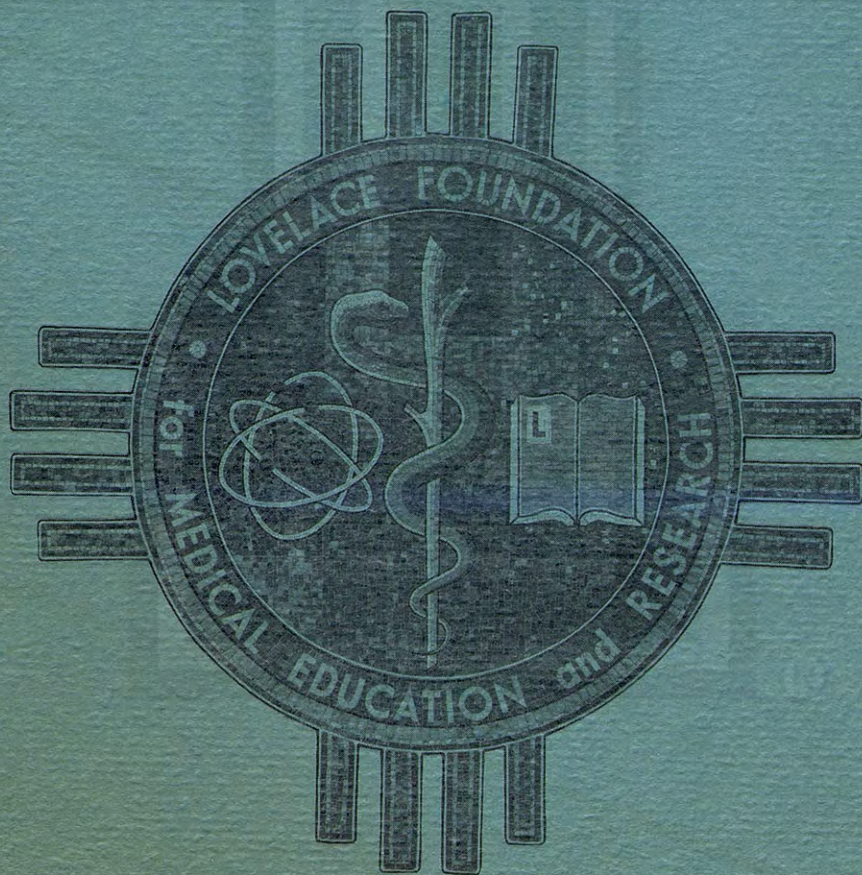
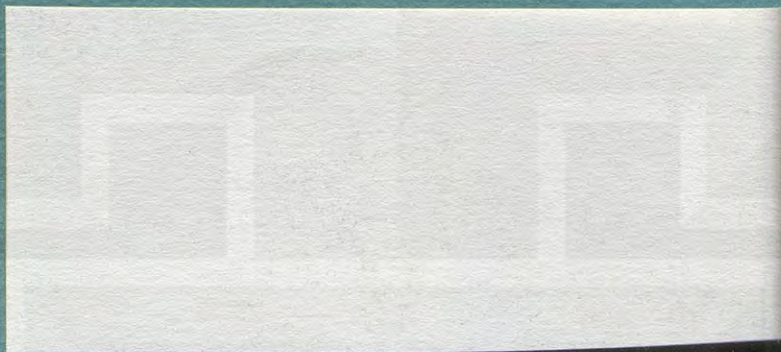




Biomedical Techniques for Use In
Manned Space Laboratories

Selected Extracts: Part 1

1. Establishment of Parameters
2. Cardiac Output
3. Blood Pressure
4. Cardiac Kinetics

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REPORT IX

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BIOMEDICAL TECHNIQUES FOR USE IN MANNED SPACE LABORATORIES

SECTION 1 - ESTABLISHMENT OF PARAMETERS

To develop a program of biomedical testing for use in manned space laboratories it is necessary to review the nature of the expected problems as they are seen today. Information from the Mercury, Vostok, Voshkod, and Gemini missions, and from U. S. and foreign laboratories, has provided a comprehensive picture of much of the requirement for manned earth-orbiting vehicles, and no doubt still further information will become available from the Apollo and future missions. By the time a large manned space laboratory can be launched, or assembled in space, more will be known about the response of man to the problems that beset him in short or medium duration earth-orbiting or lunar missions, and much will have been done to protect him from potential or actual hazard. Some is already known, and more will be known, about man's response to the accelerations of launch, re-entry, and impact, to short duration buffeting, to heat, cold and humidity, to variation in atmospheric pressure, and exposure to hyperbaric oxygen or to mixed gas atmospheres for 30 days or so. More will also be known about man's response to weightlessness, restriction and confinement. Procedures, techniques, and devices may also have been developed, if required, to protect him from any potential hazard associated with weightlessness, and from the effects of radiation. Extrapolations of such knowledge, however, even on the basis of all that is acquired in the intervening period, will provide only a speculative indication of how he will respond and how well he will perform in a very prolonged mission. Thus an organized re-examination of his response under space laboratory conditions is needed to determine the occurrence of any psychological or physiological decrement with time.

It must be assumed that the vehicle under consideration will have the requisite space, habitability, and facilities, along with an adequate environmental control system with comprehensive, reliable, environmental monitoring which will provide immediate and accurate information on the spacecraft environment to both ground control and the spacecraft occupants. Such being the case, the necessity for continuous routine physiological monitoring of the crew will become minimal, since the results would merely reflect extreme changes in the environment, better observed directly on environmental monitors. Continuous physiological monitoring is essentially second order environmental monitoring. Thus, physiological monitoring systems can be reserved for use in data collection during experimental procedures, or at regular and routine intervals. From the resulting information the extent of any time-dependent decrements can be evaluated.

In a manned space laboratory, problems of launch and re-entry will be only a routine feature, and, in fact, the vehicle might well be assembled in space. Consequently the major areas of concern will be those associated with continued orbital missions, and probably will be much the same as they are now, namely, the effects of weightlessness, radiation, confinement and work cycling, atmospheric contamination and inter-current illness, accidental injury and decompression. Primary consideration will probably be given to the psychophysiological response to weightlessness and radiation. Since each of these has an actual or potential widespread effect on body function, much incidental information will be obtained on the total body response to the total environment, which can be amplified by suitable experimentation. Thus, it need not be construed that the collection of biomedical data should be rigidly confined to certain areas, nor that it should adhere to a rigid protocol. Particularly in a long duration mission, with a high calibre of scientific observer among the crew, and a high index of curiosity, the objective and direction of research may well change, and as knowledge is gained, it will be possible to extend investigation to greater depth and wider fields.

With respect to weightlessness, studies to date have indicated the potential occurrence of detrimental effects primarily related to the cardiovascular, hematologic, locomotor and metabolic functions, with perhaps some effect on the respiratory, equilibratory, and renal systems. Further studies will determine the significance of these reactions and will separate the effects of immobility from weightlessness or reduced gravitation. Studies on radiation have shown that the major effects are observed on the alimentary, integumentary, hematological and neurological systems, with further effects on cellular repair and immunological response. In addition, the adrenocortical and adrenomedullary functions are ultimately bound up with the body response to stress, as are certain aspects of neurological function, while fluid and electrolyte balance, and perhaps changing enzyme patterns, provide an indication of the integrity of the internal body environment.

It is desirable then to devise techniques and instrumentation to measure the body response over the entire gamut of body function. To organize this approach it is advisable to examine man's capacities in terms of various related body function systems (Table 1). Numerous approaches could be made to classifying body function. It will be noted that the categories selected do not rigidly follow traditional anatomical, physiological, or clinical patterns but represent functional systems that have specific applicability to the expected problems of space flight.

Each of these functional areas is then in turn examined to determine the nature of the information that is required to provide an index of the adequacy of normal function in each area, and an indication of any change in function that may occur on exposure to the space environment. The results of these analyses are shown in Table 2, which delineates the information requirement.

In the subsequent section, each functional area is again examined to determine the means of obtaining the information outlined in Table 2. For each individual information requirement, a survey is made of all applicable measurement techniques, with the object of determining the method or methods most feasible for use in the space environment. Trade-offs are made in order to maximize the reliable information content of the measure

while minimizing subject violation and complexity of the instrumentation and execution. Recommendations are made on the most suitable techniques and on requirements for further development.

Other sections are concerned with techniques of sample collection and processing, development of specialized instrumentation, the integration of measurement systems covering several function areas, and the requirements for data handling and display.

TABLE 1

Psychophysiological Function Parameters

1. Cardiovascular
2. Respiratory
3. Anthropometric
4. Fluid and electrolyte balance, distribution
5. Alimentary
6. Metabolic
7. Thermal
8. Hematological, immunological, histological
9. Neuroendocrine
10. Neurological
11. Psychosociological

TABLE 2

CARDIOVASCULAR

CARDIAC DYNAMIC ACTIVITY

1. Pressures
 - a) Cardio-arterial
 - i) Central
 - ii) Peripheral
 - b) Cardio-venous
 - i) Central
 - ii) Peripheral
2. Volumes
 - a) Cardiac output
 - i) Minute and stroke volume
 - b) Peripheral blood flow
 - i) Plethysmographic volumes, compliance
 - ii) Circulation times
 - iii) Skin heat flow
3. Rates
 - a) Central
 - b) Peripheral

CARDIAC KINETICS

1. Dynamic contractile forces (BCG, V_b CG, etc.,)
2. Cardiac sounds
3. Pulse wave propagation

CARDIAC ELECTRICAL ACTIVITY

1. ECG
2. Vectorcardiography

TABLE 2 (Continued)

CARDIOVASCULAR (Continued)

CARDIAC MORPHOLOGY

1. Size
2. Contour

CARDIAC STRESS TESTING

1. Physiological
 - a) Response to "Flack" test
 - b) Response to hyperventilation
 - c) Response to pain, emotion
 - d) Peripheral response to skin pressure, histamine, etc.
2. Physical
 - a) Response to carotid sinus pressure
 - b) Response to cuffing of extremities
 - c) Response to lower body negative pressure
3. Environmental
 - a) Response to hypoxia
 - b) Response to hypercarbia
 - c) Response to heat
 - d) Response to sustained acceleration

TABLE 2 (Continued)

RESPIRATORY

1. Static lung volumes and capacities
2. Mechanics of breathing
 - a) Airway resistance (dynamic volumes, flow rates)
 - b) Compliance: lung, thorax
 - c) Non-elastic resistance (pressure/volume, or pressure/flow relationships)
 - d) Work of breathing
 - e) Combined functional indices (normal frequency, MVV)
3. Alveolar gas exchange
 - a) Alveolar ventilation (volume, quality, distribution)
 - b) Diffusion (Capacity)
 - c) Ventilation/perfusion ratio
 - d) Shunts (anatomic, physiologic)
4. Blood gas transport
 - a) O₂ content, capacity, saturation, tension
 - b) CO₂ content, tension
 - c) pH

TABLE 2 (Continued)

ANTHROPOMETRIC

STATIC

1. Whole body
 - a) Height
 - b) Mass (weight)
 - c) Volume
 - d) Surface area
 - e) Fat free mass
 - f) Total fat
 - g) Muscle mass
2. Circumferences, diameters, and indices
 - a) Thoracic
 - b) Abdominal
 - c) Pelvic
 - d) Limb
 - e) Skin fold

DYNAMIC

1. Muscle Function
 - a) See NEUROLOGICAL
2. Joint motion
3. Motor performance
 - a) See PSYCHOLOGICAL
4. Work capacity
 - a) Exercise loading (see also CARDIOVASCULAR)

TABLE 2 (Continued)

FLUID AND ELECTROLYTE BALANCE, DISTRIBUTION

1. Fluid intake
2. Fluid output
 - a) Urine
 - b) Feces
 - c) Respiration
 - d) Sweat
3. Fluid distribution
 - a) Total body water
 - b) Extracellular fluid
 - c) Blood (plasma) volume
 - d) Fluid partition
4. Fluid regulation
 - a) Hormonal (See NEUROENDOCRINE)
 - b) Renal function
 - i) Urine proteins
 - ii) Urine concentration, dilution
 - iii) Biochemical clearance testing of urine
5. Fluid characteristics: Urine, blood, saliva, and other
 - a) pH
 - b) Osmolarity
 - c) Refractometry (specific gravity)
 - d) Microscopy
 - e) Biochemical assay (See METABOLISM)
6. Electrolytes
 - a) Blood Na^+ and K^+ , Cl^- , HCO_3^-
 - b) Urine Na^+ and K^+ , Cl^- , HCO_3^-

See also METABOLIC, HEMATOLOGICAL, NEUROENDOCRINE,
CARDIOVASCULAR.

TABLE 2 (Continued)

ALIMENTARY

1. Intake
 - a) Protein
 - b) Carbohydrate
 - c) Fat
 - d) Minerals
 - e) Vitamins
 - f) Fluid (See FLUID AND ELECTROLYTES)
 - g) Bulk
2. Output
 - a) Fecal analysis
 - i) Composition
 - ii) Consistency
 - iii) Chemistry (See METABOLISM)
 - iv) Occult blood
3. Characteristics of content
 - a) Gastric analysis
 - i) Composition
 - ii) Consistency
 - iii) pH
4. Absorption
 - a) Labelled sugars
 - b) Labelled fats
 - c) Labelled proteins
5. Dynamics
 - a) Motility
 - b) Internal pressure
 - c) Transit times (Tagging, radiosonde, radiology)

TABLE 2 (Continued)

ALIMENTARY (Continued)

6. Hepatic function
 - a) Synthesis of protein and blood components
(See METABOLISM, HEMATOLOGY)
 - b) Bile secretion (Serum bilirubin)
 - c) Detoxification and conjugation (BSP)
 - d) Protein, fat, and carbohydrate metabolism
(See METABOLISM)
7. Pancreatic function
 - a) Exocrine (duodenal content analyses)
 - b) Endocrine (See NEUROENDOCRINE)
8. Histology
 - a) Mucosal biopsy
9. Parotid function

TABLE 2 (Continued)

METABOLIC

1. Intake and output
 - a) See ALIMENTARY
2. Energy metabolism
 - a) Corrected R.Q. (See RESPIRATORY)
3. Protein metabolism
 - a) Nitrogen balance
 - i) Blood urea nitrogen
 - ii) Blood and urine creatine
 - iii) Blood and urine creatinine
 - iv) Urine urea
 - v) Blood and urine non-protein nitrogen
 - b) Plasma protein fractionation
4. Carbohydrate metabolism
 - a) Blood sugar
 - i) Post-prandial glucose
 - ii) Glucose tolerance
 - iii) Fate of labelled sugars
 - b) Metabolites
 - i) Blood lactic acid
 - ii) Blood pyruvic acid
 - c) Correlates
 - i) Serum phosphorus
 - ii) Serum ATP
 - d) Provocative testing
 - i) Sugar response to insulin and catecholamine infusions

TABLE 2 (Continued)

METABOLIC (Continued)

5. Fat metabolism
 - a) Metabolites
 - i) Serum lipids
 - ii) Serum non-esterified fatty acids (NEFA)
 - iii) Urine ketone bodies
 - b) Correlates
 - i) Serum phosphorus
 - ii) Serum ATP
 - c) Provocative testing
 - i) NEFA Response to insulin, glucose, and catecholamine infusion
6. Mineral metabolism
 - a) Calcium and phosphorus balance
 - i) Urine and serum Ca and P
 - ii) Fecal Ca and P
 - iii) Serum alkaline phosphatase
 - iv) Urine citrate
 - b) Calcium deposition and turnover
 - i) Bone (radiology, radioisotopes)
 - ii) Kidney (radiology)
7. Blood and tissue enzymes

See also FLUID AND ELECTROLYTE BALANCE

TABLE 2 (Continued)

THERMAL

1. Heat production
 - a) Caloric value of O_2 consumption (See RESPIRATORY)
2. Heat loss
 - a) Non-evaporative (includes conductive, convective, radiative)
 - b) Evaporative:
 - i) Body calorimetry (Δ R. H.)
 - c) Convective:
 - i) Body calorimetry (air Δ T)
 - d) Conductive:
 - i) Body calorimetry (liquid Δ T)
3. Heat storage
 - a) Deep rectal or ear thermometry ("core" Δ T)
4. Heat balance
 - a) Calculated from above

TABLE 2 (Continued)

NEUROENDOCRINE

THYROID

1. Function testing
 - a) BMR (See RESPIRATORY, METABOLIC)
2. Direct assay
 - a) Circulating total thyroxine
 - b) Circulating free thyroxine
3. Indirect assay
 - a) Radioactive iodine procedures
 - b) Protein bound iodine
 - c) Tri-iodothyronine red cell uptake
 - d) Thyroxine binding pre-albumin capacity

ADRENAL CORTICAL

1. Direct assay
 - a) Free cortisol (becoming available)
 - b) Urine aldosterone
2. Indirect assay
 - a) Urine and blood 17-OHCS
 - b) Urine 17-KS
3. Provocative testing
 - a) Response to continuous parenteral ACTH

ADRENAL MEDULLARY

1. Direct assay
 - a) Circulating catecholamines
2. Indirect assay
 - a) Urine vanilmandelic acid (metanephrine) (Urinary norepinephrine)
 - b) Serum non-esterified fatty acids

See also METABOLISM

TABLE 2 (Continued)

PITUITARY

1. Direct assay
 - a) Circulating ACTH
 - b) Circulating TSH (becoming available)
 - c) Urine ADH
2. Indirect assay
 - a) ACTH reserve: Urine analysis for "compound B" after exhibition of steroid SU-4885
3. Water metabolism (See also FLUID AND ELECTROLYTES)
 - a) Urine concentration with and without pituitrin
 - b) Water and salt loading (Carter Robbins) with and without pituitrin

GONADAL

1. Direct assay
 - a) Seminal examination
 - b) Seminal phosphatase
 - c) Testicular biopsy
2. Indirect assay
 - a) Urine 17-KS

PANCREATIC

1. Direct assay
 - a) Circulating insulin
2. Indirect assay
 - a) See carbohydrate METABOLISM

PARATHYROID

1. Direct assay
 - a) Circulating parathoromone - immuno-assay
2. Indirect assay
 - a) See mineral METABOLISM

TABLE 2 (Continued)

NEUROHUMORAL

1. Direct assay
 - a) Circulating serotonin

HEMATOLOGICAL, IMMUNOLOGICAL, HISTOLOGICAL

1. Blood composition
 - a) Plasma volume - See FLUID AND ELECTROLYTES
 - b) RBC count
 - c) Hematocrit
 - d) Reticulocyte count
 - e) WBC total count
 - f) WBC differential count
 - g) Platelet count
 - h) Hemoglobin content
 - i) Abnormal pigments
2. Morphology
 - a) Microscopy of stained blood smear
3. RBC destruction
 - a) Life span
 - b) Fecal and urine urobilinogen
4. WBC activity
 - a) Leukocyte mobility
 - b) Leukocyte phagocytic capacity
 - c) Leukocyte mobilization
5. Serum immunology
 - a) Serum immunoglobulins, complement, and antibodies
6. Hemostasis
 - a) Coagulation time
 - b) Bleeding time
 - c) Capillary fragility

TABLE 2 (Continued)

HEMATOLOGICAL, IMMUNOLOGICAL, HISTOLOGICAL, (Continued)

6. Hemostasis (Continued)

- d) Clot retraction
- e) Platelet adhesiveness
- f) Fibrinolytic activity
- g) Prothrombin complex activities
- h) Plasma thromboplastin component activity

7. Cytology

- a) WBC chromosomal structure

TABLE 2 (Continued)

NEUROLOGICAL

AROUSAL AND SLEEP

1. Cortical electrical activity
 - a) EEG
2. Ocular activity
 - a) EOG
 - b) Pupillography

SENSORY FUNCTION

1. Visual
 - a) Central visual acuity (minimum detectable)
 - i) Near
 - ii) Far
 - b) Peripheral visual acuity
 - i) Static
 - ii) Dynamic
 - c) Depth perception
 - i) Near
 - ii) Far
 - d) Ocular muscle activity
 - i) Balance
 - ii) Accommodation
 - iii) Convergence
 - iv) EOG
 - e) Color perception
 - f) Refraction
 - g) Retinal activity
 - i) ERG
 - h) Provocative testing
 - i) Response to radial acceleration (LOMA, greyout, blackout)
 - i) Visual performance (See PSYCHOLOGICAL)

TABLE 2 (Continued)

NEUROLOGICAL (Continued)

SENSORY FUNCTION (Continued)

2. Auditory
 - a) Threshold and range
 - i) Audiometry
 - b) Auditory perception (See also PSYCHOLOGICAL)
 - i) Tone discrimination
 - ii) Tone pattern discrimination
 - iii) Speech perception
 - c) Auditory localization
3. Vestibular (See also Proprioceptive, visual)
 - a) Otolith function
 - i) Static
 - A. EVLH with and without pressure contact
 - ii) Dynamic (Provocative testing):
 - A. Detection of linear acceleration threshold
 - B. Response to suprathreshold linear acceleration (EOG, cinephotography)
 - b) Canal function
 - i) Static (Provocative testing)
 - A. Thermal stimulation
 - ii) Dynamic (Provocative testing)
 - A. Detection of angular acceleration threshold
 - B. Response to suprathreshold angular acceleration (EOG, visual illusions, physiologic correlates)
 - c) Combined otolith and canal function
 - i) Response to linear acceleration and head rotation (EOG, visual illusions, physiologic correlates)
4. Proprioceptive (See also Vestibular)
 - a) Static
 - i) Detection of body posture
 - ii) Limb localization

TABLE 2 (Continued)

NEUROLOGICAL (Continued)

SENSORY FUNCTION (Continued)

4. Proprioceptive
 - b) Dynamic
 - i) Detection of threshold of body motion
 - ii) Detection of threshold of limb motion
 - c) Provocative testing
 - i) Re-alignment after body or limb displacement
5. Taste, smell, touch

MOTOR FUNCTION

1. Muscle mass (See ANTHROPOMETRIC)
2. Muscle action
 - a) Force
 - i) Dynamometry
 - b) Coordination
 - i) See PSYCHOLOGICAL
3. Electrical activity
 - a) EMG
 - b) Galvanic response

AUTONOMIC ACTIVITY

1. See CARDIOVASCULAR, RESPIRATORY, METABOLIC, THERMAL, NEUROENDOCRINE.

HIGHER FUNCTION

1. See PSYCHOLOGICAL

TABLE 2 (Continued)

PSYCHOLOGICAL

1. Perception
 - a) Discrimination
 - b) Recognition
2. Cognition
 - a) Comprehension
 - b) Memory, short and long-term
 - c) Learning (aquisition and retention)
 - d) Inductive and syllogistic reasoning
 - e) Manipulation of symbols
 - i) Problem solving
 - ii) Verbal skills
 - iii) Computation
3. Task performance (including psychomotor)
 - a) Discrete response
 - i) Simple reaction
 - ii) Complex reaction
 - iii) Sequencing
 - b) Continuous response
 - i) Vigilance (monitoring)
 - ii) Attention
 - iii) Tracking
 - c) Fine motor control
 - i) Dexterity
 - ii) Manipulation
 - iii) Positioning
 - iv) Steadiness
 - d) Gross motor control
 - i) Self-maneuvering
 - ii) Complex activity
 - iii) Force application

TABLE 2(Continued)

PSYCHOLOGICAL (Continued)

- 4. Operational performance
- 5. Behavior and emotion
 - a) Sociometric rating
 - b) Observational appraisal
 - i) Visual
 - ii) Auditory
 - c) B/GSR
 - d) Physiologic correlates (See CARDIOVASCULAR,
RESPIRATORY, NEUROENDOCRINE).

