IMPEDANCE CARDIOGRAPHY IN THE ELDERLY

by

Brian Owen Williams, M.B., Ch.B.(Comm), F.R.C.P.(Glasg)

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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Most of the work detailed in this thesis presentation was carried out during three years (1979-82) in my post as Senior Lecturer within the University Department of Geriatric Medicine in Glasgow before I was appointed to the post of Consultant in Administrative Charge of the Glasgow Western District Geriatric Medical Service in October, 1982.

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DECLARATION

I declare that all of the clinical studies and statistical analysis, encompassed in this presentation, have been completed by myself. None of the original observations have previously been published except earlier studies which have been referred to in Chapter 4. The studies described in Chapter 13 and 14 required assistance to complete and I was ably assisted by Dr. Iain Lennox, M.B., M.R.C.P. (U.K.) and Professor Francis I. Caird, D.M., F.R.C.P. More detailed and extended observations on the mechanisms of postural hypotension in the elderly may be presented by the three of us in collaboration at a later date.

SUMMARY

Experience gained by performing 1250 impedance cardiograms in 362 elderly subjects has shown that the technique is simple, non-invasive and highly reproducible; it lends itself to the investigation of cardiovascular problems in the elderly. Minor modifications to the method, as applied to the elderly, may improve the validity of stroke volume estimation.

Cyclical, small changes in thoracic impedance do occur and are related to the cardiac cycle but from the evidence available it is not clear whether the change is solely related to left ventricular stroke volume or a combination of left and right ventricular stroke volumes.

The Kubicek stroke volume formula is clearly empirical but it provides an accurate though not precise estimate of the stroke volume and cardiac output. Poor accuracy is obtained in the presence of valvular regurgitation and right bundle branch block due to characteristic first derivative impedance waveform abnormalities and in atrial fibrillation because of a natural wide variation of the stroke volume on a beat to beat basis. Poor accuracy occurs in patients with chronic lung disease due to systematic effects on the basal thoracic impedance.

The impedance method tends to overestimate larger cardiac outputs and underestimate smaller cardiac output values. Absolute values for the cardiac output are, however, rarely required in medicine and despite some doubts about the validity of impedance absolute values it does provide an accurate reflection of expected relative changes. The method is a useful non-invasive technique

for the haemodynamic investigation of elderly patients with symptomatic postural hypotension where the essential problem appears to be due to a failure of the peripheral vascular system to respond to the effects of orthostatic stress.

The impedance cardiogram is useful for the measurement of systolic time intervals, changes in thoracic fluid content, assessment of myocardial contractility and the eludication of beat to beat haemodynamic changes in individual patients in atrial fibrillation. The waveform gives useful information about left atrial function, the bundle branch blocks, and it is helpful in the assessment of aortic valve regurgitation.

INTRODUCTION

Cardiovascular disease is a major cause of mortality and disability in the elderly. There is a universal reluctance to subject older patients to invasive assessment and non-invasive techniques of clinical investigation have developed largely because of the costs and necessary skills inherent in invasive methods, radiation risks, patient acceptability and the small but definite risks of intravascular instrumentation.

Most of the standard methods of measurements of the stroke volume and cardiac output lack precision. Knowledge of precise, absolute values of the cardiac output are rarely necessary in most clinical or research situations and changes in cardiac output due to the effects of physiological stresses, drugs or disease states are more important.

During the last 20 years, and especially with the development of Space Flight Programmes, a considerable amount of work has been carried out in the U.S.A. on the practical application of impedance bio-electrics in biology. There are few references to this field of research in the British literature.

With the need for a simple, bloodless method of measuring the cardiac output, early workers in the field of bio-electrics observed that electrical impedance changes in the thorax occurred in time with the cardiac cycle and adapting an empirical formula relating impedance change to volume change in a conducting solid a method of measuring the stroke volume in animals and man was developed. A relatively simple, mathematical formula is therefore available and this can be completed with knowledge of such individual test variables as the haematocrit, systolic time intervals and a simple

measurement derived from the impedance cardiogram.

Impedance cardiography appeared to be theoretically ideal for non-invasive investigation in the elderly but, after a comprehensive review of the literature, it was clear that many questions regarding the theoretical basis for the technique were unanswered and although the method appeared to be accurate, its precision was in doubt. Further clinical studies of the basic technique were performed and the results of these studies form the basis of this thesis.

Statistical analysis of the results was carried out, throughout, using a HEWLETT PACKARD HP-67 Programmable Pocket Calculator and reference was made to DOCUMENTA GEIGY SCIENTIFIC TABLES, 7th Edition (Eds. K DIEM and C LENTNER) 1970, JR GEIGY, BASLE.

CHAPTER 1

THE DEVELOPMENT OF TRANSTHORACIC ELECTRICAL IMPEDANCE CARDIOGRAPHY

RESISTANCE AND IMPEDANCE

Electrical resistance is defined in the most elementary form by Ohm's Law viz. $R = {}^{V}/I$ where V is the fall in potential in volts over the conductor and I is the current in amperes which flows through it. Electrical impedance (Z) is the opposition of the conductor to the flow of alternating current. In the measurement of electrical fields it is important to define the structures through which the current flows. This is relatively easy to achieve in volume conductors of simple geometry and homogeneous electrical properties but less simple in biological tissues e.g. the thorax with its unspecified shape and intrinsic differing electrical properties. The influence of major cyclical physiological changes e.g. cardiac activity and respiration may further complicate measurements of the intrathoracic electrical field. In the practical application of transthoracic impedance measurements, however, the absolute total impedance value is of less importance than changes in impedance which relate to altered fluid/air volumes and changes in cardiac volumes during physiological cycles (1).

Total impedance is the sum of the resistance of the tissue as an electrolyte and resistance of the tissue as a condenser (capacitance). A resistance vector quantity is expressed as follows (2).

$$Z = \sqrt{R^2 + X^2} \quad \text{..... Equation 1.1.}$$

where Z = impedance

R = resistance

X = reactance (of which capacitance is the major component)

In measuring the impedance of a tissue the reactance can be excluded by the use of a compensatory condenser in the measuring device (2). Furthermore, in mammalian tissues, the reactive component is usually very small and for the analysis of variations in thoracic impedance it is justifiable to assume that the impedance is only resistive (3) when the current frequency lies within the range of 30 to 200 kiloherz.

IMPEDANCE CARDIOGRAPHY

The well known fact that a change in the volume or in the shape of a body between two electrodes in a high frequency circuit influences the resistance or impedance has been utilized by many workers (4 -8) in an attempt to study volume changes in the heart. In 1907, Cremer (4) placed an isolated frog heart in the air between two condenser plates and obtained a cyclical change in the measured capacitance with each heart beat. In 1932, Atzler and Lehmann (6) noted similar changes in hearts placed between the insulated plates of a 100 megaherz oscillator and Rosa (7) related the changes observed in the precordial capacitance values to changes in underlying blood flow.

Nyboer (9) suggested that changes in electrical resistance were due to changes in the cardiac volume but he later regarded the impedance change as being related to fluctuations in the calibre of the major blood vessels induced by the cardiac cycle (10). This principle led to the coining of the term impedance plethysmography.

Nyboer (10) stated that the change in the volume of blood within a body segment (the finger) could be calculated from the derived expression for the volume of a cylindrical conductor.

$$V = \rho \frac{L^2}{R} \quad \text{..... Equation 1:2.}$$

where V = change in the volume of blood.

ρ = specific resistivity of blood in the segment.

L = length of segment of the conductor.

R = calculated parallel resistance of blood related to the volume change.

This formula was, however, derived theoretically and assumed a fairly uniform current density throughout the cross section of the conductor; a principle which does not apply to the thorax (11).

The advent of space flight in the early sixties stimulated the search for a non-invasive method of measuring the cardiac output. Kinnen and his co-workers developed a two electrode thoracic impedance plethysmograph and adopted a simple formula relating the stroke volume to measured impedance changes (12) although they stated that there was no theoretical justification for it.

$$\Delta V = \frac{\Delta Z}{Z} \times V \quad \text{..... Equation 1:3}$$

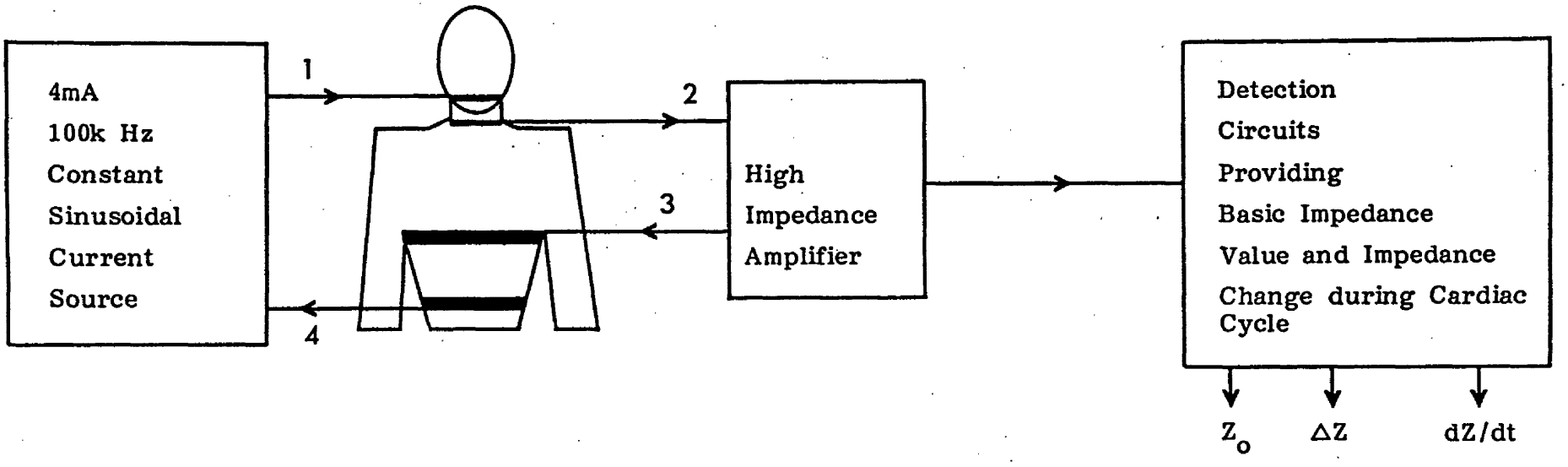
where ΔV = Stroke volume

ΔZ = Variation in transthoracic impedance due to cardiac activity.

Z = Transthoracic impedance

V = Volume of thorax

Kubicek and his colleagues later developed a tetrapolar impedance plethysmograph with circumferential band electrodes (Fig 1:1) and introduced another empirical formula for the



Z_o : Basic Impedance Value

ΔZ : Change in Impedance

dZ/dt : First Derivative of Change in Impedance

FIGURE 1:1

TETRAPOLAR IMPEDANCE PLETHYSMOGRAPHY -

FOUR CIRCUMFERENTIAL METALLIC CONDUCTIVE STRIP ELECTRODES

calculation of the stroke volume (13).

$$\Delta V = \rho \frac{L^2}{Z_o^2} \Delta Z \quad \text{..... Equation 1:4}$$

where ΔV = ventricular stroke volume (cc)

ρ = electrical resistivity of blood at 100k Hz (average value 150 ohm.cm.)

L = mean distance between the two inner electrodes (cm).

Z_o = basic impedance between the two inner electrodes (ohms).

Z = extrapolated maximum impedance change during systole.

Z was initially derived graphically from tracings of cyclical changes in basal impedance but was later derived from the product of the ventricular ejection time and the first derivative of the maximum change in impedance in order to reduce the error in calculating the change in impedance (14) (Fig 1:2).

$$\Delta V = \rho \frac{L^2 T}{Z_o^2} \quad (dZ/dt) \text{ min} \quad \text{..... Equation 1:5}$$

where ΔV = ventricular stroke volume (cc)

ρ = electrical resistivity of blood at 100k Hz (average value 150 ohm.cm.)

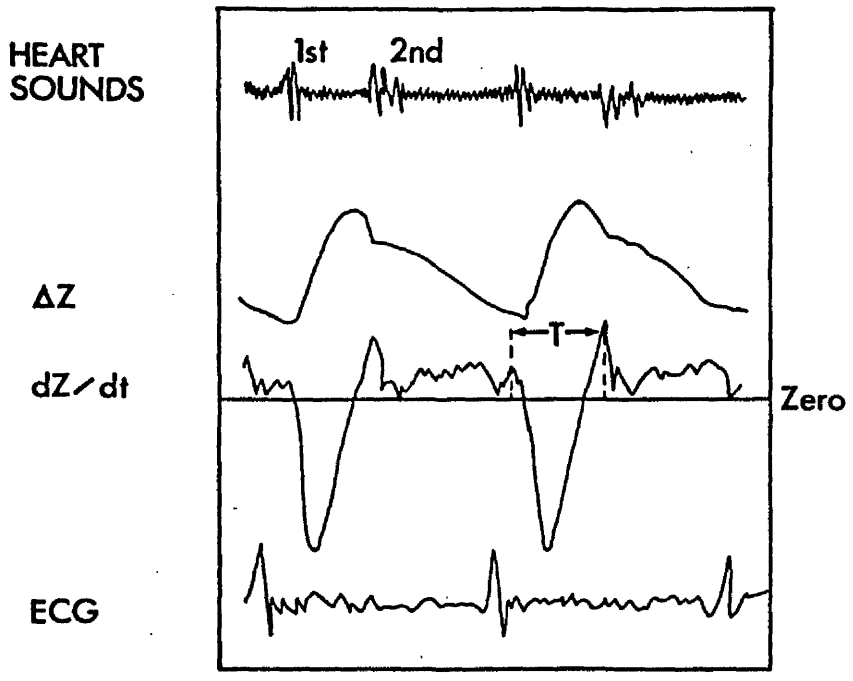
L = mean distance between the two inner electrodes (cm.) (measured front and back)

Z_o = basic impedance between the inner two electrodes (ohms.)

T = ventricular ejection time (seconds)

dZ/dt = first derivative of maximum change in impedance (ohms/sec.)

The Kubicek equation (Equation 1.5) was empirical and he made no attempt to justify the expression nor did he explain the dependence on ρ and L. He reported that the measured cardiac output was consistently overestimated by this formula. The Kubicek equation was given a certain credence which was neither deserved nor



KEY

ΔZ : BASAL IMPEDANCE WAVEFORM

$\frac{dZ}{dt}$: FIRST DERIVATIVE OF IMPEDANCE WAVEFORM

T : VENTRICULAR EJECTION TIME

FIGURE 1:2

CYCLICAL CHANGE IN BASAL IMPEDANCE AND FIRST DERIVATIVE OF IMPEDANCE (ADAPTED FROM KUBICEK ET AL (14))

intended by Kubicek and his co-workers.

The first commercially available impedance cardiograph was developed by Kubicek and his colleagues in Minnesota in the late sixties (14) and since that time the Minnesota Impedance Cardiograph has been evaluated in many centres throughout the world (Fig 1:3).

ORIGIN OF THE IMPEDANCE CARDIOGRAM TRACE

The transthoracic electrical impedance cardiogram obtained by tetrapolar plethysmography is synchronous with the electrocardiogram and related to cardiac cyclical activity (13). The impedance change (ΔZ) reaches a maximum before the start of ventricular ejection and then decreases to reach a minimum at the time of peak aortic pressure (15). That part of the impedance waveform (ΔZ) at the time of ventricular diastole begins from an apparent dicrotic notch and then shows an increase in impedance until the end of diastole (in Fig 1:2, a rise in the amplitude of the ΔZ trace is associated with a fall in impedance and vice versa). The first derivative of the impedance cardiogram (dZ/dt) forms a more useful basis for study because it has sharper demarcation points, is more stable during respiratory cycles and is used to calculate the stroke volume (16).

The cardiac impedance signal is very small (11) and accounts for approximately one per cent of the measured total basal thoracic impedance value. Blood is an excellent electrical conductor when compared with other biological tissues (17) and during systole the main haemodynamic effect in the thorax is for a redistribution of blood into the pulmonary circulation. Lesser effects are reduced blood content in the heart associated with reduced cardiac cavity dimensions, a transient increase in blood flow to the thoracic walls

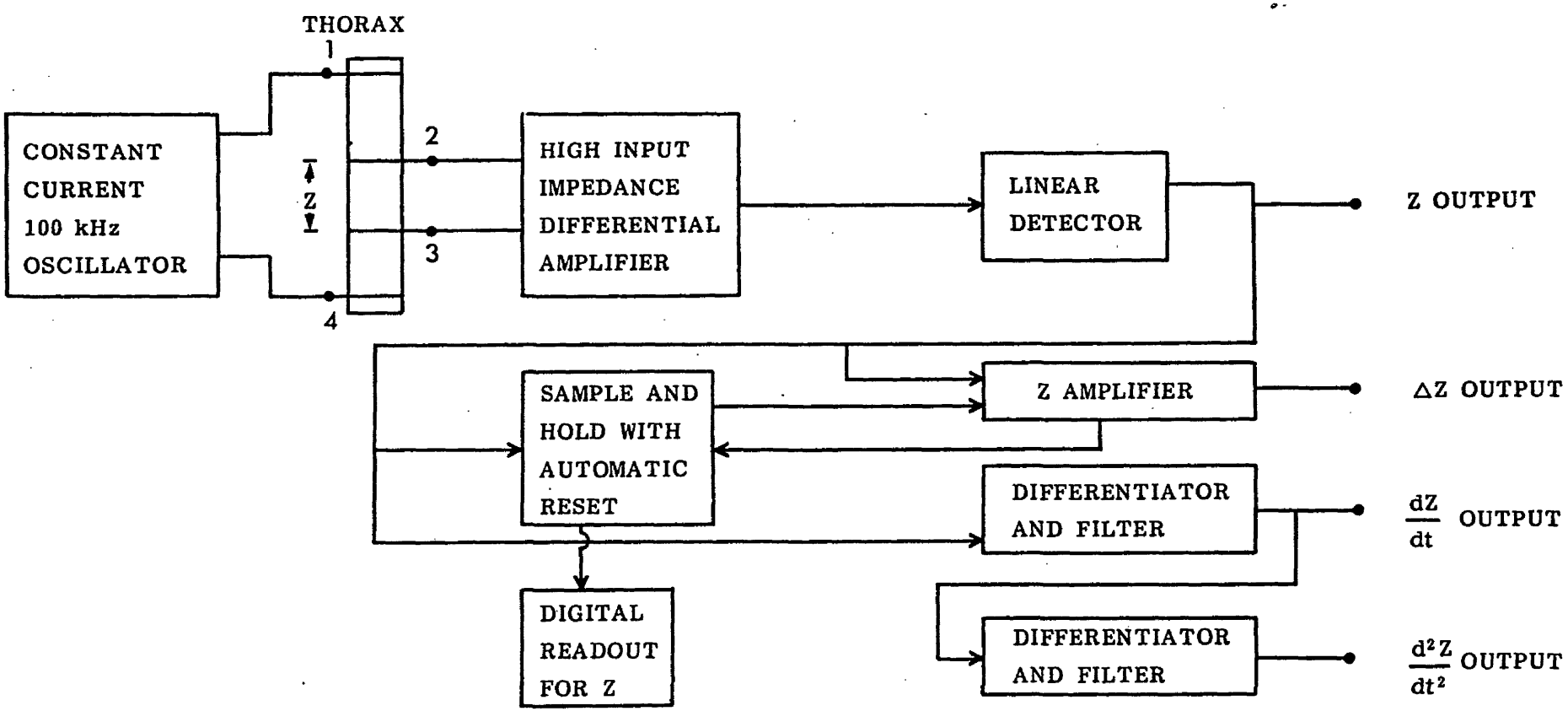


FIGURE 1:3

SCHEMATIC DIAGRAM OF THE IMPEDANCE CARDIOGRAPH

and swelling of tissues in the chest.

Various hypotheses have been proposed to explain the origin of the cyclical cardiac impedance waveform (Table I).

1. Pulmonary Circulatory Changes

The first systematic investigation of cardiac volume changes and rhythmic variations in the blood content of the major intrathoracic vessels was reported in dogs in 1952 (18). Impedance changes were associated with the expulsion of blood from the heart and the blood flow to the lungs and not to the actual volume changes of the heart. The blood content of the vascular bed between the electrodes was the principal factor in determining the extent of the impedance change and an increased blood flow was associated with a proportionate reduction in impedance values. The influence of the heart appeared to be very small but the electrodes were placed on the limbs or on each side of the chest wall and not in a circumferential tetrapolar configuration.

Kinnen and his colleagues (12) suggested that the measured impedance waveform and amplitude changes appeared to instantaneously reflect the cyclical changes in the pulmonary blood volume. Farman and Juett (19) observed that impedance variations synchronous with cardiac activity were often considered to be due to artefact and they considered that the apparent cardiac impedance wave was indicative of pulsatile changes in the intrathoracic blood volume.

Kubicek and his co-workers stated that the tetrapolar impedance measurement technique monitored pulsatile right ventricular ejection (13) into the pulmonary circulation and in 1970, Japanese experimental evidence, obtained in anaesthetised dogs, was strongly in favour of the principle that cyclical impedance changes synchronous with cardiac activity reflected mainly haemodynamic

1. Pulmonary circulatory changes.

2. Mechanical movement of the chest wall and the influence of electrode/tissue interface.

3. Changes in cardiac shape, size and movement.

4. Pulsatile blood flow in the venae cavae and pulmonary veins.

5. Pulsatile blood flow in the aorta.

6. Rate of blood flow.

TABLE I

HYPOTHESES FOR THE ORIGIN OF THE CARDIAC IMPEDANCE WAVEFORM

changes in the pulmonary circulation and bore no relation to cardiac action or blood volume changes within the great vessels (20-21). These animal experimental studies, were, however, performed using tetrapolar leads on the side walls of the chest unlike Kubicek's circumferential lead configuration.

Lababidi and his colleagues studied the Kubicek impedance technique in children with left to right cardiac shunts and observed that the derived impedance cardiac output correlated well with pulmonary blood flow but poorly with systemic flow (22).

Goto observed marked changes in the amplitude and character of the cardiac impedance waveform in dogs when he experimentally produced an excess haemodynamic load in the pulmonary circulation by artificially increasing the left atrial pressure with a balloon catheter (23) or by inducing a reversible bypass between the left ventricle and left atrium (24).

2. Mechanical Movement of the Chest Wall and Electrode/Tissue Interface

In a major critical analysis of transthoracic electric impedance plethysmography, Hill and his colleagues (25) stated that a basic error in the principle of measurement of thoracic impedance was due to the fact that the electrode tissue interface was extremely sensitive to impedance changes and that very large impedance changes might occur due to the simple outward mechanical pressure produced by ventricular systolic filling. Krohn and his co-workers (26) refuted Hill's statements and observed that if skin electrode pressure significantly influenced the impedance tracing then it should occur especially during systole when the point of maximum impulse presses against the overlying electrodes and the impedance value should decrease, but in actual tracings of a

hypertrophied left ventricle, the impedance was observed to rise during systole and the impedance changes due to the change in the shape of the heart were greater than any variation at the electrode/tissue interface, which accounts for less than 10% of the total impedance change (27).

In a further defence of electrical impedance plethysmography, Kinnen (28) commented that measured impedance values might be influenced by a variety of factors including electrode shape, size, composition, pressure and location, conductive paste, specific body segment examined and the electrical current and frequency used but his group showed no relationship between impedance changes and surface motion of the thoracic wall and Kira (20) observed rhythmical impedance changes when he applied electrodes directly to canine lungs, after thoracotomy, which were similar to the signals obtained when the electrodes were applied to the intact chest wall in the same animals.

3. Changes in Cardiac Shape, Size and Movement

Witsoe and Kottke (29) observed that cyclical impedance changes only appeared to relate to intrathoracic systemic circulatory events and that, in dogs, the rapid systolic decrease in impedance only occurred when blood was ejected from the left ventricle into the aorta; a phenomenon which appeared to be independent of right ventricular ejection. Geddes and Baker (30) injected saline into both ventricles in dogs and noted that left ventricular ejection contributed more to the change in transthoracic impedance than right ventricular ejection.

In a study of point electrode vector impedance cardiography (31) Hanish and his group noted that the greatest change in cardiac

impedance was related to the change in the shape and volume of the heart including the blood in the cardiac chambers. During ventricular ejection, the ventricular myocardium increased in thickness especially towards the base of the heart. Krohn and his colleages (26) using point electrodes concluded that the cardiac impedance waveform was due to cyclical changes of the shape of the heart and they observed that, during early systole, when the lateral ventricular walls came together the normal heart changes from a spheroid to a conoid shape. This decreases impedance across the shortened diameters and increases impedance across the long axis but changes in electrode proximity to the heart might influence the impedance tracing obtained (32).

4. Pulsatile Blood Flow in the Venae Cavae and Pulmonary Veins

The flow of blood in the venae cavae is pulsatile (33, 34) and a similar situation exists in the pulmonary veins (35). Karnegis and Kubicek (36) noted that the contraction of the atria and of the ventricles was associated with identifiable components in the impedance change waveform and they speculated that cardiac thoracic impedance changes might be related to the pulsatile flow of blood through the venae cavae and/or the pulmonary veins as well as cardiac activity.

5. Pulsatile Blood Flow in the Aorta

Kubicek and his co-workers observed that, in experimental studies in dogs, there appeared to be a linear relationship between the peak values of dZ/dt and peak aortic blood flow (14). Mohapatra and his colleagues performed experimental studies using intra-aortic balloon pumping and concluded that there was no marked contribution to the cardiac impedance signal from pulsating blood flow in the aorta (16).

6. Rate of Blood Flow

Geddes and Baker (30) observed a bigger change more quickly in the impedance waveform when 2 ml. saline was injected experimentally into a dog's left ventricle than when the same volume was injected into the right ventricle and this difference appears to be due to the higher velocity of left ventricular ejection compared with right ventricular ejection (16). Mohapatra has postulated that the rate of change of ventricular ejection of blood might be more important than the volume of ejection in explaining the origin of the cardiac impedance waveform (16).

SUMMARY

Very little is known about the electrical field and current flow paths within the thorax and it must be accepted that Kubicek's stroke volume equation is empirical. Kubicek stressed that his formula was, however, useful and that absolute cardiac output values are seldom required in medicine although relative changes in cardiac output induced by stress or drugs were important measurements and tetrapolar transthoracic impedance plethysmography might be a useful non-invasive technique for assessing cardiac output changes in individual subjects in a variety of clinical situations (15).

Cyclical small changes in transthoracic electrical impedance do occur and are related to the cardiac cycle but from published evidence it is not clear whether the impedance changes relate to left ventricular ejection, right ventricular ejection or a combination of both. More than one intrathoracic phenomenon contributes to the overall observed impedance change associated with the cardiac cycle and the impedance change is related to changes in the volume and velocity of blood motion within the electrical field

within the thorax when the tetrapolar circumferential lead system is utilized.

CHAPTER 2

METHOD OF OBTAINING THE IMPEDANCE CARDIAC WAVEFORM

THE METHOD

Transthoracic electrical impedance (Z_o) was measured by the Minnesota Impedance Cardiograph (Albury Instruments) which comprises a constant current oscillator and a high impedance voltmeter. Four aluminized Mylar Electrodes attached to an adhesive-tape backing were applied circumferentially, at the top and root of the neck, at the level of the xiphisternum, and around the upper abdomen (Fig 1:1). A 100 k Hz., 4 ma alternating current passes between the first and fourth leads and the second and third leads act as pickups at the upper and lower boundaries of the thorax. The value of Z_o is displayed continuously and the impedance signal is passed through a differentiator. The electrocardiogram, phonocardiogram, first derivative of the impedance cardiogram (dZ/dt), and an external arterial pulse trace (taken from a carotid or subclavian artery by means of a diaphragm-type tambour and Elema-Schonander 510C transducer), were recorded simultaneously on a Elema-Schonander Mingograph 34 recorder, at a paper speed of 100 mm/second (Fig 2:1).

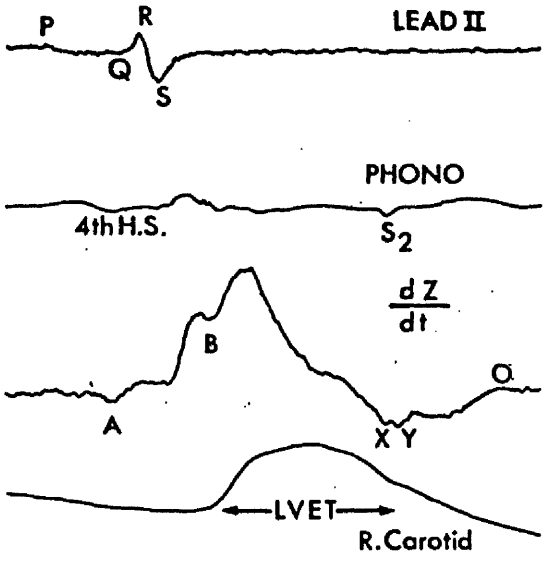
The beat to beat stroke volume was derived according to the equation of Kubicek and his colleagues (14).

$$V = \rho \frac{L^2 T}{Z_o^2} \quad (dZ/dt) \text{ min} \quad \text{..... Equation 1:5}$$

where ΔV = ventricular stroke volume (cc)

ρ = electrical resistivity of blood at 100 k Hz (Kubicek 1975) (37)

L = mean distance (cm) in the midline between the two inner electrodes (2 and 3) (measured front and back)



A: Simultaneous with 4th heart sound

B: Synchronous or almost synchronous with maximal deflection of 1st heart sound

X: Synchronous or almost synchronous with aortic valve closure

Y: Synchronous or almost synchronous with pulmonary valve closure

O: Synchronous with rapid ventricular filling phase

FIGURE 2:1

SIMULTANEOUS FOUR CHANNEL RECORDING IN 80 YEAR OLD HEALTHY FEMALE (PAPER SPEED 100 mm/sec)

Z_o = basal impedance between the two inner electrodes (ohms)

dZ/dt = first derivative of impedance change (ohms/second)

T = left ventricular ejection time from the upstroke to the dicrotic notch in the arterial pulse trace (seconds)

and the cardiac output was derived from the average stroke volume over ten consecutive beats, and the heart rate.

Cardiac Output = Stroke Volume x Heart Rate ..... Equation 2:1

For the purposes of the present studies, L in the formula for derivation of the stroke volume was taken as the mean of the distances between the second and third circumferential leads measured in the midline at the front and the back of the chest. These two measurements may differ considerably in elderly patients with kyphosis and the use of the mean of the two measurements rather than one seemed preferable. Most workers have followed the example of Kubicek and his colleagues (14) and used the mean of the two values for the back and front of the chest but other groups have only measured the distance on the front of the chest in studies in animals (38) and humans (39-42).

The left ventricular ejection time was derived from a carotid or subclavian arterial pulse tracing, rather than from the record of the dZ/dt waveform. In some tracings of dZ/dt the left ventricular ejection time is difficult to determine since neither the beginning nor the end of the ejection time may be clearly marked. Ten complexes were measured and the results averaged in order to minimize the effects of respiration on dZ/dt since many elderly patients have difficulty in prolonged breathholding.

Patient Safety and Ethical Considerations

In the tetrapolar thoracic electrical plethysmography technique, electrical current is passed into the thorax but frequencies higher than 20 k Hz provide electrical protection and do not produce any appreciable electrode polarisation (16). Electrical stimulation of the skin does not occur, there is no localized change in the tissue and there is no risk of inducing respiratory arrest or ventricular fibrillation (43).

A tetrapolar system is used in preference to a two lead system to reduce the likelihood of electrode/interface artefact and skin contact impedance. Uniform current density distribution is obtained in the segment under study and electrode polarisation is less likely to occur.

The technique is totally non-invasive and is therefore suitable for use in clinical studies in human subjects.

MODIFICATION OF THE METHOD OF OBTAINING THE IMPEDANCE WAVEFORM IN ELDERLY SUBJECTS

In the clinical application of the impedance technique, it is important that the first and second circumferential electrodes i.e. the upper current and pick-up electrodes should be placed at least three centimetres apart or invalid results may be obtained. The first lead can, however, be placed on the forehead as a strip with little apparent difference in the basal thoracic impedance value (Z_o) or the dZ/dt waveform obtained (16).

In some elderly subjects, and especially females, a tendency to kyphosis and a low hairline at the back of the neck make it difficult to achieve a constant minimum three centimetre distance between the first and second electrodes on the neck. A comparison

study of basal impedance and derived cardiac output values was carried out with 1) lead I as a strip on the neck and 2) lead I on the forehead in elderly patients.

Subjects and methods

Nine male and four female patients (age range 69-83 years) under the care of the University Department of Geriatric Medicine were studied.

Cardiovascular diagnoses are listed in Table II. Basal thoracic impedance values (Z_0) and derived cardiac output values were obtained as described in pages 14-15 with lead I placed on the neck and on the forehead. The second, third and fourth leads were placed in the standard positions.

Results

The results are detailed in Tables II and III. In most patients the basal thoracic impedance value (Z_0) was lower when Lead I was placed on the forehead (mean difference 0.53 ohms, standard deviation 0.55) and this difference was significant when analysed by a paired t test ($t = 3.47$, $p < 0.005$). There was no observed difference in the amplitude or waveform of the first derivative of impedance (dZ/dt).

The resultant effect of the change in basal impedance was reflected in the values obtained for cardiac output. Cardiac output values were on average 6% higher when Lead I was on the forehead (mean difference 0.22 1/min., standard deviation 0.22) and this was significant ($t = 3.6$, $p < 0.005$).

Discussion

It is clear that if a lead configuration with the first

PATIENT	DIAGNOSIS	AGE (YRS)	SEX	LEAD I ON NECK Zo (ohms)	LEAD I ON FOREHEAD Zo (ohms)	DIFFERENCE (ohms)
1	CVS Normal	75	M	30.6	29.5	- 1.1
2	CVS Normal	70	M	36.9	36.4	- 0.5
3	CVS Normal	74	M	26.7	26.0	- 0.7
4	Ventricular Ectopics	80	M	31.3	30.2	- 1.1
5	Ischaemic Heart Disease	76	M	23.0	22.2	- 0.8
6	Ishcaemic Heart Disease	75	M	23.7	23.0	- 0.7
7	Cor Pulmonale	75	M	27.5	27.5	0
8	Aortic Stenosis	69	M	19.3	19.1	- 0.2
9	Alcoholic Heart Disease	72	M	21.0	21.2	+ 0.2
10	Ischaemic Heart Disease	80	F	33.4	32.4	- 1.0
11	Ischaemic Heart Disease	75	F	21.4	20.5	- 0.9
12	Ischaemic Heart Disease	83	F	29.6	30.3	+ 0.7
13	Atrial Fibrillation	75	F	23.8	23.0	- 0.8

Difference in Z_o (ohms) Mean Difference = 0.53 ohms (SD 0.55) Degrees of Freedom = 12
Paired t value = 3.47 ($p < 0.005$)

TABLE II

VALUES FOR BASAL THORACIC IMPEDANCE USING DIFFERENT POSITIONS FOR LEAD I IN 13 ELDERLY SUBJECTS

PATIENT	CARDIAC OUTPUT LEAD I ON NECK L/min	CARDIAC OUTPUT LEAD I ON FOREHEAD L/min	DIFFERENCE L/min	% DIFFERENCE
1	4.3	4.6	+ 0.3	7
2	6.3	6.5	+ 0.2	3
3	7.3	7.7	+ 0.4	6
4	2.9	3.1	+ 0.2	7
5	4.4	4.7	+ 0.3	7
6	6.6	7.0	+ 0.4	6
7	7.9	7.9	0	0
8	7.7	7.9	+ 0.2	3
9	4.7	4.6	− 0.1	2
10	2.9	3.1	+ 0.2	7
11	7.0	7.6	+ 0.6	9
12	3.9	3.7	− 0.2	5
13	3.6	3.9	+ 0.3	8

Difference in cardiac output (L/min)

Mean difference = 0.22 L/min (SD 0.22)
Paired t value = 3.6 ($p < 0.005$)

TABLE III

VALUES FOR IMPEDANCE CARDIAC OUTPUT USING DIFFERENT POSITIONS FOR LEAD I IN 13 ELDERLY SUBJECTS

circumferential lead on the forehead is used then a higher value for the impedance cardiac output will be obtained due to a reduction in the measured basal thoracic impedance (Z_o). This is important in haemodynamic studies of the elderly and infants where anatomical factors may preclude positioning two circumferential leads on the neck.

Lead I should be placed on the neck where possible and if this is not practical, then serial recordings of stroke volume and cardiac output values should be measured with a constant lead configuration or unnecessary errors will occur. In most studies in individual subjects the small differences in Z_o and cardiac output although statistically significant may not be of clinical importance.

MEASUREMENT OF THE LENGTH OF THE THORAX IN THE IMPEDANCE TECHNIQUE IN THE ELDERLY

Most workers have followed the example of Kubicek and his colleagues (14) and have used L (cms) in the formula for deriving the volume as the mean of the distances beween the second and third circumferential leads measured in the midline at the front and back of the thorax (L/2). Other groups have only measured the distance on the front of the chest in studies in animals (38) and humans (39-42). Measurements of the length at the front and the back may differ considerably in elderly subjects with kyphosis and a study was undertaken to assess the importance of the difference in these two measurements in young and elderly subjects.

In one previous study L was determined from the mean of six measurements made between the two inner electrodes taken at the anterior and posterior midlines, midclavicular lines and scapular lines (41). A second study was therefore performed in elderly

patients to assess the effect of any differences between L/2 and L/6.

Subjects and Methods

First Study Twelve healthy young adults (6 males and 6 females, age range 24–48 years) and 39 elderly subjects (21 males and 18 females, age range 60–91 years) with no clinical, radiological or electrocardiographic evidence of cardiovascular disease were studied. Four circumferential electrodes were applied in the standard fashion as described in page 14 and L was measured at the front and the back in the midline between the inner two electrodes.

Second Study Seventeen elderly patients (6 males and 11 females, age range 63–86 years) under the care of the University Department of Geriatric Medicine were included in this study. Three patients had no clinical, radiological or electrocardiographic evidence of cardiovascular disease. The remainder had cardiac disorders as described in Table IV. Four circumferential electrodes were applied as in the first study and L was measured as the mean of the distances in the midline at the front and the back of the thorax between the two inner electrodes (L/2) and as the mean of six measurements made between the two inner electrodes taken at the anterior and posterior midlines, midclavicular lines and scapular lines (L/6).

Results

First Study Detailed results are displayed in Appendix 1 and a summary of the data is presented in Table V. In young men the average difference between L_{front} and L_{back} was 9.6 cm (38.5%) and very similar values were obtained in elderly males. In young women

PATIENT	DIAGNOSIS	AGE (YRS)	SEX	$L/_2$ (cm)	$L/_6$ (cm)	Difference %
1	Cardiovascular Normal	77	M	28	29	+ 3.6
2	Cardiovascular Normal	68	M	21.5	23	+ 7.0
3	Ischaemic Heart Disease	76	M	26	27	+ 3.9
4	Old Myocardial Infarction	78	M	25	26	+ 4.0
5	Left VentriculAr Failure	79	M	23.5	24.5	+ 4.3
6	Mitral Regurgitation	83	M	30	30.5	+ 1.7
7	Cardiovascular Normal	85	F	23	23	0
8	Ventricular Ectopic Activity	78	F	26	28	+ 7.7
9	Supraventricular Tachycardia	86	F	25	27	+ 8.0
10	Atrial Fibrillation	63	F	20	22	+ 10.0

TABLE IV

LENGTH OF THORAX MEASURED AS THE MEAN OF THE DISTANCES IN THE MIDLINE AT THE FRONT AND THE BACK ($L/_2$) AND AS THE MEAN OF SIX MEASUREMENTS MADE BETWEEN THE TWO INNER ELECTRODES TAKEN AT THE ANTERIOR AND POSTERIOR MIDLINES, MID-CLAVICULAR LINES AND SCAPULAR LINES ($L/_6$) IN 17 ELDERLY SUBJECTS.

PATIENT	DIAGNOSIS	AGE (YRS)	SEX	$L/_2$ (cm)	$L/_6$ (cm)	Difference %
11	Aortic Stenosis	84	F	28	30	+ 7.1
12	Aortic Stenosis	80	F	30	30	0
13	Left Ventricular Hypertrophy	72	F	27	28.5	+ 5.6
14	Congestive Cardiac Failure	78	F	27.5	29	+ 5.5
15	Mitral Regurgitation	74	F	25	27	+ 8.0
16	Hyperthyroidism	76	F	28	29	+ 3.6
17	Hypothyroidism	85	F	21	22	+ 4.8

TABLE IV (Cont'd)

YOUNG

	MEAN AGE (YEARS)	L_{FRONT} (CM)	L_{back} (cm)	Difference (cm)	$L_b - L_f$ DIFF. %	$L/_2$ (cm)
MALES (6)	33 (25-48)	25 (SD 1.5)	34.6 (SD 3.5)	9.6 (SD 3.2)	38.5	29.8 (SD 2.3)
FEMALES (6)	27 (24-31)	23.1 (SD 1.9)	26.7 (SD 2.7)	3.6 (SD 2.7)	15.8	24.9 (SD 1.9)
	Wilcoxon Test (P)	N.S.	< 0.05			< 0.02

ELDERLY

MALES (21)	76 (60-86)	24 (SD 2.8)	34.8 (SD 3.8)	10.8 (SD 3.6)	45.9	29.4 (SD 2.8)
FEMALES (18)	78 (61-91)	18.3 (SD 3.5)	30.7 (SD 4.7)	12.4 (SD 5.4)	72.3	24.5 (SD 3.1)
	Wilcoxon Test (P)	< 0.01	< 0.01			< 0.01

KEY N.S. : Not significant
SD : Standard deviation

TABLE V

MEASUREMENTS OF L_{front} AND L_{back} IN 12 HEALTHY YOUNG ADULTS AND 39 ELDERLY SUBJECTS

very similar values were obtained in elderly males. In young women the average difference was smaller than in the males at 3.6 cm (15.8%) but in elderly females L_{front} was shorter and L_{back} relatively greater because of a tendency to kyphosis; the average difference was 12.4 cm (72.3%). Males and females in both age groups had similar values for L/2 although in males L/2 was on average 5 cm greater.

In young females there was little difference between L_{front} and L/2 (8%) but in elderly females there was a considerable difference (34%). In young men the difference was 19% and elderly males 23%.

Second Study The results of this study are detailed in Tables IV and VI. Values for L/6 were systematically higher than for L/2 by 5% (range 0 - 10%) and these were significantly different by a paired t test ($t = 7.7$, $p < 0.001$). Derived values for L/6 cardiac output were observed to be systematically greater than for L/2 cardiac output by 9.8% (range 0 - 21.8%) and these values were significantly different by a paired t test ($t = 5.7$, $p < 0.001$).

Discussion

In previous studies of young or middle aged adults L_{front} was used and in two of these studies, which were correlative with other methods of cardiac output measurement, more accurate results were obtainedwith L_{front} values than with L/2 (42) or L/6 values (41). Keim et al (40) observed that values for impedance stroke index were significantly lower than dye dilution values when L_{front} was used but they commented that this might have been due to the fact that they used L_{front} instead of the greater values which obtain with L/2.

There is little difference between L_{front} and L/2 in young

PATIENT NO.	C.O. L/min ($L/_2$)	C.O. L/min ($L/_6$)	DIFFERENCE %
1	5.6	5.7	+ 1.8
2	5.5	6.7	+ 21.8
3	4.3	4.6	+ 7.0
4	3.8	4.1	+ 7.9
5	3.4	3.6	+ 5.9
6	11.3	11.6	+ 2.7
7	2.8	2.8	0
8	6.1	7.1	+ 16.4
9	3.8	4.4	+ 15.8
10	4.4	5.3	+ 20.5

TABLE VI

DERIVED IMPEDANCE CARDIAC OUTPUTS USING $L/_2$ AND $L/_6$ IN 17 ELDERLY SUBJECTS

PATIENT NO.	C.O. L/min ($L/_2$)	C.O. L/min ($L/_6$)	DIFFERENCE %
11	5.0	5.6	+ 12.0
12	8.9	8.9	0
13	8.2	9.0	+ 9.8
14	4.8	5.4	+ 12.5
15	5.2	5.9	+ 13.5
16	5.7	6.2	+ 8.8
17	2.0	2.2	+ 10.0

TABLE VI (Cont'd)

females but there is a + 19-23% difference in men and a + 34% difference in elderly females. The use of L_{front} rather than L/2 in the impedance stroke volume formula will tend to underestimate values for the stroke volume and cardiac output particularly in elderly females and the use of L/6 values will tend to overestimate the cardiac output in elderly subjects by approximately 10% compared to cardiac output values derived from L/2.

In studies of the elderly, therefore, the length should be measured as the mean of the distance between the inner two electrodes on the front and the back of the thorax in the midline to minimize the difference between L_{front} and L_{back} especially in the elderly kyphotic female. It is unlikely that the use of L/6 values will be more accurate as most workers have reported that the standard impedance technique using L/2 values tends to overestimate the stroke volume.

CHAPTER 3

REPRODUCIBILITY OF THE IMPEDANCE CARDIAC OUTPUT TECHNIQUE

The reproducibility of the technique of impedance cardiography for the measurement of the stroke volume and cardiac output has been found to be very good in studies of healthy adults (2, 13, 42, 44-46) and neonates (47), in hypertensive adults (42), adult cardiac patients (48-50), children with congenital heart disease (22, 51) and pregnant women undergoing Caesarean Section delivery (52). A study of the reproducibility of the technique was undertaken in a group of elderly subjects.

