical and the result is a relative value.

Thermal plethysmographic methods of estimating flow depend on the blood flow varying the thermal convection and conduction of tissue. Those variables are measured using a heat source and temperature sensing element a known distance apart. The values obtained are relative and the heat has a direct effect on the local blood flow (149).

The transcutaneous Doppler flow detector method measures blood velocity, and information on vessel size would be needed to calculate volume (168).

2. Alexander, R. S.: The Peripheral Venous System. Handbook of Physiology, Circulation. Washington, D.C.: American Physiological Society, 1963 Vol. II, Section 2, Chapter 31, 1075.

A general discussion of the anatomy and physiology of the veins along with methods of assessment of their motor activity. Veins differ from arteries in that they have little elastic tissue, and the wall is composed mostly of adventitia. Valves allow this low energy, high volume system to propel blood along. Although venous pressure is the most often measured parameter, venous tone is a more useful physiologic value. Veins tend to collapse when volume falls and distend when volume increases, therefore pressure does not reflect motor activity as it would with arteries. Plots of venous pressure versus venous volume reveal a series of "s" shaped curves which differ from each other as a function of the degree of constriction or venous motor tone. Noninvasive methods for measuring venous tone include pulse measurements and observations on venous distensibility using plethysmographic methods. The author lists a summary of venomotor responses to various conditions and drugs.

67. Formel. P. F. and Doyle, J. T.: Rationale of Venous Occlusion Plethysmography. Circulation Research 5:354, 1957.

A series of experiments on humans showing that water displacement plethysmography and venous occlusion fulfill the requirements of 1. complete venous tamponade 2. no reduction in initial arterial inflow, and 3. trapped blood causing the segment under study to swell proportionally to the rate of arterial inflow. It was their opinion that venous occlusion plethysmography permitted the satisfactory estimation of segmental forearm flow under normal hemodynamic conditions.

207. Wood, J. E. and Eckstein, J.W.: A Tandem Forearm Plethysmograph for Study of Acute Responses of the Peripheral Veins of Man. Journal Clin. Invest. 37:41, 1958.

A human study using a double chamber water displacement plethysmograph along with invasive measurement of venous pressure. The proximal chamber acted to distend the veins in the distal chamber so that the volume change in the segment occured at the same time as the measured intravenous pressure. Peripheral venous pressure--venous volume curves were constructed under various hemodynamic conditions. The effective venous pressure was the occluding pressure at which the first change in volume occurred.

36. Brown, E., Greenfield, D.M., Goei, J. S., and Plassaras, G.: Filling and Emptying of the Low-Pressure Blood Vessels of the Human Forearm. Journal of Applied Physiology 21:573, 1966.

Human study in which forearm volume was measured in a water filled plethysmograph pressurized to 20 mm Hg while venous pressure was measured invasively in two veins. The congesting cuff was inflated at controlled rates and the response in the veins and plethysmograph noted. Slow inflating or deflating of the cuff allowed evaluation of pressure in superficial veins and might make distensibility measurements more reliable. Ideal inflation rate was less than 0.25 mm Hg/sec and deflation rate 1 mm Hg sec.

176. Sharpey-Schafer, E. P.: Venous Tone. Brit. Med. Journal 5267:1589, 1961.

Using a plethysmograph and invasive measurement of venous pressure in over 200 humans he reported on the variations in venous tone which he defined as the change in pressure/time divided by the change in volume/time. On going from supine to upright position the increase was from 1.5 to 2.5. Valsalva increased it from 2.5 to 7.5, phlebotomy of 450 ml caused an increase from 1.5 to 3.0 and ganglion blockade caused a drop from 2.5 to 1.0.

109. Hyman, C. and Winsor, T.: History of Plethysmography. Journal of Cardiovascular Surgery 2:506, 1961.

A discussion of the methods evolved through the years. Displacement methods depend on a rigid compartment in which there is no resistance to flow of the displaced medium. The volume sensor should detect only volume changes. Methods for measurement of volume change include weight, bellows, spirometer, electrical transduction, photoelectric, photographic, and mechanical movement in a tube. The authors felt the occluding cuff should be 6-9 cm wide and should be placed close to the plethysmograph. They felt impedance and photoplethysmographic methods failed to show an increase in volume with venous occlusion. The mercury in rubber strain gauge method was felt to be satisfactory and the capacitance method did not interfere with thermal exchange in the segment.

94. Greenfield, A.D.M.: Venous Occlusion Plethysmography. Methods in Medical Research 8:293, 1960.

A discussion of the water-filled plethysmograph and venous occlusion. He stated flow measurements are best done when the whole volume under study is included in the plethysmograph. The occluding or collecting cuff should be raised to the pressure that gives the highest flow thus insuring that it is not so loose as to allow the escape of venous blood. The pressure should be reached rapidly. The limb under study should be positioned so as to collapse the veins. He suggested the mercury in rubber strain gauge method when conditions preclude use of the water displacement method. The slope used to calculate flow is measured from the volume when the occluding cuff was applied and the author cautioned against inclusion of the jump from the cuff squeezing blood into the plethysmograph, the so-called "cuff artifact."

105. Hyman, C. and Winsor, T.: The Application of the Segmental Plethysmograph to the Measurement of Blood Flow Through the Limbs of Human Beings. Am. Journal of Cardiology 6:667, 1960

An evaluation of an air filled, cone shaped section made from a cuff of light dental dam and a shell of nondistensible leather which acted to record volume changes. It was linear when related to a standard water filled plethysmograph over the range of 4-20 cc/100 ml tissue/min. It could be used on moving subjects.

133. Ludbrook, J. and Loughlin, J.: Regulations of Volume in Postarteriolar Vessels of the Lower Limb. Amer. Heart Journal 67:493, 1964.

An air filled plethysmograph on the calf and another on the foot were used to measure the changes in volume as humans were placed in different positions on a tilt table. Venous pressure was taken as being the difference in height between the heart and the middle of the plethysmograph. Passive changes in venous volume occured in the veins in the calf muscles. In general the superficial veins acted like innervated smooth muscle tubes and the deep veins like passive tubes.

205. Winsor, T.: Clinical Plethysmography: Part I. An Improved Direct Writing Plethysmograph: Part II. Plethysmographic Procedures of Clinical Importance. Angiology 4:134, 1953.

Human studies of blood flow, pulse volumes, skin temperatures of the digits and limb segments. Recording equipment consisted of three electronic segmental limb air displacement plethysmographs, three electronic digital air displacement plethysmographs and three temperature measuring thermistors. Measurements were also made after inducing vasodilation.

202. Whitney, R. J.: The Measurement of Volume Changes in Human Limbs. Journal of Physiology 121:1, 1953.

Description of the mercury-in-rubber strain gauge for measuring volume changes. He calculated that the percent change in girth was equal to one half the comparable change in volume. This is only true for small changes in the order of 5% or less. He presents an argument to prove it is also true of non cylindrical shapes. At blood flow rates of from 1.5 to 7.0 cc/100 ml tissue/min this method agreed with water displacement plethysmography. Calibration is based on recording the resistance change induced by stretching the tube a known percentage of its total length. In that way volume change is directly related to resistance change.

51. Clarke, R. S. J. and Hellon, R. F.: Venous Collection in Forearm and Hand Measured by the Strain Gauge and Volume Plethysmograph. Clin. Science 16:103, 1957.

A comparison of mercury in rubber strain gauge on one arm with water displacement plethysmography on the other. The two correlated well if the strain gauge was placed in the middle of the forearm.

155. Nyboer, J.: Plethysmograph: Impedance. Medical Physics (O. Glasser, ed.) Chicago Year Book, 1950.

Using the electrical properties of tissues which include ionic conductance, semiconductance and dielectric properties the author designed and used instruments to measure volume changes as a function of resistive and reactive impedance to an alternating current applied across the segment with two electrodes, and sensed with an additional pair.

100. Hill, R. V., Janson, J. C. and Fling, J.L.: Electrical Impedance Plethysmography: A Critical Analysis. Journal of Applied Physiology 22:161, 1967.

Using a tetrapolar system and commercially available instruments the authors felt the "impdeance signal" was due to uncalibratable pressure strain gauge effects on the plethysmograph electrodes and that the less sophisticated instruments showed the best "pseudo-signals". They felt that calibratable pressure strain gauges could do a better job of following tissue pressure effects of cardio-hemodynamic events than impedance plethysmographs.

106. Hyman, C., Burnap, D., and Figar, S. Bilateral Differences in Forearm Blood Flow as Measured with Capacitance Plethysmograph. Journal of Applied Physiology 18:997, 1963.

A human study comparing the air plethysmograph developed by Hyman with the electrocapacitance plethysmograph developed by Figar. The two were found to have a linear relationship over the flow ranges of 1-20 cc/100 ml tissue/min in six humans. The electrocapacitance measurements were made with a cone shaped cage that could be used on the calf or on an arm segment. It consisted of an insulated inner "live" screen which formed one plate of a capacitor and an outer uninsulated screen which acted as a shield and along with the skin formed the ground plate.

198. Weinman, J. and Manoach, M.: A Photoelectric Approach to the Study of Peripheral Circulation. Amer. Heart Journal 63:219, 1962.

Evaluation of the method of measuring relative changes in blood flow by measuring the transmission of light from incandescent lamps to photoconductive cells across skin or through a digit. Blood volume pulse was measured with an AC amplifier and blood volume with a DC amplifier. The methods are simple and the sensors small. Method measures only relative changes.

54. DePater, L., Vanden Berg, J. and Bueno, A.A.: A Very Sensitive Photoplethysmograph Using Scattered Light and a Photosensitive Resistance. Acta Physiol. & Pharmacol. Neerlandica 10:378, 1962.

