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In the operation of high performance aircraft, operational crews are often subject to high sustained $\pm G_Z$ acceleration. The response of the human cardiovascular system to these acceleration forces has been the object of considerable research. Numerous techniques have been used to measure important parameters of cardiovascular function; however, plethysmographic measurements of blood volume shifts have not been possible during exposure to hypergravity because of unavoidable tissue deformation. Such measurements have added

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FINAL TECHNICAL REPORT
February 1981 to September 1985

ULTRASONIC QUANTIFICATION OF BLOOD VOLUME REDISTRIBUTION UNDER HYPERGRAVITY

by

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and

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January 15, 1986

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ABSTRACT

In the operation of high performance aircraft, operational crews are often subject to high sustained $\pm G_Z$ acceleration. The response of the human cardiovascular system to these acceleration forces has been the object of considerable research. Numerous techniques have been used to measure important parameters of cardiovascular function; however, plethysmographic measurements of blood volume shifts have not been possible during exposure to hypergravity because of unavoidable tissue deformation. Such measurements have added significantly to understanding of the cardiovascular response to postural shifts and to zero-g. A multi-channel instrument has been developed which employs multiple ultrasonic depth measurements to determine the volume of blood contained in the various compartments of the circulation during exposure to hypergravity on a centrifuge. These volume measurements can be used to study the time course and quantity of blood shifts produced by exposure to selected acceleration profiles and physiological manipulations, including anti-G suit inflation. The data obtained should provide improved understanding of basic cardiovascular physiology and of the relative effectiveness of various anti-G devices.

INTRODUCTION

Time-dependent, whole body acceleration applied along the spinal (G_Z) axis of the body can produce significant alterations in arterial and venous blood circulation (1-5). With the recent development and deployment of high speed terrain following tactical aircraft and hovercraft, operational crews are subjected to sustained high accelerations. According to Leverett et al (6) future military aircraft will have performance characteristics which will expose aircrews to accelerations above 6 G for periods exceeding 2 minutes.

Accelerations of this magnitude are capable of producing severe impairment of crew performance through loss of vision, or even unconsciousness, if adequate protective techniques are not applied. The standard protective device against the effects of positive (+ G_Z) acceleration is the application of pressure to the lower part of the body (15). This pressure prevents blood from pooling in the legs and helps maintain venous return. In theory, application of pressure prior to onset of acceleration should improve G tolerance further than the normal inflation after the onset of acceleration; however, the effect of earlier inflation is controversial (2).

Various voluntary maneuvers have been used in an effort to improve G-tolerance. The M-1 maneuver in which the subject exhales against partially closed glottis while tensing his muscles is the most widely used. This maneuver provides some slight increase in G-tolerance while requiring active participation by the subject. M-2, also known as the valsalva experiment, originally referred to "blowing against a closed manometer system so as to maintain intrapulmonary pressures of 40 to 60 mm Hg for 10 sec immediately before G exposure"

(31), is also routinely used in hypergravity situations. Current protective techniques and M_1, M_2 maneuvers are capable of increasing tolerance to + G_Z loading by 2-3 G [14].

An extensive body of published literature exists on the effects of hypergravity on the cardiovascular system dating back to the early 1940's. Burton et al (12, 14) and Christy (41) have written excellent reviews of this literature. Specific topics such as effects of sinusoidal + G_Z acceleration (16), regulation of circulation during prolonged stress (17) and cardiovascular changes due to short duration exposure (18) have been studied. As part of this report only a brief review of physiologic responses is given in order to define the need for measurements of the quantity and time course of fluid shift during hypergravity exposure.

Positive acceleration shifts fluid from the head and thorax into the legs, reducing venous return to the heart. This shift produces an increased pressure in the arteries and veins of the legs and a decreased blood pressure at the level of the heart. Reflex factors are capable of partially compensating for these effects. Application of pressure to the lower parts of the body partially prevents this pooling and allows higher G-loads to be sustained without blacking-out. Negative acceleration produces increased pressures in the head and thorax. Because the vasculature of the upper part of the body is less distensible than that of the legs, the blood normally contained in the lower body cannot be accommodated in the upper; hence, the venous columns remain open throughout their entire length. This produces large hydrostatic pressures than those that occur with positive accelerations. The limiting factor in tolerance of sustained negative acceleration is the pain produced by this hydrostatic

pressure in distending the unsupported veins of the head (27). The rigid skull evidently protects the vessels of the brain from damage as a result of the increased pressure. In negative acceleration venous return to the heart is impeded by increased pressure in the thorax (27). In addition to the work directly related to hypergravity extensive literature exist concerning the effects of postural changes on the cardiovascular system (11, 21, 22, 23, 24, 25, 26). These effects have been reviewed by Gauer and Thron (3), and by Folkow et al (29). These studies provide a theoretical framework within which the effects of hypergravity can be placed.

The acceleration studies which have been reported rely upon invasive measurement of venous and arterial pressures by cannulation of vessels and upon various indirect noninvasive indicators of cardiovascular function. These noninvasive measurements include EKG, oxygen tension determination by oxymeter ("ear oximetry"), thoracic pressure determination by esophageal catheter, and, more recently, flow determination by Doppler flowmeter. Loss of eye level arterial pressure has been correlated with cessation of blood flow to the retina (7) and used as a reliable indicator of cardiovascular status. However, this technique is invasive requiring cannulation of a radial artery. Transcutaneous Doppler flowmetry was used by Kurtz et al (8) in an attempt to correlate eye-level (temporal artery) flow velocity with direct arterial pressure during + G_Z acceleration. They observed that during the rapid onset runs (ROR, 1 G/sec) zero forward flow and a mean arterial pressure of 20 mm Hg occurred 6 sec prior to blackout. It is generally assumed that 20 mm Hg is close to the critical closing pressure of the branches of temporal artery (9).

However, during the gradual onset runs (GOR, 0.1 .G/sec), blackout occurred before a sustained zero forward flow and mean pressure of 20 mm Hg had been reached. Kurtz et al (8) suggest that this could be attributed to reduced oxygenation of blood during prolonged + G_Z exposures (10). In a recent study designed to compare various current methods of assessing G tolerance Voge has reported that the doppler veloci-meter technique is most reliable in predicting impending blackout (13).

This brief review confirms that most of the effects of axial acceleration are due to shifts of blood between vascular compartments; however, few studies have been reported in which the volume of these shifts are measured (28). Knowledge of the quantities of blood shifted under experimental conditions would provide a direct indication of the effectiveness of countermeasure devices and maneuvers, without the necessity of pushing the subject near blackout. Such studies would also provide an improved understanding of basic cardiovascular physiology. In addition, such measurements might provide an improved indication of impending blackout.

The oldest and conceptually the simplest plethysmographic technique is volume displacement. The limb is immersed in a fluid, usually water, and changes in limb volume are indicated by changes in the volume of fluid displaced. In addition to the obvious technical problems involved in use of this type of system at high acceleration, this approach is unsuitable because the hydrostatic pressure in a water plethysmograph would completely alter the physiological parameters under investigation (32, 35).

The use of an air displacement plethysmograph for centrifuge measurements has been reported in abstract form (28). In this study

an attempt was made to compensate for acceleration induced distortions in tissue shape by conducting centrifuge runs in which leg volume was held constant by means of occlusive pressure cuffs. In general, air plethysmographs suffer from the high thermal expansion coefficient of air and from difficulties in maintaining fluid seal. For these reasons, air plethysmography has not been extensively used.

The standard instrument for routine volume measurement in the physiology laboratory is the Whitney ("Mercury-in-rubber") strain gauge (34). This instrument records changes in limb circumference at a single site. Data are interpreted on the assumption that the limb cross section is circular. Despite this limitation, the technique has been shown to yield volume data which are as accurate as those obtained from the water plethysmograph. However, due to the distortion of tissues during high acceleration and to the probable direct effect of acceleration on the device reading, this approach seems unsuitable for use in hypergravity research.

In recent years, a considerable effort has been expended toward development of plethysmographic techniques suitable for use in space flight. During the Skylab missions, a capacitance plethysmograph was used to determine changes in leg volume (30, 37). Although this instrument was the best available at this time, it suffered from several limitations including sensitivity to humidity and temperature and bulkiness. Bhagat et al have developed a microprocessor based plethysmograph which determines leg cross-sectional area by measuring the transit times of ultrasonic pulses across the calf of the leg (36, 38, 39). More recently, Kirsch et al (19, 20) have demonstrated that reliable measurements of blood redistribution occurring during

postural changes can be made by use of measurements of tissue depth above bone. In this approach, an ultrasonic transducer is attached to a body to location where a thin layer of skin covers a flat bone structure. An ultrasonic pulse from the transducer is reflected from the bone and returned to the transducer. The time required indicates the thickness of the tissue. This tissue thickness is directly proportional to the quantity of blood in the tissue.

These two techniques yield complementary information. The former yields a quantitative estimate of the amount of blood pooled or removed from the entire leg. The latter measures the condition of the superficial vessels and allows measurement of blood redistribution in parts of the body not accessible by any other plethysmographic technique. Combination of the two approaches will provide a sophisticated monitoring system which can be used in a variety of physiological experiments.

The major objective of this project was, therefore, to develop the authors' concept of ultrasonic plethysmography into a practical technique for measurement of blood volume redistribution under hypergravity. Related goals of the project were definition of optimum sites for monitoring blood volume redistribution, design and fabrication of necessary transducers, and development of a basis for separation of deformation induced changes from those due to the blood shift.

ULTRASONIC PLETHYSMOGRAPH

The ultrasonic plethysmograph is based on measurement of the transit time needed for an ultrasonic pulse to propagate from a given point to another. If the velocity of propagation through the medium

can be assumed to be constant, then measurement of transit time allows a computation of traversed distance. Rushmer et al (42) and others (43,44) have used this transit time measurement principle to monitor dynamic changes in left ventricular dimensions invasively in laboratory animals. The instrumentation developed in our laboratory (36) differs from that of Rushmer and others in the selection of ultrasonic frequency due to larger distances involved, circuit design and implementation for a noninvasive application. Figure 1 shows a block diagram of the ultrasonic plethysmograph. The basic units are a pulse generator, a receiver amplifier, a voltage comparator and an elapsed time counter. Two ultrasonic crystals (2 MHz resonant frequency) are mounted on opposite sides of a limb in such a manner that the generated ultrasonic pulse traverses mainly through soft tissue. One of the crystals (Transmitter) when excited by the pulse generator produces a short duration ultrasonic pulse detected by the other transducer (receiver). The elapsed time for pulse propagation is measured using a 32 MHz clock which is turned on by the transmitted pulse and off by the received signal. This transit-time, as indicated earlier, is proportional to chord length for a constant velocity of propagation (1560 m/sec for gastrocnemius muscle tissue). In a comparative study, using venous occlusion procedure, the developed instrument gave results that are comparable in accuracy and sensitivity to the double strand Whitney strain gauge (36). We have recently extended this principle to measure cross sectional area through ultrasonic measurement of two independent chord lengths at a given site (38). To provide the user with maximal flexibility in choosing measurement sites, a four channel instrument was developed as described below:

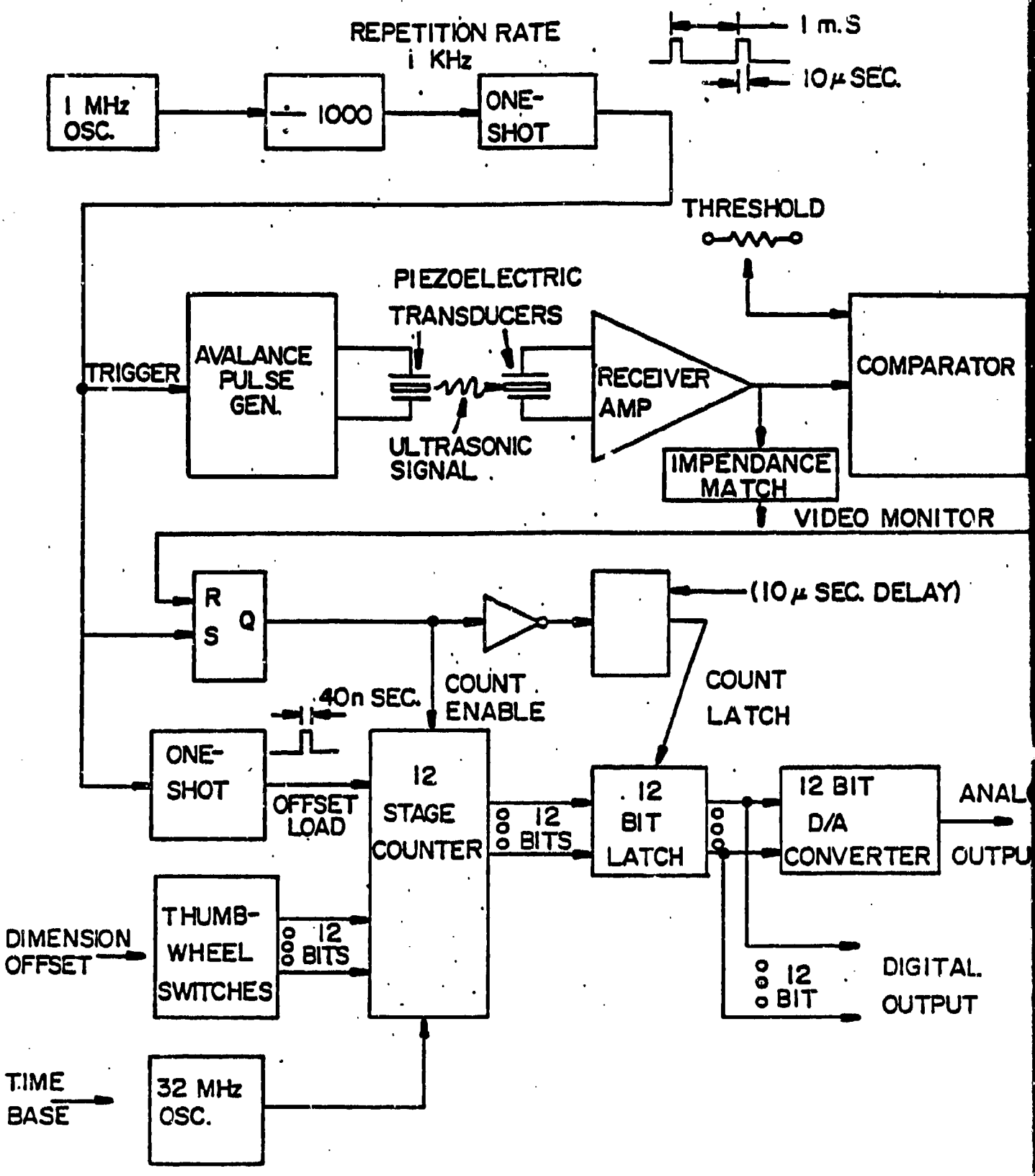


FIGURE 1 Ultrasonic Plethysmograph

FOUR CHANNEL ULTRASONIC PLETHYSMOGRAPH

The developed Ultrasonic Plethysmograph estimates the separation of up to four pairs of ultrasonic transducers by measuring the time an ultrasonic pulse takes to travel between a pair of transmitting and receiving transducers (piezoelectric crystals of compatible resonant frequencies) located on the body. This transit time is converted to a voltage proportional to the separation by a linear Time-to-Voltage convertor. At the end of the transit period, the final voltage is sampled and held for output. The output signal itself may be filtered or amplified, as required.

Referring to Figure 2, the system may be divided into six functional blocks: the Transmitter (Pinger Drive/Amp), Receiver/Comparator (RCVR/CMPR), Time-to-Voltage (T-V) convertor, Sample & Hold amplifiers, Calibration module, and Sequencing Logic/Inhibit control. Figure 2 also depicts the optional output processors. The instrument incorporates a highly multiplexed design which permits the use of a single receiver, transmitter, calibrator, and T-V convertor to service each of the four dimensioning channels. Each channel has a separate output circuit so that offset, amplitude, and filtering may be adjusted independently. The benefits of such a scheme include reduced crosstalk, size, parts count, and power requirements.

The function of each of the subsystems is described below, followed by system timing and a detailed circuit description.