Subjects and Methods

The reproducibility of the impedance method for estimation of the cardiac output was determined by a study of 41 patients under the care of the University Department of Geriatric Medicine. Twenty-one females and 20 males were included in the study (age range 61-87 years) (Table VII). Seventeen patients had no clinical, radiological or electrocardiographic evidence of cardiovascular disease. Thirteen patients had evidence of ischaemic heart disease, four had left ventricular hypertrophy, three had atrial fibrillation, one left bundle branch block, one left anterior hemiblock, one aortic stenosis and one patient had mitral regurgitation.

Two estimates for the cardiac output were obtained by the impedance method (pp 14-15) for each patient, within fifteen minutes, at rest.

Results

The results for paired values of the cardiac output are

DIAGNOSIS	FEMALES (21)	MALES (20)
Cardiovascular normal	9	8
Ischaemic heart disease	6	7
Atrial fibrillation	2	1
Left ventricular hypertrophy	2	2
Left bundle branch block	-	1
Left anterior hemiblock	1	-
Aortic stenosis	-	1
Mitral regurgitation	1	-

TABLE VII

REPRODUCIBILITY STUDY OF IMPEDANCE CARDIOGRAPHIC ESTIMATION OF CARDIAC OUTPUT IN 41 ELDERLY IN-PATIENTS

detailed in Tables VIII and IX and are displayed in Figs 3:1 and 3:2. The mean difference between the values obtained by the impedance method was 0.05 litres /minute (standard deviation 0.22). There was no significant difference in the paired values by analysis with the paired t test ($t = 1.34$) and the correlation between the paired values was high ($r = 0.99$, $p < 0.001$).

Discussion

This study has confirmed that the impedance method of estimating the cardiac output is highly reproducible in elderly adults with or without cardiac disease who are at rest. In previous studies, the reproducibility of the impedance method has been shown to be as good or better than the reproducibility of standard methods of measuring the cardiac output, i.e. the dye dilution method (13, 22, 42, 48-9), the thermodilution method (45, 52) and the technique of effective pulmonary capillary blood flow (47) (see Appendix 2).

IMPEDANCE CARDIAC OUTPUT

CARDIOVASCULAR DIAGNOSIS	AGE (YRS)	FIRST VALUE L/min	SECOND VALUE L/min	DIFFERENCE L/min
Normal	70	4.2	4.3	+ 0.1
Normal	66	3.5	3.5	0
Normal	73	3.4	3.1	- 0.3
Normal	76	5.5	5.3	- 0.2
Normal	78	6.0	6.2	+ 0.2
Normal	61	3.3	3.3	0
Normal	69	7.5	7.8	+ 0.3
Normal	83	2.5	2.6	+ 0.1
Normal	71	6.1	6.1	0
Ischaemic heart disease	78	7.6	7.1	- 0.5
Ischaemic heart disease	71	5.8	5.8	0
Ischaemic heart disease	86	4.3	4.5	+ 0.2
Ischaemic heart disease	80	2.3	2.3	0
Ischaemic heart disease	85	2.0	2.0	0
Old myocardial infarction	70	5.7	5.5	- 0.2
Left ventricular hypertrophy	79	5.2	5.1	- 0.1
Left ventricular hypertrophy	75	3.9	3.9	0
Atrial fibrillation	80	7.3	6.9	- 0.4
Atrial fibrillation	79	3.9	3.5	- 0.4
Left anterior hemiblock	85	4.4	4.3	- 0.1
Mitral regurgitation	74	4.5	4.2	- 0.3

TABLE VIII

PAIRED VALUES FOR IMPEDANCE CARDIAC OUTPUT IN FEMALE PATIENTS (n = 21)

IMPEDANCE CARDIAC OUTPUT

CARDIOVASCULAR DIAGNOSIS	AGE (YRS)	FIRST VALUE L/min	SECOND VALUE L/min	DIFFERENCE L/min
Normal	77	5.6	5.7	+ 0.1
Normal	69	5.8	6.1	+ 0.3
Normal	80	5.6	5.4	- 0.2
Normal	86	5.4	5.6	+ 0.2
Normal	76	7.1	7.4	+ 0.3
Normal	74	7.7	7.3	- 0.4
Normal	72	4.6	4.9	+ 0.3
Normal	75	3.1	2.9	- 0.2
Ischaemic heart disease	70	7.0	6.9	- 0.1
Ischaemic heart disease	73	4.7	4.6	- 0.1
Ischaemic heart disease	87	4.7	4.7	0
Ischaemic heart disease	86	3.4	3.3	- 0.1
Old myocardial infarction	79	3.8	3.4	- 0.4
Old myocardial infarction	76	4.4	4.3	- 0.1
Old myocardial infarction	71	8.2	8.2	0
Atrial fibrillation	84	3.5	3.3	- 0.2
Left ventricular hypertrophy	86	6.1	5.9	- 0.2
Left ventricular hypertrophy	70	10.6	10.7	+ 0.1
Left bundle branch block	70	4.6	5.0	+ 0.4
Aortic stenosis	69	7.6	7.6	0

TABLE IX

PAIRED VALUES FOR IMPEDANCE CARDIAC OUTPUT IN MALE PATIENTS (n = 20)

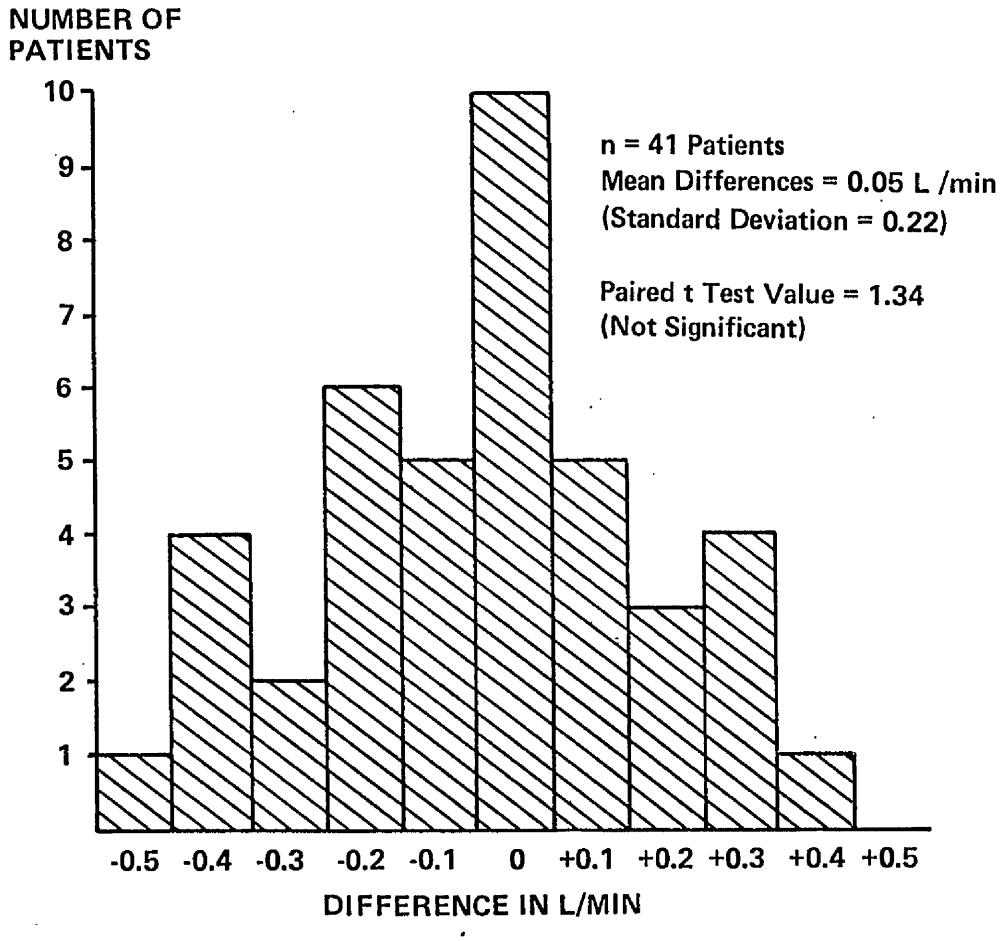


FIGURE 3:1

REPRODUCIBILITY OF IMPEDANCE CARDIAC OUTPUT METHOD

PAIRED VALUES

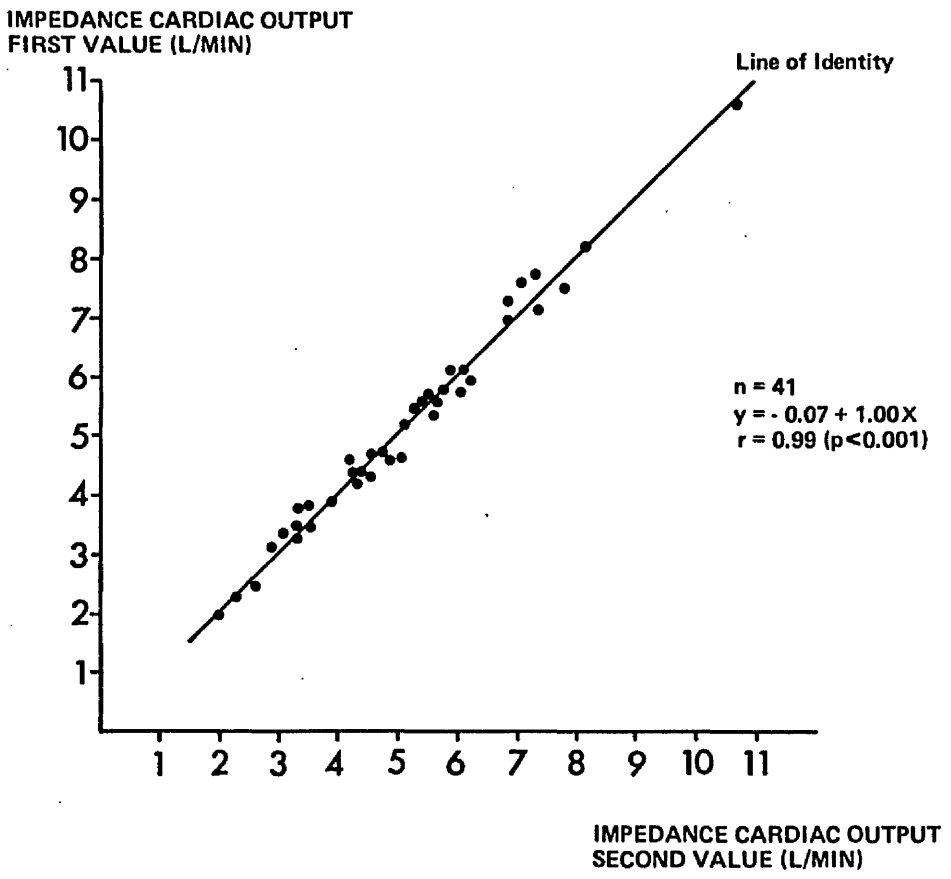


FIGURE 3:2

REPRODUCIBILITY OF IMPEDANCE CARDIAC OUTPUT

PAIRED VALUES

CHAPTER 4

ACCURACY OF THE IMPEDANCE CARDIAC OUTPUT TECHNIQUE

Since Kubicek et al (1966) developed transthoracic impedance plethysmography as a method of estimating cardiac output, its accuracy has been compared with other methods in more than fifty studies (Appendix 3). Invasive techniques of cardiac output measurement are often hazardous, time consuming and require skilled operators (16); they have therefore only a limited role in the investigation of the elderly. As the technique of impedance cardiography is non-invasive, simple and very reproducible, it lends itself to the investigation of cardiac problems in elderly patients. The first documented correlative study of this technique in the elderly was carried out in 1979 in Glasgow (53) and this study was extended to elucidate likely causes for poor correlation in some groups of elderly subjects when an isotopic indicator dilution method of cardiac output measurement was compared.

Subjects and Methods

Correlative studies were performed in 93 patients (47 females and 46 males, age range 64 - 95 years) under the care of the University Department of Geriatric Medicine. The heart was clinically, radiologically, and electrocardiographically normal in 14 patients, eight had chronic obstructive airways disease and the abnormalities present in the remaining 71 are shown in Table X.

At the same session, the cardiac output was determined by impedance cardiography as described in Chapter 2 and an isotopic indicator-dilution method with the patient semisupine.

The isotopic indicator-dilution method is based on the methods

Atrial fibrillation without valvular regurgitation	15
Atrial fibrillation with valvular regurgitation or RBBB	8
RBBB in sinus rhythm	6
LBBB in sinus rhythm	6
Complete heart block	4
Valvular disease in sinus rhythm	11
Ischaemic heart disease - no recent myocardial infarction	12
Ischaemic heart disease - recent myocardial infarction	9

TABLE X

CARDIAC DIAGNOSES IN 71 PATIENTS WITH HEART DISEASE

of Veall et al (54) and others (55-57). 100 μ Ci of ^{99}Tc-labelled human serum albumin in 2 ml saline was injected rapidly into an antecubital vein with the arm elevated and immediately flushed in with a further 10-15 ml of saline. Its passage through the heart was recorded with collimated 5 cm scintillation counter (Nuclear Enterprises DM1-2), centred over the left second intercostal space close to the sternum, and connected to a scaler-ratemeter (Nuclear Enterprises SR-3) and chart recorder. After 5 minutes, blood was taken from another arm vein for determination of specific activity and measurement of blood volume, and tissue background activity was counted over the anterior surface of one thigh (57). Duplicate measurements separated by 5-10 minutes were made and the results averaged. Calculations followed those of Donato et al (57).

Results

The results are detailed in Appendix 4 and are summarised in Table XI and Figs 4:1 to 4:10.

Cardiovascular Normals (n = 14)

Good correlation was observed over a range of cardiac output values from 2.8 - 9.5 L/min (Fig 4:1). The mean difference of the two methods was 0.2 L/min and there was no significant difference when a paired t test was applied. The correlation coefficient (r) was 0.937 ($p < 0.001$). There was a tendency for the impedance method to underestimate lower isotope cardiac output values and to overestimate higher values.

Ischaemic Heart Disease (n = 21)

Satisfactory correlation was observed over a range of cardiac output values from 2.3 - 9.4 L/min (Figs 4:2 and 4:3). There were no significant differences when paired t tests were applied to

CARDIAC DIAGNOSIS	SUBJECTS	PAIRED t TEST	MEAN DIFFERENCE (STANDARD DEVIATION) BETWEEN TECHNIQUES (L/min)	CORRELATION COEFFICIENT r	p	REGRESSION EQUATION
Cardiovascular normals	14	N.S.	0.2 (0.9)	0.937	< 0.001	y = - 0.6 + 1.2 x
Ischaemic heart disease - no recent infarction	12	N.S.	0 (1.0)	0.873	< 0.001	y = - 0.7 + 1.1x
Ischaemic heart disease - recent myocardial infarction	9	N.S.	0.2 (1.2)	0.853	< 0.01	y = 0.6 + 0.9x
Left bundle branch block	6	p < 0.05	0.5 (0.4)	0.981	< 0.001	y = 0.9 + 0.7x
Complete heart block	4	N.S.	0.4 (0.6)	0.946	< 0.05	y = - 0.3 + 1.1x
Total	45	N.S.	0.1 (0.9)	0.896	< 0.001	y = - 0.3 + 1.1x

TABLE XI

CORRELATION BETWEEN ISOTOPE (x) AND IMPEDANCE (y) CARDIAC OUTPUT VALUES IN 93 ELDERLY PATIENTS

CARDIAC DIAGNOSIS	SUBJECTS	PAIRED t TEST	MEAN DIFFERENCE (STANDARD DEVIATION) BETWEEN TECHNIQUES (L/min)	CORRELATION COEFFICIENT r	p	REGRESSION EQUATION
Right bundle branch block	6	$p < 0.01$	2.6 (1.9)	0.771	< 0.05	$y = -10.1 + 2.2x$
Atrial fibrillation without valvular regurgitation	15	N.S.	0.1 (1.0)	0.529	< 0.05	$y = 1.8 + 0.5x$
Atrial fibrillation with valvular regurgitation or RBBB	8	$p < 0.05$	2.0 (2.6)	0.295	N.S.	$y = 3.8 + 0.5x$
Valvular disease in sinus rhythm	11	$p < 0.05$	1.1 (1.8)	0.149	N.S.	$y = 4.4 + 0.2x$
Obstructive airways disease	8	N.S.	1.1 (2.4)	- 0.373	N.S.	$y = 7.4 - 0.4x$

KEY N.S. Not significant

TABLE XI (Cont'd)

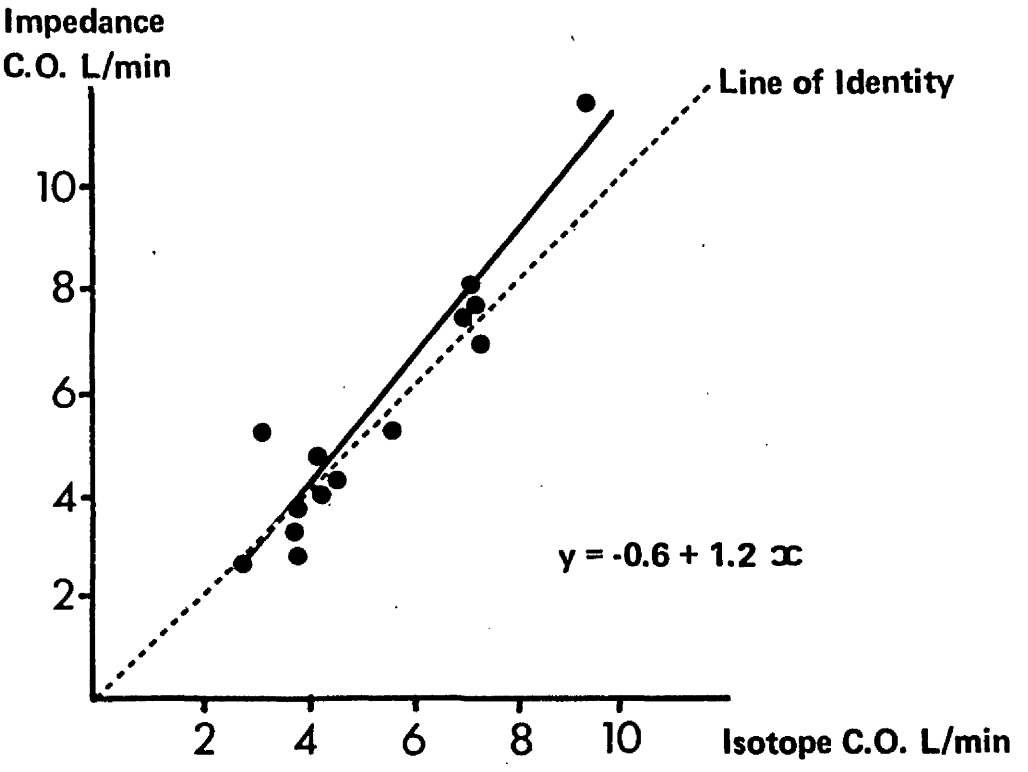


FIGURE 4:1

CARDIOVASCULAR NORMALS (n = 14)

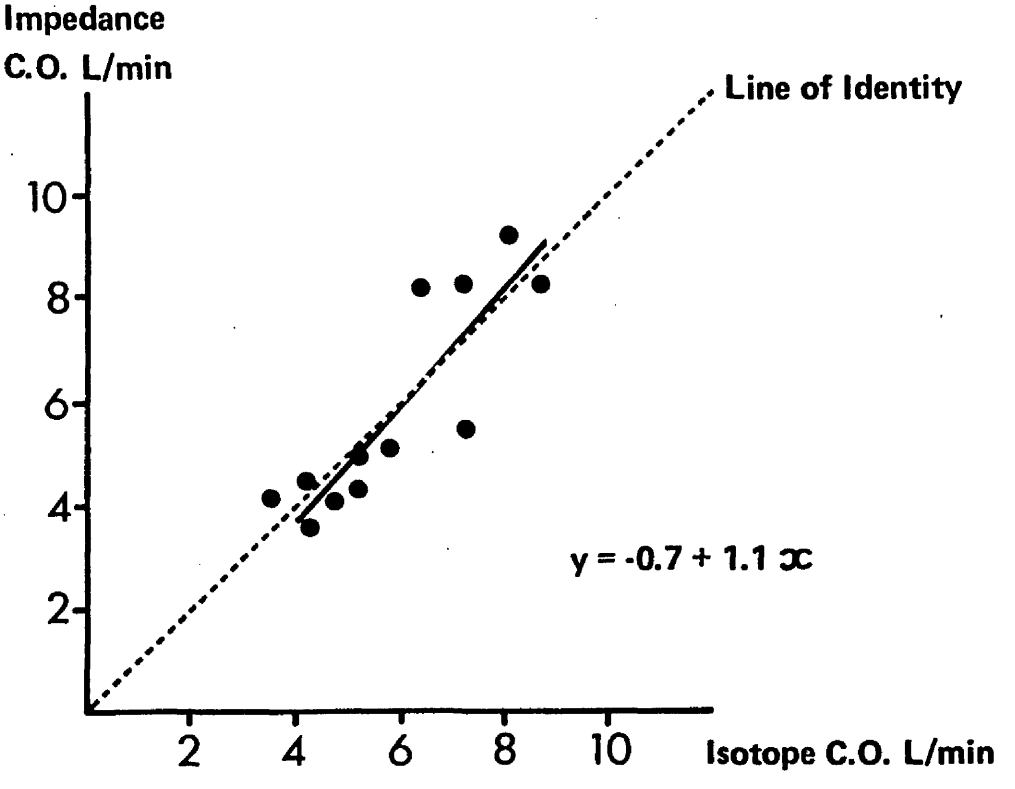


FIGURE 4:2

ISCHAEMIC HEART DISEASE (NO RECENT INFARCT) (n = 12)

values for groups of patients with or without recent acute myocardial infarction and the correlation coefficients (r) were 0.853 ($p < 0.01$) for patients with a recent infarct and 0.873 ($p < 0.001$) in those without a recent infarct.

Conduction Abnormalities (n = 16)

Good correlation was observed in six patients with left bundle branch block (Fig 4:4) ($r = 0.981$, $p < 0.001$) and in four patients with complete heart block ($r = 0.946$, $p < 0.05$) but poor correlation was noted in six patients with right bundle branch block (Fig 4:5) and in five of these patients the impedance value grossly underestimated the isotope cardiac output value.

Atrial Fibrillation (n = 23)

Poor correlation was obtained in patients with atrial fibrillation over a range of cardiac output values from 2.0 - 6.5 L/min (Fig 4:6 and 4:7). In three patients with atrial fibrillation and mitral regurgitation and one patient with tricuspid regurgitation, the impedance valves grossly overestimated the isotope values.

Valvular Disease in Sinus Rhythm (n = 11)

Poor correlation was observed over a range of cardiac output values from 2.4 - 6.3 L/min (Fig 4:8). The impedance values grossly overestimated the cardiac output in two patients with isolated severe mitral regurgitation and in one patient with tricuspid regurgitation. In two patients with mild isolated aortic regurgitation the impedance values showed a minor tendency to overestimate the cardiac output.

Obstructive Airways Disease (n = 8)

A very poor correlation was observed in patients with chronic obstructive airways disease (Fig 4:9). The impedance method

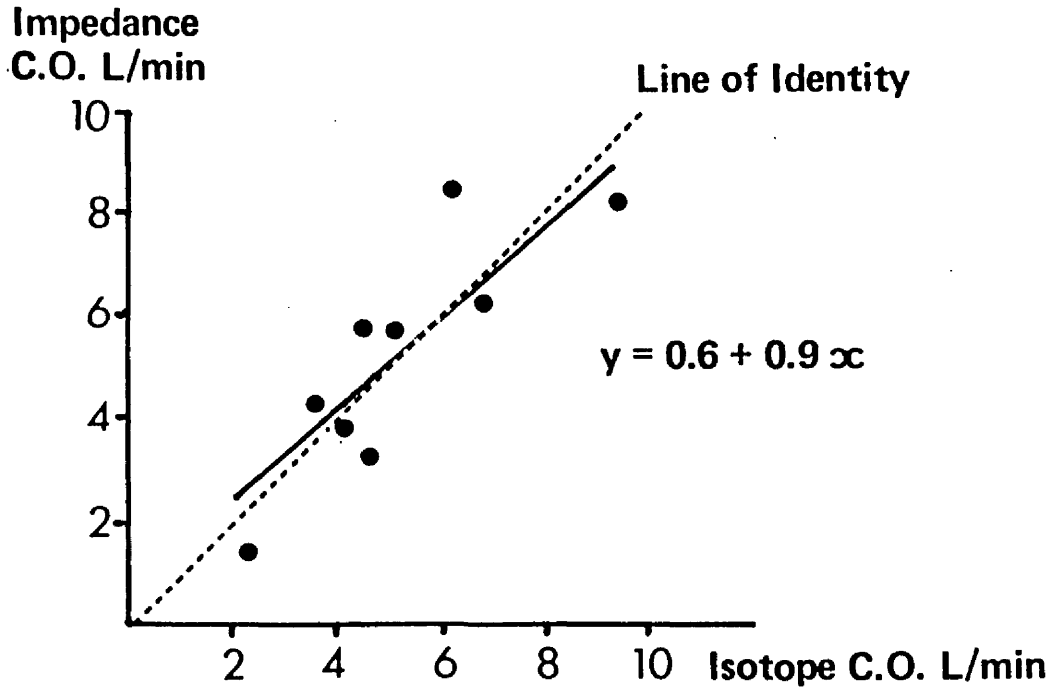


FIGURE 4:3

ISCHAEMIC HEART DISEASE (RECENT INFARCT) (n = 9)

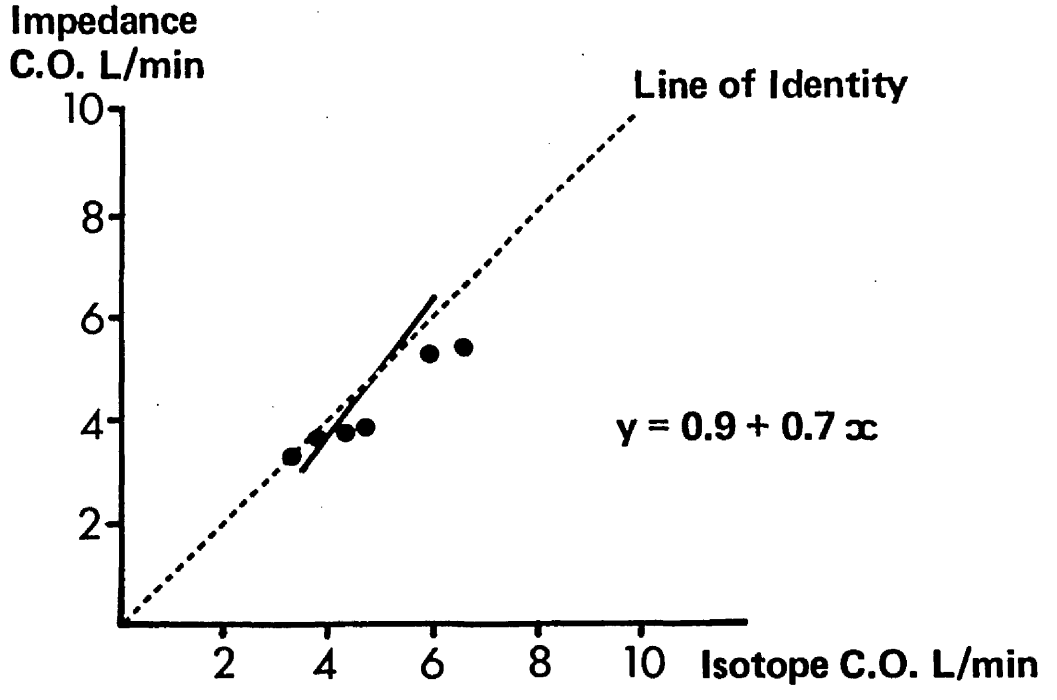


FIGURE 4:4

LBBB (n = 6)

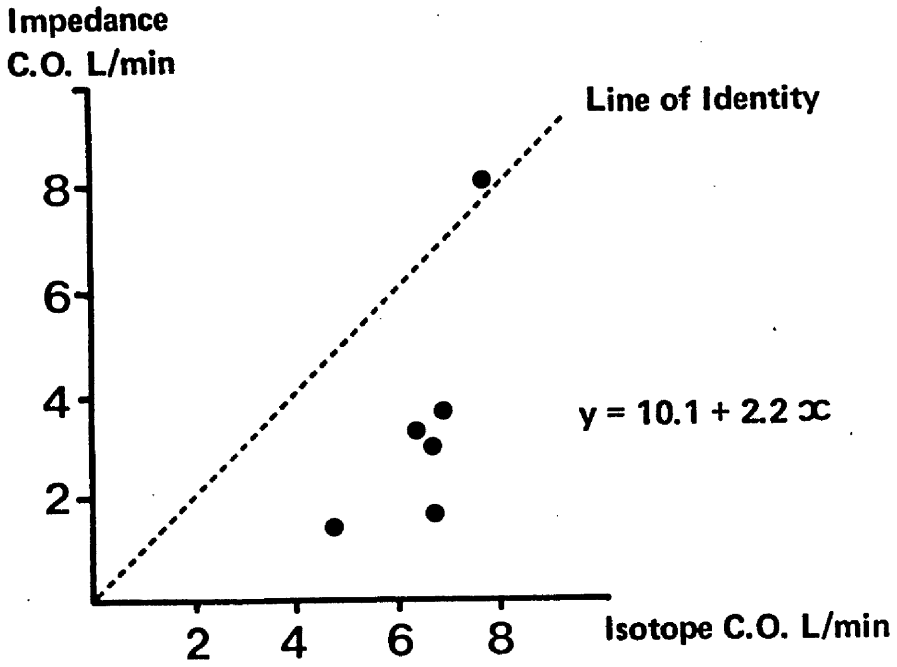


FIGURE 4:5

RBBB (n = 6)

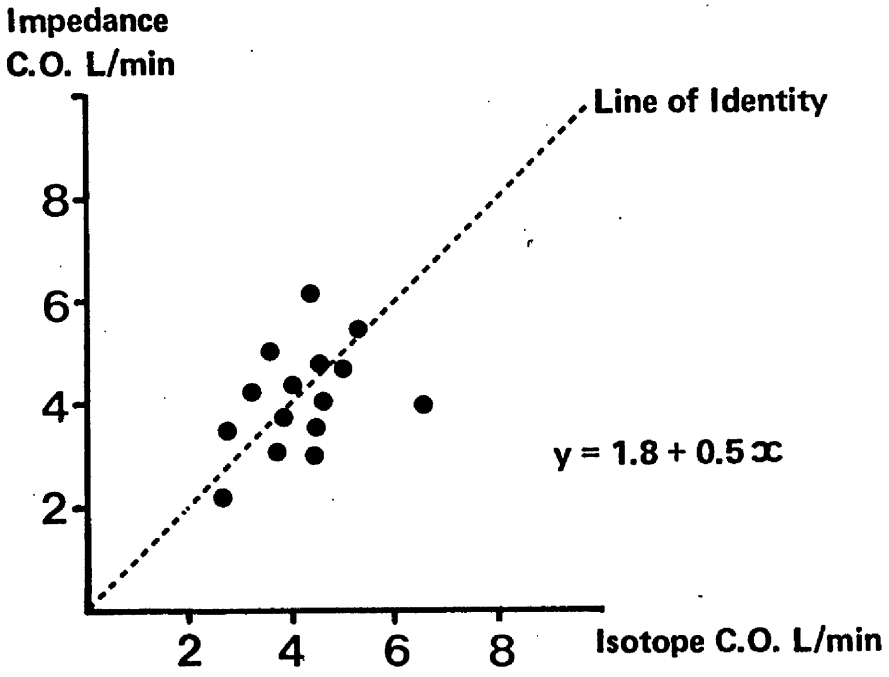


FIGURE 4:6

ATRIAL FIBRILLATION (n = 15)

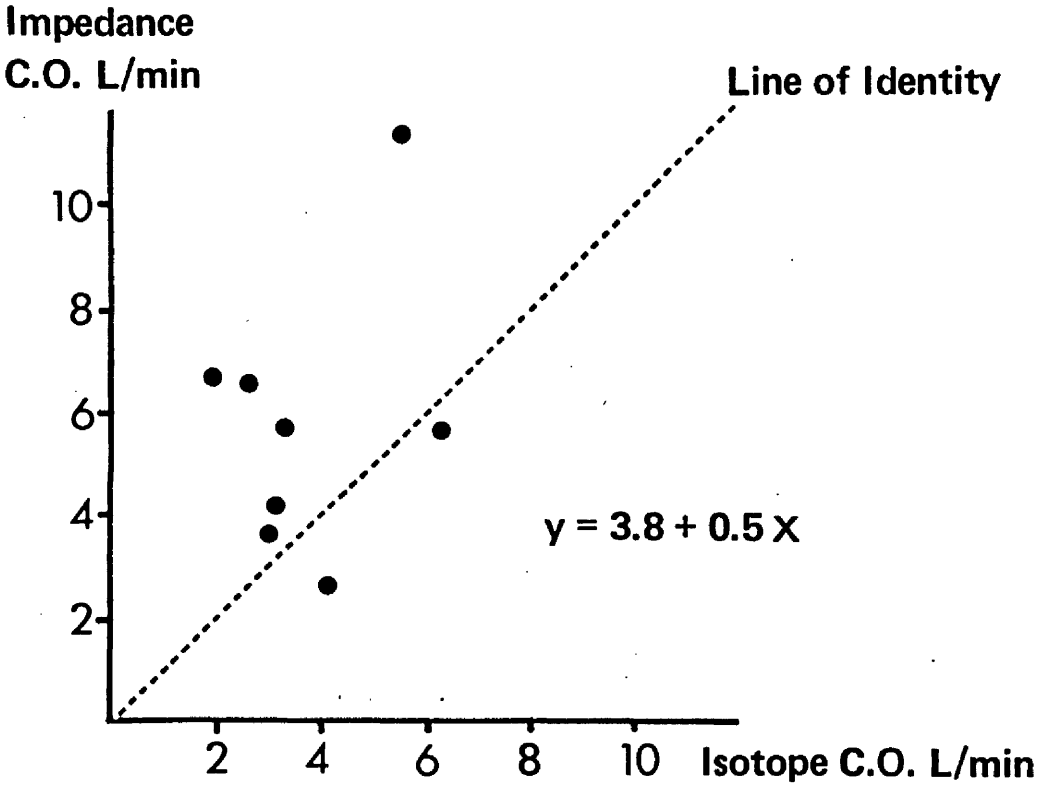


FIGURE 4:7

ATRIAL FIBRILLATION WITH VALVE REGURGITATION (n = 6)

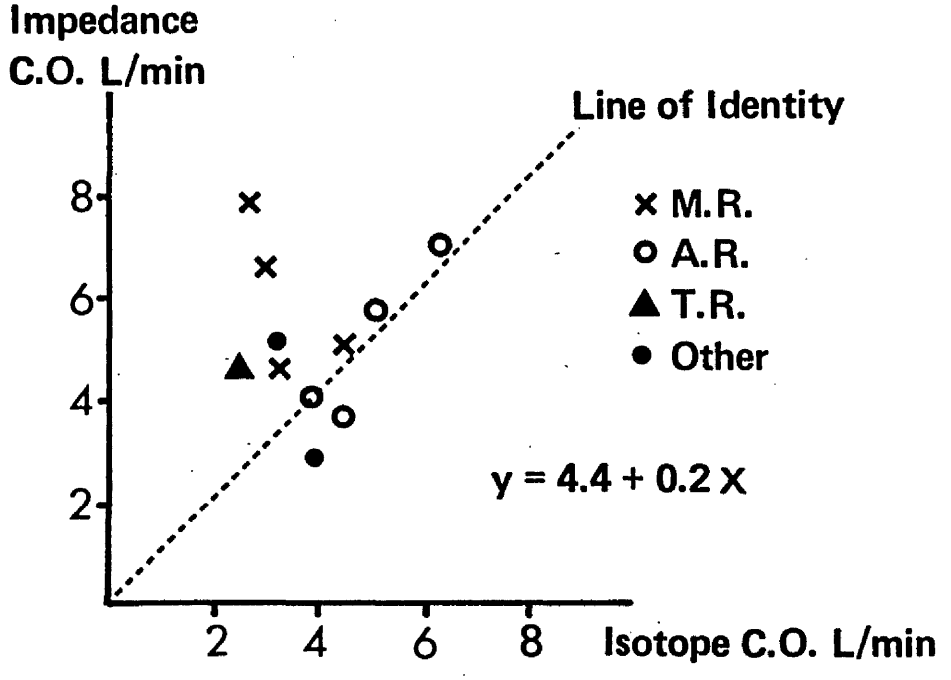


FIGURE 4:8

VALVE DISEASE. SINUS RHYTHM (n = 11)

KEY MR : MITRAL REGURGITATION
AR : AORTIC REGURGITATION
TR : TRICUSPID REGURGITATION

underestimated the cardiac output in six patients but overestimated the cardiac output in two patients with chronic obstructive airways disease complicated by lobar pneumonia.

Summary of Results

Good correlation between the impedance and isotope methods of cardiac output measurement was observed in 45 elderly subjects who were in normal sinus rhythm, in complete heart block, or in whom there was evidence of ischaemic heart disease or left bundle branch block (Fig 4:10) ($r = 0.896$, $(p < 0.001)$.

Poor correlation was associated with the presence of atrial fibrillation, right bundle branch block, valvular regurgitation, or evidence of significant chronic obstructive airways disease.

Discussion

The only function of the heart is to pump blood and the stroke volume and the cardiac output are valuable indices of cardiovascular performance. The importance of the accurate assessment of these indices has been recognised for more than 100 years, despite the many technical difficulties involved in their precise measurement (58). Heart disease is the single greatest cause of death and disability in the population over the age of 65 years in the United Kingdom and the accurate measurement of the cardiac output is therefore important in the elderly and in particular changes in the cardiac output induced by physiological stresses, drugs and disease states.

A reliable, accurate method of cardiac output measurement which is easily applied is not yet available (16) and the precision of standard invasive methods, e.g. Fick, dye dilution, thermodilution,

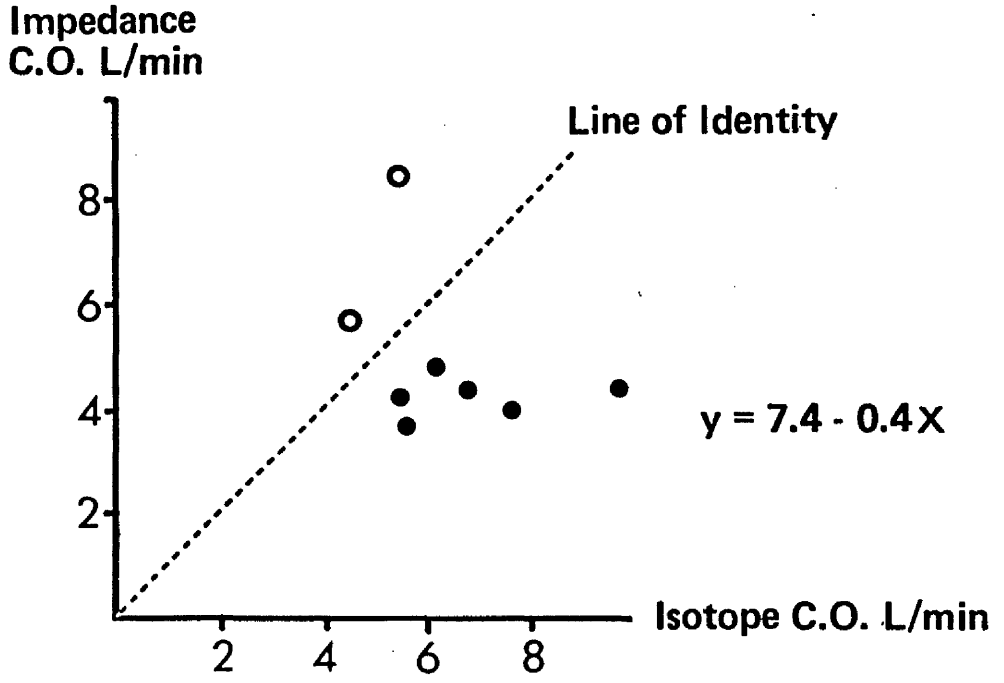


FIGURE 4:9

OBSTRUCTIVE AIRWAYS DISEASE (n = 8)

KEY : o :- LOBAR PNEUMONIA

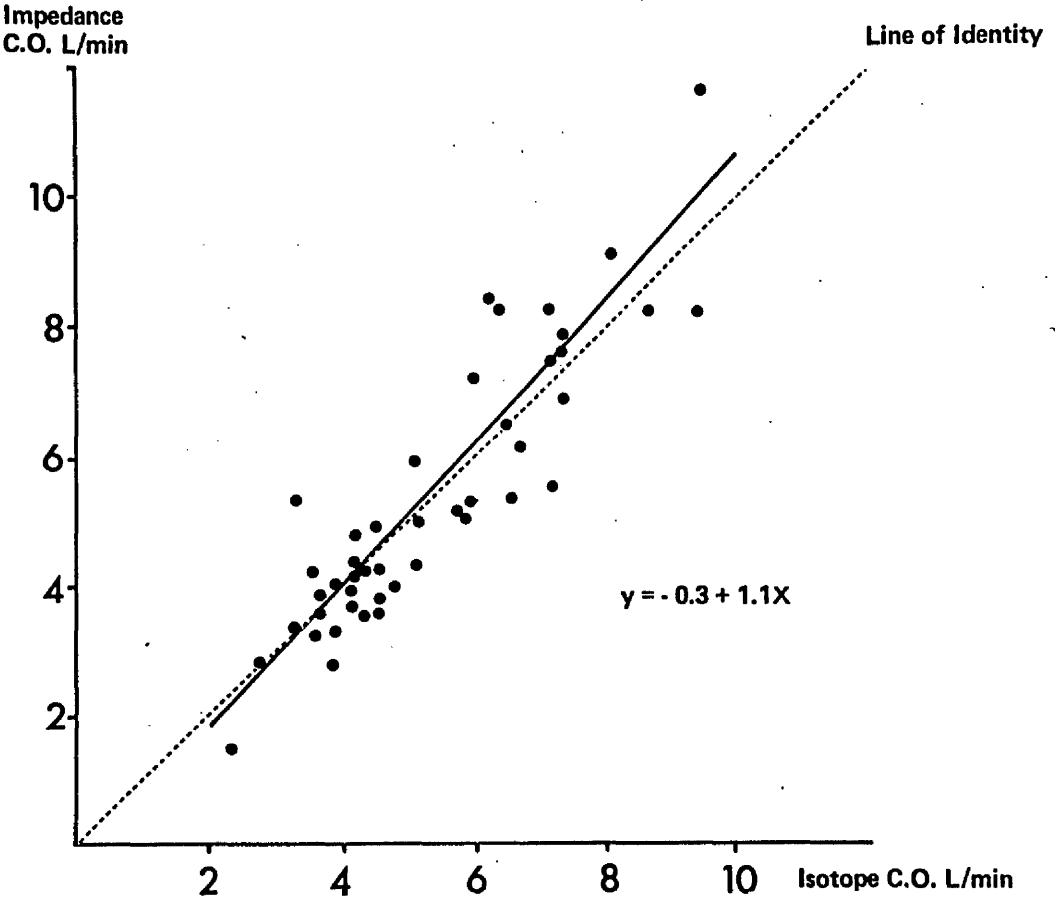


FIGURE 4:10

SINUS RHYTHM WITHOUT RBBB, VALVULAR REGURGITATION OR LUNG DISEASE (n = 45)

radioisotope, and electromagnetic flowmetry is not exactly established and the results of these methods do not show a satisfactory inter-correlation (22). Non-invasive techniques have been developed due to a need for repeated investigations, especially in physiological or pharmacological studies in individuals and this is particularly applicable to the elderly who often have advanced or multiple pathology and in whom invasive techniques are often difficult to perform and are associated with an increased risk of morbidity (59).

Echocardiography provides excellent information about cardiac functional anatomy but does not directly measure blood flow. Left ventricular stroke volume may be derived by this technique but only in patients with no evidence of valvular disease and the accuracy of this method is considerably diminished in high blood flow states and in subjects with small left ventricular volumes (60).

Many workers have adopted the empirical impedance stroke volume formula of Kubicek but have interpreted various components of the equation in different ways, e.g. different resistivity formulae, different measurements of the length of the thorax and different measurements of the first derivative of the impedance change during the cardiac cycle.

In animal work (Appendix 3A), good correlation has been observed in studies comparing the impedance method with dye dilution (38, 61-3), thermodilution (64) and the electromagnetic flowmetry technique (14, 62, 65-8) but poor correlation was observed in one dye dilution study (67) and in a study comparing the aortic systolic pressure area technique (62). The impedance values tended to overestimate the cardiac output (38, 67) especially at higher

cardiac output levels and this was thought to be due to the contribution of right ventricular stroke output in addition to the left ventricular stroke output (22, 30, 62).

In many human studies (Appendix 3B) good correlation between the impedance cardiac output technique and other methods has been obtained in neonates (47), healthy adults (12, 41, 69-71) patients with heart disease (2, 22, 49, 70, 72-81), hypertensives (42, 82), and in patients with thoracic injuries (83), obesity (84), in intensive care (85-7), with surgical conditions (88) and during dialysis (89).

Poor correlation has, however, been observed in studies of healthy subjects (40, 65, 90-92), during caesarean section (52), before and after salt depletion (46), in patients with heart disease (50, 91, 93, 94) and especially in those with valvular regurgitation or left to right shunts (22, 95).

