STUDY REPORT

ON

MODIFICATION OF THE LONG TERM CIRCULATORY

MODEL FOR THE SIMULATION OF BED REST

JULY 15, 1977

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DATE 7-15-77	WORK ORDER REF:	WORK STATEMENT PARA: NAS9-14523	REFERENCE:

SUBJECT

Study Report
Modification of the Long Term Circulatory Model
for the Simulation of Bed Rest

The attached study report documents the results of a major effort under this contract. The modifications of the circulatory, fluid, electrolyte control model (based on the model of Guyton) to include separate leg compartments, the addition of gravity dependency, and the validation studies were completed, as were the modifications for bed rest simulation, hypothesis formulation and testing, and bed rest simulation studies.

The performance of this study resulted in many suggestions for additional improvements, modifications, and future studies. These recommendations are discussed in section 7 of this report. The basic conclusion is that the recompartmented Guyton model can perform, at least as well, the simulations the previous model was capable of performing; it can simulate changes in orthostatic gradient; and it can simulate the response to the fluid shifts associated with bed rest with enough accuracy to test the suggested hypotheses.

Attachment
/db

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1.0   INTRODUCTION

Analysis of experimental data from Skylab has shown that the
changes occurring in the legs, the losses of tissue and fluid, and the
shifts of fluid from the lower to the upper body play a very important
role in the physiological adaptation to zero-g.   The data from bed rest
studies, taken as a ground-based experimental analog to zero-g, have
also shown similar important changes involving the legs.   Attempts to
analyze these physiological changes, and their underlying mechanisms,
through the use of the simulation models has been hampered by the inabil-
ity of the long term portion of the Whole-Body Algorithm and the Guyton
model of circulatory, fluid, and electrolyte regulation to simulate changes
involving the legs and gravity dependency.   The objective of this study is:
1)   to modify the long term model by recompartmenting the circulatory
representation so that leg (lower body) compartments could be identified
separately.   This recompartmentization would allow changes in the leg
compartments themselves and shifts from the lower to the upper body
compartments (and vice-versa) to occur,   2) to add gravity effects to
this representation so that removal (or zero angle) of the gravity vector
is explicitly represented in the model,   3) to verify the modified model
through comparison with previous simulations and experimental data and
4)   to develop and test hypotheses for the long term simulation of bed
rest.

Experimental studies of spaceflight and bed rest may be divided
into periods of time, each characterized by different types of physiological
response.   Thus, the sudden reduction of gravitational effects results in
an <u>acute</u> response lasting minutes, hours, or even one or two days.   This
is followed by a chronic or long term adaptation phase lasting perhaps
weeks or months in which the physiological changes occur more slowly
albeit persistently.   Similarly, the recovery-from-stress stage may
also be divided into acute and chronic periods of readjustment.

It should be recognized, however, that the Guyton model is primarily suited to the study of long term adaptation to stress. It should not be expected that the fidelity of the simulation of short term stress – particularly the dynamic response of those stresses lasting minutes – would be as great as longer term responses. This inadequacy is further compounded by the relative scarcity of good long term studies as compared to acute experiments. Thus, the ability of the improved model to meet these objectives is governed not only by the additional degree of detail added to the model under this task, but also by the basic capability of the model and the quality of data available.

The most obvious physiological changes during an acute change of posture occur in the circulatory system are a result of a moderate volume of blood shifting between the upper and lower body. Longer term changes during bed rest or zero-g exposure are also characterized by different circulatory changes occurring in the upper and lower body. In addition to intravascular fluid shifts, adaptive responses are also thought to occur in cardiac control, vascular compliance, blood flow redistribution, etc. Some of the more dramatic changes that have been observed immediately upon recovery from these type of stresses, have occurred during orthostatic tolerance stress tests which involve displacing blood from the upper part of the body to the legs either as a result of LBNP or standing. All of these considerations lead to the conclusion that the minimum change in the Guyton model must include a recompartmentalization of the circulatory compartment into upper and lower body segments.

In addition to changes in circulatory function as a result of gravity effects, secondary changes occur throughout the body both during the acute and chronic stages. Some of the most important of these changes involve plasma-interstitial fluid shifts, autonomic function, renal function, hormonal function, electrolyte concentrations, and body fluid volumes.

All of these elements are represented to some degree in the Guyton model. Whether or not most of these responses are a direct result of the initial gravitational effect is not known and, in fact, is a question which may be answered in part by simulation studies with the recompartmentalized model. Additional structural changes will most certainly have to be included to provide the necessary level of detail to test hypotheses for acute and long term zero-g adaptation.

The following determinations are associated with recompartmentation:

a)   pressures, flows, and volumes of the upper and lower circulatory compartments,

b)   redistribution of flow paths between upper and lower circulatory compartments perfusing muscle and non-muscle, non-renal tissues,

c)   levels of pressure and volume of the upper and lower body interstitial (and intracellular) compartments,

d)   redistribution of basal capillary filtration and lymph flow between upper and lower body compartments,

e)   pressure-volume function curves (compliances) of upper and lower circulatory compartments for arterial and venous segments.

f)   pressure-volume function curves (compliances) for interstitial compartments of upper and lower body.