A series of studies using measurement of scattered light and the derivation of volume and flow from the observed pulses. Application pressure was found to be critical and should be between 10 and 40 mm Hg. Measurements were limited to changes in skin blood flow.

149. Mian, E. U. Flow-Metric Values in Peripheral Vascular Diseases. Angiologica (Basel) 2:107, 1965.

Measurement of skin flow based on the principle that the convective current through a tissue is related to the blood flow. The author derived a thermophoretic index which he felt was proportional to flow. It was related to base flow by comparison with values obtained with heating the area and by arterial compression for 5-10 minutes.

168. Rushmer, R. F., Baker, D. W. and Stegall, H.F.: Transcutaneous Doppler Flow Detection as a Nondestructive Technique. Journal of Applied Physiology 21:554, 1966.

Description of an ultrasonic flowmeter which can continuously indicate changing blood velocity in superficial or deep vessels. The direction of flow is not recorded unless a double unit is employed. The velocities measured varied from 5-60 cm/sec.

In addition to the above annotated articles, the following references also contain relevent information: (16, 25, 26, 29, 27, 48, 34, 53, 88, 52, 63, 65, 66, 75, 92, 101, 107, 124, 132, 139, 146, 144, 158, 220, 79, 80, 117, 57, 64, 62, 173, 99, 183, 177, 172, 192, 196, 162, 190, 9, 102, 50, 35, 141).

C.2 Digital Plethysmography

As in a limb, the volume of blood contained in the veins of a finger or toe will increase if the venous flow is obstructed. Venous occlusion plethysmography has been used for over 30 years to measure blood flow in digits. Efforts in this field have been largely devoted to improving the methods of detecting volume changes (34).

The earliest method, still in use, employs an air or water-filled rigid capsule, tightly sealed around the finger-tip (42). The change in volume of the finger was at one time detected by using a bellows, stylus and kymograph, but more recently electronic transducers for this purpose have been introduced (113).

The electrical impedance between two points or rings on the finger has been used as an index of volume (162). This method has been criticized as one which may be seriously compromised by factors other than volume change (100).

The changes in the temperature of the digit during venous occlusion has been interpreted as flow, but this technique has not found favor among contemporary investigators (16, 48, 93). "Strain gauge" plethysmography of limbs has been in use since 1953 and successfully applied to digits at least as early as 1958. In this method it is the change in girth of the digit which is directly measured; the relationship between girth and volume has been carefully rationalized so that valid inferences about volume changes can be made (59, 60, 61).

Photoelectric plethysmography has as long a history as do the other methods, and modern components have made it increasingly popular (54). In this method, use is made of the difference in reflectivity of engorged and normal tissue so that volume changes can be inferred from color changes. The quantitative validity of the method is asserted more by good correlation with direct methods or flow measurement than by an analysis of the optical properties of skin and blood (199). As a qualitative measure it has many advantages (54).

As advances have occurred in each of these inferential methods, investigators have compared it to others (34, 48, 94). Most of these comparative studies have assumed that the results of volume plethysmography may be considered the true values, but that its lack of convenience justified the search for other valid means.

16. Arab, M.M.: A Calorimetric Study of the Digital Blood Flow in Normal Subjects and in Some Abnormal Vascular and Nonvascular Conditions. Guy Hosp. Rep. 114:45, 1963.

Describes a thermocouple monitored finger calorimeter. Finds finger blood flow varies from almost 30 to 10 ml/min/100 ml tissue as fully dilated vessels constrict.

34. Brown, C. C. et al.: Techniques of Plethysmography. Psycholophysiology 1:253, 1965.

Compares volume, electrical impedance strain gauge and photoplethysmography. Gives virtues and faults for each, noting that volume plethysmography is not without its characteristic errors. Describes use of optic fibers to minimize heating of tissue in photoplethysmography.

42. Burch, G. E.: Digital Plethysmography. New York: Grune & Stratton, Inc. 1964.

Full rationale of digital volume measurements. Describes technique and interpretation of "rheoplethysmography", a method of obtaining both the inflow and outflow of blood during a typical cardiac cycle.

48. Burger, H.C. et al.: Comparison of Some Methods for Measuring Peripheral Blood Flow. Phys. in Med. & Biol. 4:168, 1959.

Compares volume plethysmography to strain gauge, radioactive dilution and thermal methods of estimating blood flow. Finds thermal method has low accuracy, dilution requires invasive procedure, strain gauge gives good results and is practical. Points out that volume plethysmography of the digits has conflicting requirements of air-tightness and rigidity of the enclosure as well as of non-interference with the enclosed tissue.

54. De Pater, L. Vanden Berg, J. and Bueno, A. A.: A Very Sensitive Photoplethysmograph Using Scattered Light and a Photosensitive Resistance. Acta Physiol. & Pharmacol. Neerlandica 10:378, 1962.

Describes construction and use of a small photoelectric transducer for photoplethysmography. The results of an investigation of the effect of pressure between the transducer and the finger are presented and interpreted, emphasizing the importance of this factor. No difference between transmitted light and back scattered light was found. Points out that percent change in output of photoplethysmograph arising from pulsations of the finger is similar to that of volume plethysmography.

59. Eagen, C. J.: The Construction of a Small Mercury Strain Gauge. Alaskan Air Command, AAL-TN-60-14, 1960.

60. Eagen, C. J.: The Mercury Gauge Method of Digital Plethysmography. Alaskan Air Command, AAL-TN-60-15, 1961.

61. Eagen C. J.: The Physics of the Mercury Strain Gauge and of its Use in Digital Plethysmography. Alaskan Air Command, AAL-TN-60-17, 1961.

A complete description, analysis and technique for strain gauge plethysmography of fingers and toes. Discusses construction, calibration, circuits and theory of the mercury-in-rubber-tubing type of gauge.

100. Hill, R. V., Janson, J.C. and Fling, J. L.: Electrical Impedance Plethysmography: A Critical Analysis. Journal of Applied Physiology 22:161, 1967.

Suggests that electrical impedance plethysmography has often been misinterpreted, in that changes in electrode-to-tissue impedance have been thought to be caused solely by volume changes.

94. Greenfield, A.D.M.: Venous Occlusion Plethysmography. Methods in Medical Research 8:293, 1960.

Discusses volume and strain gauge plethysmography, giving practical suggestions of ways to avoid errors.

93. Greenfield, A.D.M.: Peripheral Blood Flow by Calorimetry. Methods in Medical Research 8:302, 1960.

Illustrates the simplicity and comfort of thermal measurement of finger

blood flow, but grants that it is a relative measure and incapable of following brief changes. The condition of the venous system is not revealed by this method.

113. Karpman, H. L., Payne, J. H., and Winsor, T.: A Practical Systematic Laboratory Approach to the Study of Peripheral Circulation. Annals of Int. Med. 53(2):306, 1960.

A thorough description of the clinical use of a commercially available volume plethysmograph. Studies were made of both limbs and digits in health and disease. Temperature measurements were also made. The modification of plethysmographic response due to vascular disorders of both the arterial and the venous system are discussed.

162. Powers, S. R., Schaffer, C., Boba, A., and Nakamura, Y.: Physical and Biologic Factors in Impedance Plethysmography. Surgery 1:53, 1958.

An attempt to make electrical impedance plethysmography more accurate by taking greater account on the non-resistive changes than did earlier investigators. An *in vitro* calibrator was devised to test the method, after which further validation was done on disarticulated dog's legs. It is claimed that measurements made on human toes give a good index of skin blood flow but do not include muscle blood flow.

199. Weinman, J. and Ben-Yaakov, S.: The Physical and Physiological Basis of Photoplethysmography. Digest of the 6th International Conference on Medical Electronics and Biological Engineering, Tokyo, 1965, p. 54.

Treats the principles of the technique, discussing the optical properties of tissue and blood, the effects of oxygen saturation and hemolysis and the choice of photodetector. Points out that the blood volume pulses--with each cardiac cycle--are small, contain fairly high frequencies and are almost exclusively due to arterial events.whereas the blood volume--the general engorgement of the tissue--results in large signals of low frequency and are probably highly dependent on venous condition. Explains the great difficulty involved in obtaining quantitative data. Describes several unusual applications of photoplethysmography.

200. Weinman, J.: Private Communication. Letter of February 12, 1967 to Dr. James W. Dow, c/o Biosystems, Inc.

A comparison of the arterial pulse wave with a photoplethysmographic record made during a Valsalva maneuver. Also included in this letter is a record made with the photoplethysmographic transducer on a superficial vein, showing clearly the venous distension induced by the maneuver, along with the comment, "no blood volume pulses were recorded by the transducer indicating that probably no artery was 'seen' by it."

C.3 Pulse Wave Velocity

The propagation velocity of the arterial pressure pulse has been extensively investigated because of its potential use as an index of the physical properties of the vascular wall. A number of theoretical treatments have been proposed (151, 123, 11), but the agreement between theoretical and experimental data is still unsatisfactory (127, 147, 10). Therefore, the method cannot yet be used as a reliable clinical tool, although it has considerably advanced our understanding of vascular physiology. The wave velocity depends on the elastic modulus, the vessel radius and the wall thickness and each of these parameters is pressure dependent.

In the venous system the relation between these three parameters and the wave velocity are even more complex because valves are present and the veins assume a noncircular cross section at low distending pressures (164, 165). At higher distending pressures a relationship between venous pressure and wave velocity has been established (138, 13, 11). The uncertainty of venous pressure measurements alone as an index of venous function has been emphasized (2). The pulsatility of flow in the central veins, associated with atrial and respiratory activity, as well as the volume changes occuring during respiration and under various forms of stress, have been well documented (184, 32) but are still poorly understood in terms of overall cardiovascular function. Since these volume changes are frequently non-uniform (sometimes resulting in collapsed segments), their effects on wave transmission are not yet predictable.