Effects of Cardiac Disorders

The impedance method tends to overestimate the cardiac output (13, 49, 50, 65, 79, 82), particularly in patients with valvular regurgitation (22, 70, 91), left to right shunts (22, 70) or other causes of a large stroke volume (45, 51, 80). Some workers have observed that the impedance technique underestimates the cardiac output in subjects with small stroke volumes (45, 51, 80), atrial fibrillation and mitral stenosis (91), during dialysis (89) and in markedly obese patients (84). This study in the elderly has confirmed the apparent poor correlation between the impedance method and the isotope dilution method in patients with valvular regurgitation and in those in atrial fibrillation.

Cardiac disorders may be associated with inaccuracies in the measured impedance stroke volume due to abnormalities in the

impedance cardiogram waveform. Impedance waveform distortions have been reported in mitral regurgitation (14, 96), aortic regurgitation (97-8) and right bundle branch block (44, 99-100). In elderly patients with pure mitral regurgitation in this study the impedance method overestimated the cardiac output and this supports the findings in one other study (91) but is directly contrary to the observations of two further studies (70, 95) where the impedance method underestimated the cardiac output in similar patients. There is no clear explanation for this discrepancy. In this study two elderly patients had mild isolated aortic regurgitation and there was only a minor tendency for the impedance method to overestimate the cardiac output. Unreasonably high impedance cardiac output values have been observed in aortic regurgitation in several studies (22, 70, 91, 95) and this may be due to the fact that the impedance method actually measures total aortic blood flow (95) and the distorted impedance waveform might reflect more accurately the regurgitant fraction (97).

In five of six elderly subjects with right bundle branch block the impedance cardiac output was underestimated and this was probably due to distortion of the impedance waveform (see Chapter 11).

Effects of Respiration and Chest Disease

Impedance pneumography has been used to monitor the respiratory rate and the tidal volume (19, 101-2). The basal thoracic impedance (Z_o) value fluctuates with the respiratory cycle; the Z_o rises on inspiration and falls on expiration (103-4). Impedance values may therefore be considerably affected by breathing which may distort the baseline and the waveform (105-7). A number of workers

have recommended that the stroke volume should be calculated independent of the baseline of the impedance tracing and that impedance measurements should be taken at the end of expiration or during breath-holding. This manoeuvre is difficult to achieve in many elderly subjects and it should be remembered that respiration influences both the venous return and the heart rate (106) and therefore the wisdom of using only beats at end expiration or during breath-holding could be challenged. Normal quiet respiration has little cyclical effect on the mean stroke volume (108) and it is probably advisable to average individual impedance stroke volume values during two respiratory cycles to improve the accuracy of the technique.

Elderly patients with significant obstructive airways disease had low impedance cardiac output values presumably due largely to artificially high basal thoracic impedance values associated with emphysema and this confirms the findings of previous studies (91, 103, 109). Milder forms of obstructive airways disease are not associated with false low impedance stroke volume and cardiac output values (77). In the two elderly patients in this study with obstructive airways disease and lobar pneumonia, the impedance values overestimated the cardiac output presumably due to a reduced basal thoracic impedance value associated with significant pulmonary consolidation.

Effects of Exercise

Accurate impedance stroke volume measurements may be achieved during exercise up to submaximal workloads (41, 70, 80, 110) but technical problems may occur at submaximal workloads largely due to respiratory and other artefacts producing distortion in the impedance waveform (41). These technical artefacts are usually

abolished by breath-holding or if measurements are taken at least five seconds after exercise has stopped (111).

Relative Changes in Cardiac Output

Despite some doubts about the validity of the impedance technique for measuring absolute cardiac output values it is quite clear that the method will accurately reflect expected relative changes in the cardiac output in individuals and indeed may be a more accurate method of measuring such changes than the dye dilution technique (65). This degree of accuracy has been confirmed during exercise (41, 80) after moderate exertion (2, 13, 90, 94), in pharmacological intervention studies (2, 44, 46, 49, 76, 80), during anaesthesia (84), after dialysis (89) and during the valsalva manoeuvre (45-6) and orthostatic stress tests (44, 49, 69).

If, however, the basic thoracic impedance value (Z_o) is not constant in individual subjects due to the presence of pleural effusion, pulmonary oedema, pneumothorax or overhydration then caution must be exercised in interpreting the impedance stroke volume as an absolute value and this may, as a consequence, make estimation of relative changes in the stroke volume more difficult.

CHAPTER 5

THE KUBICEK FORMULA - BASAL THORACIC IMPEDANCE (Z_o) - REPRODUCIBILITY AND SEX DIFFERENCE

In deriving values for the left ventricular impedance stroke volume most workers have adopted the empirical Kubicek formula (14).

$$\Delta V = \rho \frac{L^2 T}{Z_o^2} (dZ/dt)$$

where ΔV = ventricular stroke volume (c.c.)

ρ = electrical resistivity of blood at 100 k Hz

L = mean distance between the two inner electrodes (cm) (measured front and back)

Z_o = Basic impedance between the inner two electrodes (ohms)

T = ventricular ejection time (seconds)

dZ/dt = first derivative of maximum change in impedance (ohms/sec.)

This formula is attractive because of its simplicity and because it forms the basis for a non-invasive method of measuring the stroke volume on a beat to beat principle. It is however founded on several theoretical assumptions:-

1. The thorax is a cylindrical, uniformly conducting medium.
2. Ventricular stroke ejection is on a square wave basis.
3. There is no arterial run off during ejection.

Other more complex formulae have been proposed by Hawke and his colleagues (112) and Mapleson and his co-workers (113) but they have not been shown to enhance the accuracy of the impedance technique in practice (43).

In the next eight chapters the components Z_o, T, dZ/dt and ρ

will be studied. Aspects of L have been considered in Chapter 2.

Z_o (THORACIC IMPEDANCE)

The basal transthoracic electrical impedance value (Z_o) comprises the total of all the impedances of each separate tissue within the thorax and Z_o is a function of the volumes and ratio of the intrathoracic biological fluids and air. There are therefore two major components 1) Constant component: comprising bone, muscle, fat, connective tissue, heart and lungs, and 2) Variable component due to variation in air and fluids in association with cardiopulmonary function. The most significant variable factor is air due to the high impedance of air in comparison with the low impedance of body fluids (114).

Variations in Z_o are essentially due to changes in non-conductive volumes, mainly air, and conductive volumes which are principally intrathoracic fluids. Clinically, however, a change in Z_o is not specific and cannot necessarily differentiate between changes in air volumes or intravascular or extravascular water volumes.

Z_o values in normal adults generally lie within a range of 25 $\pm$ 7 ohms at 100 kiloherz (16) but they vary with the individual subject's height, weight, body build and chest measurements (115). Difficulties in standardizing electrode placement in multiple recordings in individuals can be partly avoided by using the function Z_o/L (ohms/cm) (15, 114).

REPRODUCIBILITY OF Z_o VALUES

Little is known about the reproducibility of the measured Z_o value in humans. Three studies were completed to clarify this point.

Methods

Study I: Paired values for Z_o were obtained, by standard technique, in 20 elderly subjects (10 males and 10 females) at the same session. Each patient was breathing normally. There was no change in the lead configuration between the readings.

Study II: Paired values for Z_o/L were obtained, by standard techniques, in four elderly subjects at the same session. L (cm) was changed between the two readings.

Study III: Paired values for Z_o/L were obtained, by standard technique, in nine elderly subjects at two separate sessions at least one week apart. L(cm) was different at the two readings.

Results

Study I: The reproducibility of 20 paired Z_o values at the same session was excellent (mean difference 0.15 (S.D. 0.15) ohms or less than 0.5%).

Study II: The reproducibility of four paired values for Z_o/L, at the same session, with a change in L(cm), showed a variation of up to 21% (average 8%) (Table XII).

Study III: The reproducibility of nine paired values for Z_o/L at at least one week's interval was good but there was an average variation of 8% (Table XIII).

Discussion

The reproducibility of Z_o readings at the same session in individual subjects is very high and the small variation of less than 0.5% may be due to respiratory excursion or even cardiac activity (11). A displacement of the circumferential lead configuration to produce a difference in L of up to 9 cm (average 4 cm) will be associated with a variation of the ratio Z_o/L by on

	First Reading			Second Reading			Difference in Z_o/L
Subject	Z_o (ohms)	L (cm)	Z_o/L ohms/cm	Z_o (ohms)	L (cm)	Z_o/L ohms/cm	
1	23.0	22.5	1.02	28.4	27.5	1.03	0.01 (1%)
2	23.6	30.0	0.79	27.7	36.0	0.77	0.02 (3%)
3	20.3	29.8	0.68	22.5	35.0	0.64	0.04 (6%)
4	16.5	26.5	0.62	18.4	33.5	0.55	0.13 (21%)
Mean Values (Standard deviation)			0.78 (0.18)			0.76 (0.18)	Mean 8%

TABLE XII

Z_o/L ohms/cm. TWO VALUES WITH DIFFERENT L VALUES IN FOUR ELDERLY SUBJECTS AT THE SAME SESSION

	First Reading			Second Reading			Difference in Z_o/L
Subject	Z_o (ohms)	L (cm)	Z_o/L ohms/cm	Z_o (ohms)	L (cm)	Z_o/L ohms/cm	
1	30.7	33.5	0.92	29.2	35.0	0.83	0.09 (10%)
2	25.7	28.3	0.91	22.4	29.0	0.77	0.14 (15%)
3	24.2	25.5	0.95	18.5	16.5	1.12	0.17 (18%)
4	29.2	25.0	1.17	28.2	24.0	1.18	0.01 (1%)
5	30.3	28.5	1.06	23.9	23.0	1.04	0.02 (2%)
6	32.7	28.0	1.17	25.2	24.0	1.05	0.12 (9%)
7	19.0	20.0	0.95	20.4	21.0	0.97	0.02 (2%)
8	29.4	23.5	1.25	21.4	18.9	1.13	0.12 (10%)
9	27.3	25.0	1.09	26.0	25.5	1.02	0.07 (6%)
Mean Values (Standard deviation)			1.05 (0.13)			1.01 (0.14)	(8%)

TABLE XIII

Z_o/L ohms/cm. TWO VALUES WITH DIFFERENT L VALUES IN NINE ELDERLY SUBJECTS AT SEPARATE SESSIONS AT LEAST ONE WEEK APART

average 8% and this is a greater variation than has been previously reported in one small study of three patients where the variation was considered to be negligible at 3% (114). It would appear appropriate to measure the function Z_o/L for each subject when multiple recordings are required and where possible the value for L should be kept constant to minimise errors due simply to changes in the lead configuration.

SEX DIFFERENCE IN Z_o VALUES

Despite a considerable literature on the subject of impedance measurement, no information is available about any sex difference in the basal thoracic impedance value. In one study (114) Z_o/L values for 30 normal males in the supine position were 0.822 (S.E.M. 0.021) and for 30 normal females, 1.094 (S.E.M. 0.0184) but the authors did not comment on the sex difference. The following studies were carried out to elucidate any sex difference in Z_o.

Subjects and Methods

Study I: Z_o values were obtained in the supine position by standard techniques, in 12 young normal adult volunteers and 39 cardiovascular normal elderly subjects.

Study II: Z_o/L values were obtained in the supine position, by standard techniques in 12 young normal adult volunteers, 45 cardiovascular normal elderly subjects, 200 elderly patients with heart disease and 16 elderly patients with chronic respiratory disease.

Study III: In 12 young normal adult volunteers (6 males and 6 females) Z_o/L values were obtained in the supine position, by standard techniques and by the application of two additional circumferential leads between the two pick up leads such that the

thorax was divided into equal thirds between the pick up leads. Z_0/L values for each of the three segments were recorded in all subjects (upper, middle and lower segments).

Results

Study I: There were no significant sex differences observed in Z_0 in young or elderly subjects although Z_0 values were higher in the elderly (Table XIV).

Study II: Systematic, significantly higher levels for Z_0/L were observed in females except in those subjects with chronic respiratory disease (Table XV) (unpaired t test).

Study III: Total thoracic and segmental Z_0/L values for upper, middle and lower segments are detailed in Table XVI and displayed in Fig 5:1. The significantly higher values obained for Z_0/L in females is due to a sex difference in the upper segment of the thorax.

Discussion

These studies have confirmed one previous observation that Z_0/L appears to be greater in females (114). The difference is confined to the upper third of the thorax where thoracic impedance values are highest (93). The sex difference is most likely to be due to the relatively greater amount of fat, which has a high resistivity (17), and the relatively smaller amount of skeletal muscle, which has a lower resistivity (17), in the upper thorax of females. This phenomenon has no apparent effect on the accuracy of derived stroke volume studies, however. The increase in Z_0/L observed in men with chronic lung disease is likely to be due to a relative increase in the air content in the thorax which may in turn be associated with artificially high basal Z_0 values and resultant artificially low

Group	Mean Z_o Value (Standard Deviation)		
Young males (n = 6)	22.1 (2.1)	)	
		)	
		)	N.S.
Young females (n = 6)	21.8 (3.6)	)	
Elderly males (n = 21)	27.8 (1.6)	)	
		)	
		)	N.S.
Elderly females (n = 18)	27.0 (5.3)	)	

N.S. Not significant by Wilcoxon Test.

TABLE XIV

Z_o VALUES IN YOUNG AND ELDERLY

Subjects	Males	Number	Females	Number	t value	p value
Young volunteers	738 (48)	6	878 (127)	6	2.5	< 0.05
Normal cardiovascular elderly	916 (184)	26	1122 (188)	19	8.3	< 0.001
Atrial fibrillation	902 (217)	17	1190 (211)	30	7.1	< 0.001
Left bundle branch block	896 (140)	14	1080 (152)	14	5.8	< 0.001
Right bundle branch block	842 (138)	6	1307 (268)	7	4.3	< 0.005
Heart block	720 (67)	6	1011 (151)	10	5.3	< 0.001
Valvular disease	782 (131)	5	1080 (185)	13	3.8	< 0.005
Ischaemic heart disease	919 (155)	35	1170 (220)	25	12.3	< 0.001
Left ventricular hypertrophy	827 (127)	9	1050 (216)	9	3.8	< 0.005
Chronic respiratory disease	1040 (128)	11	1090 (173)	5	2.1	N.S.

TABLE XV

Z_o/L milliohms/cm. SEX DIFFERENCE. GROUP MEAN VALUES (STANDARD DEVIATIONS)

	Males(n= 6)	Females (n = 6)	t value	p value	Males and Females (n= 12)
Total	738 (48)	878 (127)	2.65	< 0.01	808 (117)
Upper segment	979 (44)	1339 (218)	4.34	< 0.025	1159 (241)
Middle segment	475 (72)	517 (89)	1.02	N.S.	496 (80)
Lower segment	517 (95)	544 (108)	1.19	N.S.	525 (99)

TABLE XVI

Z_o/L milliohms/cm VALUES. TOTAL THORACIC AND SEGMENTAL VALUES IN 12 YOUNG, ADULT VOLUNTEERS (MEANS AND STANDARD DEVIATIONS)

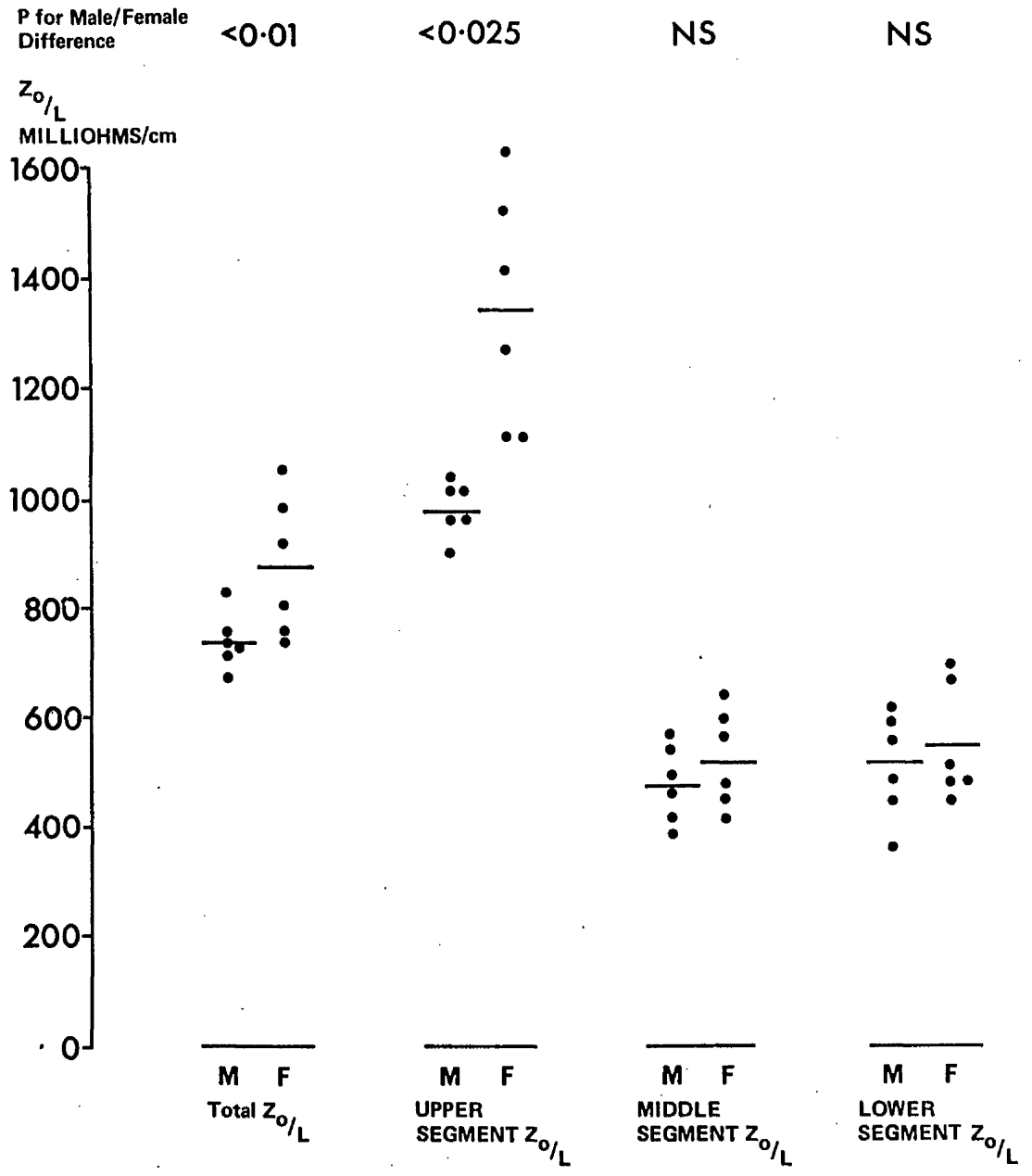


FIGURE 5:1

TOTAL AND SEGMENTAL THORACIC Z_o/L VALUES

stroke volumes measurements (91, 103, 109).

CHAPTER 6

BASAL THORACIC IMPEDANCE (Z_o)-VITAL CAPACITY AND INTRATHORACIC FLUID VOLUMES

Variations in Z_o are due to changes in non-conductive volumes, mainly air, and conductive volumes which are principally intrathoracic fluids.

VITAL CAPACITY AND Z_o VALUES

The electrical impedance technique has been used to monitor various aspects of respiration (19, 102, 104, 116-24). All of these studies have shown that Z_o increases with inspiration and decreases with expiration. The value for Z_o can vary as much as two ohms in lungs which have been inflated to total lung capacity and then deflated to residual volume level (125). Minimum Z_o values are usually observed at the end of normal expiration (126) and in experiments in dogs an almost linear relationship has been observed between the impedance change and tidal volume in a single lung (127). Kubicek and his colleagues noted that an average tidal volume of 830 ml. was associated with a change in impedance of one ohm in humans (104).

Experimental animal studies (126) have shown an increase in Z_o during the induction of an artificial pneumothorax and this observation has been confirmed in clinical studies where a small change in Z_o has proved to be a useful indicator in the early detection of pneumothorax in neonates (128).

The rise in Z_o associated with inspiration is probably largely due to changes in lung tissue resistivity as a result of aeration and also to a redistribution of blood volume within the lungs (104, 116, 118-119, 122-124).

The relationship between the vital capacity and Z_o was studied

in nine normal, young, adult volunteers as breath holding and other respiratory manoeuvres are notoriously difficult to achieve, with any degree of reproducibility, in the elderly.

Subjects and Methods

Z_o/L values were obtained in the sitting position, by standard techniques, in nine normal adult volunteers (5 males). One male had a previous history of bronchial asthma. In each subject, the vital capacity was measured by standard spirometry (three readings were averaged) and the total lung capacity was measured by the helium dilution method in the five males. Thirty values for Z_o were noted across the range of the vital capacity in each subject.

Results

The results are detailed in Tables XVII and XVIII and displayed in Fig 6:1. There was a very close linear relationship observed between the impedance change and the range of the vital capacity in both sexes (r values 0.59 - 0.97) but there was better correlation obtained in females (r values 0.90 - 0.97). Slopes for regression lines were steeper in females.

In the males, the mean total impedance for the vital capacity was 899 (S.D. 254) milliohms/cm. and the mean impedance for the total lung capacity was 1.8 (S.D. 0.39) ohms/cm.

Discussion

These studies have demonstrated a close linear relationship between the air content of the thorax and the impedance value, during respiration, and this is certainly the situation across the range of the vital capacity and probably the total lung capacity. A sex difference is again apparent, with a greater change in

	Vital Capacity (litres)	$L/_2$ (cm)	Regression Equation Impedance = a + bx % vital capacity (milliohms/cm)		r value	t value	p value
Males			a	b			
1	3.4	37.5	833	0.188	0.61	5.7	
2	4.4	36.5	899	0.207	0.82	8.3	
3	2.9	31.4	839	0.263	0.84	7.8	
4	5.3	31.5	644	0.324	0.75	6.2	
5	3.5	31.0	820	0.416	0.59	3.7	
Females							ALL < 0.01
1	2.7	27.0	1210	0.922	0.90	9.2	
2	2.7	28.0	1003	0.950	0.92	11.6	
3	2.9	27.8	982	1.064	0.91	10.5	
4	3.2	31.3	846	1.002	0.97	22.6	

TABLE XVII

VITAL CAPACITY STUDIES IN NINE HEALTHY YOUNG VOLUNTEERS

Subject	Total Lung Capacity (litres)	Vital Capacity (litres)	Total Impedance in milliohms/cm % of Vital Capacity	Total Impedance in milliohms/cm For Vital Capacity	Total Impedance in ohms/cm for Total Lung Capacity
1	-	3.4	0.188	707	-
2*	11.2	4.4	0.207	757	1.93
3	5.4	2.9	0.263	722	1.34
4	8.6	5.3	0.324	1018	1.65
5	6.1	3.5	0.416	1292	2.25
Mean (SD)			0.280 (0.09)	899 (254)	1.8 (0.39)

* Previous history of asthma.

TABLE XVIII

LUNG VOLUME STUDIES IN FIVE HEALTHY YOUNG MALE VOLUNTEERS

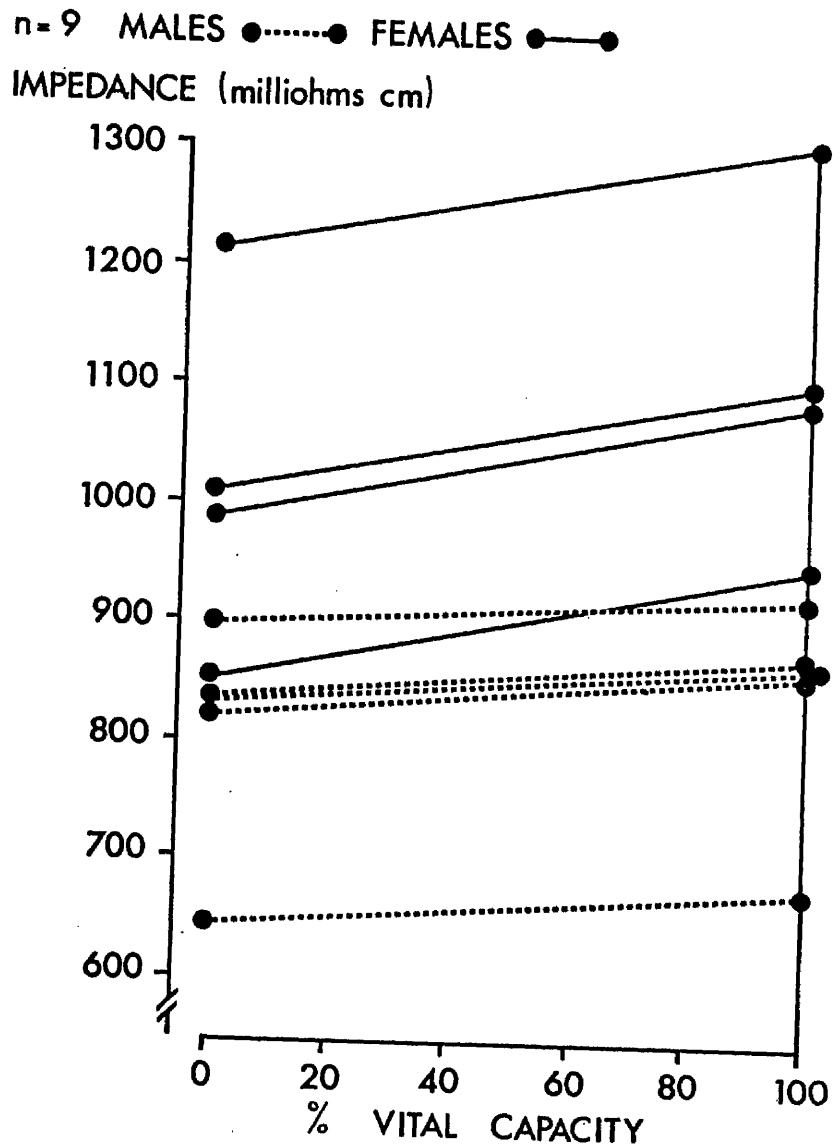


FIGURE 6:1

RELATIONSHIP BETWEEN IMPEDANCE CHANGE AND VITAL CAPACITY

impedance being observed across the range of the vital capacity in females despite their relatively smaller vital capacities (Table XVII). In males the average impedance change across the total lung capacity is of the order of two ohm/cm.

INTRATHORACIC FLUID VOLUMES AND Z_0 VALUES

Change in intrathoracic fluid volumes are associated with changes in Z_0 values. Pathological increases in fluid in the pleural space, chest wall, pericardial sac and as a result of pulmonary oedema are associated with reduced Z_0 values and the impedance method can detect fluid accumulation earlier than conventional methods (125, 129 - 132).

Three studies were completed to elucidate the relationship between Z_0 values and intrathoracic fluid volumes in elderly subjects.

Patients and Methods

Study I : Studies of the relationship between Z_0 and intrathoracic blood volume were carried out in 68 patients (31 females and 37 males, age range 64 - 90 years) under the care of the University Department of Geriatric Medicine. The heart was clinically, radiologically and electrocardiographically normal in 13 patients and the abnormalities present in the remaining 55 are shown in Table XIX.

These elderly patients were studied as part of an investigation of isotope uptake over clinically abnormal joints (133) and the cardiac outputs and pulmonary blood volumes were measured by a radionuclide indicator dilution method employing ^{99}Tc - labelled human serum albumin and external praecordial counting (53, 133). Intrathoracic blood volume values were derived from the measured

Main Diagnosis	No. of Cases
Atrial fibrillation	14
Ischaemic heart disease	8
Left ventricular hypertrophy	10
LBBB in sinus rhythm	8
RBBB in sinus rhythm	2
Left anterior hemiblock	2
First degree heart block	1
Complete heart block	1
Nodal rhythm	1
Aortic valve disease	2
Aortic valve replacement	1
Atrial flutter	1
Supraventricular tachycardia/Tricuspid regurgitation	1
Cor pulmonale	1
Hypothyroid heart disease	2

TABLE XIX

CARDIAC DIAGNOSES IN 55 PATIENTS WITH HEART DISEASE

intrathoracic transit time and cardiac output in each subject. Duplicate measurements for intrathoracic blood volumes and pulmonary blood volumes were made and the results averaged.

Z_o/L values were obtained in the supine position, by standard techniques, and values for the blood resistivity (ρ) were derived as described in Chapter 2.

Study II : Z_o/L values were obtained in the supine position, by standard techniques, in 261 elderly patients (132 females and 129 males) with evidence of cardiac disease. Thirty-nine of these patients (12 females and 27 males) had evidence of congestive cardiac failure but none of the patients studied had evidence of isolated left heart failure or significant pleural effusion.

Study III: Thoracocentesis was performed in 11 elderly patients with pleural effusions as part of their normal treatment regimens (Table XX). Z_o was measured, in each patient, after each aliquot of 50 ml of pleural fluid was withdrawn (average 14 values).

Results

Study I : 73 readings for the intrathoracic blood volume (ITBV) were measured in the 68 patients and these were correlated with derived values for $(Z_o/L)^2\ \rho$ and $\log\ (Z_o^2/L^2\ \rho)$. A poor correlation was observed for $(Z_o/L)^2\rho$ and the ITBV values but a highly significant inverse linear relationship was observed between $\log\ (Z_o^2/L^2\ \rho)$ and the ITBV in the whole group of 68 patients (Fig 6:2) ($t = 3.1$, $r = -0.353$, $p < 0.005$).

In 19 patients, whose paired pulmonary blood volume (PBV) results were within 25% of each other, a highly significant inverse linear relationship was observed between the function $\log\ (Z_o^2/L^2\rho)$ and the PBV ($r = -0.78$, $t = 5.1$, $p < 0.001$).

Clear effusion	Diagnosis	Basal Z_o (OHMS)	Fluid Removed (ml)	Impedance OHMS/L	(Z_o = a + b x fluid ml)	r value	p value
F 70 yrs	Carcinoma of breast	23.9	750	1.98	23.89 + 0.00198x	0.99	< 0.001
F 80 yrs	Mesothelioma	26.0	1500	2.24	26.47 + 0.00224x	0.98	< 0.001
F 89 yrs	Carcinoma of stomach	25.0	1000	1.87	25.18 + 0.00187x	0.98	< 0.001
F 80 yrs	Congestive heart failure	20.5	1000	2.19	20.86 + 0.00219x	0.83	< 0.001
M 81 yrs	Congestive heart failure	20.4	1250	1.80	20.46 + 0.00180x	0.74	< 0.001
M 78 yrs	Congestive heart failure	20.2	760	2.15	20.56 + 0.00215x	0.95	< 0.001
M 79 yrs	Congestive heart failure	29.0	800	1.37	29.12 + 0.00137x	0.97	< 0.001
				Mean (SD)	1.94 (0.30)		

TABLE XX

RELATIONSHIP BETWEEN CHANGES IN Z_o AND FLUID WITHDRAWN IN 11 ELDERLY PATIENTS WITH PLEURAL EFFUSIONS

Haemorrhagic effusion	Diagnosis	Basal Z_o (OHMS)	Fluid Removed (ml)	Impedance OHMS/L	(Z_o = a + b x fluid ml)	r value	p value
F 90 yrs	Mesothelioma	27.2	500	3.86	27.28 + 0.00386x	0.99	< 0.001
F 78 yrs	Carcinoma of bronchus	29.9	600	3.04	29.92 + 0.00304x	0.96	< 0.001
F 84 yrs	Pulmonary infarction	24.4	620	2.56	24.58 + 0.00256x	0.85	< 0.001
M 75 yrs	Carcinoma of bronchus	24.0	1500	2.60	23.94 + 0.00260x	0.99	< 0.001
			Mean (SD)	3.02 (0.60)			

TABLE XX (Cont'd)

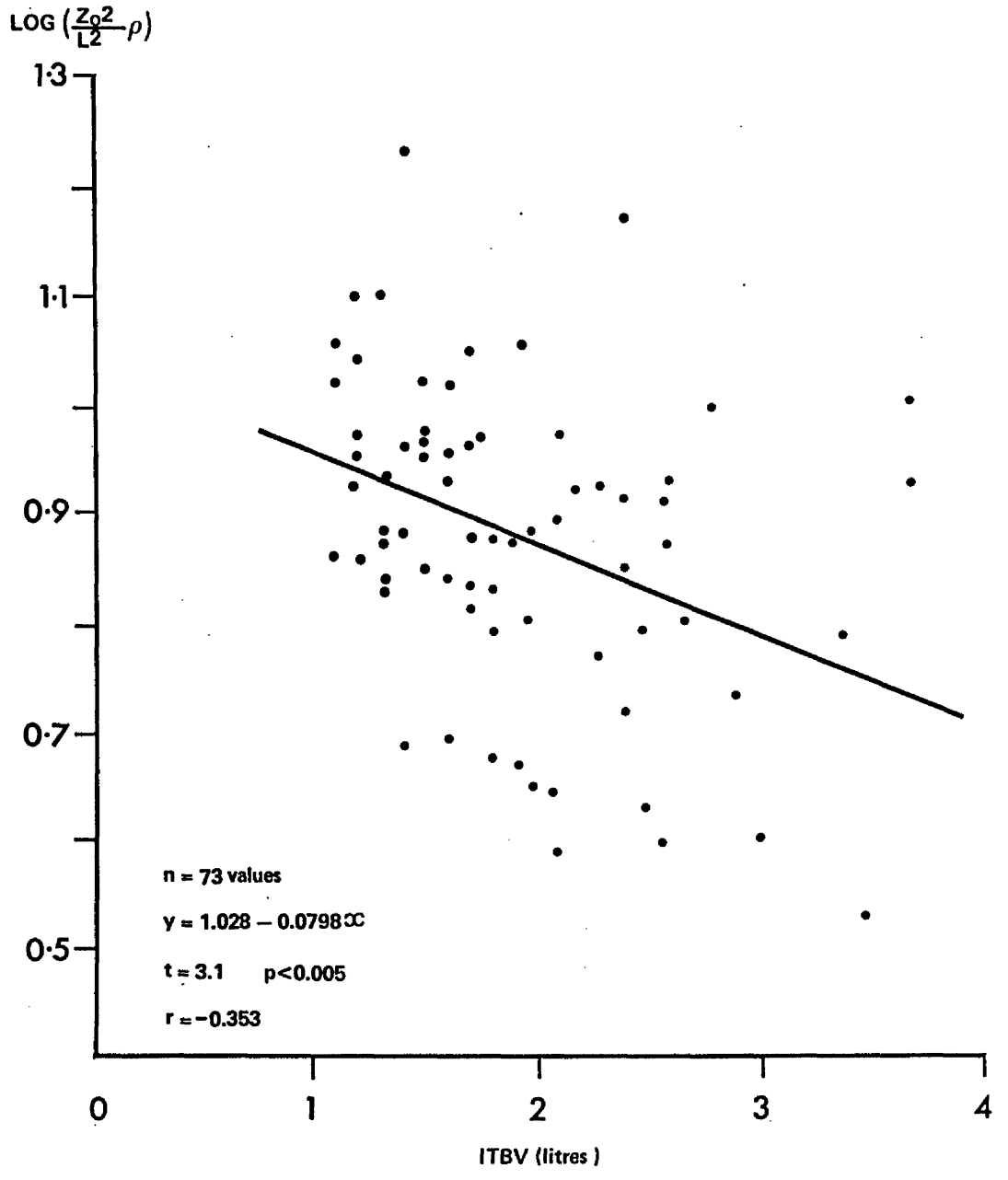


FIGURE 6:2

RELATIONSHIP BETWEEN ITBV AND IMPEDANCE FUNCTION.

73 VALUES IN 68 PATIENTS.

Study II : The results of this study are summarised in Table XXI. Patients of both sexes in congestive cardiac failure had significantly lower values for Z_o/L (for females, $t = 6.2$, $p < 0.001$; for males, $t = 3.1$, $p < 0.01$).

Study III: The relationship between impedance change and pleural fluid volume change after thoracocentesis is detailed in Table XX and Fig 6:3. There was a highly significant linear relationship between the change in Z_o and the volume of pleural fluid withdrawn in all patients (r values from 0.74 to 0.99). Slopes for haemorrhagic effusions were steeper and non-haemorrhagic effusions had a lower impedance value (mean 1.94 ohms/litre cf. haemorrhagic effusion, 3.02 ohms/litres).

Discussion

One previous experimental study in animals demonstrated an inverse relationship between changes in Z_o and artificially induced changes in ITBV in individual dogs (126). In a study of exercise testing of patients with ischaemic heart disease (115) a fall in Z_o was observed and this was considered to be due to an assumed rise in ITBV associated with transient exercise provoked left ventricular dysfunction (134). The above study has, however, clearly demonstrated a significant inverse relationship between a function of basal impedance values and ITBV measurements within a large group of human subjects and must modify the widely accepted view that absolute impedance values only apply to individuals and cannot be compared within groups (126).

An inverse linear relationship between impedance values and PBV has previously been described in individual animals and humans (79, 135-6) and Z_o is known to increase during the Valsalva manoeuvre

Diagnosis	Females (Means and S.D.)	Males (Means and S.D.)
Heart disease with congestive cardiac failure	(n = 27) 1105 (207)	(n = 12) 835 (187)
Heart disease without congestive cardiac failure	(n = 72) 1137 (216)	(n = 59) 877 (159)
	* t = 6.2 ($p < 0.001$)	* t = 3.1 ($p < 0.01$)

* Unpaired t test.

TABLE XXI

DIFFERENCE IN Z_o/L milliohms/cm IN PATIENTS IN CONGESTIVE CARDIAC FAILURE

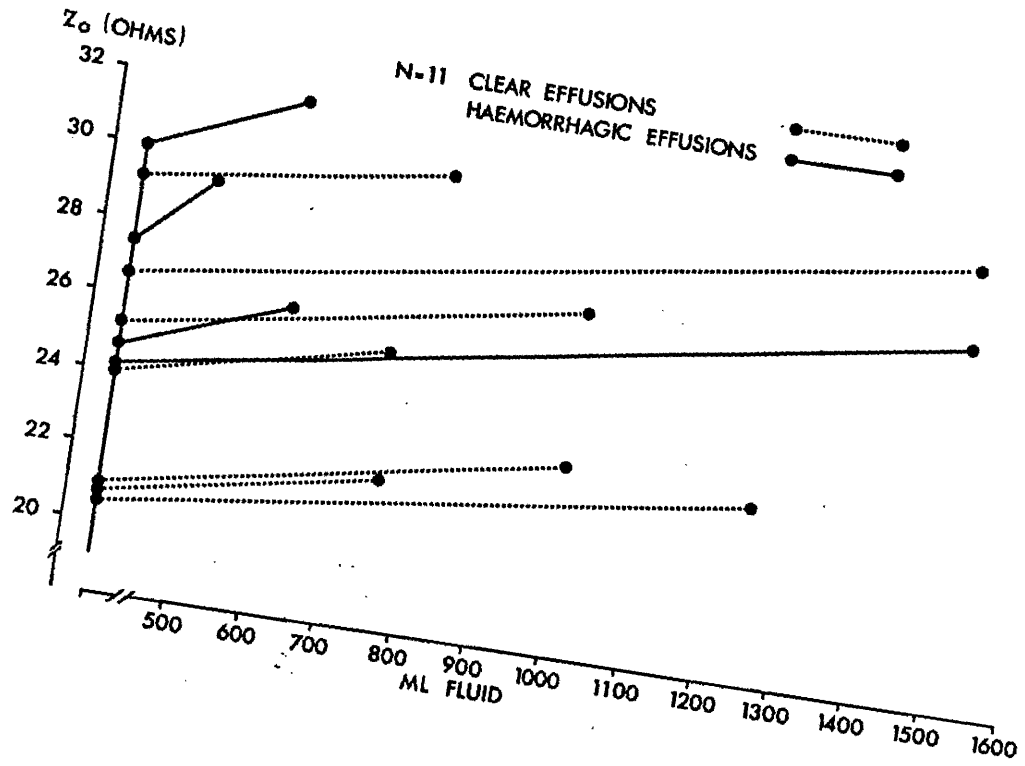


FIGURE 6:3

REGRESSION LINES FOR IMPEDANCE CHANGE AND FLUID WITHDRAWN IN 11 PATIENTS WITH PLEURAL EFFUSIONS

which may simply reflect a fall in the PBV (45). In the above studies in the elderly it has been demonstrated that the inverse relationship between impedance and absolute PBV also applies within groups.

Experimental studies in animals have shown a fall in Z_0 in association with induced pulmonary oedema provoked by alloxan (129) or autotransfusion of blood (126) and the transthoracic impedance technique has been described as a valuable means of detecting incipient high altitude pulmonary oedema (131). In one study of three patients in congestive cardiac failure a good correlation was observed between Z_0/L values and the degree of congestion (114). The above study of 39 elderly patients in congestive cardiac failure has shown a significantly reduced Z_0 value associated with congestive changes compared to the control group. The reduction in Z_0 associated with pulmonary congestion in heart failure is most likely to be due to a combination of an increase in conductivity accompanying an increase in electrolyte containing fluid and a reduction in air volume (137-138).

Accumulation of pleural effusion fluid is associated with a fall in Z_0 values and as little as 25 - 50 ml of fluid injected into the pleural space can be detected by an impedance change in animals (73, 129). Previous clinical case studies of pleural effusion in humans have shown a close linear relationship between impedance change and the volume of pleural fluid aspirated (73, 125, 130, 138) (see Table XXII) but little comment about the character of the effusion fluid has been made in these studies. The present study of 11 cases of pleural effusion has shown very similar regression lines for non-haemorrhagic effusion and steeper gradients for those which are clearly haemorrhagic.

Study	Patient	Diagnosis	Fluid Removed (ml)	Z_o = a + b x fluid ml	r value
Van de Water et al, 1970 (125)	M 60 yrs	Chest wound (6 weeks post drainage)	850	25.16 + 0.00165x	0.99
Van de Water et al, 1971 (73)	F 63 yrs	Carcinoma of bronchus	850	17.57 + 0.00240x	0.90
Van de Water et al, 1973 (138)	F 64 yrs	Leukaemia	1200	25.16 + 0.00203x	0.99

TABLE XXII

CLINICAL CASE STUDIES OF Z_o VALUES AND THORACOCENTESIS IN PATIENTS WITH PLEURAL EFFUSIONS

CHAPTER 7

BASAL THORACIC IMPEDANCE (Z_o) – EFFECTS OF POSTURAL STRESS

Previous studies have reported changes in Z_o with postural manoeuvres. Systematic rises in Z_o on foot down tilt or standing up have been noted in healthy young and elderly adults (44, 139, 140), after acute myocardial infarction (49) and in elderly subjects with postural hypotension (140). In two studies (40, 115) no Z_o change was observed on standing up from the sitting position and in another study (46) little change occurred when foot down tilt of 20^o was applied. In this chapter three studies of the effects of postural stress were carried out to confirm and further elucidate basal thoracic impedance changes which are related to postural manoevures.

Subjects and Methods

Study I: Z_o values were obtained at rest in the supine position on a tilt table by standard technique, in twelve young normal adult volunteers (6 males, 6 females). Two additional circumferential leads were applied between the two pick up leads such that the thorax was divided into equal thirds between the pick up leads. Z_o values for each of the three segments (upper, middle and lower) and for the total thorax were recorded in all subjects at rest and at eight different positions of tilt on the tilt table viz. head down 20^o, 10^o; foot down 10^o, 20^o, 30^o, 45^o, 60^o and 90^o. Values were recorded at one minute intervals.

Study II: Z_o values were obtained at rest in the supine position on a tilt table by standard technique, in six elderly subjects (4 males). Three of these subjects had no clinical, radiological or electrocardiographic evidence of cardiovascular disease, two had

left bundle branch block and one had ischaemic heart disease. Their ages ranged for 70 to 90 years. Z_o values were recorded at 5, 15, 30, 45, 60 seconds and three and five minutes after each subject was tilted instantaneously to the 60° foot down position. The tilt table was then returned to the horizontal position. The sequence of values was recorded on two separate occasions at the same session for each subject and average values for the changes in Z_o were tabulated.

Study III: Z_o values were obtained at rest, in the supine position on a tilt table, by standard technique in 79 elderly subjects (43 males). Forty-eight subjects (27 males) had significant postural blood pressure drop defined as a fall of more than 20 mm in systolic blood pressure on standing and 31 subjects (16 males) had no significant postural blood pressure drop on standing. Each subject was tilted, instantaneously, to the 60° foot down position and Z_o values were recorded at one, three and five minutes after tilting.

Results

Study I : Changes in the total Z_o and the upper, middle, and lower segment Z_o values related to postural changes are detailed in Table XXIII and Figs 7:1 and 7:2. Total and segmental Z_o values fell when the subjects were tilted head down to 10° and 20° and rose commensurately when the degree of foot down tilt was increased from 0° to 90°. The relative Z_o change was most marked in the lower segment of the thorax (Fig 7:2).