Transmitter

The Transmitter, or Pinger, is activated by the control logic and consists of a low voltage pulse generator, a high voltage pulse amplifier and its power supply, and a transducer selector. It is

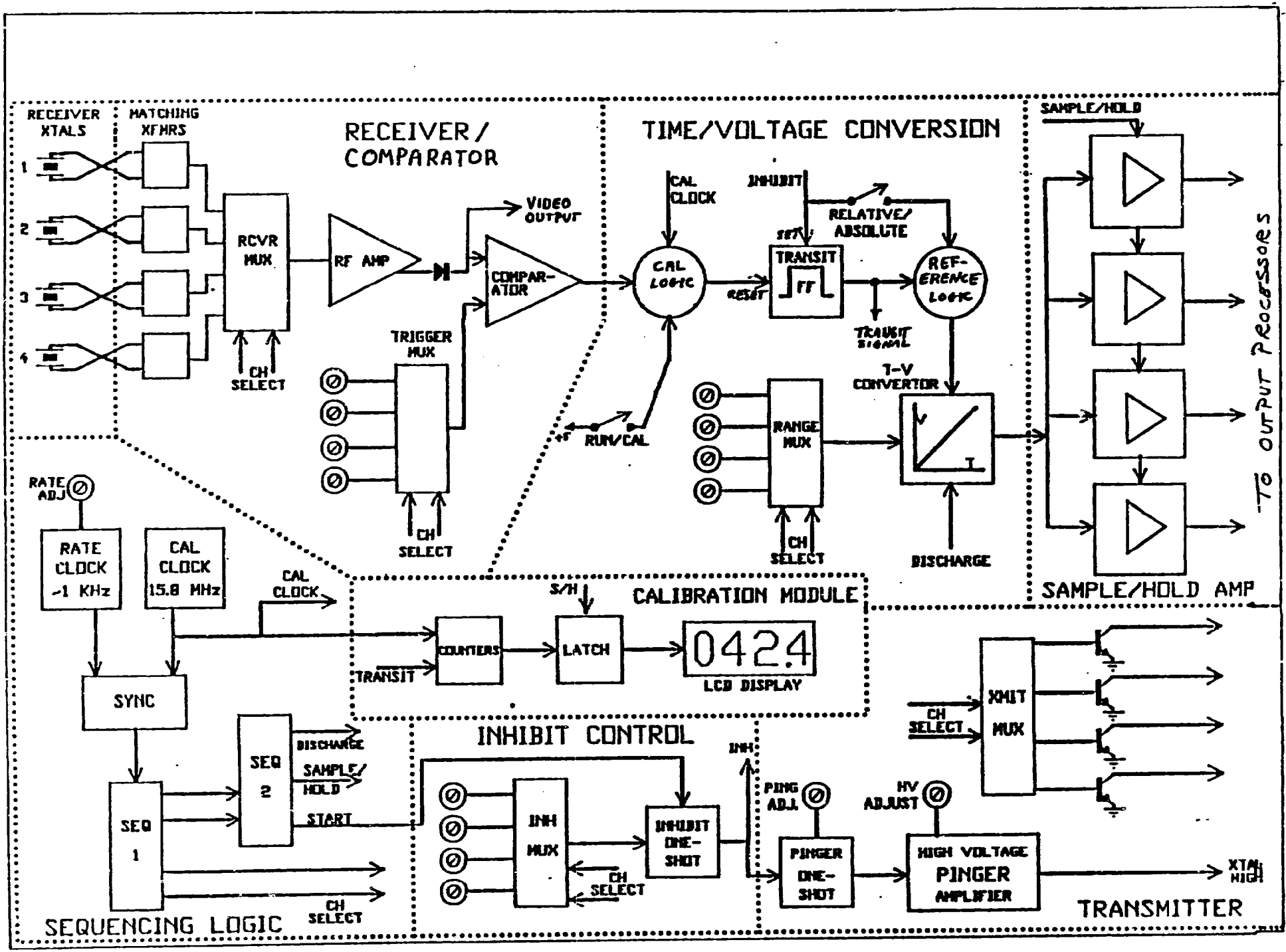


FIGURE 2. Block diagram of four channel ultrasonic plethysmograph

responsible for creating a high voltage pulse of narrow width used to excite a piezoelectric transducer at its thickness-mode resonance. Of concern here are factors such as pulse voltage, width, and damping: Voltage must be sufficient to initiate a response of desired amplitude, width must then reinforce the response to achieve a maximum first-cycle amplitude, and damping must be great enough to prevent excessive ringing.

The pulse generator drives a high voltage (up to 320 volts), high speed push-pull amplifier which sends the pulse to all four transducers simultaneously. Power is derived from the 120 VAC line by a voltage doubler which can supply 320 VDC, and is adjustable over a 0-320 volt range to attenuate reflected signals or crosstalk if necessary. One transducer, that of the selected channel, is provided a return path to ground, and so only that channel will be excited.

Of particular importance is that the output impedance of the amplifier is very low due to the nature of the VFET output stage. This results in a highly damped response from the output crystals and thus limits the number of cycles produced by the transducers while increasing the amplitude of the first few cycles.

Receiver/Comparator

The Receiver block consists of four isolation transformers, an input multiplexer, a two-stage differential receiver, and a comparator with trigger multiplexer. The signals detected by the receiving transducers are isolated, impedance matched, and band-pass filtered to some extent by the isolation transformers, then passed to an analog multiplexer which selects one of them for further processing.

The ultrasonic receiver amplifies the minute signal levels

detected by the selected receiving transducers. The receiver consists of two stages of differential amplification for a total gain of 65 dB over its passband of 1 to 8 MHz. The output is a "Video" signal in the 5 volt p-p range which may be observed on an oscilloscope as an indicator of relative transducer position, crosstalk and noise, and ping amplitude. This signal is also compared with an adjustable trigger voltage, selected by a multiplexer, to provide information regarding the arrival of an ultrasonic wavefront at the Time-to-Voltage convertor.

Time To Voltage Convertor

This block consists of a Transit Flip-Flop, a RANGE control multiplexer, a T-V convertor, and some calibration and reference logic. It is the function of this group to collect information from the control logic and the receiver, and to provide an output pulse whose width is proportional to the separation between a transducer pair. This Transit signal is also available for observation on an oscilloscope as an aid for adjustment of the trigger levels.

The output of the receiver/comparator is fed to calibration logic, and then to the Transit Flip-Flop. It is this device which monitors the progress of the pulse; its output is a rectangular waveform (the Transit signal) which is set when the Ping is issued, and reset when a signal in response is received through the receiver network. The duration of the Transit signal is thus directly related to the physical separation of the transducers.

The Time-to-Voltage convertor circuit consists of a switched constant-current source charging a capacitor at a fixed rate for superior linearity. The rate of integration may be adjusted by a

RANGE control selection through the multiplexer in order to maximize the dynamic range of the output signal. In addition, the ABS/REL switch, through reference logic, can select an absolute mode where T-V conversion is begun at the onset of a cycle, or a relative mode where conversion is delayed until after an inhibit period selected by the user. Ideally, the output should be zero volts for minimum separation and 5 volts for maximum separation, and with proper adjustment of Range and reference mode this ideal can be approached.

Sample/Hold & Output Processor

The output stage consists of four separate Sample-and-Hold amplifier (S&H), which acquire and retain the results of the above operations, and four processing networks. The S&H amps are directed to sample the output of the T-V convertor by the control logic according to the system timing, and the values are held while the other channels are measured. The output voltages are fed to optional processing networks (not shown in Figure 2) which may include filters and amplifiers. These are not multiplexed and could each be optimized for a particular channel, if necessary.

Calibrator

Provisions have been made for a calibration module, which may be attached to the main circuit board by a ribbon cable. Digital display of transducer separation is achieved by counting pulses from an oscillator while the Transit signal is active. The calibration pulses are of known duration, in this case 63.3 ns (corresponding to the time required for sound to travel through 0.1 millimeter of tissue at 25°C), allowing a simple counter to determine the distance between the

transmitting and receiving transducers by gating the pulses with the Transit signal. The count is latched, decoded, and displayed for the selected channel.

Calibration may be accomplished in two modes: RUN mode allows continual display of the transducer separation, so that fixed measurements are easily accomplished by relating separation to the display and to the output voltage. In contrast, CAL mode simulates the separation by disabling the pinger and artifically controlling the Transit signal with the INHIBIT control. The operator can set inhibit to cover the range of possible separations for a given channel, as displayed by the calibrator, and annotate the strip chart output for reference. Each channel may be calibrated independently.

Control Logic

The control logic, consisting of Sequencing Logic and Inhibit Control, is responsible for system timing and channel sequencing. The major components are a rate clock, which determines the rate at which each channel is measured; a channel selector (Sequencer 1), which switches all multiplexers to the channel selected; a state generator (Sequencer 2), which controls the sequence of operations during the dimensioning cycle; and an "Inhibit" generator to control the period during which the system will ignore signals from the receiver, typically in the range of 1mm to 150mm. Also included in the control logic is a calibration clock, used by the calibration module, and a synchronizer used to ensure that the calibrator gives consistent measurements.

System Timing

The system timing for one dimensioning cycle is presented in Figure 3. There are four states in this cycle, each state corresponding to one tick of the Rate clock. Only one of the four channels is active during this period: The channels are sampled sequentially, so that each channel is serviced in one of four dimensioning cycles, or once every 16 cycles of the rate clock. Each cycle consists of four states: Start, Wait, Sample and Discharge. A description of events during a typical cycle follows: The duty cycle of the Rate clock has little significance, since it is the leading edge of this signal that eventually does the work, but it is depicted as a square wave. This signal is synchronized to the Cal clock (not shown here) to produce a time-shifted Rate clock which controls sequencer 1. The CH Select signals are generated at this point, as well as the raw State Select signals (not shown), which are decoded by sequencer 2 to produce the four states.

The leading edge of State 1 (Start) initiates the Inhibit pulse, which in turn sets the Transit flip-flop and triggers the transmitter or "Pinger". The resulting ultrasonic pulse from the selected transmitting transducer propagates through the interposing medium, arriving at the appropriate receiving transducer in its line of travel. The mechanical energy of the pulse excites an electrical signal in the piezoelectric material, which is amplified by the receiver and passed to both a video output amplifier and a comparator. The Video signal may be observed on an oscilloscope if desired.

When the amplitude of the received signal exceeds a trigger level set by the operator, the comparator resets the Transit flip-flop.

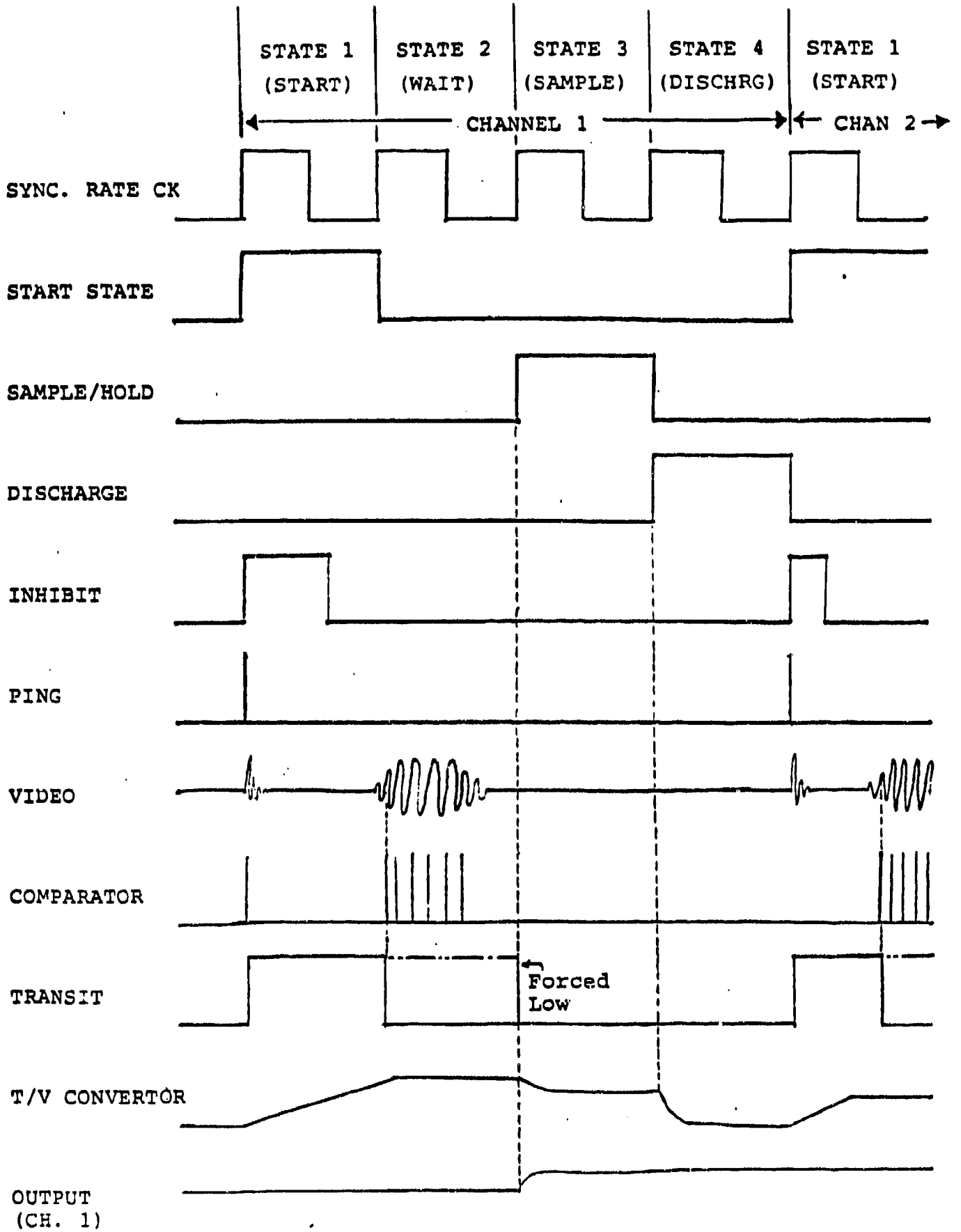


FIGURE 3. SYSTEM TIMING

(ONE DIMENSIONING CYCLE)

During this period, the calibrator counts pulses from the cal clock; when Transit ends, the final count reflects the distance travelled by the pulse in tenths of millimeters.

State 2 is a wait state which extends the range of measurements. It is not used directly, and leads into State 3 (Sample). After ample time has elapsed for the pulse, if any, to be received, State 3 begins. During this period, the result of the T-V conversion is sampled by the output section, and the final count of the calibrator is latched for display. If the Transit signal has not yet been reset by a received ultrasonic pulse, it is reset at this time in preparation for the next dimensioning cycle.

Finally, State (Discharge) causes the voltage previously recorded to be held at that level until the currently active channel is once again sampled. Also, the T-V capacitor is discharged at this time in order to reset the converter for the next cycle, and the calibration counters are reset.

The dimensioning cycle repeats as above for each of the four channels, at a frequency determined by the rate clock.

Instrument Operation and Measurement

Measurements were taken with the developed instrument in both the Absolute and Relative modes, in order to verify correct and accurate operation. The procedures used and the results obtained are outlined below, along with signal waveforms observed in both this and an earlier instrument (for comparison).

Two hemispherical 2 MHz transducers were connected to channel 1 of the instrument, mounted on a standard X-Y positioning device, and placed into a water bath containing approximately one liter of

distilled water (23°C). Styrofoam inserts were fitted to each end of the bath to attenuate ultrasonic reflections.

The receiving transducer was mounted on a positioning rod calibrated in tenths of millimeters, while the transmitting transducer was fixed such that the separation between the pair was 10mm initially. The maximum travel of the receiver positioner was 80mm, for an actual range of transducer separation of from 10mm to 90mm.

The instrument was then connected to an oscilloscope with SYNC providing the external trigger while VIDEO and TRANSIT supplied the two Vertical Input channels. The oscilloscope controls were adjusted to provide the image in Figure 4A.

The controls on the instrument were adjusted as follows: The ABS/REL switch to the ABS position, RUN/CAL to RUN, RATE and PING VOLTAGE set to maximize oscilloscope intensity (for photographic purposes) while minimizing reflections. The INHIBIT and TRIGGER levels were adjusted to permit the TRANSIT signal to follow a single leading half-cycle of the received waveform over the entire range of expected separation (Note the INHIBIT marker in the trough of the TRANSIT signal in Figure 4A).

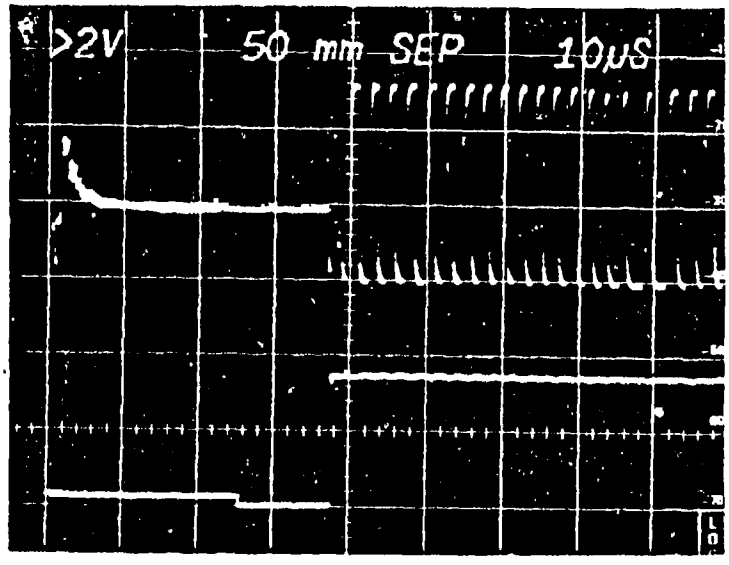
A Fluke D804 voltmeter was connected to the output terminal for channel 1in order to monitor the separation voltage, while one channel of the oscilloscope was used to observe the voltage across T/V Convertor capacitor C3 (Figure 4B). The separation between the transducers was set to maximum (80mm) and the RANGE control was then adjusted to ensure that the slope of the T/V Conversion was optimal for the range of measurements (ie, the constant-current source approached saturation at maximum separation).

The oscilloscope was then removed from C3 to prevent premature discharge, and reconnected to the VIDEO signal. Transducer separation was then reduced to relative zero (10mm dome to dome), and the OFFSET control for channel 1 adjusted for an output voltage of zero as measured on the voltmeter. Measurements were then taken at 5mm intervals over the range of 0mm to 80mm, and the results plotted in Figure 5.

The above procedure was also followed for measurements in the relative mode over a range of 30mm to 40mm, as measured on the receiver positioner. ABS/REL was set to REL, and INHIBIT was adjusted to a point just before the received signal at a separation of 30mm (see Figure 4C). The separation was then increased to 40mm, and RANGE was adjusted, as above, for a T/V Converter level just below saturation. This procedure ensures a better signal to noise ratio over this more precise range of measurements. Measurements were then taken over the 30mm to 40mm range in increments of 1mm, with the results shown in Figure 6. As can be seen from Figure 5 and 6 the developed instrument provides good accuracy in either made of operation under simulated conditions. Figure 7 shows the improvement in time to voltage conversion accuracy compared to a conventional converter. Improvements in both rise and fall time of pinger output are shown in Figure 8. This is expected to provide better overall accuracy in plethysmographic measurements.