SECTION 2 - CARDIOVASCULAR

In this section each of the function systems outlined in Table 2 of Section 1 is examined in depth. A review is made of the methods and techniques available to provide meaningful measures of the significant variables within each function system. Because of overlapping techniques of measurement, and the capacity to measure more than one variable at the same time, the order of presentation of variables outlined for each function in Table 2 is not strictly adhered to in this Section, nor is each variable necessarily considered individually.

SECTION 2 - CARDIOVASCULAR

Section 2.1a - Cardiac Output

From a teleological point of view it may be considered that the function of the cardiovascular system is to provide a continued, adequate supply of oxygenated blood to the brain, to the body organs responsible for maintenance and support, and to the musculature. From a more pragmatic point of view, if the veins, the right heart, and the lung vasculature are considered as a low pressure reservoir, and the systemic arteries as a high pressure reservoir, the function of the heart is to pump blood from the low to the high pressure reservoir. As one of the most significant measures of the integrity of this function, and of the extent of its adaptation to internal and external stimuli, the timed volume output of blood from the heart is paramount. By definition the cardiac output is the timed product of the stroke volume and the heart rate. Since heart rate is readily measured, the complexities of measurement lie in obtaining values for the stroke volume.

Since it is not practicable to measure stroke volume directly in man, and barely practicable even in animals, numerous ingenious techniques have been developed for indirect measurement. Many of these, however, are very complex and require considerable violation of the subject, such as intracardiac catheterization, arterial infusion, or arterial puncture, and cannot be considered readily acceptable. In evaluating techniques for use in an orbiting space laboratory, therefore, in conditions of weightlessness and confinement, where equipment is limited in weight and volume, where the investigator is not necessarily expert in all techniques, and where the subjects are operational astronauts, certain constraints must apply. Thus, in this particular study, while, reference may be made to techniques of considerable complexity involving severe violation of the subject, emphasis is placed on those providing optimization of subject participation, reliability of data, and simplicity of execution and instrumentation.

Methods involving the peripheral pulse

On contraction, the left ventricle ejects a volume of blood into the aorta from whence it is passed along the arterial tree. In addition to passage along the aorta, the ejected blood also produces a pressure pulse within the vessels, the amplitude of which is measurable as the difference between the systolic and diastolic pressure, or the pulse pressure. This pressure pulse distends the vessel and of course is most apparent in the aorta. There is obviously a relationship between the pulse pressure and the stroke volume, but this relationship is complicated by the varying distensibility and resistance of the arteries involved. Numerous attempts have been made to derive equations linking stroke volume and pulse pressure. Most of these have been on an empirical basis, whereby the pulse pressure reading is modified by some constant derived from the blood pressure without any deliberate allowance being made for the arterial distensibility. Examples of the type of formulae used are shown on Table (1) from the work of Warner and his associates (1953)⁶⁷.

In another approach, Bolie and his colleagues (1963)⁸ prepared a nomogram (Figure 1) for the determination of stroke volume from blood pressure on the basis of an equation developed by Starr (1954)⁶¹ which allows for modification of blood pressure by age.

These methods of course are highly empirical but provide in some cases quick and useful approximations of the stroke volume, with the minimum of measurement, particularly if carefully pre-calibrated by an indirect Fick or dye method.

Bazett and his associates (1935)⁷, advocated the use of the pulse wave velocity as an index to the percentage increase in volume of an artery over a given range and thereby hoped to account for the factor of arterial distensibility. Hamilton and his associates at the University of Georgia (Hamilton and Remington, 1947²⁸; Remington et al., 1948⁵³; Hamilton, 1962²⁶), extended the technique and found it useful for measurement of cardiac output in dogs, but observed that while there is a relationship between pulse wave velocity and arterial distensibility, the relationship is relative and not absolute, and is modified by the capacity

TABLE 1

COMPARISON OF VALUES FOR STROKE VOLUME OBTAINED BY EIGHT VARIATIONS
OF THE AORTIC PRESSURE PULSE METHOD AND BY THE FICK AND DYE METHODS IN MAN

No. of comparisons:.....	TEST CONDITION					
	Exercise		Tilt 70°		Press. applied to body and tilt in sitting position	
	10		7		12	
	Mean 128 cc.	S. D. ±15 cc.	Mean 65 cc.	S.D. ±13 cc.	Mean 82 cc.	S.D. ±14 cc.
Stroke volume by Fick or dye method ¹	% Difference from Fick or dye value					

<i>(A) Methods Using a Pressure Difference and a Proportionality Constant Only</i>						
1) Pulse pressure method, $SV = (P_s - P_d)k_1$	5	±9	38 ²	±21	3	±13
2) Dicrotic pressure method, $SV = (P_z - P_d)k_2$	-28 ²	±15	37	±41	-2	±20
3) Systolic area method, $SV = (P_{Sa})k_3$	-13 ²	±12	1	±12	0	±14
4) Mean distending pressure method, $SV = (P_{md})k_4$	-12 ²	±11	25 ²	±15	3	±13

<i>(B) Above Methods with Correction for Changes in Ratio of Systolic to Diastolic Drainage³</i>						
5) Pulse pressure method, $SV = k_5(P_s - P_d) \left(1 + \frac{T_s}{T_d}\right)$	27 ²	±10	39 ²	±23	3	±16
6) Dicrotic pressure method, $SV = k_6(P_z - P_d) \left(1 + \frac{T_s}{T_d}\right)$	-15 ²	±12	36 ²	±29	-1	±21
7) Systolic area method, $SV = k_7(P_{Sa}) \left(1 + \frac{T_s}{T_d}\right)$	6	±14	0	±17	0	±16

Definition of symbols: SV, stroke volume; P_s , systolic pressure, P_d , diastolic pressure; P_z , pressure at dicrotic notch; P_{Sa} , product of mean rise above diastolic pressure during systole times the duration of systole; k_1 through k_4 , proportionality constants obtained by dividing the resting value for stroke volume (Fick or dye) by the respective resting pressure difference; k_5 through k_7 , proportionality constants obtained by dividing the resting value for stroke volume by the product of the resting pressure difference times the value $\left(1 + \frac{T_s}{T_d}\right)$; (T_s and T_d) duration of systole and diastole.

1. Resting control values for stroke volume averaged 108cc. with S. D. of ±30cc. 2. Statistically significant systematic difference; P value less than 0.02. 3. Changes in heart rate produce changes in the relative duration of systole and diastole and thus in the relationship of systolic to diastolic drainage. This would be expected to alter the relationship between stroke volume and the pressure differences used in these methods since the pressure pulse results from the net volume increase, that is volume ejected minus the volume running off. In methods 5, 6 and 7 a time factor T_s/T_d only is used. Source: Warner et al. (1953)⁶⁷.

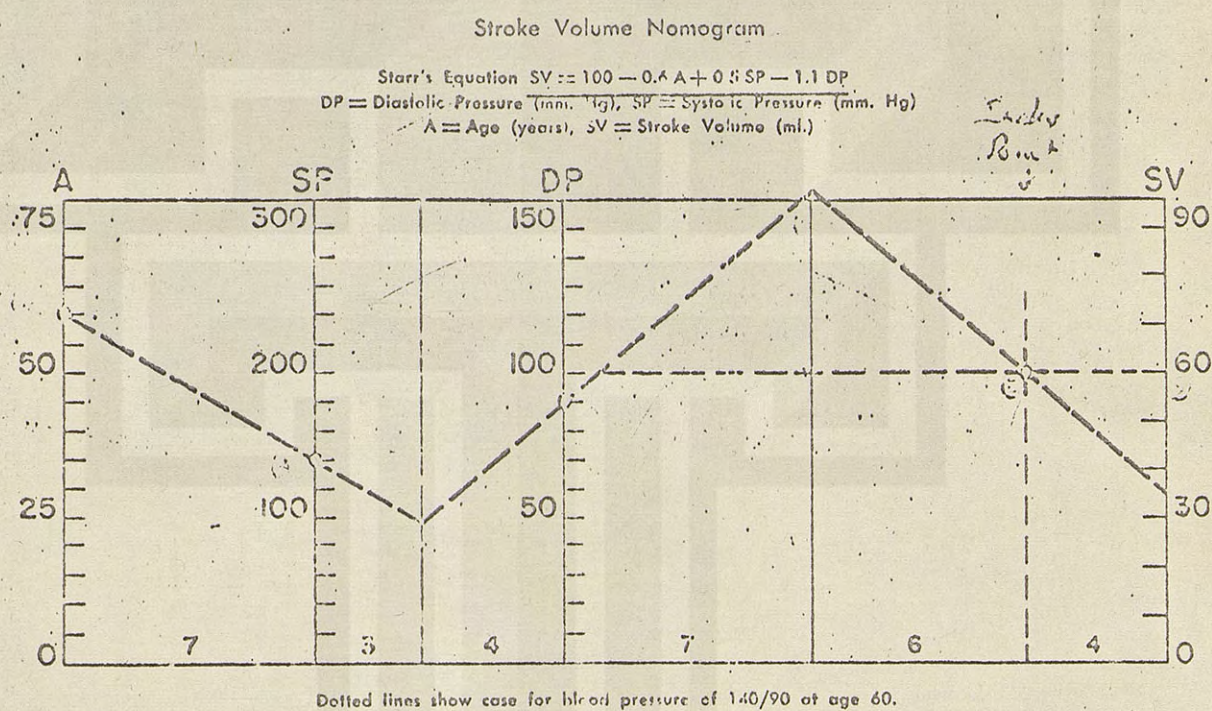


Figure 1

Source: Bolie et al. (1963)⁸

of each segment of an artery at the beginning of the pulse. Consequently pulse wave velocity cannot provide information on absolute distensibility. In man, in particular, because of wide variability in aortic size at diastolic pressure in a given individual, and because of still further changes associated with age, physiological conditions, body size, and disease, the technique is not reliable.

Consequently, this group (Remington et al., 1948⁵³) went on to develop a method independent of distensibility measures. By experimental stretching of rings cut from human aortas and measurement of pressure volume relationships, Remington showed that regardless of previous history, age, or aortic size, the average increase in aortic volume per unit pressure rise is very similar. The actual volume at any diastolic pressure will vary widely, but the change in volume with pressure is more constant. Furthermore, at pressures between 20 and 100 mm Hg there is virtually proportional relationship between pressure and volumes which tends to fall off above the upper level.

From values of stroke index derived from 83 determinations of cardiac output by the Fick principle, along with simultaneous arterial brachial pressure pulses, Remington then adjusted the values of the previously noted pressure volume curves to conform to those which would be expected on the basis of stroke index calculated by the Fick procedure. The stroke index represents stroke volume per square meter and is used to diminish differences occurring by reason of body size. The final figures are shown in Table (2) which permits prediction of the stroke volume from the difference between the volume factors associated with systolic and diastolic pressures.

In examining this method it is apparent that there is considerable room for error in prediction. The pressure-volume data used to derive the table are averaged over different age groups and physical conditions, with, in each case, fairly large standard deviations applicable to the data points. On top of this, these averaged data are then manipulated somewhat arbitrarily to accommodate to averaged Fick cardiac output data, which in turn may have an inherent error of $\pm 10\%$. (Rushmer, 1961⁵⁷). It is not surprising that Remington found a discrepancy of 18.6% between cardiac outputs obtained from his table and those obtained by the Fick principle. At the same time,

TABLE 2

Factors for the Prediction of Stroke Volume.
per m² Body Surface, from the Pulse Pressure.

Pressure	Volume Factor	Pressure	Volume Factor	Pressure	Volume Factor
mm Hg	ml	mm Hg	ml	mm Hg	ml
20	0	100	81	180	140
30	10	110	90	200	148
40	21	120	100	220	155
50	31	130	108	240	161
60	42	140	115	260	167
70	52	150	122	280	173
80	62	160	128	300	179
90	71	170	134		

Source: Remington et al. (1948)⁵³

with known individuals it would be possible, by doing Fick type cardiac output estimation at rest and under varying conditions of exercise, to develop in controlled laboratory conditions a constant (or constants) which would be applied to the table for use in an orbiting laboratory.

Warner and his associates (Warner et al., 1953⁶⁷) in Wood's laboratory, utilized this principle of pre-calibration by a Fick method to determine a constant which would link stroke volume to the systolic/diastolic pressure ratio. Using an equation, the derivation of which is clearly expressed in their paper, they showed that:

Equation 1.

$$SV = kP_{md} (1 + Sa/Da)$$

where

SV = stroke volume

k = constant

P_{md} = end systolic mean distending pressure
(measured)

Sa = area under curve of systolic arterial pressure
corrected for mean time of pulse transmission.

Da = area under curve of diastolic arterial pressure
corrected for mean time of pulse transmission.

Details of the logic and method should be consulted in the original paper. Using this technique they obtained a close correlation, with a 9% standard deviation, between their method and estimations made by direct Fick and dye methods. Since the technique calls for catheterization into the subclavian artery, however, it cannot be given much consideration for use in space vehicles.

Still more sophisticated methods have been developed by Hamilton and his group (Hamilton and Remington, 1947²⁸; Hamilton, 1953²⁷; Remington, 1952⁵²; Hamilton, 1962²⁶) using the time relationships of arterial pulse contours. Hamilton points out, however, that although pulse contour methods have applicability to dogs with a high degree of correlation with direct Fick methods, they are not suitable for use in man for the reasons previously noted. Essentially the technique requires the initial development of tables showing the net volume uptake per square meter of body surface in different portions of the arterial tree under different pressures,

along with the transmission times of the pressure pulse to these different portions under the same pressures, and the diastolic drainage times.

On the basis that the stroke index is the sum of the arterial uptake and arteriolar outflow, or drainage, per square meter of body surface the stroke index can be shown to be given by the following equation:

Equation 2.

$$SI = U + U \frac{(Ts - Tw)}{Tc - Ts + Tw}$$

where

SI = stroke index

U = arterial uptake per square meter (from tables)

Ts = time of systole

Tw = weighted average drainage time

Tc = total time of cardiac cycle.

In addition to having doubtful applicability to man, however, this method also required intra-arterial catheterization and hence cannot receive much consideration for use in orbiting laboratories.

Methods involving cardiometry

Cardiometry is the term given to the direct measurement of changes in cardiac volume occurring with the events of the cardiac cycle. Most cardiometric methods require open thoracic surgery and are not applicable to man.

The use of x-ray techniques, however, has permitted another approach to cardiometry. Hamilton (1962)²⁶ has reviewed some of the methods used. Straight thoracic x-ray with timed short exposures made during systole and diastole provides a picture of cardiac shadow through the cycle, from which volume calculations can be made. Since x-ray sees only in one plane, however, the three-dimensional action of the heart is ignored, and cardiac outputs so calculated are persistently underestimated. More sophisticated techniques using cardiac x-ray kymography suffer from the same disadvantages. Empirical constants obtained from Fick or dye methods can be applied to correct the resulting values (Johnson, 1937)³³.

Another method involves the quantification of light intensity resulting from x-rays passing through the body and impacting on a fluorescent screen. Measurement is made by means of a photomultiplier system which, with suitable processing, provides a record somewhat similar to that of a mechanically recorded ventricular plethysmogram. Again, however, calibration factors must be applied to the record from cardiac output measures calculated by other techniques (Ring et al., 1949)⁵⁴.

Further approaches have been made by the use of infusions of radio-opaque material into the left ventricle with subsequent study of the intraventricular shadow by cineangiocardiology (Rushmer and Thal, 1952)⁵⁶, Chapman et al., 1958¹¹; Gribbe et al., 1959²³) but the technique is complex and calls for catheterization of an artery.

There is no doubt that valuable information can be obtained through the use of x-rays. In the orbiting space laboratory, however, the information obtainable by straight x-ray, or even kymography, can be found more accurately, and in some cases more simply, by other methods, while that obtained by sophisticated x-ray methods would not appear to justify the violation of the subject and the complexity of the instrumentation and techniques. The additional radiation exposures, even using the most advanced techniques, would be considered generally undesirable.

Methods involving the Fick Principle

The Fick principle, which was enunciated by Fick in 1870, states that the rate of uptake of a reference material by an organ is equal to the difference in concentration of that material in the intake and output blood stream. In other words,

Equation 3.

$$\frac{dM}{dt} = F_o C_o - F_i C_i$$

where

M	=	quantity of reference material
F _o	=	rate of flow out of organ
C _o	=	concentration of material in outflow
F _i	=	rate of flow into organ
C _i	=	concentration of material in inflow.

The integrated form of the equation is shown as:

Equation 4.

$$M = \int_{t_0}^{\infty} (F_o C_o - F_i C_i) dt$$

If the flow rate and the concentration are independent of the time interval T and if $F_o = F_i$ at all times, the equation may be represented as:

Equation 5.

$$M = F(C_o - C_i) T$$

or, in its more usual form:

Equation 6.

$$F = \frac{M}{(C_o - C_i) T}$$

In determining cardiac output in relation to oxygen consumption the equation becomes:

Equation 7.

$$\dot{Q} = \frac{\dot{V}_{O_2}}{C_{a_{O_2}} - C_{\bar{V}_{O_2}}}$$

where

$\dot{Q}$ = blood flow per unit time

$\dot{V}_{O_2}$ = oxygen consumption per unit time

$C_{a_{O_2}}$ = arterial O_2 content

$C_{\bar{V}_{O_2}}$ = mixed venous O_2 content

In a very thorough analysis of the potential errors that arise in the application of this equation, Stow (1953)⁶⁴ emphasizes the requirement for constant flow and concentration, and observes that even in "steady state" conditions changes occur in both the lung volume and pulmonary blood volume. He observes further that in practice when a needle or catheter is used for withdrawal of blood samples at a constant rate, the resulting samples yield a time average concentration and not the volume average concentration that the equation demands. He goes on to illustrate other potential errors arising from irregular mixing in the blood stream, inconstancy of flow volume, and velocity. Fishman and his associates (1952)¹⁹.

have also commented on the unreliability of the Fick equation in the unsteady state engendered by entering or leaving a hypoxic condition, a point which may have some application to the determination of cardiac output in a space laboratory.