Study II: Changes in the Z_o values related to time after instantaneous 60° foot down tilt are detailed in Table XXIV. All of the change in Z_o occurred within the first five seconds and little change occurred thereafter up to five minutes. On resuming

		Head Down Tilt		Foot Down Tilt					
		20°	10°	10°	20°	30°	45°	60°	90°
Total Z_o	M	- 1.6	- 1.0	+ 0.2	+ 2.5	+ 2.7	+ 4.2	+ 5.8	+ 7.7
		(1.8)	(2.2)	(2.9)	(2.4)	(2.1)	(2.6)	(2.5)	(3.3)
	F	- 0.2	+ 0.3	+ 1.1	+ 1.3	+ 2.0	+ 4.2	+ 6.7	+ 8.7
		(1.7)	(1.4)	(1.5)	(1.2)	(2.5)	(2.6)	(2.5)	(1.9)
	M + F	- 0.8	- 0.3	+ 0.7	+ 1.9	+ 2.3	+ 4.2	+ 6.2	+ 8.2
		(1.8)	(1.9)	(2.2)	(1.9)	(2.2)	(2.4)	(2.4)	(2.6)
Upper Segment	M	- 2.8	- 2.4	0	+ 1.3	+ 2.8	+ 5.2	+ 7.2	+ 10.7
		(4.9)	(3.0)	(3.0)	(3.6)	(3.6)	(4.7)	(3.5)	(6.0)
	F	+ 1.2	+ 1.3	+ 0.7	+ 1.2	+ 1.7	+ 3.7	+ 5.7	+ 7.5
		(2.9)	(2.7)	(2.7)	(2.7)	(2.1)	(1.9)	(1.9)	(1.8)
	M + F	- 0.6	+ 0.3	+ 0.3	+ 1.3	+ 2.3	+ 4.4	+ 6.4	+ 9.1
		(2.5)	(2.7)	(2.7)	(2.7)	(2.9)	(3.4)	(2.8)	(4.5)
Middle Segment	M	0	+ 0.4	+ 0.3	+ 1.2	+ 2.2	- 1.2	+ 1.3	+ 4.5
		(5.4)	(3.1)	(4.3)	(4.4)	(4.8)	(7.2)	(7.2)	(4.3)
	F	- 2.3	- 2.7	+ 1.5	+ 3.0	+ 4.3	+ 5.7	+ 10.5	+ 14.2
		(4.5)	(4.8)	(3.4)	(2.8)	(3.9)	(4.0)	(6.3)	(4.1)
	M + F	- 1.3	- 1.3	+ 0.9	+ 2.1	+ 3.3	+ 2.6	+ 5.9	+ 9.3
		(4.8)	(4.2)	(3.8)	(3.6)	(4.3)	(6.4)	(8.0)	(6.4)
Lower Segment	M	- 3.6	- 0.6	+ 3.8	+ 6.3	+ 7.3	+ 7.4	+ 11.3	+ 8.7
		(6.3)	(3.5)	(2.7)	(4.7)	(2.9)	(4.9)	(7.3)	(5.6)
	F	- 3.7	- 3.3	+ 1.8	+ 2.7	+ 2.5	+ 4.5	+ 6.3	+ 5.2
		(1.2)	(2.3)	(1.5)	(3.3)	(2.6)	(2.5)	(3.3)	(6.0)
	M + F	- 3.6	- 2.1	+ 2.8	+ 4.5	+ 4.9	+ 5.8	+ 8.8	+ 6.9
		(4.1)	(3.1)	(2.3)	(4.3)	(3.7)	(3.9)	(6.0)	(5.8)
Total	M	- 1.6	- 1.0						

TABLE XXIII

MEAN CHANGES IN Z_o IN % (S.D.) IN 12 YOUNG NORMAL ADULTS WITH TILTING

Time after Tilt	0 secs	5 secs	15 secs	30 secs	45 secs	60 secs	3 min	5 min
Mean change in Z_o (%)	+ 5.3	+ 4.5	+ 5.3	+ 5.5	+ 5.5	+ 5.7	+ 5.7	+ 5.7
	(3.4)	(2.9)	(1.6)	(1.1)	(1.1)	(1.3)	(1.3)	(1.3)

TABLE XXIV

Z_o CHANGES (MEAN % AND S.D.) IN SIX ELDERLY PATIENTS TILTED TO 60° FOOT DOWN

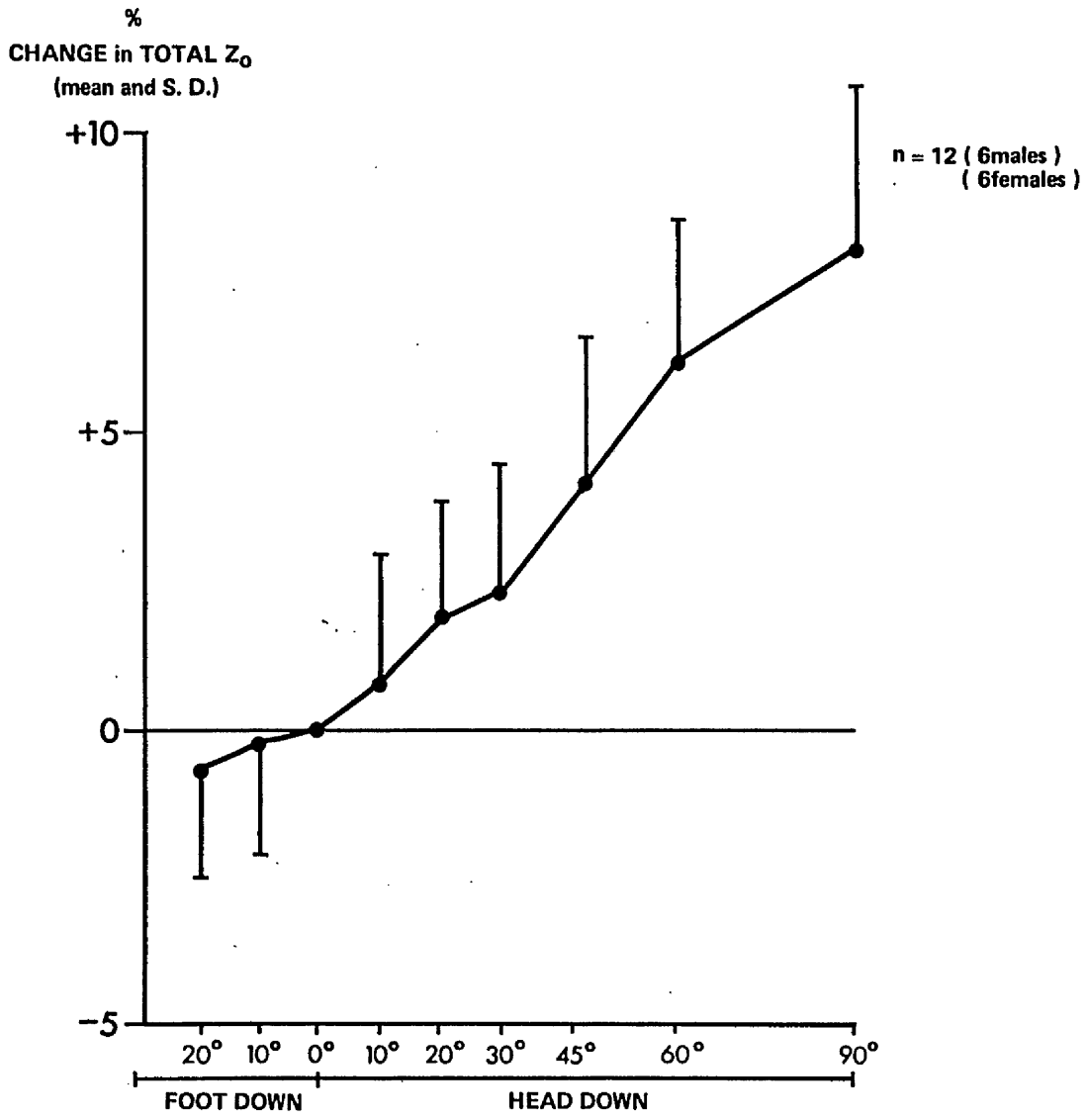


FIGURE 7:1

TILT TEST EFFECT ON Z_o IN 12 YOUNG ADULTS

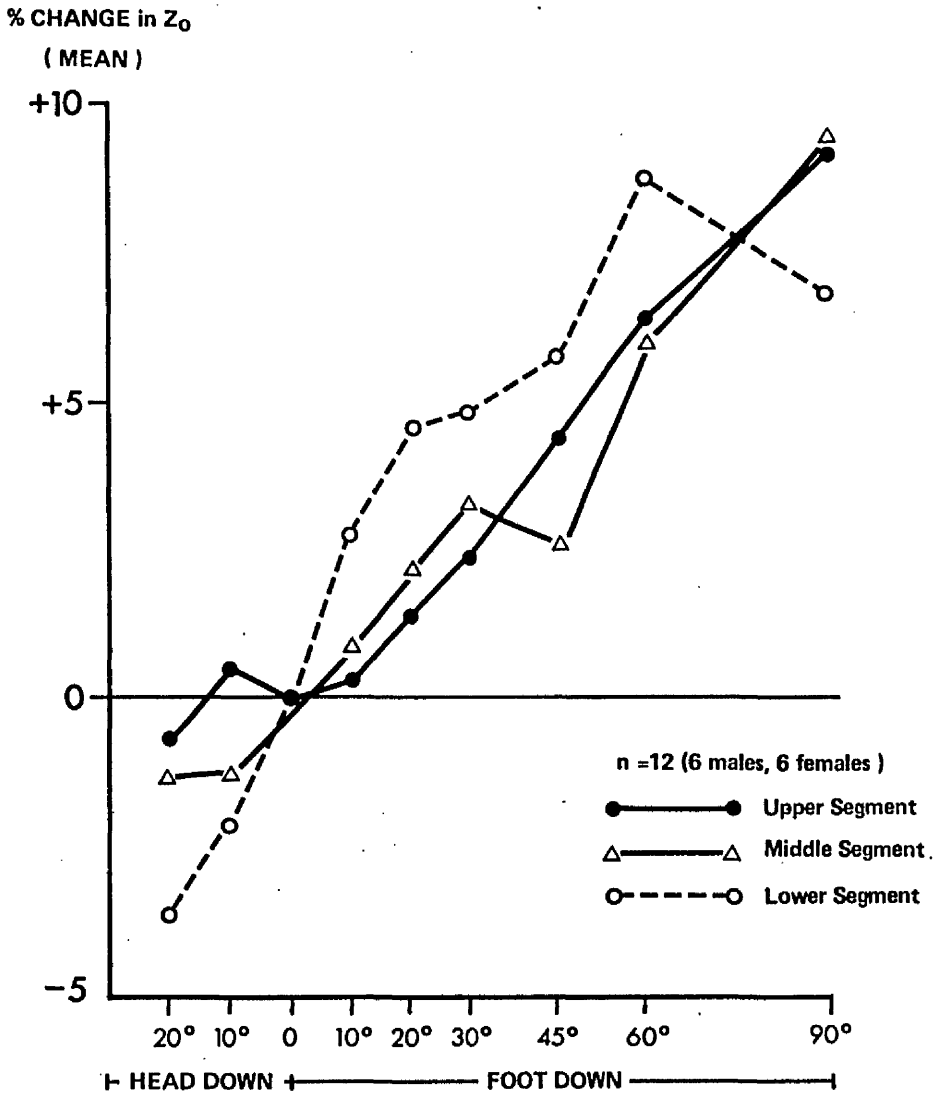


FIGURE 7:2

TILT TEST EFFECTS ON Z_o IN THORACIC SEGMENTS IN 12 YOUNG ADULTS

the horizontal position, Z_0 values returned to basal readings within five seconds.

Study III: Changes in Z_0 values related to instantaneous 60^o foot down tilt are detailed in Table XXV. In all of the four groups there was a significant rise in Z_0 which continued to rise until three minutes (all groups, paired t test $p < 0.05$) and the rise continued until five minutes in elderly females who had no postural blood pressure drop. At one minute, males and females with significant postural blood pressure drop had a significantly greater increase in Z_0 values (males, $t = 13.9$, $p < 0.001$; females, $t = 9.0$, $p < 0.001$) and this was more apparent in females.

Discussion

These studies confirm that there is a systematic, significant increase of 5 - 6% in the value of Z_0 on tilting to 60^o foot down in young and elderly subjects. Previous similar studies in young and elderly adults have shown Z_0 increases of 14 - 15% (140) and it is likely that the apparent failure to demonstrate any significant change in Z_0 in one hypertensive patient (40) in five young men (46) and in ten patients after acute myocardial infarction (49) was due to the fact that tilting only took place to a maximum of 35^o foot down and changes are more likely to appear between 45 - 60^o foot down (Fig 7:1).

Z_0 changes occur throughout the thorax but these are more marked in the lower segment. Postural induced changes in Z_0 occur almost immediately after tilting and values return to normal, as quickly, when the tilt table is returned to the horizontal position.

Elderly subjects with postural hypotension have a greater increase in Z_0 on tilting and this confirms the work of Lye and

Subject Group	Z_o Change (%) 1 min	3 min	5 min	Paired t test for values at 1 minute
Males - no postural BP drop (n = 16)	4.7 (4.3)	5.6 (4.3)	6.9 (5.7)	
				t = 13.9 ($p < 0.001$)
Males - significant postural BP drop (n = 27)	4.8 (3.2)	5.8 (4.1)	5.6 (3.6)	
Females - no postural BP drop (n = 15)	5.5 (3.1)	6.3 (3.5)	7.6 (4.3)	
				t = 9.0 ($p < 0.001$)
Females - significant postural BP drop (n = 21)	7.9 (7.0)	9.3 (6.4)	9.9 (6.9)	
Paired t test	All groups $p < 0.05$	Only females with no postural BP drop ($p<.05$)		

TABLE XXV

Z_o CHANGES (MEAN % AND S.D.) IN 79 ELDERLY SUBJECTS TILTED TO 60^o FOOT DOWN

Vargas (140).

It is therefore likely that the Z_0 change on tilting is genuine and not an artefact due to positional changes of the circumferential leads or lead drag during the tilt manoeuvre. The Z_0 change may be due to blood pooling in the legs due to gravity (44, 139) with associated reduced cardiac venous return and a reduction of the intrathoracic blood volume. Other causal factors may be due to movement of the diaphragm and a relative increase in the lung air volumes particularly as the Z_0 change is most marked in the lower thoracic segment. The relatively greater change in Z_0 in postural hypotension may simply reflect a failure of venous return and a fall in peripheral vascular resistance.

CHAPTER 8

DERIVATION OF SYSTOLIC TIME INTERVALS FROM THE IMPEDANCE CARDIOGRAM

Systolic time intervals have been established as reliable noninvasive indicators of myocardial function in health and disease (142-3). The systolic time intervals include a number of temporal relationships between events in the electrocardiogram, the phonocardiogram and the arterial pulse wave. The two most frequently quoted intervals are the left ventricular ejection time (LVET) and the pre-ejection period (PEP). The LVET is the duration of left ventricular ejection of blood into the aorta, viz. the time between the opening and closure of the aortic valve. The PEP is the time between the start of ventricular depolarisation and the opening of the aortic valve.

Indirect measurement of these time intervals is carried out conventionally by simultaneous recording of the electrocardiogram, phonocardiogram and the carotid arterial pulse wave at a paper speed of 100 mm per second. Total electromechanical systole (QS_2) is obtained by measuring the time interval between the start of the QRS complex (Q) and the aortic valve closure (S_2) in the phonocardiogram. The LVET is measured from the start of the upstroke to the dicrotic notch of the carotid pulse wave. The PEP is conventionally derived by subtraction of the LVET from QS_2.

The derivation of the LVET from a carotid pulse surface transducer is not always easy and the pulse wave may be difficult to find in obese subjects, in the elderly and in those with thick necks, restlessness or dyspnoea. Conventional methods require technical skills of a high order and three transducer systems, viz.

electrocardiogram, phonocardiogram and carotid tracing. Recent modifications have reduced the need for the phonocardiogram (144).

The principle of using the differentiated impedance cardiogram $(dZ/_{dt})$ for the derivation of systolic time intervals has been utilized by several group of workers in anaesthetized dogs (63), healthy adults (105, 145-50) and in patients with ischaemic heart disease (146, 150). A study was undertaken to validate the use of the differentiated impedance cardiogram for the derivation of LVET and PEP in elderly cardiovascular normal subjects and patients with left or right bundle branch block. Values obtained by the differentiated impedance cardiogram and conventional transducer methods were compared.

Subjects and Methods

Systolic time intervals were measured in 50 patients under the care of the University Department of Geriatric Medicine. Twenty-five females and 25 males were included in the study (age range 61-90 years). Thirty patients had no clinical, radiological or electrocardiographic evidence of cardiovascular disease. Ten patients had left bundle branch block and 10 patients had right bundle branch block.

Each subject had the LVET and PEP determined by the two methods in the supine position, at rest, and during quiet breathing.

Simultaneous recordings of the electrocardiogram, phonocardiogram, $dZ/_{dt}$ and carotid pulse wave were made in each patient (Fig 2:1) at a paper speed of 100 mm/second (see Chapter 2).

The following measurements were made using ten consecutive complexes for each patient (total 500 complexes).

1. RR interval and heart rate.

2. Electromechanical systole (QS_2).

3. Left ventricular ejection time derived from the carotid pulse ($LVET_c$).

4. Left ventricular ejection time derived from the $^{dZ}/_{dt}$ waveform ($LVET_z$). The onset of $LVET_z$ was at the point where the calibration line crossed the upslope of the $^{dZ}/_{dt}$ waveform and the end point was located at the X point as defined by LABABIDI (151) synchronous or just following the first high frequency component of the second heart sound.

5. Pre-ejection period derived from the formula QS_2-$LVET_c$.

6. Pre-ejection period derived from the $^{dZ}/_{dt}$ waveform was measured from the onset of the Q wave on the ECG to the start of the $LVET_z$.

Results

The carotid pulse was obtained with little difficulty in all subjects and the impedance cardiogram end points were usually easily identified. The X point of the $^{dZ}/_{dt}$ waveform was not clearly identifiable in 5 subjects (10%) and in these the end point for measurement of the $LVET_z$ was taken as the first high frequency component of the second heart sound on the phonocardiogram.

The results obtained by the measurement of 500 complexes in 50 patients are displayed in Table XXVI. Over a heart rate range of 48-113 beats/minute, the $LVET_c$ and $LVET_z$ were identical in 42 subjects (84%) and the remainder were within 10 milliseconds. The PEP_c and PEP_z were identical in 38 subjects (76%) and the remainder were within a margin of 12 milliseconds.

Number of complexes	500
Mean Heart rate range	48–113 beats/minute
Mean $LVET_c$	263.8 (SD 39) millisecs
Mean $LVET_z$	264.6 (SD 39) millisecs
Mean PEP_c	129.0 (SD 28.6) millisecs
Mean PEP_z	129.0 (SD 28.2) millisecs

SD = Standard deviation

TABLE XXVI

COMPARISON OF SYSTOLIC TIME INTERVALS DERIVED BY CONVENTIONAL METHODS AND IMPEDANCE CARDIOGRAPHY IN 50 ELDERLY SUBJECTS

Discussion

The measurement of LVET is used in the Kubicek formula for the calculation of the impedance stroke volume. Kubicek and his co-workers (13) measured the ventricular ejection time as the interval from the zero baseline crossing of the $^{dZ}/_{dt}$ waveform at the start of systole to either the X point on the $^{dZ}/_{dt}$ trace or the second heart sound on the phonocardiogram. Most workers have used this technique for measuring the LVET (51, 145-146, 148, 150) and it was applied in this study in elderly subjects.

The X point was clearly defined in the majority (90%) of elderly subjects in this study although this end point may not always be as easily recognized (105).

The LVET derived from the $^{dZ}/_{dt}$ waveform has been shown to closely correlate with the LVET derived from invasive measurements in peripheral arteries (16) and the aorta (63) and from non-invasive surface carotid artery tracings (105, 146, 149). The PEP measured directly from the $^{dZ}/_{dt}$ trace has been shown to closely correlate with the PEP derived from QS_2 - LVET by an invasive method (63) and from non-invasive conventional recordings (146, 149). In this study a similar satisfactory correlation for LVET and PEP was observed in elderly subjects free from cardiac disease and with ECG evidence of right or left bundle branch block.

The impedance tracings technique has clearly distinct advantages over conventional methods of measuring the LVET and PEP in that both of these systolic time intervals can be measured directly as there is no delay related to pulse transmission time. No hand held transducers are required and prolonged monitoring over several days is feasible in critically ill patients. The $^{PEP}/_{LVET}$ ratio, which is a very sensitive measurement of left ventricular

function (142), is therefore easily derived by this technique.

During exercise, conventional methods of measuring the systolic time intervals are technically very difficult and although the impedance waveform is liable to be distorted by motion artefacts during strenuous exercise (146), the effect of these artefacts can be minimized by computerized ensemble averaging (147, 149). Valid measurement of the LVET and PEP can be obtained during quiet respiratiion as has been demonstrated in this study and breathholding is unnecessary (146) and may be undesirable as respiratory manoeuvers may influence both the venous return and the heart rate with a consequent effect on the systolic intervals.

CHAPTER 9

RELATIONSHIP BETWEEN THE PRECEDING CYCLE LENGTH AND THE LVET, IMPEDANCE WAVEFORM AMPLITUDE AND STROKE VOLUME IN ATRIAL FIBRILLATION

There is little detailed information available about the effects of atrial fibrillation (AF) on cardiac function in old age. The effects of the dysrhythmia on the circulation are of the same order as those of frank cardiac failure with sinus rhythm (133) and the cardiac output may be reduced by 20-30% below normal values in elderly subjects with controlled AF. Cardiac performance is altered by removal of the consequences of atrial contraction and the introduction of an irregular variation in the ventricular cycle length. AF therefore provides a useful model for the examination of the effects of beat to beat variations in the stroke volume and systolic time intervals. Beat to beat changes in the circulation generally require invasive measurements but the technique of impedance cardiography lends itself to the study of these changes in a non-invasive manner. In this chapter, the beat to beat variation in preceding cycle length (R-R interval), LVET, first derivative impedance cardiogram waveform amplitude ($^{dZ}/_{dt}$) and stroke volume were studied in a group of elderly subjects in AF.

Subjects and Methods

Twenty patients (11 females and 9 males; age range 63-95 years) under the care of the University Department of Geriatric Medicine were studied. None of these patients had evidence of valvular heart disease, left bundle branch block, or cardiac failure. All were in atrial fibrillation and were receiving maintenance digoxin therapy.

Each patient had simultaneous recordings of the

electrocardiogram, phonocardiogram, $^{dZ}/_{dt}$ and carotid pulse wave at a paper speed of 100 mm/second in the supine position at rest and during quiet breathing. The following measurements were made using 15 consecutive complexes for each patient (total 300 complexes).

1. Previous cycle length (R-R interval) in milliseconds.
2. Left ventricular ejection time derived from carotid pulse (LVET) in milliseconds.
3. Amplitude of impedance waveform ($^{dZ}/_{dt}$) in ohms/second.
4. Stroke volume (impedance method: see Chapter 2) in ml.

Results

The relationship between the R-R interval and the LVET in the 20 patients is detailed in Table XXVII and demonstrated in four individual cases in Figs 9:1 - 9:4. A signficant linear relationship is apparent (r = 0.42 - 0.92) in all of the cases of AF, but the relationship appears to be curvilinear with a consistent plateau effect occurring above cycle lengths of 600-800 milli-seconds (Figs 9:1, 9:2, 9:4). No plateau effect is present in patients with faster heart rates (Figure 9:3).

The relationship between the R-R and the amplitude of $^{dZ}/_{dt}$ in the 20 patients is detailed in Table XXVIII and demonstrated in four individual cases in Figs 9:5 - 9:8. A significant linear relationship is apparent (r = 0.41 - 0.93) in all of the cases of AF.

The relationship between the R-R interval and the stroke volume in the 20 patients over a range of R-R intervals of 340-1640 milliseconds is detailed in Table XXIX. A significant linear relationship is apparent (r = 0.60 - 0.94) in all subjects and the regression lines are all different and appear in Fig 9.9.

PATIENT NUMBER	LVET (y) AND R-R (x)	r
1	y = 101 + 0.1x	0.79
2	y = 132 + 0.2x	0.75
3	y = 160 + 0.1x	0.85
4	y = 177 + 0.1x	0.79
5	y = 137 + 0.2x	0.81
6	y = 213 + 0.1x	0.59
7	y = 228 + 0.1x	0.75
8	y = 194 + 0.1x	0.84
9	y = 165 + 0.1x	0.92
10	y = 117 + 0.1x	0.87
11	y = 164 + 0.1x	0.90
12	y = 47 + 0.3x	0.82
13	y = 197 + 0.6x	0.70
14	y = 76 + 0.2x	0.69
15	y = 133 + 0.1x	0.72
16	y = 183 + 0.02x	0.42
17	y = 97 + 0.2x	0.60
18	y = 242 + 0.04x	0.78
19	y = 146 + 0.1x	0.61
20	y = 188 + 0.04x	0.78

r = Correlation coefficient

TABLE XXVII

RELATIONSHIP BETWEEN PRECEDING CYCLE LENGTH (R-R) AND LVET IN 20 ELDERLY PATIENTS IN ATRIAL FIBRILLATION

PATIENT NUMBER	dZ/dt (y) R–R (x)	r
1	y = −0.2 + 0.004x	0.80
2	y = −1.3 + 0.006x	0.82
3	y = 0.1 + 0.002x	0.49
4	y = 1.4 + 0.002x	0.85
5	y = 0.3 + 0.002x	0.87
6	y = −0.7 + 0.002x	0.71
7	y = 0.5 + 0.001x	0.57
8	y = 1.4 + 0.0004x	0.41
9	y = 1.1 + 0.001x	0.69
10	y = −0.2 + 0.003x	0.93
11	y = 0.1 + 0.002x	0.81
12	y = −0.1 + 0.003x	0.72
13	y = 1.2 + 0.001x	0.51
14	y = −0.7 + 0.004x	0.86
15	y = 0.6 + 0.001x	0.82
16	y = −0.2 + 0.002x	0.63
17	y = −0.3 + 0.003x	0.69
18	y = 0.5 + 0.001x	0.89
19	y = 0.04 + 0.003x	0.76
20	y = −0.1 + 0.002x	0.86

r = Correlation coefficient

TABLE XXVIII

RELATIONSHIP BETWEEN PRECEDING CYCLE LENGTH (R–R) AND THE AMPLITUDE OF dZ/dt IN 20 ELDERLY PATIENTS IN ATRIAL FIBRILLATION

PATIENT NUMBER	STROKE VOLUME (y) AND R-R (x)	r	p
1	y = -25 + 0.2x	0.81	< 0.001
2	y = -34 + 0.1x	0.87	< 0.001
3	y = -9 + 0.1x	0.60	< 0.05
4	y = 16 + 0.1x	0.88	< 0.001
5	y = -14 + 0.2x	0.92	< 0.001
6	y = -77 + 0.2x	0.76	< 0.01
7	y = 13 + 0.04x	0.63	< 0.05
8	y = 45 + 0.03x	0.64	< 0.05
9	y = 9 + 0.1x	0.90	< 0.001
10	y = -28 + 0.1x	0.94	< 0.001
11	y = -12 + 0.1x	0.84	< 0.001
12	y = -33 + 0.2x	0.84	< 0.001
13	y = 31 + 0.03x	0.61	< 0.05
14	y = -50 + 0.19x	0.83	< 0.001
15	y = 16 + 0.1x	0.91	< 0.001
16	y = -8 + 0.1x	0.63	< 0.05
17	y = -34 + 0.2x	0.73	< 0.05
18	y = 14 + 0.1x	0.93	< 0.001
19	y = -8 + 0.1x	0.78	< 0.001
20	y = -18 + 0.1x	0.86	< 0.001

r = Correlation coefficient
p = Statistical significance

TABLE XXIX

RELATIONSHIP BETWEEN PRECEDING CYCLE LENGTH (R-R) AND THE STROKE VOLUME IN 20 ELDERLY PAIENTS IN ATRIAL FIBRILLATION

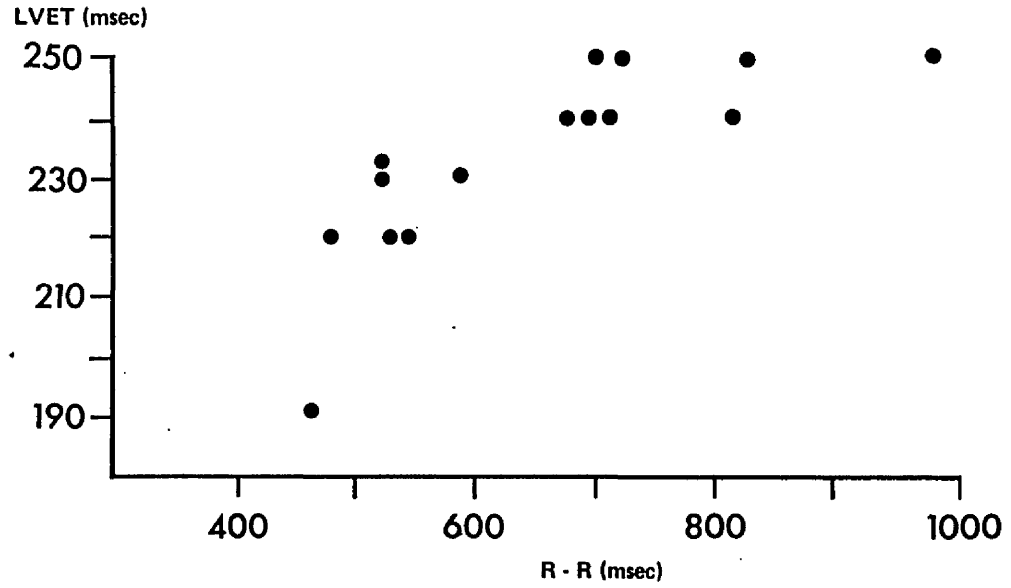


FIGURE 9:1

PATIENT NO. 4 FEMALE 89 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND LVET

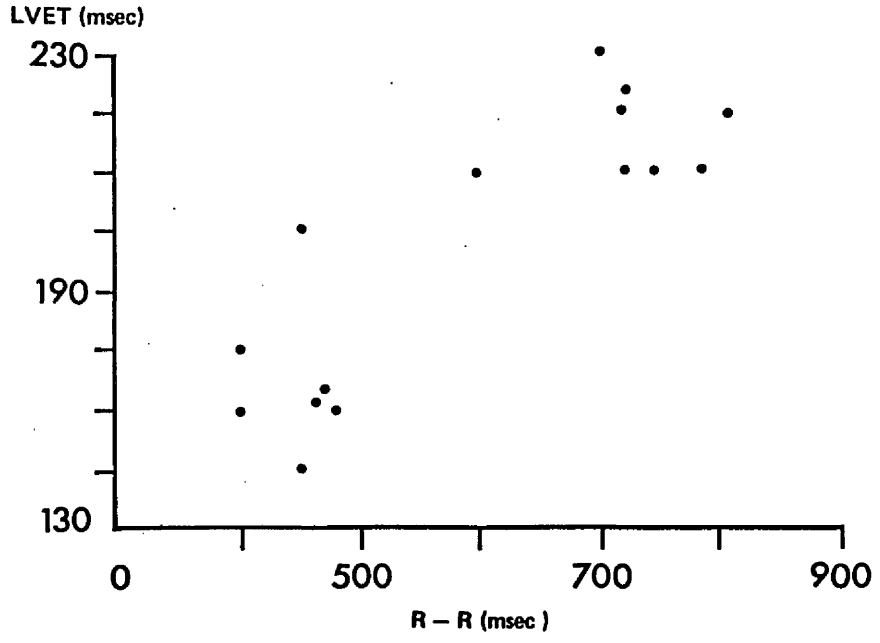


FIGURE 9:2

PATIENT NO. 10 FEMALE 86 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND LVET

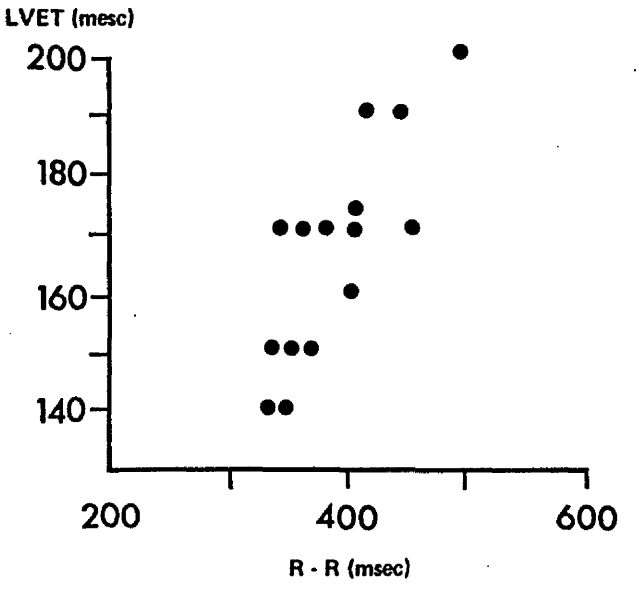


FIGURE 9:3

PATIENT NO. 12 MALE 75 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND LVET

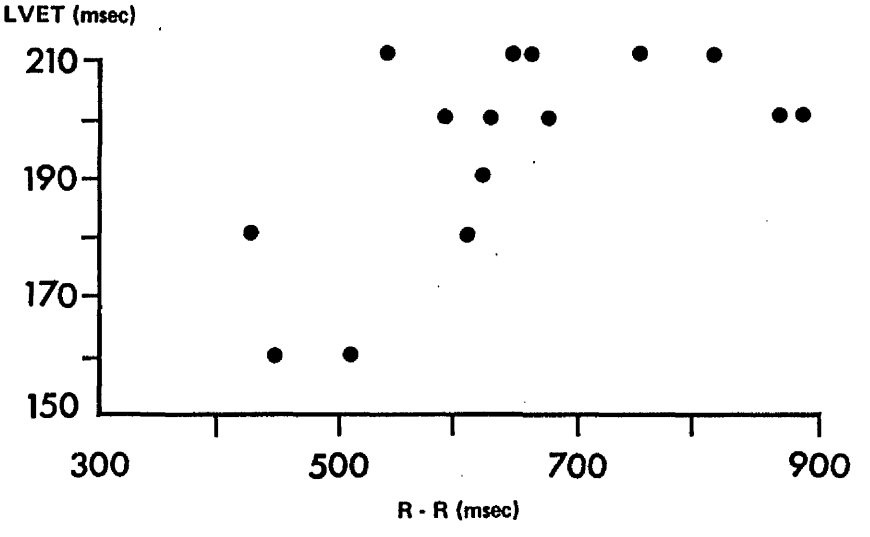


FIGURE 9:4

PATIENT NO. 19 MALE 82 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND LVET

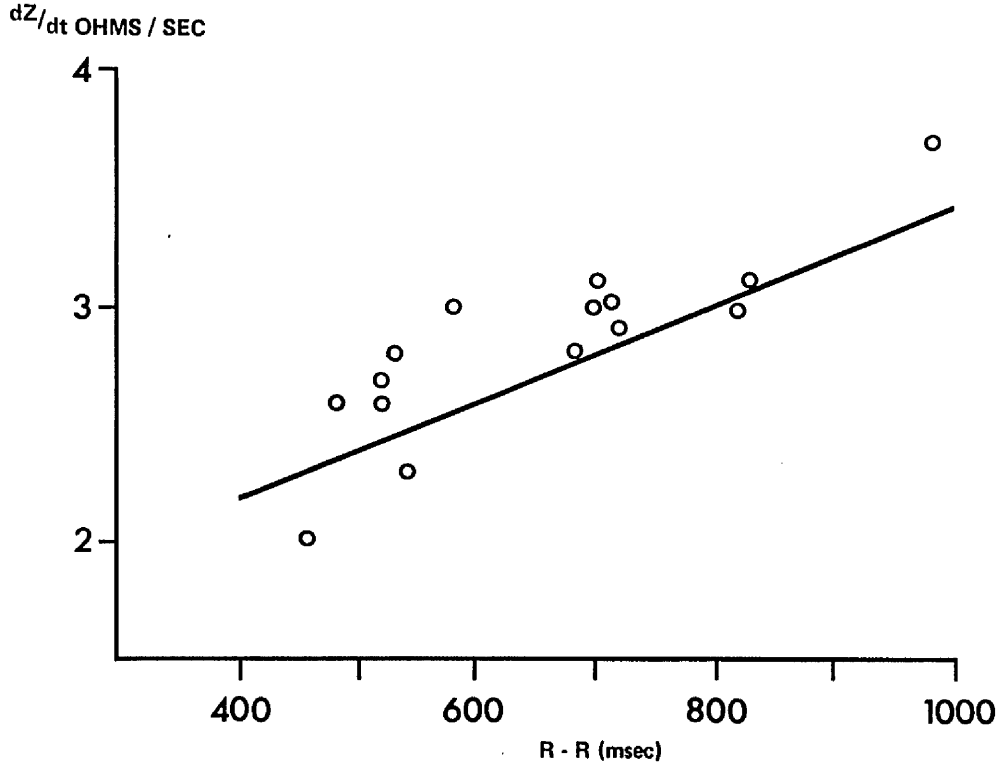


FIGURE 9:5

PATIENT NO. 4 FEMALE 89 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND dZ/dt

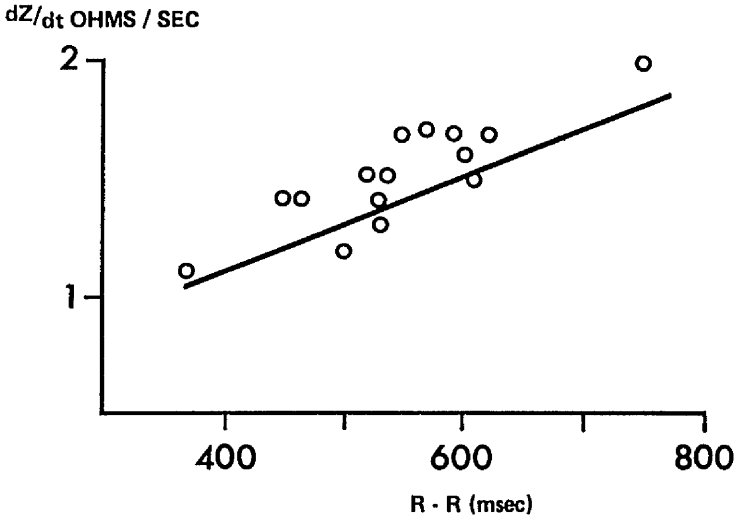


FIGURE 9:6

PATIENT NO. 5 FEMALE 79 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND dZ/dt

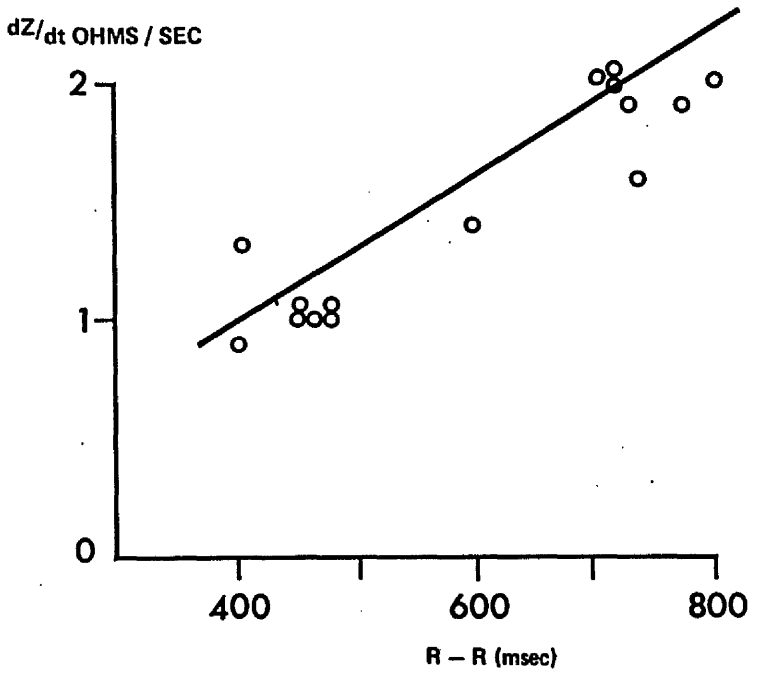


FIGURE 9:7

PATIENT NO. 10 FEMALE 86 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND dZ/dt

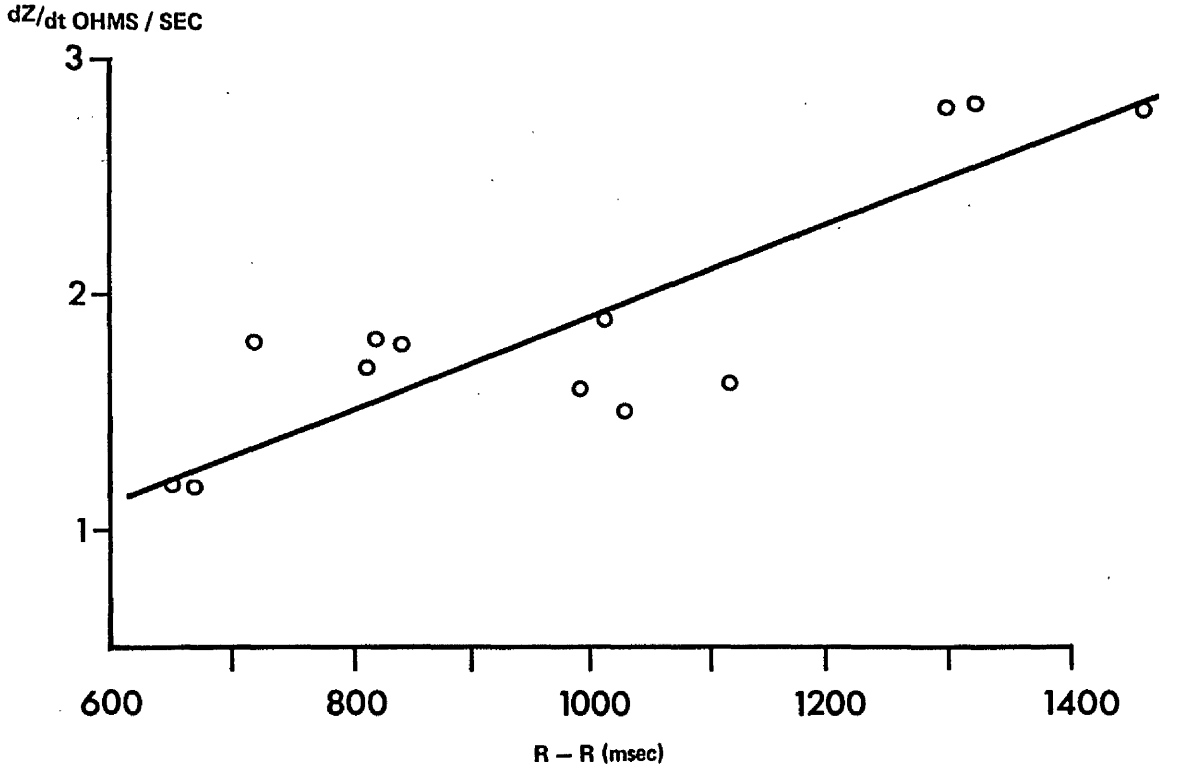


FIGURE 9:8

PATIENT NO. 20 MALE 65 YEARS.

RELATIONSHIP BETWEEN R-R INTERVAL AND dZ/dt

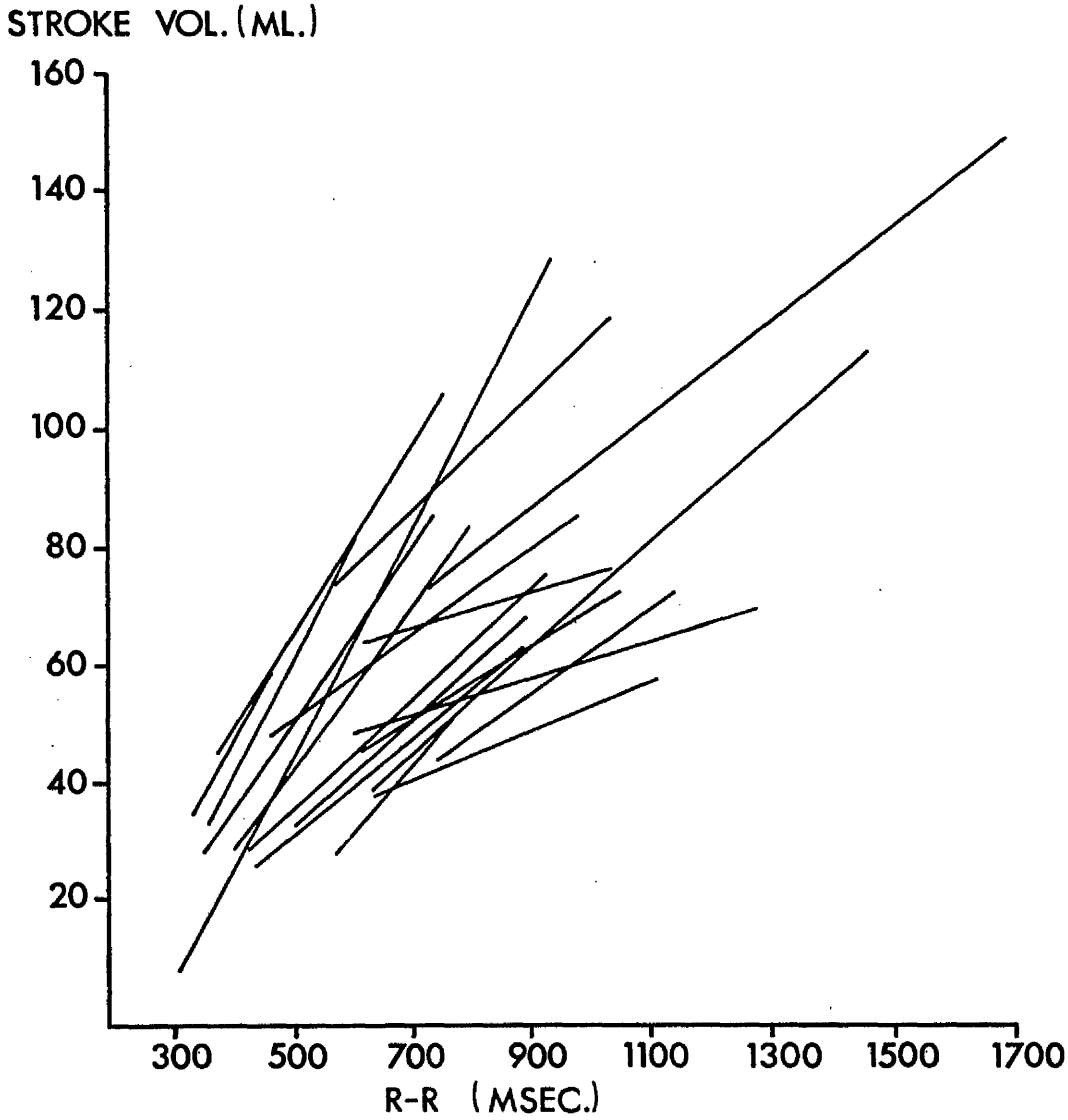


FIGURE 9:9

RELATIONSHIP BETWEEN R-R AND STROKE VOLUME IN 20 ELDERLY PATIENTS IN ATRIAL FIBRILLATION

Discussion

Previous studies have demonstrated that the LVET and the stroke volume are directly and significantly related to the preceding R-R interval in normal hearts in sinus rhythm (152-3). Similar findings have been observed in AF (154) but the relationship between LVET and the R-R interval is generally curvilinear with reduced lengthening of the LVET at longer R-R intervals of more than 800 milliseconds (155-6). In AF in association with mitral stenosis however, a straight line relationship is apparent (155-6) and this may be due to a persistent elevation of left atrial pressures which produces a persistent head of pressure forcing blood into the left ventricle and continuation of this pressure differential throughout relatively long diastolic periods might account for continued filling of the ventricle even in late diastole (155). In those patients with AF in the absence of significant mitral stenosis, the plateauing effect of the LVET as a function of the preceding R-R interval above values of 800 milliseconds may be due to the fact that left ventricular volume increases rapidly in early diastole in response to free flow through the mitral orifice but as soon as the early passive filling is completed, the low atrial pressure is unable to further augment filling and therefore the LVET will increase no further.