Additional elements must be added to the model to represent gravity dependency. The most basic addition entails determining the locations in the model which should be responsive to the direct effect of hydrostatic gradients and choosing the most appropriate means of including this effect. Other determinations of gravity effects include:

a)   baroreceptor pressure,

b)   autonomic function,

c)   pressures, flows, and volumes of the upper and lower cir-
      culatory compartments,

d)   pre- and post-capillary resistances in muscle and non-
      muscle tissues in the upper and lower circulatory com-
      partments,

e)   venous tone in both upper and lower body segments as the
      result of stress relaxation, autonomics, and angiotensin

f)   renal flow,

g)   capillary filtration and lymph flow in both upper and lower
      compartments,

h)   renal function (urine flow, electrolyte excretion),

i)   hormonal secretion rate including ADH, angiotensin, and
      aldosterone

j)   metabolic rate

The following guidelines , and criteria were used to test the final models:

a)   Supine Model at Rest

      Steady-state values for the gravity dependent model in the
supine and unstressed mode should agree with those of the original model
with respect to such important quantities as cardiac output, mean
arterial pressure, blood volumes, extravascular volumes, electrolyte
concentrations, renal excretion, salt and water intake, etc. In addition,
values of flows, pressures and volumes of the new lower body compart-
ment should favorably compare with the pulsatile cardiovascular model
and with available data on human subjects supine for relatively short
periods of time.

b)   Supine Mode Under Stress

The behavior of the restructured model in response to stresses of interest should be essentially similar to that of the original model with respect to basic physiological parameters. The stresses that will be performed will include the relatively short term responses to fluid infusions, hemorrhage, dehydration, and longer term salt loading with impaired renal function. These are stresses which have been used to validate the original Guyton model. In addition, the capability will be included in the new model to perform LBNP simulations. Simulation results for this stress will be compared with that of the pulsatile cardio-vascular model which has already been validated for LBNP.

c)   Standing Mode at Rest

Steady-state values of basic circulatory parameters in the standing mode should agree with data from human subjects performing quiet standing or tilt for relatively short periods of time. The model will have the ability to vary the angle of tilt with respect to gravity. Differences between passive tilting and erect standing may suggest new elements in the model to account for muscle pumps, venous valves, abdominal compression reflex, and venoconstriction, all of which are important in the real system to prevent orthostatic collapse. The additional lower body compartment should realistically simulate blood pooling, extravascular filtration and peripheral vasoconstriction. Comparison of responses will be made not only with human data, but with simulation responses of the model of Croston and that of Leutscher and co-workers. Extremely long term effects of standing at rest without leg activity results in continued pooling of blood in the legs and will not be considered. The emphasis will rather be on long term effects of the supine position.

d)   Long Term Bed Rest

Proper validation of the longer term bed rest experiment will entail testing hypotheses by adding other elements or modifying existing

elements. The incorporation of the lower body segments into the Guyton model and the successful completion of the studies outlined above will provide a solid foundation and the necessary level of detail with which to test theories of long term adaptation.

2.0 MODIFICATIONS FOR POSTURAL (GRAVITATIONAL) CHANGES

There have been only a few studies in which the gravitational effects of posture on the body fluid compartments have been modeled. Snyder (1969), and Croston, et al (1973) have described models of the circulatory system in which gravity effects have been included as well as some of the physiological mechanisms (such as muscle pumping, abdominal compression, venous valves) that act to prevent orthostatic collapse. Responses to tilt-table experiments have been simulated by these investigators. However, these models do not account for fluid exchange with extravascular compartments, and moreover have been designed for describing only short term responses. Another intravascular model with gravity effects has been reported by Green and Miller (1974) for describing the response of the circulatory system to acceleration stress. The emphasis in this study was in investigating changes in circulatory function in the head during centrifuge studies and does not include a separate lower body compartment. Only one published study was found that models circulatory responses to postural change and which includes the effects of intravascular-interstitial fluid shifts (Boyers, Cuthbertson and Luetscher (1972). Their seven compartment circulatory subsystem lacks the detail found in some of the other models mentioned above, but on the other hand has a degree of complexity greater than Guyton's model on which it is based. The absence of lymph return, extravascular protein circulation, hormonal effects, etc., preclude using this model for other than short term simulations. A more recent version of this model (Luetscher, et al (1973)) includes the addition of a renin-angiotensin subsystem. A previous, unpublished attempt to include gravity effects in the Guyton model was made by White (1974), but it was only a feasibility study and lacked the detail necessary for the present task. One other model that was useful in this study is that of Luetscher, et al (1970) in which the effects of posture on renal circulation and function was simulated.