Because of the various actual and potential errors, cardiac output as estimated by the direct Fick principle is considered reliable at best only to within $\pm 10\%$. The direct Fick procedure, using oxygen as a reference material, would nevertheless appear to be the most reliable method available. Its application calls for a measure of O_2 consumption, a measure of arterial O_2 content, and of mixed venous O_2 content. While the O_2 consumption is a relatively simple measure, that for arterial O_2 content requires a sample of arterial blood; while in order to obtain a representative sample of mixed venous blood intracardiac catheterization is necessary. These complexities render the procedure impracticable for use in an orbiting space laboratory.

An obvious respiratory application of the Fick principle lies in utilizing CO_2 as the reference material instead of O_2 . In this situation the equation becomes:

Equation 8.

$$\dot{Q} = \frac{\dot{V}_{CO_2}}{C_{\bar{V}CO_2} - C_{aCO_2}}$$

where

- $\dot{V}_{CO_2}$ = carbon dioxide production
- $C_{\bar{V}CO_2}$ = mixed venous carbon dioxide content
- C_{aCO_2} = arterial carbon dioxide content

Carbon dioxide production is readily measurable. Arterial CO_2 content can be very closely approximated by measuring the P_{CO_2} in a sample of end-tidal air and subsequently deriving the CO_2 content from a prepared CO_2 dissociation curve. The major problem lies in obtaining a value for the mixed venous carbon dioxide content.

One approach towards obtaining this value is to rebreathe oxygen in a closed system until the CO_2 concentration in the system reaches a plateau representing equilibrium with the mixed venous concentration. Because of problems arising from the recirculation of the CO_2 produced, and slowing of the evolution of CO_2 from the venous lung blood as rebreathed air tension approaches that of blood (Hamilton, 1962)²⁶, it is difficult to establish where this end point occurs. A technique for determining this end point was proposed by Defares and his colleagues (1961)¹³, and has been still further developed by Garza (1963)²² and Luft. This method is currently in regular use and continued development in Luft's laboratory at the Lovelace Foundation.

To provide values approaching equilibrium concentration at an early stage of rebreathing, a known quantity of CO_2 (4-6%) is added to the oxygen in the rebreathing bag. The ideal initial mixture is still being investigated. Rebreathing at a controlled rate is permitted for about 10 breaths, or less than 15 seconds (the approximate recirculation time). With each expiration into the bag, the expired CO_2 concentration approximates more closely to the inspired. At some point the CO_2 concentration in breath n will equal that in the succeeding breath $n + 1$. Thus, if the CO_2 in breath n is plotted against the CO_2 in breath $n + 1$ the resulting plot can be extrapolated to meet the identity line (Figure 2) from the points obtained during the period prior to equilibration. The point of meeting represents a very close approximation to the concentration of CO_2 at equilibrium. In point of fact, the actual CO_2 curve from the rebreathing maneuver is an asymptote whose intercept with the identity line is infinity. Since there is a constant production of CO_2 in the body, the $n + 1$ breath will never have the same amount of CO_2 as the n breath. Under exercise the difference will be even greater but the actual quantitative difference is sufficiently small that the extrapolation procedure can be applied. Thereafter, CO_2 content can be derived from a dissociation curve and the Fick equation completed.

Garza (1963)²² draws attention to the errors that can arise in the use of this method and notes the requirement for steady state conditions, accurate calibration and precision, rapid response CO_2 measures, care in protocol,

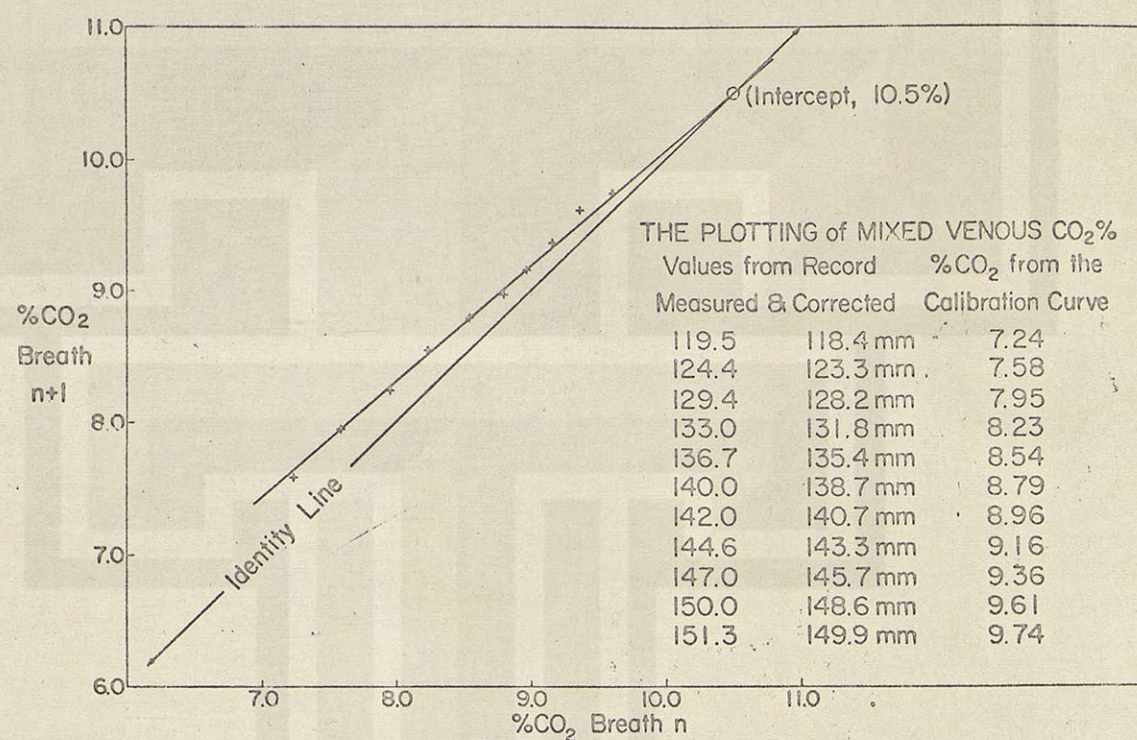


Figure 2
The plotting of mixed venous CO₂%. This shows the method used to extrapolate a CO₂% level from which the P_{VCO₂} is calculated.

Source: Garza, (1963)²²

and positioning of subjects. He refers to the work of Dubois and his colleagues (1952)¹⁵ who showed that lung tissue and fluids have the capacity to absorb evolved and inspired CO₂ and that the movement of stored CO₂ into the lung fluids causes a more slowly rising P_{CO₂} in the alveolar air than would be predicted from the volume of air in the lungs and the rate of CO₂ output. Nevertheless, the reproducibility of the results obtained in Luft's laboratory, and comparison with other methods of obtaining cardiac output indicates the applicability of the method. Table (3) shows a comparison with other methods (Garza, 1963)²².

TABLE 3

Method	Position	Cardiac Index (mean)
CO ₂	Supine	3.50 liters/min/m ²
	Seated	4.89 liters/min/m ²
Direct Fick	Supine	3.62 liters/min/m ²
Foreign gas	Seated	4.80 liters/min/m ²

In a recent study by Klausen (1965)³⁶, a comparison was made between cardiac output determined by CO₂ rebreathing and by the acetylene technique of Grollman (1929)²⁴. The values obtained by the two methods were highly comparable, with a standard deviation over all experiments of $\pm 7.3\%$, and were of the same magnitude as those obtained by others with dye-dilution or direct Fick techniques.

Although originally sampling of the rebreathing bag and measurement of CO₂ concentration by the Scholander method were required, the use of an on-line rapid response CO₂ measuring device provides highly satisfactory results. The technique would be very applicable to space laboratory use because of its inherent simplicity, reliability, and reproducibility, and minimal violation of the subject.

Besides oxygen and carbon dioxide, other gases have been used as reference materials. The amount of an introduced gas which is absorbed is dependent on the pulmonary blood flow; hence if its solubility in blood is known and its rate of absorption is measured, the cardiac output can be calculated. Several gases, including nitrogen, nitrous oxide, ethyl iodide, ethylene, and acetylene have been used for this purpose. Of these, the acetylene technique of Grollman (1929)²⁴ has probably been the most popular, but also suffers from problems arising from recirculation and absorption in the lung fluids. In any event, the use of foreign gases in space laboratory conditions would seem inadvisable both from the point of view of possible atmospheric contamination and because of difficulties in storage.

Dilution methods

Dilution methods of determining cardiac output involve a modification of the Fick principle first suggested by Stewart (1897)⁶³, and modified by Hamilton and his associates (1928)³¹. The methods depend on the fact that if a material is introduced into the blood stream, and is uniformly mixed, the concentration becomes dispersed and can be represented as a function of time $c(t)$, where c is the concentration, and t the time. Moody and his colleagues (1963)⁴² analyse the resulting relationship as follows:

In any time, Δt , the amount of dye passing the sampling point is:

$$F c(t) \Delta t, \quad \text{where } F = \text{flow}$$

and since the whole of the dye, I , will eventually pass the sampling point, Equation 9.

$$I = \int_0^{\infty} F c(t) dt$$

If the flow, F , is constant, then :

Equation 10.

$$F = \frac{I}{\int_0^{\infty} c(t) dt}$$

If the flow and the concentration are independent of the time interval, the cardiac output in liters per minute can be represented in the more common form of the equation:

Equation 11.

$$F = \frac{60 I}{ct}$$

In practice, a dye or other indicator is injected into the right heart or the venous system and its timed course of appearance and build-up is monitored in the arterial blood. The injected substance begins to appear after a delay of 6 to 15 seconds, builds up to a peak concentration and rounds off. After an apparent exponential descent for a time, a secondary build up occurs as recirculation begins. The occurrence of recirculation provides a problem in determining the actual time concentration of the material in its first circulation. Advantage, however, is taken of the apparent exponential descent of the curve, and by extrapolating the descending limb of the curve linearly on a semi-log plot of concentration versus time a measurable area can be defined (Figure 3) from which the necessary calculations can be made.

Doubt has been expressed as to whether the descending limb of the curve actually is exponential. Experiments with analog models of the circulation have shown that the curve becomes exponential only when a mixing chamber is incorporated in the analog (Hamilton et al., 1932³⁰). As compared with direct Fick methods, however, the results have shown an acceptable agreement, which tends to indicate that any deviation from a true exponential decay is not sufficient to negate the use of the method.

Sampling procedure has provided a continued problem. Early methods required samples of arterial blood at one-second intervals for analysis of dye content. Development of the arterial cuvette, which allows continuous analysis of the blood passing through it, reduced the sampling problem considerably, but created new problems in dye selection and in blood loss. The cuvette contains a light source and a photoelectric cell, the output of which varies according to the amount of absorption of light that takes place by the blood and by the dye carried by the blood. The

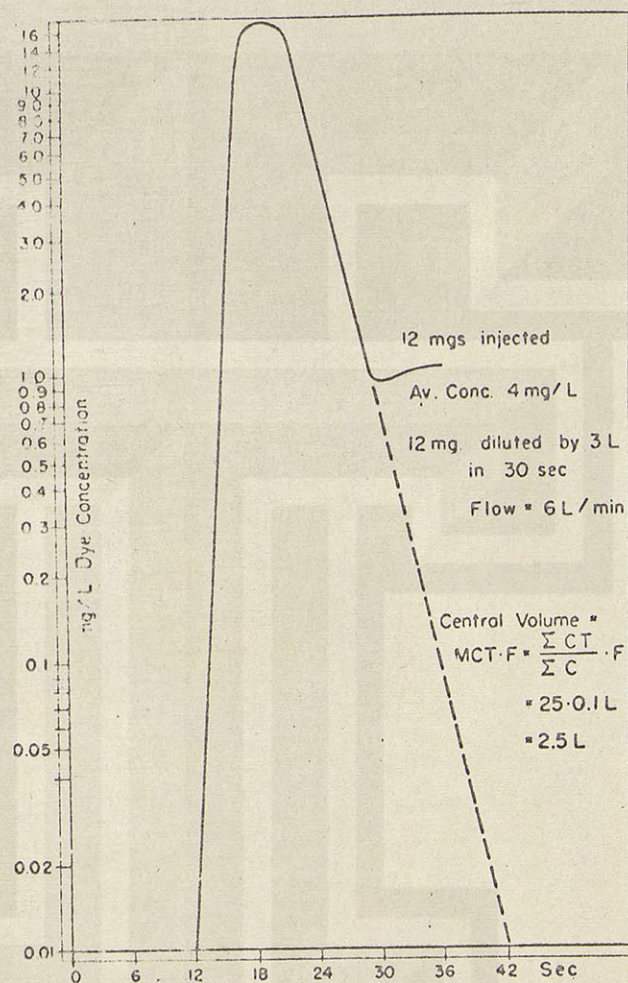


Figure 3

Changes in arterial dye concentration after injection into a vein. Cardiac output is calculated from data given on the figure.

Source: Hamilton, (1962)²⁶

cuvette, however has certain disadvantages. Distortion of the dye curve may result from the passage of blood through the connecting polyethylene tubing, although this can be reduced by maintaining a flow rate greater than 0.71 ml/sec (Lacy et al., 1957³⁸). Stray light may enter the photoelectric cell; the response of the recorder may not be linearly proportional to the dye concentration throughout the entire range, and drift of the recorder may occur. In addition, there are limitations inherent in the photometry of blood, largely due to its heterogenous character, with a tumbling mass of red cells, a clearer peripheral area, and streaks of protein stained by dye (Dow, 1956¹⁴).

The requirement to distinguish between the absorption characteristics of hemoglobin and dye raises problems in dye selection, compounded by the requirement to ensure minimum toxicity, and ideal diffusibility. Numerous materials have been used, but one of the more popular dyes is Evans blue or T-1824, (Dawson et al., 1920¹²). It is relatively non-toxic but very slowly excreted. Tissue staining may last for several days following a dose greater than 50 mg, (Payne and Armstrong, 1962⁴⁹). Use of this dye is further complicated by the fact that its absorption spectrum, maximum at 620 to 640 millimicrons, is similar to that of reduced hemoglobin and necessitates continuous oxygen administration during recording. This problem can be overcome by utilizing a dye such as indocyanine green ("Cardiogreen") the sensitivity of which is minimal at about 800 millimicrons and maximal at about 925 millimicrons. This dye, however, is removed from the circulation so rapidly that some workers, at least, maintain that proper calibration of the dye curve cannot be obtained (Taylor and Shillingford, 1959⁶⁵). Certainly one of the most suitable dyes is Coomassie blue (Taylor and Thorp, 1959⁶⁶) which is a water-soluble compound of low toxicity with a half-life, in the circulation, of 15 to 20 minutes, and maximal absorption sensitivity around 580 millimicrons, which reduces its interference by hemoglobin.

Procedures involved in the calculation of cardiac output from dye curves are cumbersome and tedious. In essence they require transfer of the data from the first portion of the curve onto semi-log graph paper, extrapolation of the descending portion of the first curve to meet the base line, planimetry of the resulting area, extraction of a value representing

mean concentration, and calculation of the flow which would provide such a concentration. Moody et al., (1963)⁴² described a method whereby an electronically generated curve could be matched against the dye concentration curve. The results can be read in terms of cardiac output and mean transit time. Such an instrument is manufactured by the Waters Corporation (Bulletin CO-63) who claim their method is three to four times more accurate than hand calculation. Another device manufactured by the Sanborn Company (Cardiac Output Computer Model 130) integrates the output of a densitometer and provides a digital read-out of cardiac output. The Gilson Company also make a suitable computer.

The above noted dye techniques require arterial puncture, with discrete or continuous arterial sampling. These factors reduce their applicability for use in manned space operations. To overcome this difficulty Wood and his associates at the Mayo Foundation have been using an ear cuvette which measures changes in absorption of light transmitted through the ear lobe. Although this method has met with some controversy, it has been used with considerable success by Wood and his colleagues. A recent paper (Reed and Wood, 1964⁵¹) describes refinements in the technique using a dichromatic earpiece densitometer containing two photocells, one of which is sensitive to dye (indocyanine green) and one which is insensitive to dye. The use of a dichroic mirror allows both cells to view the same optical pathway of the ear. Both cells are approximately equally reactive to changes in transilluminance of the ear caused by changes in blood content, hematocrit, or other non-specific effects, but one is sensitive to dye, the other not. Both cells are relatively insensitive to changes in oxygen saturation of the transilluminated blood. Compensation for non-specific changes in the ear unrelated to dye is obtained by using these cells in reverse polarity to each other. The "bucking" of the detecting cell against the compensating cell provides a stable baseline from which the end-tail method of calibration of a dye such as indocyanine green can be measured even though the removal rate of dye from the arterial blood is rapid.

To determine cardiac output from the earpiece densitometer a calibration factor is required. Originally this was obtained by independent analysis of an arterial sample, or averaged arterial samples. Using this method Reed and Wood found no systematic difference between cardiac output determined by the earpiece and by arterial cuvette, although the standard deviation in the former was large (31%). They also showed that an acceptable calibration factor could be obtained from venous rather than arterial samples, with, in this case, a systematic under-estimation of 7%. They further went on to show that once the earpiece has been calibrated by blood sample in terms of cm. deflection of the galvanometer per mg. of dye per liter of blood, any further calibration could be made from a factor related to the amount of blood actually being trans-illuminated. This measure can be obtained by measuring the difference in output of the infrared cell when the ear is in the normal blood containing state and when the transilluminated portion is rendered essentially blood-less by inflating the pressure capsule on the apparatus to over 200 mm Hg.

Thus, after pre-calibration of the instrument, it is possible to obtain a measure of cardiac output without arterial puncture and without venous puncture other than to inject the dye. It is emphasized that a high degree of familiarity with the method is necessary and that the standard deviation of the results is large, but it is believed that allowing for further development, the technique may have application in a manned space laboratory. The earpiece cuvette, however, suffers from the same disadvantages as the arterial cuvette. In addition, head movements may cause irregularity of the base line, and vasodilation must be ensured by heat or a rubifacient, otherwise vasoconstriction may interfere with registration of the dye curve (Payne and Armstrong, 1962⁴⁹).

Electrical conductivity

The original application of the Stewart principle by Stewart in 1897 involved the incorporation of a segment of an artery into a Wheatstone bridge. Injection of salt solution changed the electrical conductivity of the artery which was signalled by the automatic ringing of a bell. At

this time the arterial flow was diverted into a tube for sampling. Although accurate in principle the technique is not very practicable. White (1947)⁶⁹ modified the method for continuous recording of conductivity by devising minature conducting cells which could be inserted into an artery by way of a modified hypodermic needle. Using this system White successfully measured cardiac output in isolated preparations and intact dogs. There is no record of its having been used in man and it also does not now appear very acceptable for space use.

Thermal dilution methods

The use of temperature change in the blood flow has been suggested as another modification of the Stewart principle. One such approach is that of Fegler (1954)¹⁸ who calculated cardiac output from the temperature difference between saline at room temperature and at the equilibrium temperature which developed after injection of the saline into the right atrium. The theory is based on the assumption that heat exchange takes place only between the saline and the blood. Doubt, however, has been cast on the adequacy of the mixing that takes place, and it has been suggested that heat exchange also takes place in the lungs, although the possibility of the latter is minimized by Webb and Crocker (1963)⁶⁸. Using very careful techniques and calculating for all potential sources of heat exchange, Goodyer and associates have shown a close correlation between the thermodilution method of obtaining cardiac output and the direct Fick in animals. However, the method is complex and currently requires cardiac and arterial catheterization. Consequently, it would not be suitable for use in space.

Another form of thermodilution technique is being currently examined in Paul Webb's laboratory (Webb and Crocker, 1963⁶⁸), in which attempts are being made to apply a "slug" of heat to an artery by way of high intensity ultrasound and thereafter measuring the change in temperature by a thermistor in the nose. So far the results have been somewhat discouraging but the principle appears to present a hopeful potential.

Radioisotope methods

The use of injected radioisotopes as reference material began with Prinzmetal and his associates in 1949⁵⁰. The most commonly used material has been human serum albumin tagged with I^{131} (RISA). The method depends fundamentally on utilization of the Stewart-Hamilton principle to compute the cardiac output from measured concentration of the RISA. Two main approaches have been made to obtain the measurement. MacIntyre and his associates (1951)⁴⁰ utilized a method whereby the radioactive count rate at peak concentration was obtained from a sample of arterial blood withdrawn by way of a tube coiled round a rate counter. Calibration in terms of concentration was achieved by obtaining a further count rate when equilibrium had been reached and matching that against a dilution of the injected indicator.