The study described in this chapter has confirmed the significant relationship between the LVET and the R-R interval and the curvilinear association in patient's with AF without mitral stenosis.

The impedance stroke volume technique has been applied to studies of AF in small numbers of patients by three groups of workers (91, 156-7). All of these studies have demonstrated a

significant direct linear relationship between the stroke volume and preceding R-R interval, on a beat to beat basis, in individual patients. Harley and Greenfield (91) demonstrated this relationship in six cases including two patients with mitral stenosis over R-R intervals of 300 to 1500 milliseconds and Kitamura and his colleagues (156) demonstrated similar findings in three cases including one patient with mitral stenosis over R-R intervals of 400 to 2200 milliseconds. Thomsen and Fabricius (157) reported a signficant correlation between the impedance stroke volume and the R-R interval in three patients in AF. This significant continuous direct linear relationship over R-R intervals of 340-1640 is well demonstrated in Table XXIX and Fig 9.9.

The significant relationship described between the R-R interval and the amplitude of $^{dZ}/_{dt}$ further supports the assumed relationship between cardiac activity and the first derivative waveform of the impedance cardiogram.

CHAPTER 10

MYOCARDIAL CONTRACTILITY AND THE HEATHER INDEX

The essential part of the heart as far as the systemic circulation is concerned is the left ventricle and most attention is concentrated on the performance of this chamber and its alteration by disease or drugs (58). Contractility has been defined as the capacity for becoming short in response to a suitable stimulus (158) and cardiac contractility as the rate of shortening or contraction of the heart muscle fibres (15).

Indices of myocardial contractility include estimates of muscle function, e.g. left ventricular pressure, left ventricular wall tension, rate at which left ventricular pressure is developed ($^{dp}/_{dt}$ max) and the time taken to reach the peak of $^{dp}/_{dt}$ max and estimates of pump function, e.g. peak aortic blood velocity, peak aortic blood acceleration and ejection fraction.

The ejection fraction (EF) provides a good overall index of left ventricular performance (159-160) and change in it is a sensitive measure of change in myocardial function due to disease or drugs (161). EF is defines as:

$$\frac{\text{VENTRICULAR END-DIASTOLIC VOLUME - END-SYSTOLIC VOLUME}}{\text{END-DIASTOLIC VOLUME}}$$

or in the absence of valvular regurgitation:

$$\frac{\text{STROKE VOLUME}}{\text{END-DIASTOLIC VOLUME}}$$

EF may be measured in man by left ventricular angiocardiography (162), echocardiography (163) and radionuclide cardiography, by first-pass or equilibrium methods (164). The first technique is

highly invasive, the second is difficult to interpret (165) and the third needs expensive and complex equipment. Latour et al (166) have however described a simple, reproducible virtually non-invasive, radionuclide method of measurement of the EF in the elderly using a single scintillation counter and eclipse collimation based on the techniques described by Steele et al (167) and Berndt et al (168).

The ratio of $^{PEP}/_{LVET}$ has been adopted as a popular single expression of ventricular performance (142). Diminished left ventricular efficiency results in an increase in $^{PEP}/_{LVET}$ and is a more sensitive index of left ventricular dysfunction than the cardiac index or stroke index (143).

Siegel and his colleagues (99, 169), in their early experimental work, observed that impedance change might be associated with an estimate of myocardial contractility and that $^{dZ}/_{dt}$ bears a direct relationship to the time taken from onset of contraction to the maximum $^{dp}/_{dt}$. This phenomenon was confirmed by Moritz and his co-workers (87).

In 1969, Heather proposed a new index of left ventricular function (95). As the R-Z interval was similar to the PEP and the $^{dZ}/_{dt}$ related to the maximum velocity of the ejection of blood into the aorta the following index was derived:

$$\text{INDEX} = \frac{^{dZ}/_{dt}}{q - Z}$$

where $^{dZ}/_{dt}$ is the amplitude of the first derivative of impedance change in ohms/second and $q - Z$ is the time from the start of the Q wave on the electrocardiogram to the peak of the $^{dZ}/_{dt}$ waveform.

This Heather Index was later applied by most workers in the

following modified form:

$$\text{HEATHER INDEX (HI)} = \frac{dZ/dt}{R - Z} \quad \text{ohms/sec}^2$$

where R - Z is time from the R wave on the electrocardiogram to the peak of the dZ/dt waveform. This modification apparently produced higher reproducibility in the derived index (16).

The first comparison of the HI and other indices of myocardial function derived from systolic time intervals in a study of five human subjects was reported in 1976 (105). In this chapter the HI was compared with the EF and the $PEP/LVET$ in a group of elderly patients with and without overt cardiovascular disease.

Subjects and Methods

Fourteen elderly patients (age range 67-82 years) under the care of the University Department of Geriatric Medicine were studied. All were in sinus rhythm and cardiovascular diagnoses are displayed in Table XXX. These patients were already under investigation by the technique of first pass area-of-interest radionuclide measurement of the EF and this study has been recorded by Latour and her colleagues (166).

A lead disc 5.5 cm in diameter was placed 3.5 cm in front of a 5 cm collimated scintillation counter (Nuclear Enterprises CM1-2), and 11.6 cm from the counter face. With the patient semi-supine, the counter was centred over a point midway between the midline and the cardiac apex (as determined by palpation, or if impalpable, in its normal anatomical position), and oriented directly backwards at right angles to the frontal plane. 200 μCi of ^{99}Tc-labelled human serum albumin in 2 ml of saline was rapidly injected into an

PATIENT NUMBER	AGE (YEARS)	SEX	DIAGNOSIS
1	76	M	Emphysema
2	74	M	Cardiovascular Normal
3	80	F	Anaemia
4	67	M	Left Ventricular Hypertrophy
5	74	F	Anaemia
6	69	F	Cardiovascular Normal
7	80	F	Ischaemic Heart Disease
8	82	M	Asthma
9	68	M	Anaemia
10	76	M	Ischaemic Heart Disese
11	70	M	First Degree Heart Block
12	74	M	Left Ventricular Hypertrophy
13	72	M	Ischaemic Heart Disease
14	75	F	Hypertension, Left Ventricular Hypertrophy

M: Male

F: Female

TABLE XXX

CARDIOVASCULAR OR OTHER DIAGNOSIS IN 14 ELDERLY PATIENTS

antecubital vein with the arm elevated, and immediately flushed in with a further 10-15 ml of saline. A time-activity curve was recorded with a scalar-ratemeter (Nuclear Enterprises SR-3) with a time-constant setting of 0.4 seconds, and chart recorder. After 5 minutes, blood was taken from another arm vein for determination of specific activity and measurement of blood volume.

The lead disc was then replaced by a 1.3 cm lead shield with a control orifice 3.5 cm in diameter placed over the aperture of the counter, which was repositioned as before. 400 μCi of ^{99}Tc-labelled human serum albumin was then similarly injected, and a time-activity curve recorded with a time constant setting of 0.2 seconds.

The first record was placed over a horizontal viewing box and the second record placed over it, so that the vertical time-marks were parallel, and the times of injection, the peaks of right and left heart activity, and the tails of left heart washout curves were superimposed. A line corresponding to the left heart washout on the first record was then traced on to the second. The EF for at least five cardiac cycles from the initial two-thirds of the left heart washout was then calculated as described by Latour et al (166).

Simultaneous recordings of the electrocardiogram, phonocardiogram, $^{dZ}/_{dt}$ and carotid pulse wave were made in each patient at the same session as the EF estimation.

The following measurements were made using five consecutive complexes for each patient (total 70 complexes).

1. EF (%)
2. Electromechanical systole (QS_2) millisecs.

3. Left ventricular ejection time derived from the carotid pulse (LVET) millisecs.

4. Pre-ejection period derived from the formula QS_2-LVET millisecs.

5. $^{PEP}/_{LVET}$

6. $^{dZ}/_{dt}$

7. R-Z interval millisecs.

8. $HI = \frac{^{dZ}/_{dt}}{R-Z}$ ohms/sec^2

Results

Values for the EF, HI and $^{PEP}/_{LVET}$ for the 14 individual patients are detailed in Table XXXI. A significant direct linear relationship between the EF over a range of 41-87% and the HI is displayed in Fig 10:1 ($r = 0.69$, $t = 3.3$, $p < 0.01$). A significant negative linear relationship was observed between the HI and the $^{PEP}/_{LVET}$ (Fig 10:2) ($r = -0.55$, $t = -2.27$, $p < 0.05$) and between the EF and $^{PEP}/_{LVET}$ (Fig 10:3) ($r = -0.69$, $t = -3.3$, $p < 0.01$).

Discussion

Five of the 14 elderly subjects in this study had an EF which could be considered as in the normal range of more than 70% when measured by the technique employed (166). None of the patients had a particularly low EF and in those with overt heart disease the EF was in the range of 41-74%.

Garrard and his colleagues have demonstrated the close correlation ($r = -0.90$) between the EF as measured by quantitative angiocardiography and the $^{PEP}/_{LVET}$ (170) in humans and this has been confirmed in the present study although the correlation is not as good ($r = -0.69$) and this may highlight the fact that first pass

PATIENT NUMBER	EJECTION FRACTION (%)	HEATHER INDEX (ohms/sec^2)	PEP/LVET
1	51	14.0	0.57
2	87	21.5	0.41
3	70	21.3	0.38
4	74	19.5	0.35
5	83	33.5	0.35
6	74	23.5	0.31
7	51	13.6	0.41
8	66	20.0	0.37
9	61	11.7	0.38
10	41	16.9	0.47
11	44	12.3	0.64
12	69	18.3	0.32
13	67	11.8	0.45
14	69	18.4	0.39

TABLE XXXI

EJECTION FRACTION, HEATHER INDEX, AND PEP/LVET IN 14 INDIVIDUAL PATIENTS

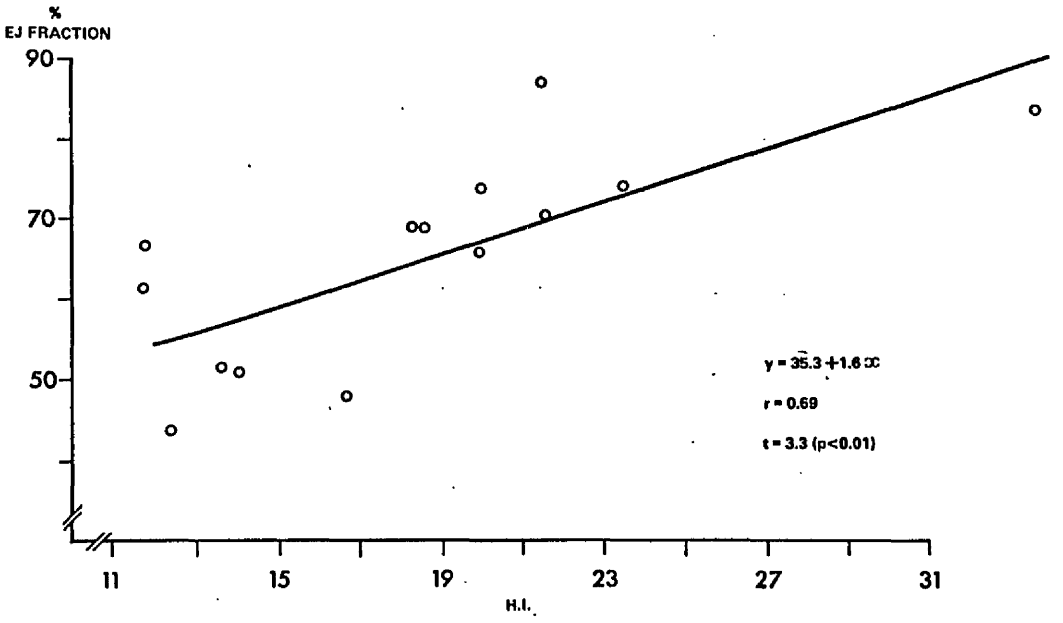


FIGURE 10:1

RELATIONSHIP BETWEEN EJECTION FRACTION AND HEATHER INDEX IN 14 INDIVIDUAL SUBJECTS

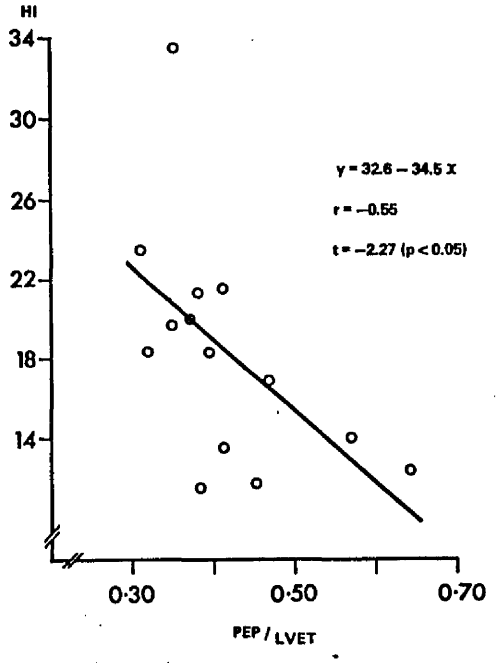


FIGURE 10:2

RELATIONSHIP BETWEEN HEATHER INDEX AND PEP/LVET IN 14 INDIVIDUAL SUBJECTS

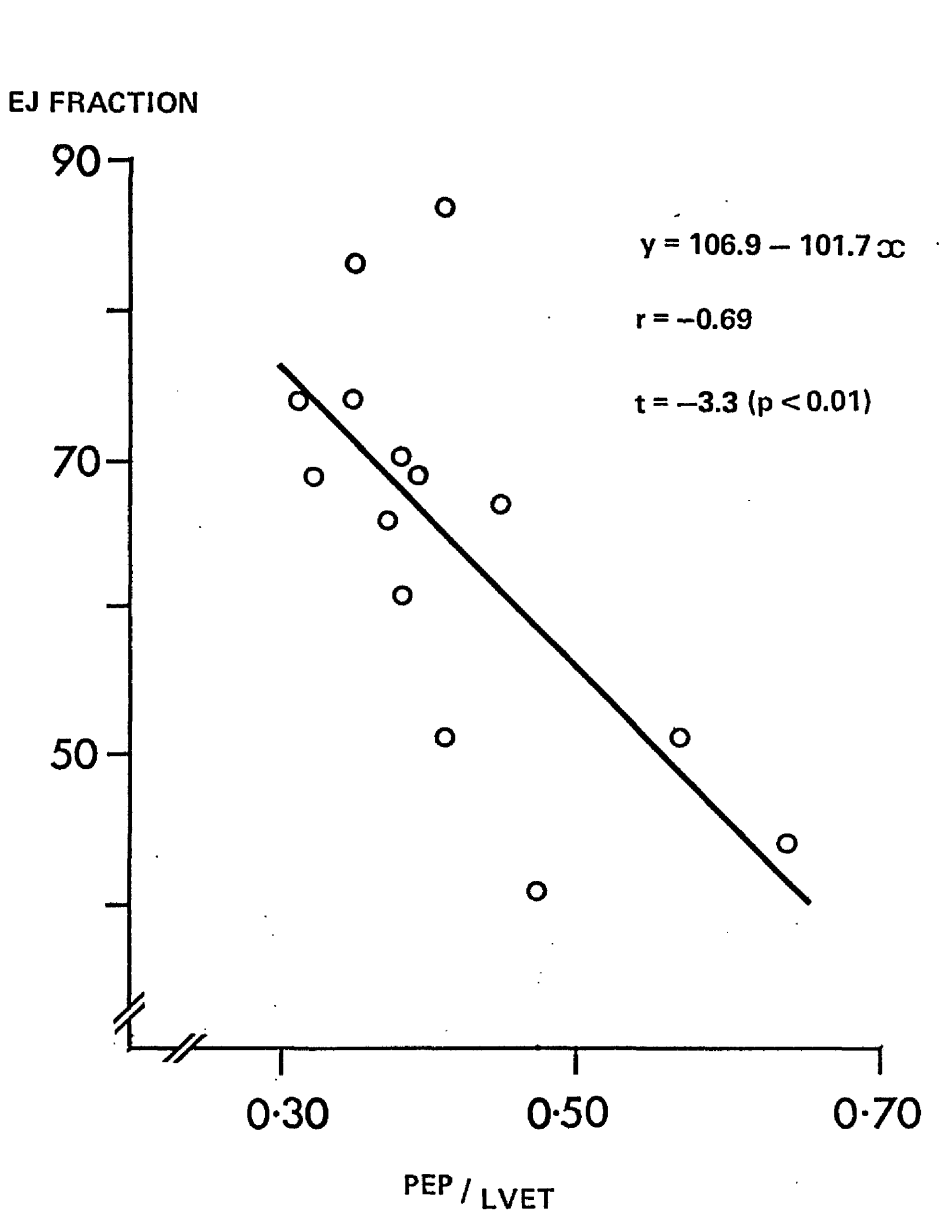


FIGURE 10:3

RELATIONSHIP BETWEEN EJECTION FRACTION AND PEP/LVET IN 14 INDIVIDUAL SUBJECTS

area-of-interest radionuclide measurement of the EF is less precise than the benchmark technique. The most likely explanation for the concordant changes in the EF and the $^{PEP}/_{LVET}$ is that both measurements reflect a common disorder of left ventricular contractility.

A good correlation has been observed in animal studies between the HI, and the maximum rate of change of left ventricular pressure, peak aortic blood velocity and acceleration (171). Hill and Merrifield (1976), in their study of five healthy human volunteers, observed that the HI correlated best with the $^{PEP}/_{LVET}$ ($r = -0.79$) and less well with the stroke volume, cardiac output, PEP, $^{1}/_{PEP^2}$, or LVET (105). The correlation has been confirmed in this study ($r = -0.55$) but a wide degree of scatter can be seen in Fig 10.2.

This study has shown as good a correlation between the EF and the HI ($r = 0.69$) as there appears to be between the EF and the $^{PEP}/_{LVET}$ ($r = -0.69$) in a group including elderly subjects with or without evidence of cardiac disease.

The temporal aspects of the impedance pulse reflect alterations in the time course of iso-volumetric pressure development and an estimate of myocardial contracility related to the isometric time tension index can be quantified using the impedance technique (99). The HI is easy to measure using an ECG trace and a $^{dZ}/_{dt}$ trace only and this index gives a useful guide to the state of myocardial contractility and changes with the effects of postural stress, drugs or disease. The HI has been utilized to assess myocardial contractility in steady state exercise testing in fit subjects (172), wheelchair dependent patients (173) and after acute myocardial infarction (15).

The normal ageing process may be accompanied by changes in left

ventricular function although the results of studies of age associated changes in systolic left ventricular function have been contradictory (174). The HI may form a useful non-invasive tool in the assessment of alteration of myocardial contractility with ageing and further studies should be directed in this area of research.

CHAPTER 11

THE FIRST DERIVATIVE OF THE IMPEDANCE CARDIOGRAM WAVEFORM

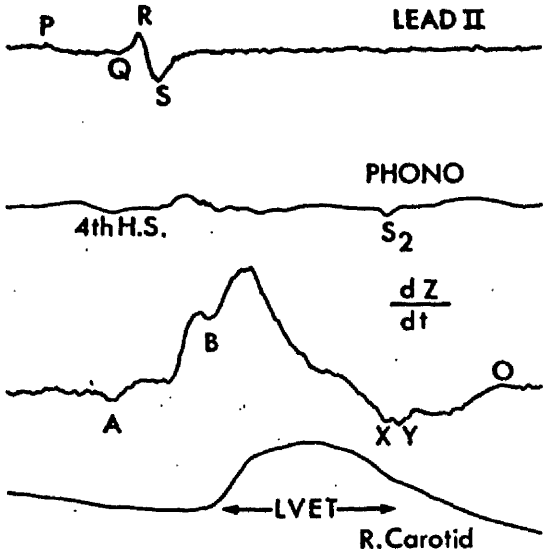
The temporal relationships of the waveform of the first derivative of the impedance cardiogram were first clearly described by Lababidi and his colleagues in 1970 (151) and their nomenclature has been followed by most other workers (Fig 11:1).

ATRIAL COMPONENT

In 1959, Nyboer noted a cyclical change in thoracic impedance corresponding to atrial mechanical activity (175). Krohn and his group observed undulations in the scalar impedance cardiogram which related to simultaneous ECG atrial changes in atrial flutter (26). In 1969, in a study of five patients with complete heart block, Bache et al (93) observed that the first component of the usual systolic upstroke of the impedance wave really represented the ascending limb of a negative deflection which accompanied atrial activity and could be seen independently of ventricular contraction. Atrial deflection begins usually at 100 to 120 milliseconds after the P wave on the ECG.

The maximum $^{dZ}/_{dt}$ amplitude could theoretically be increased by coincident atrial and ventricular contractions but Bache et al observed that atrial impedance changes only produced distortion of the $^{dZ}/_{dt}$ waveform in patients with abnormally short P-R intervals or when the P wave was superimposed upon the QRS complex in the ECG (93).

Lababidi and his colleagues described the A wave (Fig 11:1) which was related to atrial activity and was simultaneous with the beginning of the fourth heart sound (151). This observation was



A: Simultaneous with 4th heart sound

B: Synchronous or almost synchronous with maximal deflection of 1st heart sound

X: Synchronous or almost synchronous with aortic valve closure

Y: Synchronous or almost synchronous with pulmonary valve closure

O: Synchronous with rapid ventricular filling phase

FIGURE 11:1

SIMULTANEOUS FOUR CHANNEL RECORDING
IN 80 YEAR OLD HEALTHY FEMALE

(PAPER SPEED 100 mm/sec)

confirmed by other workers (36, 176-177) and it is evident that A waves are absent in the impedance cardiograms of patients in atrial fibrillation.

Takada et al (176) completed the first study of the quantitative aspects of the A wave which appeared to occur between 40 and 100 milliseconds after the P wave in subjects in normal sinus rhythm, first degree heart block or complete heart block. The amplitude of the A wave showed a small correlation with the pulmonary artery wedge pressure ($r = 0.47$; $p < 0.05$) but a much higher correlation with the left atrial ejection fraction ($r = 0.91$: $p < 0.005$) and the impedance technique is probably a useful non-invasive method of estimating the left atrial function or booster pump function of the left ventricle.

VENTRICULAR COMPONENT

In 1969, Karz et al observed qualitative abnormalities in the ventricular component of bipolar lead impedance cardiograms in 10 of 12 patients with acute myocardial infarction. The initial abnormality improved progressively over six weeks (178). The $^{dZ}/_{dt}$ waveform shows variable amplitude in ectopic activity (35, 44) and this is demonstrated in Fig 11:2.

Valvular lesions frequently distort the $^{dZ}/_{dt}$ waveform (14) and changes have been described in patients with mitral regurgitation (15, 48, 96, 179), aortic regurgitation (48, 97-8) and mitral stenosis (179).

MITRAL REGURGITATION

In 1970, Kinnen (48) and later in 1974, Kubicek et al (15) observed abnormalities in the impedance cardiogram in patients with mitral regurgitation. Parulkar et al (1980) described an apparent

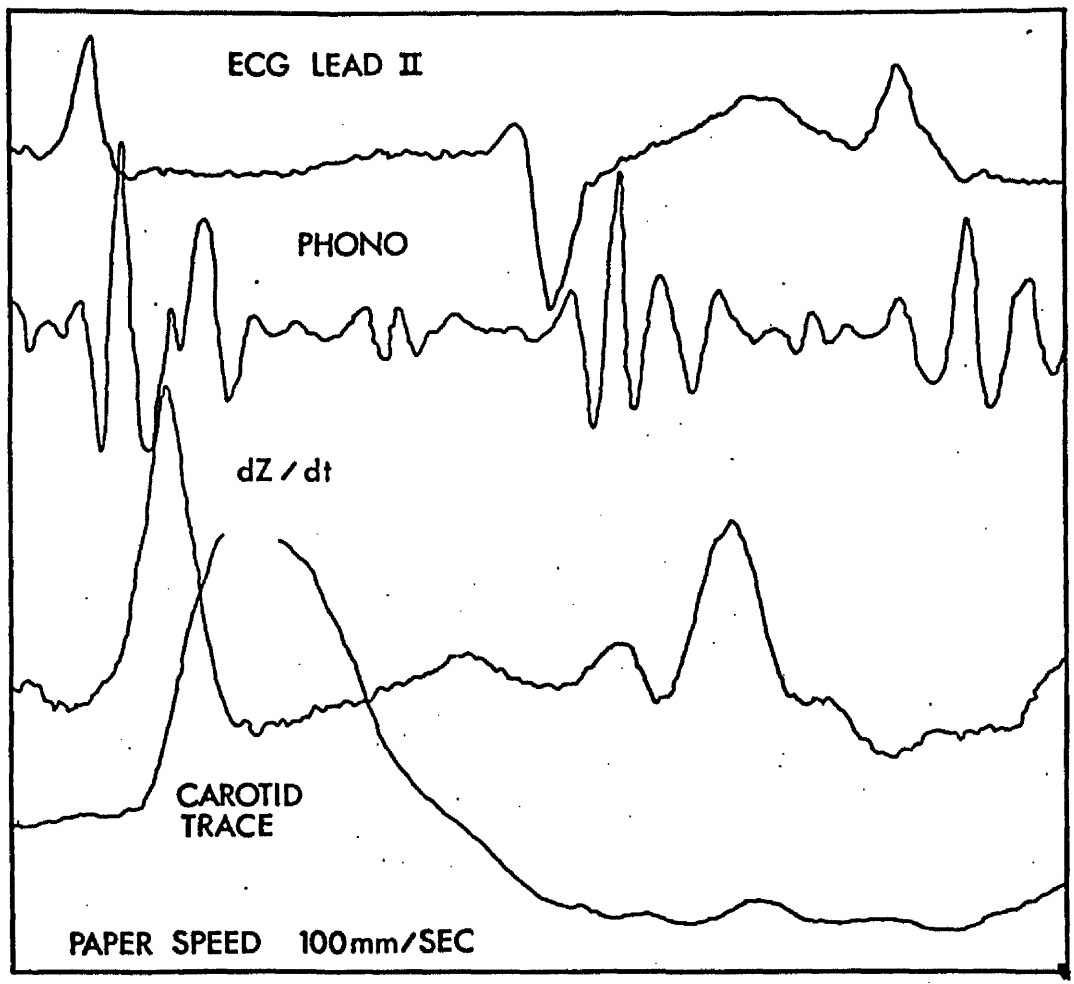


FIGURE 11:2

VARIABLE AMPLITUDE OF IMPEDANCE WAVEFORM IN VENTRICULAR ECTOPIC ACTIVITY IN A 77 YEAR OLD MALE WITH MITRAL REGURGITATION

distortion of the $^{dZ}/_{dt}$ ventricular component during its fall time (179). Karnegis et al (1981) further described this characteristic abnormality of the waveform in 35 cases of severe isolated mitral regurgitation (96). They also derived an index which can be easily obtained from the impedance tracing and which may be useful in identifying patients with mitral regurgitation but probably only in severe cases. The waveform abnormality returns to normal contours after valve replacement (96, 179).

MITRAL STENOSIS

In patients with mitral stenosis the O wave, at the time of rapid ventricular filling, is often more prominent than normal and may show a bifid pattern which returns to normal contour after mitral valvotomy (179). The O wave is however pronounced in patients with an enlarged left atrium due to other causes, e.g. left ventricular failure, large left to right cardiac shunts and after exercise, deep inspiration, in myocarditis or high cardiac output states (180, 181). The apparent exaggeration of the O wave may simply represent the inability of the ventricles to accommodate the venous return presented to them during early diastole. In patients with ischaemic heart disease an abnormally large O wave is associated with a significantly poorer prognosis in terms of mortality and functional disability (181).

AORTIC REGURGITATION

The impedance cardiogram X point occurs at or near the time of the aortic component of the second heart sound (Fig 11:1). The X point is deeper in subjects with aortic regurgitation (97) (Fig 11:3). The waveform appears to be affected in contour and magnitude by aortic regurgitation (48, 97) and this may reflect total left ventricular systolic output including the regurgitant

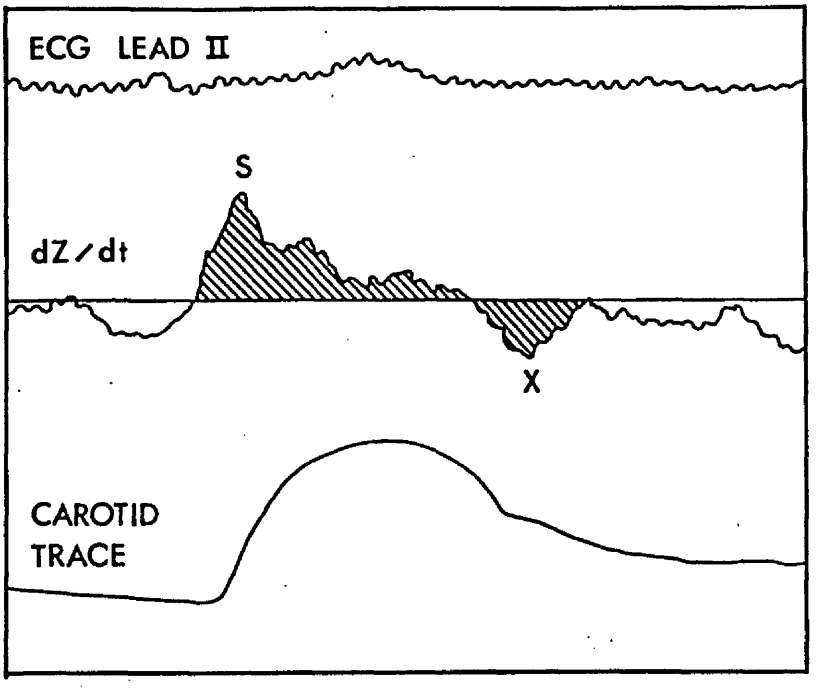


FIGURE 11:3

85 YEAR OLD FEMALE WITH MILD ISOLATED AORTIC REGURGITATION.

THE X WAVE IS DEEPER THAN NORMAL

fraction. This may in turn lead to an overestimate of the stroke volume and cardiac output as measured by the impedance technique (Chapter 4).

Quantification of aortic regurgitation is valuable not only in deciding on surgical intervention but also in planning mitral valve surgery when associated aortic reflux may cause flooding of the operative field. Clinical evaluation of aortic regurgitation is unreliable (182) and non-invasive quantification of aortic reflux is difficult to achieve. Echocardiography provides only indirect pointers to the diagnosis (183) but Doppler echocardiography may be a more promising technique (184).

Schieken and his colleagues have shown, in experimental animal studies, that both the ratio $\frac{X}{dZ/dt}$, where X is the amplitude of the X wave and dZ/dt is the amplitude of the impedance waveform, and the ratio of $\overline{X}/\overline{S}$, or aortic regurgitant fraction (AORTIC RF_I), where $\overline{X}$ is the area of the X wave and $\overline{S}$ is the area of the dZ/dt waveform are highly correlated with the severity of aortic regurgitation (185-186) (Fig 11:3). In further clinical studies (97) the AORTIC RF_I was highly correlated with the angiographically determined aortic regurgitant fraction ($r = 0.90$). In a more recent study in anaesthetized dogs, Schieken et al have observed that the aortic RF_I may be quantitatively related to the degree of aortic reflux induced by artificial means (98).

The results of these experimental and clinical studies would suggest that the impedance cardiogram may be a valuable sensitive non-invasive tool in assessing the severity of aortic regurgitation.

BUNDLE BRANCH BLOCKS

Early impedance cardiography studies observed bizarre or bifid

systolic waveform patterns in single clinical cases of left and right bundle branch block (44, 99, 187-8). Luisada and his colleagues completed a systematic study of the first derivative waveform in patients with the bundle branch blocks and described apparent characteristic systolic abnormalities (100). A further study was therefore carried out in a group of elderly patients with left or right bundle branch block to clarify the findings of Luisada et al (100).

Patients and Methods

Ninety-nine elderly patients under the care of the University Department of Geriatric Medicine were studied (52 males and 47 females, age range 61-96 years). Twenty patients had no clinical, radiological or electrocardiographic evidence of cardiovascular disease, 18 patients had left bundle branch block and 17 patients had right bundle branch block. The cardiac diagnoses in the remaining 44 patients are detailed in Table XXXII.

Simultaneous recordings of the electrocardiogram, phonocardiogram, $^{dZ}/_{dt}$ and carotid pulse wave were made in each subject, at rest, at a paper speed of 100 mm/second. Systolic time intervals were determined as described in Chapter 8.

Results

CARDIOVASCULAR NORMAL SUBJECTS. The cardiac first derivative impedance systolic waveform had a normal single peak contour in all 20 normal subjects.

LEFT BUNDLE BRANCH BLOCK. In all 18 cases of left bundle branch block the systolic wave was bifid (Table XXXIII) and an example of this phenomenon is displayed in Fig 11:4. The second peak was invariably taller than the first peak and the nadir between

DIAGNOSIS	NO. OF CASES
Cardiovascular normal	20
Left bundle branch block	18
Right bundle branch block	17
Ischaemic heart disease	11
Old myocardial infarction	8
Recent myocardial infarction	1
Aortic stenosis with left ventricular hypertrophy	12
Aortic regurgitation	4
Mitral regurgitation	8

TABLE XXXII

CARDIAC DIAGNOSIS OF 99 ELDERLY SUBJECTS IN IMPEDANCE CARDIOGRAM WAVEFORM STUDY

Patient	Sex	Age (Years)	Diagnosis	R-R (msec)	PEP (msec)	LVET (msec)	Systolic Waveform
1	F	77	Ischaemic heart disease	850	200	260	Bifid
2	F	74	Hypothyroid	600	200	240	Bifid
3	M	70	Emphysema	850	160	230	Bifid
4	F	78	Hypothyroid	1020	180	320	Bifid
5	F	76	Angina	690	180	260	Bifid
6	F	74	Stroke	650	140	220	Bifid
7	F	76	Diabetes	750	140	260	Bifid
8	M	82	Adenocarcinoma	870	220	230	Bifid
9	M	69	Cardiac failure	670	150	210	Bifid
10	F	70	Cardiac failure	1430	130	300	Bifid

TABLE XXXIII

RESULTS OF IMPEDANCE CARDIOGRAM WAVEFORM STUDY IN 18 PATIENTS WITH LEFT BUNDLE BRANCH BLOCK

Patient	Sex	Age (Years)	Diagnosis	R-R (msec)	PEP (msec)	LVET (msec)	Systolic Waveform
11	M	75	Ischaemic heart disease	860	210	250	Bifid
12	F	89	Ischaemic heart disease	950	210	250	Bifid
13	F	90	Ischaemic heart disease	690	170	260	Bifid
14	F	74	Cranial arteritis	830	140	310	Bifid
15	M	96	Left ventricular hypertrophy	1040	180	310	Bifid
16	F	90	Astrocytoma	740	200	240	Bifid
17	M	70	Alcoholic cardiomyopathy	720	150	250	Bifid
18	F	75	Ischaemic heart disease	980	180	280	Bifid

TABLE XXXIII (Cont'd)

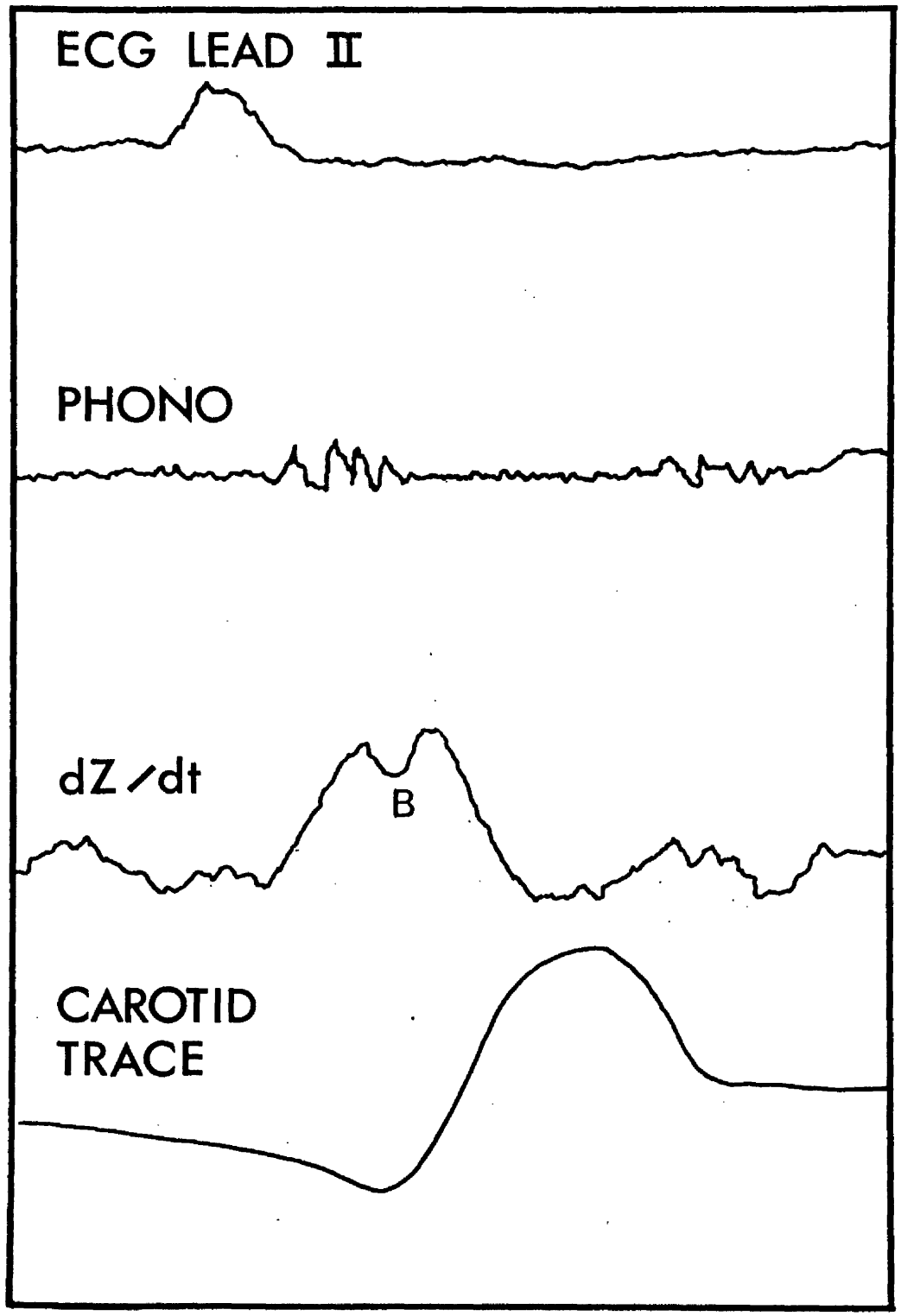


FIGURE 11:4

FOUR CHANNEL RECORDING OF PATIENT NO. 2 WITH LBBB.

FEMALE 74 YEARS WITH HYPOTHYROIDISM.

THE START OF THE SECOND PEAK OF SYSTOLIC WAVE IS SYNCHRONOUS WITH THE START OF LEFT VENTRICULAR EJECTION

the peaks, which is probably the B point, was synchronous or nearly synchronous with the start of left ventricular ejection.

RIGHT BUNDLE BRANCH BLOCK. In 7 of the 17 cases of right bundle branch block the systolic wave was bifid (Figure 11:5) and in the remainder the waveform peak was splintered and prolonged (Table XXXIV). The B point was synchronous or nearly synchronous with the beginning of left ventricular ejection.

OTHER CARDIAC DISORDERS. In 20 patients with ischaemic heart disease and 24 patients with valvular lesions and no electrocardiographic evidence of conduction defects, the systolic waveform had a normal single peak contour with no evidence of splintering.

Discussion

In this study the bundle branch blocks were associated with characteristic changes in the systolic impedance waveform and no such abnormalities were observed in cardiovascular normal subjects or in patients with other forms of cardiac disease. The bifid appearance of the wave pattern in bundle branch block is most likely to be due to asynchrony of the ventricles and this has already been postulated by Kubicek et al (15), Keller and Imhof (44) and Keller and Blumberg (189). The first systolic peak in left bundle branch block (Figure 11:4) is probably related to right ventricular activity as is the second systolic peak in right bundle branch block (Figure 11:5).

Luisada et al (100) observed, however, a bifid systolic wave in two elderly subjects with no clinical evidence of heart disease and in six patients with previous myocardial infarction and no evidence of bundle branch block. It may be that these abnormalities were

Patient	Sex	Age (years)	Diagnosis	R-R (msec)	PEP (msec)	LVET (msec)	Systolic Waveform
1	F	80	Ischaemic heart disease	1120	100	350	Splintered
2	F	90	Ischaemic heart disease	860	110	290	Spintered
3	M	69	Acute myocardial infarction	950	90	290	Splintered
4	M	87	Anaemia	800	110	250	Bifid
5	F	87	Anaemia	950	110	260	Bifid
6	F	81	Atrial fibrillation	670	130	200	Splintered
7	F	82	Atrial fibrillation	860	120	300	Splintered
8	F	90	Cardiomegaly	730	120	410	Splintered
9	F	84	Hypothyroid	1120	170	320	Splintered
10	M	85	Cardiac failure	650	140	260	Splintered

TABLE XXXIV

RESULTS OF IMPEDANCE CARDIOGRAM WAVEFORM STUDY IN 17 PATIENTS WITH RIGHT BUNDLE BRANCH BLOCK

Patient	Sex	Age (years)	Diagnosis	R-R (msec)	PEP (msec)	LVET (msec)	Systolic Waveform
11	M	79	Atrial fibrillation	750	140	270	Bifid
12	F	83	Right ventricular hypertrophy	1150	180	330	Splintered
13	F	79	Emphysema	530	90	200	Bifid
14	F	75	Ischaemic heart disease	890	100	310	Bifid
15	M	73	Cardiovascular normal	710	120	270	Splintered
16	M	78	Alcoholic neuropathy	670	130	220	Bifid
17	M	75	Old myocardial infarct	880	120	280	Bifid

TABLE XXXIV (Cont'd)

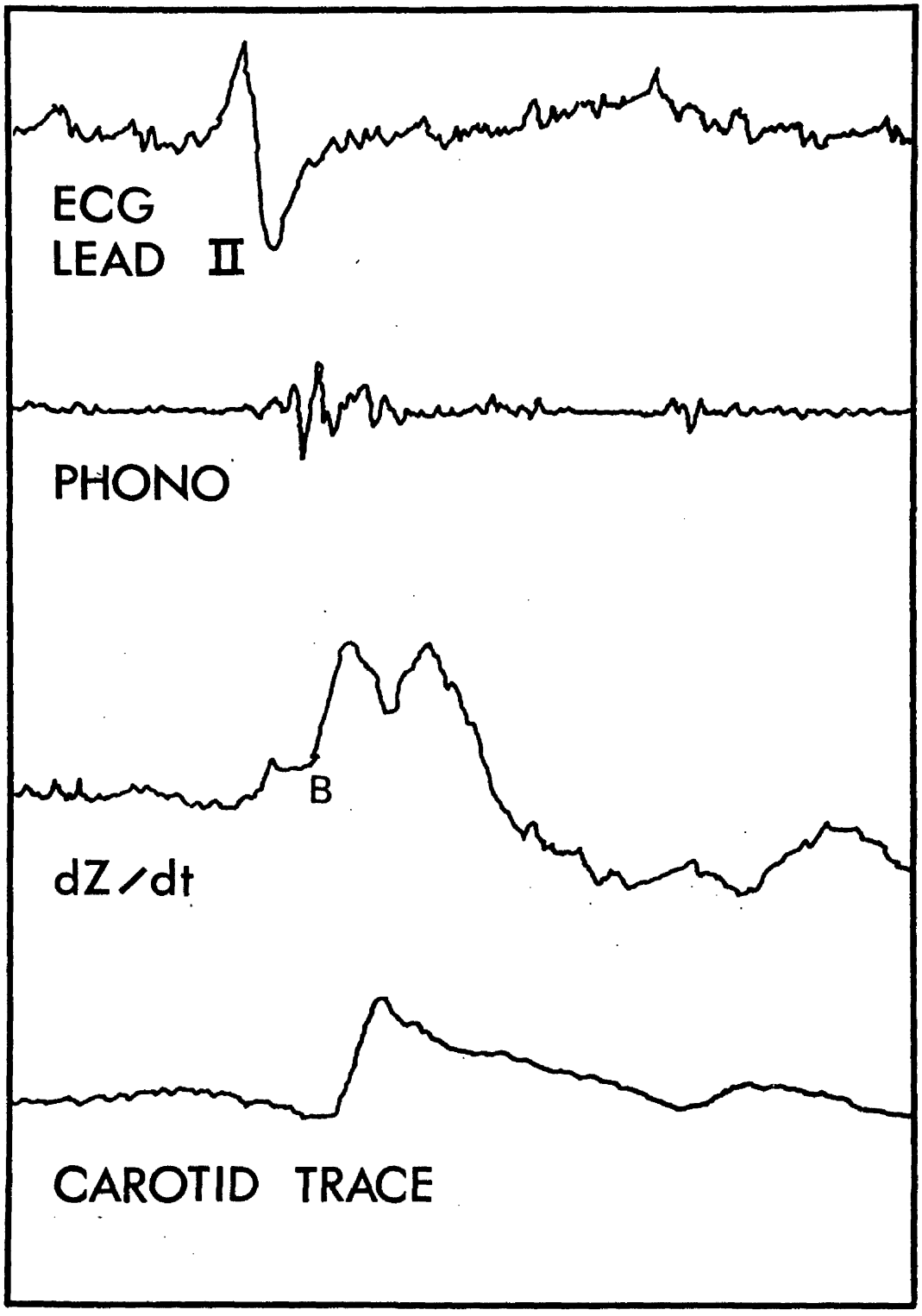


FIGURE 11:5

PATIENT NO. 5 WITH RBBB. FEMALE OF 87 YEARS WITH ANAEMIA.