The recompartmentation of the circulatory, fluid, and electrolyte control model based upon the model of Guyton (1972), was accomplished by drawing from and improving upon these earlier studies. These modifications and others described in Section 3.0 were performed first on the stand-alone model and verified by comparison with other model simulations and experimental data. These modifications were then incorporated in the Whole-Body Algorithm.
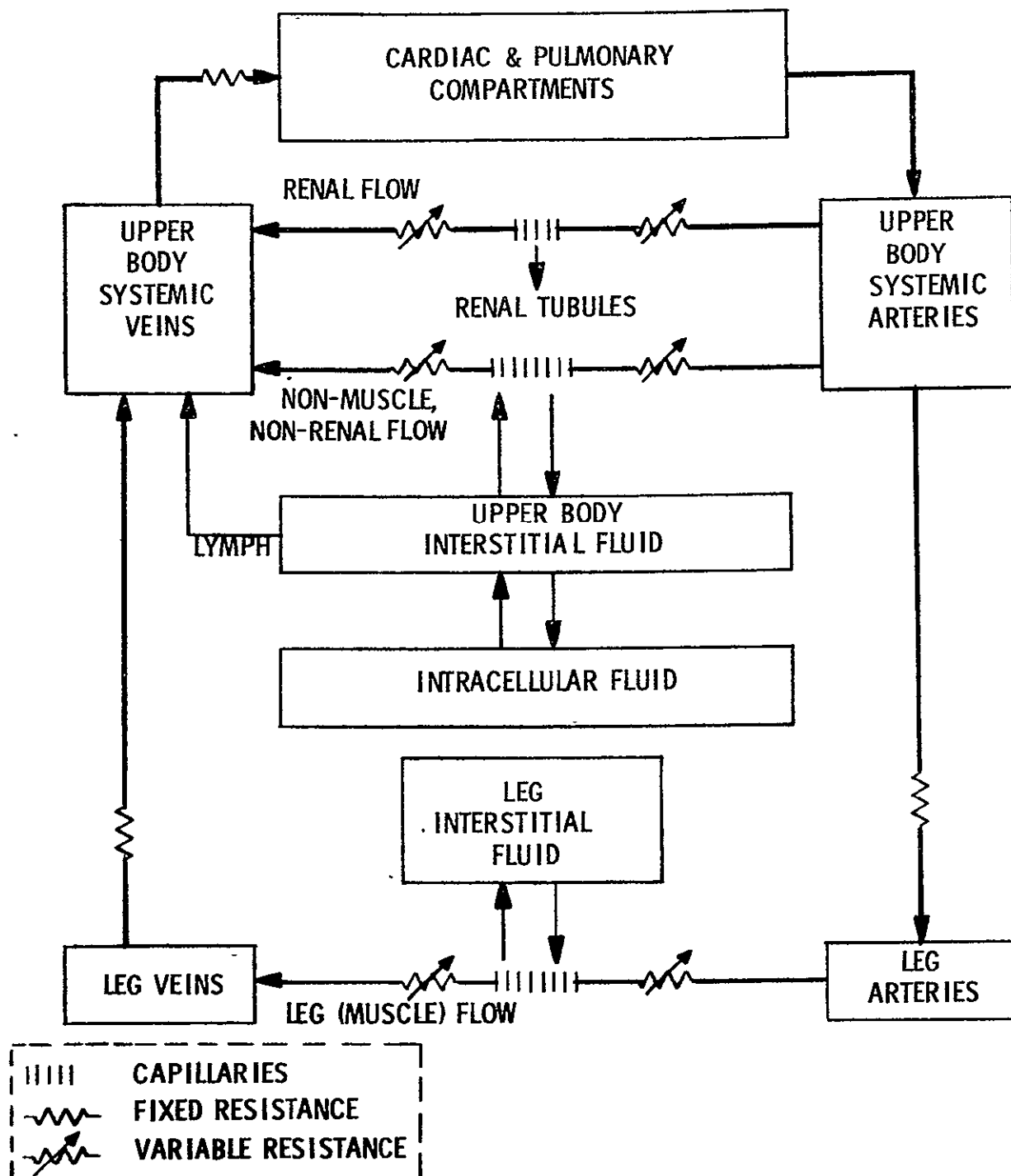
2.1   RECOMPARTMENTING THE MODEL

Leg Circulatory Compartment

Two compartments have been added in the circulatory system representing leg arteries and veins. Each compartment is characterized by a total blood volume, blood pressure and compliance (see Figure 2.1 and Table 4.1). The values for volumes and compliances of the leg compartments were derived from the 28-compartment pulsatile cardiovascular subsystem of the whole-body algorithm. The blood volumes and compliances of the upper circulatory compartments were adjusted to keep the total volume and compliance of the arterial and venous vessels nearly identical to that of the original Guyton model.

Blood Flow Pathways and Metabolic Rates

The original Guyton model contained three blood flow pathways: renal, muscle, and non-renal, non-muscle. In the modified version these three pathways remain intact; however, the muscle flow pathway represents the entire leg flow and the non-muscle, non-renal pathway together with the renal flow represents total upper body flow (see Figure 2.1). In other words, in this modified model, leg blood flow and muscle blood flow are identical. Muscle and non-muscle, non-renal flows were readjusted (by changing their basic resistances RALZ and RVLZ) so that cardiac output was similar to that of the unmodified version of the Guyton

CIRCULATORY AND FLUID COMPARTMENTS IN MODIFIED GRAVITY DEPENDENT
MODEL OF CIRCULATORY, FLUID AND ELECTROLYTE REGULATION

FIGURE 2.1

model and leg flow was similar to that of the leg blood flow of the short term pulsatile cardiovascular model of the whole0body algorithm (see Table 4.1). Metabolic demand in terms of oxygen consumption were also readjusted in proportion to the new blood flow rates.

Resistances of the Leg Blood Vessels

Two fixed resistances were added (RVZ and RAZ) to provide a small pressure gradient between upper and lower arteries and veins (see Figure 2.1).