FABRICATION OF APPROPRIATE TRANSDUCERS

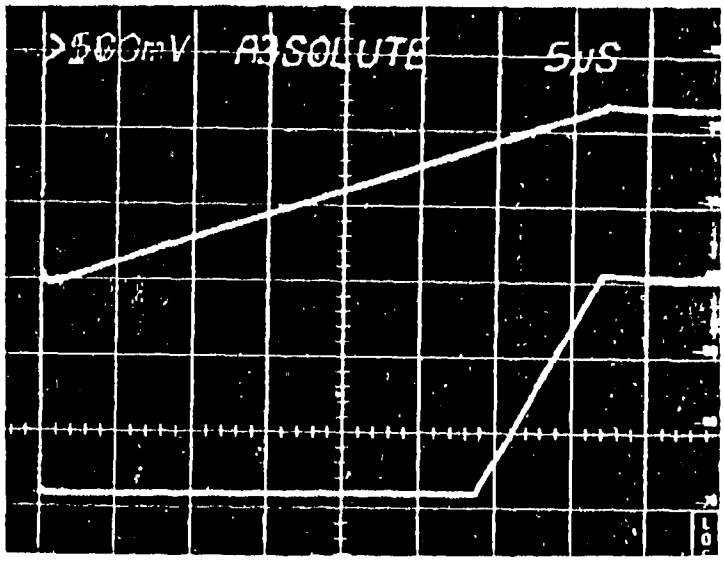
Because of unique requirements of operation under hypergravity, it is essential that low mass transducers be used. In addition, due to specific geometries at the chosen sites, the shapes of the



A: VIDEO and TRANSIT Signals as observed under normal operating conditions.

Note INHIBIT indicator in trough of TRANSIT.

Note position of trigger



B: T-V Convertor Signal Absolute Mode

C: T-V Convertor Signal Relative Mode

FIGURE 4. TYPICAL SIGNALS OBSERVED DURING SETUP

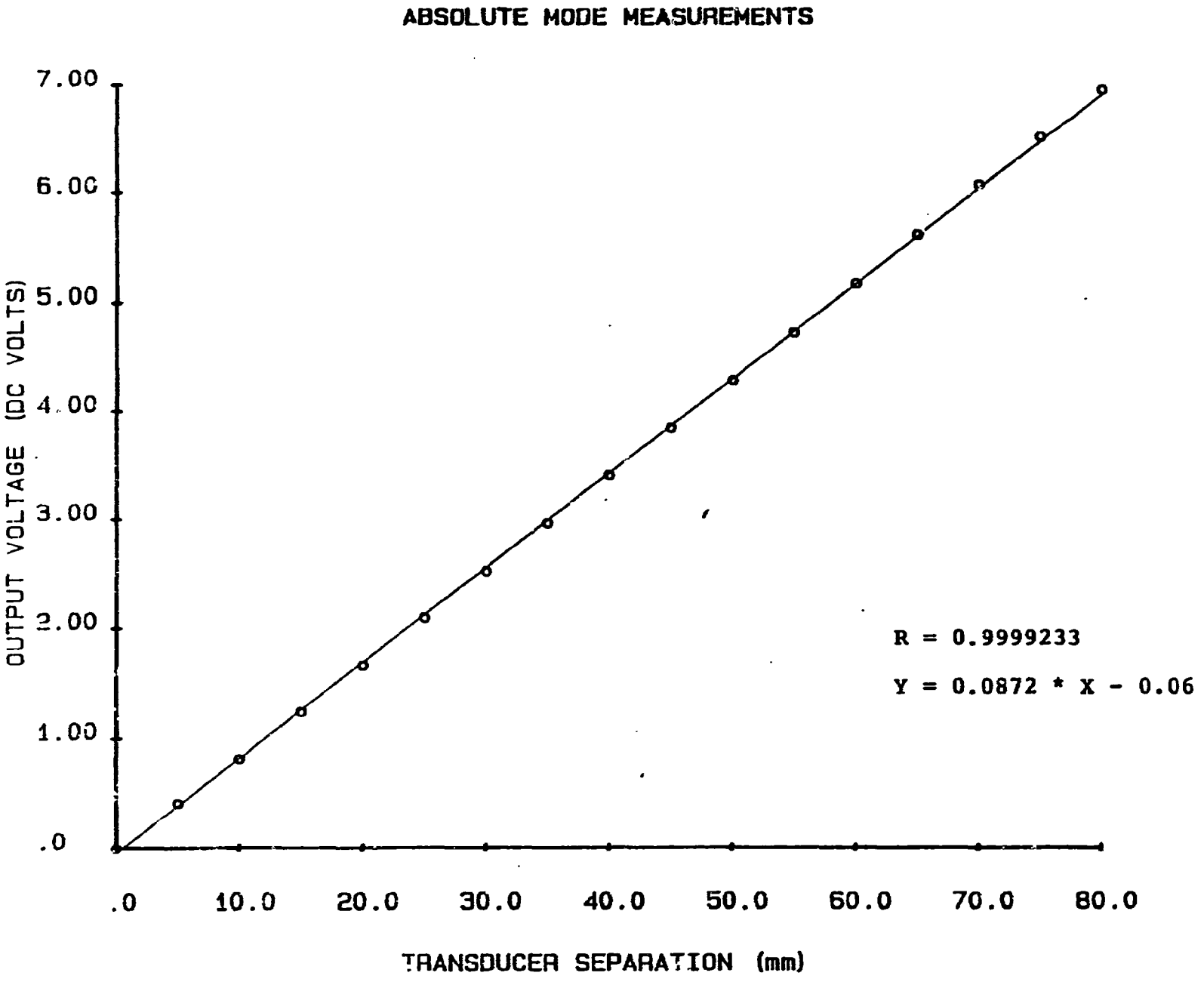

ABSOLUTE MODE MEASUREMENTS
7.00
6.00
5.00
4.00
3.00
2.00
1.00
.0
OUTPUT VOLTAGE (DC VOLTS)
R = 0.9999233
Y = 0.0872 * X - 0.06
.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
TRANSDUCER SEPARATION (mm)

FIGURE 5.

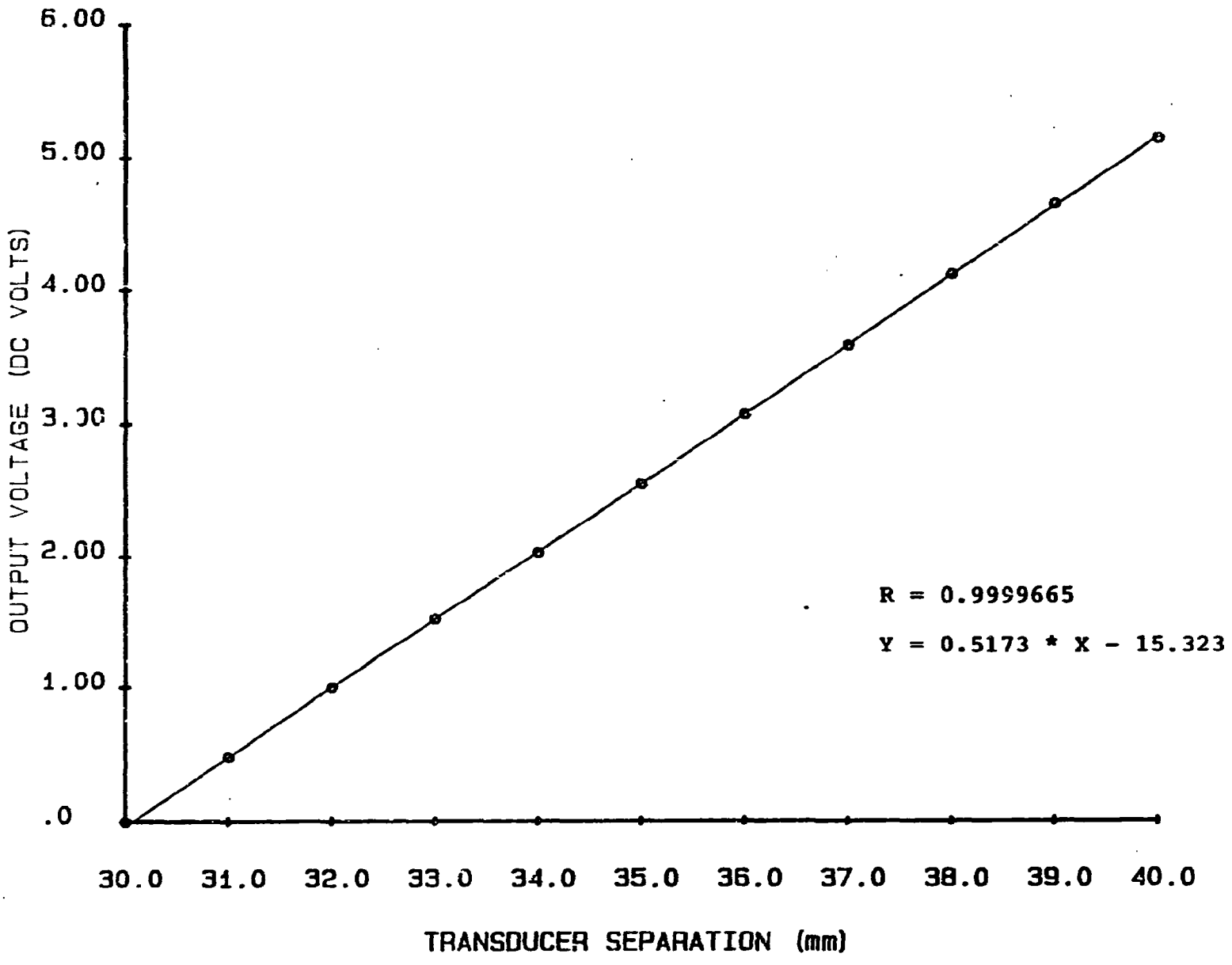
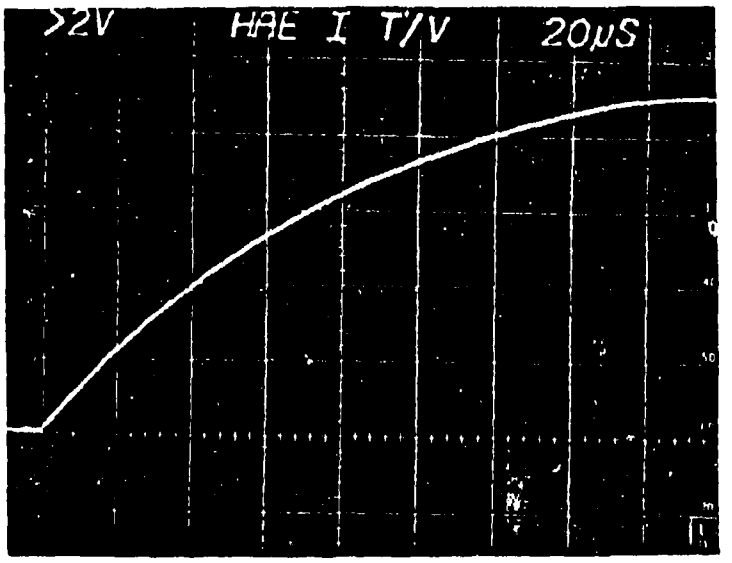
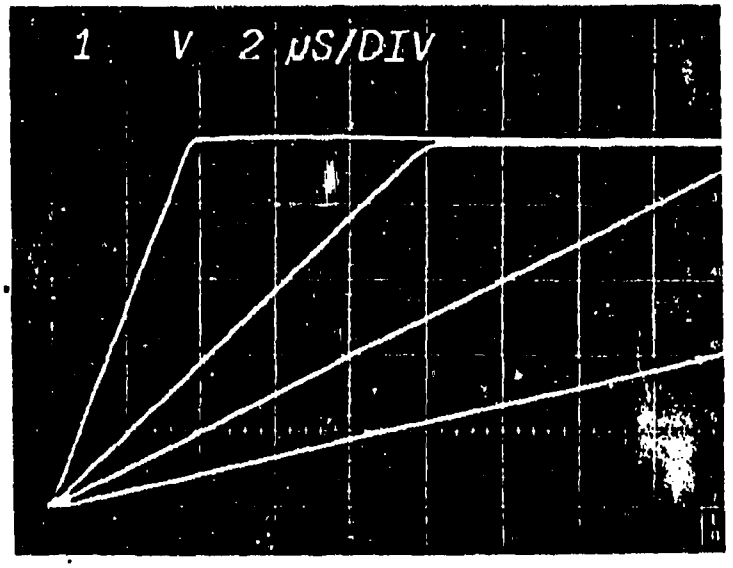

RELATIVE MODE MEASUREMENTS
6.00
5.00
4.00
3.00
2.00
1.00
.0
OUTPUT VOLTAGE (DC VOLTS)
R = 0.9999665
Y = 0.5173 * X - 15.323
30.0
31.0
32.0
33.0
34.0
35.0
36.0
37.0
38.0
39.0
40.0
TRANSDUCER SEPARATION (mm)

FIGURE 6



A: Old T/V Convertor

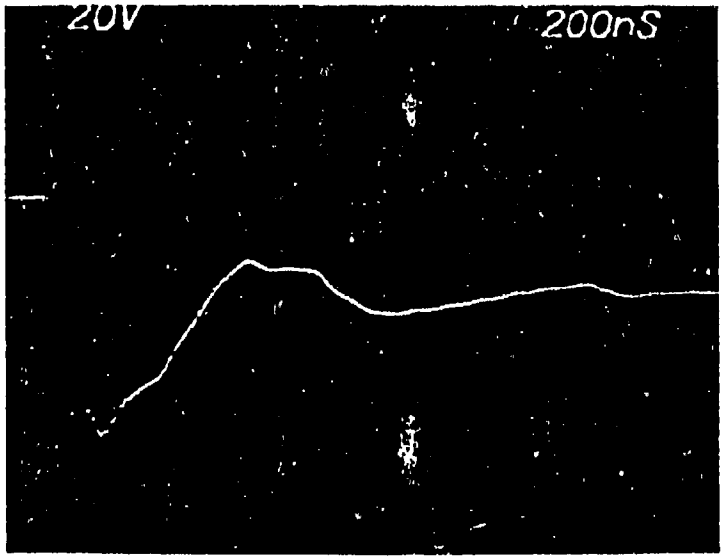
Switched R/C Network
Time Constant Fixed
Common to all channels



B: New T/V Convertor

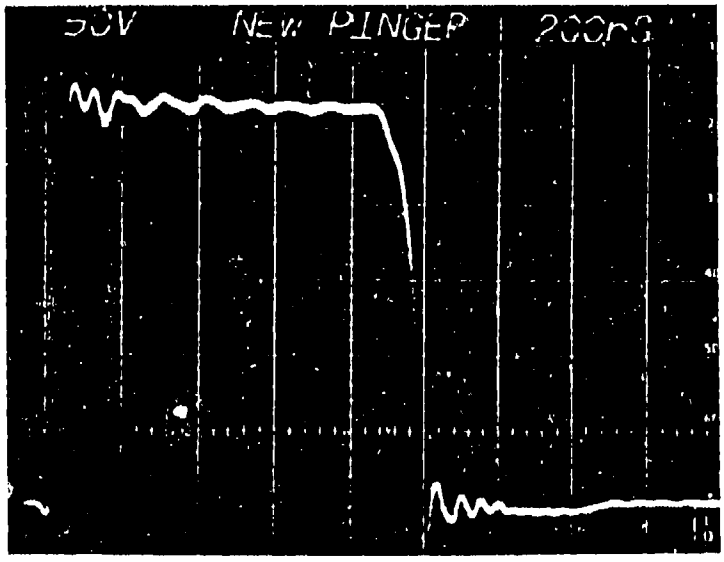
Switched Current Source
Adjustable Slope
All channels shown

FIGURE 7. COMPARISON OF T/V CONVERTOR SIGNALS



A: Old Pinger Output
(Under Load)

Rise Time: 75 nS
Fall Time: 300 nS to 30%
6 uS to 10%
Hold Time: 100 nS Approx
Peak Out : 60 V. Fixed



B: New Pinger Output
(Under Load)

Rise Time: 40 nS
Fall Time: 60 nS
Hold Time: 850 nS Adj.
Peak Out : 265 V. Adj.

FIGURE 8. COMPARISON OF PINGER OUTPUT SIGNALS

transducer mountings must be defined for specific measurements. In the following, we shall describe the salient features of transducers for:

(i) Calf dimension measurement

(ii) Measurement across digits

(iii) Skin depth measurement

Transducers previously developed for calf dimension measurements in zero-g appear suitable for the proposed experiments. A photograph of one of these transducers is included in Figure 9D. The most critical problem with calf dimension transducers is to provide sufficient beam width to allow easy placement and to prevent small changes in orientation from altering the received pulse shape. Two types of unit are used for the calf dimension measurement. Transmitting transducers consist of a 3 mm diameter flat disc of LTZ-2 ceramic. This element is embedded 1 mm behind a plastic convex lens, which serves to diverge the beam and to provide good contact with the tissue. Receiving transducers are constructed from hemispherically shaped transducer elements, which are completely non-directional. The transducers are embedded 1 mm deep in plastic. The combination of the two transducers produces a system which provides for ease in transducer placement and in obtaining satisfactory signals.