THE B POINT IS NEARLY SYNCHRONOUS WITH THE START OF LEFT VENTRICULAR EJECTION

due to left ventricular dyssynergy (100) but the explanation might also be that mechanical asynchrony of the ventricles can occur without electrocardiographic evidence in all cases. Bifidity or multiple splintering may be induced by pressure overload using phenylnephrine infusions in human pharmacological studies (188) but the significance of this finding is not clear unless it relates to stress dyssynergy of the left ventricle or asynchrony.

These studies in bundle branch block further explain the origin of the first derivative systolic waveform of the impedance cardiogram and suggest that the waveform comprises elements representing haemodynamic activity in both the left and right ventricles.

SUMMARY

The first derivative of the impedance cardiogram is useful in the non-invasive assessment of left atrial function. Abnormalities of the systolic waveform occur in acute myocardial infarction, the bundle branch blocks and in severe mitral regurgitation. The severity of isolated aortic regurgitation may be assessed by an index derived from the $^{dZ}/_{dt}$ waveform and an exaggerated O wave may have prognostic significance in patients with ischaemic heart disease.

CHAPTER 12

RESISTIVITY OF HUMAN WHOLE BLOOD

Blood is a good conductor of electrical current. The earliest studies of the electrical conducting properties of blood were published by Bugarsky and Tangl in 1898 (190) and they demonstrated that the conductivity of whole blood is less than that of serum and that it decreases progressively with the concentration of red cells. Blood may be thought of therefore as a suspension of cells, which are very poor conductors, and plasma whose conductivity depends on the concentration of its constituent electrolytes (191). Several studies have confirmed that the resistivity of blood (ρ) is directly proportional to the haematocrit (17, 37, 191-7).

In the Kubicek equation for the derivation of the impedance stroke volume, it is necessary to know the accurate resistivity of blood. Geddes and Baker have demonstrated that the resistivity of human whole blood with a haematocrit of 40% lies in the range of 148-176 ohm centimetres at body temperature (17). The early studies of human whole blood resistivity were however based on samples drawn from blood bank time expired supplies (37, 194). In view of the importance of obtaining as accurately as possible the resistivity of blood in clinical impedance cardiography, three studies were performed using fresh venous whole blood samples to validate the standard resistivity/haematocrit nomogram of Kubicek provided by the manufacturers of the Minnesota Impedance Cardiograph (37).

Patients and Methods

Fresh venous blood samples were obtained from elderly patients under the care of the University Department of Geriatric Medicine.

Each 10 ml. sample was collected in a plastic container, with lithium heparin as the anti-coagulant, and stored in a water bath at 37°C until required.

Resistivity measurements were made with a variable path length conductivity cell devised by the staff of the West of Scotland Health Boards Department of Clinical Physics and Bioengineering at the Southern General Hospital and West Graham Street, Glasgow. The cell was based on a modification of the technique of Hill and Thompson (195) and design improvements included an improved temperature control mechanism and digital display. The blood resistivity bridge was connected to the resistivity cell mounted on a shaker, the temperature controlled water bath and an oscilloscope, digital ohmeter and thermometer.

The cell was calibrated using a 0.9% solution of physiological saline (resistivity 50 ohm cm. at 37°C and 100 kHz).

Blood was carefully injected into the cell by means of a plastic syringe without a needle. The cell was carefully filled to a maximum of approximately 4 ml. without the introduction of air bubbles. The resistivity bridge was then balanced within 6 seconds and a resistance measurement taken. The length of blood in the cell was then shortened by 1 cm. by adjustment of the plunger in the chamber and the resistance value for the smaller volume of blood was noted. The resistivity (ρ) of the sample was thereafter derived as follows:-

$$= A \times \frac{\Delta R}{\Delta l} = 0.597 \times R \text{ ohm cms.}$$

where A is the cross sectional area of the cell chamber, Δl is the distance (cm) between the two plunger positions and ΔR is the difference in resistance measured at the two positions.

STUDY I

The resistivities of whole fresh venous blood in samples from 64 individual elderly patients were obtained over a haematocrit range of 20-57% at 37°C. The haematocrits were measured by centrifuging the blood at 11,000 rev./min. in a Hawksley Micro-centrifuge. Two resistivity values were obtained for each sample and the mean value was noted.

STUDY II

The resistivities of whole fresh venous blood in four samples from each of ten individual elderly patients were measured over a haematocrit range of 35-53% (total 40 samples). In each patient, resistivity values were taken at blood temperatures of 36°C, 37°C, 37.5°C and 38°C.

STUDY III

The effect of bench ageing on the resistivities of blood samples from 21 individual subjects was studied. Nine fresh samples were stored in the water bath at 37°C and resistivity values were measured initially, and after two, four and six hours (Group A). Six fresh samples were stored on the bench at room temperature and resistivity values were taken initially, and two, four and six hours after rewarming each sample to 37°C (Group B). In each of a further six patients, five fresh blood samples were studied. Resistivities were measured initially and after two, four, six and 24 hours; during this period the samples were stored on the bench at room temperature and rewarmed to 37°C as required such that each sample was only rewarmed on one occasion (Group C).

Results

STUDY I: Relationship between resistivity and haematocrit

The technique for measuring the whole blood resistivity was highly reproducible as the mean difference between the 64 paired values was less than 1%. Values for haematocrit and resistivity are detailed in Appendix 5 and displayed in Fig 12:1. A curvilinear relationship is apparent and this is best described by the exponential function

$\rho = e^{(4.3866 + 0.003186H^{1.45})}$ ($r = 0.978$) where H is the haematocrit.

STUDY II: Resistivity and Temperature Change

The values for resistivities of whole blood in 10 subjects at 36°C, 37°C, 37.5°C and 38°C are detailed in Appendix 6 and summarized in Table XXXV. The resistivity value reduced with a rise in blood temperature across the range of 36-38°C (average change 3% per 1C°).

STUDY III: Resistivity and Sample Ageing

The effects of bench ageing on resistivity are detailed in Appendix 7 and summarized in Table XXXVI.

Group A In the nine samples which were stored in the water bath for six hours, the resistivity fell on average by 1-2% per hour but there was little change apparent in six samples.

Group B In the six samples which were stored on the bench and rewarmed to 37°C on three occasions, over six hours, the resistivity fell on average by 2-4% per hour.

Group C In the 30 samples (five for each of six subjects) which were stored on the bench and in which four samples for each subject were rewarmed only once to 37°C over 24 hours, the

TEMPERATURE	36°C	37°C	37.5°C	38°C
Mean change in resistivity (%)	- 3.2	- 1.5	- 1.9	

TABLE XXXV

EFFECT OF TEMPERATURE CHANGE ON RESISTIVITY (ρ)

OF WHOLE BLOOD IN 10 SUBJECTS

	TIME	IMMEDIATE*	2 HRS	4 HRS	6 HRS
GROUP A					
(9 subjects)	Mean change in resistivity (%)		- 2.2	- 2.3	- 3.7

	TIME	IMMEDIATE*	2 HRS	4 HRS	6 HRS
GROUP B					
(6 subjects)	Mean change in resistivity (%)		- 3.4	- 5.5	- 7.4

	TIME	IMMEDIATE*	2 HRS	4 HRS	6 HRS	24 HRS
GROUP C						
(6 subjects)	Mean change in resistivity (%)	- 0.1	- 0.1	- 0.4		+ 7.4

* Immediate: within half an hour.

TABLE XXXVI

EFFECT OF BENCH AGEING ON RESISTIVITY (ρ)

OF WHOLE BLOOD IN 21 SUBJECTS

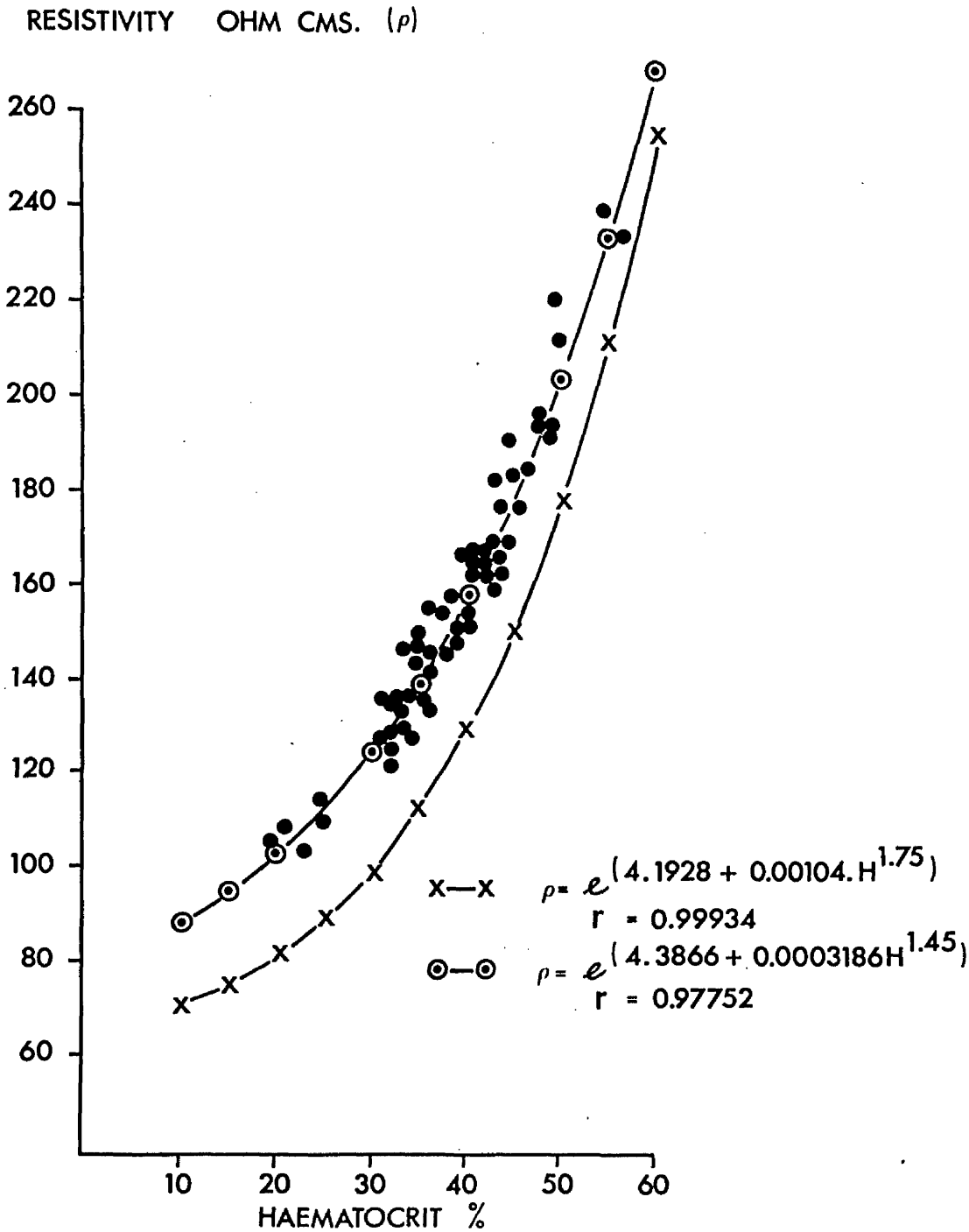


FIGURE 12:1

VALUES FOR HAEMATOCRIT AND RESISTIVITY IN 64 SAMPLES OF WHOLE VENOUS BLOOD AT 37°C

(x——x : KUBICEK (37))

resistivity showed no real change over six hours, but rose by 7.4% on average over 24 hours.

Discussion

The technique used for measuring blood resistivity in the study described in this chapter has been found to produce highly reproducible results (mean difference between paired values < 1%). The variable path length cell was used to compensate for the presence of electrode/electrolyte impedance (195).

The positive haematocrit coefficient of resistivity of whole fresh blood has been confirmed (17, 27, 190-7) but higher values of resistivity have been observed than in two previous studies of time expired blood bank specimens (37, 194) and two studies of fresh blood samples (195-6) (Table XXXVII). Geddes and Sadler (194) and Kubicek (37) studied time expired, reconstituted blood from transfusion banks and Kubicek used a two electrode resistivity measuring device which did not include any compensatory mechanism for electrode/blood interface impedance which might well introduce an important source of error (195). Hill and Thompson (195) employed fresh blood samples and derived resistivity values which were consistently 10% lower than those of Geddes and Sadler (194) or Kubicek (37). In Mohapatra and Hill's study (196) blood samples from haemodialysis patients were studied and artificially low values of resistivity may have occurred due to high blood concentrations of electrolytes and urea.

The resistivity values in the present study were lower than those obtained by Mohapatra and his colleagues in fresh adult blood samples (197) but these workers stored the blood, at 5^{o}C in a refrigerator until measurements were made up to 24 hours after,

HAEMATOCRIT %	GEDDES AND SADLER 1973 (194)	KUBICEK 1975 (37)	HILL AND THOMPSON 1975 (195)	MOHAPATRA AND HILL 1975 (196)	MOHAPATRA COSTELOE AND HILL 1977 (197)	WILLIAMS
15	74	75	62	57	100	94
20	83	82	72	69	114	103
25	92	90	83	82	128	118
30	103	100	93	94	142	125
35	115	113	104	106	163	139
40	128	127	114	118	185	157
45	143	146	125	130	206	177

TABLE XXXVII

HAEMATOCRIT RANGE 15–45% AND WHOLE BLOOD RESISTIVITY IN SIX STUDIES OF HUMAN BLOOD

In vivo animal experimental work has, however, shown that blood resistivity may actually rise with an artificially induced reduction in the haematocrit (68). This phenomenon is likely to be related to alterations in red cell velocity rather than simple haematocrit changes as flowing blood has a lower resistivity than stationary blood (198-9).

The exciting frequency used in the study in this chapter was 100 kHz and although Schwan and Kay observed that blood resistivity tends to fall slowly with rising electrical frequencies (200), Mohapatra and his colleagues have reported that impedance bridge measurements of resistivity appears to be unaffected by frequency changes over the range of 1-100kHz (197).

Like other electrolyte solutions, blood has a negative temperature coefficient of resistivity (17, 196, 201). In the current study (Table XXXV) over a temperature range of 36 to 38^{o}C, the resistivity fell by, on average, 3% for each centigrade degree change but the rate of resistivity decrease was not the same for all of the samples studied (Appendix 6) and this confirms the observation of Mohapatra and Hill (196).

Storage of the samples in the water bath at 37^{o}C was associated with a 1-2% reduction in resistivity per hour (Group A, Table XXXVI) but storage at room temperature and rewarming the same sample several times to 37^{o}C was associated with an acceleration of the fall in resistivity to 3-4% per hour and this may have been related to red cell changes due to repeated heat damage (Group B). In Group C in which each sample was rewarmed from room temperature on one occasion only, the resistivity values did not change significantly over six hours but increased by 7% between six and 24 hours. This latter effect may account for the higher resistivity values observed

by Mohapatra et al (197).

If one accepts the assumptions inherent in the Kubicek formula for impedance stroke volume measurement, then the accuracy of the calculation will depend on an appropriate value for ρ. A variety of factors may influence the resistivity of blood samples including the haematocrit, temperature and blood velocity. Fresh blood clearly differs from reconstituted blood as far as electrical properties are concerned. When comparative studies between the impedance technique and other methods of cardiac output measurement are being described the following information about resistivity values must be clearly described:-

1. Whether fresh blood or reconstituted blood is used.
2. How the samples are stored before measurement.
3. The delay before resistivity measurements.
4. The measurement technique.
5. The frequency of excitation.
6. The temperature of the blood samples.

CHAPTER 13

RESPONSE TO POSTURAL STRESS TESTING IN THE ELDERLY

Homeostatic abilities reduce with ageing and one of the characteristics of increasing age is that more time is required to adjust to physiological stresses (202). Passive upright tilting is a useful test of cardiovascular status because it quickly imposes a predictable set of circulatory changes (203). Traditional physiological studies in tilted subjects have involved catheterization techniques of the heart and the great vessels but artificial haemodynamic values may be achieved due to intravascular instrumentation and the effects of anxiety (204), particularly in elderly subjects.

The impedance method for measuring the stroke volume and cardiac output during orthostatic stress testing has been validated in three studies (49, 69, 139). The technique has been shown to produce reproducible results in elderly subjects (140). A study of the haemodynamic changes associated with standardized tilt testing in elderly subjects was performed to elucidate the physiological effects of orthostatic stress in old age.

Subjects and Methods

Six elderly subjects were studied (4 males, 2 females: age range 70–86 years). They were all ambulant and had no clinical, electrocardiographic or radiological evidence of heart disease. None had clinical cerebrovascular disease, parkinsonism, diabetes mellitus, anaemia or were receiving drugs affecting the cardiovascular or central nervous systems.

The studies were conducted in a well-lit, warm, quiet

laboratory. The subjects were all at least three hours post prandial and were rested for 15-30 minutes before the test procedure.

Each subject was placed in the supine position on the tilt table and the feet rested on a footrest. Three supporting belts were applied comfortably but securely to the knees, hips and chest. The following measurements were taken at rest in the supine position (mean of two values), after immediate tilt to 60° foot down at one minute, three minutes and five minutes, and finally after one minute back in the supine position.

1. Blood pressure (mmHg) in the right arm by standard sphygmomanometry.
2. Heart rate (beats per minute).
3. Stroke volume (ml) by impedance cardiography.

The cardiac output was derived from the formula -

$$\frac{\text{Stroke volume x heart rate}}{1000}$$

The mean blood pressure was calculated as the diastolic + 1/3 pulse pressure (145). The total peripheral resistance was derived by dividing the value for the mean blood pressure by the cardiac output at each stage of the test (205).

Results

The cardiovascular effects of 60° foot down tilt in the six elderly subjects are detailed in Appendix 8 and summarized in Table XXXVIII and Figure 13:1. Haemodynamic changes were complete within one minute and there was little further change apparent during the remaining four minutes of the tilt test. Considerable variations in the degree of response between individuals were apparent.

BLOOD PRESSURE The mean blood pressure fell by an average of 3% on

		60° FOOT DOWN TILT			
	SUPINE*	1 MINUTE	3 MINUTES	5 MINUTES	SUPINE
MEAN BLOOD PRESSURE (mmHg)	101.2 (14.1)	- 3%	- 3%	- 1%	+ 3%
HEART RATE (beats/min)	75.8 (9.4)	+ 8%	+ 8%	+ 8 %	+ 1%
STROKE VOLUME (mls)	70.0 (8.4)	- 18%	- 18%	- 17%	+ 1%
CARDIAC OUTPUT (L/min)	5.2 (0.5)	- 11%	- 11%	- 12%	+ 1%
TOTAL PERIPHERAL RESISTANCE (mmHg/L/min)	19.6 (4.0)	+ 9%	+ 9%	+ 12%	+ 2%

* Mean (Standard deviation)

TABLE XXXVIII

CARDIOVASCULAR EFFECTS OF 60° FOOT DOWN TILT IN SIX ELDERLY SUBJECTS (GROUP MEAN VALUES AND PERCENTAGE CHANGE)

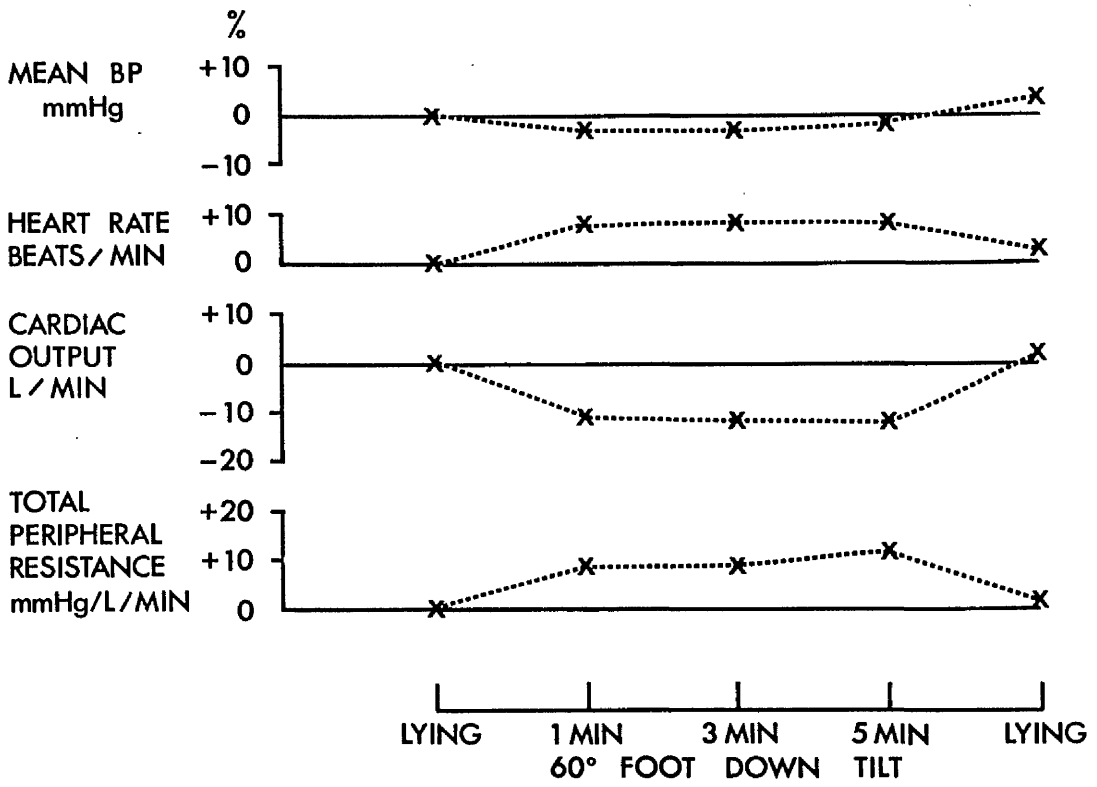


FIGURE 13:1

MEAN HAEMODYNAMIC CHANGES IN SIX CARDIOVASCULAR NORMAL ELDERLY SUBJECTS DURING TILT TEST

tilting and one minute after the tilt test, the blood pressure exceeded the original resting value by 5% in four of the six subjects.

HEART RATE The heart rate increased by an average six beats per minute (8%) and this occurred in all of the subjects within the first 10 seconds after tilting.

STROKE VOLUME The stroke volume fell by 18% on average during tilting and returned to pre-test values within one minute after the test.

CARDIAC OUTPUT The derived cardiac output fell by 11% on average and returned to pre-test values within one minute after the test.

PERIPHERAL VASCULAR RESISTANCE The derived total peripheral resistance rose by 9% on average during tilting.

Discussion

The normal physiological haemodynamic responses to postural stress in healthy young adults are well known (206-7). A change in posture from the supine to the upright position is followed immediately by an increase in venous pressure, below the level of the heart, with peripheral blood pooling and reduced cardiac venous return. Both the right and left ventricular filling pressures are decreased and the stroke volume and cardiac output are reduced (208). In normal man, the mean blood pressure is usually maintained within narrow limits (206, 210); the systolic blood pressure responds variably (210) and the diastolic pressure rises with a fall in pulse pressure. The main compensatory mechanisms involved result from the initial tendency to a fall in blood pressure which activates the baroreceptor reflex arc and this is associated with an adrenergic vasoconstrictor response on both the

arterial and venous sides of the vascular bed and cardioacceleration with an increase in myocardial contractility.

In young adults, the heart rate increases within the first ten seconds (150, 203) by 19-35% (90, 139, 141, 206-7, 210) although wide individual variations may occur (207). Stroke volume falls by 22-47%, cardiac output by 14-36% and total peripheral vascular resistance rises by 30-40% (206) (Tables XXXIX, XL).

The 60^{o} tilt test is used for maximum measurable haemodynamic effect (206). All significant changes occur in the first minute and little change thereafter. Various ways of deriving the peripheral vascular resistance have been devised and the quotient of mean blood pressure and cardiac output as an index of the vascular resistance is helpful but must, however, be subject to some reservation (145).

In the study of elderly subjects described in this chapter, the heart rate response was an increase of only 8% and this occurred within ten seconds in all subjects. This reduced response to orthostatic stress in the elderly has been observed before (211-3). The stroke volume and cardiac output reductions are less marked in the elderly and the rise in the peripheral vascular resistance is much less than would be expected in younger adults. It is known that increased tolerance to tilt occurs in patients with heart disease with or without cardiac failure (150, 207), and this is probably due to the associated rise in intravascular volume, raised peripheral vascular resistance and increased ventricular filling pressures. Increased tolerance to the normal effects of postural stress has also been observed in subjects taking beta adrenergic blocking drugs (214) and this is probably because the expected functional changes during tilt can be supported at a lower heart

STUDY	REFERENCE	SUBJECTS	HEART RATE (beats/min)	STROKE VOLUME (mls)	CARDIAC OUTPUT (L/min)
1	Judy et al (90)	Young Men	+ 32%	- 31%	- 12%
2	Asayama et al (139)	Young Men		- 40%	- 35%
3	Jung et al (141)			- 30%	
4	Asayama et al (210)	Young Men		- 43%	- 34%

Key + : Increase

- : Decrease

TABLE XXXIX

STUDIES OF HAEMODYNAMIC RESPONSES TO POSTURAL STRESS TESTS IN HUMAN SUBJECTS (LYING TO STANDING ERECT) IMPEDANCE STROKE VOLUME MEASUREMENT

STUDY	TILT	REFERENCE	SUBJECTS	HEART RATE (beats/min)	STROKE VOLUME (mls)	CARDIAC OUTPUT (L/min)	PERIPHERAL RESISTANCE (mm/L/min)
1	20°	BOER et al (46)	Young men	No change	- 22%	- 25%	+ 41%
2	30° and 55°	HILL AND MERRIFIELD (105)	Healthy men	+ 23%	- 47%	- 36%	
3	30°	GABRIEL et al (49)	Post myocardial infarct	+ 15%	- 23%	- 13%	
4	60°	THANGARAJAH et al (219)	Young subjects			- 27%	
5	70°	SMITH et al (145)	Young men	+ 35%	- 40%	- 18%	+ 40%
6	70°	SMITH et al (69)	Young men	+ 25%	- 45%	- 18%	+ 40%
7	70°	ZAMBRANO AND SPODICK (150)	Healthy men	+ 26%	- 32%	- 14%	
8	70°	ZAMBRANO AND SPODICK (150)	Ischaemic heart disease	+ 1%	- 1%	- 1%	
9	60°	THANGARAJAH et al (219)	Elderly			Variable	

KEY + : Increase - : Decrease

TABLE XL

STUDIES OF HAEMODYNAMIC RESPONSES TO POSTURAL STRESS TESTS IN HUMAN SUBJECTS (TILT TEST). IMPEDANCE STROKE VOLUME MEASUREMENT

rate.

It is known that the sensitivity of the cardiac beta adrenergic responses wane with the ageing process (215-7) and baroreceptor sensitivity probably declines with age (218).

The reduced haemodynamic responses of apparently healthy elderly individuals subjected to postural stress may be due to occult heart disease, reduced left ventricular wall compliance (174), a reduced beta adrenergic response to tilt or an abnormally high resting peripheral vascular resistance (219).

CHAPTER 14

HAEMODYNAMIC STUDIES IN POSTURAL HYPOTENSION

Postural blood pressure drop of more than 20 mmHg on standing is known to be common in the elderly (Table XLI). The prevalence appears to increase with age (222) although this has been disputed (223). In younger patients, a variety of single causes have been reported including diabetic neuropathy (226) and intermediolateral column degeneration (227). In the elderly the literature suggests that multiple causes predominate (205, 222, 228).

Most elderly people tolerate postural blood pressure drop unless some other stress is introduced. Prolonged bed rest will produce some degree of cardiovascular deconditioning and difficulty in maintaining the blood pressure on standing (229). A reduction in blood volume, varicose veins, acute myocardial infarction, anaemia, infections or biochemical upsets may aggravate the elderly patient's tendency to postural hypotension and neurological disorders, especially cerebrovascular disease or parkinsonism, are common associations. Many commonly prescribed drugs interfere with circulatory reflexes (230) and together they probably constitute the commonest cause of symptomatic postural hypotension in geriatric medical practice (205).

The impedance cardiography technique is a useful non-invasive method for measuring changes in the cardiac output and the study described in this chapter was performed to investigate the problem of symptomatic postural hypotension in elderly hospital patients in an attempt to determine the haemodynamic mechanisms involved.

Patients and Methods

Forty hospital inpatients with symptomatic postural

STUDY	POPULATION STUDIED	PREVALENCE
RODSTEIN AND ZEMAN (220)	Old People's Home	10%
JOHNSON et al (221)	Geriatric Unit	17%
CAIRD et al (222)	At home	24%
MYERS et al (223)	Geriatric Unit	11%
MacLENNAN et al (224)	At home	22%
LENNOX AND WILLIAMS (205)	Geriatric Unit	10%
WILLIAMS AND AMERY (225)	Untreated hypertensives	11%

TABLE XLI

PREVALENCE OF POSTURAL BLOOD PRESSURE DROP IN THE ELDERLY

(SYSTOLIC BLOOD PRESSURE FALLS > 20 mmHg ON STANDING)

hypotension were studied. These included 39 elderly subjects (21 males and 18 females with a mean age of 76 years and a range of 65-86 years) and one 41 year old insulin dependent diabetic male patient. Severely ill patients, who could not stand, were excluded from the study.

Lying and standing blood pressures were measured by standard syphygmomanometry and all 40 patients had evidence of a postural systolic blood pressure drop of 20 mmHg or more at one minute after standing up. A detailed drug history was obtained and a full clinical examination performed. Investigations included a full blood count, plasma glucose concentration, blood urea and electrolytes, electrocardiogram and chest radiograph.

Detailed haemodynamic studies were performed in all subjects as described in Chapter 13, and the following measurements were taken at rest in the supine position (mean of two values), after immediate tilt to 60^{o} foot down at one minute, three minutes and five minutes, and finally after one minute back in the supine position.

1. Blood pressure (mmHg) in the right arm by standard sphygmomanometry.
2. Heart rate (beats per minute).
3. Stroke volume (ml) by impedance cardiography.

The cardiac output, mean arterial blood pressure and total peripheral resistance were derived as described in Chapter 13.

Results

Symptoms of postural hypotension including dizziness or lightheadedness, tremor, weakness, poor balance or falls were reported in all of the patients studied. The associated causes of postural

hypotension are detailed in Appendix 9 and summarised in Table XLII. Only one subject, a 65 year old man with parkinsonism and gross postural hypotension, could not tolerate tilt to 60^{o} foot down for more than one minute.

Thirty-three patients (83%) manifest maximal postural blood pressure drop within the first minute of tilting, two patients within the third minute (one patient with widespread lymphoma and one patient with diuretic induced hypotension) and five patients after five minutes (two with drug related causes, one with peripheral neuropathy, one with diabetes mellitus, and one with no clear cause).

Symptomatic postural hypotension was associated with a fall of peripheral vascular resistance on tilting in 33 (83%) of the patients studied. Five (13%) had a rise in the peripheral resistance and this group included two parkinsonian patients taking levodopa/carbidopa therapy, one patient with hypokalaemia and a large reduction in the cardiac output, one patient taking multiple drugs and one patient with a past history of cervical sympathectomy.

Eight patients (20%) had a significant increase in the cardiac output on tilting and all of this group had a reduction in the peripheral vascular resistance. Four of these patients had evidence of congestive cardiac failure.

There was a wide individual variation in the heart rate response to tilt (range 0-37%, mean 11.1 (standard deviation 8.3) beats per minute).

PARKINSONISM

Ten patients had postural hypotension associated with parkinsonism (7 males, 3 females). Two of these patients were

ASSOCIATED CAUSE	MALES	FEMALES
Parkinsonism	7	3
Diabetes mellitus	1	–
Alcoholic neuropathy	1	–
Pneumonia	1	–
Cerebrovascular disease	0	1
Lymphoma	1	–
Severe ischaemic heart disease	1	–
Hypokalaemia	1	–
Cervical sympathectomy	–	1
Thiazide diuretics	1	4
Frusemide	1	–
Thioridazine	1	2
Multiple drugs	4	4
No clear cause	2	3

TABLE XLII

SYMPTOMATIC POSTURAL HYPOTENSION IN 40 PATIENTS.

ASSOCIATED CAUSES

receiving no drug therapy and the remaining eight were taking stable doses of levodopa combination preparations.

CASE 1. Male of 70 years of age with evidence of ischaemic heart disease and parkinsonism on no drug therapy. Postural hypotension was associated with an 8% rise in the heart rate, an 8% fall in the cardiac output and a small reduction in the peripheral vascular resistance (Fig 14:1).

CASE 2. Male of 65 years with no evidence of heart disease but parkinsonism and receiving no drug therapy. In this case gross postural hypotension on tilting (100% mean blood pressure fall) was associated with a 19% rise in the heart rate, a 7% rise in the cardiac output and a 100% reduction in the peripheral vascular resistance.

CASES 3-8. Six patients (4 males, 2 females) with parkinsonism treated with levodopa and benserazide (Madopar) in an average daily dose of 417 mg had postural hypotension. Systematic haemodynamic changes were noted within the first minute of tilting in this group (Fig 14.2). The mean blood pressure fell by 23% (9-39%) and this was associated with a mean heart rate rise of 10% (0-37%), mean reduction in the cardiac output of 21% (11-39%) and a mean fall in the peripheral vascular resistance of 8% (1-18%).

CASES 9 and 10. Two patients (one male, one female) had postural hypotension associated with parkinsonism treated with levodopa and carbidopa (Sinemet). Both were taking a total daily dose of 220 mg of the drug. Both had a significant drop in the mean blood pressure (8% and 22%) associated with a small rise in the heart rate (2% and 4%), a fall in the cardiac output (13% and 33%) and a rise in the peripheral vascular resistance (5% and 16%) (Fig 14:3).

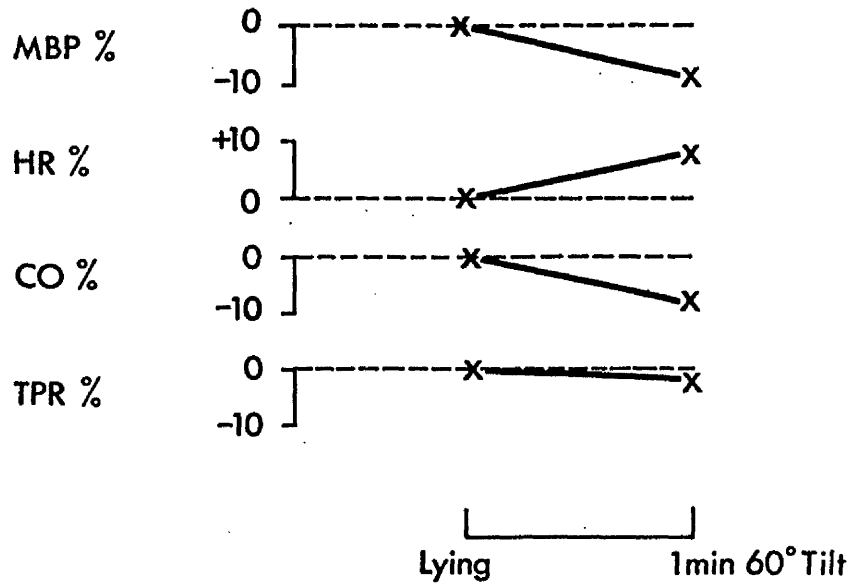


FIGURE 14:1

POSTURAL HYPOTENSION IN AN UNTREATED PARKINSONIAN PATIENT

(CASE 1)

KEY FOR FIGS. 14:1 - 14:6

MBP : MEAN BLOOD PRESSURE
HR : HEART RATE
CO : CARDIAC OUTPUT
TPR : TOTAL PERIPHERAL RESISTANCE

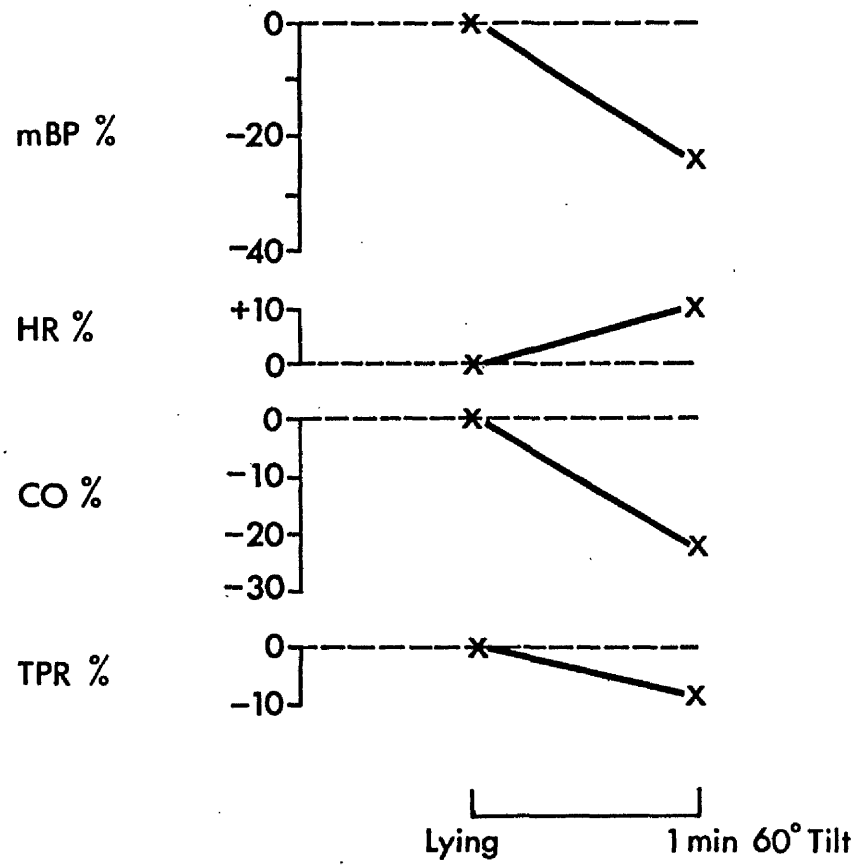


FIGURE 14:2

POSTURAL HYPOTENSION IN SIX PARKINSONIAN PATIENTS ON MADOPAR

(CASES 3 - 8)

DIABETES MELLITUS

CASE 11. Male of 41 years of age with stable insulin dependent diabetes and no evidence of cardiac disease or clinical signs of peripheral neuropathy. The blood pressure continued to fall until five minutes after tilting (Fig 14:4). The mean blood pressure drop of 41% at five minutes was associated with a substantial heart rate increase (21%), no change in the cardiac output and a large reduction in the peripheral vascular resistance (42%).

PERIPHERAL NEUROPATHY

CASE 12. Male of 78 years of age with alcoholic peripheral neuropathy and chronic obstructive airways disease. The blood pressure continued to fall until five minutes after tilting (Fig 14:5). The mean blood pressure drop of 47% at five minutes was associated with a 15% increase in the heart rate, a 38% reduction in the cardiac output and a 15% reduction in the peripheral vascular resistance.

PNEUMONIA

CASE 13. Male of 77 years with resolving left lower lobe pneumonia. The mean blood pressure drop of 14% was accompanied by a heart rate increase of 27%, an increase in the cardiac output of 12% and a fall of 24% in the peripheral vascular resistance (Fig 14:6).