The single muscle flow resistance of the original version was replaced by two variable resistances in series to permit capillary filtration to occur in the muscles which is driven by a muscle capillary pressure. The two leg resistances are a precapillary arteriolar resistance (RAL) and a postcapillary (venule) resistance (RVL), each mathematically defined as follows:

Leg arteriolar resistance:

RAL = RALZ x AUM x ANU x ARL x VIM * PDAL

where RALZ = arteriolar basic resistance

AUM = autonomic effect

ANU = angiotensin effect

ARL = autoregulatory effect

VIM = blood viscosity effect

PDAL = pressure distention effect

Leg venule resistance:

RVL = RVLZ x CEL x PDVL x (1+(AUM-1)AULZ) x (1+ANU-1)ANLZ)

where TVLZ = basic leg venule resistance (constant)

PDVL = passive distention effect due to venous pressure

$$= (4.89/PVL)^{.3}$$

CEL = capillary pressure waterfall effect

AUM = autonomic effect with gain constant AULZ

ANU = angiotensin effect with gain constant ANLZ

The total resistance to blood flow through the leg muscle is given by the sum of these two variable resistances.

$$RL = RAL + RVL$$

The blood flow rate of the leg is taken to be the difference of pressure between the leg arteries (PAL) and veins (PVL) divided by the resistance.

$$QL = (PAL - PVL)/RL$$

The pre- and post capillary resistances (i. e., arteriolar and venule) of the non-muscle, non-renal tissues were renamed RAN and RVN, respectively although their formulation remains unchanged from the original model. However, their steady-state resistance values were readjusted (by changing their basic resistances RANZ and RVNZ) in accord with the logic discussed above in "Blood Flow Pathways." The formulations for RAL and RVL given above for the leg muscle tissue are similar to that of the non-muscle, non-renal pre- and post capillary resistances presented in the original Guyton model with the following exceptions:

a) The passive distention effect due to hydrostatic pressure was removed from the leg arterioles (i. e., PDAL set to 1. 0). This was justified by the fact that upon standing it is believed that a strong myogenic local reflex acts to constrict arteriolar vessels (as well as capillary sphincters) in response to the high hydrostatic load. The myogenic reflex opposes the passive distention effect. It was felt that until the myogenic effect is included in the model the passive distention effect should be removed. Otherwise, the effect of standing would create arteriolar distention great enough to overcome autonomic vasoconstriction, a condition that does not seem to exist in the real physiological system.

b) The veins are not known to participate in the myogenic response, but rather, should be highly responsive to passive distention under the high

hydrostatic pressures of standing. Therefore, a passive distention effect (PDVL) has been added to the leg venule resistance. The formulation defining PDVL permits a 1 mm Hg change in pressure to cause a 1% change in resistance in accordance with data reviewed by McDonald (1960). The net effect of excluding the passive distention effect in the leg arterioles and adding this effect to the leg venules is to favor a higher pre/post capillary resistance ratio· upon standing which tends to reduce leg capillary pressure towards leg venous pressure. According to Mellander (1971), this is an appropriate response to limit outward filtration of plasma in the erect posture.

Effect of Gravity on Pressure Gradients

The average hydrostatic pressure gradient (PGH) in the legs due to gravity has been expressed as:

$$PG = ZML \times 0.77252 * \sin (PHI/57.295)$$

where ZML is taken as the distance (in cm.) from the heart to the knees. The factor 0.77252 converts cm H_2O to mm Hg while PHI/57.295 is the angle (in radians) of tilt measured from the horizontal (i.e., PHI = 0° for supine and PHI = 90° for fully erect). PG is introduced into the formulation for leg flow in two locations: a) at the input to the leg arterial compartment where it aids flow and b) at the output of the leg venous compartment where it opposes flow.

The effect of gravity on the carotid baroreceptors must also be included since the angle of tilt changes the hydrostatic pressure at these important sensors. The hydrostatic gradient at the baroreceptors is given by:

$$PG1 = ZB * 0.77252 * \sin (PHI/57.295)$$

where ZB is the distance between the heart and the carotid receptor.

PG1 is <u>subtracted</u> from the effective pressure sensed at the carotid body (PA1) during a tilt simulation. The values for ZML and ZB are set at present to 76.2 cm and 13 cm, respectively.