To avoid the necessity of withdrawing arterial blood, Shipley and his associates (1953)⁶⁰, Huff and his associates (1955)³², and others, extended the work of Prinzmetal by using scintillation equipment with careful positioning over the precordium, and eventually with more refined collimation of the detector head. With the precordial equipment, calibration again offered difficulties. These have been tackled in a manner somewhat similar to the computations required in determining dye concentration. The average intensity of radioactivity is obtained from a semi-log plot of intensity versus time of the first portion of the radioactive curve. If the final concentration of the curve is determined when the RISA is uniformly mixed throughout the intravascular space (10 - 20 min), the average intensity during registration of the curve compared to the intensity at equilibrium represents that portion of the blood volume which must have traversed the site of the detector during the primary circulation. If the blood volume is known, the flow rate per minute may be calculated as follows:

Equation 12.

$$F = \frac{BV \times c_e \times 60}{c_{av} \times t}$$

where

F = flow (cardiac output)

BV = blood volume

c_e = concentration of isotope at equilibrium

c_{av} = average concentration of isotope in primary circulation

t = time of primary circulation in seconds from extrapolated plot

These relationships have been presented by MacIntyre and his associates (1952)⁴¹, Huff and his associates (1955)³², and Schreiner and his associates (1959)⁵⁹. In a further analysis, MacIntyre and his group (1958)³⁹ point out that the blood volume measured is not necessarily the circulating blood volume as usually calculated by dilution methods, but is actually the volume of dilution of the injected material at the time when the sample was withdrawn. In most cases, after a 10 minute mixing time this volume would approximate the total blood volume.

A problem arises from difficulty in determining the actual downslope which should be extrapolated. The curve obtained from a precordial detector normally presents in two peaks, representing the outflow from the right and left ventricles respectively, but including elements of pulmonary and coronary flow. However, the first part of the left ventricular curve and the last part of the right ventricular curve are superimposed and it is not always possible to find a downslope of the right heart curve which can be extrapolated. Where a suitable downslope is not obtainable the method is invalidated.

Doubt has been cast on the validity of the technique because of differences in results obtained with varying positions of the detector, varying collimations, and differences in "focussing" distance that may occur with chest movement during respiration. In particular, Carter and her associates (1959)¹⁰ in experiments with dogs found that an uncollimated precordial scanning technique gave results averaging 1.8 times greater than

those obtained by continuous counting of a peripheral artery; with a collimator there was a closer approximation. Changing the position of the detector on the precordium gave results which produced variations up to twice control.

Despite these findings, good correlations have been found with direct Fick and arterial methods in other circumstances and the method has received considerable acceptance. In a study of 44 subjects Schreiner et al., (1959)⁵⁹ found the mean precordial value of the stroke index was 3.53 liters/min/M² and the arterial value 3.46 liters/min/M²; while in 25 instances the mean values for precordial, arterial, and Fick methods were 2.97, 2.91, and 3.01 liters/min/M² respectively. Furthermore, the estimated standard deviation between duplicate measures with the precordial technique compared favorably with that from the Fick.

The use of radioisotope techniques has much to commend it in space operations. The application depends upon effective compromises among factors of detector sensitivity and positioning, dosage of radioactive materials, collimation, and sampling rates. It has the advantages of simplicity in execution, rapidity, and avoidance of arterial puncture or catheterization. At the same time the instrumentation is complex, the repeated exposure of astronauts to radioactive materials is inadvisable, and the storage of the materials would present problems. It would consequently seem unwise to consider it a method of priority.

As an addendum, it might be noted that Cournand and his colleagues (1960) (quoted in Hamilton, 1962²⁶) have made precordial measures of radioactive krypton injected intravenously. Since the krypton is highly diffusible it is eliminated in the lungs before reaching the left ventricle and consequently provides a clear picture of concentration in the right heart only. Unfortunately the half-life of K⁸⁵ is so short that storage for space operations would not be practicable.

Methods involving measures of cardiac kinetics

Ballistocardiography

Concepts governing the use of ballistocardiography for other aspects of cardiac evaluation are considered elsewhere in a general discussion of cardiac kinetics.

Beginning with Starr and his colleagues (1939)⁶² with the high frequency ballistocardiographic table, several workers have developed formulae relating events of the ballistocardiographic trace to the stroke volume (Nickerson et al., 1947⁴⁵; Hass, 1955²⁵; Klensch, 1956³⁷; Rodenbeck, 1959⁵⁵). It is not proposed to discuss and derive the individual formulae which are highly complex and include constants to take into account factors such as peripheral resistance, systolic ejection time, pulse wave velocity, age, body dimensions, table coupling, etc., as well as measurements of amplitudes and time dimensions of the trace. Formulae will be found in the original papers quoted.

The method depends on equating the acceleration forces developed by the mass of the blood ejected from the right and left ventricles with the acceleration forces developed by the recoil of the body and modified by the motions of the heart and vasculature. From these equations, calculations can be made to provide values representative of stroke volume.

In a review of the field, Hamilton (1962)²⁶ points out that there is no simple quantitative relationship between the recorded trace and the forces of ejection from which the stroke volume can be derived. In the first place the recoil which is recorded is responsive not to the steady flow but to the acceleration of that flow, as can be demonstrated by experiments with models. Furthermore during systole there are many forces generated at the same time, some of which are contrary to each other and tend to cancel out. As Rushmer (1961)⁵⁷ notes, the blood ejected from the two ventricles moves simultaneously in several directions after leaving the heart, and its energy is imparted vectorally to the body at every turn. In addition, Hamilton (1945)²⁹ has shown that accelerative forces in the venous return contribute to the total picture.

Thus, it would appear that although correlations have been shown between stroke volumes derived by ballistocardiographic methods and those by Fick or modified Fick methods (Starr, 1939⁶²; Nickerson, 1958⁴⁴; and others) the respective formulae tend to be somewhat empirical and have a doubtful inherent validity, which, however, does not render them less useful.

With respect to manned space laboratories, it would not seem reasonable to justify inclusion of ballistocardiographic apparatus solely for the purpose of performing measures of cardiac output. However, if it is deemed advisable to include such apparatus for other purposes, cardiac output determinations could readily be made. Under those circumstances, however, it would seem necessary to undertake a comparative study to determine which of the various methods of calculation would provide the most reliable data.

Precordial kinetics

Very little attempt has been made to correlate records of precordial traces with determinations of stroke volume. As noted in the section on cardiac kinetics, Agress (1964b) utilizes measurements of the ejection phase (J_2 -L) of the precordial vibrocardiogram to determine relative changes in stroke volume. However, because of considerable extraneous variation in the wave form of the vibrocardiogram, and because of some doubt as to what manifestation of energy the trace is actually reflecting, controversy has arisen over the interpretation of the stroke volume measure. Should the vibrocardiogram be used as a routine measure in space operations it will of course be advantageous to make the calculation if only for comparative purposes.

Measurement of precordial acceleration appears to show more potential. In an unpublished study in which 12 subjects were stressed by exposure in step fashion to hypoxia at 25,000 feet in an altitude chamber, Proper and Nevison (1962) showed a linearly proportional relationship between the amplitude of the "E" peak of the accelerogram and the increase in stroke volume occurring with hypoxia. Under the conditions of the

experiment it will be observed from Figure (4) that as the stroke volume rose from 52 to 106 cc with increase in altitude, the amplitude of the accelerogram trace doubled from an arbitrary value of 1 to an arbitrary value of 2. It must be noted here that stroke volume in this case was calculated from the displacement ballistocardiogram formula of Klensch, and was not determined by Fick or dye procedures. Thus, the relationship must be considered relative. With quantification of the accelerogram trace, such as would be possible with an accelerometer calibrated in terms of g versus stroke volume, it would seem feasible to develop a technique for determining stroke volume from the accelerogram tracing. If, as is recommended in the section on cardiac kinetics, accelerogram tracings are employed in manned space operations, the potential of obtaining stroke volume determinations therefrom would be a useful dividend.

Methods involving ultrasonic techniques

While the use of ultrasonic methods of determining blood flow and cardiac output has proven of significant value in animals, the technique currently demands implantation of ultrasonic generating and sensing devices. Consequently no application to man is seen for the near future. A brief review, however, is probably in order to permit evaluation of potential developments. Useful studies of ultrasonic physics in relation to biology have been made by Nelson et al., (1950)⁴³, Edler et al., (1961)¹⁷, and Joyner and Reid (1963)³⁴.

Ultrasonic frequencies currently employed in biological investigation and treatment range from above 20 kilocycles per sec (Kc) to around 1 million Kc. For investigative and diagnostic purposes the frequency is commonly of the order of 700 - 1000 Kc. At these frequencies ultrasonic waves tend to behave more like light waves than sound waves. Like audible sound waves they travel through a conducting medium as longitudinal vibrations with alternate compression and rarefaction within the medium, but travel with considerably less scatter. Like

- Precordial Accelerographic Tracing - Amplitude
- Stroke Volume - Displacement Ballistocardiograph (Klensch).

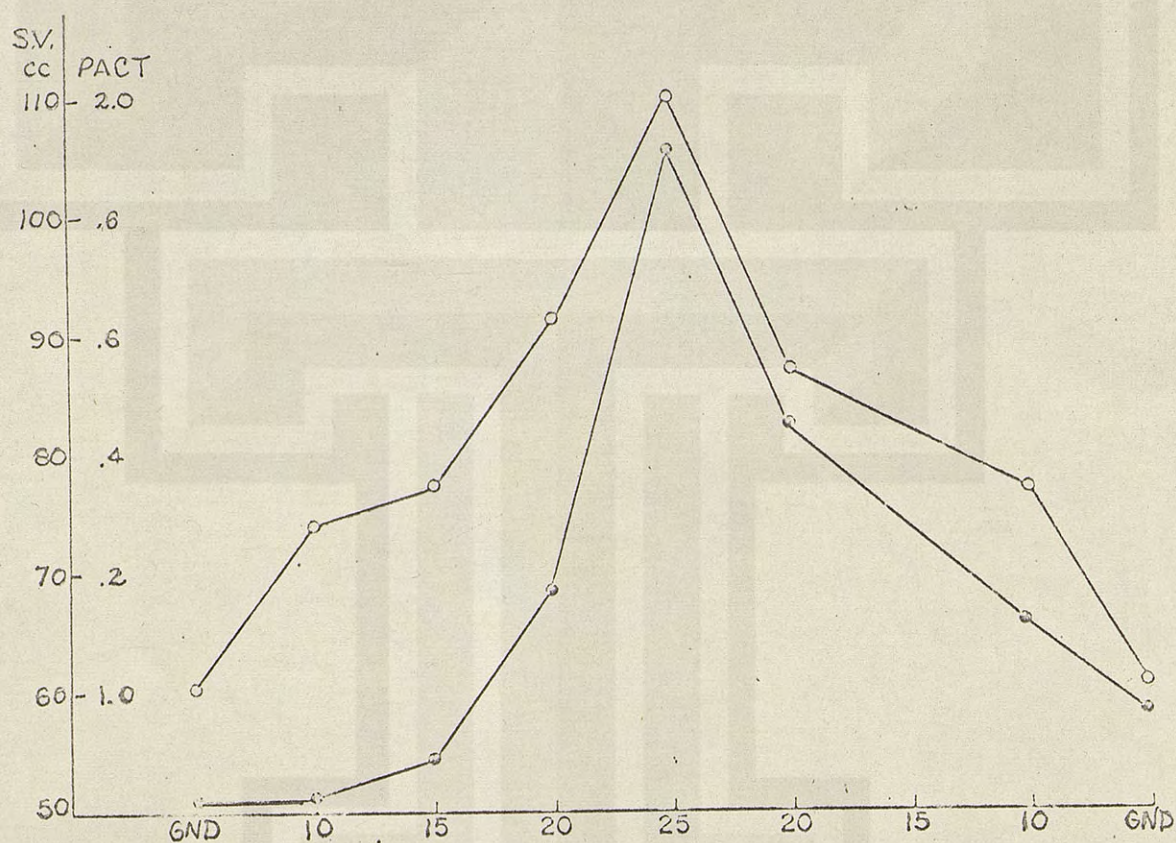


Figure 4

Source: Proper and Nevison (1962) (Unpublished report)

light waves, ultrasonic waves may be reflected and refracted under suitable conditions, and may be focussed by an acoustic lens.

The velocity of sound in a medium is a constant dependent on the characteristics of the medium, while the transmission in a medium is dependent upon the acoustical impedance, which in turn is related to the frequency of the sound, the velocity, and the density of the medium. When a sound wave travelling through an acoustically uniform medium reaches an interface with a medium with a different acoustical impedance, a greater or less degree of reflection of the sound will occur dependent on the magnitude of the difference of the impedance. There is a large difference between the impedance of a generating crystal, the impedance of air, and the impedance of different tissues. These differences lead firstly to the necessity of having a coupling medium, generally water or oil, between the generator and the tissue, and also to the difficulty of transmission of ultrasonic waves into organs surrounded by air, such as the heart.

The most commonly used generator of ultrasonic waves in biological investigation is the piezoelectric crystal. These crystals have the ability to become electrically charged on opposite surfaces when subjected to pressure. Conversely, such a crystal will undergo vibration at very high frequency when opposite sides are subjected to an alternating electric field.

With these and other transducers, ultrasonic waves of different intensity and frequency have been applied to tissue in vivo and in vitro for investigative, diagnostic, and therapeutic purposes. The whole field of ultrasonics in medicine is discussed by Edler and his colleagues (1961)¹⁶ who have pioneered the field in Sweden. Notable exponents in this country are Howry at the University of Colorado, Wild in Minneapolis, and Reid and Joyner at the University of Pennsylvania, while much work has been done in Rushmer's laboratory in the measurement of blood flow.

Several different techniques have been used to determine blood flow. Rushmer, Franklin, and Ellis (1956)⁵⁸ attached crystals to each side of the left ventricle of an animal and obtained a virtually continuous record

of change in diameter of the heart chamber from which output of the ventricle could be calculated. Other devices are based on ultrasound transit times. Franklin and his associates (1959)²¹ in Rushmer's laboratory attached a transducer to the aorta in such a manner that the signal was transmitted diagonally back and forward across the flow. The difference in transit time between signals travelling with and against the flow provided a measure of flow rate. Out of the same laboratory Franklin et al., (1961)²⁰ devised a flow meter which utilized the back-scattering of ultrasound by the moving stream to measure a Doppler frequency shift which also provided a measure of flow rate.

All these methods utilize implantable transducers which can be left in situ and used for continuous and repetitive measures, but, of course, because of the surgery involved, they are not at this time considered applicable to man.

External ultrasonic techniques are used extensively in diagnosis. The simplest (the "A" scan) presents a sonar type of display whereby a reflected echo is shown on a time scale proportional to the distance between the origin and the reflecting surface. It is used among other purposes to determine shifts in the midline of the brain. In the "B" scan technique, echoes are displayed as dots; by moving the transducer around the part to be examined both a horizontal and circular motion the echo-produced dots are scanned in a two-dimensional display to produce a somagram which represents the underlying structure. Various other complex compound scans are employed. The echo-cardiogram was developed by Edler and Herz (1954)¹⁷ and is described in Edler's comprehensive review (1961)¹⁶. With the transducer suitably placed on the precordium, signals attributable to heart motion can be obtained. Pulsations can also be observed when the beam is directed to the aortic arch via the root of the neck. Although no attempt would seem to have been made to relate the latter signals to aortic flow, a relationship of this kind might exist, and lend itself to calibration in terms of flow rate.

Ultrasonic investigative methods are still in a very early stage of development. It is possible that in time reliable external techniques will become available for the determination of blood flow rates and cardiac output.

Methods involving impedance plethysmography

The use of impedance plethysmography in the measurement of segmental volumes depends upon the relationships defining the electrical volume of a volume conductor, and on the concept of parallel resistive impedances introduced by Nyboer (1950)⁴⁷.

The volume of an electrical conductor can be defined as follows: (Nyboer, 1959⁴⁶):

Equation 13.

$$V = \frac{l^2}{R}$$

where

V = volume (ml)

l^2 = length (cm)

ρ = specific resistivity (ohm centimeters)

R = resistance (ohms)

Using models, Nyboer (1950)⁴⁷ showed that the physical change of volume over a limited range within a cylindrical elastic membrane (rabbit aorta) is directly proportional to the change in electrical conductance of its electrolyte contents, if measured between fixed points in the longitudinal axis of the cylindrical system. Expansion of a blood vessel within a given length of body segment, such as an arm, results in an increase in cross section and volume. The material (blood) expanding a segment has a different specific resistivity than the surrounding material. The effective relations of the volume change can be expressed as those of an added resistance in parallel to the resistance of the other tissues.

According to the theory of parallel resistance,

Equation 14.

$$R_{\text{total}} = \frac{R_1 \cdot R_2}{R_1 + R_2}$$

Equation 15.

Rearranging,

$$R_2 = \frac{R_1 \cdot R_{\text{total}}}{R_1 - R_{\text{total}}} = \frac{R_1 \cdot R_{\text{total}}}{\Delta R}$$

When radio frequency signals (50 - 120 kc) are passed into the tissues, the resulting impedance is almost entirely resistive (Nyboer, 1959⁴⁶) and the equation expressing the pulse volume can be written as:

Equation 16.

$$R_b = \frac{R_n \cdot R_o}{\Delta R}$$

where

R_b = calculated parallel resistive impedance equivalent to given pulse volume

R_n = new resistive impedance during segmental distribution of blood pulse

R_o = original segmental resistive impedance

The calculated value of R_b can be incorporated into Equation 13 to determine the change in volume (ΔV) after measuring length (l) and using a previously determined specific resistivity (ρ), usually considered to be 150 ohm cm at body temperature.

These relationships have been verified by Allison (1960)¹ and Allison and Nyboer (1965)⁶ in carefully controlled models. Using an ionic fluid in a graduate jar with a constant hindrance to outflow, and also with an expansible segment in the outflow tract, they measured the changes in resistive impedance resulting from changes in volume, and showed that: (1) the resistance in an electrolyte solution to a constant current varies directly as the length between the detecting electrodes when the cross-sectional area is constant, (2) the resistance varies inversely as the cross-sectional area when the length is constant, (3) a new ionic volume increasing the cross-sectional area acts electrically as though in parallel with the non-expanded segment.

In practice, (Allison et al., 1964^{2, 3}; Allison et al., 1965^{4, 5, 6}) to determine volume in a segment, an oscillator feeds a 100 kc current to a

buffer amplifier stage. The buffer is coupled through a transformer to a modified Kelvin double bridge of which the segment is a part. The signal is introduced to the segment through a pair of outer electrodes and detected between two inner electrodes. A two-electrode system can be used for both input and output but it is not so satisfactory due to inclusion of electrode contact resistance at balance. Impedance is measured as an imbalance of the bridge, the output of which is amplified and led to a recorder. On completion of the record, electrode leads are electrically switched to a decade substitution box. Null balance by substitution provides a measure of the impedance between the inner electrodes and expresses the gross resistive impedance of the system (R_o). 1 ohm and 0.1 ohm standards are also recorded for calibration purposes.

In measuring the change in resistive impedance occurring with change in volume it is necessary to bear in mind that the pulse volume contains systolic and diastolic components separated by the dicrotic notch. During both systole and diastole, drainage is taking place. From the beginning to peak of systole, arterial inflow exceeds venous outflow. The peak of systole represents the maximum arterio-venous volume exchange. Following closure of the aortic valve, represented by the occurrence of the dicrotic notch, outflow from the segment occurs as venous run-off. To allow for venous drainage when making a measure, the systolic downslope of the curve before the dicrotic notch is extrapolated backwards to the point representing the beginning of systole, as suggested by Nyboer and illustrated in Figure (5) from the work of Allison (1965)⁵. The beginning of systole is obtained from a concurrent ECG, phonocardiogram, and vibrocardiogram. The validity of this extrapolation procedure has been verified in the model experiments previously noted (Allison, 1960¹ and Allison and Nyboer, 1965⁶). The calculated flows agreed very closely with the actual measurement of the volume flow in the graduate jar. Patterson and his associates (1964)⁴⁸ from the University of Minnesota use a different measure of the same duration, extrapolating forward along the upslope from the onset of systole to the closing of the pulmonary valves.

