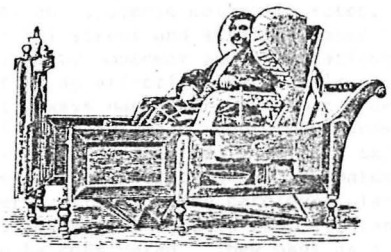

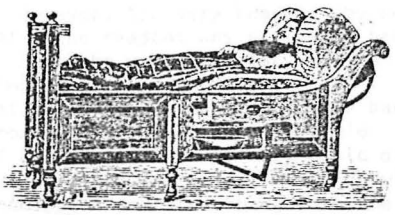

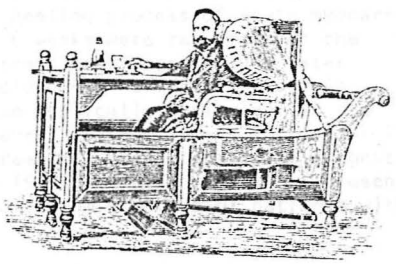

PARKLAND MEMORIAL HOSPITAL
MEDICAL GRAND ROUNDS, JUNE 18, 1981.

CARDIOVASCULAR CONSEQUENCES OF BED REST

C. GUNNAR BLOMQVIST, M.D.

INTRODUCTION.

The clinical indication for bed rest is a need to minimize the functional demands on a diseased organ or organ system. Bed rest will effectively reduce local and systemic metabolic rates, cardiac and respiratory work, and the mechanical stress and strain imposed on the musculo-skeletal system and other tissues by movement and gravitational forces. However, the very reasons why bed rest is an effective therapeutic regimen are also the reasons why prolonged bed rest always has severe systemic side effects. Even the most sedentary person will normally spend about two-thirds of his time in the upright position and achieve an average daily caloric expenditure at least 40 per cent above the basal rate. Any condition that attenuates these normal stimuli will have multiple adverse effects. The cardiovascular effect of bed rest is the primary topic of this review but results from studies during space flight and water immersion will also be considered. They have as a common denominator profound changes in the distribution of hydrostatic pressures and body fluids.

CLINICAL IMPLICATIONS: A HISTORICAL PERSPECTIVE.

The evolution of the current therapeutic regimen in acute myocardial infarction clearly illustrates how the perception of the relative merits and demerits of bed rest has changed during the past 40 years. During the 1930's and 40's most patients with acute myocardial infarction were treated with strict bed rest for at least 6 weeks (Lewis, 1937). The early empirical treatment was reinforced by two classic studies by Paul White. Mallory, White, and Salcedo-Salgar (1939) described the time course of the healing process of acute myocardial infarction. They concluded that at least 6 weeks were required for the transformation of necrotic myocardium into a firm fibrous scar. In a later paper, Jetter and White (1944) noted a high incidence of cardiac rupture in patients with mental disease who continued to be physically active during the course of an acute myocardial infarction. However, another famous Boston cardiologist, Dr. Sam Levine, had begun arm chair treatment of patients with congestive heart failure as early as 1937 (first reported 1944) and he later (1951) presented favorable results relative to historical controls from a series of patients with acute myocardial infarction.

The serious general side effects of bed rest - loss of muscle mass and strength, cardiovascular deconditioning, metabolic abnormalities, and an increased risk of venous thromboembolism - received wider attention during the early 1940's. The AMA Annual Meeting 1944 included a symposium on the "Abuse of Rest in the Treatment of Disease." The chairman's address was delivered by the Chief of Medicine at Southwestern Medical School, Dr. Tinsley R. Harrison. Dr. Harrison suggested that activity should be limited only to the extent necessary to keep the patient asymptomatic. In support of this view he cited a study of his own on the unfavorable effects of strict immobilization in experimental thermal myocardial injury and a series of clinical observations. At the same symposium, a second paper on heart disease, entitled "The Evil Sequelae of Bed Rest," was given by William Dock (1944). Both speakers discussed the hemodynamic advantages of the upright position, i.e. decreased pulmonary congestion and decreased myocardial work, and the role of activity in the prevention of venous thromboembolism and pneumonia. The psychological disadvantages of strict bed rest were also emphasized.

The publications by Levine, Harrison, and Dock, later supported by a series of physiological studies, initiated a marked change in the treatment of myocardial infarction. The duration of bed rest and hospital stay was progressively reduced. Wenger et al. (1973) surveyed management practices of more than 2,000 physicians in 1970 and found at that time an average hospital stay of 21 days and mobilization by the third day in uncomplicated cases. A recent follow-up study (Wenger et al., 1980) showed a further reduction of the average hospital stay to 14 days.

Table I. Controlled Clinical Trials of Early Mobilization and Hospital Discharge after Uncomplicated Acute Myocardial Infarction.

Author		N	Mobilization, days after onset	Discharge, days after onset
Harpur et al. (1971)	Treatment	95	8	15
	Control	105	21	28
Lamers et al. (1973)	Treatment	102	10	30
	Control	100	20	30
Hutter et al. (1973)	Treatment	69	7	14
	Control	69	10	21
Boyle and Lorimer (1973)	Treatment	269	7	21
	Control	269	21	28
Bloch et al. (1974)	Treatment	77	2	21
	Control	77	21	33
Hayes et al. (1974)	Treatment	107	2	9
	Control	82	9	16

None of the studies demonstrated significant differences between treatment and control groups with respect to early and late morbidity or mortality. Morbidity includes the incidence of venous thrombi as judged from a ^{125}I-labelled fibrinogen scan in the study by Hayes et al. (1974). Only Bloch et al. (1974) were able to show a significantly increased rate of return to work in the treatment group.

A number of controlled clinical trials (Table I) have convincingly demonstrated that early mobilization in uncomplicated infarction is a safe procedure which facilitates early hospital discharge. The psychological benefits have been well documented (Hacket and Cassem, 1973), and the economic advantages are obvious. There are no demonstrable favorable or unfavorable long-term effects on myocardial function, mortality, or morbidity.

The principle of early mobilization and discharge has been widely accepted with few dissenting opinions (Scherf and Cohen, 1978) and extended into carefully quantitated formal in-hospital exercise programs (Wenger, 1973).

Prolonged bed rest is now rarely used in the treatment of cardiovascular disease. However, prolonged immobilization is sometimes unavoidable in other conditions, e.g. multiple fractures. The physiology of bed rest should still be part of the clinical core curriculum.

PRINCIPAL EFFECTS OF PROLONGED BED REST IN NORMAL SUBJECTS.

A recent summary published by NASA (Nicogossian et al., 1979) lists more than 500 American, European, and Russian bed rest studies performed between 1921 and 1978. Early experiments concerned the metabolic effects of bed rest and immobilization and documented increased nitrogen excretion (Campbell and Webster, 1921), calcium loss (Cuthbertson, 1929; Albright et al., 1941), and decreased glucose tolerance (Blotner, 1945). The principal effects on body fluid distribution and cardiovascular function, i.e. decreased blood volume, orthostatic intolerance, and decreased exercise capacity in the upright position, were described by Taylor et al. (1945 and 1949), and Dietrick et al. (1948). The establishment of the U.S. Manned Space Program in 1958 and the use of bed rest as a model of weightlessness produced a very large number of studies during the 1960's.

Overview.

The results of a comprehensive study performed at this institution (Saltin et al., 1968) may serve as an introduction to current approaches and an overview of the principal features of the adaptation to bed rest.

The study group included 5 young men, 19 to 21 years old. Two were athletes and 3 were sedentary. The protocol called for a set of baseline studies followed first by a 20-day period of bed rest and then by a 60-day period of vigorous physical training. The control studies were repeated at the end of the bed rest and the training periods. The bed rest was closely supervised. The subjects were at no time allowed to support their own weight standing but they had bathroom privileges and were permitted to sit up in bed for eating and reading. The effectiveness of the immobilization was verified by measurements of heart rate, oxygen uptake, and caloric intake. During repeated 24-hour monitoring periods less than 5% of all heart beats were at a rate higher than 100 beats/min.

Table II. Effects of a 20-Day Period of Strict Bed Rest in Young Normal Men.

Mean values, n = 5.

	Control	Bed Rest	Change, Percent
Total Body Mass (kg)	76.7	76.4	-0.4
Lean Body Mass (kg)	66.3	65.3	-1.5
Calcium Excretion (urine, mEq/day)	15.9	25.6	+61
Total Blood Volume (l)	5.07	4.70	-7
Maximal Oxygen Uptake (l/min)	3.39	2.43	-28

Saltin et al. (1968).