For small distance measurement across digits or other body parts, the directional characteristics of the transducer are less critical because of larger signal amplitude available; however, the transducer housings must be specially shaped for the location of interest. A photograph of transducers intended for measurements across digits is included in Figure 9B. These transducers consist of 2 mm diameter

discs of LTZ-2 transducer material embedded in plastic. The mounting is curved with radius of a 5 cm to give improved contact with the digit.

Because of the small distance involved in measuring the depth of skin, and the proximity of the receiving and transmitting transducers, the most difficult technical problem in design of skin depth transducers is providing sufficient damping so that the returning echo is not obscured by oscillations remaining from the transmitting signal. The damping achieved largely determines the signal-to-noise ratio of the system. Commercially available transducers, such as those used by Kirsch et al (19) provide damping by use of an extensive backing plate; however, the use of this backing material makes the transducer too heavy for hypergravity use. We have explored several alternative approaches to providing adequate damping.

In an early approach, we used a single flat plate of LTZ-2 piezoelectric material. The conductive coating of the ceramic was cut so a to form two exectrically isolated transducers. Damping is achieved by embedding the ceramic transducer in a mixture of tungsten powder and epoxy. The housing of the unit is ensolite foam; this material is light in weight and will not conduct acoustic vibrations. This transducer gave satisfactory results; however, the received signal was not as clean as desired. Figure 9C represents an attempt to achieve damping by directing energy away from the transducer element. In this design, a 4 mm diameter transducer element is attached to the top of a cone. The transducer element is damped by a mixture of tungsten powder and epoxy. A dimple on the face of the element scatters the energy reflected from the skin-plexiglass interface against the sides of the cone, where it is reflected in a direction nearly normal to the

axis of the cone, thus minimizing the effects of scattered energy.

Figure 9A represents a transducer in which two separate transducer elements are placed at an angle such that energy from the first, which is reflected from bone with a depth of 5 mm, is returned to the second transducer. The transducers are mounted in balsa wood, which provides lightweight and mechanical isolation. In tests with human subjects, this third design (Figure 9A) gave better performance than the other two approaches. Echo amplitude was greater and coupling between the two transducers were low. The production of a better signal by this design is probably due to discrimination against signals reflected from the skin surface by the directional characteristics of the crystals and to excellent isolation between the receiver and transmitter.

LABORATORY BASED STUDIES

We conducted several laboratory experiments to provide baseline data towards interpretation of hypergravity data. Both venous occlusion and head up tilt experiments were carried out on healthy subjects, 18-40 yrs., drawn from University of Kentucky student and staff population. Venous occlusion and tilt were used to produce a controlled change in limb volume and local circulation. A pressure cuff was applied to the proximal portion of the limb and pressure in the cuff increased above the venous pressure but below the diastolic arterial pressure (usually between 40-60 mmHg). The rate of volume change with respect to time immediately after occlusion provides a measure of the arterial flow. The limb volume stabilizes at a compliance level where the pressure in the veins equals the pressure in the cuff.

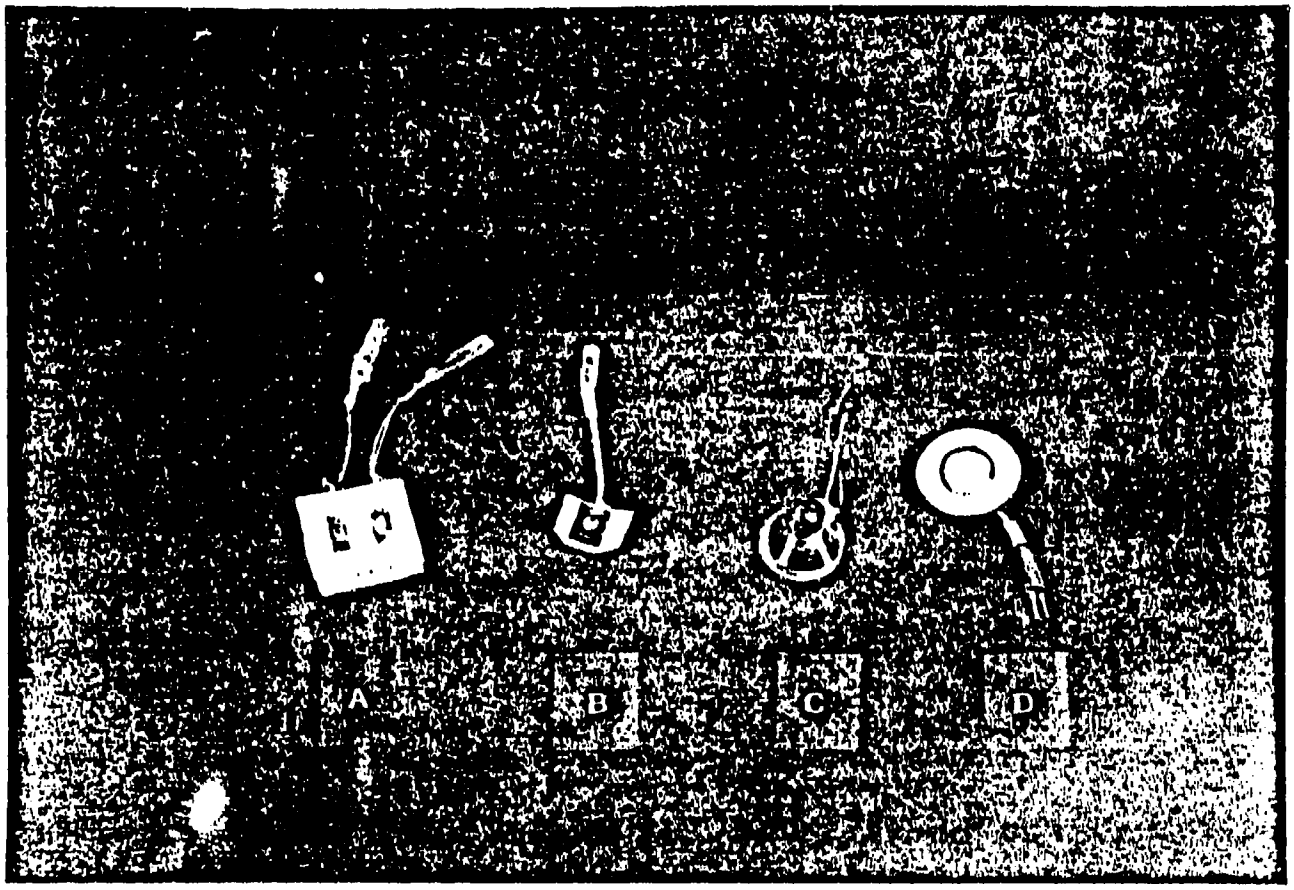


FIGURE 9. TRANSDUCERS

A. Skin depth transducer using angled transducer element.

B. 'Toeducer' transducer designed for attachment to a digit.

C. Cone type skin depth transducer.

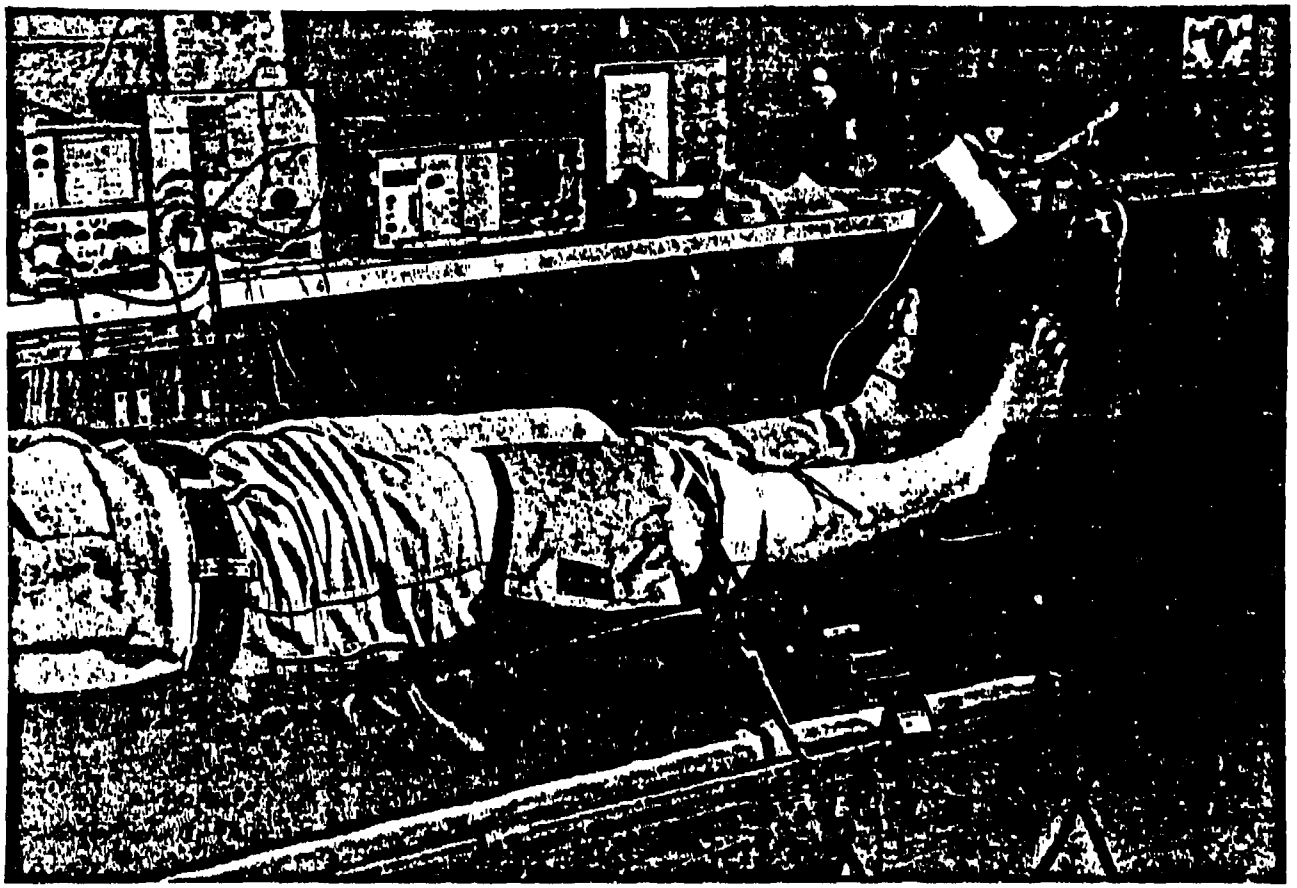
D. Calf transducer.

With the subject relaxed in a supine position on the tilt-table, the calf transducers are positioned on the lower leg at the midcalf region, the skin depth transducers are located above the tibia near the midcalf region and the digit transducers are located across the great toe. The transducers are positioned with the aid of an oscilloscope so that the received signal quality is satisfactory. A thigh cuff is placed on the leg above the knee and a toe cuff is placed proximal to the transducers on the great toe. Figure 10 is a photograph of an instrumented subject on a tilt table.

Briefly, our experimental procedures are (details are given in Appendix A):

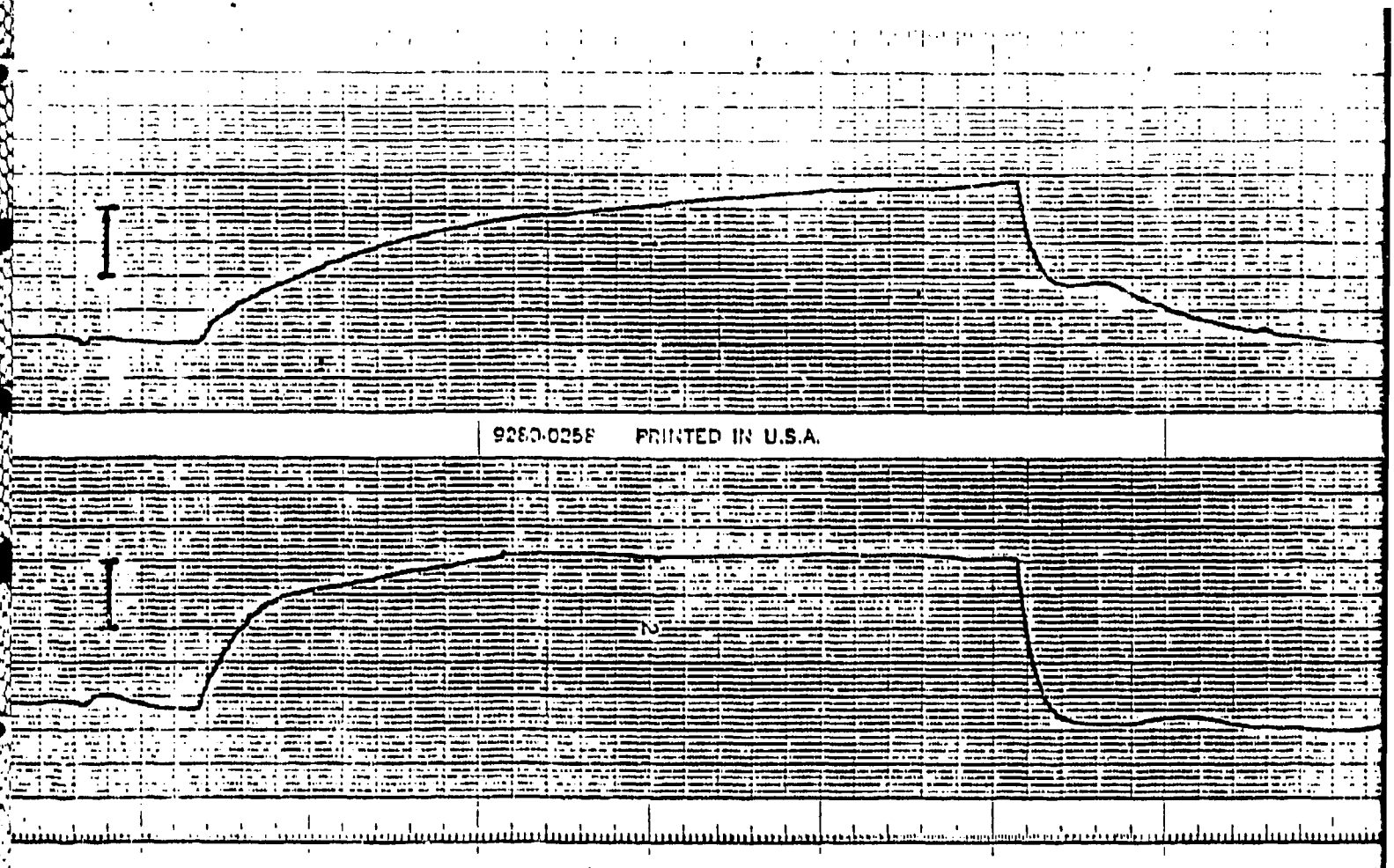
1. Venous occlusion experiments: Obtain stable baseline at -5 Degrees head down position. Inflate thigh cuff to 50 mmHg, hold for two minutes, deflate. Continue recording data until stable baseline is obtained. Repeat the procedure for the toe cuff.
2. Tilt experiments: Obtain stable baseline at -5 Degrees head down position. Tilt to 50 Degrees head up position. Continue recording data until stable baseline is obtained.
3. Localized heat/cold exposure experiments: With the subject in the -5 Degrees head down position obtain stable baseline data. Apply heat to the toe region using a forced air heater. Carry out toe venous occlusion experiments at one minute intervals.

Figure 11 shows the results of a venous occlusion experiment to simultaneously measure skin and muscle blood volume. Transducers were attached at midcalf so as to measure the depth of skin above the tibia



INSTRUMENTED SUBJECT

FIGURE 10



LEGEND: Simultaneous measurement of skin and muscle blood volume.

TOP: Muscle, Calibration Bar 1.11%

BOTTOM: Skin, Calibration Bar 0.72%

TIME: 1 Sec/mm

FIGURE 11

and the distance across the soleus muscle. Limb expansion was produced by inflation of a thigh cuff to 50 mmHg. Because the skin is a very small fraction of the thickness of the muscle, the lower trace records, for practical purposes, only changes in the volume of muscle mass.

In this record pressure was applied to the occlusion cuff at the first arrow and released at the second arrow. In the muscle (top) record the initial slope of the volume increase is an accurate measurement of the blood flow into the soleus muscle. In the case of the skin volume record presented here, the flow cannot be determined with comparable confidence because an unknown quantity of blood may have flowed from skin to muscle through perforator channels. While the quantity of blood available is certainly insufficient to affect the muscle volume determinations, further study is required to determine whether this flow is sufficient to invalidate the determination of skin blood flow in the calf segment by this technique. In any case, the data shown here give important information concerning the state of the skin vasculature: the total volume change measures the "venous compliance" of the bed; changes in the compliance or in the baseline volume produced by hyperemia are directly related to the ability of the bed to respond to sympathetic outflow.

Similar records can be obtained by measuring chords, for example, from top to sole of the foot or across the width of the great toe. If the occlusion cuff is properly placed, these records will produce an accurate indication of blood flow in the measured member in ml per 100 ml of total tissue; however, interpretation of the resulting blood

flow in terms of soft tissue flow is complicated by the presence of an unknown quantity of bone and by the anatomy of the great toe. Fortunately, the proportion of bone in the great toe is small and will have a negligible effect on the flow measurement. The anatomical shape of the toe is important because it is not possible to make the assumption that the tissue expands only in cross-section. This will produce a systematic error which will probably be relatively constant; however, the blood flow derived by these measurements cannot be considered absolutely quantitative.