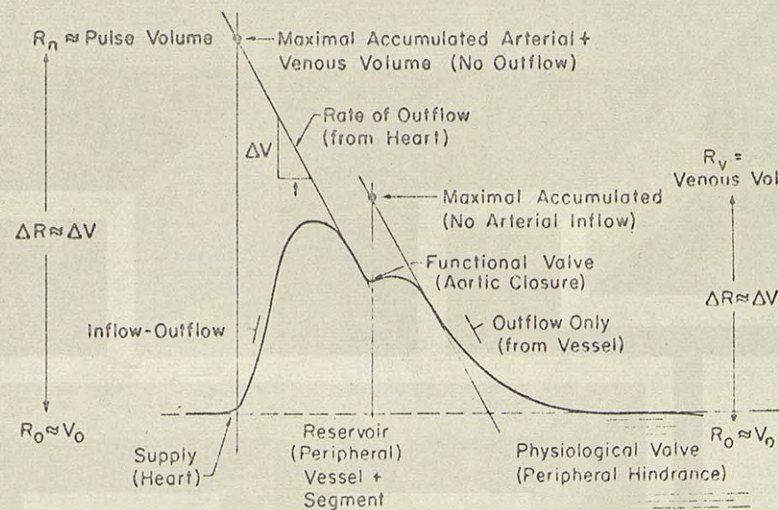


Figure 5

Systolic and Diastolic Pulse Volume Components

Peripheral Pulses depend on a blood supply, a reservoir and variable physiological hindrance to outflow. From the beginning to peak of systole, arterial inflow exceeds venous outflow. The peak of systole represents the maximal arterial-venous volume exchange. Following closure of the aortic valve (dicrotic notch) outflow from the segment is represented as venous run-off. Extrapolation of the systolic slope to beginning systole predicts the maximal volume delivered to the segment for one cycle and corrects for venous run-off (9). Extrapolation of the end-diastolic slope to beginning of diastole predicts the maximal venous volume at peak systole.

Source: Allison (1965)⁴

So far consideration has centered on the general aspects of impedance plethysmography, and in this field the leading exponents have been Nyboer from Wayne State University, Allison from the Lovelace Foundation, and Kubicek and his associates from the University of Minnesota. Application of the technique to the determination of cardiac output raises other considerations. When input electrodes are placed across the base of the neck and at a level between the subcostal and intertubercular planes, and when detecting electrodes are placed 30 cm apart across the crest of the shoulders and the level of the diaphragm, the record shows excursions synchronous with respiration, and also smaller excursions synchronous with the cardiac cycle. Pulses are similar in form to peripheral pulses, but are 180° out of phase with peripheral pulses, indicating increased resistance during systole, unlike peripheral pulses which demonstrate decreased resistance following systole. Electrodes are placed on the posterior thorax to minimize change in distance between the electrodes that might occur with respiration. Breathholding abolishes the excursions associated with respiration.

Patterson and his associates (1964)⁴⁸ undertook a series of experiments, which are also reported in part by Kinnen et al., (1964)³⁵ to determine if in fact the lesser changes in impedance observed reflect pulses of pulmonary blood flow representative of cardiac output. Using a fixed electrode, a small movable electrode, and catheter electrodes in the carotid artery, jugular vein, aorta, heart, esophagus, trachea, and large bronchi, they determined the current flux distribution in the thorax. They showed that impedance decreased during systole and increased during diastole except when electrodes were placed over the heart. With electrodes in the standard position, the rapid decrease of impedance during systole suggested movement of blood into the pulmonary volume or into the large vessels. Since, however, the major current flow was to the right of the spine and the large vessels are located to the left, the pulmonary blood flow would appear to provide the main path. This was confirmed by measuring the total impedance of a portion of a dog's aorta (3100 ohms), and comparing it with the total impedance measured externally over the same portion (5 ohms). On the

basis of their experiments they concluded that the preferred current flux path in the thorax with a 100 kc excitation signal is the lung blood volume, and the impedance wave from may be reflecting the pulmonary blood volume changes.

They then extended their experiments (Kinnen et al., 1964³⁵) to measure cardiac output on 5 subjects before and immediately after exercise, using Bonjer's (1950)⁹ form of the impedance equation which gives a value for change in volume, as follows:

Equation 17.

$$\Delta V = \rho (L/Z)^2 \Delta Z$$

It might be noted that this equation calls for measure of total impedance (Z) whereas in point of fact they were measuring resistive impedance. However, with this technique they showed a close relationship between cardiac output measured by plethysmography and representative cardiac outputs on 50 subjects made by the foreign gas technique and reported by Grollman, with an average difference of 8%. They also showed a close correlation between the O₂ consumption of their subjects and the cardiac output obtained by plethysmography, (r = 0.962).

Allison, who pioneered in this measure, has undertaken numerous determinations in both animals and man. He emphasizes, however, that the technique provides a measure of pulmonary pulsatile flow rather than stroke volume. The distinction may seem academic, but Allison argues that once the blood flow leaves the right ventricle and passes into the pulmonary circulation it becomes responsive to factors which affect the peripheral circulation. Thus, for example, during thoracic impedance plethysmography, changes in apparent stroke volume may be observed during extreme respiratory excursions and during Valsalva and Mueller maneuvers (Allison and Luft, 1964²). Again, with subjects breathing a gas mixture equivalent to an altitude of 23,000, a 39% reduction in pulmonary pulse volume can be demonstrated (Allison and Luft, 1965⁵). With subjects in the seated position, there is a greater reduction in the lower thoracic segments than the upper although this difference is not so pronounced in the supine position. The same postural dependence is very marked in

blood flow in limb segments (Allison, 1965⁴). However, with the subject at rest, under stable conditions, the measure can provide a close index of stroke volume.

Comparative analysis of stroke volume in dogs, determined by impedance plethysmography, and a direct Fick method, have been carried out by Allison (personal communication), the results of which are shown in the following Table (4). These indicate an acceptably close relationship between the two methods. In addition, he has also carried out impedance measurements of cardiac output in man with results (currently not available) which compare favorably with those generally regarded as standard.

For use in manned space missions the method shows considerable merit. The execution is relatively simple; the instrumentation, although electronically complex, is mechanically simple, and can be miniaturized into small weight and volume; the time to accomplish a measure is brief, and the violation of the subject is negligible. At the same time, the method has disadvantages. The balance of the amplifiers is readily lost and is affected by movement of the subject and by the presence of other electrical fields. Use of the system is restricted to conditions involving minimal movement. With continued development, however, it should provide a very valuable means of making reliable and simple determinations of pulmonary pulsatile blood flow representative of cardiac stroke volume.

Recommendation

In making recommendations concerning techniques for the determination of cardiac output in a manned space laboratory it is necessary to bear in mind the limitations previously noted, namely, weight, volume, available skills, violation of subject, weightlessness, available time, confinement, etc., which act to influence a selection.

From the foregoing discussion it is apparent that the most fundamental, reliable, and thoroughly examined method is the direct Fick using oxygen, or its derivative the dye dilution technique using a cuvette and suitable dye, such as indocyanine green or Coomassie blue. Of these two methods, the

TABLE 4

	<u>Fick Cardiac Output</u>	<u>Impedance Calculated Cardiac Output</u>	<u>% Diff.</u>
1.	3.090	3.100	3.2
	3.750	3.200	14.6
2.	1.23	1.100	10.6
	1.064	1.100	3.6
3.	2.710	2.828	4.2
	2.778	2.744	1.3
4.	2.930	2.731	6.8
	2.984	2.395	2.1
5.	3.090	3.500	1.2
	3.750	3.600	4.0
6.	.840	.810	3.6
	1.11	.910	1.8
7.	2.51	2.200	1.24
	2.60	2.300	1.2
8.	2.98	2.630	11.7
	2.78	2.730	18.0

Source: Allison (1965)⁴

dye dilution can be performed with less complexity, less discomfort, and less hazard. Thus, excluding the constraints applied by the space cabin environment, the dye dilution technique would seem to offer the most suitable standard method.

Consequently it would seem advisable, that prior to proceeding on a space laboratory mission, all the astronauts concerned should undergo a careful determination of cardiac output at rest and exercise under simulated space flight conditions with the exception of weightlessness. In addition to providing baseline values, this measure, with suitable additional instrumentation, will provide the means of obtaining proportionality constants for application to pulse pressures, empirical tables, ear oximeters, accelerogram traces, etc., and will allow for ground-based comparison and validation of various techniques.

For use in space, it is probably necessary to consider the requirements on two levels, namely, day-to-day evaluation, and routine regular determination.

For day-to-day evaluation it would seem reasonable to accept that accuracy and reliability can be sacrificed for simplicity. For this purpose, the simple relationships between stroke volume and blood pressure would probably suffice as an index of cardiac function. In fact, pulse pressure alone, without any further calculation, might well be considered to provide an adequate index. Should a little more sophistication be deemed advisable, the table prepared by Remington et al., (1948)⁵³ (Table 2) offers a reasonable approximation to stroke volume from blood pressure measurements, particularly if a proportional adjustment is available from the pre-flight dye dilution studies.

For more accurate, reliable, routine determinations of cardiac output under space conditions, it is difficult, if not impossible, at this time to select a technique which has clear-cut advantages over all the others. As has been demonstrated in the foregoing discussion, several acceptable techniques are available, each of which has its advantages and disadvantages. It is still far from clear how favorably one compares with another even in ideal terrestrial conditions, and how much the

consistency of the results is affected by the skill of the user and his familiarity with his own favorite technique. More is needed in the way of comparison studies on the ground, but even after adequate objective comparison it will still not be possible to say with certainty which is the most appropriate technique for use in space since the orbital conditions may not only influence the implementation of the technique but could conceivably also modify some of the supposed constant factors on which a given technique is based.

Thus, despite the complexity of execution, and the violation of the subject, it would seem necessary that for the initial experiments the most reliable and accurate technique feasible, namely, dye dilution monitored by an arterial cuvette, should be employed to obtain baseline values. A valuable adjunct to the arterial cuvette would be a curve-matching computer presenting a read-out of cardiac output. Thereafter, other potentially acceptable techniques could be tested for routine use against it. As a possible alternative to the dye dilution method, and mearing in mind that it is not acceptable to all investigators, the CO₂ rebreathing method would provide much more simply and with considerably less subject violation, results which are probably as reliable as those from dye dilution.

Subsequent to, or in some cases, concurrent with determination of these baseline values, other potentially useful techniques can be evaluated. These could include impedance plethysmography, dye stuies using an ear oximeter with and without arterial calibration, radioactive isotope methods, and methods of x-ray cardiometry. As mentioned in the earlier text, ear oximetry, in skilled hands, has much to commend it, particularly if no arterial puncture is required, and merits investigation in orbital conditions. Isotope methods, with carefully controlled protocol, produce consistently reliable results but suffer from the handicap of difficulty in storage, radiation exposure to the subject, and the requirement for sophisticated instrumentation. X-ray cardiometry similarly necessitates radiation exposure and demands highly sophisticated equipment; if the latter is available for other purposes, however, the technique should be investigated.

The most potentially valuable technique would appear to be impedance plethysmography, and it might well be used in conjunction with dye dilution in the initial experiments. In addition, the possibility of quantifying cardiac accelerography has been mentioned, to provide at least a relative value for stroke volume, while if ballistocardiography is going to be undertaken for other purposes, incidental calculations can be made from the trace. Ultrasonic methods, particularly those being developed by Rushmer's group, should be borne in mind for possible future application, while the thermal ultrasonic technique of Webb may yet prove useful. In all cases, however, it is essential that the orbital investigator be thoroughly familiar with the techniques he is using.

In summary, day-to-day evaluations of the cardiac output can be approximated by estimations and subsequent calculations derived from the blood pressure. Routine determinations of the cardiac output initially demand establishment of baseline values by the most reliable feasible method - dye dilution with an arterial cuvette and a curve-matching computer. Alternatively close approximations can be obtained by the CO_2 rebreathing technique. Concurrent with, or subsequent to the dye dilution studies, other potential useful techniques should be investigated. Of these the most valuable is probably impedance plethysmography, but other investigations should include ear oximetry, the use of radioisotopes, accelerography, x-ray cardiometry, and ballistocardiography. Future developments show promise in ultrasonics, and perhaps also in thermal dilution methods. After comparative studies in orbit have been made a routine technique or techniques can be selected.

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SECTION 2 - CARDIOVASCULAR

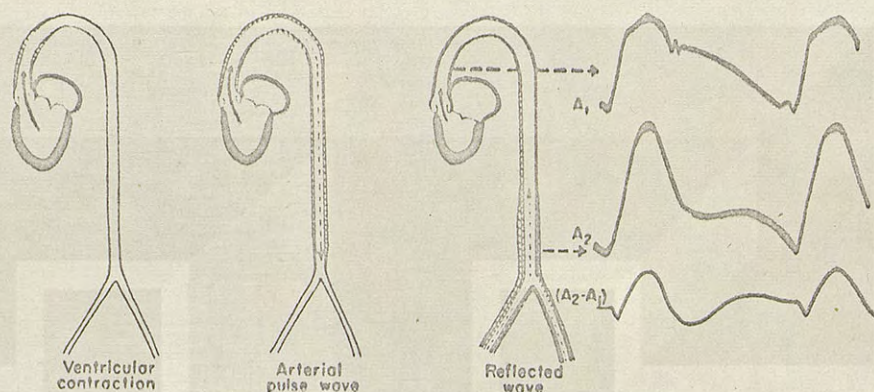
Section 2.1b - Blood Pressure

As a major factor determining the maintenance of circulation in the systemic and pulmonary vascular systems, the blood pressure provides a readily available index of the adequacy of cardiac function. The blood pressure is pulsatile and is composed of a large sustained (dc) component, the mean systolic blood pressure, about which a pulsating (ac) component, the pulse pressure, fluctuates. Major determinants of the form and magnitude of the blood pressure are: a) contractile energy of the heart, b) the quantity of blood in the arterial system, c) the volume flow of blood per beat (stroke volume), d) the elasticity or distensibility of vessel walls, e) the viscosity of the blood, and, f) the peripheral resistance, which is largely determined by the variable caliber of the small vessels. Mean systolic blood pressure can, in fact, be defined as the product of the cardiac output and the peripheral resistance.

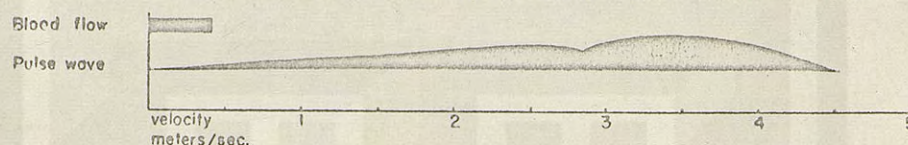
Because of the numerous interacting factors, blood pressure is not a simple sustained load. It is characterized by a pressure pulse, the shape of which is the resultant of both the cardiac output flow waveform and the nature of the vascular load impedance. In his analysis of the arterial pulse, Rushmer (1961)³⁸ observes that at the onset of ventricular ejection, blood flows into the aorta faster than it leaves through the arterioles. Ejected blood accumulates in the first portion of the aorta, thereby increasing the local tension (Fig. 1). The increased pressure and wall tension in the root of the aorta force blood into the adjacent segment of aorta which, in turn, is stretched and develops increased tension. In this way, a pulse of pressure moves rapidly down the aorta at a velocity determined by the elasticity of the walls and the pressure of the blood. This pulse wave is transmitted much more rapidly than the velocity of the blood flow. Normal pulse wave velocity in the aorta approaches 3 to 4 meters per second although in the limbs it may be 7 to 14 meters per second. On the other hand the average velocity of blood

ARTERIAL PRESSURE PULSE

A. DISTORTION OF THE ARTERIAL PULSE WAVE ALONG THE AORTA



B. THE VELOCITY OF BLOOD FLOW AND ARTERIAL PULSE IN THE AORTA



A, The arterial pressure pulse is a wave of pressure which passes rapidly along the arterial system. Blood suddenly ejected into the ascending aorta at the beginning of systole has insufficient energy to overcome all the inertia of the long columns of blood in the arteries. Therefore, blood tends to pile up and distend the ascending aorta, causing a sudden local increase in pressure. Blood is then forced into the next portion of the aorta, extending the region of distention and initiating a pulse of pressure which travels rapidly along the arteries toward the periphery. These waves of pressure, reflected by peripheral structures, travel back toward the heart and become superimposed on the advancing pulse wave. This produces a higher peak of systolic pressure, a slurring of the incisura and a lower diastolic pressure in the femoral artery. If the peripheral arterial pulse wave is subtracted from the pulse recorded at the arch of the aorta, the resulting wave form ($A_2 - A_1$) suggests a natural frequency of the peripheral arterial system.

B, The pulse wave velocity (4 to 5 m. per second) is much faster than the velocity of blood flow (less than 0.5 m. per second). The pulse wave velocity is determined by the elasticity of the arterial walls which, in turn, depends upon their distensibility in relation to the blood pressure.

Figure 1

Source: Rushmer (1961)³⁸

flow in the systemic circulation is less than 0.5 meters per second. Thus, although the pressure wave may reach the vessels of the foot in 0.2 seconds it requires several heart beats for the blood entering the ascending aorta to reach the foot vessels (Gregg, 1961)¹⁸.

Toward the end of systole, ventricular pressure falls below aortic pressure. The aortic valves close and the resulting back flow of blood produces the characteristic incisural notch in the pressure pulse pattern. As pressures are recorded in arteries progressively further from the heart, the pressure pulse changes in shape and increases in peak to peak magnitude until the smaller arteries are reached. Various causes for these changes are discussed by Rushmer (1961)³⁸, from different sources, and include the effects of reflected pressure waves rebounding from the periphery, attenuation or damping of various frequency components of the pulse wave, differences in propagation velocity of different frequencies in the pressure-pulse and steady-state oscillation of the arterial system.

The rapid spread of pulse waves and their modification as they pass through the system lead to difficulties in interpretation of blood pressure measurements. Systolic pressure in the peripheral arteries is considerably higher and diastolic pressure lower than at the root of the aorta. Consequently, measurements of blood pressure represent instantaneous values at the site measured only. Furthermore, because of the nature of the waveform, it is necessary to measure both the maximum pressure during systole and the residual pressure during diastole. The difference represents the pulse pressure. Since the waveform is not sinusoidal, the mean systolic pressure is not a simple average, but may be approximated by a value calculated from the diastolic pressure plus one-third of the pulse pressure.

In considering methods for the measurement of blood pressure it is necessary to examine the physical parameters of measurement as well as the physiological. Shirer (1961)³⁹ has prepared a table outlining some of the relevant parameters (Table 1) which is of particular usefulness in the design and selection of electronic and mechanical transducers.

TABLE I
PARAMETERS ASSOCIATED WITH CARDIOVASCULAR PRESSURE

1) Magnitude	Range	-10 to +300 mm Hg		
	Typical Adult Man	Systolic/diastolic: 130/80 mm Hg Mean: 100 mm Hg		
2) Frequency Spectrum	Mean (dc) Component plus Fundamental (heart rate) plus 6 to 30 harmonics			
	Man Dog Shrew	1-3.3 beats/sec 1.5-5 beats/sec 12-22 beats/sec	20 cps 30 cps 72 cps	66 cps 100 cps 440 cps
3) Source Impedance	Resistance		Volume Elasticity	
	Man Dog	1 mm Hg-sec/ml, 3 mm Hg-sec/ml,	(Aorta) 0.3-10 mm Hg/ml, [7]. (Arterial system) 0.1-1.0 mm Hg/ml [6].	
4) Noise	Turbulence			
	Acceleration Temperature	Position, $\pm 1g$; Ascending aorta, 1-8g; Heart, 0.1-2g. Ambient to body, 20° C		
	Stray electric currents, electric and magnetic fields			
5) Blood	Viscosity	3-4X water; temperature, composition, and tube diameter dependent		
	Coagulable			
6) Accessibility	Indirect via elastic and viscous tissue			
	Direct via vessel puncture			

Source: Shirer (1961) ³⁹

The table indicates that pressures in the circulation range from about -10 mm Hg at the very lowest to 300 mm Hg at the highest, above atmospheric pressure. The negative pressures, of course, are found only momentarily in the large thoracic veins and the heart chambers. The table also indicates the fundamental frequencies and their harmonics. It is generally agreed that high fidelity reproduction of a waveform requires a system which will respond linearly to the tenth harmonic of the fundamental frequency (Green, 1950)¹⁶. At a maximum heart rate of 240 per minute the pulse frequency is 4 per second and the tenth harmonic 40 cps. Consequently, an ideal system should have a frequency response linear to at least 40 cps, although this is only occasionally achieved.

The table also indicates the source impedance, which has a resistive, an elastic, and a mass component, although only the first two are normally considered. The source impedance is considered in determining the degree to which the measurement variable will be disturbed by the measurement load. In dog and man, the source impedance is negligible compared with that of measurement devices.