Table II shows that total body mass remained constant. Caloric intake was reduced to match the lower demands during bed rest. There was a small but significant loss of total body water and lean body mass, reflecting a loss of muscle mass and extracellular, i.e. interstitial and intravascular volume. Light and electron microscopy of skeletal muscle biopsy samples showed no significant changes in capillary supply or in ultrastructure. There was a very large and progressive increase in the rate of urinary calcium excretion on a constant dietary intake. Total blood volume decreased by 370 ml or 7%. Maximal oxygen uptake, which is an index of the overall functional capacity of the cardiovascular

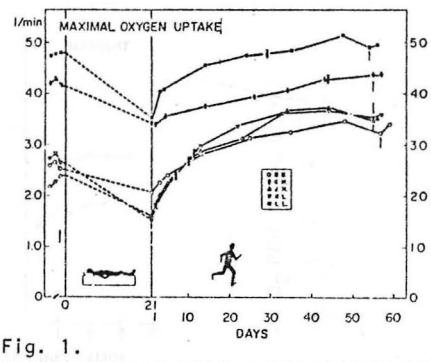

Fig. 1.

Changes in maximal oxygen uptake with bed rest and training. Individual data before and after bed rest and at various intervals during training. Arrows indicate circulatory studies. Heavy bars mark the time during the training period at which the maximal oxygen uptake had returned to the control value before bed rest.

Saltin et al. (1968)

system, decreased by 28% (Figure 1). Salient cardiovascular data are presented in Figures 2 and 3. The most important change was a marked reduction in stroke volume at rest and during exercise, particularly in the upright position but highly significant also in the supine position. There was after bed rest relative

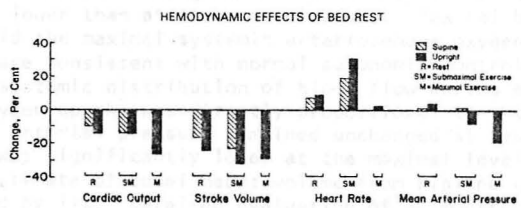

Fig 2. Data from Saltin et al. (1968)

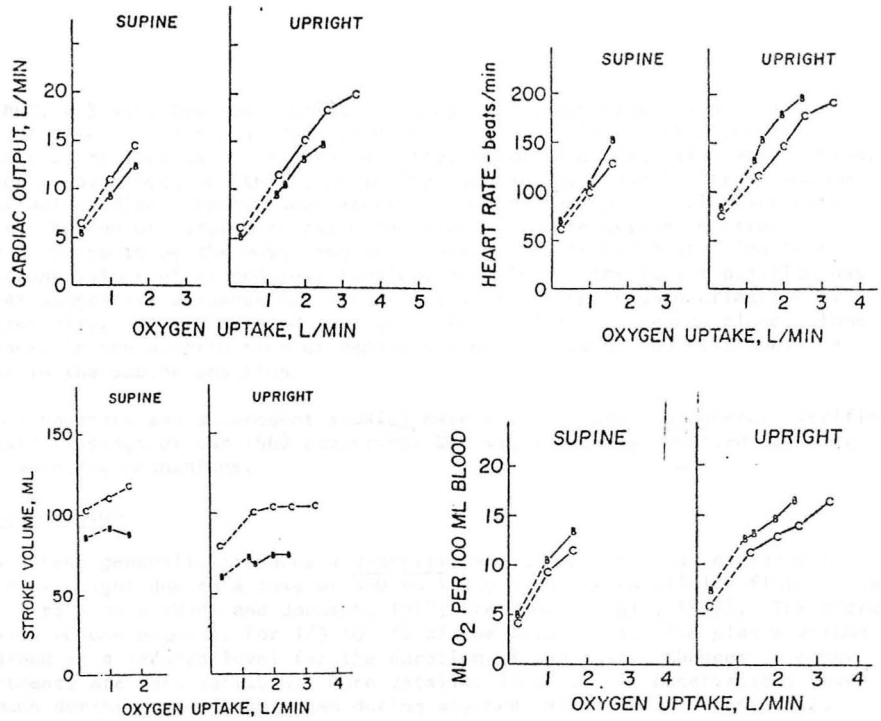

Fig. 3. Cardiac output, heart rate, stroke volume, and systemic A-V O_2 difference before (c) and after bedrest. Supine rest and submaximal bicycle exercise, upright rest (sitting), submaximal and maximal treadmill exercise. Mean values, n = 5. From Saltin et al. (1968).

tachycardia at rest and during submaximal exercise but cardiac output was still significantly lower than at the control study. Maximal heart rate did not change, nor did the maximal systemic arteriovenous oxygen difference. These two observations are consistent with normal autonomic control mechanisms for heart rate and the systemic distribution of blood flow during exercise. The reduction in maximal oxygen uptake was directly proportional to the decrease in stroke volume. Mean arterial pressure remained unchanged at rest and during submaximal exercise but was significantly lower at the maximal level. Other measurements included an estimate of total heart volume from biplane chest X rays. The heart size decreased by 11%. Detailed evaluation of pulmonary function showed no significant bed rest induced changes.

All functions returned to or surpassed baseline levels during the training program following bed rest. Recovery was significantly slower in the two athletes than the three sedentary subjects (Figure 1).

Thus, a 3-week bed rest period in young normal men caused significant losses of calcium, lean body mass, and blood volume. There was evidence for orthostatic intolerance. Exercise capacity, measured as maximal oxygen uptake, was reduced by almost one-third, primarily due to a decrease in stroke volume and maximal cardiac output. Regulatory mechanisms for control of heart rate and distribution of cardiac output were intact. The reduction in stroke volume appeared to be the most important consequence of bed rest. The fact that stroke volume after bed rest remained low also in the supine position was taken as suggestive evidence for myocardial dysfunction, caused primarily by the inactivity. It was assumed that any effects of the decreased blood volume or changes in the distribution of venous volume induced by bed rest would be minimal in the supine position.

Contemporary and subsequent studies have extended and, in general, verified the basic findings of our 1968 experiment but significantly modified our view of the adaptive mechanisms.

Body composition.

Bed rest generally produces a diuresis, and a rapid initial decrease in total body weight due to a loss of 500 to 1,000 ml of extracellular fluid, usually within 3 to 4 days (Vogt and Johnson, 1967; Greenleaf et al., 1977). The decrease in plasma volume accounts for 1/3 to 1/2 of the total loss. The plasma volume is maintained at a reduced level for the duration of bed rest. Changes in other compartments are more variable. More detailed longitudinal observations have been made during space flight than during any bed rest study. Leach et al. (1979) identified three components of the changes in total body mass: (a) an obligatory water loss of about a liter as a consequence of a headward fluid shift, (b) loss of muscle mass due to disuse atrophy and, (c) variable change in the amount of body fat. Overall losses of potassium, nitrogen, and protein are directly proportional to the degree of muscle atrophy.

Disuse atrophy preferentially affects postural muscles (which contain a high proportion of red or slow twitch fibers) (Saltin et al., 1977) and red fibers in general (Booth and Seider, 1979). The atrophy is reversible. Muscle mass is restored relatively rapidly (about 2 weeks) after experimental immobolization but postural muscles, e.g. the soleus, may require as long as 3 to 4 months to regain full strength (Booth and Seider, 1979).

Loss of calcium is a consistent feature of the response to bed rest and weightlessness. Periods of bed rest up to 36 weeks have produced losses at the rate of 0.5% of total body calcium per month. The decalcification process is progressive, and, if anything, the rate tends to accelerate with increased exposure (Dietrick et al., 1948; Donaldson et al., 1970). The calcium loss appears to be more severe during weightlessness than during bed rest. Balance studies during the Skylab flights demonstrated combined urinary and fecal losses at a rate as high as 2.5% of total body calcium per month (Rambaut and Johnston, 1979). The threshold for clinically important osteoporosis is about 20%. There is strong evidence indicating that the triggering event is the absence or attenuation of forces related to gravity, i.e. compression forces acting on bone and shearing and tensile forces acting on periosteal surfaces. Bone growth is markedly inhibited in space. Vigorous exercise in the supine position fails to prevent the calcium loss during bed rest but it can be reversed by weightbearing (Donaldson et al., 1970), e.g. three hours of quiet standing each day (Issekutz et al., 1966).