Shifts of blood out of the thorax affect cardiac output through a reduction in filling pressure of the heart; thus, the meaning of measured blood volume shifts can be better understood with reference to the compliance of the intra thoracic compartment. Koubennec et al (21) measured compliances of different compartments of the circulation by the direct method of hemorrhage and transfusion of blood. These workers report the following compliances for the supine and sitting postures:

	whole circulation	intra thoracic compartment
supine	2.3	1.0
sitting	3.3	1.9

ml/(mmHg x KgBW)

For present purposes, it is convenient to convert these values to those for a specific body weight. Compliances for a 180 pound (82 kg)

body weight are:

	whole circulation	intra thoracic compartment
supine	189	82
sitting	271	156

ml/mmHg

Thus, for an 82 kg subject, a shift of 100 ml of blood out of the thorax results in a decrease in venous pressure in the thorax of 0.64 mmHg for a sitting subject, or 1.2 mmHg for a supine subject.

Application of $+1g_z$ acceleration by a posture shift results in a shift of several hundred ml of blood into the legs (26), thus reducing central venous pressure significantly.

Higher accelerations may be expected to produce larger fluid shifts; however, the quantities shifted may not be directly proportional to the increased acceleration. Physiological experiments are conducted with the subject relaxed; in hypergravity experiments, subjects will almost certainly contract the muscles of the legs during acceleration even when not performing active countermeasure maneuvers.

This conclusion is consistent with the little data available on the quantity of blood shifted into the legs during acceleration. Thus Slaughter and Lambert, using a pneumatic plethysmograph and occlusion cuffs, measured a shift of only 50 ml into the legs during acceleration (28). British workers have determined that omitting calf cuffs from the anti-g-suit produces little reduction in g-tolerance.

Kirsch, et al (20) have measured the increase in skin volume produced by tilt. These authors found an increase of 2.2 to 4.4 ml/100 ml tissue occurred with til With reasonable assumptions as of the total volume of superficial tissues in the lower body, this shift represents 60 to 120 ml total volume shift into the skin with 1 g acceleration. This quantity is, however, very much affected by the subject's sympathetic tone.

Figure 12 shows the effect of warming on blood flow in the toe. Transducers were placed on either side of the toe and a digital occlusion cuff (Hokanson, Inc.) was placed around the base of the toe. Inflation of the cuff produces volume increases characteristic of venous occlusion. Heating the toe with a 45°C air stream produces an increase in blood flow and venous compliance over period of several minutes. Cooling the toe produces a profound decrease in flow. The data shown is for 50 mmHg pressure in occlusion cuff. Figure 12A is the control record with digit at room temperature while Figure 12B shows data at 45°C with the arrow showing the start of heating (scale 2ml/100ml).

The warming experiments described above also demonstrate the advantage of an instrument which is relatively insensitive to ambient temperature and humidity. In warming experiments, the temperature of the tissue bulk, which chiefly determines transit time, will probably not increase more than one or 2°C because of the transfer of heat by the blood. In cooling experiments, where blood flow is markedly reduced, a greater temperature reduction will occur, but the change will still be much smaller than the change in ambient temperature. Although there appear to be little data concerning the temperature coefficient of sound velocity of tissues IN SITU, it is unlikely that

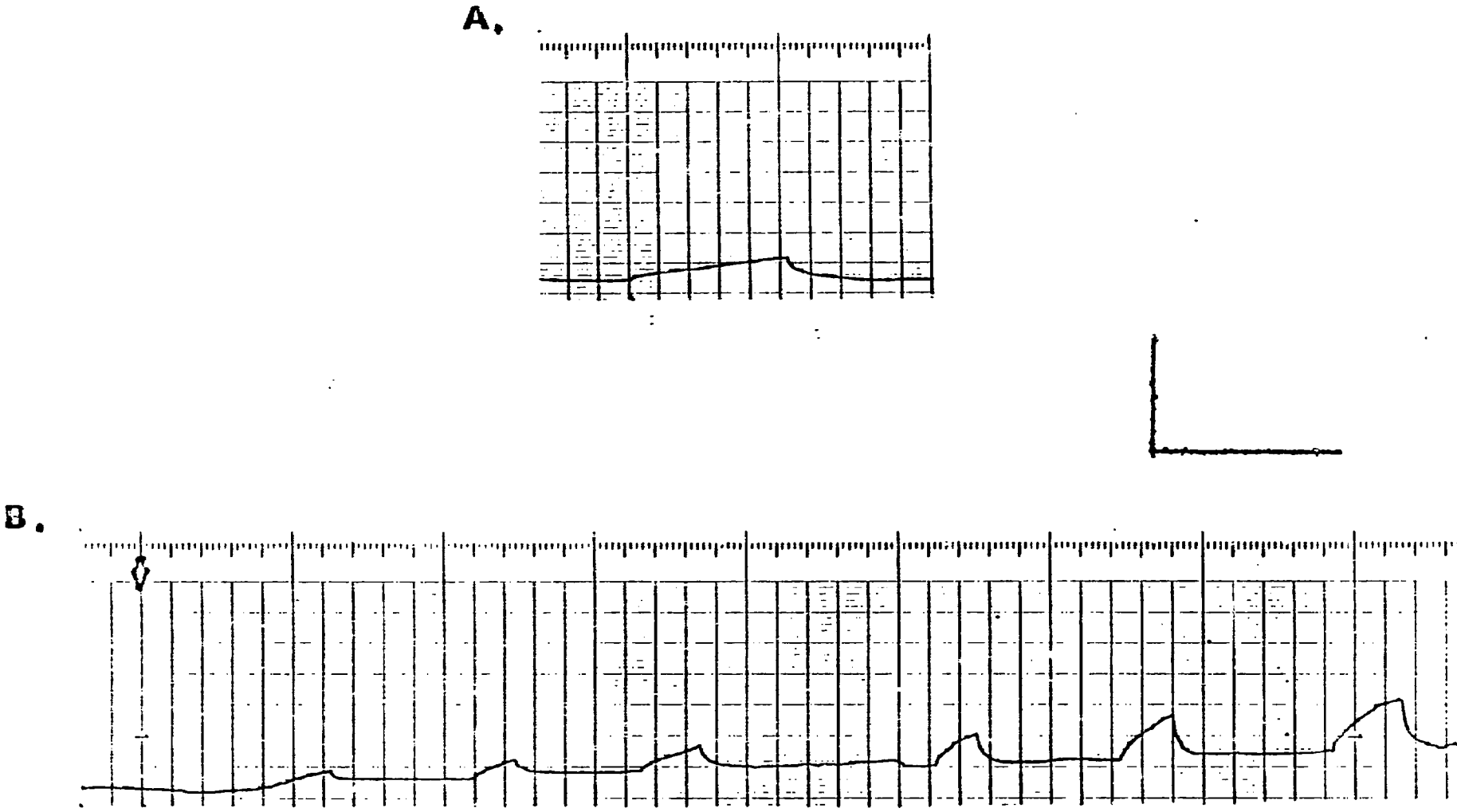


FIGURE 12. VENOUS OCCLUSION ON THE TOE AND WARMING EXPERIMENT

these small temperature changes significantly affect sound velocity. Thus, under physiological conditions, ambient temperature will have a negligible effect on the measured distance. Ambient humidity is without effect on the ultrasonic dimension gauge.

LBNP RESULTS

To assess the effects of LBNP on limb volumes, we determined the changes in horizontal calf distance during LBNP with negative pressures ranging from -20 mmHg to -60 mmHg in 11 experiments on six subjects. In all the experiments there was an initial linear increase in calf distance which lasted approximately four to six seconds, followed by the calf distance exponentially approaching a steady-state. These two responses combined usually approximated a first order system. In about half of the experiments there was also a paradoxical abrupt decrease in calf distance immediately following LBNP. This decrease is probably due to a mechanical tissue distortion resulting from the LBNP; however, the precise mechanism is not clear. Figure 13 shows the change in calf distance during LBNP in an experiment in which all three responses occurred. The graphs in Figure 13 were generated by a computer program specifically developed to collect and analyze the experimental data in this project. This data collection and analysis program is described in Appendix B.

To quantitate calf distance changes following LBNP, we determined in all subjects at each negative pressure 1) the total distance changes, 2) the slope of the initial linear response, 3) the time constant or rise time of the distance change, and 4) the baseline change in calf distance. These averaged parameters are shown in Figures 14-17.

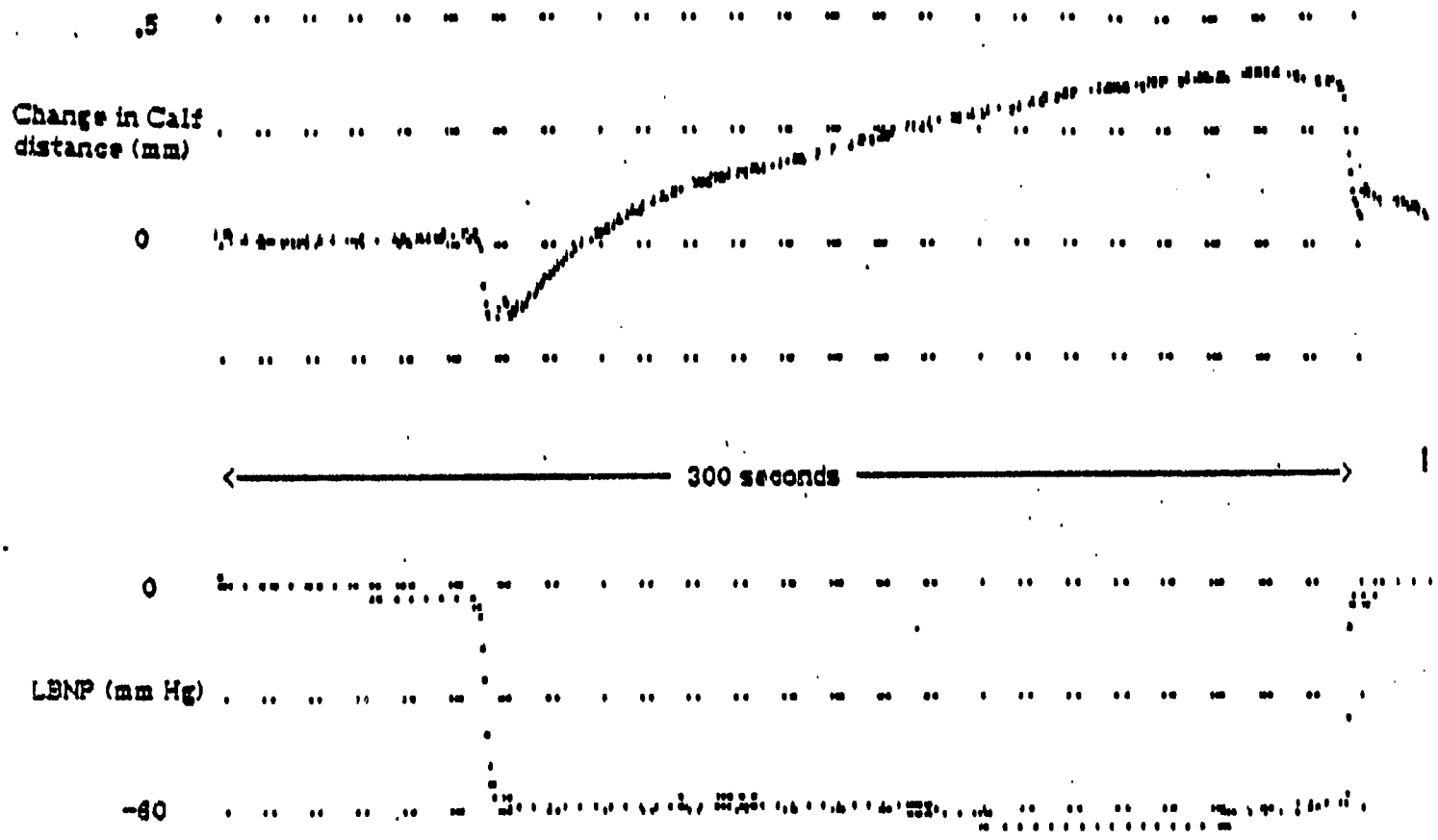


FIGURE 13. The computer produced graph of an LBNP of -60 mm Hg and the response in calf distance to this experimental provocation. Upper graph is the change in calf distance (mm) and the lower graph is the LBNP (mm Hg) perturbation.

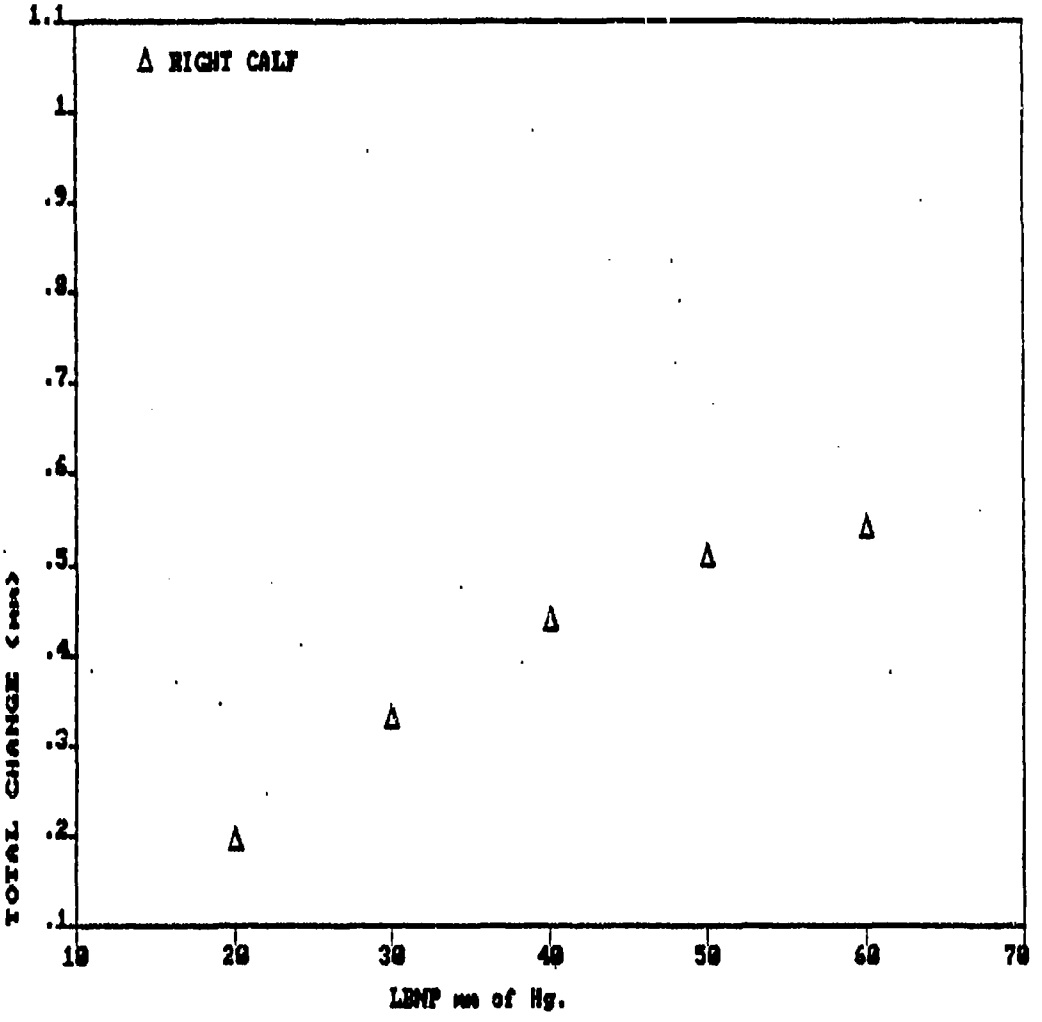


FIGURE 14. The averaged total calf distance changes (mm) following LBNP ranging from -20 to -60 mm Hg.

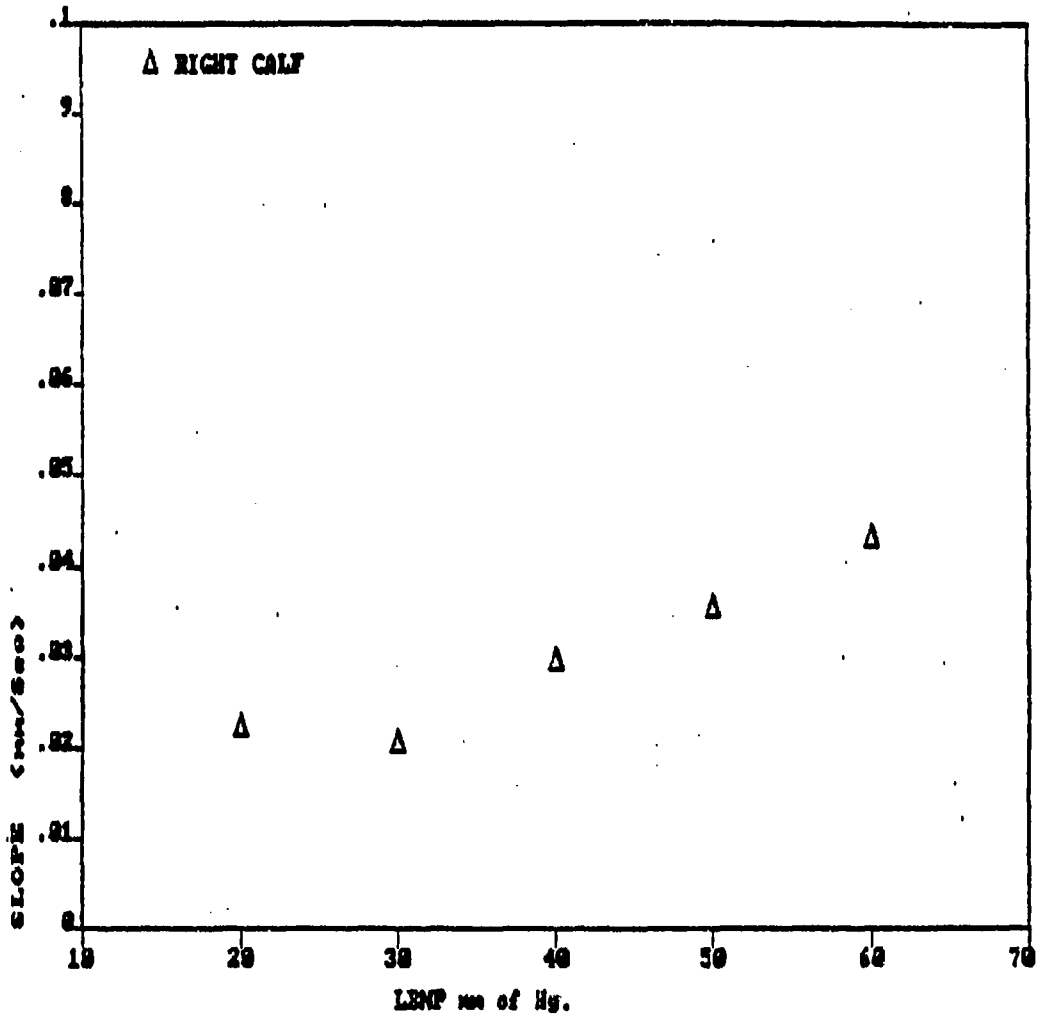


FIGURE 15. The averaged slopes (mm/second) of the initial linear response of calf distance following LBNP.