164. **Rodenbeck, M.:** Beitrage zur Modell-Theorie des Arteriellen und Venosen Systems. Ph.D. Thesis, Karl-Marx University, Leipzig, 1963.

Arterial hemodynamics are analyzed on the basis of a tube model. The latter is characterized by anisotropic, and viscoelastic wall properties, a circular cross section and surrounded by an elastic material. Flow is laminar and the fluid is newtonian. The resulting differential equation of motion is linearized by neglecting higher order quantities. In contrast to other work in this field, longitudinal and radial displacement of the wall are considered simultaneously.

The technique yields two solutions for the propagation of the pressure wave:

a) The first solution, depending primarily on the transverse elastic modulus, corresponds to the classical relation, such as that of Moens-Korteweg.

b) The second solution describes a wave of much higher propagation velocity. Here, longitudinal displacement is larger than the radial displacement. In contrast to the first solution, the wave velocity depends primarily on the longitudinal modulus of elasticity, the longitudinal constraint (tethering) and the velocity profile of the fluid. The theoretical results indicate that the statically determined stress-strain relations cannot be used with confidence for the calculation of the wave velocity, particularly in the presence of longitudinal displacement of the tube or in the presence of stress relaxation or creep. Wall damping is considered as a series arrangement of strongly and weakly dampened components. For higher frequencies the influence of the strongly dampened part decreases, resulting in an effective smaller dynamic distensibility. Correspondingly, the wave velocity is larger than that predicted from the static modulus of elasticity. The influence of wall damping on the propagation of the pressure pulse is stressed.

The general conclusions of this section appear to be justified, since they are in agreement with experimental and theoretical data presented by other investigators (97, 23, 159, 185, 20, 18, 15, 119).

In the second part of his thesis, Rodenbeck considers venous hemodynamics. His analysis is based on a partially collapsed tube, whose wall is practically indistensible, so that pressure changes lead to changes in cross section with <u>constant</u> perimeter. The mathematical treatment leads to elliptic integrals which are solved by various approximations. He concludes that for low frequencies the difference between dynamic and elastic modulus of elasticity are negligible.

In conclusion, this work represents a most interesting theoretical development of arterial hemodynamics. However, as in the case of other sophisticated theories in this field*, it is at present not possible to determine experimentally the physiological range of values for many of the coefficients and parameters which appear in these equations. Since comparisons of experimental data with those predicted from the simpler Womersley theory show satisfactory agreement,

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* For review see: Attinger, E.O.: Analysis of Pulsatile Blood Flow, in <u>Advances in Biomedical Engineering and Medical Physics</u>, Vol. 1, John Wiley Interscience.

it appears fruitless to further refine theoretical approaches before the instrumentation necessary for the evaluation of such theories becomes available, particularly for parameters which appear as power functions in the physical formulation (i.e. radius, etc.).

Rodenbeck's analysis of the venous system represents the first attempt at a mathematical description of non-circular vessels and will be reviewed in conjunction with his other two papers.

166. Rodenbeck, M.: Voraussetzunger fur die Gultigkeit Linearer Differential Gleichungen bei Schlauchwellen. Physik Grundlagen der Medizin 1:34, 1960.

The classical equations of motion for fluid and vessel wall as well as their electrical analogs are described. The question of linearity is explored by comparing measured wave velocities with those predicted from the modulus of volume elasticity in two pressure ranges:

a) Gravity is negligible. The cross section is circular and an increase in cross section is associated with an increase in perimeter (distensible tube).

b) Gravity is not negligible. The cross section is flat and a change in cross section is associated with a change in shape while the perimeter remains constant. In this case the volume distensibility is independent of the physical properties of the wall material.

The theory is evaluated experimentally by means of rubber tubes. In the low pressure range, the wave velocity increases nearly linearly with increasing pressure. In the high pressure range, the wave velocity is relatively pressure independent.

165. Rodenbeck, M.: Modell Untersuchung zur Entstehung des Venen Pulses. Wiss. Ztschr. Karl-Marx Univers. Leipzig 15:327, 1966.

In this paper, Rodenbeck emphasizes the basic differences in the analysis of arteries and veins, in terms of pressure pulse propagation, as follows:

	Arteries	Veins
Cross Section	Circular	Non-circular (partially collapsed)
Change in cross section related to	Distensibility	Change in shape for $p < 2\rho gr$
Transmural pressure	$p > 2\rho gr$	$p \,\bar{<}\, 2\rho gr$
Dynamic changes in cross sectional area	Small with respect to mean cross section	May be large with respect to mean cross section

Neglecting flexural rigidity the author formulates an expression for the cross section as a function of pressure, and calculates from this relation the pressure dependences of the modulus of volume elasticity and wave velocity.

Although this analysis is based on a highly simplified system (no flexural rigidity, a collapsible tube resting on a flat surface, no distensibility of the wall material) it is apparent that the wave velocity is not related to the physical properties of the vessel wall for non-circular cross sections. The volume elasticity which is used for the calculation of the wave velocity, apparently corresponds essentially to a shape factor for this pressure range.

We are not aware of any experimental work which has been done in this area and which would give some indication of the validity of this theoretical treatment. We have attempted to measure the pressure-volume characteristics of veins at low distending pressures in the laboratory but have encountered serious technical difficulties.

2. Alexander, R. S.: The Peripheral Venous System. Handbook of Physiology, Circulation. Washington, D.C.: American Physiological Society, 1963, Vol. II, Section 2, Chapter 31, 1075.

Only the pertinent sections of this authoritative review will be discussed. Alexander emphasized that the lack of heavy elastic investment of the media constitutes the major structural difference between arteries and veins. (These structural particularities associated with the low distending pressures account, of course, for the easy collapsibility of the venous system. Furthermore, more or less competent valves are located throughout the venous system, not only in the largest veins as previously thought [the implication of this for the physical behavior of veins and the blood flow within is not well understood except for the most elementary analysis.]) The author stresses repeatedly that inferences about venous tone based solely on venous pressure are virtually meaningless. Large portions of the venous bed are in a state of partial collapse in which case pressures are not conditioned by vascular tone but by the interplay of extravascular pressures with intravascular dynamics. The small magnitude of venous pressure further complicates the problem since an adequate definition of zero reference levels is often extremely difficult. In situations where venomotor activity exhibits any significant changes, there are usually associated changes in cardiac activity and blood flow which produce passive changes in venous pressure, thus further confounding any valid assessment of venous tone. The present evidence on the distribution of venous capacity is confusing. On one hand it is estimated that the venous system comprises 70-75% of the vascular volume, 50-60% in veins with a diameter greater than 1 mm (215, 124). On the other hand, Knisely, et al (217). found 80% of the blood volume in vessels with a diameter of less than 200μ . Similar data have also been presented by M. Wiedeman (Proc. 18 ACEMB, 1965).

Finally, the author discusses the changes in the distensibility patterns occuring with changes in "venous tone". In the constricted state, the pressure volume curve assumes a sigmoid shape, while in the dilated state the form is convex toward the pressure axis. (Note that these relations have been obtained primarily on excised vessels with rather large transmural pressure and are therefore difficult to relate to the physiological behavior of the venous system at low distending pressures.) Further complexities are introduced by non-uniform constriction, stress relaxation and creep.

Alexander has spent some twenty years studying the venous system and his pessimistic attitude is not to be taken lightly. It would seem that much more experimental and theoretical work is needed before the relations between stress, strain and rate of strain in the venous system are as well understood as the equivalent relations in the arterial bed.

175. Schoop, W.: Pulsatorische Druckschwankungen in den Extremitatenvenen. Ztschr. Kreislauffrschg. 9:937,1966.

This is a clinical investigation of pressures in arm and leg veins in supine man. In normals, the venous pulsations were between .1 and 2.2 mm Hg in the femoral vein and less than 0.5 mm Hg in the veins below the knee. The author concluded that the venous pulsations in the extremities are the results of venous flow changes caused by the rhythmic heart action. The pulsations are increased by right heart failure and by prolongation of the diastole. Significant centripetal pulses were observed only in aortic insufficiencies and in post-thrombotic syndromes. Large pulsations caused by retrograde pressure waves were found in patients with tricuspid insufficiency. With insufficient valves of the leg veins such pulsations can also be seen in the veins of the calf. Retrograde pressure waves in the proximal femoral vein can also be induced by atrial action.

It is not clear how the direction of the pressure propagation was determined. In the present context, the paper is only of interest because it illustrates the large variations in venous pressure pulses in normals and the possible use of these pulsations and their propagation as a diagnostic criterion. However, from the presented data, it does not seem promising to use these pulsations for a determination of the wave velocity.

151. Mirsky, I.: Wave Propagation in a Viscous Fluid Contained in an Orthothropic Elastic Tube. Report TM-874, Data Processing, Aerospace Group, Hughes Aircraft Company.

The problem is considered in connection with arterial blood flow. The results indicate an increase in the peak value of the pressure pulse and a decrease in the flow rate as the pulse propagates away from the heart. The pulse wave velocity depends mainly on the tangential modulus of elasticity of the arterial wall and anisotropy of the wall accounts in part for the reduction of longitudinal movements.

The simultaneous solution of the six homogeneous equations yields a polynomial of the 14th degree, if the Bessel function is represented in polynomial form. (This is permissible because of the physical constraints in the system; in the transcendental form there would be an infinite number of values for the wave velocity.) Mirsky considers only the lowest two values which he calculates for three hypothetical cases finding significant differences between the two velocities for the case of the anisotropic tube. Klip and Anliker (119, 10-15) have found theoretically similar arrays of wave velocities associated with different propagation modes. However, nobody has been able to measure experimentally these postulated higher propagation modes in the vascular system using pressure pulses generated by the heart. On the other hand, Landowne in his work (125) observed very high wave velocities in human arteries using an impulse for the generation of the wave. This may well represent one of these other modes, but at present it is not possible to reliably relate such modes to the physical properties of the vascular wall.