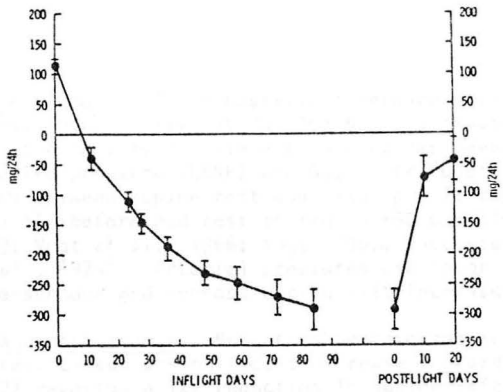

Fig. 4. Calcium balance as a function of Skylab flight duration (mean ±SE).
Raumbaut and Johnston (1979)

The exact cellular mechanisms mediating the calcium loss and the net absorption of bone are unknown. Blood levels of calcium are usually slightly elevated and plasma levels of parathyroid hormone are low. The negative calcium balance during bed rest is readily reversible by mobilization. Prolonged bed rest or space flight may nevertheless cause irreversible skeletal damage. Urolithiasis is another well-documented clinical complication. Young patients immobilized with multiple fractures occasionally develop severe hypercalcemia with systemic manifestations, including massive renal calcification with depressed function and hypertension (Albright et al., 1941; Conley, 1979). This condition is readily reversed by mobilization but largely unaffected by any other therapeutic approach. The lack of effective countermeasures has also placed calcium loss as the primary biological factor limiting the safe duration of space flight.

Cardiovascular function.

Maximal oxygen uptake during upright exercise is an important reference point in the evaluation of cardiovascular function. Only limited data on the effect of bed rest are available. Convertino et al. (paper in print) recently reported a decrease of 15% after 10 days of bed rest in a group of 50-year old men. Two-week bed rest periods produced a reduction of 9% in groups of young men and women studied by Georgiyevskiy et al. (1966) and Convertino et al. (1977). Measurements were in both studies performed during supine exercise. Slightly larger changes, -13 to -17%, (upright exercise) have been recorded after 3 weeks (Birkhead et al., 1963; Kakurin et al., 1966; Taylor et al., 1949). Miller et al. (1965) found a decrease of 22% after 4 weeks, also in a group of young normal men.

Stroke volume and cardiac output. Hyatt (1971) studied a series of 16 subjects before and after a 2 week bed rest period. Results obtained at rest and during submaximal exercise in the supine position paralleled our findings. The stroke volume was significantly reduced also in the supine position, particularly during exercise (-20%), and associated with compensatory tachycardia. Changes of equal magnitude were seen during passive head-up tilt. Similar results have also been reported from 3 subjects by Birkhead et al. (1963). Chobanian et al. (1974) also found markedly reduced stroke volume (-50%, 24 ml compared to 53 pre- bed rest) during 70° head-up tilt. There were no significant changes at supine rest.

Orthostatic tolerance. Changes in orthostatic tolerance have been evaluated in most bed rest studies. Head-up tilt at 70° for 5 to 20 minutes is the most widely used method but a variety of alternate procedures have also been employed, e.g. lower body negative pressure (LBNP) and G_{z+} centrifugation. The maximal heart rate difference between supine rest and head-up tilt typically increases from about +25 beats/min before bed rest to +40 to +50 beats/min after bed rest (Taylor et al., 1949; Vogt et al., 1966; Vogt, 1967; Lancaster and Triebwasser, 1971, Chobanian et al., 1974). Arterial pressures are lower after bed rest and the incidence of pre-syncope and syncope during tilt increases significantly.

Cardiac dimensions and performance. Recent echocardiographic studies have confirmed that bed rest causes a significant decrease in cardiac dimensions. Sandler et al. (1977) reported a 12% reduction in supine left ventricular end-diastolic volume in young men and women after a 2-week bed rest period. Hung et al. (1981) studied 50-year old men and found a corresponding decrease (-17%) at supine rest. Scintigraphic studies demonstrated significantly increased left ventricular ejection fraction at rest and during exercise both in the supine and in the upright position. Relative tachycardia was present during upright and supine exercise but absent at rest supine. The combined data virtually rule out intrinsic myocardial dysfunction after bed rest and indicate that an increased ejection fraction combines with relative tachycardia to offset the effects of the decreased end-diastolic left ventricular volume after bed rest.

DETERMINANTS OF THE DEGREE OF CARDIOVASCULAR DECONDITIONING: DURATION, STATE OF FITNESS, AGE AND SEX.

Methodological differences generally make it difficult to compare quantitatively the results from different bed rest studies but changes in plasma volume have been evaluated by similar techniques in many studies, often by multiple determinations. Red cell mass changes little during the initial 4 weeks of bed rest (Greenleaf et al., 1977) and changes in plasma volume approximate the changes in total blood volume.

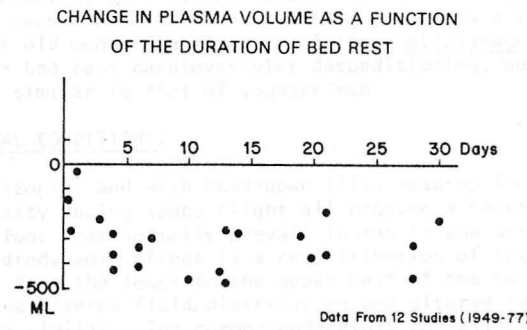

Figure 5 summarizes data from 12 studies 1949-77 with a duration of bed rest ranging from 6 hours to 30 days (Taylor et al., 1949; Saltin et al., 1966; Stevens, Miller, Gilbert et al., 1966; Stevens, Lynch, Gilbert et al., 1966; Torphy, 1966; Vogt et al., 1966; Vogt, 1967; Vogt and Johnson, 1967; Vogt et al., 1967; Johnson

et al., 1971; Chobanian et al., 1974; Greenleaf et al., 1977). A significant decrease in plasma volume occurs within 6 hours after the onset of bed rest (Torphy, 1966), preceded by a short transient phase of expanded plasma volume. The volume contraction appears to be progressive during the first 3 days but a plateau is then reached at an average loss level of 350 ml or about 12%. Greenleaf et al. (1977) performed a similar analysis of the literature and derived a non-linear regression equation indicating a progressive loss through 60 to 80 days. However, their estimate was heavily influenced by data from a single long-term study (Donaldson et al., 1969) with very large losses, 600-1,000 ml at a duration of 70 to 200 days. A similar long-term Russian study (Pak et al., 1973) showed a loss of 12% after 120 days, a value equal to the typical loss after 4 to 30 days.

Lack of sequential intragroup observations and greater variations in methodology makes it more difficult to map the time course of the changes in cardiovascular function. In general, the development of orthostatic intolerance and impaired exercise capacity seem to parallel the time course of the blood volume changes with relatively little progression after the first one or two weeks.

The rate of recovery will, to a large extent, be determined by the activity pattern after bed rest. The level of physical activity before bed rest may also be important. Very fit subjects appear to recover more slowly if their own pre-bed rest exercise performance is used as a basis for comparison (Saltin et al., 1968, see Figure 1). They are nevertheless likely to outperform sedentary subjects also in a deconditioned state. Athletes have often been considered to be more sensitive to short- and long-term orthostatic stress than sedentary subjects (Klein et al., 1977) but objective measurements comparing athletes and non-athletes have produced highly variable results. Conclusive data are lacking (Stegeman et al., 1974; Myrhe et al., 1976; Brock et al., 1979).

Most bed rest studies have been performed in normal men in their twenties but the NASA-Ames Research Center has during the past few years conducted a series of studies in women, 20-35 years old. These studies have in general failed to reveal any significant sex differences (Newsom et al., 1977; Greenleaf et al., 1977; Goldwater et al., 1978). DeBusk and co-workers (Hung et al., 1981; Convertino et al., paper in print) have recently completed a 14 day bed rest study in 12 50-year old men. The response of these middle-aged men, including the degree of post- bed rest cardiovascular deconditioning, were qualitatively and quantitatively similar to that of younger men.

RELATED EXPERIMENTAL CONDITIONS.