Any angle of tilt may be simulated by adjusting PHI and other postures such as sitting may be studied by adjusting ZML.
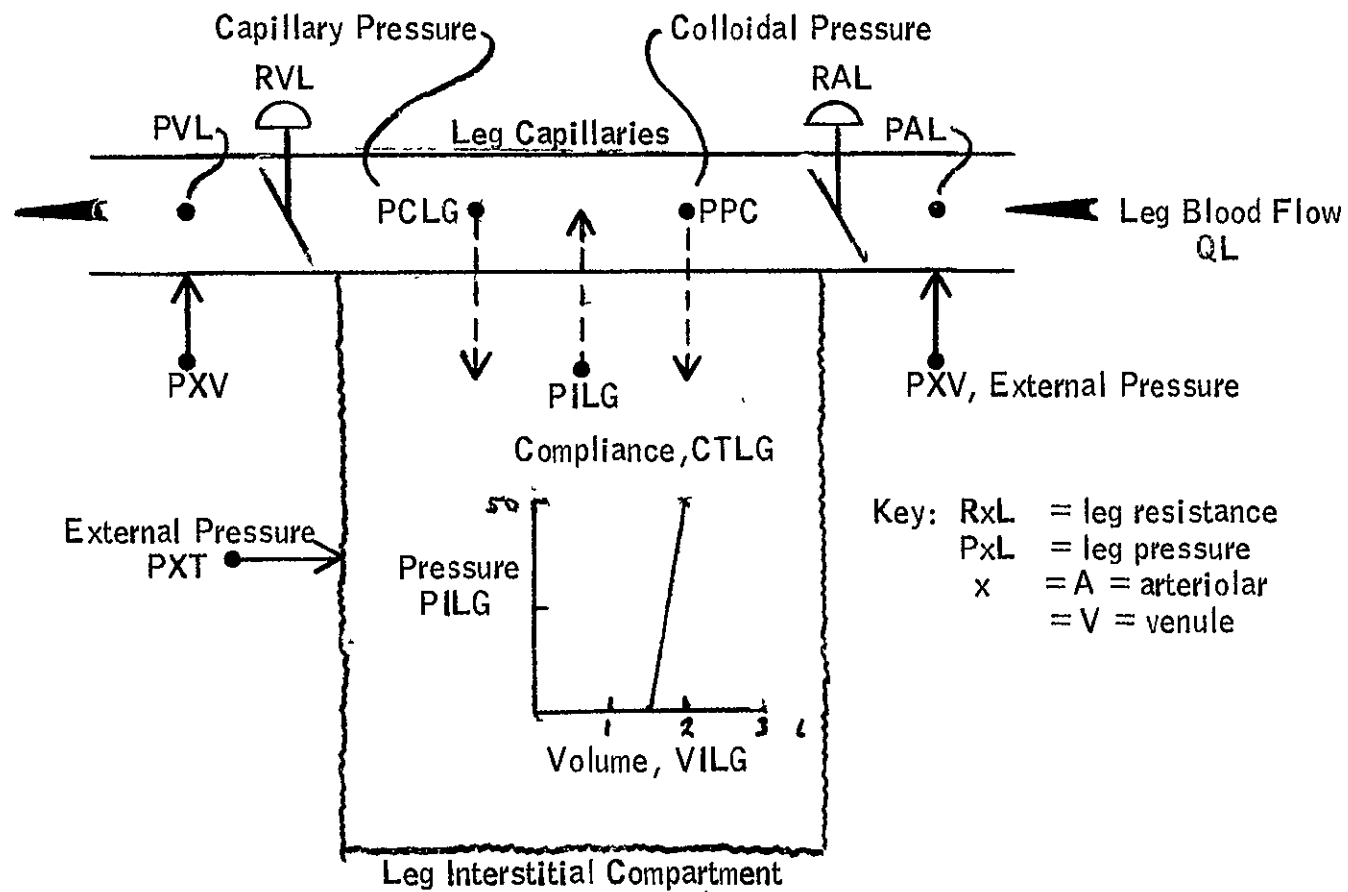
Venous Valves

The effect of venous valves has been added by permitting blood flow from the venous leg compartment (QVL) to assume only positive values. Because this leg compartment can only be filled by arterial blood (rather than reverse venous flow from upper body veins) transient conditions can exist in which inflow from the leg arteries are approximately normal, but outflow to the veins is zero. This occurs, for example, during the onset of lower body negative pressure simulation. This situation was not possible in the original Guyton formulation. In order to insure that the approach toward equilibrium of inflow and outflow occurs correctly, it was necessary to insert an additional "equilibrium criteria" at the end of the short term cardiovascular-autonomics loop of the Guyton model. The statement

IF (QLM-QVL) .LE. 0.10) GO TO 100

does not permit calculations to exit from the short term loop until the flow differential in the leg venous compartment is less than or equal to 0.10 liters/min.

Leg Plasma/Interstitial Filtration

A mechanism was added to permit plasma to filter into a new interstitial leg compartment. This is illustrated in Figure 2.2 in schematic form. Blood flow in the leg tissues is driven under an arterial-venous pressure gradient (PAL - PVL) across an arterial resistance RAL and venous resistance RVL. The capillary pressure (PCLG) is computed

Capillary Pressure

Colloidal Pressure

Leg Capillaries

Key: RxL = leg resistance
PxL = leg pressure
x = A = arteriolar
= V = venule

Leg Blood Flow QL

Compliance, CTLG

Volume, VILG

Leg Interstitial Compartment

SCHEMATIC OF LEG FILTRATION MECHANISMS

FIGURE 2.2

as a function of upstream and downstream pressures and the pre-/post capillary resistance ratio, in accordance with the Landis-Pappenheimer formulation:

PCLG = RCLG*PAL + (1-RCLG)*PVL

where   RCLG = RVL/(RVL+RAL)

Filtration rate into the leg interstitium (QLEG) is based on the transcapillary hydrostatic pressure and oncotic pressure gradients multiplied by a leg capillary filtration coefficient (CFLG):

QLEG = (PCLG - PILG - PPC)*CFLG

where PILG is the leg interstitial pressure and PPC is the plasma colloid osmotic pressure.   It is assumed that interstitial colloid osmotic pressure is negligible.   The value of PILG is determined from the leg interstitial volume (VOLG) and the tissue compliance (CTLG).