127. Landowne, M.: Pulse Wave Velocity as an Index of Arterial Elastic Characteristics. Tissue Elasticity (J. W. Remington, ed.), Amer. Physiol. Soc., 1957.

Landowne uses the simple Moens-Korteweg relationship to relate elastic modulus and wave velocity. Using data obtained in experiments with rubber tubes and umbilical arteries, he shows that:

a) The directly measured stress-strain relationship depends upon the rate of strain applied. (This is to be expected because of the viscoelastic properties of the wall material.)

b) The stress-strain relationship calculated from the wave velocity depends upon the nature of the traveling wave. For sinusoidal pressure waves, the pressure rises less for a given volume increment if the frequency is lower. The highest moduli are obtained with "impact waves" (impulses).

c) He was unable to measure wave propagation below mean pressure of 13 mm Hg because the waves were too quickly attenuated.

This paper clearly points out the problems associated with the complex relations between the distending pressure and the propagation of an arterial pressure pulse. Despite the fact that much theoretical and experimental work has been devoted to these relationships in arteries it is not yet possible to use the measured wave velocity as an index of arterial wall properties except in a qualitative way. The additional problems involved in the venous system appear to eliminate such an approach at the present time.

123. Lambossy, P.: Apercu Historique et Critique sur le Problème de la Propagation des Ôndes dans un Liquide Compressible Enfermé dans un Tube Elastique. Helv. Physiol. Pharm. Acta 8:209, 1950.

This fascinating review covers all the pertinent literature up to 1950. The author discusses in particular the pressure dependence of the wave velocity using the Moens-Korteweg relation and predicts a decrease in wave velocity with an increase in pressure (r increases more than E • h). The predictions are confirmed with data obtained by Muller on rubber tubes. In the vascular system, however, wave velocity increases as pressure rises. Lambossy relates this to the poorly understood properties of elastomers and emphasizes the uncertainty which still exists in our understanding of these relationships.

147. McDonald, D. A. and Taylor, M. G.: Hydrodynamics of the Arterial Circulation. Progr. in Biophys. and Biophysic. Chem 9:107, 1959.

One section of this review is devoted to the question of what one means by pulse wave velocity. Since the propagation velocity is frequency dependent (increasing as frequency increases), it has sometimes been difficult to compare values from different authors. The foot-to-foot velocity possibly represents the group velocity, i.e. the velocity at which the energy of the wave travels. If an arterial pressure pulse is decomposed into its Fourier components, the different components travel with different velocities (see also Landowne, ref. 127). Furthermore, what one really measures is an apparent phase velocity, i.e. the composite velocity resulting from a forward and a reflected backward traveling wave. Attinger (19) discussed the additional effects which damping of the pulse wave introduces on the propagation of a pressure pulse in the presence of reflections. McDonald and Taylor (147) proposed that the wave velocity estimated from the higher frequency components more nearly reflects the true phase velocity since the wave length is shorter with respect to the length of the system and reflection effects are more likely to cancel out. This whole discussion refers, of course, only to the classical wave propagation and does not consider any of the other propagation modes discussed earlier.

138. Mackay, I.F.S. et al.: A Technique for the Indirect Measurement of the Velocity of Induced Venous Pulsations. Am. Heart Journal 73:17, 1967.

Referring to Alexander's statement (2) concerning the need for more adequate venous pressure measurements, Mackay attempted to measure venous pulse-wave velocities under physiological conditions. Note, however, that he carefully specified his subjects: "subjects were chosen who had prominent superficial veins on their arm". Pressure was then applied by means of a pressure cuff and the propagation of an artificially induced pulse was measured. The results of this study indicate a linear relationship between pressure and wave velocity. Comparing his data against our own (18) the following table results:

Venous pressure	E_t (Mackay)	E_t (Attinger et al.)
20 mm Hg	$2.5 \cdot 10^6$	$6 \cdot 10^6$
80 mm Hg	$42 \cdot 10^6$	$60 \cdot 10^6$

These data would indicate that measurements of venous wave velocity yield data on the elastic modulus of the right order of magnitude. Note, however, that this relation holds only for venous pressures above 20 mm Hg and we see no way in which this could be extrapolated to normal venous pressures.

134. Mackay, I.F.S. and Walker, R.L.: An Experimental Examination of the Factors Responsible for the 'h' (d") Wave of the Jugular Phlebogram in Human Beings. Amer. Heart Journal 71:228, 1966.

The authors conclude that the "h" wave is a low pressure tidal wave of central origin related to the filling of the right heart during diastole. They could not associate it with any dynamic cardiac event. This paper again points out the degree of our nonunderstanding of the dynamics of the venous system, which is characterized by qualitative descriptions of individual parameters without much regard to the interrelationships between pressure, flow and volume.

184. Tafur, E. and Guntheroth, W.G.: Simultaneous Pressure, Flow and Diameter of the Vena Cava with Fright and Exercise. Circulation Research 19:42, 1966.

Excellent records of simultaneous pressures, flow and diameter are presented. Although uncalibrated they permit at least a qualitative interpretation of the relationships between these variables and their changes during various maneuvers. For instance, during inspiration, effective venous pressure fell while diameter and flow increased. During exercise, flow increased, diameter decreased but vasoconstriction could only be demonstrated in 26% of the runs. They illustrated the characteristic morphology and timing of events in the superior vena cava during the cardiac cycle. In one diagram the c-pressure wave bears no relation to changes in diameter or flow, which clearly is impossible from physical principles. It is most unfortunate that such excellent experimental data have not been exploited more analytically. If such data became available in quantitative form it would be possible to separate the active and passive mechanisms responsible for changes in venous dynamics.

32. Brecher, G.A., Mixter, G. and Share, L.: Dynamics of Venous Collapse in SVC System. American Journal of Physiology 171:194, 1952.

In well designed experiments the authors studied the emptying and filling of extrathoracic veins related to respiratory activity. They observed that venous collapse during inspiration does not occur at one distinct point but involves more or less extensive segments of extrathoracic veins.. With greater venous filling the transition zone extends farther into the periphery. Rising right atrial pressure prolongs the duration of the depletion stage and postpones the onset of the collapsed stage with inspiration.

The interposition of collapsed segments between two measuring points introduces additional factors into the interpretation of the physiological significance of wave velocity which are poorly understood. Venous collapse is promoted by the acceleration phase of venous flow associated with inspiration, but may not always be present. The phenomenon is similar to that described as the "vascular waterfall" in the pulmonary circulation or as bronchial collapse during expiration in emphysematous patients. Any justifiable interpretation of venous wave velocity must be restricted to venous segments for which the same physical relationships hold. If one wants to argue this on theoretical grounds, we have found no evidence that such measurements would permit any extrapolation to normal physiological conditions.

In the series of papers by Anliker and his collaborators (13, 14, 10, 12, 11) they investigate wave propagation both theoretically and experimentally. Their theoretical analysis is based on thin walled cylindrical shells, consisting of homogeneous isotropic material and containing an inviscid fluid. The results predict axisymmetric waves which are only mildly dispersive and nonaxisymmetric waves, which travel at much higher speeds, are highly dispersive and have a cutoff frequency. Both transmural pressure and axial stretch have marked effects on phase velocity.

The experimental data are somewhat confusing. Axisymmetric waves were generated by stepwise injection of fluid into the IVC of dogs. It was found that the wave velocity varies with location, being lowest in the segments closest to the heart. Various drugs as well as lethal doses of pentothal and minerals produced a 2 - 5 fold increase in wave velocity which persisted for hours after death and was not clearly related to changes in transmural pressure or radius. It was therefore assumed that the modulus of elasticity had changed. The observed wave velocities varied between 2 and 7 m/sec and the calculated moduli of elasticity between 10^6 and $5 \cdot 10^7$ dyn cm^{-2}. These values are considerably higher than our own, but the pertinent distending pressures are not given. In one paper the authors state that the wave velocity changes little with change in pressure below 20 cm H_2O (14) and in another (12), that an increase in venous pressure from 5 to 40 cm H_2O augmented the pulse speed by as much as 100% or more. No mention is made of the shape of the cross section at the lower distending pressures and it is not clear to what reference level pressures are referred, although this is of major importance for the evaluation of transmural pressure in low pressure systems subjected to cyclic variation of extravascular pressure.

138. MacKay, I.F.S. et al.: A Technique for the Indirect Measurement of the Velocity of Induced Venous Pulsations. Am. Heart Journal 73:17, 1967.

Experimental application of pulse wave velocity technique to superficial veins, using artificial pulse and non-invasive pressure pickups. Correlates measured with intravenous pressure and confirms nature of pulse by direct invasive measures. Important for data, treatment of extravascular factors, and practical details.

125. Landowne, M.: A Method Using Induced Waves to Study Pressure Propagation in Human Arteries. Circulation Research 5:594, 1957.

Experimental treatment of pulse wave velocity in arteries using externally induced impacts as the source, rather than arterial pulse. Technique used invasive pickups. A good treatment of relations between wave velocity and pressure over wide pressure range (20-160 mm Hg) and discussion of repeatability. Dispels the possibility that wave is transmitted through extravascular material.

18. Attinger, E. O. et al.: Modeling of Pressure Flow Relations in Arteries and Veins. Proc. 1st Int. Conf. Hemorheology, July 1966.

A distributed parameter model of the circulatory system has been programmed on a digital computer. Of particular interest is the dependence of pulse wave velocity on various parameters including wall elastic modulus, radius, blood density, wall thickness, poisson ration, as well as pressure. Experimental measurement as well as model.