Bed rest, horizontal and with head-down tilt, head-up immersion, and exposure to zero gravity during space flight all produce a marked change in the hydrostatic conditions that normally prevail in man in the upright position. The principal acute hydrodynamic effect is a redistribution of intravascular and interstitial fluid from the lower to the upper half of the body. The mechanisms of adaptation to the altered fluid distribution and altered intravascular pressures are basically similar. The common end-result for all these conditions is actual and functional hypovolemia with a significant loss of plasma volume, orthostatic intolerance, and decreased exercise capacity, primarily due to a decrease in maximal stroke volume and cardiac output.

Immersion.

Head-up immersion in thermoneutral water, saline, or silicone has been used as a means of simulating weightlessness. Immersion regularly produces a larger

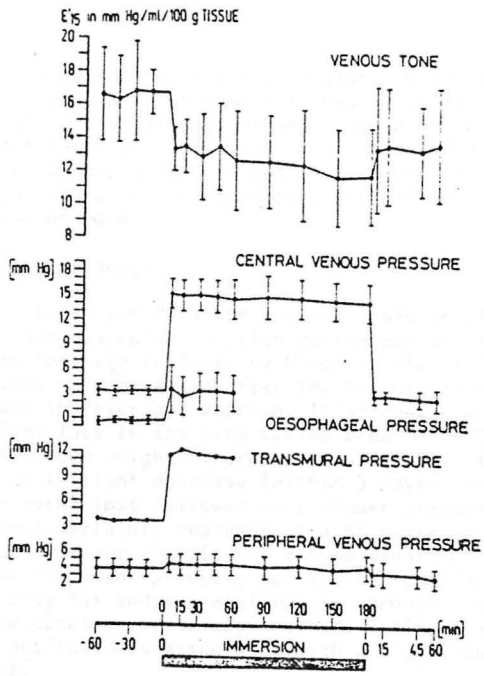

Fig. 6. The effects of whole body immersion on various parameters: peripheral venous tone; central venous pressure, oesophageal pressure, central venous transmural pressure, peripheral venous pressure. Recording of oesophageal pressure was discontinued after 1 hour immersion. N = 5.

Echt et al. (1974).

diuresis, weight loss, and blood volume loss and a greater degree of cardiovascular deconditioning than bed rest or head-down tilt of equal duration. The acute hemodynamic effects are also more prominent. Central venous pressure increases by about 15 mmHg (12 mmHg corrected for the change in intrathoracic pressure). There is a large increase in central blood volume (about 700 ml), and heart volume (+180 ml), stroke volume and cardiac output (+30 to 35%), no consistent changes in heart rate and only a minor (+10 mmHg) increase in arterial pressure. A hyperkinetic state is sustained for the duration of immersion, at least according to experiments lasting 3 to 4 hours (McCally et al., 1968; Aborelius et al., 1972; Echt et al., 1974; Lange et al., 1974, Epstein et al., 1975 and 1976; Begin et al., 1976; Epstein, 1978; Shulzhenko et al., 1979; Katkov et al., 1979; Bonde-Petersen et al., 1980).

Head-down tilt.

Bed rest with head-down tilt, usually at -4° to -6° (antiorthostatic bed rest), was introduced by Russian investigators as a more effective means of simulating zero gravity than horizontal bed rest (Kakurin et al., 1976). Several Russian and American studies (Kakurin et al., 1976; Volicer et al., 1976; Nixon et al., 1979; Katkov et al., 1979; Schulzhenko et al., 1979; Blomqvist et al., 1980; Convertino et al., 1981) support the validity of the technique. The effects of head-down tilt are qualitatively similar to those of bed rest but the adaptation is accelerated. Head-down tilt also produces a greater degree of cardiovascular deconditioning than horizontal bed rest of equal duration. Only a single study (Hyatt and West, 1976) has failed to demonstrate any difference between the two modes.

Experiments in our laboratory (Nixon et al., 1979; Blomqvist et al., 1980), based on a 24-hour period of head-down tilt at -5°, produced blood volume and weight losses of -350 ml and 1 kg and a decrease in maximal oxygen uptake of 22%. Heart rates at submaximal exercise and during orthostatic stress (LBNP) were about 20 beats higher than at the control study. These changes are of the same magnitude as those observed after bed rest or space flight of a duration of 2 weeks or more.

Weightlessness.

Extensive data are now available on fluid and electrolyte shifts and changes in cardiovascular function during and after space flight. The principal findings were recently reviewed by Nixon et al. (1979). Significant postmission weight losses were observed after the Mercury flights of a duration of less than 24 hours (Hoffler and Johnson, 1975; Pestov and Geratewohl, 1975). The average weight loss in the nine Skylab crew members was 3 kg, corresponding to 4% of total body weight (Thornton et al., 1977; Thorton and Ord, 1977). There was a rapid inflight decrease (within 3 days) that accounted for approximately one-half the total loss followed by a slower gradual decline. The rapid initial loss almost certainly represented a decrease in extracellular fluid. The intracellular fluid compartment did not change significantly (Leach and Rambaut, 1977). The slow component probably reflected a combination of caloric deficiency with loss of body fat and skeletal muscle atrophy. The pattern was reversed postflight. Data obtained by several methods during the Skylab flight documented that the weight loss was associated with a significant headward redistribution of body mass.

Data on orthostatic tolerance during and after the Apollo Skylab missions were obtained from measurements during lower body negative pressure (LBNP). Skylab 4 astronauts showed an average postflight increase in heart rate during LBNP at -50 mmHg of 27 beats/min after 89 days in space. In-flight LBNP measurements demonstrated similar changes. Decreased tolerance developed during the first few days without further changes or even some improvement toward the end of the flight (Johnson RL et al., 1976 and 1977). The Apollo astronauts (Hoffler and Johnson, 1977) had a mean heart rate during LBNP at -50 mmHg of 76 beats/min preflight and 109 postflight, i.e., a difference of 33 beats/min.

Pre- and postflight exercise data are also available from the Skylab and Apollo missions (Rummel et al., 1975; Buderer et al., 1976; Michel et al., 1977). The Apollo astronauts demonstrated a postflight increase in heart rate by 20 beats/min during exercise in submaximal levels of oxygen uptake and the crew of Skylab 4 showed an average increase of 15 beats/min. Changes of similar magnitude were seen after the 5-day Soyuz 6, 7, and 8 mission (Kakurin et al., 1976).

The Skylab experiments provided new and important data on exercise performance during and after flight. Time and equipment were available for frequent exercise sessions during flight. Preflight performance levels were maintained or improved in space (Michel et al., 1977). Nevertheless, postflight studies showed significantly reduced exercise capacity and decreased stroke volume after return to normal gravity. Orthostatic intolerance was also evident during the postflight LBNP studies (Buderer et al., 1976; Johnson et al., 1976 and 1977). Echocardiographic studies (Henry et al., 1977) demonstrated a reduced left ventricular end-diastolic volume and stroke volume postflight, consistent with a negative Starling effect without any change in contractile state.

Chair rest.

Chair rest has been used in attempts to separate adaptations related to inactivity from those due to the altered hydrostatic conditions and volume redistribution during bed rest and weightlessness. Short-term chair rest (6 hours) causes an increase in plasma volume and no change in orthostatic tolerance (McCally et al., 1968). However, Lamb et al. (1964) demonstrated orthostatic intolerance after 4 days of chair rest. The regimen included horizontal bed rest during sleep. In a later study (1965), the same group extended their series and examined 23 subjects over periods of 4 to 10 days. Orthostatic intolerance developed by Day 6 and became progressively more prominent at Days 8 and 10. Blood volume did not decrease significantly until after 10 days but the change was then comparable to that after bed rest of equal duration (-376 ml). There were no significant changes in exercise performance and maximal oxygen uptake actually increased slightly in the 10-day group.

COUNTERMEASURES.

A wide variety of interventions have been tested in attempts to prevent the cardiovascular deconditioning that is induced by bed rest. Principal approaches include exercise, redistribution of venous volume, and blood volume expansion.

Even vigorous exercise in the supine position fails to prevent orthostatic intolerance. The effects on exercise capacity in the upright position have been variable. A significant decrease is rarely prevented but the reduction tends to be smaller than in non-exercising controls (Brannon et al., 1963; Chase et al., 1966; Vogt, 1966; Birkhead et al., 1964 and 1966; Miller et al., 1964 and 1965; Lancaster and Triebwasser, 1971; Stremel et al., 1976). Most investigators have used dynamic exercise but static exercise had unexpectedly favorable effects in the study by Stremel et al (1977).