HYPOKALAEMIA

CASE 14. Male of 77 years with a history of a previous anterior myocardial infarction and evidence of a proximal myopathy associated with hypokalaemia (serum potassium 2.9 mmol/l). He had not been taking diuretics. The mean blood pressure fell by 12% and this was associated with a heart rate increase of 12%, a reduction in the cardiac output of 29% and a rise in the peripheral vascular

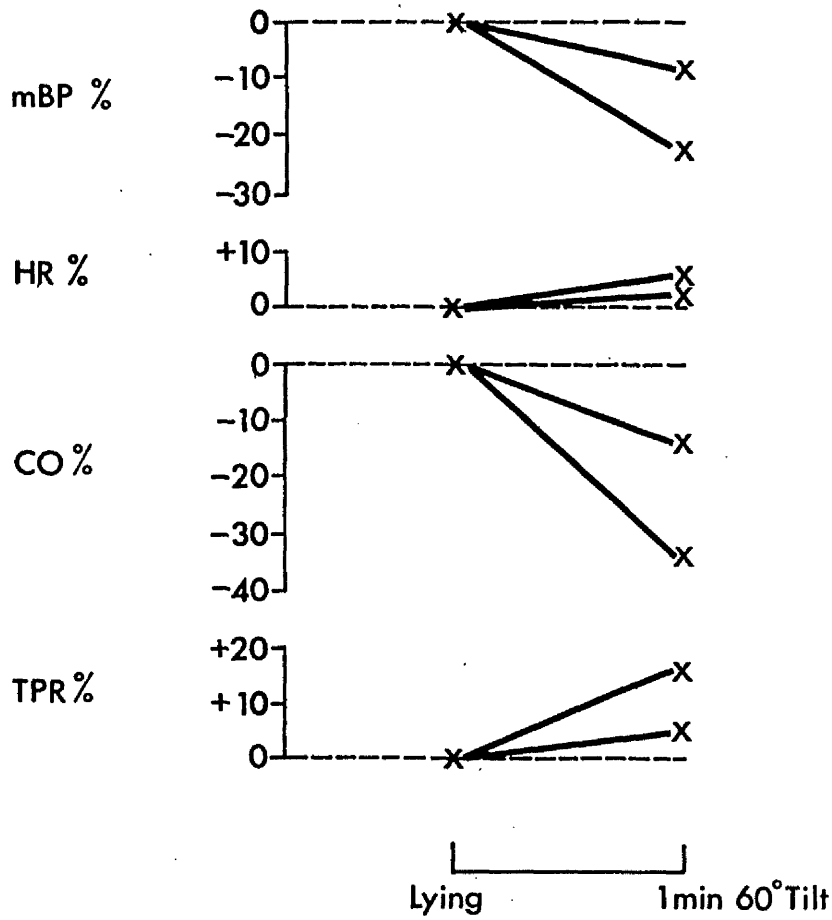


FIGURE 14:3

POSTURAL HYPOTENSION IN TWO PARKINSONIAN PATIENTS ON SINEMET

(CASES 9 AND 10)

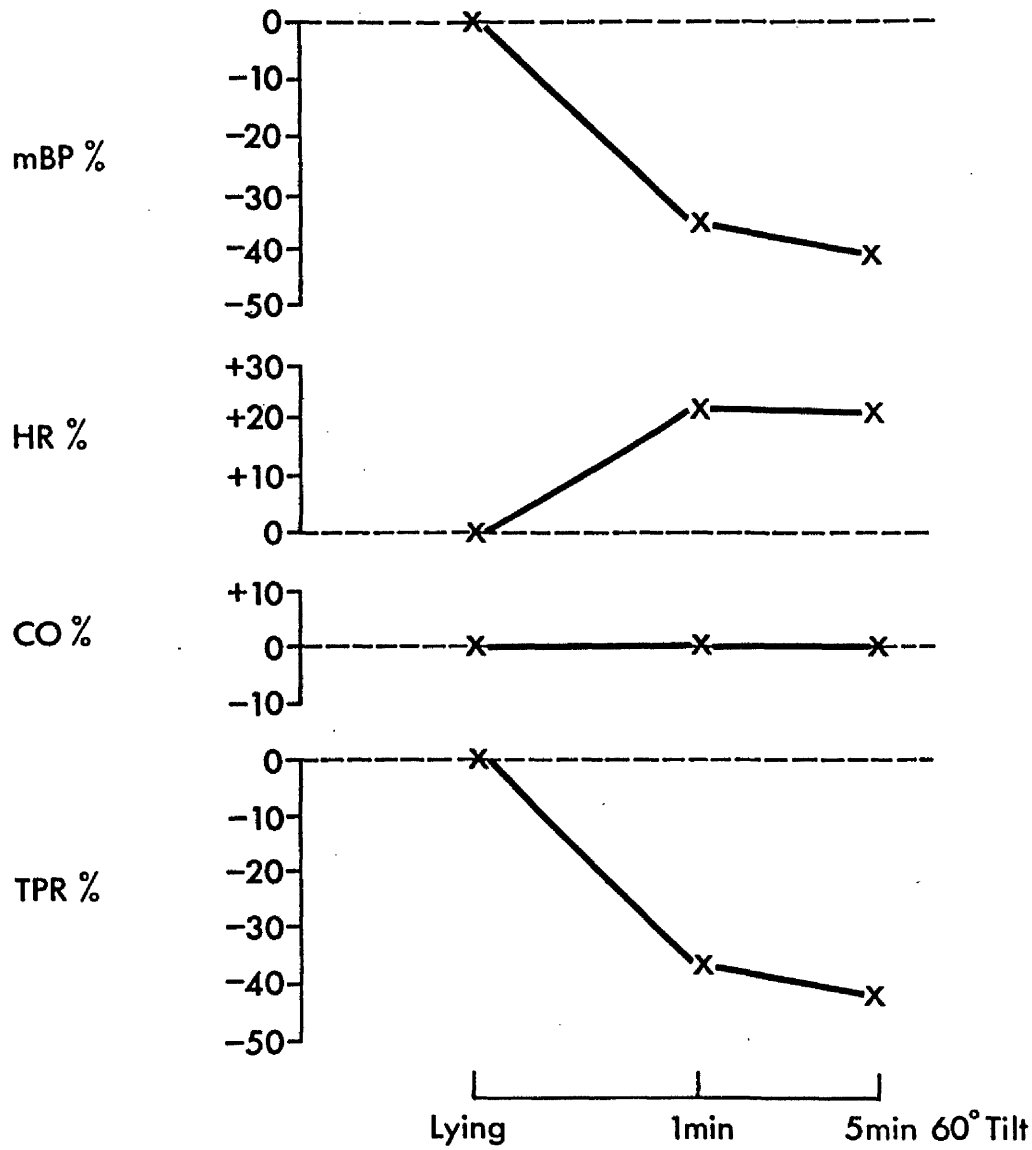


FIGURE 14:4

POSTURAL HYPOTENSION IN AN INSULIN DEPENDENT DIABETIC

(CASE 11)

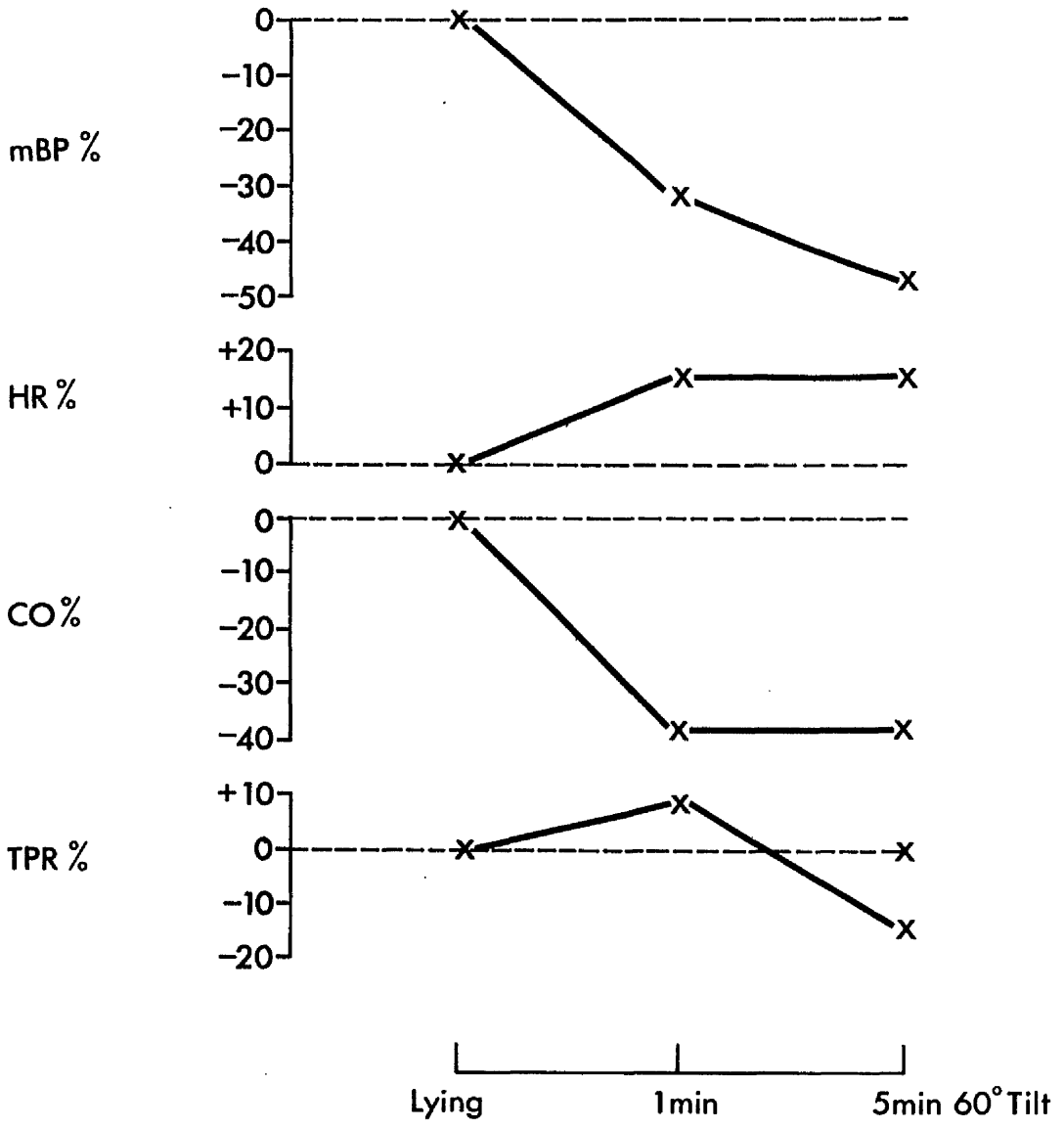


FIGURE 14:5

POSTURAL HYPOTENSION IN A PATIENT WITH ALCOHOL ASSOCIATED PERIPHERAL NEUROPATHY

(CASE 12)

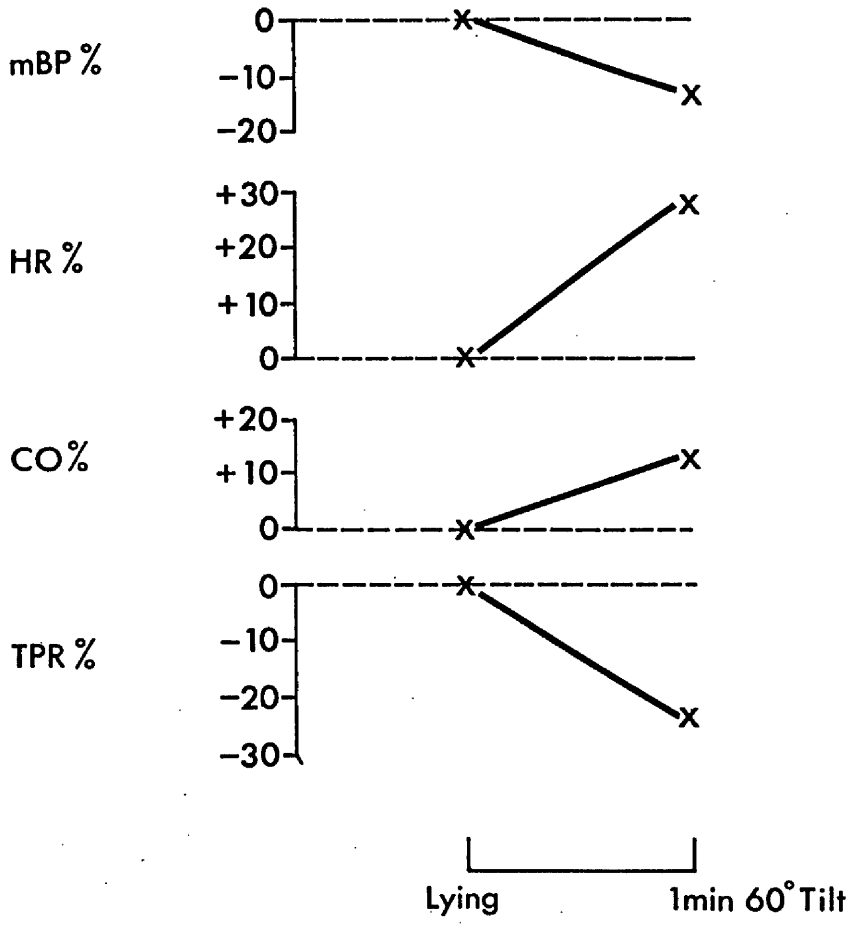


FIGURE 14:6

POSTURAL HYPOTENSION IN A PATIENT WITH LEFT LOWER LOBE PNEUMONIA

(CASE 13)

resistance of 25% (Fig 14:7).

THIAZIDE DIURETICS

CASES 15-18. Four patients (one male, three females) had postural hypotension and were receiving the diuretic combination of amiloride/hydrochlorothiazide (Moduretic). The 70 year old male (Case 15) had evidence of dehydration and uraemia but none of the four patients had evidence of hyponatraemia (serum sodium < 130 mmol/l) or hypokalaemia (serum potassium < 3.5 mmol/l). Systematic changes were observed in this group (Fig 14:8). The mean blood pressure fell by 22% on average and this was associated with a heart rate increase of 16% and a reduction in the peripheral vascular resistance of 18%. The cardiac output fell in three patients but rose in one subject (Case 16).

CASE 19. Female of 77 years with cardiac failure who was receiving one tablet of cyclopenthiazide/potassium daily (Navidrex K). A fall of 12% in the mean blood pressure was accompanied by a heart rise of 11%, a cardiac output fall of 15% and a rise in the peripheral vascular resistance of 3%.

THIORIDAZINE

CASES 20-22. Three patients (one male, two females) had evidence of mild Alzheimer's type dementia and were receiving thioridazine in a dose of 25 mg thrice daily. An average fall in mean blood pressure of 16% was accompanied by a 5% rise in the heart rate, a 15% increase in the cardiac output and a fall in the peripheral vascular resistance of 26% (Fig 14:9).

MULTIPLE DRUG THERAPY

CASE 23. Male of 65 years with a diagnosis of hypertension and epilepsy. He was receiving propranolol 40 mg thrice daily,

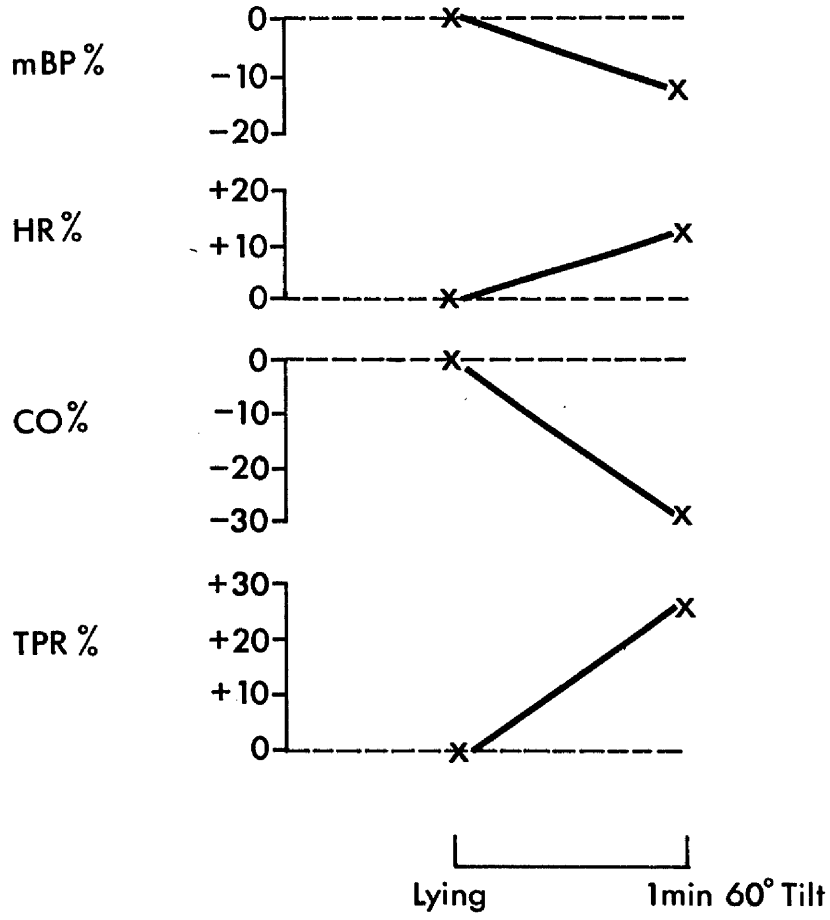


FIGURE 14:7

POSTURAL HYPOTENSION IN A PATIENT WITH HYPOKALAEMIA

(CASE 14)

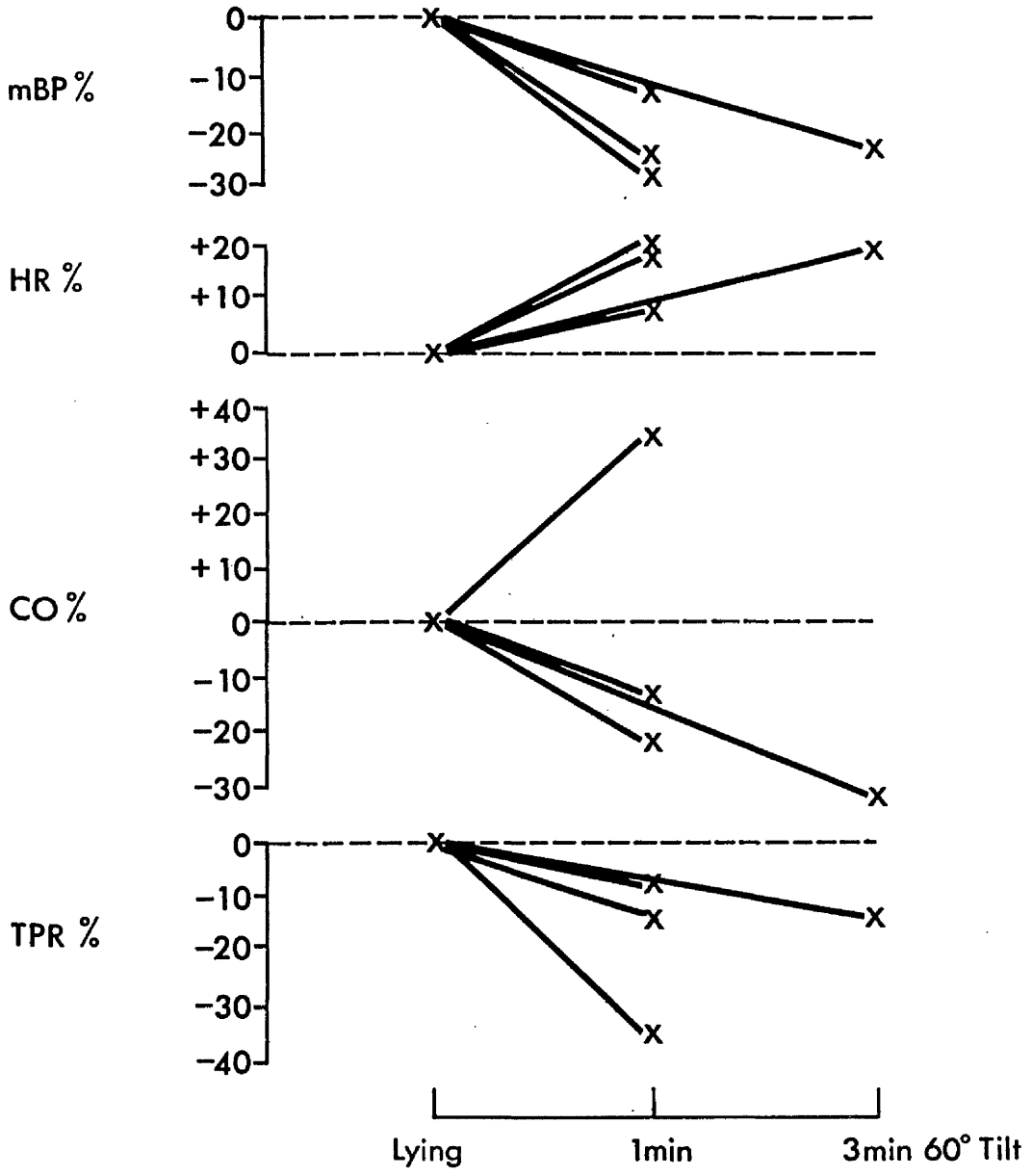


FIGURE 14:8

POSTURAL HYPOTENSION IN FOUR PATIENTS TAKING MODURETIC

(CASES 15 - 18)

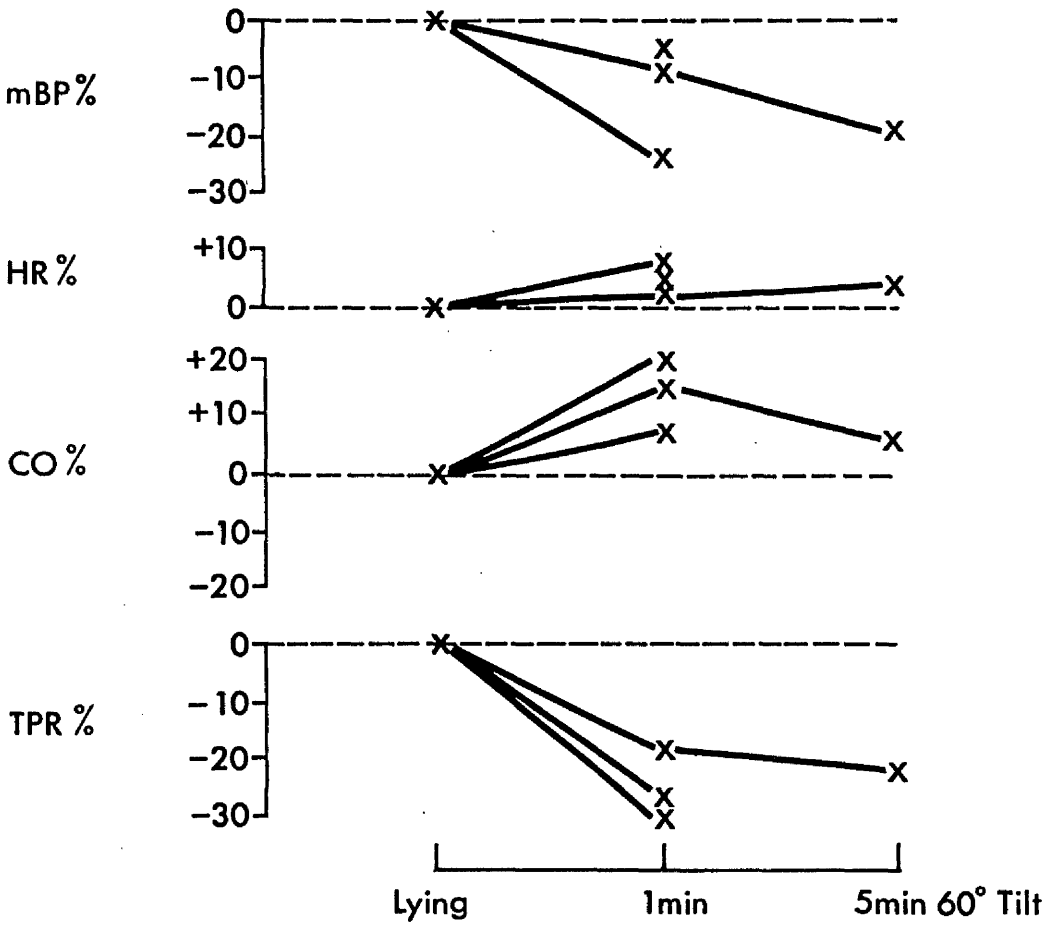


FIGURE 14:9

POSTURAL HYPOTENSION IN THREE PATIENTS TAKING MELLERIL

(CASES 20 - 22)

bendrofluazide and potassium (neonaclex K) once a day and phenytoin 100 mg thrice daily. The mean blood pressure fell by 7% and this was accompanied by a 7% rise in the heart rate, no change in the cardiac output and a 6% reduction in the peripheral vascular resistance.

CASE 24. Male of 76 years with a diagnosis of hypertension and cardiac failure. He was receiving bumetanide 2 mg daily, disopyramide 200 mg twice daily and methyldopa 250 mg twice daily. A fall of 20% in the mean blood pressure was associated with a heart rate increase of 2%, a cardiac output increase of 14% and a fall of 30% in the peripheral vascular resistance.

CASE 25. Female of 79 years with a diagnosis of ischaemic heart disease and cardiac failure. She was receiving propranolol 40 mg twice daily, frusemide 40 mg once a day and potassium supplements. The mean blood pressure fell by 16% and this was accompanied by a 15% increase in the heart rate, a 27% increase in the cardiac output and a 34% reduction in the peripheral vascular resistance.

CASE 26. A male of 71 years with a previous history of acute myocardial infarction and a recent history of depressive illness and oedema. He was receiving amitriptyline in a dose of 50 mg at night and he had been taking spironolactone in a dose of 25 mg four times a day for one week. The serum sodium level was 129 mmol/l. The mean blood pressure fell by 77% and this was accompanied by a rise in the heart rate of 24%, a rise in the cardiac output of 67% and a fall in the total peripheral vascular resistance of 85%.

CASE 27. Female of 78 years with a diagnosis of depressive illness. She was receiving thioridazine 25 mg thrice daily, flurazepam 15 mg at night and doxepin 25 mg three times a day. Two separate studies were performed in this patient (Fig 14:10). In

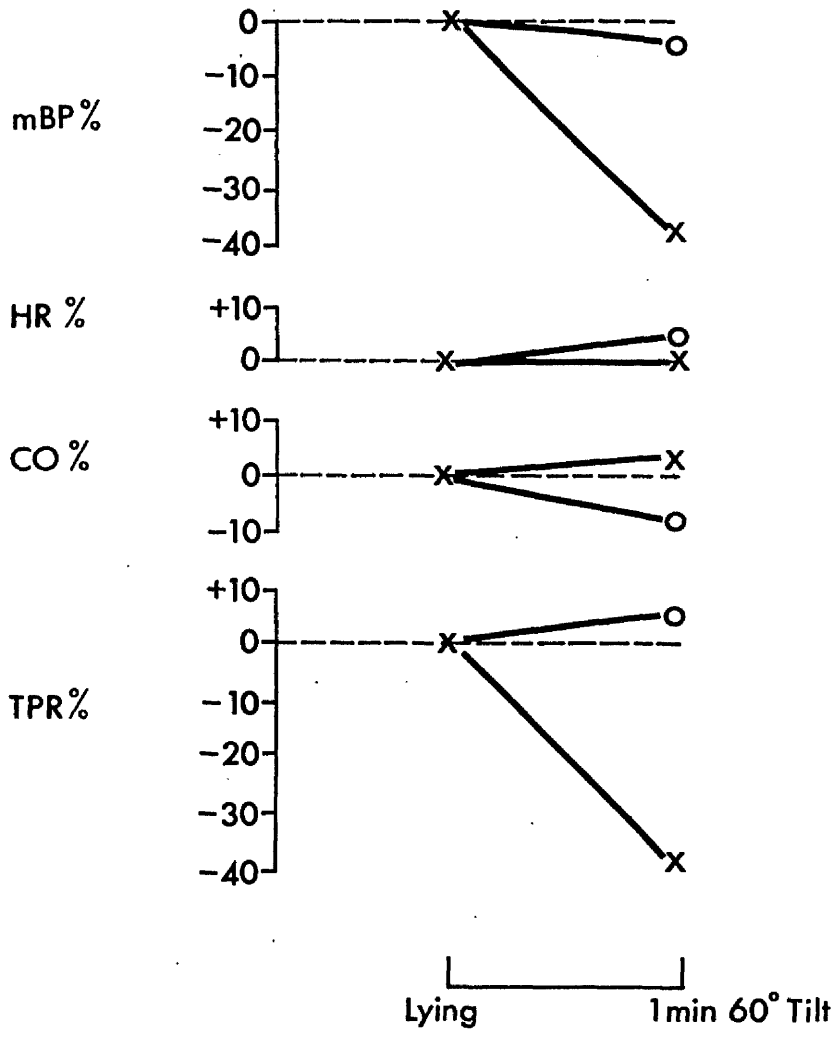


FIGURE 14:10

POSTURAL HYPOTENSION IN ONE PATIENT (CASE 27)

KEY x——x THIORIDAZINE, FLURAZEPAM, DOXEPIN
x——o NO DRUGS FOR SEVEN DAYS

the first study, the mean blood pressure fell by 37% and this was accompanied by no change in the heart rate, an increase of 2% in the cardiac output and a fall of 38% in the peripheral vascular resistance. The second test was performed after stopping all drug treatment for seven days. The mean blood pressure fell by only 4% on tilting and there were no postural symptoms. The heart rate rose by 4%, the cardiac output fell by 9% and the peripheral vascular resistance increased by 5%.

CASE 28. A male of 75 years with a diagnosis of cor pulmonale, cardiac failure and depressive illness. This man was receiving frusemide 120 mg daily, spironolactone 25 mg four times a day and dothiepin 25 mg thrice daily. Two separate studies were performed in this patient (Fig 14:11). In the first study, the mean blood pressure fell by 29% and this was accompanied by a rise in the heart rate of 11%, a rise in the cardiac output of 31% and a fall in the peripheral vascular resistance of 45%. The second test was performed after the spironolactone and dothiepin had been discontinued for 11 days. The postural symptoms were virtually abolished and the mean blood pressure fell by 8%. This was accompanied by a heart rate increase of 7%, a rise in the cardiac output of 32% and a fall in the peripheral vascular resistance of 30%.

CASE 29. A male of 69 years with a diagnosis of stroke, depressive illness and peripheral oedema. This man was receiving amiloride with hydrochlorothiazide (Moduretic) once daily, amitriptyline 50 mg daily and dantrolene 25 mg thrice daily. Two separate studies were performed in this patient (Figure 14:12). In the first study, the mean blood pressure fell by 43% and this was accompanied by a 10% rise in the heart rate, a 32% fall in the cardiac output and a fall

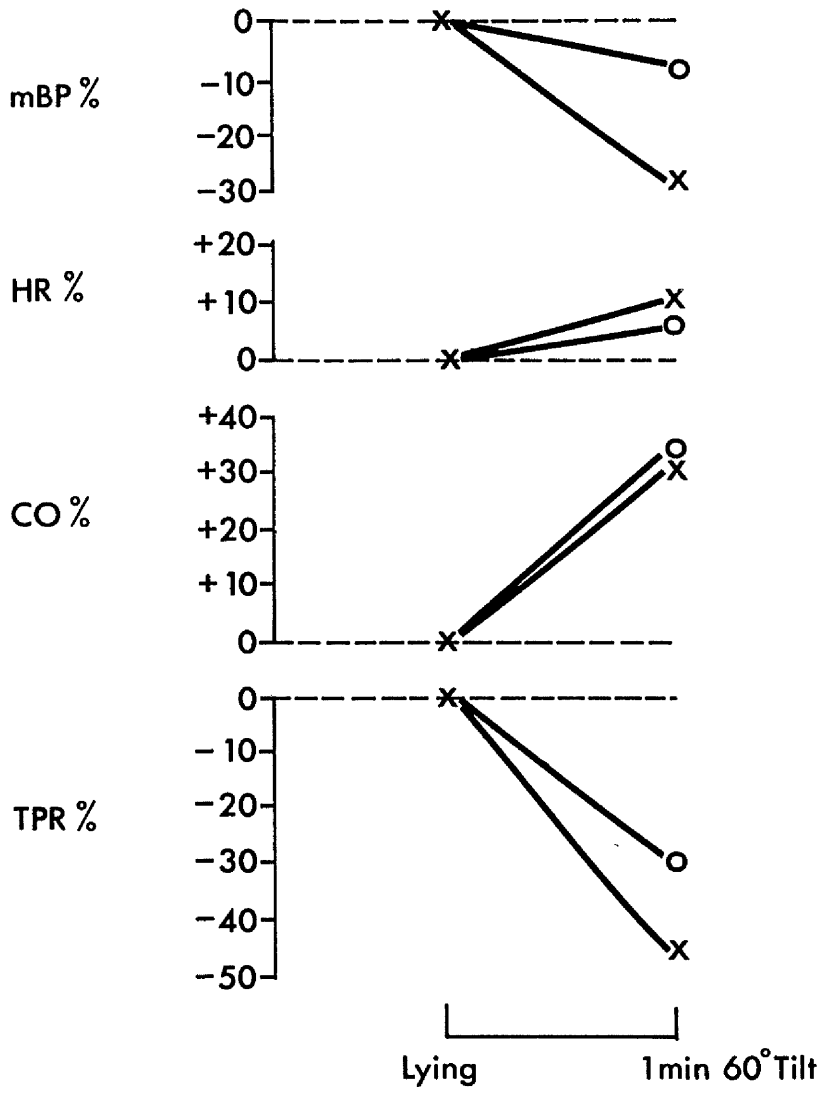


FIGURE 14:11

POSTURAL HYPOTENSION IN ONE PATIENT (CASE 28)

KEY x——x FRUSEMIDE, SPIRONOLACTONE, DOTHIEPIN
x——o SPIRONOLACTONE, DOTHIEPIN STOPPED FOR 11 DAYS

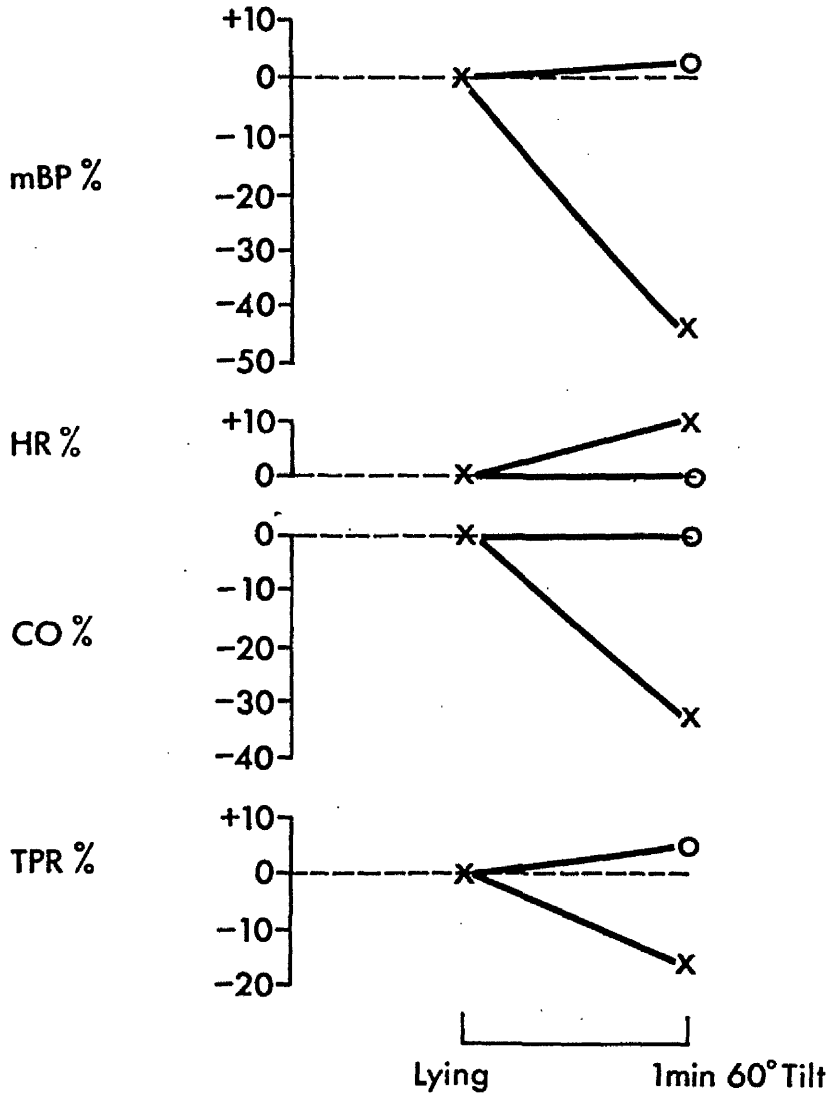


FIGURE 14:12

POSTURAL HYPOTENSION IN ONE PATIENT (CASE 29)

KEY x——x MODURETIC, AMITRIPTYLINE, DANTROLENE
x——o NO DRUGS FOR FOUR DAYS

in the peripheral vascular resistance of 16%. The second study was performed after all drugs had been discontinued for four days. Postural symptoms were abolished and the mean blood pressure rose by 3% on tilting. This was accompanied by no change in the heart rate or cardiac output and a rise of 5% in the peripheral vascular resistance.

CASE 30. Female of 71 years with a diagnosis of angina, cardiac failure and depressive illness. This patient was receiving imipramine 25 mg thrice daily, frusemide 40 mg daily, potassium supplements and diazepam 2 mg twice daily. Two separate studies were performed in this patient (Fig 14:13). In the first study, the mean blood pressure fell by 19% and this was accompanied by a 2% rise in the heart rate, a 29% reduction in the cardiac output and a 14% rise in the peripheral vascular resistance. In the second study which was performed two weeks after imipramine was discontinued, the mean blood pressure fell by 8% and this was accompanied by a 4% rise in the heart rate, a 33% reduction in the cardiac output and a 37% increase in the peripheral vascular resistance.

POSTURAL HYPOTENSION WITH NO CLEAR CAUSE

CASES 31-35. Five patients (two males, three females) had symptomatic postural hypotension with no clear associated cause apparent. Systematic haemodynamic changes were noted in this group during the tilt test (Fig 14:14). The average mean blood pressure fell by 24% and this was accompanied by a 10% increase in the heart rate, a 10% reduction in the cardiac output and a 20% reduction in the peripheral vascular resistance in four patients. In one patient (Case 32) the peripheral vascular resistance rose by 2%.

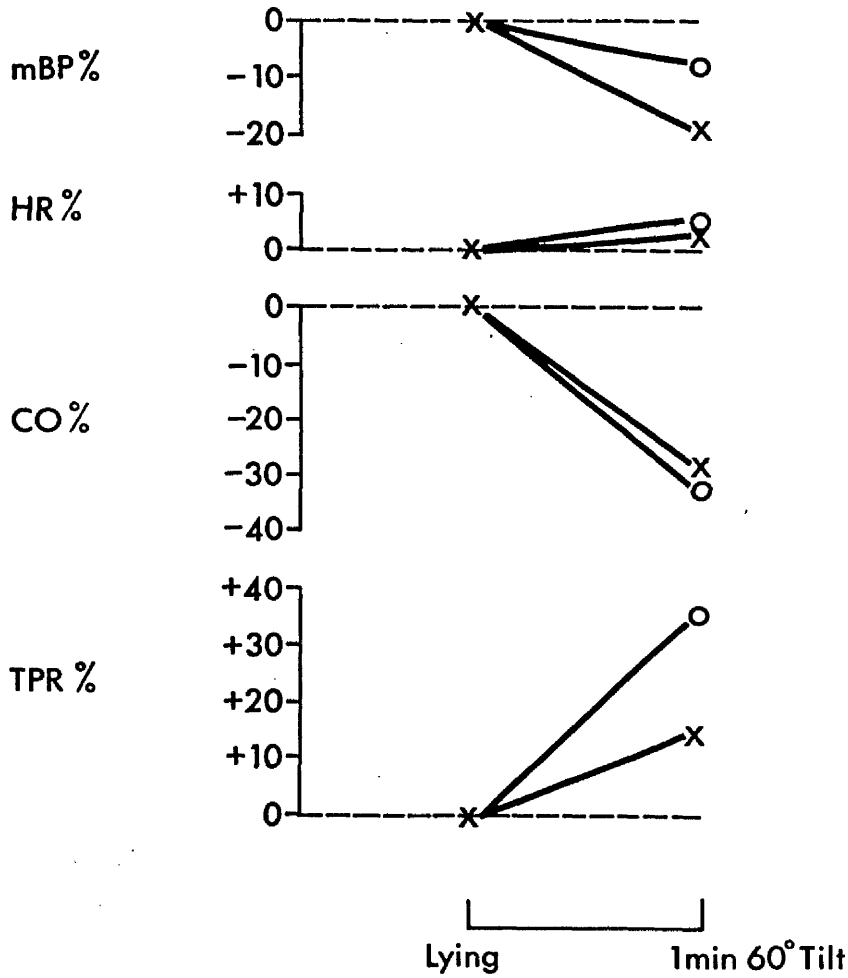


FIGURE 14:13

POSTURAL HYPOTENSION (CASE 30)

KEY x——x FRUSEMIDE, DIAZEPAM, IMIPRAMINE
x——o IMIPRAMINE STOPPED FOR 14 DAYS

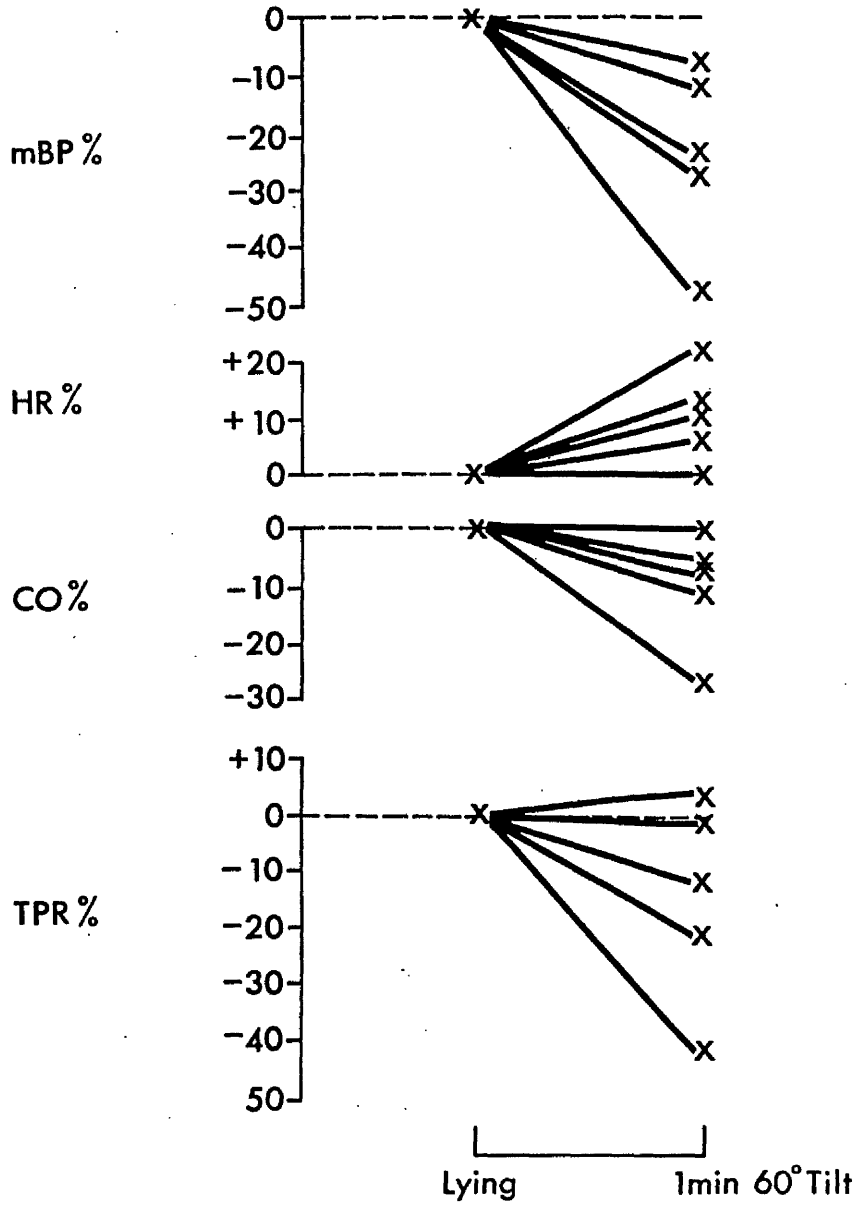


FIGURE 14:14

POSTURAL HYPOTENSION IN FIVE PATIENTS WITH NO CLEAR CAUSE

(CASES 31 - 35)

EFFECTS OF FLUDROCORTISONE

CASES 36–39. Four patients (three males and one female) had symptomatic postural hypotension and required treatment by fludrocortisone acetate (Florinef) to control their symptoms. Fludrocortisone was given in daily doses of 0.1–1 mg for periods of one to three weeks. Two studies were performed in each patient before and after the exhibition of fludrocortisone (Fig 14:15). Systematic haemodynamic changes were observed in the group. Before fludrocortisone treatment, the average mean blood pressure fell by 31% and this was accompanied by a heart rate rise of 11%, a cardiac output reduction of 8% and a fall in the peripheral vascular resistance of 24%. In the second test, after treatment with fludrocortisone, the average mean blood pressure fell on tilting by 7% and this was accompanied by a heart rate increase of 6%, a cardiac output reduction of 16% and a rise in the peripheral vascular resistance of 12%. Postural symptoms were uniformly improved.