Due to the lack of detailed information regarding the leg tissues and tissue pressure changes during standing, this represents a highly simplified model of leg filtration whose major assumptions are:

a) A leg tissue fluid volume equal to 1.5 liters in supine steady-state.

b) A linear compliance that permits tissue pressures to rise by about 40 mm Hg during standing when the fluid volume is increased by approximately 500 ml due to plasma filtration. This large pressure increase is necessary to oppose excessive filtration because of the equally high change in capillary pressure.

c) Neither the effects of lymph flow, tissue colloidal concentration, nor tissue gel have been studied.

The model allows changes in leg filtration to be reflected in the total plasma and total interstitial volumes of the whole-body model.

External Leg Vascular Pressure

An external pressure term (PXV, mm Hg) has been included in the formulation for leg arterial and venous pressure, and an external tissue pressure term (PXT, mm Hg) has also been added. These terms are normally zero. By setting PXV and/or PXT to values less than zero the effects of lower body negative pressure can be simulated. Values higher than zero will simulate various events such as positive pressure leg garments, water immersion, drying up the legs, and a muscle pump mechanism all of which have the effect of reducing venous leg blood volume and aiding in venous return during standing.

Instantaneous Stress Relaxation Effect

A term representing instantaneous stress relaxation was added to the stress relaxation block of the original model. This appears as a constant factor (normally zero) which was found to be necessary to aid venous return during tilt simulation. In that case, reverse stress relaxation was used (VSRI < zero). Its physiological counterpart may be a combination of stress relaxation, the abdominal compression postural reflex, as well as a central venoconstrictor effect. It is represented in a more complete form in White's latest (unpublished) version of Guyton's model. It is suggested that at a later date this more complete version be added to the present model.

2.2   PASSIVE TILT SIMULATION

Testing the response of the model to head-upward tilt was used during the course of the recompartmentation effort as a relatively simple means of assuring that the new formulations were basically correct. Tilting or standing is the most obvious gravity dependent stress and an abundance of information exists describing the short term (10 – 30 minutes)
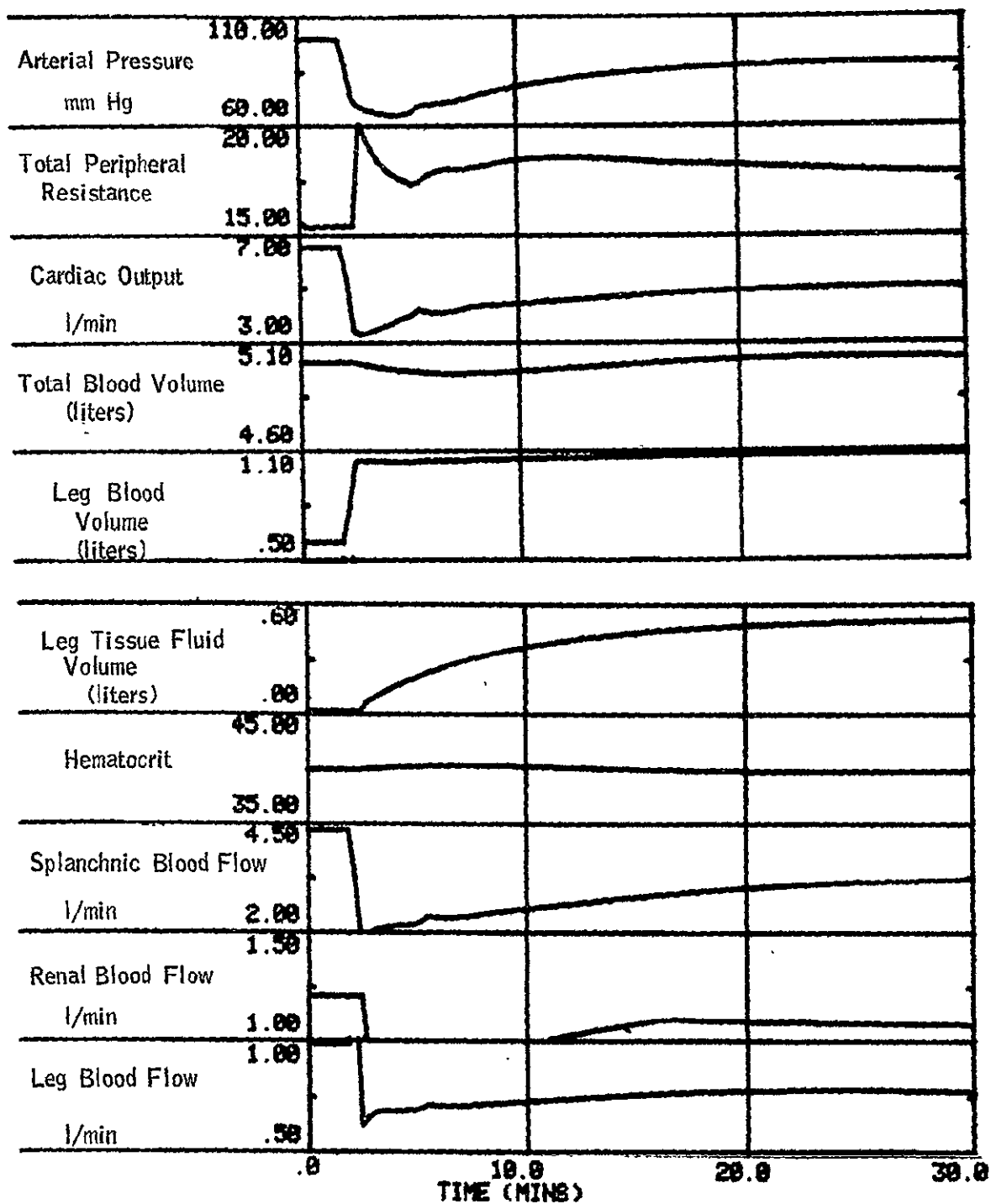
response. However, this stress is a rather complex one and all the mechanisms which participate in creating orthostatic tolerance are not quantitatively understood (Guyton, et al, 1973; Shepherd & Van Houtte, 1975).