C.4 Superficial Vein Pressure Chamber

The method of estimating central venous pressure by observing the height of the pulsation of the external jugular vein is a widely taught and accepted clinical test (1). The theoretical basis for the validity of this test is described by Holt (103) and by Ryder (169). The possibility that peripheral veins will be filled under the conditions of space flight and will reflect central venous pressure has been pointed out by Seiker (178). Simple pressure chamber methods of noninvasive measurement of venous pressure have been described by several authors (189,39). Several other approaches using strain transducers have been studied by Okino without success (157).

1. Adams, F.D.: Physical Diagnosis. Baltimore: Williams and Wilkins, 1958

The method of estimation of venous pressure by observing the height of the jugular pulsation is explained.

103. Holt, J. P.: Flow of Liquids Through "collapsible" Tubes. Circulation Research 7:342, 1959

This is a theoretical paper which describes the flow of viscous fluids through collapsible elliptical tubes.

169. Ryder, H. W., Molle, W. E., and Ferris, E. B. Jr.: The Influence of the Collapsibility of Veins on Venous Pressure Including a New Procedure for Measuring Tissue Pressure. Journal Clin. Invest. 23:333, 1944.

The authors measure the distensibility curves of vein segments and find them to be sigmoid in shape, with the steepest portion of the curve to be very near zero transluminal pressure.

178. Sieker, H.O., Pryor, W.W. and Hickam, J.B.: A Comparative Study of Two Methods for Measuring Central Venous Pressure. W.A.D.C. Tech. Report 55-6, 1955.

This careful study shows that the pressures in the arm veins vary directly with the pressure in the central veins when the arm is dependent and the veins are filled. The authors point out that the pressure in all veins outside the chest will be greater than zero under weightless conditions during rest.

189. von Recklinhausen.: Archiv. F. Experimentelle Pathologie und Pharmacologie 1:463, 1906.

This early paper describes a pressure chamber consisting of a rubber balloon which is used to measure venous pressures in the arm.

104. Hooker, D.R.: Observations on the Venous Blood Pressure in Man. Amer. Journal of Physiology 35:73, 1914.

This simple paper describes a noninvasive method of measuring peripheral venous pressure by cementing a small pressure chamber to the skin with collodion and increasing the pressure in the chamber until the vein is observed to collapse. The author discovers that the venous pressure measured by this technique is not affected by venous tone.

83. Goldmann, H.: Abflussdruck, Minutenvolumen und Winderstand der Kammerwasserstromung des Menschen. Documenta Ophthal. 5/6:278, 1951.

Goldmann describes an ingenious method of noninvasive measurement of the venous pressure in small veins of the conjunctiva using a torsion balance equipped with an applanation surface of known area. His method has been used by Brubaker (39) who finds the endpoint difficult to determine.

130. Linnér, E.: Measurement of the Pressure in Schlemm's Canal and in the Anterior Chamber of the Human Eye. Experientia 5:451, 1949.

Linnér describes a pressure chamber method of measuring venous pressure in the conjunctival and episcleral vessels of the eye. His method has been used by Brubaker (39) who finds excellent correlation of the values obtained by Linnér's method when compared to values obtained by invasive cannulation.

39. Brubaker, R. F.: Determination of Episcleral Venous Pressure in the Eye: A Comparison of Three Methods. Arch. Ophthal. 75:110, 1967.

The author compares Goldmann's and Linnér's methods of venous pressure measurement to direct cannulation. He finds that the pressure chamber method is quite reliable although the method is appropriate only for use by a highly trained examiner.

157. Okino, H.: Measurement of Intraluminal Pressure from External Pressure with Strain Transducers. Journal of Applied Physiology 19:546, 1964.

Several ways in which one may attempt to obtain the intraluminal pressure of collapsible tubes by partially occluding them with strain transducers is described. He concludes that such methods are not easily used because of problems with calibration and nonlinearity. He does not evaluate the chamber method, however.

C.5 Intraocular Pressure, Tonometry and Tonography

The relationship between the intraocular pressure and the pressure in the venous system near the eye has been clearly defined by Goldmann and accepted by his colleagues (84, 83). Episcleral venous pressure is given by the equation $P_e = P_i - (R \times F)$. The intraocular pressure, P_i has been measured by many noninvasive techniques which are known collectively as tonometry (174, 85, 142, 58). Tonography, on the other hand, is a method whereby the resistance to outflow of aqueous humor, R, and the rate of outflow of aqueous humor of the eye, F, can be measured (89, 128, 153). These methods depend on the relationship between volume changes in the eye and the corresponding change in intraocular pressure, worked out by Friedenwald (74).

The intraocular dynamics measured by tonometry and tonography are not always constant, but may vary somewhat, depending on the individual and the time of the day at which they are measured (150, 186, 55, 56, 24). The relationship between episcleral venous pressure and changes in other body parameters such as systemic blood pressure or body position have been studied, but their relationship has not been consistently and clearly established (40, 77).

84. Goldmann, H.: Die Kammerwasservenen und das Poiseuille'sche Gesetz. Ophthalmologica 118: 496, 1949.

This is a mathematical paper which considers the relationship between the intraocular pressure and the pressure in the various branches of its anatomic drainage system which include Schlemm's Canal, the aqueous veins, and the episcleral veins. Calculations are based on the application of Poiseuille's Law to laminar flow in elliptical tubes.

83. Goldmann, H.: Abflussdruck, Minutenvolumen und Winderstand der Kammerwasserstromung des Menschen. Documenta Ophthal. 5/6:278, 1951.

The relationship between the pressure in the eye, the pressure in the episcleral veins outside the eye, the resistance to outflow of fluid from the eye, and the flow rate from the eye is given as a simple formula which is analogous to Ohm's Law. This equation, "Goldmann's Equation," is well accepted among ophthalmologists. The paper also contains descriptions of noninvasive methods for measuring the episcleral venous pressure and the outflow rate of aqueous humor from the eye.

174. Schiotz, H.: Ein Neuer Tonometer; Tonometrie. Archiv. F. Augenh. 52: 401, 1905.

This is the first description of the Schiotz tonometer which is still the standard instrument for the noninvasive measurement of the intraocular pressure.

85. Goldmann, H.: A New Applanation Tonometer. Glaucoma, Transactions of the Second Conference. Josiah Macy, Jr. Foundation, p. 167, 1956.

Dr. Goldmann describes the "Goldmann Applanation Tonometer" which is now recognized as the most accurate noninvasive instrument for the measurement of intraocular pressure, against which other methods are calibrated.

142. Mackay, R. S., Marg, E. and Oechsli, R.: Automatic Tonometer with Exact Theory. Science 131:1668, 1960.

The Mackay-Marg electronic tonometer is described. It is an accurate instrument for measurement of intraocular pressure noninvasively. It has the advantage that it is self-recording, and it has been used by Moses (153) in performing tonography as well.

58. Durham, D. G., Bigliano, R. P., Masino, J. A.: Pneumatic Applanation Tonometer. Tr. Amer. Acad. Ophthal. and Otol. 69:1029, 1965.

A new tonometer is introduced which may be used against the sclera instead of against the cornea and does not require topical anesthesia. Like the Mackay-Marg tonometer, the Durham tonometer is self-recording.

89. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes. Arch. Ophthal. 44:204, 1950.

Grant introduces tonography, which is a noninvasive method of measuring the resistance to outflow of the aqueous humor of the eye. He uses an electronic Schiötz tonometer to make a continuous pressure recording of the intraocular pressure for four minutes. This pressure curve, along with the Friedenwald nomogram of scleral rigidity, is used to calculate the resistance to outflow, R. Assuming a value for episcleral venous pressure, he calculates the rate of outflow of the eye.

128. Langham, M. E. and Maumenee, A. E.: The Diagnosis and Treatment of Glaucoma Based on a New Procedure for the Measurement of Intraocular Dynamics. Tr. Amer. Acad. Ophthal. and Otol. 68:277, 1964.

Langham introduces a new method for measuring the resistance to outflow of aqueous humor from the eye. He applies a suction cup contact lens to the eye for a few minutes, and after removal, follows the rate of decrease of intraocular pressure by Goldmann applanation tonometry. Suction cup analysis, as Langham's method is called, does not offer any advantages over Grant's method and is more cumbersome to carry out.

153. Moses, R. A.: Constant Pressure Applanation Tonography with the Mackay-Marg Tonometer. Arch. Ophthal. 6:20, 1966.

Moses introduces a method of measurement of the resistance to outflow of aqueous humor from the eye which offers the greatest likelihood of being applicable to space flight.

74. Friedenwald, J. S.: Standardization of Tonometers: Decennial Reports by the Committee on Standardization of Tonometers. Chapter VII, American Academy of Ophthalmology and Otolaryngology, 1954.

This important report gives the most recently accepted values of the relation between volume and pressure in the living human eye, expressed as the "Friedenwald Nomogram."

150. Miller, D.: The Relationship Between Diurnal Tension Variation and the Water-Drinking Test. Amer. Journal Ophthal. 58:243, 1964.

A simple water-drinking test is described from which the height of the diurnal variation in intraocular pressure may be determined.

186. Thomassen, T. L., Perkins, E. S. and Dobree, J. H.: Aqueous Veins in Glaucomatous Eyes. Brit, Journal Ophthal. 34:221, 1950.

The authors discuss the variation in episcleral venous pressure which occur in a diurnal fashion and which they believe to cause the diurnal variation in intraocular pressure. Their opinion has not been substantiated by others, however. This is a poorly written paper, but represents one point of view regarding the cause of diurnal variation.

55. De Rotth, A.: Effect of Changes in Osmotic Pressure of Blood on Aqueous Humor Dynamics. A.M.A. Arch. Ophthal. 52:571, 1954.

The author shows that the diurnal variation in the intraocular pressure is probably due to diurnal variation in the osmolarity of the blood, and hence must be due to different outflow rates from the eye.