EFFECTS OF DIHYDROERGOTAMINE

CASE 40. Female of 71 years with a history of cervical sympathectomy performed 20 years before for likely Raynaud's phenomenon. Three studies were performed in this patient (Fig 14:16). In the first study, the patient was not receiving any drug treatment and had troublesome postural symptoms. The mean blood pressure fell by 8% (supine mean blood pressure 87 mmHg). This was associated with a heart rate increase of 17%, a fall in the cardiac output of 23% and a rise in the peripheral vascular resistance of 16%. A second test was performed after treatment with dihydroergotamine in a dose of 2.5 mg daily for one week. On this occasion, the mean blood pressure fell by 4% (supine mean blood

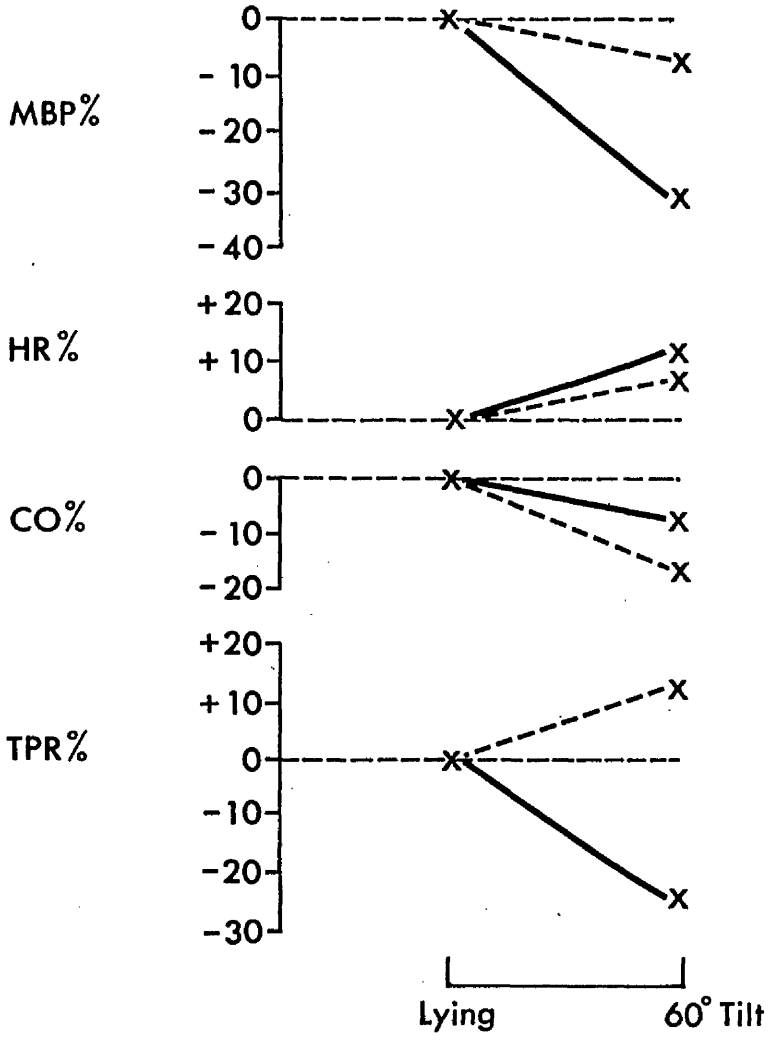


FIGURE 14:15

FOUR PATIENTS WITH POSTURAL HYPOTENSION CORRECTED BY FLORINEF

(CASES 36 - 39)

KEY x——x BEFORE TREATMENT (MEAN VALUES)
x- - -x AFTER FLORINEF (MEAN VALUES)

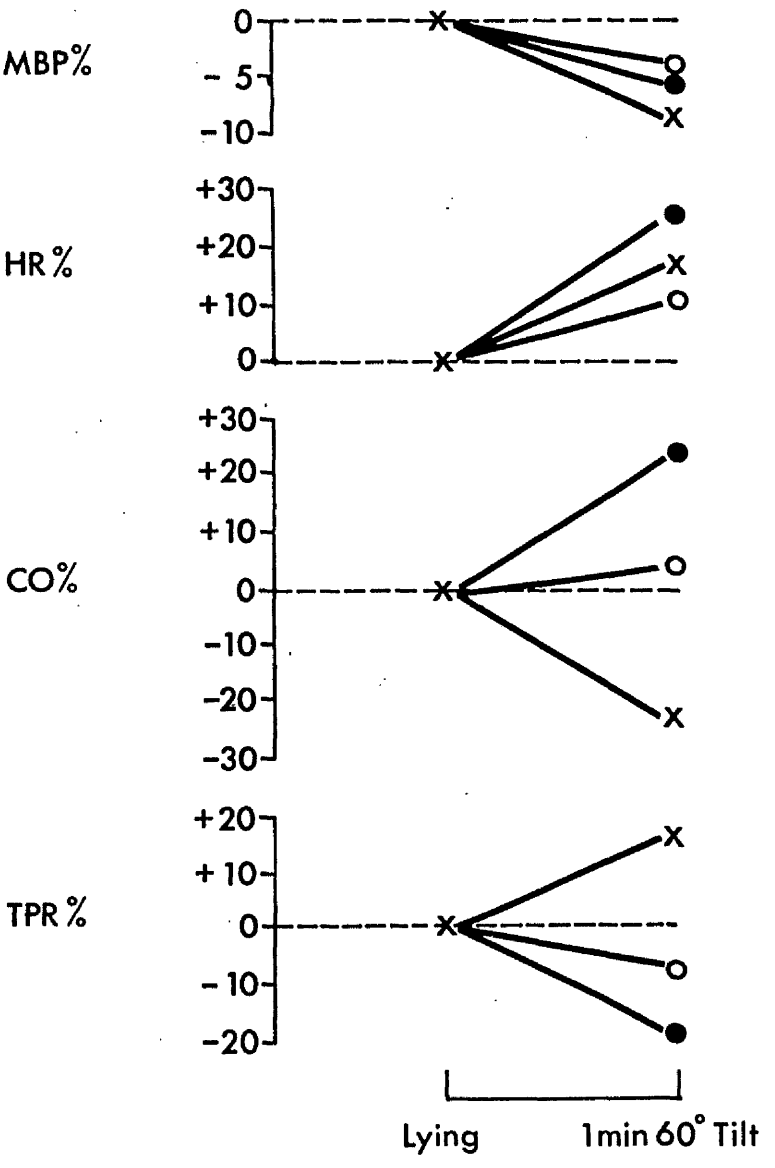


FIGURE 14:16

TREATMENT OF POSTURAL HYPOTENSION WITH DIHYDROERGOTAMINE (D.H.E.) (CASE 40)

KEY x——x SYMPTOMATIC POSTURAL HYPOTENSION
x——o ONE WEEK OF D.H.E.
x——● TWO WEEKS OF D.H.E.

pressure 99 mmHg) and this was accompanied by a heart rate increase of 11%, a rise in the cardiac output of 4% and a fall in the peripheral vascular resistance of 8%. The third test was carried out after treatment with dihydroergotamine in a dose of 2.5 mg twice daily for two weeks. The mean blood pressure fell by 5% (supine mean blood pressure 107 mmHg) and this was accompanied by a heart rate increase of 28%, a cardiac output increase of 24% and a fall in the peripheral vascular resistance of 19%. Symptoms of postural hypotension were abolished for a period of more than three months of follow up on the stable dose of dihydroergotamine.

Discussion

Postural hypotension has been described in untreated Parkinsonism (231-2), particularly in the elderly (233), although symptoms do not tend to be troublesome (233) and also in the Shy-Drager syndrome when symptoms are commanding (234-5).

The mechanism for the development of postural hypotension in Parkinsonism is not clear but it has been variously attributed to a general failure of baroreceptor function (231), a central defect above the level of the medulla (232) and a defect in peripheral vasoconstriction (231) which may be due to a lesion in the efferent sympathetic system (236).

Oral levodopa therapy has a tendency to lower the supine blood pressure and induce postural blood pressure drop either by itself or in combination with benserazide or carbidopa (233, 237-41). This is, however, usually a transient, asymptomatic phenomenon (233, 238) and rarely leads to the cessation of therapy (242). Levodopa associated postural hypotension has been attributed to the fact that dopamine competitively inhibits noradrenaline at receptor sites on

peripheral blood vessels and the vasconstrictor efficacy of dopamine is much less than that of noradrenaline (243).

Eight of 10 of the patients with Parkinsonism in the study described in this Chapter had evidence of a large reduction in the peripheral vascular resistance on tilting but two patients had an increase and both of these were taking the levodopa/carbidopa combination in small doses. There is no clear reason for this difference in response.

Diabetes mellitus is a known association with postural hypotension in the elderly (220). Diabetic patients with autonomic neuropathy show a gradual or lack of heart rate response after standing and this has been attributed to early parasympathetic and later sympathetic nerve damage (244). The vagus nerve mediates the heart rate response to orthostatic stress (245).

The 41 year old male diabetic patient included in the study had however a marked heart rate response to tilt and the postural blood pressure fall was due to a considerable reduction in the peripheral vascular resistance.

Many currently prescribed drugs may produce or aggravate a tendency to postural hypotension (227, 230). Chronic diuretic use in the elderly is very common and drug surveys in geriatric medical institutions (223, 246) and the community (247) have shown that almost one third of the elderly take some form of diuretic therapy. There has, as yet, been no clear relationship established between diuretic use and postural hypotension in the elderly in the community (223-224) but troublesome diuretic associated symptomatic postural hypotension has been observed in elderly patients admitted to hospital (205, 248).

The mechanism causing diuretic induced postural hypotension is

not clear but it may be related to diuretic induced hyponatraemia (228), hypokalaemia (249), blood volume depletion or a direct effect on the peripheral blood vessels.

The amiloride/hydrochlorothiazide (Moduretic) combination diuretic preparation may have a greater tendency to produce hyponatraemia than other diuretics in the elderly (248) and this may be a major factor in the production of postural hypotension. Of the four patients with moduretic associated postural hypotension in this study, however, none had biochemical evidence of hyponatraemia or hypokalaemia and only one had evidence of dehydration and uraemia. The mechanism for postural blood pressure drop in this group appeared to be due to a systematic reduction in the peripheral vascular resistance and this may be the result of direct effects of the thiazide on the arterioles.

Phenothiazines and particularly thioridazine (Melleril) commonly produce postural hypotension as a side effect in the elderly although tolerance to this effect usually develops rapidly (227, 250). This may be related to the tendency of phenothiazines to induce the Parkinsonian syndrome and in this study the peripheral vascular resistance fell and the cardiac output paradoxically increased on tilting.

The studies including serial tilt tests in those patients with postural hypotension receiving multiple drugs and in particular combinations include antihypertensives, diuretics, sedatives and tricyclic antidepressants have shown that the major mechanism for the production of postural blood pressure drop is a failure of the response of the peripheral vascular resistance to tilt stress and this can be reversed by withdrawal of the offending drug or drugs.

Idiopathic symptomatic postural hypotension is probably uncommon in the elderly. The five patients in this study who had no clear reason for their postural drop appeared to have a normal increase in the heart rate and reduction in the cardiac output but an abnormal response of the peripheral vascular resistance in that four patients had a significant fall and one had a minor rise which was insufficient to maintain the blood pressure. It is therefore likely that the main underlying mechanism is an inability of the peripheral resistance to rise and compensate for the normal physiological tilt response of venous pooling and a reduction in the cardiac output and this would parallel the mechanism underlying the postural hypotension of chronic autonomic failure (251).

Autonomic failure may occur due to a variety of causes including systemic illness e.g. diabetes mellitus, rare familial disorders, functional disorders due to toxic agents or drugs or the ageing process itself (212, 222). An early fall in the blood pressure on standing in the elderly with postural hypotension (252) which may be exaggerated by the presence of cerebrovascular disease (253) may reflect rigidity and inelasticity of the blood vessels (224) as it occurs before baroreceptor mediated circulatory reflexes have begun to act i.e. within eight seconds of standing. Postural hypotension after this time is more likely to be due to baroreceptor inefficiency or a failure of reflex vasoconstriction.

Johnson and his colleagues in a study of nine elderly patients with postural hypotension and cerebrovascular disease reported that the defect of postural blood pressure control was likely to be central and within the brain because the baroreceptor afferent arc, post ganglionic sympathetic outflow and blood vessel sensitivity to noradrenaline all appeared to be normal (221). There may, however,

be an underlying failure of the peripheral sympathetic nerve endings to release noradrenaline in response to orthostasis (254).

The elderly also have a known resistance to the beta adrenergic mediated responses to exercise and isoprenaline (255). The initial demonstration of reduced beta receptors on human lymphocyte membranes with ageing (256) has been disputed (257) but it has raised the possibility that these receptors might be reduced in other sites such as the heart and peripheral blood vessels. A decrease in beta receptors might produce an apparent age associated loss of adrenergic responsiveness. Less is known about the effect of age on the alpha adrenoceptor function in man, although it has been reported that the contractile response of human arterial strips to noradrenaline in vitro is not influenced by age (258). Ageing is associated with an increase in circulating plasma noradrenaline levels (259) however and this may compensate for reduced receptor sensitivity. Basal high circulating levels of noradrenaline in the elderly may preclude a normal response to an increased noradrenaline release in orthostasis.

A variety of pharmacological agents are currently advocated for the management of symptomatic postural hypotension (260) and these include fludrocortisone acetate, monoamine oxidase inhibitors, prostaglandin inhibitors, beta adrenergic blocking drugs and ergotamine derivatives.

Fludrocortisone acetate (Florinef) is perhaps the best and most widely used agent in those patients who require drug treatment (261-262). Its precise mechanism of action is unclear and it probably has several pharmacological effects. An initial expansion in the plasma volume occurs (251) but this may only be a minor

effect (262). Other effects include potentiation of the sensitivity of blood vessels to the action of circulating noradrenaline and enhanced vasoreactivity related to changes in vascular wall electrolyte concentrations (262).

Only a minority of elderly patients with postural hypotension will require fludrocortisone acetate and a good response can be achieved with minimal side effects (205). In the four patients who received fludrocortisone acetate in this study, systematic haemodynamic changes were observed in serial studies. After treatment, the cardiac output reduction response to tilt was greater and the peripheral vascular resistance was significantly raised. This is more likely to be due to the effect on the peripheral vessels than any increase in circulating blood volume.

Dihydroergotamine produces selective constriction of capacitance vessels due to alpha adrenoceptor stimulation and limits venous pooling on assuming the upright posture. This is associated with a rise in the cardiac output and peripheral vascular resistance which implies that there is also some effect on resistance vessels (263-264). These changes were confirmed in the case study of the elderly female whose symptomatic postural hypotension was abolished largely by a considerable increase in the cardiac output, which was likely to be due to venoconstriction, despite a progressive fall in the peripheral vascular resistance during two weeks of dihydroergotamine therapy.

Conclusion

Postural blood pressure drop is a common phenomenon in the elderly and troublesome symptoms may result. Elderly patients are

less efficient, than their younger counterparts, in maintaining their erect blood pressure.

Several mechanisms may contribute to the development of postural blood pressure drop. In most patients, it is due to a fall in the peripheral vascular resistance and this may be associated with an excessive reduction in the cardiac output on standing up. The failure of the peripheral vascular resistance to respond adequately to orthostasis may be due to age changes affecting the baroreceptor apparatus, changes in circulating noradrenaline levels, a reduction in peripheral vessel alpha adrenoceptors, altered vasoreactivity, irreversible changes in the vascular tree or other neurohumeral factors not yet elucidated.

The studies described in this chapter emphasize the importance of judicious drug prescribing in elderly patients and support the view that the blood pressure should be taken in the erect and supine positions in all ill elderly subjects where this is practical.

Symptomatic postural hypotension is a common clinical problem in elderly patients admitted to hospital but this can usually be corrected by the withdrawal of inappropriate or excessive drug therapy. A minority of patients may however require more specific drug treatment in the form of fludrocortisone acetate.

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APPENDIX 1

MEASUREMENT OF THE LENGTH OF THE THORAX

YOUNG MALES - CARDIOVASCULAR NORMALS (n = 6)

AGE (YEARS)	L_{front} (cm)	L_{back} (cm)	Diff (cm)	$L_b - L_f$ Diff. %	$L/_2$ (cm)
32	26	39.5	13.5	52	33
48	26	38	12	46	32
29	23.5	31	7.5	32	27
32	23.5	32	8.5	36	28
31	27	32	5	19	29.5
25	24	35	11	46	29.5
Mean (SD)	25 (1.5)	34.6 (3.5)	9.6 (3.2)	38.5 (12)	29.8 (2.3)

APPENDIX 1 (Cont'd)

YOUNG FEMALES – CARDIOVASCULAR NORMALS (n = 6)

AGE (YEARS)	L_{front} (cm)	L_{back} (cm)	Diff (cm)	$L_b - L_f$ Diff. %	$L/_2$ (cm)
31	25	29	4	16	27
29	22	23	1	5	22.5
24	24	26	2	8	25
26	22	24	2	9	23
26	25	29	4	16	27
24	20.5	29	8.5	41	25
Mean (SD)	23.1 (1.9)	26.7 (2.7)	3.6 (2.7)	15.8 (13.1)	24.9 (1.9)

APPENDIX 1 (Cont'd)

ELDERLY MALES – CARDIOVASCULAR NORMALS (n = 6)

AGE (YEARS)	L_{front} (cm)	L_{back} (cm)	Diff (cm)	$L_b - L_f$ Diff. %	$L/_2$ (cm)
75	25.5	38.5	13	50	32.0
77	21.5	35.5	14	65	28.5
83	25.5	29.5	4	16	27.5
80	24.0	34.0	10	42	29.0
69	19.0	24.0	5	26	21.5
86	25.0	32.0	7	28	28.5
76	21.0	30.0	9	43	25.5
73	22.0	36.0	14	64	29.0
80	25.0	37.5	12.5	50	31.25
60	29.0	37.0	8	28	33.0
65	27.5	40.5	13	47	34.0
82	24.0	30.0	6	25	27.0

APPENDIX 1 (Cont'd)

AGE (YEARS)	L_{front} (cm)	L_{back} (cm)	Diff (cm)	$L_b - L_f$ Diff. %	$L/_2$ (cm)
78	25.0	37.0	12	48	31.0
80	25.0	37.0	12	48	31.0
75	21.0	36.0	15	71	28.5
74	20.0	38.0	18	90	29.0
78	26.0	35.5	9.5	37	30.75
68	27.0	38.0	11	41	32.5
86	22.0	36.0	14	64	29.0
80	28.0	35.0	7	25	31.5
77	22.0	34.0	12	55	28.0
Mean (SD)	24 (2.8)	34.8 (3.8)	10.8 (3.6)	45.9 (18.2)	29.4 (2.8)

APPENDIX 1 (Cont'd)

ELDERLY FEMALES – CARDIOVASCULAR NORMALS (n = 18)

AGE (YEARS)	L_{front} (cm)	L_{back} (cm)	Diff (cm)	$L_b - L_f$ Diff. %	$L/_2$ (cm)
91	14.0	26.0	12	86	20.0
78	15.5	29.5	14	90	22.5
77	19.0	20.0	1	5	19.5
70	18.0	29.0	11	61	23.5
85	19.0	31.0	12	63	25.0
73	16.0	23.0	7	44	19.5
76	17.0	32.0	15	88	24.5
61	19.0	29.0	10	53	24.0
69	28.0	34.0	6	21	31.0
87	16.0	33.0	17	106	24.5
74	21.0	34.0	13	62	27.5

APPENDIX 1 (Cont'd)

AGE (YEARS)	L_{front} (cm)	L_{back} (cm)	Diff (cm)	$L_b - L_f$ Diff. %	$L/_2$ (cm)
80	17.0	32.5	15.5	91	24.75
83	15.0	41.0	26	173	28.0
83	17.0	32.0	15	88	24.5
85	21.0	29.0	8	38	25.0
77	14.0	31.0	17	121	22.5
69	22.0	36.0	14	64	29.0
80	21.0	31.0	10	48	26.0
Mean (SD)	18.3 (3.5)	30.7 (4.7)	12.4 (5.4)	72.3 (38.7)	24.5 (3.1)

APPENDIX 2

REPRODUCIBILITY OF IMPEDANCE CARDIAC OUTPUT TECHNIQUE

STUDY	SUBJECTS	REPRODUCIBILITY	
		IMPEDANCE METHOD	OTHER METHODS
Kubicek et al 1966 (13)	10 healthy adults	Single observations. Cardiac output ± 12% for 95% confidence limits	Dye dilution single observations ± 23% for 95% confidence limits
Sova 1970 (2)	10 persons	Repeated measurements. Cardiac output values ranged from 2–9% (mean 5.5%) related to first value.	
Kinnen 1970 (48)	61 cardiac patients	Paired values. Cardiac output r = 0.93 in 61 patients.	Dye dilution paired values r = 0.87 in 56 patients.
Lababidi et al 1971 (22)	20 children with congenital heart disease but no shunts or valvular	Paired values. Cardiac index. Mean difference 3.1% (range −15% to + 3.2%). SD 0.192 1/min/metre^2.	Dye dilution paired values. Cardiac index. Mean difference 6.6% (range −12% to +13%). SD 0.259 1/min/metre^2.
Keller and Imhof 1975 (44)	12 healthy subjects	34 paired values. Stroke index. Mean difference 7.3%.	
Gabriel et al 1976 (49)	10 patients after acute myocardial infarction.	36 paired values. Cardiac output. Mean difference 0.03 1/min. SD 0.271 1/min.	Dye dilution 36 paired values. Cardiac output. Mean difference 0.048 1/min. SD 0.313 1/min.
Secher et al 1977 (45)	7 young normal adults	Stroke volume. Mean coefficient of variation 7.7%.	Thermodilution. Stroke volume. Mean coefficient of variation 8.1%.

APPENDIX 2 (cont'd)

REPRODUCIBILITY

STUDY	SUBJECTS	IMPEDANCE METHOD	OTHER METHODS
Costeloe et al 1977 (47)	32 healthy neonates	Cardiac output 40 paired values. Coefficient of variation of paired estimates 5.68.	Effective pulmonary capillary blood flow. 40 paired values. Coefficient of variation of paired estimates 3.01.
Betz et al 1977 (51)	13 children without cardiac shunts.	Stroke volume 13 paired values $r = 0.9654$.	
Judy et al 1978 (42)		Cardiac output coefficient of variation.	Dye dilution cardiac output. Coefficient of variation.
	6 normotensive adults	5.9% $\pm$ 4.2 (SD)	9.5% $\pm$ 7.0 (SD)
	11 hypertensive adults	6.1% $\pm$ 4.4 (SD)	11.7% $\pm$ 6.1 (SD)
	6 reno vascular hypertensive adults	6.3% $\pm$ 3.1 (SD)	10.6% $\pm$ 6.5 (SD)
Secher et al 1979 (52)	12 females before and during Caesarean Section.	Paired stroke volumes Coefficient of variation 9.7%.	Thermodilution paired stroke volumes. Coefficient of variation 10.8%.
Boer et al 1979 (46)	12 healthy young people.	Paired stroke volumes $r = 0.96$ ($p < 0.001$)	
Enghoff and Lovheim 1979 (50)	14 patients (aged 38-66) with advanced heart disease but no shunts or valve insufficiency.	Coefficient of variation 7.8%. For stroke volume.	

APPENDIX 3A

ACCURACY OF IMPEDANCE CARDIAC OUTPUT TECHNIQUE - ANIMAL STUDIES

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Kubicek et al 1970 (14)	54 values in anaesthetized dogs.	Electromagnetic flowmeter	$r = 0.94$ ($p < 0.001$)	Stroke volume in individual heart beats
Namon and Gollan 1970 (61)	14 anaesthetized greyhound dogs.	Dye dilution	$r = 0.91$	Stroke volume
Baker et al 1971 (65)	214 values in 11 anaesthetized dogs.	Electromagnetic flowmeter	$r = 0.92$	Cardiac output
Khatib et al 1975 (64)	10 anaesthetized dogs	Thermodilution	Good correlation	Cardiac output
Rasmussen et al 1975 (63)	8 anaesthetized dogs	Dye dilution	$r = 0.81$	Cardiac output
Pate et al 1975 (62)	9 anaesthetized dogs	Electromagnetic flowmeter	$r = 0.855$	Stroke volume
		Aortic systolic pressure area	$r = 0.552$	Stroke volume
		Dye dilution	$r = 0.789$	Cardiac output
Hill et al 1976 (38)	4 anaesthetized dogs	Dye dilution	$r = 0.788$-0.941	Cardiac output

APPENDIX 3A (Cont'd)

Grogler 1976 (66)	15 anaesthetized pigs	Electromagnetic flowmeter	r = 0.96	Cardiac output
Zatzman and Ray 1978 (67)	6 anaesthetized marmots	Dye dilution Electromagnetic flowmeter	r = 0.566 r = 0.905	Cardiac output Cardiac output
Quail et al 1981 (68)	6 greyhound dogs	Electromagnetic flowmeter	82% values within $\pm$ 20%	Stroke volume

APPENDIX 3B

ACCURACY OF IMPEDANCE CARDIAC OUTPUT TECHNIQUE - HUMAN STUDIES

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Lababidi et al 1971 (22)	21 children with left to right shunts	Fick	r = 0.21	Impedance values for cardiac output systematically greater but r = 0.96 for impedance cardiac output values compared with pulmonary blood flow in children with shunts.
	13 children with aortic insufficiency	Fick	r = - 0.31	
Triulzi et al 1973 (75)	34 patients with acquired heart disease and heart failure	Fick		
	27 patients with acute myocardial infarction	Fick	Analysis of variance showed no signficant differences in cardiac output	At least 21 of these patients had valve regurgitation or left to right shunts.
	25 patients with old myocardial infarction	Fick		
	7 congenital heart disease and heart failure	Fick		
Ritz et al 1974 (85)	10 critically ill patients	Fick	r = 0.93	Cardiac output study

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Naggar et al 1975 (77)	14 patients (aged 15–69 years) undergoing diagnostic cardiac catheterization. No shunts or valve insufficiency.	Fick	r = 0.91 ($p < 0.001$)	Stroke index
Knapp 1976 (70)	30 athletes	Fick	r = 0.94 ($p < 0.001$)	
	15 patients with mitral stenosis	Fick	)	
	5 patients with aortic stenosis	Fick	)	Impedance values for cardiac output in 37 patients with valve regurgitation or left to right shunts considerably over-estimated the Fick values.
	4 patients with combined aortic valve disease	Fick	) r = 0.91) ($p < 0.001$))	
	11 patients with no valve disease	Fick	)	
Betz et al 1977 (51)	36 children without left to right shunts	Fick	Poor correlation	Impedance values for cardiac output systematically greater.
Enghoff and Lovheim 1979 (50)	4 patients with advanced heart disease but no shunts or valve insufficiency. All in sinus rhythm.	Fick	Poor correlation in 2 patients	Impedance values for stroke volume greater than Fick values in 2 patients.

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Kozev et al 1980 (71)	20 healthy youths	Fick	Differences in values all within ± 10%	
Kubicek et al 1966 (13)	10 healthy young adults	Dye dilution		Impedance generally overestimates cardiac output
Harley and Greenfield (91)	13 healthy males	Dye dilution	r = 0.68	Impedance gives very high values for cardiac output in valvular insufficiency.
	24 cardiac patients (aged 31-72) (8 with valvular insuff. 6 with atrial fibrillation)	Dye dilution	r = 0.26	
Heather 1969 (95)	38 cardiac patients (15 with valvular insufficiency)	Dye dilution	Poor correlation	Impedance gives very high cardiac output values in valvular insufficiency.
Smith et al 1969 (69)	8 healthy young males during tilt test	Dye dilution	r = 0.91	Cardiac output study.
Kinnen and Duff 1970 (72)	51 adults including cardiac patients. No cardiac shunts.	Dye dilution	r = 0.88	Cardiac output study.
Sova 1970 (2)	20 healthy adults	Dye dilution	r = 0.78	Cardiac output study.
	9 heart disease (no valve disease)	Dye dilution	r = 0.80	

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Lababidi et al 1971 (22)	20 children with congenital heart disease, but no shunts or valvular insufficiency	Dye dilution	Mean difference cardiac output 5.5%	
Baker et al 1971 (65)	10 normal adult males before and after exercise	Dye dilution	r = 0.68	Impedance values for cardiac output generally overestimated.
Pomerantz et al 1971 (83)	17 patients with thoracic injuries. 20 values	Dye dilution	85% of values within $\pm$	Cardiac output study.
Van de Water et al 1971 (73)	52 year old female with atrial fibrillation	Dye dilution	r = 0.92 ($p < 0.001$)	Impedance values grossly overestimate cardiac output.
Demange et al 1972 (74)	19 adults (aged 20-59) with cardiac disease. 8 mitral stenosis 2 mitral/aortic disease 1 cardiomyopathy 1 carotid stenosis 10 pulmonary disease	Dye dilution	r = 0.85	Cardiac output study.
Ritz et al 1974 (85)	22 critically ill patients 37 values	Dye dilution	r = 0.97	Cardiac output study.
Hiltmann et al 1974 (76)	8 patients (aged 50-65) No cardiac shunts or valvular insufficiency.	Dye dilution	r = 0.90	Stroke volume study.

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Moritz et al 1975 (87)	Intensive care patients	Dye dilution	Within ± 20%	Stroke volume study.
Gabriel et al 1976 (49)	10 patients (aged 43-70) after myocardial infarction. Sinus rhythm. No valve disease. 86 values.	Dye dilution	$r = 0.85$ ($p < 0.001$)	Impedance cardiac output values overestimated cardiac output by 9.7%.
Keim et al 1976 (40)	3 healthy adults (mean age 24) 14 hypertensives (mean age 43) 122 values	Dye dilution	$r = 0.49$	Stroke index underestimated by impedance.
Denniston et al 1976 (41)	10 healthy men (mean age 20) at rest and after exercise 38 values.	Dye dilution	$r = 0.9$ ($p < 0.001$)	Cardiac output study.
Lofstrom and and Wranne	30 adults in intensive care unit most on artificial ventilation	Dye dilution	50% within ± 5% 90% within ± 20%	Cardiac output study.
Rasmussen et al 1977 (84)	3 obese anaesthetized patients undergoing jejuno-ileostomy	Dye dilution	$r = 0.90 - 0.98$	Impedance value underestimated stroke volume.

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Judy et al 1978 (42)	11 hypertensives 6 renal hypertensives 6 normotensives 122 values	Dye dilution	 r = 0.98 r = 0.94	Cardiac output study. Short length Mean length
Enghoff and Lovheim 1979 (50)	15 adults (aged 38-66) all in sinus rhythm, no valvular insufficiency, or cardiac shunt. (all had ischaemic heart disease or valve stenosis) 14 values	Dye dilution	Poor correlation	Impedance value overestimated cardiac output in 2/3 of patients
Judy et al 1969 (90)	17 cardiovascular normal adult males. 28 values	Isotope	r = 0.58	Cardiac output study impedance value gave 30% overestimate.
Milleret and Barbe 1972 (88)	9 surgical patients 31 values	Isotope	27/31 within ± 20% 16/31 within ± 10%	Stroke volume study.
Hill and Thompson 1975 (82)	20 patients (aged 25-45) Hypertensives or on dialysis Cardiovascular normals	Isotope	Cardiac output study.	
	a) Resistivity constant 150 ohm.cm.		r = 0.60	Impedance 14.5% overestimates.
	b) Resistivity - Kubicek		r = 0.86	Impedance 5.1% overestimates
	c) Resistivity - Geddes and Sadler		r = 0.87	
	d) Resistivity - Hill and Thompson		r = 0.88	

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Sakai et al 1977 (78)	71 patients (mean age 35.5) No shunts, dysrhythmias or bundle branch block	Isotope	r = 0.76	
Williams and Caird 1980 (53)	40 patients (aged 64-95) 8 atrial fibrillation 8 myocardial infarction 9 cardiac failure 4 left bundle branch block 2 aortic stenosis 2 mitral stenosis 7 obstructive airways disease 2 cardiovascular normals	Isotope	r = 0.77	Cardiac output study.
Hiltmann et al 1974 (76)	8 patients (aged 50-65) No shunts or valvular insufficiency.	Thermodilution	r = 0.90	Stroke volume study.
Nechtwatal et al 1976 (94)	57 patients (mean age 50) Sinus rhythm, no shunts or valvular disease	Thermodilution	r = 0.63	Cardiac output study.
Secher et al 1977 (45)	7 patients (aged 19-29) (4 hyperkinetic 3 cardiovascular normals) 67 values at rest 62 values at valsalva	 Thermodilution Thermodilution	 r = 0.88 r = 0.77	Stroke volume studies. Impedance overestimates at stroke volumes > 140 ml.
Handt et al 1977 (89)	10 chronic uraemic patients on dialysis (aged 28-45) 30 values	Thermodilution	No significant difference on paired t test.	Cardiac output study. Impedance values underestimated cardiac output.

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Haffty et al 1977 (79)	26 patients in C.C.U. or undergoing cardiac catheterisation 59 values.	Thermodilution	r = 0.82 ($p < 0.001$)	Cardiac output study. Impedance values signficantly higher.
Slany et al 1978 (80)	33 patients (aged 22-66) Sinus rhythm 21 ischaemic heart disease 4 congestive cardiac failure 1 constrictive pericarditis 7 no organ.heart disease	Thermodilution	r = 0.98 mean difference in stroke volume = 3.3 ml	Stroke volume study Impedance underestimated small stroke volumes and overestimated large stroke volumes.
Secher et al 1979 (52)	12 normal females (aged 20-37) undergoing elective Caesarean Section 220 values before anaesthesia during anaesthesia	Thermodilution	 r = 0.77 r = 0.55	Stroke volume study. Impedance values overestimated. Stroke volumes > 100 ml.
Boer et al 1979 (46)	3 hypertensive patients before and after 4 days of salt depletion	Thermodilution	r = 0.61 ($p < 0.001$)	Cardiac output study.
Arinchin and Vasiltseva 1980 (81)	6 children (aged 7-10)	Thermodilution	r = 0.877	Cardiac output study

APPENDIX 3B (Cont'd)

STUDY	OBSERVATIONS	TECHNIQUE COMPARED	CORRELATION	COMMENTS
Harley and Greenfield 1968 (91)	2 patients with mitral stenosis and atrial fibrillation	Pressure gradient	r = 0.93 one patient r = 0.91 second patient	Impedance values Underestimated stroke volume.
Bache et al 1969 (93)	8 males (aged 34-54) with cardiomegaly but no conduction defects, valve lesions, sinus rhythm	Pressure gradient	r = 0.28 (0.58 - 0.96) for individual patients	Stroke volume study.
Costeloe et al 1977 (47)	32 newborn infants (41 occasions) 109 values	Nitrous oxide Uptake method	r = 0.79 - 0.94	Impedance method underestimated cardiac output in patients with haematocrits under 35% using standard resistivity data (Kubicek et al). Geddes and Sadler using Mohapatra et al data impedance method overestimated cardiac output in patients with haematocrits over 35%.
Miles et al 1981 (92)	10 healthy young females (mean age 29)	Carbon dioxide Rebreathing method	r = 0.57 ($p < 0.01$) 80% were within $\pm$ 20%	

APPENDIX 4

CARDIAC OUTPUT MEASUREMENT IN 93 ELDERLY SUBJECTS

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
Cardiovascular Normal	F	78	3.9	4.0
	F	83	4.2	4.8
	F	68	2.8	2.8
	F	69	9.5	11.6
	F	80	4.5	4.2
	F	75	7.3	7.9
	F	80	3.3	5.3
	M	93	5.7	5.2
	M	72	7.4	6.9
	M	72	3.9	3.3
	M	77	4.4	4.2
	M	81	3.9	2.9
	M	68	7.1	7.5
	M	75	7.2	7.6

APPENDIX 4 (Cont'd)

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
Ischaemic Heart Disease No Recent Infarct	F	71	6.4	8.2
	F	70	5.8	5.1
	F	69	4.2	3.6
	F	78	8.0	9.2
	F	88	4.3	4.2
	M	70	7.1	8.3
	M	77	8.6	8.3
	M	73	3.6	4.2
	M	75	5.1	4.3
	M	69	7.2	5.5
	M	73	4.7	4.0
	M	76	5.1	4.9

APPENDIX 4 (Cont'd)

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
Ischaemic Heart Disease Recent Myocardial Infarction	F	80	6.7	6.1
	F	80	4.5	5.9
	M	66	6.2	8.4
	M	78	4.1	3.9
	M	70	5.1	5.9
	M	71	9.4	8.2
	M	77	2.3	1.5
	M	74	4.5	3.6
	M	87	3.6	4.3
LBBB	F	84	6.5	5.4
	F	77	3.3	3.3
	M	78	3.7	3.6
	M	75	4.5	3.8
	M	85	5.9	5.3
	M	86	4.1	3.7

APPENDIX 4 (Cont'd)

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
Complete Heart Block	F	69	6.5	7.2
	F	82	3.7	6.5
	F	90	4.2	3.9
	M	75	6.0	7.2
RBBB	F	87	6.3	3.3
	F	79	6.8	5.7
	F	89	4.9	1.5
	F	82	6.6	3.0
	M	67	7.7	8.1
	M	68	6.7	1.7

APPENDIX 4 (Cont'd)

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
Atrial Fibrillation No Valvular Regurgitation	F	79	2.8	3.5
	F	69	3.8	3.0
	F	73	4.5	3.5
	F	74	4.0	4.3
	F	76	4.7	5.0
	F	67	6.5	4.0
	F	86	5.2	5.4
	F	80	4.4	6.2
	F	95	3.4	3.0
	F	80	4.7	4.7
	M	82	2.7	2.2
	M	64	4.9	4.6
	M	78	3.9	3.8
	M	65	3.3	4.2
	M	82	4.6	4.1

APPENDIX 4 (Cont'd)

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
AF/TR	F	78	3.3	5.6
AF/MR	F	73	2.6	6.6
AF/MS/MR/RBBB	F	68	3.1	3.8
AF/MS/MR	F	75	4.1	2.6
AF/MR	M	82	5.5	11.3
AF/MS/MR/RBBB	M	78	3.1	4.0
AF/MR/RBBB	M	88	2.0	6.7
AF/RBBB	M	79	6.3	5.6

APPENDIX 4 (Cont'd)

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
Valvular Disease in Sinus Rhythm				
MR	F	84	5.0	6.6
AR	F	80	6.3	6.9
AR	F	84	3.8	4.0
AR/LBBB	F	80	4.4	3.7
AS/AR	F	81	5.0	5.7
AS/AR	F	80	4.0	2.5
TR	F	75	2.4	4.7
AS	F	84	3.2	5.0
MR	M	74	4.6	5.0
MR	M	80	2.6	7.9
MR	M	76	3.3	5.0

APPENDIX 4 (Cont'd)

DIAGNOSIS	SEX	AGE (YRS)	ISOTOPE CARDIAC OUTPUT L/MIN	IMPEDANCE CARDIAC OUTPUT L/MIN
Obstructive Airways Disease	F	74	6.6	4.4
	F	81	6.1	4.9
	M	74	7.5	4.0
	M	79	5.5	3.8
	M	73	5.3	4.2
	M	83	8.9	4.5
Also Lobar Pneumonia	M	77	4.5	5.7
Also Lobar Pneumonia	M	76	5.3	8.4

APPENDIX 5

HAEMATOCRIT VALUES AND RESISTIVITIES (ρ) IN FRESH WHOLE VENOUS BLOOD SAMPLES IN 64 ELDERLY SUBJECTS AT 37°C

HAEMATOCRIT (%)	RESISTIVITIY (ρ) IN OHM CM
20	105
21	108
23	104
25	110
25	114
31	127
31	135
32	128
32	134
32	125
32	121
33	129
33	135
33	134
34	128
34	136
34	146
35	142
35	147
35	147
35	136
36	155

APPENDIX 5 (Cont'd)

HAEMATOCRIT (%)	RESISTIVITY (ρ) IN OHM CMS
36	141
36	145
36	133
37	154
38	145
39	157
39	150
39	148
39	148
40	155
40	166
40	158
40	153
41	164
41	165
41	162
42	164
42	164
42	161
42	166
42	166
43	168
43	165
43	164
43	182
43	163

APPENDIX 5 (Cont'd)

HAEMATOCRIT (%)	**RESISTIVITIY (ρ) IN OHM CMS**
44	167
44	176
44	169
44	167
45	190
45	183
46	176
47	184
48	193
48	195
49	193
49	192
50	212
50	220
55	239
57	233

APPENDIX 6

EFFECT OF TEMPERATURE CHANGE ON RESISTIVITY (ρ)

OF WHOLE BLOOD IN 10 SUBJECTS

HAEMATOCRIT%	36°C	37°C	37.5°C	38°C
35	146	142	140	136
39	159	156	152	147
40	155	149	146	144
40	165	161	158	156
41	167	165	163	160
42	164	160	157	150
46	179	170	168	167
47	196	180	179	176
48	192	188	186	187
53	236	230	228	229

APPENDIX 7

EFFECT OF BENCH AGEING ON RESISTIVITY (ρ)

OF WHOLE BLOOD IN 21 SUBJECTS

HAEMATOCRIT %		IMMEDIATE*	2 HOURS	4 HOURS	6 HOURS	24 HOURS
34		136	131	128	110	-
40		153	149	135	126	-
	GROUP A					
42		164	164	164	163	-
	ONE SAMPLE					
43		165	164	164	162	-
	IN					
43		163	163	164	162	-
	WATER BATH					
43		164	163	163	162	-
	AT 37°C					
43		163	163	164	162	-
47		184	161	146	138	-
48		193	193	192	188	-
20		105	106	106	99	-
	GROUP B					
32		128	129	128	120	-
	ONE SAMPLE					
32		134	127	117	114	-
	STORED ON BENCH					
36		141	138	134	122	-
	AND REWARMED TO					
49		193	180	160	142	-
	37°C THREE TIMES					
50		212	196	176	162	-
36		133	134	133	134	141
	GROUP C					
39		157	156	156	155	162
	FIVE SAMPLES					
40		166	167	166	165	180
	STORED ON BENCH					
42		164	162	164	162	171
	EACH REWARMED ONLY					
44		167	167	167	167	180
	ONCE TO 37°C					
49		192	194	195	193	216

* Immediate: within half an hour.

APPENDIX 8

CARDIOVASCULAR EFFECTS OF 60° FOOT DOWN TILT IN SIX ELDERLY SUBJECTS

	SUPINE	1 MINUTE	3 MINUTES	5 MINUTES	SUPINE
PATIENT 1, MALE 80 YEARS					
Mean blood pressure (mmHg)	107	105	103	105	107
Heart rate (beats/min)	68	71	71	72	71
Stroke volume (mls)	81	72	75	75	82
Cardiac output (litres/min)	5.5	5.1	5.3	5.4	5.8
Total peripheral resistance (mmHg/L/min)	19.5	20.6	19.4	19.4	18.5
PATIENT 2, MALE 86 YEARS					
Mean blood pressure (mmHg)	90	87	87	88	92
Heart rate (beats/min)	72	75	75	73	70
Stroke volume (mls)	76	69	72	67	89
Cardiac output (litres/min)	5.5	5.2	5.4	4.9	6.2
Total peripheral resistance (mmHg/L/min)	16.4	16.7	16.1	18.0	14.8

APPENDIX 8 (Cont'd)

	SUPINE	1 MINUTE	3 MINUTES	5 MINUTES	SUPINE
PATIENT 3, FEMALE 76 YEARS					
Mean blood volume (mmHg)	80	77	80	83	83
Heart rate (beats/min)	79	92	92	92	80
Stroke volume (mls)	68	49	52	49	68
Cardiac output (litres/min)	5.4	4.5	4.8	4.5	5.4
Total peripheral resistance (mmHg/L/min)	14.8	17.1	16.7	18.4	15.4
PATIENT 4, FEMALE 70 YEARS					
Mean blood pressure (mmHg)	113	110	110	110	117
Heart rate (beats/min)	67	75	73	73	69
Stroke volume (mls)	64	47	44	44	58
Cardiac output (litres/min)	4.3	3.5	3.2	3.2	4.0
Total peripheral resistance (mmHg/L/min)	26.3	31.4	34.4	34.4	29.3

APPENDIX 8 (Cont'd)

	SUPINE	1 MINUTE	3 MINUTES	5 MINUTES	SUPINE
PATIENT 5, FEMALE 76 YEARS					
Mean blood pressure (mmHg)	117	114	114	115	126
Heart rate (beats/min)	75	80	80	80	75
Stroke volume (mls)	73	63	61	63	68
Cardiac output (litres/min)	5.5	5.0	4.9	5.0	5.1
Total peripheral resistance (mmHg/L/min)	21.3	22.8	23.3	23.0	24.7
PATIENT 6, FEMALE 86 YEARS					
Mean blood pressure (mmHg)	100	97	97	97	97
Heart rate (beats/min)	90	96	95	97	90
Stroke volume (mls)	58	50	50	51	59
Cardiac output (litres/min)	5.2	4.8	4.7	4.9	5.3
Total peripheral resistance (mmHg/L/min)	19.2	20.2	20.6	19.8	18.3

APPENDIX 9

SYMPTOMATIC POSTURAL HYPOTENSION IN 40 PATIENTS. ASSOCIATED CAUSES

CASE NO.	SEX	AGE (YRS)	MAIN DIAGNOSIS	DRUG	SYSTOLIC BLOOD PRESSURE LYING	SYSTOLIC BLOOD PRESSURE STANDING
1	M	70	Parkinsonism	Nil	120	100
2	M	65	Parkinsonism	Nil	100	0
3	M	76	Parkinsonism	Levodopa/ Benserazide	130	80
4	F	70	Parkinsonism	Levodopa/ Benserazide	134	110
5	M	78	Parkinsonism	Levodopa/ Benserazide	114	68
6	F	83	Parkinsonism	Levodopa/ Benserazide	180	80
7	M	75	Parkinsonism	Levodopa/ Benserazide	126	90
8	M	74	Parkinsonism	Levodopa/ Benserazide	134	102
9	M	76	Parkinsonism	Levodopa/ Carbidopa	150	100
10	F	78	Parkinsonism	Levodopa/ Carbidopa	110	80
11	M	41	Diabetes Mellitus	Soluble Insulin	110	90
12	M	78	Alcoholic Neuropathy	Nil	116	60
13	M	77	Lobar Pneumonia	Ampicillin	150	110
14	M	77	Hypokalaemia	Nil	170	150
15	M	70	Oedema	Amiloride/ Hydrochloro-thiazide	172	110

APPENDIX 9 (Cont'd)

CASE NO.	SEX	AGE (YRS)	MAIN DIAGNOSIS	DRUG	SYSTOLIC BLOOD PRESSURE LYING	STANDING
16	F	71	Cardiac failure	Amiloride/ Hydrochloro-thiazide	136	116
17	F	86	Cardiac failure	Amiloride/ Hydrochloro-thiazide	100	70
18	F	83	Oedema	Amiloride/ Hydrochloro-thiazide	148	98
19	F	77	Cardiac failure	Cyclopen-thiazide/ Potassium	140	112
20	M	80	Dementia	Thioridazine	116	80
21	F	66	Dementia	Thioridazine	160	130
22	F	85	Dementia	Thioridazine	114	84
23	M	65	Hypertension Epilepsy	Propranolol Bendrofluazide Potassium Phenytoin	160	138
24	M	76	Hypertension Cardiac failure	Bumetanide Disopyramide Methyldopa	120	96
25	F	79	Ischaemic heart disease Cardiac failure	Propranolol Frusemide Potassium	174	118
26	M	71	Depression Oedema	Amitriptyline Spironolactone	110	60
27	F	78	Depression	Thioridazine Flurazepam Doxepin	112	0
28	F	75	Depression Cardiac failure	Frusemide Spironolactone Dothiepin	90	54

APPENDIX 9 (Cont'd)

CASE NO.	SEX	AGE (YRS)	MAIN DIAGNOSIS	DRUG	SYSTOLIC BLOOD PRESSURE LYING	STANDING
29	M	69	Stroke Depression Oedema	Amiloride/ Hydrochloro- thiazide Amitriptyline Dantrolene	120	80
30	F	71	Depression Cardiac failure	Imipramine Frusemide Potassium Diazepam	130	100
31	M	76		Nil	138	116
32	M	73		Nil	180	116
33	F	80		Nil	164	130
34	F	69		Nil	170	116
35	F	79		Nil	110	60
36	F	83	Cerebrovascular disease	Fludrocortisone	224	160
37	M	74	Ischaemic heart disease	Fludrocortisone	110	60
38	M	82	Lymphoma	Fludrocortisone	116	74
39	M	81	Atrial fibrillation Cardiac failure Bronchiectasis	Frusemide Potassium Digoxin Fludorcortisone	112	84
40	F	71	Cervical Sympathectomy	Dihydro-ergotamine	170	110