The Guyton model is primarily suited to the study of long term adaptation to stress over the course of weeks rather than minutes. Inasmuch as the major changes of the modified model were associated with the controlled system (i.e. , adding new circulatory compartments), it was important to assure that the controllers in the model (autonomic, local, and humoral mechanisms) were sufficient to regulate changes in the new fluid compartments in the face of an orthostatic challenge. (The original design of the controller system did not include considerations regarding gravity dependent stresses.) Thus, the intent of performing head-upward tilt validations was to produce a response that was more qualitatively than quantitatively correct so as to: a) assure that the new gravity dependent formulations were basically appropriate, and b) to identify any controller components which should be included in the model to improve the response not only to short term tilt, but to long term bed rest and weightlessness, simulation of these latter conditions being the ultimate goal.

Basic Model Response to Tilt and Recovery

The response of the recompartmentalized model to a 90° head upward tilt is shown in Figure 2. 3. Many other variables other than those shown were monitored, but the general accuracy of the response and the main problem areas can be identified from this output.

Fluid pooling occurred nearly instantaneously in the leg vessels and more gradually in the leg tissues due to hydrostatic forces. This reduction in central blood volume lowered cardiac output, blood pressures and curtailed flows through the three major pathways: legs, upper body, and renal. Pressures and flows would have been reduced even further if compensatory

SIMULATE 90° TILT RESPONSE OF BASIC
GRAVITY DEPENDENT MODEL
FIGURE 2.3

feedback mechanisms were not present in the model which decreased venous capacitance and increased peripheral resistance. However, these mechanisms were apparently not as effective as in the real system because the reduction in arterial pressure and cardiac output were much lower than observed in man.

Another shortcoming that was observed was the blood volume response. Although blood pooling in the legs and fluid shifting into the interstitium was appropriate with regard to direction and dynamic behavior, the blood volume only decreased transiently by about 50 ml instead of showing a net sustained loss of several hundred milliliters. Upon further examination, it was found that fluid was being absorbed from the capillaries in the upper body nearly as fast as it was filtering from the leg capillaries. Thus, although the model's response was generally in the appropriate direction the magnitude of this response and its dynamic behavior was not consistent with observations of the real system.

Additional Orthostatic Mechanisms

It became apparent that any mechanism added to the model to allow blood volume to fall would worsen the blood pressure and cardiac output response. Therefore, a combination of mechanisms would be necessary that would: a) inhibit inward fluid absorption in the upper body capillaries, and b) increase venous return and, therefore, blood flow and pressures. A preliminary series of trial simulations resulted in the following modifications which, when added to the model in concert, improved the tilt response to acceptable levels:

a)   Enhanced venoconstriction. The sensitivity (gain) of the venous resistance element to efferent baroreceptor signals was increased. This change increased the postcapillary resistance in the upper body capillaries (the major blood flow pathway) in the face of a decreased baroreceptor pressure. This permits an increase in capillary filtration pressure and limits the inward filtration that

would otherwise occur. Too much of an effect would cause blood volume to fall severely producing unrealistic reduced levels of blood pressures and flows.

b) <u>Enhanced reverse stress relaxation.</u> The original Guyton model contained a stress relaxation element which causes gradual reduction of venous capacitance in the face of reduced blood volume. A term was added to produce an instantaneous effect which reduces upper body venous capacitance to approximately half of the reduction in central blood volume. This effect, which is present in a more realistic fashion in a recent unpublished version of Guyton's model, was simulated by reducing the unstressed venous volume at the moment of tilt. Its effect is to increase venous return, cardiac output, and systemic blood pressures. However, too great an effect could actually raise pressures and flows unrealistically above control values during tilt.

c) <u>Reduced area available for capillary filtration.</u> The filtration coefficient for the upper body capillaries was reduced in value at the time of tilt. The direct effect was to limit the rate at which interstititial fluid enters the circulation and thereby produce a reduced blood volume.

d) <u>Muscle Contraction effect in legs.</u> A parameter was added which would provide a pressure, external to the leg blood vessels, simulating the muscle contraction effect that occurs during tilting and to a much greater extent during standing. The effect is to reduce leg venous pressure, reduce the amount of fluid pooled in the legs and increase venous return. Too great an effect will reduce blood pooling to unrealistically low values for a tilt stress.