Redistribution of venous volume by pressure gradients applied externally to approximate the normal intravascular pattern during sitting or standing has generally proved helpful. Prolonged application of LBNP is cumbersome but prevents or minimizes plasma volume loss and orthostatic intolerance (Lamb et al., 1965; Stevens et al., 1966 a and b). Other devices, designed to simulate normal hydrostatic gradients, e.g. an "elastic reverse gradient garment," have been effective in short-term (less than 4 hours daily) applications (Convertino et al., 1978) as judged from exercise performance in the supine position.

Much more relevant from a clinical point of view is the observation by Birkhead et al. (1964 and 1966) that a daily 3-hour period of standing or 8-hours of quiet sitting prevented the development of orthostatic intolerance.

Reexpansion of the blood volume to pre- bed rest levels was achieved by oral administration of 9-α-fluorohydrocortisone during the last 3 days of a period of prolonged bed rest but orthostatic intolerance persisted (Stevens et al., 1965 and 1966). Hyatt (1971) administered daily doses of 0.4 mg during a 10-day bed rest study and produced a blood volume expansion relative to control values before bed rest. The heart rate during post- bed rest tilt nevertheless remained slightly elevated. Later rehydration experiments by Hyatt and West (1977) also tested the effects of oral administration of saline (154 mEq) at the end of a 1-week bed rest period. Saline alone was ineffective in terms of restoring plasma volume and orthostatic tolerance but the combination of saline and a 4-hour period of LBNP produced a transient return to pre- bed rest levels. In a recent

study in our laboratory (Blomqvist et al., 1980) i.v. saline infusion sufficient to bring central venous pressure back to pre- bed rest levels failed to restore orthostatic tolerance but minimized the loss of exercise capacity in the upright position. Normalization of CVP required a volume corresponding to twice the blood volume loss.

Other countermeasures, including exposure to simulated high altitude (Stevens et al., 1966) and devices designed to introduce sudden fluid shifts (Chase et al., 1966), have generally been ineffective.

SALIENT FEATURES OF THE CARDIOVASCULAR RESPONSE TO PROLONGED BED REST AND RELATED CONDITIONS.

A critical analysis of the descriptive material that has been presented in the sections on the effects of prolonged bed rest and related conditions and on countermeasures identifies the following salient points:

1. Prolonged bed rest (horizontal and with head-down tilt), water immersion, and exposure to zero gravity produce actual and functional hypovolemia.

2. Post-intervention cardiovascular dysfunction is characterized by orthostatic intolerance and decreased exercise capacity in the upright position. Left ventricular end-diastolic volume and stroke volume are reduced in both the upright and in the supine position. There is no depression of intrinsic myocardial function.

3. The degree of cardiovascular dysfunction is more severe than expected from the magnitude of the blood volume loss. Volume for volume replacement causes a significant improvement but does not fully restore normal function.

4. The altered distribution of body fluids with a head-ward shift is a more important factor than inactivity in the development of cardiovascular dysfunction. Intermittent redistribution of venous volume to match the conditions that normally prevail in the upright position provides full protection against orthostatic intolerance whereas even vigorous exercise in the supine position has little or no effect.

MECHANISMS INVOLVED IN THE ACUTE AND CHRONIC CARDIOVASCULAR ADAPTATIONS TO BODY FLUID SHIFTS.

Multiple and complex mechanisms are involved in the acute and chronic cardiovascular adaptations to body fluid shifts. Acute responses are determined by basal intravascular pressure-volume characteristics, by cardiovascular reflex responses, and by the principles governing cardiac pump performance. Renal and hormonal mechanisms dominate the long-term control of blood volume and interact with the cardiovascular control systems during chronic adaptations.

Distribution of intervascular volume and functional characteristics of the venous system.

Total blood volume in normal man approximates 7% of the total body weight. The systemic veins normally contain more than two-thirds of the volume. The arterial volume amounts to only 10% (Figure 7, Shepherd and Vanhoutte, 1979).

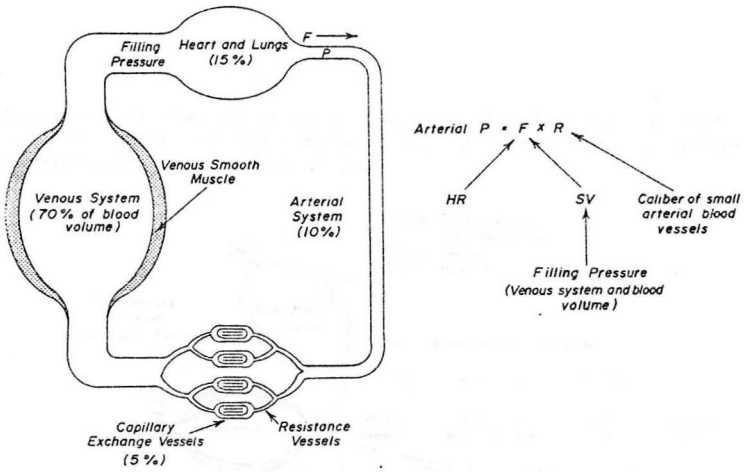

FIG. 7. Distribution of blood volume and the role of the venous system in regulating the filling of the heart. The normal values for total blood volume in humans range from 5 to 6 liters. The largest part of the blood volume is contained in the systemic veins. The capacity and pressure in this venous reservoir is continuously adjusted by contraction and relaxation of the smooth muscle in the venous wall. This permits the filling pressure of the heart to be continuously regulated so that an appropriate stroke volume is maintained. F = cardiac output. P = arterial blood pressure. R = total systemic vascular resistance. HR = heart rate. SV = stroke volume.

Passive and active control mechanisms combine to regulate central venous pressure and the regional distribution of venous volume. Passive volume changes - which dominate in the pulmonary vasculature - are a function of changes in the effective transmural distending pressure, i.e. the difference between intravenous pressure and tissue pressure. The venous pressure is in turn determined by arterial pressure and arteriolar resistance, the pressure in the right atrium and central veins, and the hydrostatic load. The down-stream pressure gradients within the venous system (disregarding hydrostatic pressures) are small, 10 mmHg or less. This means that the venous component of total peripheral resistance is small. Arteriolar pressure is therefore the major determinant of distending pressure, and, indirectly, of venous volume. Arteriolar dilatation increases venous pressure and volume. Vasoconstriction has the opposite effect and displaces venous volume centrally.

Active changes in venous capacity are mediated by cardiovascular reflexes and circulating catecholamines. The level of α-adrenergic stimulation is the primary control mechanism. Active regulation is made more effective by the basic muscle length-tension relationship that applies also to the venous wall. A distended vein will contract more effectively when stimulated than a nearly empty vessel. True autoregulatory changes (Bayliss effect) with increased myogenic activity in response to increased intravascular pressure are probably not functionally important. However, the opposite effect, i.e. relaxation after a prolonged increase in distending pressure (delayed compliance or viscoelastic creep) may be significant (Wyss et al., paper in print).

Veins differ with respect to their response to active stimulation (Figure 8). Muscle veins respond weakly, if at all, to neural stimulation. The capacitance of the cutaneous veins is primarily determined by thermoregulatory stimuli. Increased temperature causes dilatation. The splanchnic veins respond

with dilatation to stimulation of carotid and cardiopulmonary receptors and with contraction to activation of the metabolic muscle receptors (e.g. during exercise) and the chemoreceptors of the carotid body.

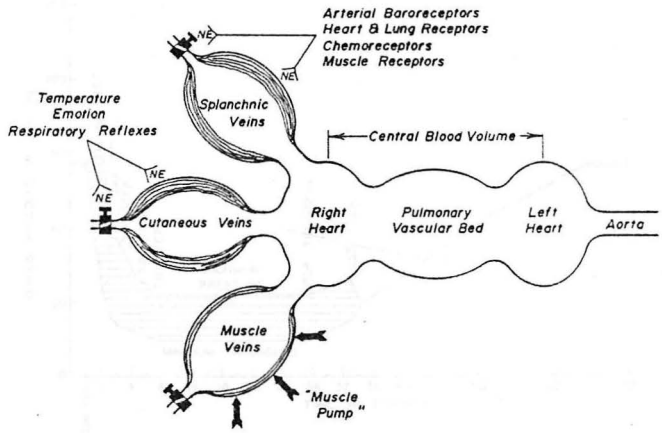

FIG. 8. Control of central blood volume and cardiac filling pressure by the systemic veins. Active changes in filling of the heart are brought about by contraction of the smooth muscle cells of the venous wall, in particular the splanchnic veins. The cutaneous veins play a role mainly in thermoregulation. Passive changes in capacity result from any change in distending pressure whether due to gravity or to changes in arteriolar resistance.
Shepherd and Vanhoutte (1979).