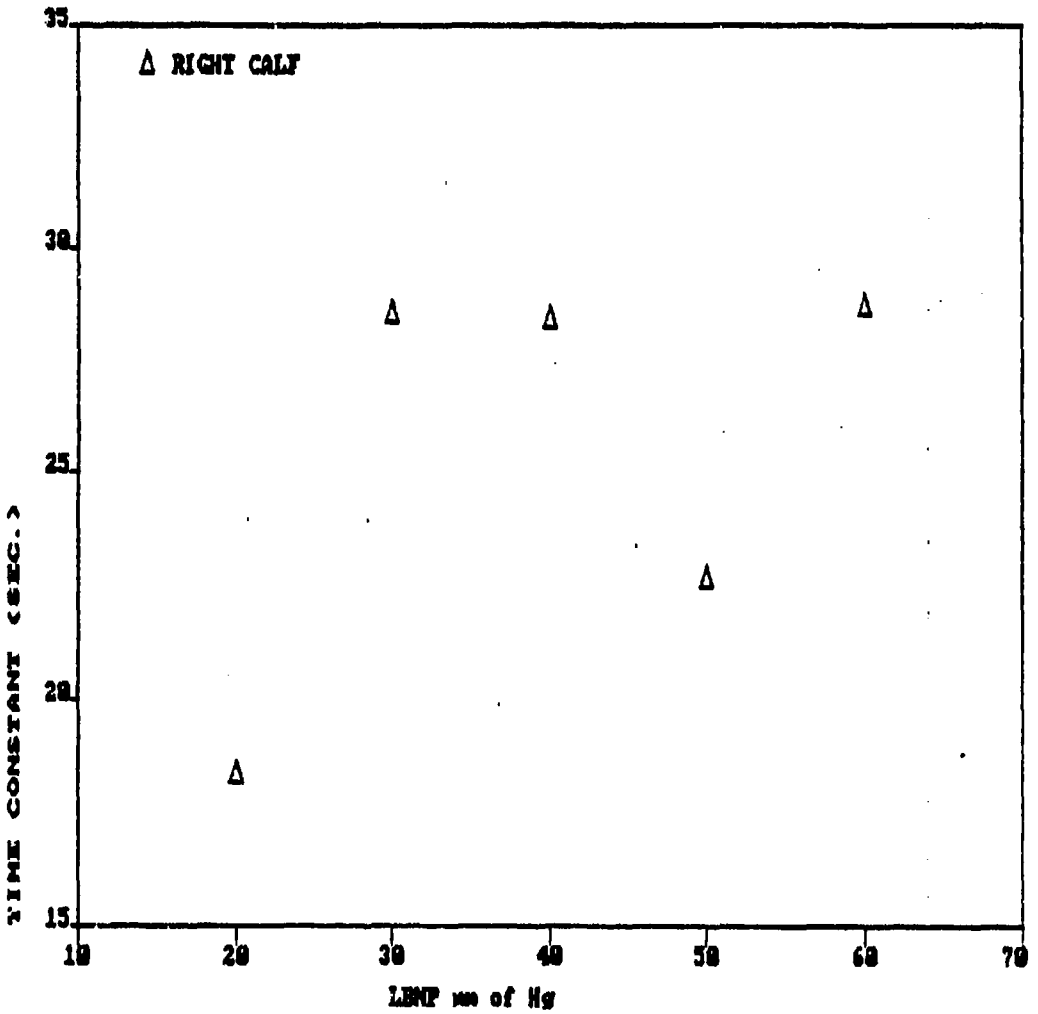


FIGURE 16. The averaged time constant (seconds) for the LBNP perturbations ranging from -20 to -60 mm Hg.

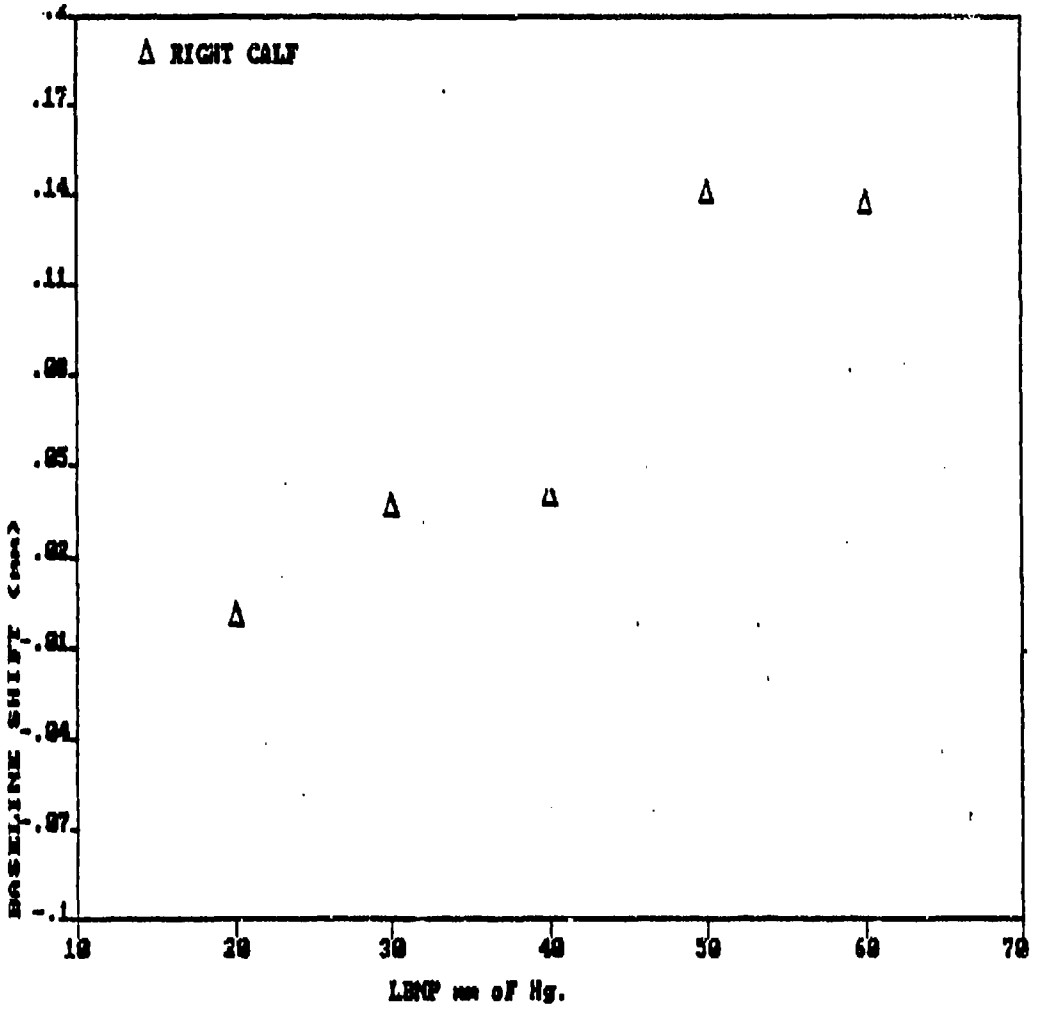


FIGURE 17. The averaged baseline shifts (mm) following the LBNP perturbations ranging from -20 to -60 mm Hg.

The total distance change is probably the result of tissue distortion from fluid shifts to the lower body while the slope of the initial linear response reflects arterial to venous blood flow minus venous return in the lower extremities. Increasing LBNP reduces venous return from the lower body thus accruing fluid either vascular or interstitial. Of course LBNP also pulls blood from the upper body into the lower vasculature; however, since the arterial system is not very compliant and the valves in the veins obstruct such a caudal movement of blood, it is likely that the primary driving force for the increase in calf distance is arterial to venous flow. As shown in Figures 14 and 15 the total changes in distance at all the pressures and the slopes of the initial linear response at pressures from -30 to -60 mmHg demonstrated a reasonably linear relationship with LBNP, thus suggesting that the initial rate of change and the total volume shift were proportional to the magnitude of negative pressure. The slope of the relationship of total changes in calf distance with LBNP was .0088 mm per mmHg LBNP while the slope of the relationship of the initial linear slopes with LBNP was .00057 mm/second per mmHg LBNP (-30 to -60 mmHg).

After cessation of the LBNP, the measured calf distance decreased toward pre-LBNP values but usually did not return to control. Figure 17 shows the averaged baseline shift with LBNP. These results suggest a reasonably linear relationship between the magnitude of LBNP and the baseline shift resulting apparently from fluid shifts to the lower body. The slope of this relationship was .0037 mm per mmHg LBNP. An explanation for these baseline shifts is that the subjects were essentially inactive reducing the fluids returned to the circulatory

system by the venous and the lymphatic pumps, thus permitting an accumulation of blood and/or interstitial fluid in the lower body.

In contrast to total change and the slope of the initial response the time constants calculated by finding the time required to reach 63 percent of the maximum response did not approximate a linear relationship with the magnitude of LBNP. This is expected since the calf distance responses approximated a first order system and thus may be essentially independent of the magnitude of the forcing function.

The results from these experiments indicate that LBNP is a useful experimental technique for mimicking the volume shifts occurring with hypergravity fields without the accompanying mechanical distortion. These experiments also indicate that the ultrasonic transducer is a useful tool for measuring tissue dimension changes occurring during volume shifts.

HYPERGRAVITY EXPERIMENTS

As has been described elsewhere in this report, one of the major effects of positive ($+G_Z$) acceleration is reduced cerebral perfusion, which often results in loss of vision and blackout. In the literature, therefore, loss of peripheral vision, temporal arterial flow velocity and percent arterial oxygen saturation have been used as indicators of the reduced cerebral perfusion. During experiments on the human centrifuge most of the above measurements are complicated by tissue distortion or sensor displacement due to hypergravity.

Quantitative data on tissue blood content can be obtained by measuring changes in tissue thickness with ultrasonic micrometry. A site convenient for measurements on the centrifuge is the earlobe. Blood content of the earlobe measured in the laboratory is affected by

respiration and by postural changes in the expected directions: forced expiration increases tissue volume, a downward tilt of the legs decreases the volume. The earlobes are relatively unaffected by hypergravity and should provide a reliable indicator of changes in blood content during acceleration. We conducted several experiments on the NADC Warminster centrifuge facility to obtain results using earlobes a data sites.

Three mm diameter discs of piezo-electric ceramic insulated with silastic were used as transducers (Figure 18). The transducers were taped to either side of the earlobe using a small piece of surgical tape. The flexible leads from each transducer were taped at the top of the ear to avoid possible deformation of the tissue from straining at the leads. Total set-up time was less than two minutes. The distance between the two transducers could then be monitored by use of an ultrasonic dimension gauge. An operational amplifier circuit attached to the dimension gauge subtracted away the baseline dimension and produced an output proportional to percent change in tissue thickness. This signal was transmitted to an external strip-chart recorder through the centrifuge slip rings. Both the dimension signal and its derivative were recorded. Subjects were exposed to increasing acceleration at a rate of .067g/sec. and rapid onset (4 sec. haversine to 15 sec. plateau) (Figures 19 and 20). The run as terminated at loss of peripheral vision. Subjects were instructed to remain relaxed or to perform the M-1 maneuver. Six subjects were studied. Useable data were obtained in twenty two centrifuge runs.

In the laboratory, blood content of the earlobe measured with the ultrasonic dimension gauge is affected by respiration and by postural changes in the expected directions; forced exhalation increases tissue