56. Drance, S. M.: The Significance of Diurnal Tension Variations in Normal and Glaucomatous Eyes. A.M.A. Arch. Ophthal. 64:494, 1960.

The author shows that diurnal variations in the intraocular pressure are exaggerated in patients with decreased resistance to outflow (glaucoma) and less marked in patients with normal eyes. His work supports the conclusions of De Rotth.

24. Bettman, J. W. Jr., McEwen, W.K., and McBain, E. H.: Venous Pressure Opposing Aqueous Outflow in Patients With and Without Chronic Open Angle Glaucoma. Invest. Ophthal. 5:624, 1966.

By doing tonography and tonometry with noninvasive techniques, the authors show how it is possible to calculate episcleral venous pressure in humans.

40. Brubaker, R. F. and Kupfer, C.: Determination of Pseudofacility in the Eye of the Rhesus Monkey. Arch. Ophthal. 75:693, 1966.

This is an experimental paper using anesthetized monkeys which shows that the pressure measured in the episcleral veins is dependent on the height of the arterial pressure.

77. Gartner, S. and Beck, W.: Ocular Tension in the Trendelenburg Position. Amer. J. Ophthal. 59:1040, 1965.

The intraocular pressure is shown to change an average of 0.42 mm Hg from lying flat to the Trendelenburg position (head 8" below feet). This figure is much less than one would expect on the basis of hydrostatic changes alone.

In addition to the above annotated articles, the following references also contain relevent information: (131, 73, 143, 72, 90, 116, 22, 86, 115).

C.6 Venous Dynamics

The capacitance system adjusts the circulating blood volume and maintains venous return by alterations in tone or distensibility. Though central venous pressure is a major determinant of cardiac output, peripheral or central pressures alone give little information about the tone of the capacitance system because most veins are in a state of partial collapse . An understanding of venous dynamics can be obtained only by studying the reflex responses of the veins to physiologic stress. In this portion of the annotated bibliography, papers are grouped under the following headings:

C.6.1 Review Articles

C.6.2 Reactions to Exercise, Hyperventilation, Deep Breath

C.6.3 Hydrostatic Effects

C.6.4 Effect of Carotid Sinus Stimulation

C.6.5 Effect of Increased Intrathoracic Pressure

C.6.6 Miscellaneous

a) Response to Autonomic Nervous System Stimulation

b) Response to Carotid Chemoreceptor Stimulation

c) Response to Adrenergic Drugs

d) Venous Tone in Disease States

C.6.1 Review Articles

2. Alexander, R.S.: The Peripheral Venous System. Handbook of Physiology, Circulation. Washington, D.C.: American Physiological Society, 1963, Vol. II, Section 2, Chapter 31, 1075.

See expecially for a discussion of the distensibility of veins.

95. Guyton, A.C.: Venous Return. Handbook of Physiology, Circulation, Washington, D.C.: Americal Physiological Society, Vol II, Chapter 32, p. 1099.

A comprehensive analysis of hemodynamic factors which effect venous return.

177. Shepherd, J. R.: Role of the Veins in the Circulation. Circulation 33: 484, 1966.

A discussion of current knowledge and concepts of the control of venous tone.

176. Sharpey-Schafer, E. P.: Venous Tone. Brit. Med. Journal 5267:1589, 1961.

An excellent paper which experimentally documents factors which alter venous tone.

C.6.2 Reactions to Exercise, Hyperventilation, Deep Breath

148. Merritt, F. L. and Weissler, A.M.: Reflex Venomotor Alterations During Exercise and Hyperventilation. Am. Heart Journal 58:382, 1959.

Exercise, deep breath, hyperventilation, passive leg motion, and reactive hyperemia were studied. Only the first three were found to produce consistent venoconstriction. A Ganglionic blocker abolished the response.

173. Samueloff, S. L. et al.: Temporary Arrest of Circulation to a Limb for the Study of Venomotor Reactions in Man. Journal of Applied Physiology 21:341, 1966.

Venoconstriction was demonstrated in response to hyperventilation, deep breath, leg exercise, and breathing 7% CO_2 in oxygen.

26. Bevegord, B. S. and Shepard, J. T.: Changes in Tone of Limb Veins During Supine Exercise. Journal of Applied Physiology 20:1, 1965.

General peripheral venoconstriction was shown to occur during leg exercise. Forearm venoconstriction associated with leg exercise was not effected by simultaneous arm exercise. It was concluded that the local metabolic effects of exercise do not effect venous tone. No forearm venoconstriction occurred in a patient who had previously undergone a cervical sympathectomy for relief of vascular symptoms.

80. Gauer, O.H. and Thron, H. L.: Postural Changes in the Circulation. Handbook of Physiology, Circulation. Washington, D. C.: American Physiological Society, 1963, Vol. III, Chapter 67.

An excellent review of hydrostatic effects on hemodynamics including a discussion of the hydrostatic indifference point and the response of the veins to passive tilt.

207. Wood, J. E. and Eckstein, J. W.: A Tandem Forearm Plethysmograph for Study of Acute Responses of the Peripheral Veins of Man. Journal Clin. Invest. 37:41, 1958.

Environmental and local cooling were shown to produce peripheral venoconstriction. Pooling blood in the legs by 30^{o} head-up tilt and cuffs (about 750cc sequestered) produced prompt arteriolar constriction; venoconstriction took place later and took longer to reach a maximum. It was concluded that the threshold to arterial response was lower than that to venous response.

170. Salzman, E. W. and Leverett, S. D. Jr.: Peripheral Venoconstriction During Acceleration and Orthostasis. Circulation Research 4:540, 1956.

Tilt table studies showed less clear cut venoconstriction than $+G_z$ acceleration, suggesting a threshold factor in the constrictive response to venous pooling.

172. Samueloff, S. L., Browse, N. L. and Shepherd, J. T.: Response of Capacity Vessels in Human Limbs to Head-Up Tilt and Suction on Lower Body. Journal of Applied Physiology 21:47, 1966.

Head-up tilt and suction to the lower body produced transient increases in venous tone and sustained constriction of resistance vessels. If the stimulus was applied gradually, there was no response of the capacitance system. It was concluded that the veins played no active role in the response to gravitational stress.

171. Salzman, E. W.: Reflex Peripheral Venoconstriction Induced by Carotid Occlusion, Circulation Research 5:149, 1957.

Carotid sinus hypotension produced venous and arteriolar constriction "similar in time course and magnitude". Carotid sinus denervation abolished the venous response, deafferentation of the aortic arch by cervical vagotomy increased it.

38. Browse, N. L., Donald, D. E., and Shepherd, J. T.: Role of the Veins in Carotid Sinus Reflex. American Journal of Physiology 210:1424, 1966.

Carotid sinus hypotension was shown to produce a marked constrictor response of the resistance vessels, but only a minimal increase in venous tone. Stimulus-response curves of resistance and capacity vessels were determined by graded stimulation of the lumbar sympathetic chain. The average arterial response to hypotension was equivalent to sympathetic stimulation at a rate of 3 impulses/sec, the venous to 0.2 impulses/sec.

27. Bevegord, B. S. and Shepherd, J. T.: Circulatory Effects of Stimulating the Carotid Arterial Stretch Receptors in Man at Rest and During Exercise. Jour. Clin. Invest. 45:132, 1966.

Stimulation of carotid sinus strech receptors by applying negative pressure to the neck vessels did not result in venous dilation. Exercise caused venoconstriction despite carotid stretch receptor stimulation. The reduction in blood pressure and heart rate were related linearly to the stimulus.

C.6.5 Effect of Increased Intrathoracic Pressure.

196. Watson, W. E.: Venous Distensibility of the Hand During Valsalva's Maneuver. Brit. Heart Journal 24:26, 1962.

A marked decrease in venous distensibility was produced by the Valsalva maneuver and demonstrated by pressure/volume curves of isolated venous segments.

195. Watson, W. E., Smith, A. C. and Spalding, J.M.K. Transmural Central Venous Pressure During Intermittant Positive Pressure Respiration. Brit. Journal Anaesth. 34:278, 1962.

Increased intrathoracic pressure stimulated reflex peripheral venous constriction to maintain central venous pressure in the face of obstruction to venous return. Maintainance of central venous pressure could not be accomplished in patients with polyneuritis and spinal cord transections.

C.6.6 Miscellaneous

a) Response to Autonomic Nervous System Stimulation

167. Ross, J. C., Hickman, J. B., Wilson, W.P., and Lowenback, H.: Reflex Venoconstrictor Responses to Strong Autonomic Stimulation. Am. Heart Journal 57:418, 1959.

Electroconvulsive shock therapy in patients premedicated with thiopental and succinylcholine was shown to increase central venous pressure within 10 seconds. It was felt that this rapid response indicated peripheral venous constriction by a reflex rather than a humoral mechanism.

(See also (38) above for lumbar sympathetic stimulation.)

b) Response to Carotid Chemoreceptor Stimulation

37. Browse, N. L. and Shepherd, J. T.: Response of Veins of Canine Limb to Aortic and Carotid Chemoreceptor Stimulation. American Journal of Physiology 210:1435, 1966.

Stimulation of the carotid and aortic chemoreceptors with cyanide caused both increases and decreased in venous tone. Atropinization did not abolish the responses which were therefore considered due only to variation in sympathetic vasoconstrictor activity.

c) Response to Adrenergic Drugs

62. Eckstein, J. W., Wendling, M. G., and Abboud, F. M.: Forearm Venous Responses to Stimulation of Adrenergic Receptors. J. Clin. Invest. 44:1151, 1965.

Infusion of Isuprel, a beta adrenergic stimulus, was shown to have no effect on veins. Epinephrine which stimulated both alpha and beta receptors caused venoconstriction only.