The hydrostatic pressures due to gravity have little effect on flow since gradients in general apply equally to arteries and veins. The valves in the veins rapidly become incompetent when exposed to high pressures. The venous pressure in the foot during standing closely approximates the open-column hydrostatic pressure (Pollack and Wood, 1949; Gauer and Thron, 1965). However, the tissue pressure in the leg during standing has a considerably smaller hydrostatic component than the intravascular pressure. This should cause an increased driving pressure and increased capillary filtration during standing but tissue filtration rates are controlled by resistance changes at the microvascular level (Haddy et al., 1976). Significant dependent edema rarely develops in healthy individuals. Abdominal tissue pressures closely parallel the intravascular hydrostatic pressures. The abdominal viscera act as a water-filled jacket. There is little postural change in the net or transmural venous pressure in the splanchnic bed (Gauer and Thron, 1965). These properties of the splanchnic vasculature have important consequences. Most of the venous volume - 500 to 600 ml - that is pooled in the legs during a change from the supine to the upright position is derived from the intrathoracic vascular volume (Tenney, 1959; Gauer and Thron, 1965).

Leg muscle contractions introduce important external pressure variations that markedly reduce venous pooling as illustrated in Figure 9, taken from the classical study by Pollack and Wood (1949). The action of the muscle pump

restores the competency of the valves in the leg veins and facilitates flow also in the superficial veins by lowering pressures (Shepherd and Vanhoutte, 1979).

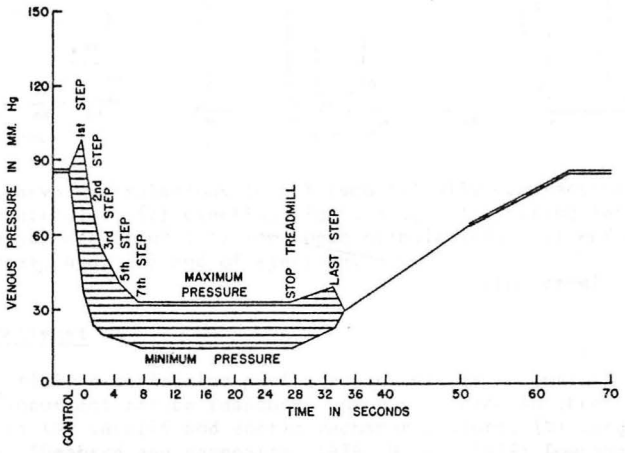

FIG. 9. Changes in venous pressure at the ankle of a normal man produced by walking, illustrating how compression of the deep veins causes a decrease in pressure in the superficial veins. (From Pollack and Wood: *J. Appl. Physiol.*, 1:649, 1949.)

Cardiac pump performance.

Cardiovascular responses are ultimately determined by the interaction between peripheral mechanisms and the basic principles regulating cardiac pump performance. A comprehensive analysis of ventricular function must be based on simultaneous consideration of force, velocity, and fiber length (Mitchell et al., 1972). The velocity axis is usually disregarded in clinical applications. The ventricular pressure-volume diagram (Suga and Sagawa, 1974; Sagawa, 1978; Weber et al., 1981) provides a useful approximation. The pressure-volume diagram defines contractile state as the maximal tension or pressure that can be developed at any given fiber length or volume (Figure 10). This implies that the amount of shortening or stroke volume that can be achieved from any given end-diastolic length or volume can be increased only by reducing afterload or by enhancing contractile state, e.g. by β-adrenergic stimulation. Similarly, any increase in the amount of shortening at a given afterload requires either an increased end-diastolic volume or an increased contractile state. Decreased filling pressure, e.g. due to venous pooling on the transition from supine to standing position, will therefore cause a decrease in stroke volume unless compensated for by an increased contractile state and/or decreased afterload. However, the systolic reserve capacity is limited. The left ventricular ejection fraction at rest is about 70% and the maximum during inotropic stimulation will rarely exceed 95% (Poliner et al., 1979). A large decrease in preload will inevitably cause a decrease in stroke volume. Cardiac output can only be maintained by increasing heart rate.

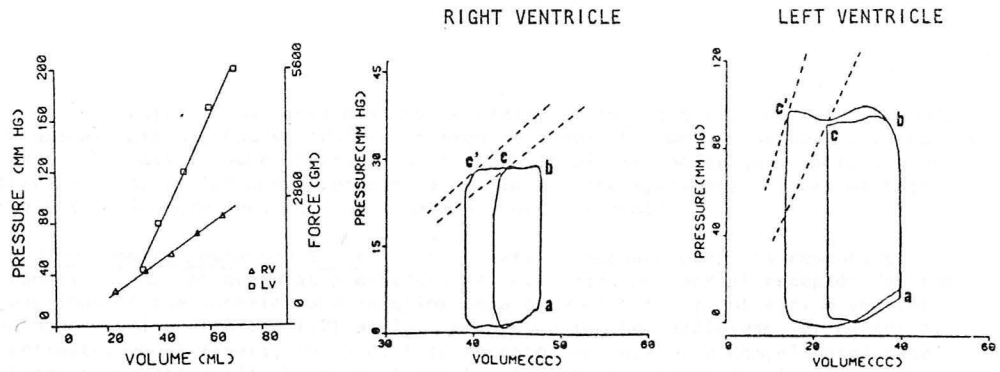

Fig. 10. Pressure-volume relations in (1) isometrically contracting right and left ventricles, (2) ejecting right, and, (3) ejecting left ventricles before (c) and after (c') inotropic stimulation. (a) end-diastole, (b) onset, and, (c) end of ejection.

Weber et al. (1981).

Cardiovascular reflexes.

The altered fluid distribution during acute changes in posture and prolonged bed rest causes important reflex responses which originate in three different sets of receptors: (a) carotid and aortic mechanoreceptors, (b) cardiopulmonary mechanoreceptors (Shepherd and Vanhoutte, 1979; Brown, 1979; Downing, 1979; Korner, 1979), and, (c) hypothalamic osmoreceptors and angiotensin II receptors. The third group of receptors interacts with the first two in the control of blood volume (Shepherd and Vanhoutte, 1979; Epstein, 1979).

Carotid and aortic mechanoreceptors. The mechanoreceptors in the walls of the carotid sinus and the aortic arch are stretch receptors. They are stimulated when distended. The degree of deformation and the rate of impulse flow is a function of transmural pressure. Afferent impulses travel in rapidly conducting myelinated and slowly conducting unmyelinated nerves with the glossopharyngeal nerve and the vagus to the cardiovascular center. Adrenergic and cholinergic efferent fibers reach the sinus and atrioventricular nodes, the ventricles, veins and arterioles by spinal cord pathways. Table III provides a summary of the effects of a fall in arterial pressure producing decreased stretch and decreased afferent impulse flow.

Table III. Hemodynamic Effects of a Decrease in Activity of the Mechanoreceptors in the Carotid Sinus, Aortic Arch, and the Cardiopulmonary Region.

Function	Change	Mechanism
Heart rate	+	ACh-, NE+
Stroke volume	± or +	NE+
Cardiac contractility	+	NE+
Venous capacitance	-	NE+
Coronary flow	+	Metabolism
Muscle flow	-	NE+
Skin flow	-	NE+
Kidney flow	-	NE+
Splanchnic flow	-	NE+

(+ increase, - decrease, ACh = acetylcholine, NE = norepinephrine).

Shepherd and Vanhoutte (1979).

The carotid sinus receptors are generally silent at pressures below 60 mmHg. A maximal rate of impulse traffic is seen at about 180 mmHg. The aortic receptors have - at least in some species - a steeper stimulus-response curve with a higher threshold (about 100 mmHg) but similar maximum. The myelinated fibers of both regions, which are less numerous, have a lower threshold.

Cardiopulmonary mechanoreceptors. Three sets of mechanoreceptors respond to changes in the intracardiac pressures: (a) discrete endocardial receptors at the junctions of the superior and inferior vena cava with the right atrium and the pulmonary veins with the left atrium, connected to the cardiovascular center by myelinated vagal fibers, (b) a diffuse receptor network with unmyelinated vagal fibers, connecting all chambers of the heart with the cardiovascular centers, and, (c) a similar network of receptors with afferent sympathetic spinal cord fibers. The function of the members of the last group is largely unknown, but some are probably pain receptors.