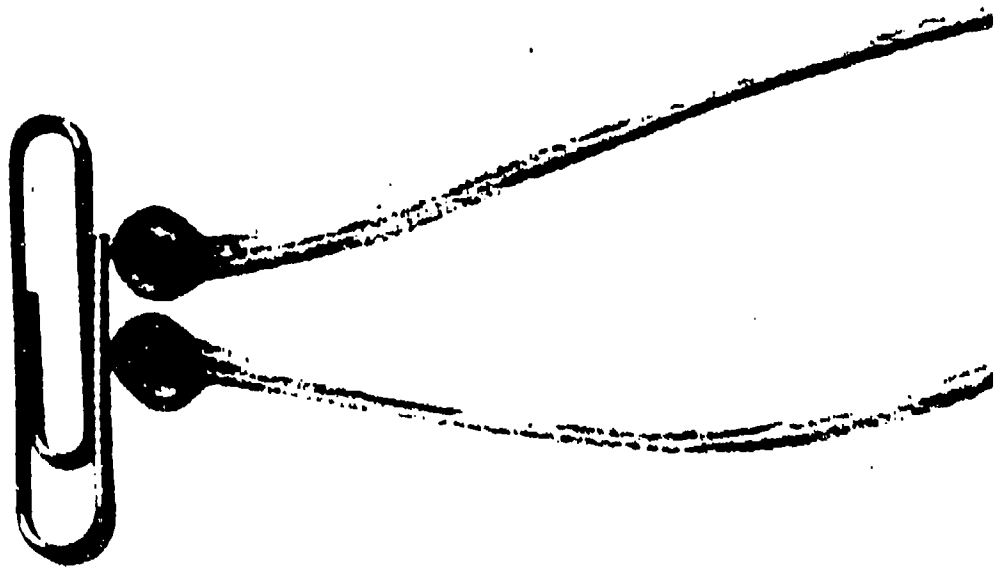


FIGURE 18. Ear transducers

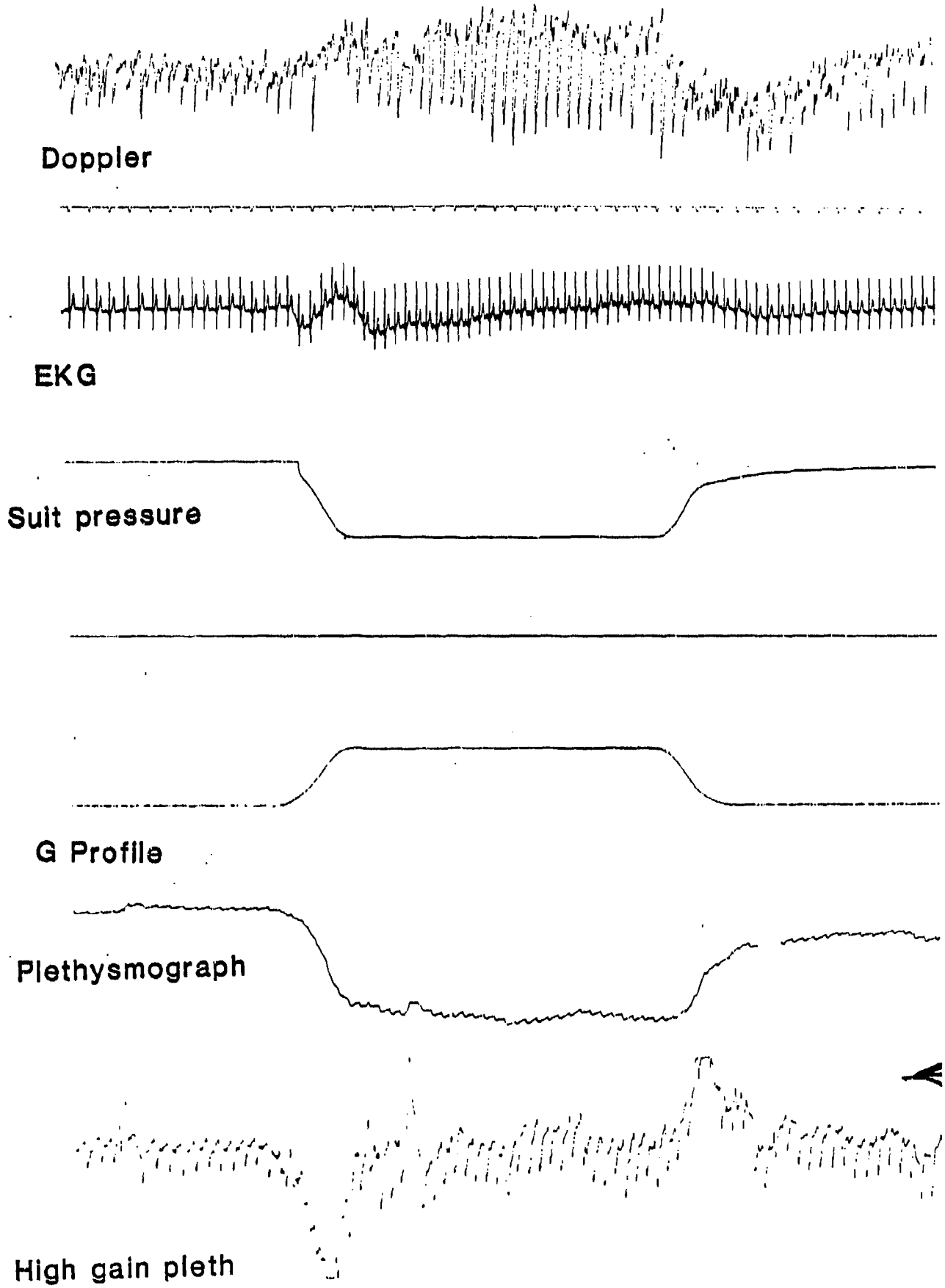


FIGURE 19. Rapid onset run

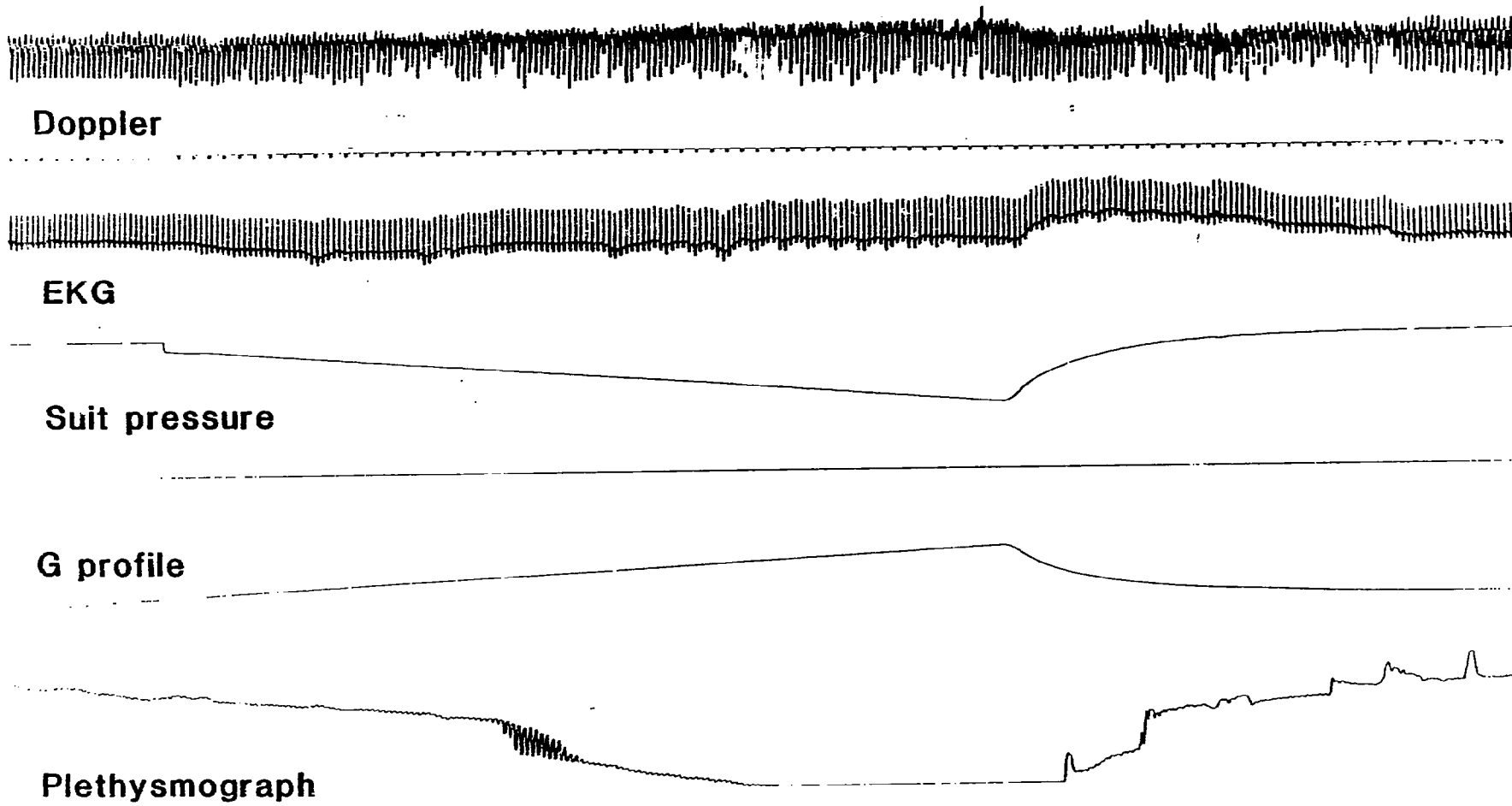


FIGURE 20. Gradual onset run

volume, a downward tilt decreases the volume. By increasing recorder gain, or by computing this derivative of the signal, changes in volume produced by the arterial pressure pulse may be observed. These pulsations are reduced by changes which reduce arterial pressure in the head, such as tilting from horizontal to vertical. Similar observations have been reported from other sites by workers using the photo-plethysmograph.

The vascular tone in all cutaneous tissues exhibits periodic spontaneous variations which are most readily evident in the amplitude of the arterial pressure pulsations. The earlobe participates in these oscillations to a lesser extent than other skin areas, but appreciable variations is present. Insofar in both laboratory tests and on the centrifuge, we find considerable variation in pulse amplitude from subject to subject and from day-to-day in one subject. Over the course of one minute, however, conditions are relatively stable.

On the centrifuge, interpretation of the dimension record is complicated by the possibility of tissue deformation at high acceleration levels. With the gradual onset rate used in these experiments, it was not possible to distinguish between possible deformation and actual changes in volume. With rapid onset of acceleration, the physical deformation would occur immediately, while changes in blood volume would occur more slowly. Any change in dimension at plateau is presumably the result of blood volume changes.

Based upon the above discussion we offer the following sequence of events as a working hypothesis in a subject without a g-suit: On acceleration, the muscles of the calf and thigh will be contracted.

This contraction will increase intramuscular pressure, reducing blood flow into the muscle and preventing filling of the deep veins. Significant shift into the skin will occur; the quantity will depend upon the subject's emotional state and the ambient temperature. Simultaneously, a relatively large shift into the unsupported vascular structures of the abdomen will occur. With prolonged acceleration, there will be extravasation of fluid into the intercellular spaces of the muscle mass of the legs. Thus, the leg muscles will be a more significant reservoir for prolonged accelerations than for short accelerations. On removal of acceleration extravasated fluid will return slowly to the circulation; hence, limb volume will show a long declining phase following a centrifuge run.

Several trends were apparent in the data from these centrifuge runs. For most subjects earlobe volume decreased, as expected, under positive acceleration. During strained breathing, oscillations corresponding to the respiratory cycle were seen. Performance of the M-1 maneuver often produced increases in volume during the straining phase (Figure 21). As the subject approached his G-tolerance limit, the increases in volume became smaller, or disappeared.

In most subjects, arterial pressure pulsations were observed in the earlobe. It might be expected that positive acceleration would reduce the amplitude of these pulsations by reducing the pressure in the head, and this is often observed in tilt experiments at 1 G. On the centrifuge, however, the pulsation amplitude did not decrease, but stayed constant or increased. In some subjects, short periods of very large pulsations (<2 ml blood/100 ml tissue) were observed. These observations may be explained by autonomic vasodilation of the peripheral vessels of the head under acceleration, or by physical

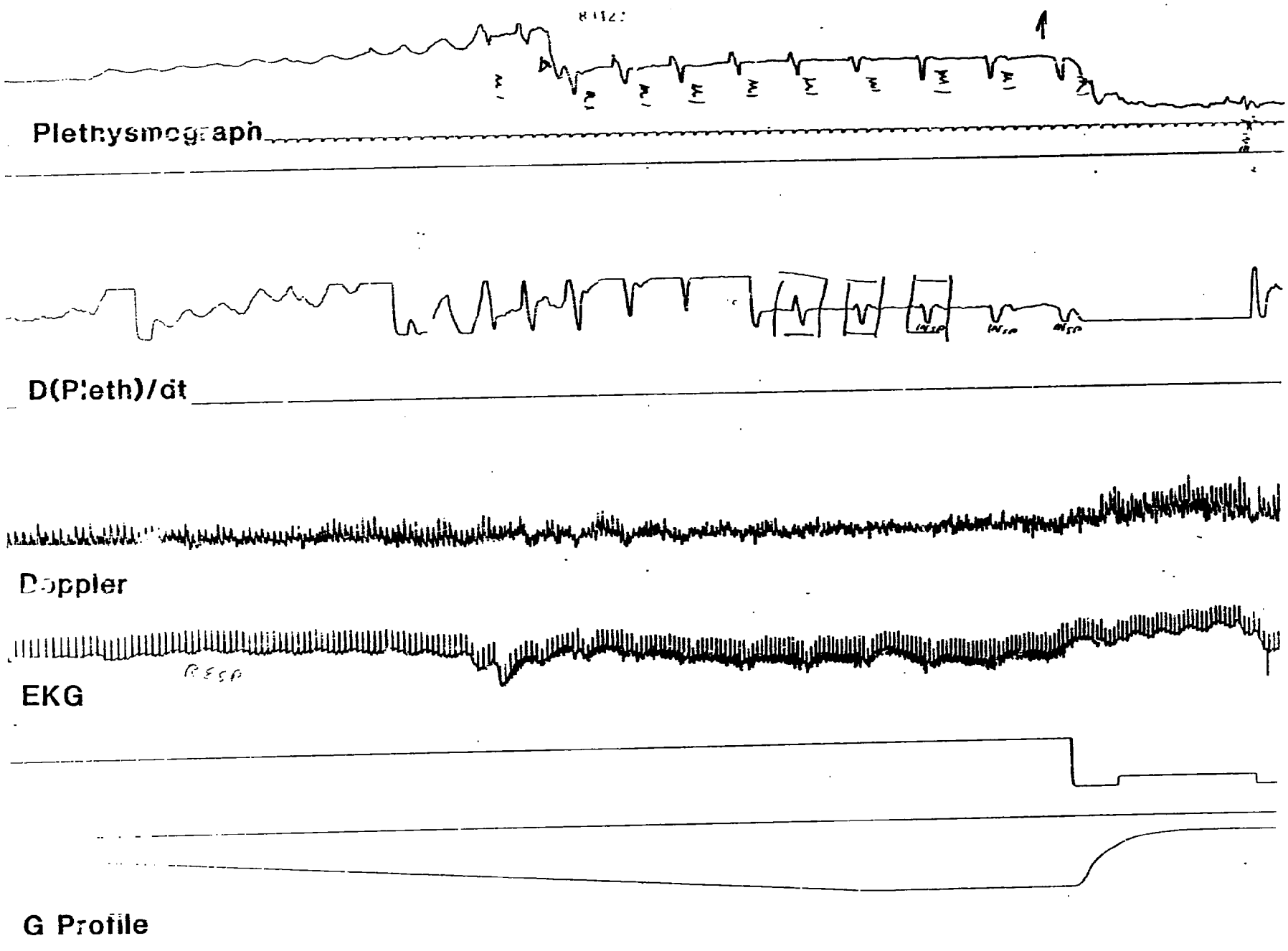


FIGURE 21. Successful M-1 maneuvers

mechanisms related to the draining of blood from the capacitance vessels.

MAJOR ACCOMPLISHMENTS

We have now fabricated a complete multi-site ultrasonic dimension measuring unit. Conversion of electronic circuits from TTL to CMOS logic has resulted in both improved signal to noise ratio (S/N) and savings in power consumption. Each receiver channel can now be individually tuned for measurements at a particular defined site on the body (earlobe, toe, midcalf). Multiplexing of the pinger circuit has resulted in greatly reduced interference. We now have the capability of making either absolute or relative measurements of dimensional changes.

We have also fabricated a lower body negative pressure (LBNP) chamber capable of providing up to 80 mm of Hg (Negative). The subject lies supine on a movable platform (on rollers). He/she can then be rolled into the vacuum chamber (3/4" plexiglass 24" wide X 17" high, 51" deep). An adjustable post is provided to prevent lateral movement of the subject when negative pressure is applied. Adjustable seals are provided to fit the subject's body contour at the abdomen level. Preliminary experiments indicate that negative pressures can be maintained at any desired level (> 80 mm Hg) for a specified length of time. The designed unit can also accommodate positive pressures of up to 80 mm Hg above ambient pressure.

SIGNIFICANCE OF RESEARCH

There appears to be little information on actual quantities of blood shifted during the application of acceleration or during the various procedures for preventing blackout. Acquisition of this

information would allow development of improved models of circulatory system behavior under acceleration. In addition, further improvement in the ability of crewmembers to sustain G_Z loading will depend upon improved understanding of the cardiovascular response to acceleration. The study reported here seeks to improve the understanding of this response through measurement of the volume of blood shifted in response to axial acceleration. The instrumentation already developed by the authors is noninvasive, nonconfining to limbs under study and simple to use. The conversion of these instruments for use in hypergravity experiments has been relatively straightforward and posed few technical problems.

A plethysmographic instrument which can be operated on a centrifuge has many features which are needed in the clinical situation but are not necessary in the laboratory. The instrument must be rugged, simple to use, and reliable. Thus, the present development effort may result in a plethysmograph suitable for clinical use. We are cooperating with clinical staff of UKMC in testing the instrumentation for noninvasively evaluation of deep venous thrombosis and arterial insufficiency in human subjects.

A particular clinical situation in which quantitative plethysmographic techniques may be useful is in the assessment of arterial disease in diabetics. In non-diabetic patients, measurement of segmental blood pressures provides a reliable indication of arterial obstruction. In diabetics, however, arterial walls are often diffusely calcified and rigid, producing falsely elevated blood pressures readings. Maximal calf blood flows produced by exercise or ischemia have been shown to correlate well with the degree of

blockage, although the accuracy of venous occlusion plethysmography in the presence of very low arterial pressures has been questioned (Lorentsen, et al, 1970). This measurement is not routinely used clinically, however, possibly because of the difficulty of use of the Whitney Strain Gauge. The warming experiments (Figure 12) represent a convenient method of obtaining maximum blood flow which may be more practical in many patients than exercise or arterial occlusion.

A second area where these techniques may be clinically useful is in the diagnosis of problems of the sympathetic nervous system. The response of the vascular bed of the skin to heat or cold is easily monitored by the techniques presented here. The reduction in skin flow produced by a controlled cooling of the skin may be developed into a quantitative test for such conditions. In cases where sympathetic ablation is considered for relief of chronic ischemia, the measurement of skin flow before and after a temporary sympathetic blockade may provide an indication of the outcome of surgery.

CONTRACT SUPPORTED PUBLICATIONS

1. Bhagat, P.K., W.T. Nickell and V.C. Wu
   Ultrasonic Measurement of Body Fluid Redistribution Under Hypergravity, 1982 Review of AFOSR and NAVY Biomechanics Programs, San Antonio, Texas, March 1982.
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APPENDIX A

EXPERIMENTAL PROTOCOL FOR LABORATORY BASED STUDIES

Subjects for the laboratory based studies defined in the proposed research program, will be drawn from University of Kentucky student/staff population, between the ages of 18 and 35. Subjects will be required to fill out medical history questionnaires and will be excluded on the basis of any cardiovascular problems, history of motion sickness, acute illness of any kind, or any musculoskeletal problems. All subjects will be carefully screened and given information about the experimental procedures. After signing the informed consent form, the subjects will be given a familiarization session, consisting of a venous occlusion procedure followed by a head-up tilt and LBNP session. Measurements will be carried out at the mid-calf region, earlobes, upper arms, finger tips and toes.

At the beginning of an experimental session, the subject will be asked to lie down quietly on a tilt table. During this quiet period, approximately ten minutes duration, a set of ultrasonic transducers will be placed across the mid-calf region on one of the legs. A water soluble gel, Aquasonic Gel, will be used to provide good contact. In some cases, it may be necessary to shave a small region around the mid-calf to facilitate transducer placement. The transducers will be secured on the limb using standard stomaseal discs. A double strand Whitney strain gauge may also be place around the mid-calf region over the ultrasonic transducers. This procedure involves no known risks or hazards. A pressure cuff will be placed around the subject's thigh for venous occlusion experiments. For tilt-table and lower body negative pressure (LBNP) experiments, the subject will be strapped to

the table. Following the ten minute quiet period, one of three experimental protocols will be carried out. Each of these procedures is a method of producing a shift of blood between the legs and the upper part of the body.

Venous Occlusion Experiments

Following this ten minute period, the pressure cuff will be inflated to a pressure of 30 mm of Hg. This pressure will be maintained until the limb cross-section changes indicate a steady value, approximately two minutes. The pressure will then be released. During the occlusion period, the output signals from the ultrasonic plethysmograph and the Whitney Strain gauge will be collected on strip-chart recorders. The occlusion will be repeated a total of six times, with a three minute rest period between each occlusion.

This procedure will be repeated with the cuff inflated to 35 and to 50 mm Hg.

The maximum pressure of 50 mm Hg should provide essentially complete venous occlusion, but is not high enough to affect arterial flow. This procedure, similar to that used in recording blood pressure, ordinarily produces slight discomfort but is not hazardous; however, the pressure will be released immediately if the subject complains of pain or excessive discomfort.

Tilt-Table Experiments

Following the ten minute quiet period, the subject will be tilted to a position where his head is slightly below his feet (-5 degrees from horizontal). He will be held in this position for ten minutes. Following this period, the subject will be tilted to a nearly vertical position (85 degrees from horizontal) and held in this position for

ten minutes. The subject will then be returned to a horizontal position and allowed five minutes rest. The procedure will be repeated five (5) times.