The question of noise interference is considered in the table in terms of the effect of turbulence, acceleration, and temperature, along with the effects on the measuring system of stray electric currents, magnetic and electric fields.

Actual measurement of arterial blood pressure can be undertaken using either direct or indirect techniques. Direct techniques involve the cannulation of arterial vessels, which is a procedure both painful and to some extent hazardous. Consequently they cannot be considered for anything other than exceptional use in a manned space laboratory. At the same time, a brief consideration of the principles involved in direct measurement is in order.

Direct Method

Mercury manometers have been traditionally used for the direct recording of mean systolic blood pressure, via an arterial cannula containing a solution of saline or heparin separating the blood from the mercury. Because of the inertia of the fluid and the resistance to its flow into the manometer, the latter is inadequate for the precise and continuous recording of systolic and diastolic blood pressure. This inadequacy led to the development of devices with a frequency response adequate for the task. These devices initially were mechanical transducers such as that of Hürthle (1888) (quoted by Green, 1950)¹⁶ who used a mechanical lever system to amplify movements of a membrane. The frequency response of this system, however, was still very low. Improvement came with the development of optical systems in which a weightless light beam was used as the lever, reflecting the movements of a miniature mirror mounted on a rubber or metallic membrane (Frank, 1925¹¹; Hamilton, 1934¹⁹; and others).

With the development of electronics came the use of devices in which the minute movement of a high frequency membrane is employed to produce changes in resistance, capacitance, or conductance, which can be detected, amplified, and displayed on some form of permanent record.

The resistance principle is used in the Statham gauge (Lambert and Wood, 1947)²⁴ in which displacement of a metal bellows produced by increase of pressure is transmitted to a metal slide supported by four sets of strain-sensitive wires wound under tension and connected to form a Wheatstone bridge.

The capacitance principle is employed in a transducer designed such that a metal membrane in contact with the blood flow forms one plate of a condenser, the other being rigid. Changes in the air gap between, cause changes in capacitance (Lilly et al., 1947)²⁶.

An inductance manometer was described initially by Motley et al., (1947)²⁷. In the early form the movable membrane and the secondary coil were placed in the field of a primary coil supplied with high frequency ac current. In later types, the membrane is connected to an iron core

located within the coils. Movement of the iron core produces changes in the magnetic flux (Gauer and Gienapp, 1950)¹³. The latter device can be attached to the end of a cardiac catheter and inserted directly into the heart and great vessels.

All these methods require electronic amplification and display by optical galvanometer, direct writing galvanometer, or oscilloscope and camera, and in each case careful consideration has to be given to the frequency response of the total system. Theory and techniques of analysis of the frequency response are discussed in detail by Shirer (1961)³⁹.

Still another system of measurement was developed by Clemedson and his associates in Sweden (1959)⁸ using the RCA No. 5734 mechano-electric pressure transducer. The latter is a subminiature triode vacuum tube with a movable anode which is attached to the liquid-containing membrane manometer. Since the anode current is proportional to the distance between the anode and the cathode, any movement of the anode from pressure fluctuation will cause a change in the resulting current and a subsequent variation in voltage over a resistor in the anode circuit, which can be interpreted in terms of pressure.

Direct registration of blood pressure is open to error from such occurrences as impaction of a catheter or cannula against the vessel or heart wall, false readings occasioned by catheter movement in the stream, differences in reading according to whether the catheter is sampling by way of an end or side opening, and problems created by improper frequency response or inadequate damping, but there is little doubt that direct methods must be inherently superior to indirect, and in fact the direct mercury manometer technique can be regarded as a standard. However, because of difficulty in execution, discomfort, and potential hazard to the patient, the use of direct methods of blood pressure measurement would not seem justifiable in a manned space laboratory.

Indirect Methods

Indirect methods avoid the problems of cannulation and provide a measure of blood pressure by the use of devices designed to match the pressure within the artery or to reproduce the pulsatile distension of the artery. Systolic pressure is recognized as being that pressure just less than that required to occlude flow in an artery. Diastolic pressure is the maximum amplitude of the residual pressure when flow is re-established.

Manual Sphygmomanometry

The manually operated sphygmomanometer is the most common, simplest, and, when properly used, probably the most reliable method available for indirect measurement of blood pressure.

It is not necessary to detail the technique, which depends on occlusion of an artery by way of pressure applied through a suitable inflatable cuff, visual estimation on a manometer or aneroid scale of the pressure at which the flow is re-instituted, and further estimation of the pressure at which flow is established.

Recognition of these two pressure points depends on perception by stethoscope over the brachial artery of the sounds described by Korotkow in 1905, which are alleged to be caused by turbulent flow occurring in the vessel partially compressed by gradually reducing pressure in the cuff. Four phases of these sounds are described:

Phase 1. Sudden appearance of clear, but often faint, tapping sound growing louder during the succeeding 10 mm Hg fall in pressure.

Phase 2. The sound takes on a murmurish quality during the next 15 mm Hg fall in pressure.

Phase 3. Sound changes little in quality but becomes clearer and louder during the next 15 mm Hg fall in pressure.

Phase 4. Muffled quality lasting throughout the next 5 to 6 mm Hg fall. Thereafter the sound disappears (Gregg, 1961)¹⁸.

Systolic pressure is measured at the onset of phase 1. According to the American Heart Association (Bordley et al., 1951)⁵ diastolic pressure

is measured at the cessation of sounds. This recommendation has been questioned, particularly by Roberts and his colleagues (1953)³³ and by Burton (1953)⁷, who in comparison studies between sphygmomanometry and direct manometry produced strong evidence to indicate that diastolic pressure is better indicated by the point at which muffling occurs.

Several sources of error exist in measuring blood pressure by sphygmomanometer, in addition to subjective errors in interpretation of the sound. One relates to the relative size of the cuff and the arm. The standard cuff is 13 cm wide. If the cuff is small relative to the arm the pressure around the artery when the cuff is inflated may be considerably less than that recorded by the manometer (Thompson and Doupe, 1949)⁴². Similarly, if the cuff is too loosely applied it tends to become more cylindrical when inflated, with a reduced area of application, thus producing the same effect (Rushmer, 1961)³⁸. Reading errors can also occur because of too rapid deflation. Another source of error is known as the auscultatory gap (Berry, 1940³; Ragan and Bordley, 1941³⁰) which describes the phenomenon in which the auscultatory sounds in some cases disappear over a fairly large range between systolic and diastolic pressures, although the radial pulse is preserved. The occurrence of the gap is related to a slow rate of inflation of the cuff. It may be eliminated in some subjects by inflating the cuff with the arm elevated. The cuff should be inflated as rapidly as is feasible to a point about 30 mm Hg over the point at which the radial pulse disappears and then deflated at the rate of 2 to 3 mm Hg per heart beat (Bordley et al., 1951)⁵.

Despite the potential errors, the method when properly used is very reliable and strongly supported by tradition. Several studies have been undertaken comparing blood pressure values obtained by a sphygmomanometer with those obtained by direct means (Roberts et al., 1953³³; Ragan and Bordley, 1941³⁰; Hamilton et al., 1936²⁰). Differences would appear to be of the order of ± 8 mm Hg. Both the apparatus and the technique of sphygmomanometry are simple, and the method deserves strong consideration for use in a manned space laboratory.

Automatic Sphygmomanometry

While the manual system is convenient for discrete and discontinuous readings, it is unsuitable for monitoring purposes, and during limb movements. Several approaches have been made towards modifying the technique for automatic continuous registration. These may be considered in three major groups, namely; a) those in which Korotkow sounds from an artery below the cuff are recorded visually in conjunction with cuff pressure, b) those in which pressure pulsations from the artery are recorded graphically from a subsidiary pressure bag under the cuff, along with cuff pressure, and, c) those in which cuff pressure is controlled at systolic level by a feedback mechanism sensed from an artery distal to the cuff. The last named method, as exemplified by the work of Doupe et al., (1939)¹⁰ and Green (1955)¹⁷, is probably the least satisfactory since not only does it require constant pressure on the limb over a prolonged period, but it is not suitable for the measurement of diastolic pressure.

Recording of Korotkow sounds along with pressure began with Gilson et al., (1941)¹⁴. Other developments on the technique have been made by Rose and his colleagues (1953)³⁷, and a step forward was taken when Currens and his group (1957)⁹ from the Massachusetts General Hospital obtained the pressure and arterial sounds on the same calibrated trace. Continued development culminated in the systems produced by the Wright Air Development Division (Johnson, 1959²¹), by the School of Aviation Medicine (Ware and Kahn, 1963⁴⁴; Smedal et al., 1960⁴⁰; Roman et al., 1965³⁶) and by AiResearch, for use in the Mercury and Gemini project.

All the devices work on the same principle, but differ in sophistication, pick-up, and filtering. The WADD device (Model 16) is the most sophisticated, and correspondingly the most complicated. It utilizes a computer-controlled programmer to inflate the cuff, search for a diastolic pulse sound, confirm the latter by a coincident pressure pulse, reconfirm, and go on through a series of steps to identify and confirm a systolic pulse. Auditory ambient noise is minimized by the use of a contact type microphone. The equipment is fairly large and heavy (11" x 11" x 11", 35 lbs.) and, although elegant in concept and use, would not appear to be altogether suitable in its present

form for conditions of manned space flight.

The system developed at SAM employs a cuff inflated electromechanically by a bypass type gas pressure regulator with a pressure compensation system to allow for changes in cuff pressure with muscle movement. Readings can be made every minute as follows: inflation (0 - 225 mm Hg), 3 sec; leak down to dump pressure level, 25 sec; dump (20 - 0 mm Hg), 2 secs; interval to next inflation, 30 sec. The slower the leak down rate the more accurate is the reading. At the same time the longer the cuff pressure is held, both for the duration of a given reading, and in accumulated duration, the more likely is the pressure affected by the measuring device. Thus, an inevitable compromise arises between duration of leak down and duration between readings.

A contact piezoelectric microphone is firmly "potted" in the cuff along with a miniature preamplifier, and the cuff is so placed that the microphone is held over the antecubital fossa, or the medial aspect of the upper arm, preferably the latter to permit easier movement. Electronic filtering of the signal from the Korotkow sounds is so designed as to permit selection of several narrow wave bands for amplification and display. The bands that have been used are those centered on 40, 90, and 150 cps. With suitable selection of a band or bands it has been found that environmental noise rarely interferes with the signal even in the presence of F-100F engine noise at 125 db. Cuff pressure is displayed as a separate simultaneous trace.

In a test with the system in F-100F aircraft, 874 recordings were made during 19 flights with 85% successful records in conditions that include $\pm 4G$ and short periods of weightlessness (Ware and Kahn, 1963)⁴⁴. With continued attention to the system such as would be possible in an orbiting laboratory, the expectation of success would probably be higher.

Other testing on a T-33 aircraft has been carried out at Ames Research Center using a different microphone and a filter with a bandpass between 150 and 200 cps. (Smedal et al., 1960)⁴⁰. The accuracy of the system was stated to be within ± 4 mm Hg, assuming a steady heart rate.

Roman and his colleagues (1965)³⁵ undertook a comparison, under flight conditions in the X-15 aircraft, between the SAM system and a direct arterial method utilizing a Statham strain-gauge transducer. Although only one subject was used, the indirect system was found to be highly accurate and reliable. The values tended to read low, with an average systolic error of -6.7 mm Hg and a diastolic error of -3.3 mm Hg.

Less information unfortunately is available on the AiResearch system. It works on the same principle. A special directional contact microphone is held in the pocket of a cuff positioned over the brachial artery. The cuff is automatically cycled with a rapid rise time and a bleed off over a period of about 20 seconds, and a further 30 second delay before repeating. Readings can be made every minute. The microphone signal is passed through a very narrow bandpass filter centered at 35 cps. Body motions and ambient noise affect the signal very little. A major advantage in display over the SAM system is that the sound signal is presented on the same trace as the cuff pressure, which renders reading of the pressure simpler and more accurate. The accuracy of the system is stated to be ± 6 mm Hg. Reading is occasionally complicated by difficulty in identifying the first systolic pulse. Satisfactory performance has been found under conditions of environmental stress, including 50 G impact shock, 30 G vibration to 2000 cps, sustained acceleration of 10 G, and a temperature range of 0 - 160° F. A prototype system has been used widely under conditions of rest and exercise by Luft at the Lovelace Foundation and has been found highly satisfactory. The system actually used in the Gemini mission has a manually operated cuff, activated by the astronaut as desired, with a miniature signal conditioner weighing 1.6 ounces, from which signals are telemetered to ground-recording oscillographs. Performance has been highly satisfactory.

It is apparent that there is little if anything to chose between the SAM and the AiResearch systems. In each case the weight, volume, and power requirements are compatible with the facilities of a manned space laboratory. The signals of each are suitable for telemetry. The SAM system has been operationally tested under severe flight conditions and the AiResearch system

has been operationally tested, at least in part, under orbital conditions, and widely on the ground. The SAM system has an advantage of selective filtering, but presents the cuff signal separate from the arterial signal. The AiResearch system has a single, although effective, bandwidth, but presents a combined cuff and arterial signal.

As mentioned earlier, another approach to automatic sphygmomanometry lies in sensing the pressure pulse by way of a bag underneath the occluding cuff. This approach has been used by Zuidema and his associates (1956)⁴⁹ at WADD, and in another form by Richardson et al., (1964)³¹ in Oxford. In Zuidema's system, a fluid filled plastic balloon situated underneath the cuff and overlying the brachial artery transmits the pulse waves by way of a polyethylene catheter to a Statham pressure transducer from which they are recorded simultaneously with the automatically controlled cuff pressure. Control of cuff pressure is similar to that described for the microphone system. With 90 determinations on 10 seated subjects, a correlation of 0.97 was found with auscultatory sphygmomanometry.

In Richardson's system, the underlying bag and the cuff are both inflated simultaneously with air. Oscillations from the underlying bag, synchronous with the pulse, are amplified pneumatically and recorded along with cuff pressure during one minute in every five. Comparison with an intraarterial method showed that in 87% of simultaneous measure the cuff value differed from the intraarterial value by 10% or less, and in 99.8% by less than 20%.

Not much work, however, has been done with "bag" methods and there seems to be little reason at this time to consider they have any advantage over microphone pickup systems which have been more fully investigated.

Methods Using Photoconduction

The volume of blood in a vascular network fluctuates cyclically with each pressure pulse. The change at the periphery is slight but it may be detected by observing changes in the transmittance of a beam of light passing through the tissue. Using a sensitive crystal photocell, a low

intensity light source, and an amplifier, fluctuations can be picked up from any mass of tissue which has a vascular supply and through which the light can be transmitted. Following occlusion of the blood supply to the tissue by applied pressure, and subsequent reduction of pressure, re-instatement of the pulse can be observed at a pressure corresponding to systolic pressure, while maximum amplitude of the pulse wave is noted at diastolic pressure.

Wood and his colleagues (1950)⁴⁸ at the University of Rochester, estimated the arterial blood pressure by measurement of the externally applied pressure required to obliterate the ear opacity pulse. For this purpose they used a modified oximeter earpiece with a translucent pressure capsule along with masking which permitted light access through two irises 8 mm in diameter. The pressure capsule was inflated by a bulb connected to a manometer. Blood pressure was also simultaneously measured by intra-arterial and auscultatory methods in the brachial artery. In 20 subjects a closer correlation in systolic pressure was found between the ear pulse and the intra-arterial method than between the auscultatory and intra-arterial, while the values for the diastolic correlated without significant difference in all methods.

While the use of this method is not specifically advocated for manned space use, it should be borne in mind if the ear oximeter system is considered for use in determining cardiac output (see Cardiac Output).

Other applications of the principle have been used for measurement of blood pressure in the finger or toe (Robinson and Eastwood, 1959³⁴; Weinman et al., 1960⁴⁷). The greatest protagonists of this technique, however, are probably Gowen and Bolie (Gowen, 1962¹⁵; Bolie et al., 1964⁴).

In their technique, the finger is placed in a device which incorporates an inflatable finger cuff around the base of the finger and a photoelectric sensor at the nail bed. On activation, and controlled by a complex electronic system, cuff pressure is permitted to rise until the finger pulse disappears. A diastolic detecting circuit observes the point where the pulse amplitude begins to decrease, and displays the information on a

digital meter from the output voltage of a pneumatic pressure transducer at the cuff. Simultaneously the information is automatically printed out. When the finger pulse disappears the systolic pressure is displayed on another meter and printed out. Pressure is then automatically released, and a few seconds later the meters are reset. Up to ten pressure measurements can be made per minute. As an alternative to the digital read-out, the information can be displayed as a trace of arterial pulsation along with a calibrated trace of cuff pressure.

Using a small number of subjects, Gowen found a fairly good agreement between systolic pressures obtained by the auscultatory method over the brachial artery, and the finger method with the cuff around the proximal phalanx. A less good agreement was observed with diastolic measures. Statistical analysis was not attempted.

The system has been employed under exercise, but digital read-out or interpretation of the record, particularly for diastolic pressure, is handicapped by noise which occurs with any appreciable hand motion or finger tremor, while, in addition, changes in peripheral motor tone are readily reflected.

While the system has potential for space use, it would appear to be most suitable for monitoring under quiet steady conditions such as sleep or anesthesia. The fact that readings are grossly disturbed by movement, and that immobilization of the hand is required during measurement, renders it less valuable for measurement under active conditions. The equipment meantime is bulky, although it could no doubt be miniaturized.

Pulse Sensing Devices

Direct external sensing of a peripheral pulse without cuffs or cannulae is an obvious challenge. Analytically and experimentally, cyclical arterial distension varies in a near-linear manner with fluctuating systolic and diastolic pressure. There is a straight line relationship over a large range of pressures although the functional relationships vary from patient to patient and with age. In sensing pressure externally, however, problems

arise because of the necessity for transmission of the waveform through the vessel wall, overlying tissue, and skin. Changes occur dependent upon the geometry and properties of the intervening tissue. Factors involved include elasticity, viscosity, mass, friction, degree of artery occlusion, vasoconstriction or dilation, and muscle movement (Rieke, 1964³²).

Several early attempts at pressure sensing using spring mechanical transducers were unsatisfactory, largely because of the mass and inertia of the mechanical systems. Adams, Corell, and Wolfeboro (1960)¹, however, on the basis of work done by Corell on capacitance transducers, developed a system whereby deformation of skin surface overlying an artery was used as an index of the diametric change in the artery with the pressure pulse. The system recorded reproducible pressure pulses which could be calibrated in terms of blood pressure and gave, under best conditions, an accuracy within 3% to 8% of that obtained by a direct intra-arterial method. The system, however, was readily open to error resulting from limb movement, transducer motion, and transducer location, while calibration was readily lost. In addition, physiological influences on skin tension, tissue tension, and muscle tone were found to exert a profound effect on the reading. Thus, although certain drugs would reduce arterial pressure the accompanying effect on tissue would be such that the sensor would read a relative increase in arterial distension. Consequently, while the system has advantages, these are largely nullified by the disadvantages.

Another form of capacitance device is marketed by Gulton Industries (The Infracor pickup, Model B) and described by Gaffey (1962)¹². It incorporates in the system a manually operated finger cuff on line with a manometer. The cuff is used both for holding the transducer in place and for calibration purposes. The system has been used at several hospitals and research institutes for blood pressure recording, but, at least on theoretical grounds, it would seem to suffer from the above noted disadvantages.

To overcome these disadvantages, Pressman and Newgard (1965)²⁸ tried a different and more hopeful approach. Instead of sensing the skin deformation over an artery they applied a controlled pressure over the area sufficient to flatten the skin and tissues under the transducer and remove tissue tension effects, and at the same time, in the center of the flattened area directly overlying the vessel, they independently applied pressure sufficient to flatten the vessel slightly. They then sensed the force required to maintain the vessel slightly flattened in the face of the internal pressure pulse. In their initial device, the mechanics of which they justified by an elegant mathematical model (Pressman and Newgard, 1963²⁹), they used a strain gauge transducer with pneumatic pressure loading. The transducer could be mounted over, for example, the radial or temporal artery. Pressure was applied from an air pressure chamber in the transducer via a rubber diaphragm to the skin. Sideplates, integral with the housing, lay on each side of the artery, and the center plate, or rider, which was in communication with the strain gauges, lay directly over and partially compressed the artery (Figure 2). A satisfactory method of calibration was developed, using an artery simulator which could be pressurized in a controlled manner. The initial devices were sensitive to temperature, positioning of the transducer, motion, and size of the rider as compared to the artery, but changes in design and care in application produced results in man comparable with those from a sphygmomanometer, and at the same time allowed continuous beat-to-beat blood pressure evaluation.