The discrete receptors at the venoatrial junction are activated by atrial contraction (Type A) and atrial filling (Type B). Stimulation produces: (a) increased sympathetic flow to the sinus node, (b) decreased sympathetic flow to the kidney, and, (c) inhibition of the secretion of antidiuretic hormone (ADH) from the posterior pituitary lobe. The net effects are tachycardia, increased renal blood flow, and a diuresis.

The diffuse receptors with unmyelinated vagal fibers are also activated by distension. The effects of stimulation are equal to those of distension of the aortic and carotid mechanoreceptors, i.e. the inverse of those listed in Table III.

The effects of both systems on renal sympathetic drive and renal blood flow are identical but the heart rate effects are opposite. Decreased stretch of the venoatrial receptors causes bradycardia and decreased stretch of the diffuse mechanoreceptors and of the carotid sinus/aortic arch receptors causes tachycardia. Covariations in atrial and ventricular/arterial pressures, e.g. reduced pressures during hemorrhage, will combine the effects generated by both receptor networks whereas a dissociation, e.g. high atrial pressures and low arterial pressures in severe congestive heart failure will buffer the effects (Shepherd and Vanhoutte, 1979). The cardiopulmonary and venoatrial receptors also interact with the metabolic muscle receptors (Abboud et al., 1981).

DYNAMIC RESPONSES TO CHANGES IN POSTURE AND TO PROLONGED BED REST.

Immediate responses to changes in posture.

Gauer has argued forcefully that in man the upright position should be regarded as the normal reference because basic vascular pressure-volume characteristics are regulated to provide optimal tissue perfusion in the upright position (Gauer and Thron, 1965). Nevertheless, the supine position continues to serve as the basal or control state in most human hemodynamic studies. Very few investigators have concerned themselves with the immediate circulatory adjustments to a change from a standing or sitting to a lying position. It is likely that a careful study would reveal hysteresis but it will - for the purposes of this discussion - be assumed that the hemodynamic responses to the transitions supine-standing and standing-supine are mirror images.

The primary stimulus to the postural cardiovascular responses is the translocation of a venous volume of about 500 ml. A redistribution similar to that which occurs during standing can be achieved by the application of lower body negative pressure (LBNP). Use of LBNP rather than tilt or standing facilitates many cardiovascular measurements and eliminates confounding effects due to skeletal muscle activity. Comparison of the responses suggest that the hemodynamic stress imposed by LBNP of -50 mmHg is the equivalent of quiet standing and passive head-up tilt at 70° (Wolthuis et al., 1974).

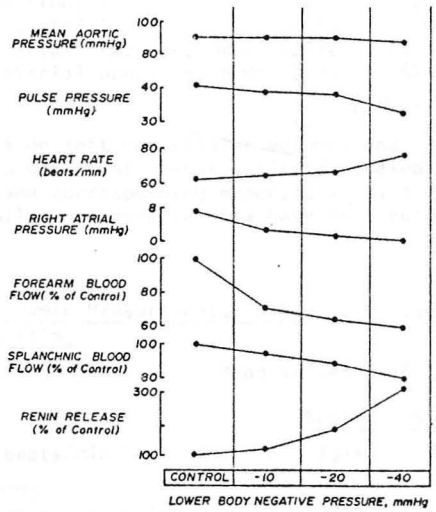

Fig. 11. Principal features of the hemodynamic response to lower body negative pressure (Shepherd and Vanhoutte, 1979, based on data from Fasola and Martz (1972), Johnson et al. (1974), and Zoller et al. (1972)).

Figure 11 (from Shepherd and Vanhoutte, 1979) shows the principal hemodynamic effects of LBNP. The degree of venous pooling is linearly related to the negative pressure. Stroke volume (not shown) also decreases in a linear fashion to a level 25-50% below that at rest. Cardiac output decreases by 20 to 40% (Ahmad et al., 1977; Nixon et al., 1979; Gaffney et al., 1979; Raven et al., 1980). Initially there are no changes in heart rate or arterial pressure. Peripheral and splanchnic arteriolar constriction compensates for the decrease in systemic flow. The splanchnic veins also constrict but there is, paradoxically, no measurable constriction of superficial or muscular veins. Progressive peripheral venous pooling eventually causes tachycardia. An increase in plasma renin is apparent after about 2 minutes and there are parallel changes in plasma norepinephrine (Fasola and Martz, 1972; Zoller et al., 1972; Johnson et al., 1974; Ahmad et al., 1977; Gaffney et al., 1979 and 1980; Raven et al., 1980). Echocardiographic studies in our laboratory (Ahmad et al., 1977) have demonstrated a marked decrease in end-diastolic volume with a parallel change in stroke volume (-20% at -40 mmHg). End-systolic volume also decreases (Sandler et al., 1977; Nixon et al., paper in print) but there is no change in contractile state until tachycardia develops. Thus, the primary cardiac response is a negative Starling effect.

Table IV. Left Ventricular Dimensions and Performance in Normal Subjects at Rest Supine and Sitting.

Mean values ± SE, n = 7

	Supine	Sitting	p
End-diastolic volume, ml	107±10	85±6	<0.02
End-systolic volume, ml	34±4	32±5	-
Stroke volume, ml	76±8	55±5	<0.05
Ejection fraction, %	76±2	72±4	-
Heart rate, beats/min	71±6	89±5	<0.05
Systolic arterial pressure, mmHg	125±8	125±5	-
Diastolic arterial pressure, mmHg	76±4	84±4	-

Poliner et al. (1980).

Scintigraphic data on left ventricular volumes and performance at rest supine and sitting in a series of normal subjects studied by Poliner et al (1980) are shown in Table IV and corresponding hemodynamic data (Thadani and Parker, 1978) in Table V. Similar hemodynamic data have been published by others, e.g. Bevegard (1962).

Table V. Direct Hemodynamic Measurements in Normal Subjects at Rest Supine and Sitting.

Mean values ± SE, n = 10

	Supine	Sitting	p
Heart rate, beats/min	73±4	84±4	<0.001
Pressures, mmHg			
Brachial artery, systolic	130±5	132±5	-
Brachial artery, diastolic	76±3	82±3	<0.05
Pulmonary artery, mean	13±1	13±1	-
Pulmonary capillary wedge	6±1	4±1	<0.001
Left ventricular, end-diastolic	8±1	4±1	<0.001
Stroke index, ml	50±5	35±3	<0.001
Cardiac index, l/min	3.5±.3	2.0±.2	<0.001

Thadani and Parker (1978).

The combined data on the cardiovascular response are consistent with a generalized vasoconstriction due to a decreased level of stimulation of the atrial receptors when pressures and volumes fall. Increased renal sympathetic drive produces decreased flow and a release of renin. Progressive pooling with decreasing stroke volume and cardiac output eventually causes a fall in arterial pressure with compensatory tachycardia, increased contractility and further vasoconstriction, mediated by the arterial baroceptors. The vasoconstriction is caused by reflex α-adrenergic stimulation and circulating norepinephrine. The relative importance of parasympathetic withdrawal and β-adrenergic stimulation in the regulation of heart rate is less clear. Bjurstedt et al. (1976), who performed LBNP during autonomic blockade, concluded that both systems contributed significantly, whereas Ewing et al. (1980) found that the heart rate response to standing was mediated primarily by vagal withdrawal.

The organization and response characteristics of the receptors may explain the relative lack of compensatory tachycardia at a time when venous pooling has caused a large decrease in stroke volume and cardiac output and falling arterial pressures. It is possible that the relatively slow heart rate is the resultant of opposing drives originating in the venoatrial and in the cardiopulmonary and arterial receptors. This dissociation may also have a role in hypovolemic syncope. More likely, reduction of ventricular dimensions during the pre-syncopal state progresses to a point at which the end-systolic volume approaches zero and the ventricular mechanoreceptors are stimulated during systole, causing bradycardia and vasodilatation, a Bezold-Jarisch reflex (Epstein et al., 1968). Echocardiographic studies (Sandler et al., 1977; Ahmad et al., 1977; Nixon et al., in print) provide some support for this mechanism. The unstable autonomic state during pre-syncope with large oscillations in heart rate may reflect opposing drives from atrial and ventricular/arterial receptors. (Stimulation of endocardial receptors due to high left intraventricular pressures and wall tension may precipitate exercise-induced syncope in aortic stenosis (Mark et al., 1973)).