The subject will be allowed to request a break following any of the 10 minute head-down tilt phases. On return from the break, the five minute horizontal period and the ten minute head-down tilt will be repeated to establish a new baseline.

This procedure could cause fainting or dizziness in some people. If the subject should complain of such symptoms, the experiment will be terminated immediately. The subject will then be asked to remain in the laboratory until the experimenter is confident that the subject is capable of walking or driving.

LBNP Experiments

With the transducers located at appropriate positions, the subject will be placed on the Wenner-Gren lower body negative pressure device. A five minute quiet period will be observed to stabilize the data readings. Following this period, the subject will be exposed to a 30 minute LBNP test protocol as follows: 1 minute exposure to -10 mm Hg, 1 minute exposure to -20 mm Hg, 3 minute exposure to -30 mm Hg, 5 minute exposure to -40 mm Hg, 5 minute at -50 mm Hg, 5 minutes at ambient pressure. This protocol will be repeated two (2) times in a session.

The subject will be allowed to request a break following a session. On return from break, the LBNP protocol will be implemented after a five minute quiet period.

This procedure could cause fainting or dizziness in some people. If the subject should complain of such symptoms, the experiment will

be terminated immediately. The subject will then be asked to remain in the laboratory until the experimenter is confident that the subject is capable of walking or driving.

Approval for this study from the University of Kentucky Human Investigations Committee is enclosed on the following page.

SUMMARY OF RESEARCH PROPOSAL

1. What are your research objectives, their scientific significance and their possible human benefits?

In the operation of high performance aircraft, operational crews are often subject to high sustained $\pm G_z$ acceleration. The response of the human cardiovascular system to these acceleration forces has been the object of considerable research. Numerous techniques have been used to measure important parameters of cardiovascular function; however, plethysmographic measurements of blood volume shifts have not been possible during exposure to hypergravity because of unavoidable tissue deformation. Such measurements have added significantly to understanding of the cardiovascular response to postural shifts and to zero-g. A research program is proposed which will employ multiple ultrasonic depth measurements to determine the volume of blood contained in the various compartments of the circulation during exposure to hypergravity on a centrifuge. These volume measurements will be used to study the time course and quantity of blood shifts produced by exposure to selected acceleration profiles and physiological manipulations, including anti-G suit inflation. The data obtained will be to provide improved understanding of basic cardiovascular physiology and of the relative effectiveness of various anti-G devices.

The human experimentation proposed here is required to develop the instrumentation which will be required. No exposure to hypergravity is proposed at this time. Hypergravity experiments will be conducted in cooperation with Navy personnel experienced

in centrifuge studies. Detailed experimental protocols will be developed in conjunction with these Navy personnel and approval of these protocols by appropriate authorities will be obtained at the Navy installation.

2. Who will be your subjects and how will they be selected?

Subjects used in this study will be healthy volunteers, both male and female, 18-35 years of age chosen from University student and staff population. The subjects will be chosen on the basis of physical examination and medical history. Candidates with a known acute or chronic illness will be excluded from this study. High-blood pressure, or any history of dizziness or fainting will be specific reasons for excluding subjects. Persons with peripheral arterial and venous disease will be excluded.

Dr. A. M. Fried, chief, diagnostic radiology, U. K. Medical Center, will act as the medical monitor for this study. All medical examinations will be performed by or under the supervision of Dr. Fried. He will also be present or available on call whenever experiments are to be performed.

3. Procedures to be used

Ten subjects will be selected for the proposed research. All selected subjects will participate in a short orientation session during which the purposes and procedures of the research will be presented. All potential risks and discomforts will be discussed at this session. Each subject will then be asked individually to come into the Wenner-Gren Biomedical Research Laboratory for experimental sessions, scheduled during weekdays, of three hour durations.

At the beginning of an experimental session, the subject will be asked to lie down quietly on a tilt table. During this quiet period, approximately ten minutes duration, a set of ultrasonic transducers will be placed across the mid-calf region on one of the legs. A water soluble gel, Aquasonic Gel, will be used to provide good contact. In some cases, it may be necessary to shave a small region arouud the mid-calf to facilitate transducer placement. The transducers will be secured on the limb using standard stomaseal discs. A double strand Whitney strain gauge will also be placed around the mid-calf region over the ultrasonic transducers. This procedure involves no known risks or hazard. A pressure cuff will be placed around the subject's thigh for venous occlusion experiments. For tilt-table and lower body negative pressure (LBNP) experiments, the subject will be strapped to the table. Following the ten minute quiet period, one of three experimental protocols will be carried out. Each of these procedures is a method of producing a shift of blood between the legs and the upper part of the body.

Venous Occlusion Experiments:

Following this ten minute period, the pressure cuff will be inflated to a pressure of 20 mm of Hg. This pressure will be maintained until the limb cross-section changes indicate a steady value, approximately two minutes. The pressure will then be released. During the occlusion period, the output signals from the ultrasonic plethysmograph and the Whitney Strain gauge will be collected on strip-chart recorders. The occlusion will be repeated a total of six times, with a three minute rest period

between each occlusion.

This procedure will be repeated with the cuff inflated to 35 and to 50 mm Hg.

The maximum pressure of 50 mm Hg will provide complete venous occlusion, but is not high enough to affect arterial flow. This procedure, similar to that used in recording blood pressure, ordinarily produces slight discomfort but is not hazardous; however, the pressure will be released immediately if the subject complains of pain or excessive discomfort.

Tilt-Table Experiments:

Following the ten minute quiet period, the subject will be tilted to a position where his head is slightly below his feet (-5 degrees from horizontal). He will be held in this position for ten minutes. Following this period, the subject will be tilted to a nearly vertical position (85 degrees from horizontal) and held in this position for ten minutes. The subject will then be returned to a horizontal position and allowed five minutes rest. The procedure will be repeated five (5) times.

The subject will be allowed to request a break following any of the 10 minute head-down tilt phases. On return from the break, the five minute horizontal period and the ten minute head-down tilt will be repeated to establish a new baseline.

This procedure could cause fainting or dizziness in some people. If the subject should complain of such symptoms, the experiment will be terminated immediately. The subject will then be asked to remain in the laboratory until the experimenter is confident that the subject is capable of walking or driving.

LBNP Experiments:

With the transducers located at appropriate positions, the subject will be placed on the Wenner-Gren lower body negative pressure device. A five minute quiet period will be observed to stabilize the data readings. Following this period, the subject will be exposed to a 30 minute LBNP test protocol as follows: 1 minute exposure to -10 mm Hg, 1 minute exposure to -20 mm Hg, 3 minute exposure to -30 mm Hg, 5 minute exposure to -40 mm Hg, 5 minute at -50 mm Hg, 5 minutes at ambient pressure. This protocol will be repeated two (2) times in a session.

The subject will be allowed to request a break following a session. On return from break, the LBNP protocol will be implemented after a five minute quiet period.

This procedure could cause fainting or dizziness in some people. If the subject should complain of such symptoms, the experiment will be terminated immediately. The subject will then be asked to remain in the laboratory until the experimenter is confident that the subject is capable of walking or driving.

4. What risks are involved? What precautions will be taken?

The most likely source of injury to the subjects is a fall from the tilt-table. This table is a motorized commercial unit designed for the purpose for which it is being used. Experimental personnel will be present at all times when a subject is on the table. In addition, during the tilt-table experiments, the subject will be strapped to the table.

The experimental procedures are not considered hazardous.

Release of negative or occlusion pressure or return to a horizontal position should relieve any distress. The tilt-table/LBNP experiments will be terminated any time that there is an indication the subject is feeling dizzy. The venous occlusion experiment will be terminated any time the subject complains of excessive discomfort or pain. Where appropriate, the venous occlusion experiments may be resumed after a rest period. Tilt-table/LBNP experiments will not be resumed after the subject has experienced dizziness. The subject will be asked to remain in the laboratory until the experimenters are satisfied that he has recovered completely.

If a serious problem should develop, the medical monitor will be on call. Transportation will be available at all times.

No drugs or invasive procedures will be used in these experiments. No placebos will be used.

5. Will subjects be paid?

Subjects will be temporary U.K. employees. They will be paid not more than $5 per hour, which is the rate suggested by the U.K. Research Foundation. They will be paid by PAR and will be eligible for workman's compensation, plus the usual University of Kentucky insurance coverage.

6. Confidentiality and anonymity:

Data will be recorded by subject's initials or first name. Any published reports will not identify subjects other than by initials.

INFORMED CONSENT FORM

The purpose of this project is to evaluate the performance of an instrument which will be used to measure the shift of blood which occurs upon exposure to hypergravity and to determine the effectiveness of various techniques which may be used to reduce this shift.

My selection as a subject will involve a physical examination and a health history. The examination will be conducted by Dr. A. M. Fried of Diagnostic Radiology, or under his supervision. All procedures will be conducted under the general supervision of Dr. Fried and he will be on call at all times when experimental procedures are being conducted.

During each experimental session, several ultrasonic transducers will be attached to the calf of one of my legs. A Whitney Strain gauge, which is a standard device for measuring changes in limb volume will also be attached to my calf.

At each experimental session, one of three procedures will be used to produce changes in the amount of blood pooled in my leg. In the first procedure, a venous occlusion cuff, which resembles a standard blood pressure cuff except that it is larger, will be placed around my thigh. This cuff will be inflated to as much as 50 mm Hg as many as 18 times during each session. Inflation of the cuff to this pressure will prevent return of blood from my leg, but will not affect the flow of blood into the leg through the arteries. The discomfort experienced will be comparable to that encountered during a blood pressure measurement. If at any time during the procedure I report

feeling pain or excessive discomfort, the pressure will released immediately.

In the second procedure, the tilt-table on which I will be lying will be tilted ten (10) times between a position where my head is slightly below my feet (-5 degrees) to a position where I am nearly vertical with my feet down (70 degrees from horizontal). This procedure will probably cause no symptoms, but could cause dizziness and fainting in a few people. For this reason, I will be strapped to the table during this phase of the procedure and I will be observed carefully by the experimenters. If I experience any discomfort during this procedure, the experiment will be terminated immediately.

In the third procedure, I will be placed in a lower body negative pressure (LBNP) device which applies negative pressure to portions of the body below the diaphragm. Maximum negative pressure of -50 mm Hg can be applied with use of this device.

This procedure usually results in no adverse symptoms, but could cause dizziness and fainting in some people. For this reason, the experimenters will observe me very carefully and at the slightest discomfort the experiment will be terminated immediately.

The ultrasonic transducers will expose the tissues of my leg to ultrasound having a frequency of approximately 2-3 million cycles per second. The intensity of these vibrations will be comparable to those routinely used in medical diagnosis. There is no known hazard associated with this exposure.

Data from this study may be published in scientific journals or the news media at some future without further consent or notification. My name will not be used in any publication or disclosed to other persons.

I am free to withdraw my consent and discontinue participation in the project at any time.

I have the right to ask questions at any time before, during or after any phase of the project and to receive answers to these questions which are satisfactory to me before proceeding.

As a part-time, temporary U.K. employee, I will be covered by the University's workman's compensation and blanket bond liability.

I,_____, having read and understood the above, volunteer to participate in this project, and give consent to publication of the results of this study.

_____ _____

SIGNATURE DATE

I have explained and described in detail the research procedure in which the subject has consented to participate.

_____ _____

P. K. BHAGAT/G. PROFFITT DATE

SUBJECT SCREENING DATA

FOR

ULTRASONIC QUANTIFICATION OF BLOOD VOLUME REDISTRIBUTION

The intent of this questionnaire is to evaluate your suitability as a subject for the above named study. Your selection as a subject will be made by the Principal Investigator and the Medical Monitor based on the data provided here. To be a subject you will also be required to sign an "Informal Consent Form" which details the scientific and technical aspects of this study.

I. Personal Data

1. Name _____

2. Address _____

_____

3. Home Telephone _____

4. Business Telephone _____

5. Age _____ Date of Birth _____

6. Male _____ Female _____

7. Height _____ Weight _____

II. Health History

Did/do you have any of the following health problems?

A. General:

		Yes	No
1.	Allergies or asthma	( )	( )
2.	Bone or joint problems	( )	( )
3.	Cancer or tumor	( )	( )
4.	Diabetes	( )	( )
5.	Frequent infections	( )	( )
6.	Bleeding tendencies or anemia	( )	( )
7.	Epilepsy or seizures	( )	( )
8.	Eye problems	( )	( )
9.	High blood pressure	( )	( )
10.	Stomach or liver problems	( )	( )
11.	Kidney or bladder trouble	( )	( )
12.	Nervous breakdown or other disorders	( )	( )
13.	Lung problems	( )	( )
14.	Heart trouble	( )	( )
15.	Other (specify)	( )	( )

B. Hospitalization:

1. Have you ever been hospitalized for any serious medical illness or operation? Yes ___ No ___

Year of hospitalization _____ Type of illness or operation _____

C. Medicine:

Write the names of any medicine that you are now taking or that you are allergic to.

D. Personal Habits:

1. Do you smoke? Yes ___ No ___ How much _____

2. Do you drink alcohol? Yes ___ No ___ How much _____

III. Specific Questionnaire

	Yes	No
1. Are you troubled with stiff or painful muscles, joints or spine?	( )	( )
2. Are your joints ever swollen?	( )	( )
3. Do you have any skin problems?	( )	( )
4. Do you ever faint or feel faint?	( )	( )
5. Have you ever had fits or convulsions?	( )	( )
6. Have you gained or lost much weight recently?	( )	( )
7. Do you have a tendency to be to hot or cold?	( )	( )
8. Do you drink more than six cups of coffee or tea a day?	( )	( )
9. Do you easily become nauseated?	( )	( )
10. Have you had an earache lately?	( )	( )
11. Have you been troubled by running ears?	( )	( )
12. Do you feel a repeated buzzing or other noises in your ears?	( )	( )
13. Do you get motion sickness riding in a car or plane?	( )	( )
14. Have you ever been told that you have high blood pressure?	( )	( )
15. Have you ever been bothered by a thumping or racing heart?	( )	( )
16. Do you ever get pains or tightness in your chest?	( )	( )
17. Do you have trouble with dizziness or lightheadedness?	( )	( )
18. Do little efforts leave you short of breath?	( )	( )
19. Do you get cramps in your limbs at night?	( )	( )
20. Have you ever been told that you have a heart murmur?	( )	( )
21. Special problems or symptoms?	( )	( )

Specify:

IV. Questions Related to the Present Research

1. You will be available for experiments between ____ and _____

2. Will you be able to spend a total of 4 hours at each meeting?

   Yes ___ No ___

3. Do you do any exercises (jogging, weight lifting, etc.)?

   Yes ___ No ___

   Specify:

4. Is there any additional information you wish to provide which might be helpful in this study?

_____
Signature of Subject

_____ _____
Signature of Screener Date

APPENDIX B

MICROPROCESSOR DATA COLLECTION AND ANALYSIS SYSTEM

A data acquisition and analysis workstation was developed on an inexpensive microprocessor to facilitate data manipulation during this project. We anticipated this workstation would 1) increase the accuracy in data reduction by eliminating the manual abstraction of data from mechanically generated strip charts, 2) efficiently store and retrieve data, and 3) reduce the time required for analysis.

An IBM PC with a Tecmar A/D convertor was programmed in Fortran 77 (Microsoft) and Assembly language (IBM Macro) to digitize, scale, and store in active memory as 16 bit integers, eight channels of data. The eight channels of data were sampled as rapidly as the system would permit with a 0.5 second interval inserted between each sampling burst of eight data points. The scaled data was immediately displayed on an Amdek video display terminal using a high resolution color graphics card (IBM) to allow real time inspection of the data acquisition. Since there are no systems calls for graphics using this card, the display was accomplished by direct calls to the graphic functions in the BIOS located in the PC's read only memory.

At the conclusion of data acquisition the collected parameters were stored on a 360 Kilobyte 5 1/4 inch diskette. Even though these data were in a binary format for efficient storage, the 360 Kilobyte capacity of the diskettes limited the data collection period to slightly over 3 hours. Because the collected data is buffered in active memory before storage on diskettes, the amount of data that can be collected at one time is also contingent on the amount of memory

available. However, the PC used in this project had 640 K of active memory, so the limiting factor for data acquisition was the 360 K diskettes.

Another program written in Fortran 77 and Assembly language retrieved the appropriate data file previously stored on the 5 1/4 inch diskettes and displayed the first 640 points of any two channels of this data. Keyboard selectable options allowed the data displayed to be advanced or moved backwards 640, 320, or 100 data points. The two variables displayed could also be selected from the keyboard. Thus, using this workstation the previously acquired data could be rapidly scanned in its entirety. For final data reduction it was necessary to delineate the single data point or the data epoch to be analyzed. Vertical line cursors whose positions were controlled by function keys selected either a data point or by fixing one cursor and moving a second cursor, a data epoch. The analytical techniques applied to data selected by the vertical line cursors were:

1) The value of the data point at the vertical cursor was displayed.

2) The average of the data points between the two cursors were given.

3) The time constant or rise time was calculated for the variable between two cursors by determining the time required to reach 63 percent of the maximum value when starting from the minimum value. To reduce errors resulting from background variability the maximum response was calculated from a five point moving average. Since the immediate response of the parameters following the experimental perturbation was often a sudden decrease followed by the expected exponential rise,

attempts to average out background variability could possibility cause an error in the determination of the minimum data value, so a moving average was not used to find the minimum point.

4) The slope of the first six data points occurring after the minimum value was calculated to assess the initial parameter change following the experimental perturbation.

5) The slope of data between the two cursors was calculated.