(See also (2, 95, and 176) above for further discussion of humoral agents).

d) Venous Tone in Disease States

49. Caliva, F. S. et al.: Digital Hemodynamics in the Normotensive and Hypertensive States. II. Venomotor Tone. Circulation 28:421, 1963.

Increased venous tone was demonstrated to be part of the overall increase in peripheral vascular resistance in hypertension.

(See also (177) above for a discussion of congestive heart failure, beriberi, and anemia.)

In addition to the above annotated articles, the following references also contain relevant information: (114, 161, 178, 120, 188, 78, and 98.)

APPENDIX D

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APPENDIX E

RESULTS OF QUESTIONNAIRE MAILING

In the course of the program we have prepared and mailed 226 form letters and questionnaires, copies of which are shown in Figures E-1 and E-2. These were sent to individuals whom we believed to be active in the relevant areas of the cardiovascular function and measurement field. The mailing list was compiled from many sources including personal knowledge of our staff, individuals uncovered during the literature search, those suggested by respondents to the questionnaire and individuals brought to our attention by the various people we have contacted and visited in conjunction with this program.

The results of this mailing were most gratifying in that we not only received an overwhelming response (109 replies out of the 226 questionnaires sent), but we also obtained much useful information in the form of specific ideas and suggestions, relevant publications and work, and additional individuals to contact.

The following list summarizes both the more significant and the typical questionnaire replies.

NO.	NAME AND ADDRESS	AREA OF WORK AND SUGGESTIONS
1	Robert S. Alexander Albany Medical College Albany, N.Y.	Has done extensive work in central and local controlling mechanisms and their relationship to basic properties of the venous system. Feels venous pressure is not a homogeneous entity and, therefore, that the project is "misdirected".
2	Julia T. Apter Presbyterian St.Luke's Hospital 1753 W. Congress Pkwy Chicago, Illinois	Has studied visco-elastic properties of veins with experiments guided by a three parameter model. The parameters are obtained experimentally, fitted into the differential equations of

BIOSYSTEMS, INC.

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Subject: Venous Pressure Measurement

The National Aeronautics and Space Administration would like to find out what happens to the venous blood pressure of astronauts during space flight. We are conducting a program for NASA under contract NAS W-1559 to locate, evaluate and develop techniques for noninvasive measurements of venous pressure. We feel that you can help us in our role as a collecting agency for suitable measurement techniques and ideas.

The purpose of this letter is to enlist your aid in bringing to our attention any new measurement techniques on which you may be working or with which you may be familiar so that they may be evaluated and included in the study. Any ideas or data you supply would be given full credit in any resulting publications or projects. Furthermore, complete protection will be afforded any proprietary information supplied to us.

As part of the program we are conducting a literature search and developing an annotated bibliography of medical and engineering works relevant to venous pressure measurement. In order to make this bibliography as up-to-date as possible, as well as to insure that we include all promising work, we have undertaken to contact people in the field, such as yourself, and request that they fill out and return the attached short questionnaire. Since you would be undoubtedly interested in the results of our literature survey, we would be happy to make a copy of our final bibliography available to you. A prompt reply would help us greatly since we are working on the fairly strict time schedule of the Apollo Application program

Thank you in advance for your cooperation and assistance.

Sincerely,

James W. Dow, M.D.
Principal Investigator

Figure E-1

Biosystems, Inc.

Venous Blood Pressure Measurement Questionnaire

If address shown is inaccurate, please correct here.

____

____

____

____

	Yes	No
1. Have you worked in the area of venous pressure control or measurement?	___	___

If so, please describe your work briefly. Use additional sheets if desired.

____

____

____

____

2. If you have published or reported any of this work please enclose reprints. If these are not readily available please list the references here.

____

____

____

____

3. Can you suggest other individuals or organizations who are active in the area of venous pressure measurements?

____

____

____

4. In your opinion which, if any, venous pressure measurement techniques show promise?

____

____

____

5. Name of individual completing the questionnaire ______________________________;

Date ______________________; Phone No. ______________________.

Thank you for your assistance. Completed copies of our annotated bibliography will be sent to those who complete and return this questionnaire. If you desire this material please check here _____.

Figure E-2

NO.	NAME AND ADDRESS	AREA OF WORK AND SUGGESTIONS
2	Julia T. Apter (cont.)	motion of the model and then used to analyze venous pressure curves. Aim is to find a transfer function.
3	E. O. Attinger Res. Inst. Pres. Hosp. U. of Pennsylvania Philadelphia, Pa.	Has done extensive work in analysis of pressure-flow relations and vessel wall characteristics of the venous and arterial tree. Suggested another individual to be sent questionnaire. Subsequently assisted in this program (See App. A),
4	Hermann Bader Dept. of Pharmacology U. Medical Center Jackson, Miss.	Recommended two names for questionnaire.
5	Ernest Barany Inst. of Pharmacology U. of Uppsala Uppsala, Sweden	Has worked with cannulation of saggittal sinus in monkeys. Pressure breathing with a pressure suit enclosing the monkey and helping expiration. Recommends Erik Linner, Umea University in Sweden who developed a noninvasive method for the small veins on the eye.
6	Henry Barcroft Sherrington Sch. of Physiology St. Thomas Hosp. Med. Sch. London, England	Recommends two other people.
7	G. Octo Barnett, Lab. of Computer Science Mass. General Hospital Boston, Mass.	Recommends two other people.
8	Jan E. W. Beneken Dept. of Physiology & Biophysics U. of Miss. Sch. of Med. Jackson, Miss.	Designing electronic analog computer model of human blood circulation system.

NO.	NAME AND ADDRESS	AREA OF WORK AND SUGGESTIONS
9	Mr. Anders Bill Dept. of Pharmacology U. of Uppsala Uppsala, Sweden	Has studied pressure in the intrascleral veins in rabbits and cats and also pressure in the small veins in the eye of cats. Suggests direct cannulations using very thin polyethylene tubes.
10	Stanley E. Bradley Dept. of Med. Columbia U. College of Phys. & Surg. N.Y., N.Y.	Has studied effect of gravitation shifts in man, effect of shock in man and dog with special reference to portal venous system and also effect of venal hepatitis on man and dog including splanchirc venous pressure.
11	Gerhard A. Brecher Dept. of Physiology U. of Oklahoma Med. Ctr. 800 N.E. 13th Street Oklahoma City, Okla.	Has worked with intravascular venous pressure measurements. Sent reprints. Author of "Venous Return". Suggests Ian Mackay.
12	Dr. Ellen Brown U. of Calif. Med. Ctr. San Francisco, Cal.	Has done extensive work in venous system. Suggests plethysmographic technique. Sent reprints and bibliography. Suggests two other people.
13	Alan C. Burton Dept. of Biophysics U. of W. Ontario London, Ontario, Canada	Suggests digital plethysmography. Sent detailed note explaining approach. Recommends we contact G. Burch.
14	Jose L. Duomarch Servicio de Fisiologia Obstetrica U. de la Republica Hospital de Clinicas, Piso 16 Avenida Italia, S/N Montevideo, Uruguay	Sent two monographs on venous pressure.
15	Walter Feder Dept. of Medicine U. of Chicago Chicago, Illinois	Has developed a simple narrow bore plastic tube attached to a needle which would give mean pressure as well as some idea of pulsitile changes.
16	J. D. Fewings Senior Research Off. Dept. of Human Physiol. & Pharmacy U. of Adelaide Adelaide, S. Australia	Has measured venous pressure via a polyethelene catheter introduced into the cephalic veins and connected to a conventional pressure transducer.

17	Otto Gauer Der Freien U. Berlin Berlin, Germany	Has little confidence that a noninvasive technique of satisfactory accuracy will be found.
18	M. Jay Goodkind Div. of Cardiology Philadelphia Genl. Hosp. Philadelphia, Penna.	Has done clinical measurements by cardiac catherization. Suggests A. Guyton.
19	A.D.M. Greenfield et al Dept. of Physiology St. Mary's Hosp. Med. Sch. London W 2, England	Has made measurements of central venous pressure during lower body negative pressure suction manoeuvre using catheters and electrical pressure transducers. Results will be published shortly. Knows of no promising noninvasive methods.
20	Warren G. Guntheroth Dept. of Pediatrics U. of Wash. Sch. of Med. Seattle,Washington	Worked in the area of venous return. Has been studying the superior vena cava with simultaneous distending pressure and diameter and flow in relation to exercise. Are using silastic tubing and silastic balloons in the pleural cavity. Has worked reasonably well. See reprint.
21	Chester Hyman Prof. of Physiology U. of S. California School of Medicine Los Angeles, Calif.	Sent patent and reprint. Suggested other articles of interest.
22	John W. Irwin Mass Eye & Ear Infirmary 243 Charles Street Boston, Mass.	Working with pressures of microcirculation. Developing a method for securing dynamic pressuregrams on arterioles of approx. 50 micra. Suggested five other individuals.
23	John Jones U. of Nebraska College of Medicine Omaha, Nebraska	Has measured venous pressure on hundreds of patients using simple infusion set.
24	R. T. Kado Space Biology Lab Brain Research Inst. U. of California Los Angeles, Calif.	Has used strain gage pressure transducer with catheter miniaturized for intra-vascular use. Suggests two other sources.
25	H. Kanai Dept. of Electrical Engrg. Sophia U. Chiyoda-Ku Tokyo, Japan	Has worked on pulsatile blood pressure measurement by catheter method. Suggests optical method, the infrared plethysmograph.