Orthostatic intolerance.

Orthostatic intolerance is caused by two principal mechanisms: hypovolemia and abnormal reflex regulation. The hemodynamic and regulatory patterns in the hypovolemic group represent an exaggeration of the normal response, including increased adrenergic drive (sympathicotonic orthostatism). The second group is heterogenous and includes patients with generalized autonomic disorders and more specific abnormalities of mechanisms controlling cardiac and peripheral vascular responses.

The orthostatic intolerance induced by prolonged bed rest and related conditions may be due to a combination of these factors. As previously noted, the degree of intolerance is disproportionate relative to the magnitude of the hypovolemia. Autonomic dysfunction is likely to contribute.

Abnormal blood volume or blood volume distribution. Measurable orthostatic intolerance appears after an acute blood volume loss of 200-250 ml (Murray et al., 1967). Women have larger increases in heart rate and decreases in arterial pressure and stroke volume than men at a given degree of venous pooling, probably due to a smaller basal end-diastolic ventricular volume and limited systolic reserve (Sandler et al., 1977; Gaffney et al., 1977). Some women with mitral valve prolapse and small ventricles have severe orthostatic intolerance. They have less venous pooling and more intense vasoconstrictor responses than normal subjects but total blood volume is low, perhaps due to a chronically vasoconstricted state. The hypovolemia combines with the mechanical characteristics of the valve to produce severely impaired ventricular filling and low stroke volume in the upright position (Gaffney et al., 1980).

Conditions that cause increased venous pooling are also associated with central hypovolemia and with orthostatic intolerance. Data on venous compliance after bed rest and space flight are inconclusive (Blomqvist, 1980). The most important physiological mechanism that affects the degree of pooling is linked to thermoregulation. Venous compliance and pooling is proportional to skin temperature. Heat significantly reduces and cold increases orthostatic tolerance (Henry and Gauer, 1950; Henry et al., 1955; Raven et al., 1980). Patients with massive venous varicosities or congenital absence of the venous valves have decreased orthostatic tolerance and decreased exercise capacity in the upright position. These patients also have an increased compliance of non-varicose veins (Zsoter and Cronin, 1966).

A large number of vasoactive drugs will affect venous properties by direct effects on smooth muscle, on adrenergic nerve endings, or the central nervous system (Shepherd and Vanhoutte, 1975).

Abnormal autonomic responses. A small group of patients have postural hypotension caused by idiopathic failure of the adrenergic system. Catecholamine release and vasoconstrictor responses are impaired due to widespread degeneration of neurons in the brain and spinal cord. The etiology is unknown (Bevegard et al., 1962; Shepherd and Vanhoutte, 1975 and 1979; Chobanian et al., 1974). A variety of neuropathies, including diabetic, may interfere with sympathetic and parasympathetic control mechanisms (Donald and Shepherd, 1979; Ewing et al., 1980; Eckberg, 1980; Abboud et al., 1981). Defective heart rate control due to local abnormalities, e.g. complete heart block or sick sinus node syndrome, may also impair orthostatic intolerance.

The nature of the regulatory abnormalities that may contribute to the orthostatic intolerance after bed rest and space flight is unknown. Chobanian et al. (1977) found no bed rest-induced changes in the pressor responses to the infusions of norepinephrine and angiotensin. Plasma catecholamines were reduced during bed rest but the response to tilt was unchanged. The apparent turnover rate of norepinephrine was also normal. However, Stone and co workers (Dickey et al., 1979; Billman et al., 1981) have demonstrated reduced baroceptor sensitivity and altered responses to vasoactive drugs after long-term horizontal immobilization in rhesus monkeys.

A detailed review of all conditions and interventions that modify orthostatic tolerance is outside the scope of this presentation. However, it may be noted that orthostatic tolerance often is increased in hypertension and congestive heart failure (Murray et al., 1969; Abelman and Fareeduddin, 1969; Shepherd and Vanhoutte, 1979). Cardiac performance characteristics, decreased venous compliance and increased total and central blood volumes combine to counteract autonomic dysfunction with blunted afferent and efferent regulatory responses (Donald and Shepherd, 1979; Downing, 1979; Eckberg, 1980).

Dynamic responses to prolonged bed rest.

Many studies of prolonged bed rest and related conditions have been limited to static before-and-after comparisons. There is relatively little information on the dynamic response. It is nevertheless evident that the stimulus that triggers both the short-term and long-term adaptations is the shift of intravascular and interstitial fluid from the lower to the upper half of the body, particularly to the central circulation. The absolute magnitude and exact time course of the responses to bed rest, head-down tilt, immersion, and weightlessness, may vary as they relate to specific functions, but a critical review of the literature (Blomqvist, 1980) justifies the use of one particular condition, head-down tilt, as a model for an analysis of the general features of the adaptation to a central fluid shift.

Figure 12 is based on 2 experiments with 24-hour head-down tilt, each including 5 young normal men (Nixon et al., 1979; Blomqvist et al., 1980). Another experiment in a group of 50-year old men produced similar data.

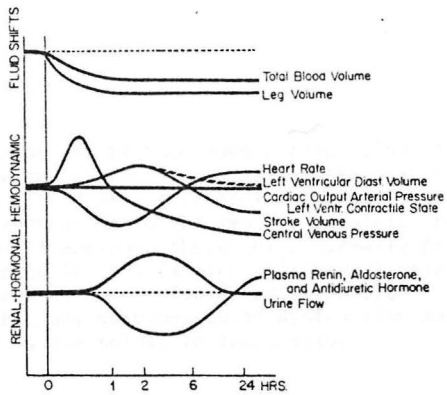

Fig. 12. Diagrammatic representation of the time course of human adaptation to a central fluid shift (head-down tilt).

Blomqvist et al. (1980).

The time course of the adaptations to weightlessness and head-down tilt is similar. Changes generally occur more slowly during bed rest. A 24-hour period of head-down tilt is the approximate equivalent of 3-4 days of bed rest.

The baseline for all measurements represented in Figure 12 was supine rest. A central fluid shift is indicated by a decrease in leg volume of about 1 liter during the initial 2 hours. Central venous pressure increased significantly by 2.5 cm H_2O but returned to baseline within 1 hour. This decrease was associated with a transient increase in venous compliance whereas systemic and peripheral venous compliances were normal at the end of 24 hours. Stroke volume and left ventricular end-diastolic volume also increased transiently and reached a maximum somewhat later than CVP, or at about 2 hours. There was no change in contractile state. Cardiac output did not change. The decrease in stroke volume was offset by relative bradycardia. Arterial pressures also remained unchanged.

Plasma renin, aldosterone, and antidiuretic hormone levels decreased transiently during the initial 6 hours and there was a diuresis that produced a weight loss equal to the loss in leg volume, and, more importantly, a decrease in total blood volume of 350 ml. There was no change in plasma osmolality or electrolyte concentrations but the urinary sodium/potassium excretion ratio increased. Central venous pressure and stroke volume were at 24 hours below baseline and the heart rate was slightly elevated.

The events are consistent with a central fluid shift that activates atrial and ventricular receptors and results in a decreased sympathetic drive acting on peripheral vessels and the kidney with inhibition of renin and aldosterone. The crucial diuretic effect is partially due to a Henry-Gauer reflex, i.e. reflex inhibition of ADH secretion by impulses originating in the atrial receptors. Epstein (1978) has analyzed in detail the renal effects of water immersion and demonstrated similar changes, i.e. combined effects on renal handling of water (ADH inhibition) and electrolytes (inhibition of the renin-angiotensin system with a natriuresis). There is no evidence for significant changes in renal hemodynamics or an important role of the osmoreceptors.

The apparent overshoot of the hemodynamic adaptation at 24 hours with a reduced filling pressure and stroke volume may be taken as support for Gauer's view that the upright position is the set-point for basic cardiovascular regulation in man. When the adaptation to bed rest is complete, hemodynamic conditions in the supine position will approach those which normally prevail sitting or standing. A system adapted in this fashion will have little reserve capacity to deal with additional stresses due to fluid redistribution. This view also renders untenable the concept that any cardiovascular dysfunction manifest in the supine position after bed rest is due solely to inactivity.

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