Continued development, particularly with respect to the operation of a temporal sensor, led to the use of a much smaller rider which in turn utilized a smaller fraction of the energy derived from the blood pressure and dictated the requirement for a transducer other than the strain gauges previously used. Consequently, a new device was developed (Pressman and Newgard, 1965²⁸) which used as a sensor a miniature differential transformer. This transducer in turn suffered from a high acceleration sensitivity, amounting initially to as much as 50 mm Hg per g. Design changes and mechanical compensation reduced this to a measured value of less than 2 mm Hg per g. The new model is not temperature sensitive,

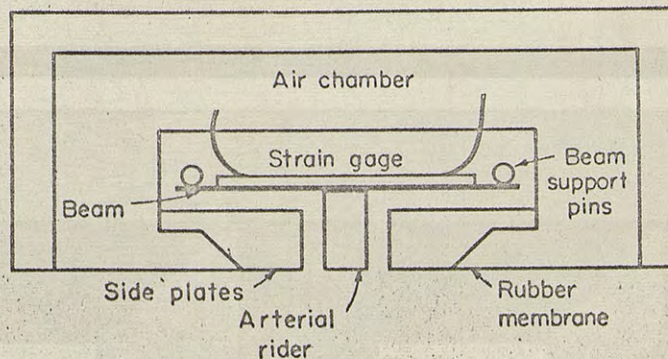


Figure 2

Source: Pressman and Newgard (1963)²⁹

and in addition methods are being devised to permit accurate semi-automatic positioning of the transducer in the optimum location over an artery.

This system for external sensing of blood pressure is still under development and cannot yet be considered for use in space conditions. It shows great potential, however, as a method for continuous, non-cuff, non-cannula, beat-to-beat, external sensing of arterial blood pressure via the temporal artery.

Ophthalmodynamometry

In a very comprehensive review of the subject of ophthalmodynamometry, Koch (1945)²³ observes that the eye may be converted into a natural sphygmomanometer. With application of external pressure, a pulsation in the retinal vessels is induced. Initially venous pulsation is observed. As intraocular tension arises to equal diastolic pressure, collapse of the retinal arteries occurs in diastole, and pulsation of the arteries becomes visible. Further increase of intraocular pressure to systolic level causes total collapse of the arteries and disappearance of pulsations. Pressures applied to the living human eye can be registered by a standardized tension spring instrument. Numerous modifications of the instrument have since been developed. With this, or similar,

apparatus, pressure is applied horizontally to the sclera while the retina is observed by ophthalmoscope. The applied pressure at diastolic and systolic levels is read from a scale on the instrument.

Another modification of the principle was developed by Thorner (1961)⁴³, who devised a transducer called the ophthalmic Pulsensor, by which air pressure is applied to the eye and the resulting pulsations transduced and recorded on a trace which is interpreted in a manner similar to a digital pulse trace. Use of the instrument in over 700 cases is reported by Kimura and Kaslow (1962)²².

A third modification relies on the plethysmographic goggles developed by Weeks and his associates (1964)⁴⁶, and depends on the subjective response of the subject viewing a target. It has been suggested by Lewis and Duane (1956)²⁵ that the occurrence of greyout is associated with an increase in intraocular tension to diastolic level, while the occurrence of blackout is associated with increase to systolic level. Consequently, by increasing the pressure over one eye to greyout level and then to blackout level, an estimation of diastolic and systolic pressures can be made. These assumptions have not been validated.

These three methods all suffer from inadequacies. The existence of a natural intraocular tension of some 20 mm Hg confuses the readings, while there is some possibility that the application of external pressure per se may affect the arterial pressure locally or centrally. In addition, application of pressure by the spring tension instrument method and subsequent reading of the record is open to considerable subjective error on the part of the investigator, while differences would also appear to occur by reason of different designs of the instrument. In any event, a wide range of results has been observed with the spring technique, up to as much as 100%. Koch (1945)²³ states that the average retinal artery pressure so obtained is 30 to 45 mm Hg diastolic, and 65 to 75 systolic.

The Thorner technique suffers from the same problems in utilizing the eye as a sphygmomanometer, but is probably more reliable in its reproducibility. Kimura and Kaslow (1962)²² state that comparisons of

Pulsensor data with readings derived from a catheter in the common carotid artery show agreements within 10%. It must be noted, however, that both the spring tension and the Pulsensor methods are preferably conducted with local anesthesia of the eye, a fact which renders them very unsuitable for a space use.

The plethysmographic goggle technique is as yet not validated. It seems doubtful, however, if it would provide useful general information on blood pressure more simply than other techniques, although it might well be used to obtain information on retinal circulation.

Electrical Impedance Plethysmography

Plethysmography of various types has been extensively investigated from the point of view of providing measurements of blood flow. An excellent review of the techniques in use was completed by Allison (1960)². In point of fact, many of the methods previously described for determination of blood pressure employ the principles of venous occlusion plethysmography, in that external pressure is applied to a body segment and initially occludes venous flow before going on to occlude arterial flow.

The technique of segmental limb electrical impedance plethysmography, the principles of which are described in the section on Cardiac Output, also shows potential in this area. Allison (1960)² demonstrated that if pressure is applied to a limb by way of a sphygmomanometer, changes in the electrical impedance waveform downstream could be read in terms of blood pressure. From some points of view the technique shows more reliability in measuring diastolic pressure than do the more common oscillometry methods. Ideally, diastolic pressure is measured at the level of appearance of the dicrotic notch from the pulse waveform. In the standard oscillometry techniques, where the pulse is sensed from a transducer under the sphygmomanometer cuff, the pressure actually sensed is a function of both the intraarterial pressure and the externally applied transmural pressure. Because of the associated pressure-volume relationships under the cuff, and the accompanying changes in segmental compliance, the disappearance of the dicrotic notch is unreliable under these circumstances as an index of diastolic pressure, and the maximum amplitude of the pulse is used instead. With the impedance system, however, sensing takes place downstream of the cuff where these altered relationships do not apply, and the dicrotic notch can be used as a reproducible index of diastolic level.

Very little has been done to develop impedance techniques for the measurement of blood pressure, but if impedance instrumentation is available on a spacecraft for other purposes, as is recommended, the potential of using this instrumentation for blood pressure measures would be a useful dividend. It would be particularly valuable to develop independent calibration measures so that the waveform could be used for determining blood pressure without the need for a sphygmomanometer cuff.

Venous Pressure

Measures of venous pressure may assume considerable significance in space operations where cardiac decompensation arising from weightlessness and/or confinement may be reflected in venous pooling. Although information is desirable on both peripheral and intrathoracic venous pressures it is considered that measures of the latter, which require cannulization from the periphery to the great veins, are inadvisable and unjustified under the circumstances. Useful qualitative information, however, can be obtained by applying a transducer (microphone, capacitance) over the jugular vein and obtaining a trace of the venous pulse. It is probable that methods could be developed for calibrating this pulse in terms of pressure.

Peripheral pressure can be evaluated by means of a simple manometer attached by a three-way stopcock to a syringe and needle. Saline is ejected from the syringe into the manometer to a level above expected venous level, and then, by use of the stopcock allowed to enter a peripheral vein. Final saline level in the manometer represents venous pressure which, in turn, should be related to the phlebostatic level. In an alternative method, saline from a capillary tube with a pre-established meniscus is allowed to run horizontally into a vein by way of a needle on the capillary tube. The position of the meniscus moves outward and is returned to its original position by air pressure applied via a rubber tube and pressure bulb attached to the other end. A manometer in series with the bulb provides a reading of the pressure level. (Burch and Winsor, 1943⁶). A further modification of this technique by Sodeman (1952)⁴¹ obviates the

requirement for a manometer by the use of a system in which the restoring pressure is applied by controlled increase of tension on the bulb through rotating a knob on a calibrated dial. This last system, which seems to be that of choice, is probably open to further development in miniaturization.

Recommendations

In making recommendations on techniques for determination of blood pressure in manned space laboratories it is necessary to consider the requirements for these measures. As an index of the adequacy of the cardiovascular system, blood pressure measures can be used in three ways: continuous monitoring, routine discrete determination, and short duration observation. In the early stages of space exploration such as is exemplified by the Mercury, and Gemini missions, continuous or nearly continuous monitoring of vital functions, of which blood pressure is one, has been the practice wherever possible. As knowledge of man's immediate response to the space environment increases, as missions become longer and more sophisticated, and as environmental control systems more nearly perfect, the requirement for continuous monitoring of blood pressure, in particular, disappears. In the space laboratory situation, however, there will still be a requirement for both discrete measurements to identify trends and for short duration observations during physiological experiments, and perhaps during extra-vehicular activity.

For discrete measures, there seems no reason to doubt that the manually operated aneroid sphygmomanometer and cuff, when properly used, is the simplest, most reliable, and most thoroughly investigated of all techniques, and can provide values of acceptable accuracy.

For short duration observation, a continuous readout, preferably on a beat-to-beat basis is desirable. Beat-to-beat methods include techniques involving photoconduction (Wood et al., 1950⁴⁸; Gowen, 1962¹⁵; Bolie et al., 1964⁴), pulse sensing (Pressman and Newgard, 1965²⁸) and perhaps impedance plethysmography, but none of these

methods as yet appear to be developed to a stage of superiority, although obviously they deserve continued application and might well be used in an experimental manner, particularly if the instrumentation is already available for other purposes.

Consequently, for short duration observation the methods of choice would appear to lie with devices sensing a pulse from beneath an automatically inflated sphygmomanometer cuff. As previously noted there is little if anything to choose between the SAM development and the AiResearch development. Each would appear to perform an adequate function and each has advantages not possessed by the other.

While the automatic sphygmomanometer appears to be the method of choice at this time it is obviously not an ideal piece of apparatus. It is bulky, very indirect, mechanically complex, sometimes difficult in systolic reading, and provides only partially continuous observations. It seems probable that greater potential lies with direct pulse sensing devices not requiring a cuff. Continued improvement and development of these methods, particularly with respect to temporal artery sensing, would be desirable.

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SECTION 2 - CARDIOVASCULAR

Section 2.1c - Cardiac Kinetics

Traditionally it has been the practice for the clinician to place a hand on the thorax over the point or area of maximum cardiac impulse and thereby obtain by way of a complex indefinable judgmental process an indication of cardiac function. To the trained and experienced clinician this is a reliable and informative technique. Obviously, however, it is subjective, non-quantifiable, and impermanent.

Towards the end of the 19th century, Gordon (1877)⁷, in Edinburgh, while engaged in careful body weight measurements with a spring balance, observed rhythmic fluctuations in the balance movement which he showed were correlated with the cardiac cycle. From that point on, evolution of techniques for the representation of cardiac kinetics was slow. With the appearance and subsequent development of electronic techniques of transduction and recording interest was re-awakened, but the development of these same techniques led in turn to great confusion in nomenclature and interpretation of the records obtained.

Rosa (1962)¹⁶ points out that the pulsation which is experienced over the chest and elsewhere is derived from contraction of the heart, and can be expressed as the resultant of several vectors. At the same time the heart cannot be vectorally separated from the totality of the vibrating body, which includes the blood mass and the vascular tree. The major contribution to the energy input is derived from the left ventricle which provides most of the energy of cardiac contraction (Agress et al., 1964³).

One representation of the resulting forces is found in the ballistocardiogram (BCG), modified from Gordon's spring balance, which reflects some aspects of the relative motion between the heart and the body that results from heart action. As a result of heart activity, blood is displaced from the ventricles, the position of the heart in the thorax changes, and a pressure wave develops along the long axis of the vessels. Ballistocardiography examines the end result, a shift in the body's center of gravity,

which can be registered as a displacement, velocity, or acceleration, measurable in three mutually perpendicular axes. From its original inception, BCG technique has undergone considerable evolution, culminating in the high frequency BCG of Starr et al., (1939)¹⁸ which tended to produce distortion of the record at the natural body frequency of 5 cps, and the still later ultra-low frequency systems of Klensch and others. Notable contributions in this field are currently being made by Scarborough of the Aviation Medical Service of the FAA, and there is no doubt that in the hands of experienced experts valuable information can be obtained from ballistocardiography.

Ballistocardiography, however, has inherent disadvantages. Chief among these are the requirements for bulky and costly equipment, distortions of waveform attributable to different body masses, distortions induced by the masses of the limbs, changes in impedance inherent in the coupling between the body and the table or suspension, and perhaps inconsistent abnormalities occurring in the records of subjects over age 40 (Agress et al., 1964³). Theoretically, some of these disadvantages can be overcome by obtaining records during the weightless state. To this end 6-degree of freedom free-floating ballistocardiography has been suggested by Lockheed researchers as a possible technique for use in space missions (Lockheed, 1964¹¹). The Lockheed group presumably bases its suggestion on the work of Tannenbaum, et al., (1954)¹⁹ in spatial vector ballistocardiography, but has not so far carried out any experiments in this field. They envisage a light platform, of the nature of a tubular frame, on which the subject is mounted free-floating. Six accelerometers record in three linear and three rotational vectors. The record is then integrated by computer into a single measure recording a spatial vector ballistocardiogram. A somewhat similar technique has been utilized by Hixson and Beischer (1964)⁸, of the U. S. Navy of School of Aviation Medicine, who have undertaken measurements on subjects flying a Keplerian trajectory in a KC-135 aircraft. Using a custom-moulded fiberglass couch, and three orthogonally mounted linear accelerometers along with one angular accelerometer, they

obtained data on the triaxial ballistocardiograph in the free-floating state. Signals were conditioned on board and telemetered to an airborne receiving station. At the same time they obtained triaxial electrocardiographic data for correlation of the electrical and mechanical events of the cardiac cycle. The resulting data were voluminous and difficult to interpret. Acceleration patterns were displayed in loop form and in a three-dimensional model to assist in visual analysis, and, in addition, a computer analysis of the data was undertaken. It is interesting to observe that the longitudinal BCG component in the flight data conformed closely to that found in terrestrial ultra-low frequency systems with close body-suspension coupling. The absence of comparative data, in other vectors unperturbed by gravitation, renders interpretation difficult, and much more baseline data is required.

It is apparent, however, that the system shows great potential, despite the complexity of the procedures required in continuing investigation in a nulled-gravitational environment. It seems reasonable to assume that in conditions of actual space flight the restraint and instrumental complexity will be to some extent reduced. The main considerations at this time appear to be refinement of instrumentation, collection of baseline data, and development of a simplified form of data analysis.

The disadvantages inherent in ballistocardiography in terrestrial gravitational conditions have led to closer consideration of techniques of recording and analysis of precordial vibrations. Since the characteristics of these vibrations reflect heart motion, analysis of the waveforms can be used to assess the events of the cardiac cycle, and the rate of contraction and relaxation, as well as correlative data pertaining to blood flow and cardiac output.

In the process of pumping blood, work is performed and energy developed. Some of this energy can be appreciated over the precordium as vibrations in a range from below 2 cps to above 1000 cps. Figure 1, modified by Agress from Butterworth, indicates that the spectrum has a wide range of energy distribution, being markedly more intense at the lower frequencies. The high-speed components (murmurs) are produced by acceleration and impaction of high-speed jets of blood or from turbulence

HEART VIBRATIONS FREQUENCY-ENERGY DISTRIBUTION

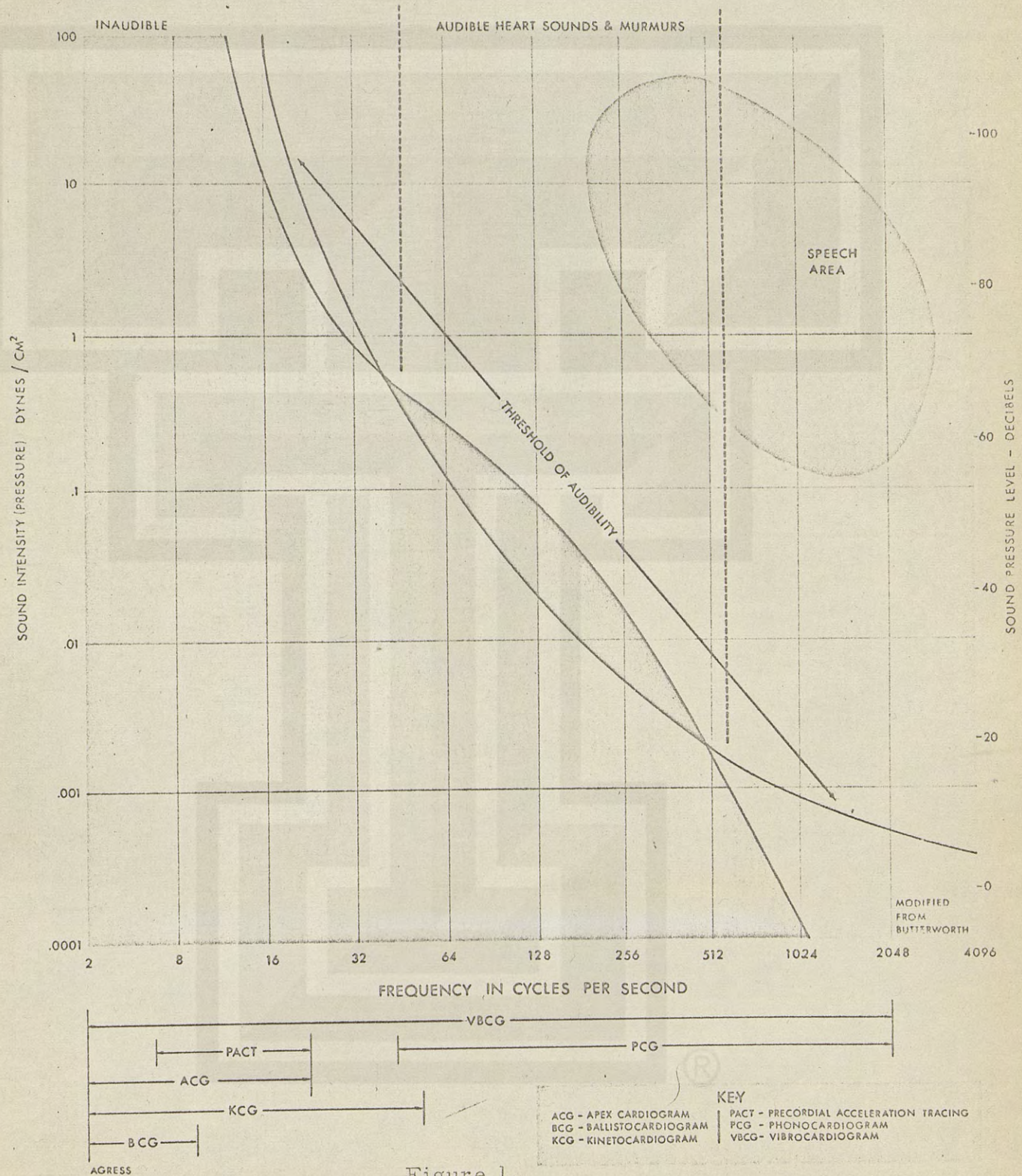


Figure 1.

Source: Agress and Fields, (1961)¹

around small masses of tissue or valves. The lowest frequencies, those approaching the fundamental frequency of heart rate (about 1 cps), are generated by the motion of the heart in conjunction with, and coupled to, the major volume of blood moved (Agress and Fields, 1961¹).

As can be observed from the figure, the measurable range of audible vibrations (40 to 500 cps), occupies about 1% of the total. Since the original work of Marey (1878)¹³, who developed a system of recording chest motion from a bellows tambour over the precordium, numerous techniques have been developed to investigate the remainder of the vibrational field. In general, however, five distinct, though related, techniques have evolved, namely, the apexcardiogram, the kinetocardiogram, the precordial acceleration tracing, the phonocardiogram, and the vibrocardiogram. The frequency ranges explored by these techniques are indicated in Figure 1.

The apexcardiogram, recording displacement at the cardiac apex, has received much attention since its inception by Marey, and has been found of particular value in the study of hypertrophy, valvular lesions, constructive pericarditis, bundle branch block, and cardiac aneurysm. Notable exponents in this field are Eddleman and Harrison at the University of Alabama Medical School, and Benchimol and Dimond at the Scripps Clinic, LaJolla.

The kinetocardiogram was described by Eddleman, et al., (1953)⁵. It utilizes a technique whereby a bellows pickup is suspended from a fixed point above the chest wall. The air coupling ensures reproducibility, avoids phase distortion occasioned by differential motion between the tissue and transducer, and records pure displacement tracings, as well as picking up diffuse precordial motions that might be poorly registered by a transducer directly on the chest wall. Kinetocardiography has been used in the investigation of valvular heart disease, and ischemic heart disease with some success (Eddleman, 1962⁶), but its limitations for use in space vehicles seem to be prohibitive.