26	E. Kinnen Dept. of Elect. Engrg. U. of Rochester Rochester, N.Y.	Working with venous flow, particularly pulmonary venous flow. Suggested two other individuals.
27	H. H. Kopald Mass General Hospital Fruit Street Boston, Mass.	Measured venous pressure by use of inlaying polyethelene catheters in dogs. Suggested another person.
28	Chauncey D. Leake U. of California San Francisco Med Ctr. San Francisco, Calif.	Suggests water manometer and cuff. Recommends another person.
29	Erik Linner Dept. of Opthalmology University Hospital U. of Umea, Umea, Sweden	Has developed a method for measuring the episcleral venous pressure in human beings and rabbits. Feels that this is a suitable technique for noninvasive measurements of the episcleral venous pressure.
30	Ian F. S. Mackay Baldorioty Plaza 1404 Calle Diez De Andino 212 Santurce, Puerto Rico	Has done extensive pertinent work. Has assisted significantly in this program (See Appendix B).
31	Frank Macri Nat. Inst. of Neurol. Diseases & Blindness Clinical Center N.I.H., Bethesda, Maryland	Has measured venous pressure of the eye and suggests microcannulation techniques.
32	John M. Moran Dept of Surgery Tufts U. School of Medicine Boston, Mass.	Familiar with venous pressure measurements in clinical applications to major surgery and postoperative management. Aspects of percutaneous catherization have been studied clinically. Knows of no noninvasive technique.
33	Raymond Murray Indiana University Cardiopulmonary Lab. 6570 AMRL (MRBB) W.P.A.F.B., Ohio	Has measured central venous pressure changes during environmental stresses. Suggests height of blood column in neck veins.
34	Y. Nose Dept. of Artificial Organs Cleveland Clinic Found. 2020 E. 93rd Street Cleveland, Ohio	Monitors the venous pressure of the vena cava (superior-inferior) and the r & l atrium. Use strain gauge transducers via silicone tubing.

35	Jorge Perez-Cruet Pavlovian Lab. Johns Hopkins U. School of Medicine Baltimore, Md.	Has measured venous pressure in dogs, rt. ventricular pressures in dogs and venous pressure in humans. He suggests rt ventricular pressure by direct catheter and also venous pulse waves (osillographic).
36	Richard M. Rauch Smith Kline Instrument Co. 1500 Spring Garden St. Philadelphia, Pa.	Has used catheters and strain gage transducers. Has considered other direct methods. Has also worked with IR pickups similar to ear oximeters. Suggests transcutaneous Doppler flow system, and try to derive pressure from flow.
37	S. R. M. Reynolds P.O. Box 6998 Chicago, Illinois	Has measured systemic and venous pressures in the lamb fetus in utero (without gravity pull).
38	Robert F. Rushmer Professor of Physiology U. of Washington Seattle, Washington	Points out that there appears to be good evidence for a region of partial venous occlusion at the entrance of veins into the thorax. This implies that the peripheral venous pressure is very apt to be substantially different from the venous pressure within the thorax.
39	Allen M. Scher Dept. of Physiol & Biophys. U. of Washington School of Medicine Seattle, Washington	Attempted to find venous reflexes, but found none. Suggests another individual.
40	Marvin Sears Prof. of Opthalmology Yale U. of Medicine New Haven, Conn.	Measured venous pressure in the eye and its outflow channels. Suggested several other people.
41	Ewald E. Selkurt, et al Dept. of Physiology Indiana U. Sch. of Med. Indianapolis, Indiana	Venous pressure measurement during shock, homorrhages, A-V fistulas, cardiac function in shock, etc. Feels direct measurement by implanted transducers is best.
42	John T. Shepherd Section of Physiology Mayo Clinic Rochester, Minn.	Studies on men and dogs using invasive techniques. Suggested two other people.
43	Merrill P. Spencer Virginia Mason Res. Ctr. 1202 Terry Avenue Seattle, Washington	Suggests that a small inflatable chamber, like a plethysmograph over an extremity might be calibrated in terms of resistance so that there might be a change in resistance when the veins are emptied as the pressure of the chamber is elevated.

44	Robert L. Van Citters Dept. of Physiology & Biophysics U. of Washington Sch. of Med. Seattle, Washington	Has developed a system for telemetry of blood flow and blood pressure in the arterial system. Feels it is applicable to the venous system with small modifications.
45	J. Weinman Rogoff Lab. for Med. Elect. The Hebrew U. Hadassah Med. School Jerusalem, Israel	Feels problem is very complicated and not immediately soluble. Suggests photoplethysmographic recording of effects ot Valsalva maneuver. Gives noninvasive recording of changing venous vasomotor tone.
46	J. R. Whiteman Instrumentation Field Sta. 2121 K Street, N.W. Washington, D.C.	Suggests a form of venous occlusion plethysmography.
47	Fred Wiener IBM, Advanced Systems Dev. Div. 2651 Strong Blvd. Yorktown Heights, N.Y.	Worked on models of wave propagation in the pulmonary circulation relating the oscillation of venous pressure and flow to right ventricular pressure propagated through the pulomary capillaries into the veins.
48	Travis Winsor 4041 Wilshire Blvd Los Angeles, Calif.	Normal values and establishment of reference levels. Also venous pressure in children. Suggested contacting Burch et al.
49	J. Edwin Wood III U. of Virginia Hospital Box 146 Charlottesville, Va.	Suggests measurement of the natural volume of the extremity followed by deflation of the veins to minimal volume, then re-inflation of veins by congestion techniques through a series of pressures with simultaneous measurement of volume. Has done work in plethysmography. Suggests four other individuals.

APPENDIX F.

SUMMARY OF CONTACTS AND VISITS

No.	Individuals	Affiliation	Conducted By	Type of Contact*	Discussions & Results
1.	Akers, W.W. & Bourland, H.M.	Rice Univ. Houston, Tex.	L. Stark	V	Discussed modeling of venous pulse, importance of venous pressure to left heart bypass work. Suggested references and other contacts.
2.	Attinger, E.O.	Presbyterian-Univ. of Penn. Philadelphia, Pa.	R. Brubaker, D. Worthern, S. Molner, L. Young, J. Pines, J. Newman	P,B	Discussed various techniques involving pulse wave transmission. Reviewed the analytical and experimental work on this program performed by Dr. Attinger.
3.	Barnett, G.O.	Mass. Gen. Hospital, Boston,Mass.	L. Young	V	Discussed various noninvasive measurement possibilities, significance of venous pressure and tone measurements, and modeling of venous system.
4.	Brown, Ellen	Univ. of Calif. Med. Ctr. San Francisco, Calif.	D. Worthen	P	Interested in venous pressure relative to heart action. Has been recently concentrating on measurement of venous compliance and tone. Suggests venous occlusion plethysmography as a good technique.

*V - visit to, P - phone conversation, B - visited Biosystems

No.	Individuals	Affliation	Conducted By	Type of Contact*	Discussions & Results
4.	Brown, Ellen (Continued)				Feels central venous pressure measurement is important to understanding of vascular dynamics. Suggested C. Hyman for capacitance plethysmography.
5.	Burch, G. E.	Tulane Med. Sch. New Orleans, La.	D. Worthen & S. Molner	P	Discussed his extensive work in digital plethysmography and in particular methods, techniques and hardware.
6.	Currier, R.	Space Labs, Inc. Van Nuys, Calif.	L. Stark & L. Young	V	Talked about the pulse wave velocity hardware developed for AFFTC (Edwards AFB) and described in FTCTR 66-7. Also discussed difficulties associated both with correlating pressure and pulse velocity and with utilizing a phonocardiogram in flight.
7.	Frazier, T.M. et al.	Lovelace Found. Albuquerque, N. Mexico	L. Young	V	This group favors the P-A delay technique. Suggested tests in which the transducers be implanted at the atria. Also suggested use of thermal flow meters for end-point detection.
8.	Fromer, P.	Nat. Heart Inst. Bethesda, Md.	L. Young	V	Discussed several noninvasive venous measurement techniques as well as the significance of venous pressure and tone measurements, especially in terms of cardiac function.

No.	Individuals	Affliation	Conducted By	Type of Contact*	Discussions & Results
9.	Heckman, H.	Office of Surgeon Gen. Wash., D.C.	L. Young	V	Reviewed the significance of venous pressure and tone measurements, particularly with respect to shock and in surgery.
10.	Irwin, J.	Mass. Eye & Ear Infirmary Boston, Mass.	R. Brubaker	V	Felt that noninvasive techniques for venous pressure measurement are not yet practical.
11.	Mackay, I.F.S.	Univ. of Puerto Rico Med. Sch. San Juan, P. R.	R. Brubaker, D. Worthen, L. Young, J. Newman	P,B	Discussed Dr. Mackay's experience and thoughts relating to application of venous occlusion plethysmography, P-A delay, pulse wave velocity, A wave obliteration, pulse contour determination, measurement of cerebral blood flow and several other techniques. Dr. Mackay subsequently performed a number of experiments for us which greatly assisted us in evaluating several of the proposed techniques.
12.	Mount, J. et al.	IBM Res. Ctr. Houston, Tex.	L. Stark	V	Reviewed work done by this group in modeling and analysing the arterial pressure pulse and related phenomena.
13.	Reed, J.M.	Dept. of Phys. & Biophysics Univ. of Wash. Seattle, Wash.	L. Stark	V	Discussed various noninvasive venous measurement techniques including schemes for inferring vessel diameter, flow and pressure.

No.	Individuals	Affliation	Conducted By	Type of Contact*	Discussions & Results
14.	Vogt, F.B.	Tex. Inst. for Rehab. & Res. Houston, Texas.	L. Stark	V	Discussed various noninvasive techniques for monitoring venous system status. Reviewed the significance of venous pressure and distensibility measurements.
15.	Weltman, G.	Univ. of Calif. Los Angeles, Calif.	L. Young	V	Reviewed his work on arterial pulse wave velocity measurements, discussed the problems of pulse wave velocity measurements as applied to the venous system.