The precordial acceleration tracing (PACT) was developed by Rosa, et al., of the Chicago Medical School, although some of the original observations were made by Landes (1940)¹⁰. The technique employs an electromagnetic accelerometer operating in a defined frequency band (2 - 30 cps) and uses standardized procedures for obtaining reproducible data. Rosa and his colleagues have undertaken considerable work with this system and have described criteria for the normal PACT (Rosa, 1961¹⁵), and its use in clinical interpretation (Rosa, 1962¹⁶).

The output voltage tends to vary with the tissue, and presumably the impedance of the tissue, over which the vibrations are being registered. As a result, with the electromagnetic microphone type transducer used by Rosa, records registered over soft tissues may in fact represent reflections of velocity and not acceleration. Notwithstanding allowances for resonance vibrations, however, and attenuation by intermediate structures, Rosa has shown that the PACT offers a reproducible standard for comparative studies. Time sequence, frequency pattern, and relative amplitude of the consecutive oscillations reveal a pattern equivalent to the second derivative of the pressure curve obtained from the pulmonary artery and the aorta, and the time tracings relate to mechanical events in the cardiac cycle.

Noting the phase relationships in tracings representing displacement, which is proportional to the ventricular pressure pulse, velocity of vibration, and acceleration, Rosa maintains that the acceleration tracing is richer in useful detail than displacement tracings, as well as being less subject to distortion from respiratory movement. During ventricular isometric tension, contractile forces without motion are paramount, and thereafter, there is a phase difference between the velocity of the resulting motion and the acceleration component of the force during it. The acceleration tracing reflects forces in the antero-posterior vector rather than motions, and shows details absent in displacement tracings during isometric contraction.

The transducer used by Rosa, however, which is manufactured by the Decker Corporation, is cumbersome, with a weight of 100 Gm and

a diameter of 40 mm, and it is doubtful if the technique would have direct application to space use. In addition, its output is not quantifiable in absolute terms, and, as has been noted, there can be some doubt as to whether the transducer reflects velocity or acceleration.

The use of a strain gauge accelerometer has much to commend it. Proper, of the Lovelace Foundation (personal communication)¹⁴, is using a light-weight, miniature (1 cm diameter) Statham strain gauge accelerometer which records in the range of 0.1 to 20 cps. In that range its response is linear, reflecting only acceleration, and is quantifiable to $\pm 5g$. A considerable body of data has been accumulated with this technique, defining normal precordial acceleration patterns in selected subjects of varying ages. The simplicity of the sensor and signal conditioners, and the reproducibility of the tracings renders the technique of particular advantage in space operations. Further application of this technique will be considered later.

Much work has been done with the phonocardiogram since the initial description of the technique of recording heart sounds was made by Einthoven and Geluk in 1897. Development of suitable electronic pickups, amplifiers, and filters, has led to more and more refinement in defining, through various frequency bands from about 40 - 1000 cps, various heart sounds, murmurs, snaps, and friction rubs, and in utilizing these sounds to time events in the cardiac cycle.

Numerous authors, including Landes (1940)¹⁰, have observed relationships between the phonocardiogram, particularly in the low frequencies, and other recordings of precordial vibration, notably the PACT (Schutz, Dieter, and Rosa, 1959¹⁷). The resemblance to the PACT is particularly obvious, since in the frequency range below 20 cps the microphones used in phonocardiography do not have a linear response, and in fact probably reflect distorted acceleration complexes (Rosa, 1962¹⁶). As will be noted later, the phonocardiogram is, in fact, a filtered apexcardiogram.

While phonocardiographic techniques could be utilized in space operations and render useful information, it is doubtful if the information

so obtained would warrant the additional complexity, particularly when a large portion of that information can be obtained by the stethoscope and other methods to be described.

As will be observed from Figure 1, the techniques of vibrocardiography explore the whole frequency range of precordial vibrations. Although the term was originally coined by Kountz, Gilson, and Smith in 1940⁹, the most comprehensive work in this field has been done by Agress and his colleagues at the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles. In addition, clinical application of the techniques has been effectively undertaken by Proper at the Lovelace Foundation. Essentially, the vibrocardiogram (VbCG) trace is a time function of the total vibrational energy appreciated over the precordium in frequencies ranging from less than 1 cps to over 2000 cps. Initially an Altec capacitance microphone was used as the sensor, but more recently miniature microphones with signal conditioning transistorized for minimal size, manufactured by Ling Temco Vought, have been utilized with even greater success. This equipment has a linear response in the frequency range 1.6 cps to 3000 cps (± 3 db) and a dynamic range of 90 db. Still further refinements of the equipment are currently under study.

Figure 2 illustrates the form and standardized nomenclature of the VbCG trace, although it must be noted that the form, although not the timing, tends to change with the position of the transducer on the chest, and the position and physical characteristics of the subject. Figure 3 illustrates the time sequence of the VbCG in relation to the ECG, the phonocardiogram, and pressure events in the cardiac cycle.

According to Agress, measurement of the phases of isometric contraction, ejection, systole, and diastole can be obtained from the precordial VbCG with an accuracy as good as that realized with direct cardiac catheterization. This belief, however, is open to question, by other cardiologists. In addition, comparison of these phase intervals in stressed and unstressed subjects has shown significant changes which serve to differentiate the normal from the cardiac injured subject, and

THE VIBROCARDIOGRAM

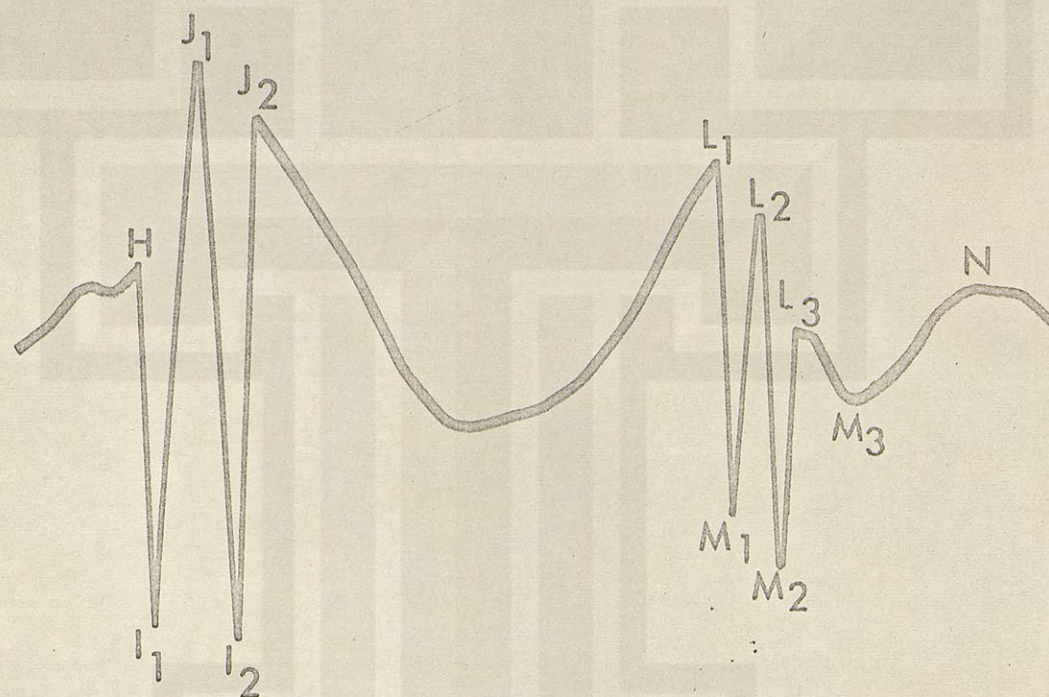


Figure 2

Source: Agress and McInnis, (1964)⁴

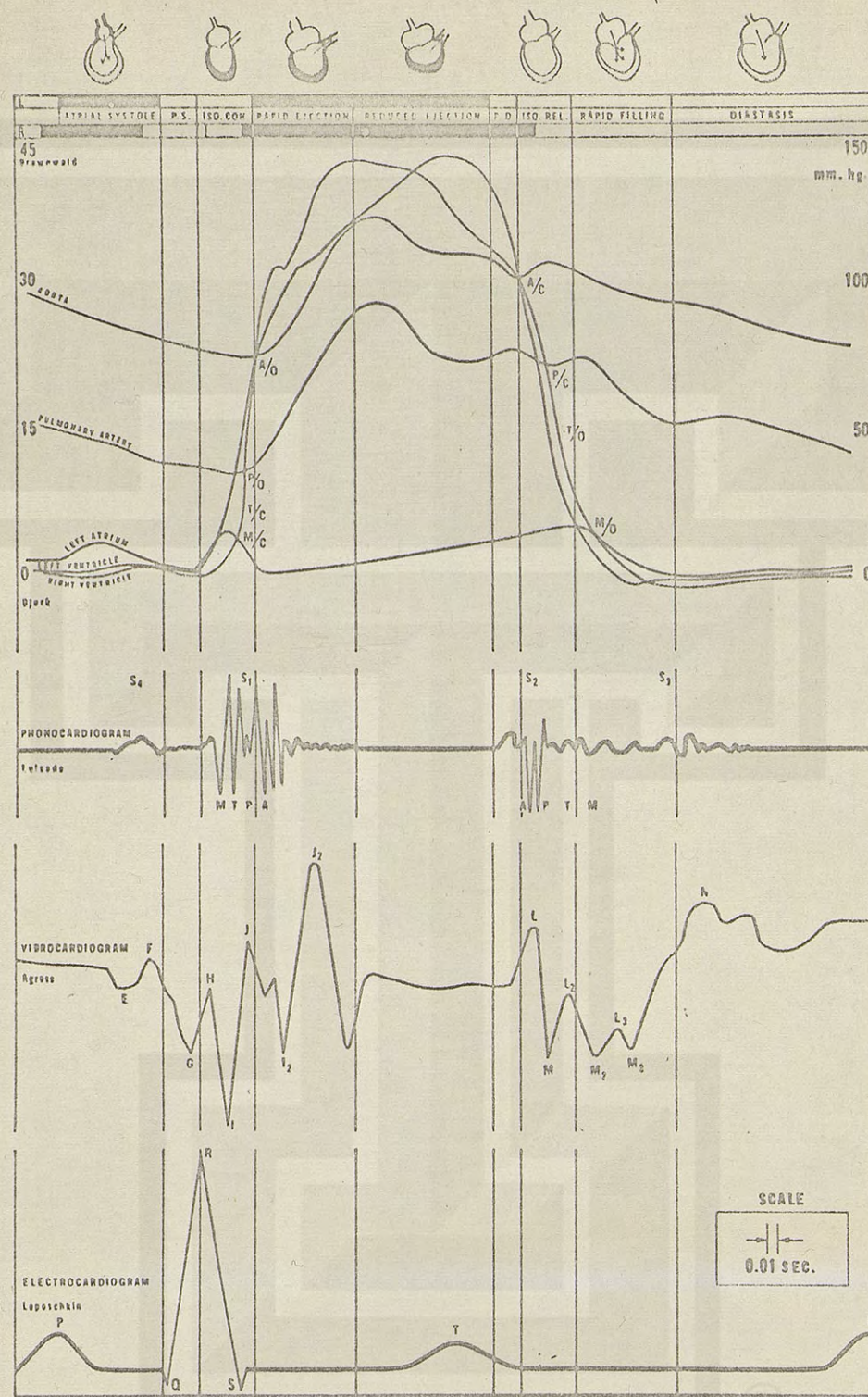


Figure 3

Source: Agress and McInnis, (1964)⁴

can be correlated with other physiological parameters expressing stress.

The VbCG waves "H", "J", "J₂", and "L" have been shown by Agress (1964)⁴ to correlate with: the initial rise of left ventricular pressure, the juncture of the slow and rapid phases of isometric contraction, and the opening and closing of the aortic valve, respectively.

The essential interval measures involved are the isometric contraction interval (H - J₂), and the ejection interval (J₂ - L). These intervals bear a relationship to each other best expressed as the ratio H-J₂/J₂-L. In normal subjects changes in this ratio parallel O₂ consumption and pulse rate, with an increase after exercise, while in subjects with clinically established heart disease the ratio has been observed to decrease (Agress, 1964⁴). However, not all stresses act in the same fashion. Proper and Nevison (1963), in an unpublished report, found that in normal subjects under hypoxia, the isometric contraction time was reduced, although only to the extent of 5 milliseconds in a 50 millisecond total time, while the above noted ratio was decreased.

Other measures which have been employed in this field include the time-tension index, which is the product of the mean systolic pressure and the ejection time and has been shown to be directly related to myocardial oxygen consumption; the ventricular slope, which is the quotient of the isometric pressure gradient and the isometric contraction time and indicates the rate of development of pressure during isometric contraction; and the mean systolic ejection rate which is the stroke volume divided by the ejection time and indicates the rate at which ejection is occurring. Significant changes have been found in these indices under exercise.

In another area of measurement, Agress (1964)⁴ has developed techniques which he uses for determining cardiac energy level, or mechanical force, and relative stroke volume, from which can be calculated cardiac output. In his work he has shown good correlations with the results of these measures obtained by other methods. In each case, the values are derived from measurements of areas under different portions of the VbCG curve. For energy measures, the entire area

under the systolic portion of the curve is used, while for stroke volume measures the area under the ejection phase (J_2 -L) is employed. Because of the variation in waveform previously noted, and because of doubt as to what the VbCG is actually reflecting, some controversy has arisen over the interpretation of these measures. Lohr et al., (1962)¹² in Utrecht, maintain strongly that precordial tracings cannot be used for estimations of cardiac force or stroke volume. They note the distortion that occurs with various positions of the transducer, and analyze the result of placing the transducer over different areas of the precordium. They recognize four major areas of the precordium: a) the cardiac apex; b) a zone of retraction around the apex where the tracing may demonstrate a mirror image of the apex trace; c) a zone of relative tranquility found especially in the third and fourth intercostal spaces along the left sternal border; and finally, d) the zone of the base of the heart. In each case, however, they find inconsistencies of measurement which preclude the use of that area for the quantitative measurements required. They conclude that... "no area of the precordium would seem to be suitable for the derivation of either stroke volume or the force of cardiac contraction from the accelerographic excursions." In the light of the above, a re-examination and verification of the techniques of Agress in this field would be well justified.

From consideration of all the foregoing, it is apparent that numerous techniques are employed for the investigation of precordial vibrations. This has led to much confusion in nomenclature and interpretation, and there is a tendency to consider that each technique investigates a different phenomenon. This in fact, is not so, and in a timely paper Agress and his colleagues (1964)³ have examined the common origin of precordial vibrations and have shown that the various records of precordial vibrations represent different attributes of chest wall motion resulting from, and proportional to, the rate of change of pressure within the cardiac chambers. Heart vibration recordings by any technique contain inherently the same information, the graphic differences in the records being dependent primarily on the response characteristics of the transducer and its recording system.

Thus, a displacement transducer responds primarily to the amplitude of the vibrations and is largely independent of frequency. On the other hand velocity transducers have signal output proportional to the frequency of the input, while acceleration transducers have an output proportional to the square of the frequency. Thus, the resulting trace will vary with the transducer used to record it.

At the same time, by use of suitable integrating and differentiating electronic circuitry and band-pass filters, one form of signal can be transformed into another, with, in some cases, remarkable fidelity. Agress et al., (1963)² showed that the vibrocardiogram trace could be reconstructed from the first time derivative of ventricular pressure (Figure 4), and in the same paper showed that a trace resembling that of left ventricular pressure could be reconstructed by electronically integrating the VbCG trace.

Similarly, by suitable filtration of the VbCG, traces could be obtained similar to that of the kinetocardiogram (0.1 - 20 cps), the accelerogram (5 - 200 cps), and the phonocardiogram (60 - 120 cps) (Figure 5). It is perhaps surprising that the accelerogram of Rosa can be obtained by a simple process of filtering when one would expect that integration would be necessary. This may indicate, as already suggested, that Rosa's accelerogram does not truly reflect acceleration, or alternatively that the output of the vibrocardiogram in that range is responsive primarily to the square of the frequency.

However, although all implications and potentialities of the vibrocardiogram are by no means defined, it is obvious that with suitable signal conditioning vibrocardiography provides a simple technique from which a large amount of information on cardiac function can be derived. It should be given strong support as a measure for use in space operations.

As an extension of vibrocardiography, Proper of the Lovelace Foundation, in conjunction with Ling Temco Vought Western Research Division, is developing a combined vibrocardiograph microphone and miniature accelerometer. With miniaturized band-pass filter circuitry, integrating and differentiating networks, this miniature combined transducer will provide information readable as an apexcardiogram, vibrocardiogram, phonocardi-

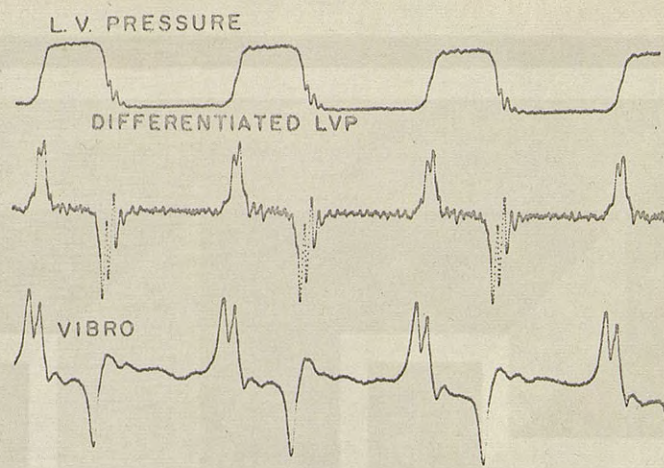
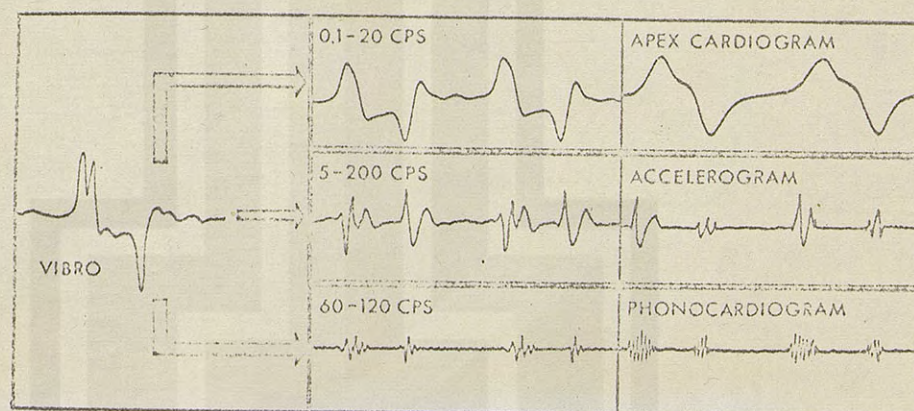


Figure 4

Source: Agress et al. (1963)²



This figure illustrates the derivation of other types of cardiographic tracings from the vibrocardiogram by use of a variable band pass filter.

Figure 5

Source: Agress et al. (1964)³

gram, and accelerogram. The accelerometer will provide quantifiable data in terms of G loading, and where the accelerometer is inactivated by an impressed G field the vibrocardiogram will continue to present useful information. In other situations the electronic circuitry will permit mutual validation of the respective tracings. As a bonus, Dr. Proper observes that the vibrocardiogram microphone will act as a voice back-up should there be a failure in other audio systems. This combined approach would appear to be the most potentially useful of all techniques in the investigation of cardiac kinetics.

Recommendations

From the above discussion it would appear that useful information can be derived from a study of cardiac kinetics. Three-dimensional ballistocardiography shows very hopeful potential, although much work seems necessary yet in refining instrumentation, collecting baseline data in a nulled gravitational environment, and developing simplified systems of data analysis.

Precordial measurements, which are simpler and require less in the way of instrumentation, seem to be more applicable at this time. Of these, the phonocardiogram has received the greatest attention. It is, however, limited in the range of frequencies encompassed, and when compared with other precordial recording methods, albeit less thoroughly examined, it does not appear to provide so much useful information.

The precordial acceleration tracing and the vibrocardiogram would seem to offer the widest range of information on precordial kinetics, particularly if combined into a conjoined transducer, and provided with suitable electronic processing from which can be derived other precordial traces. The PACT is most advantageously recorded from a miniature strain gauge accelerometer and not from the electromagnetic variety. Further validation of some of the VbCG interpretations would in addition seem to be advisable, particularly with respect to their usefulness in providing measures of, for example, stroke volume, cardiac force.

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