The first three of these effects are in accord with the generalized splanchnic venoconstriction that has been observed following reduction in central blood volume either due to hemorrhage or tilting (Folkow and Neil, 1971; Rowell, 1974. The first two modifications (a and b) could also be as a result of abdominal compression, autonomic, or local meta-bolic effects. The last modification (d) could represent a proprioceptive tilt reflex which is simulated as a small increase in external pressure (≈ 10 mm Hg). These effects, regardless of the underlying mechanisms, appear reasonable and are supported in the literature on tilt table experiments. While arterial constriction affects resistance by reducing vessel caliber, venoconstriction reduces the capacity of the blood reservoirs (thus shifting fluid toward the heart) and increases postcapillary resistance. An increase in postcapillary resistance has less of an influence on overall systemic resistance than it has on capillary filtration by its effect on capillary pressure. The evidence for a decrease in capillary coefficient has been inferred from studies of hemorrhage, infusions, and standing (Mellander, et al, 1967, 1971).

The model response with these mechanisms added either singly or in combination at the beginning of tilt is shown in Figures 2.4A to 2.4E and Figure 2.5. The dashed line in each of these figures represents the simulation response to tilt of the basic gravity dependent model without these additional orthostatic effects (see Figure 2.3). The symbols at the right margin indicate those responses which have been improved due to the additional mechanisms. The first two mechanisms listed above resulted in the greatest improvements and Figure 2.5 shows the tilt response as well as recovery from tilt during a simulation in which these effects have been added. The transient "spike" effect at the start of each tilt simulation is an artifact that would not be present if the tilt had not been performed instantaneously.

SIMULATED 90° TILT RESPONSE: EFFECT OF INSTANTANEOUS
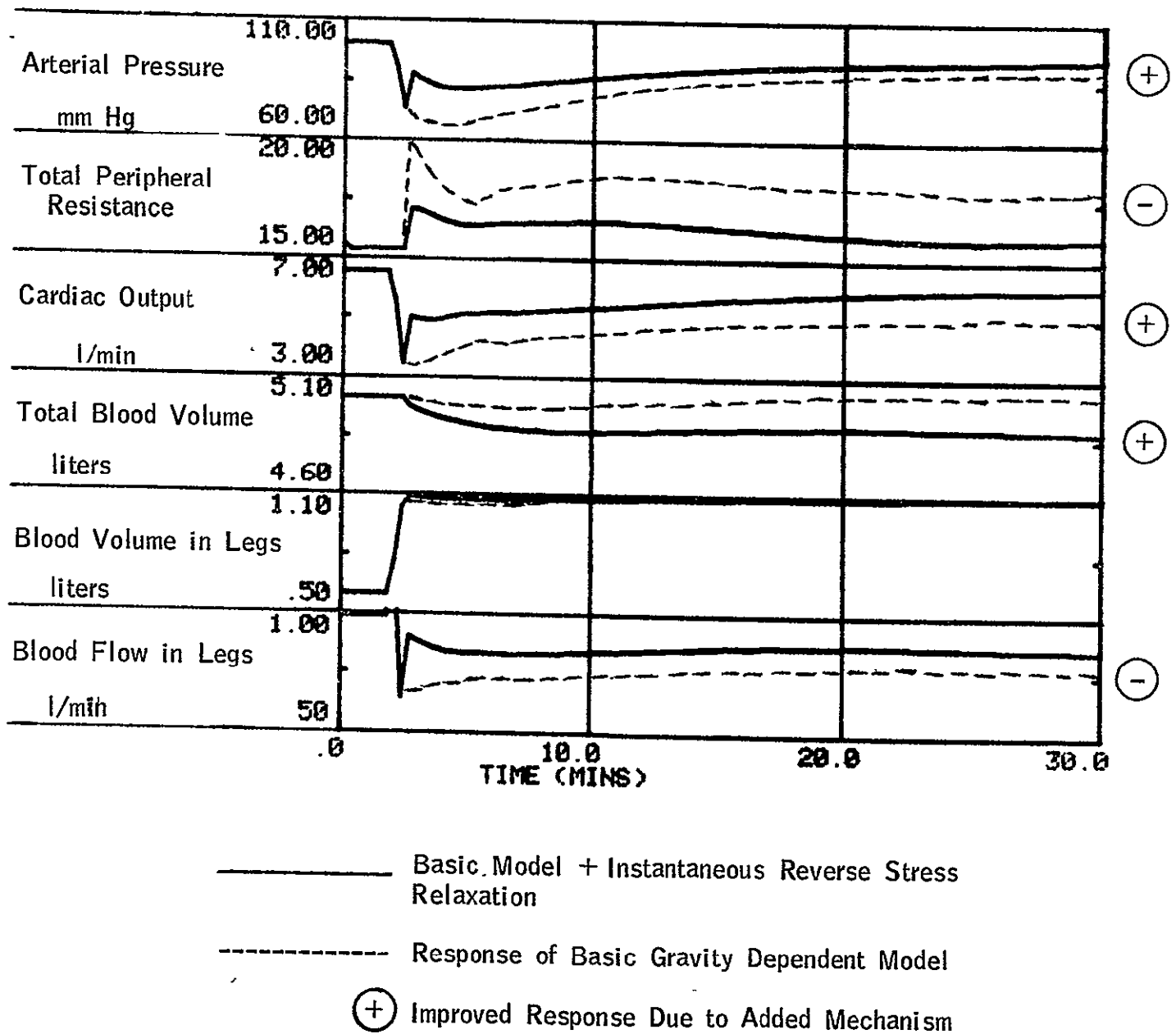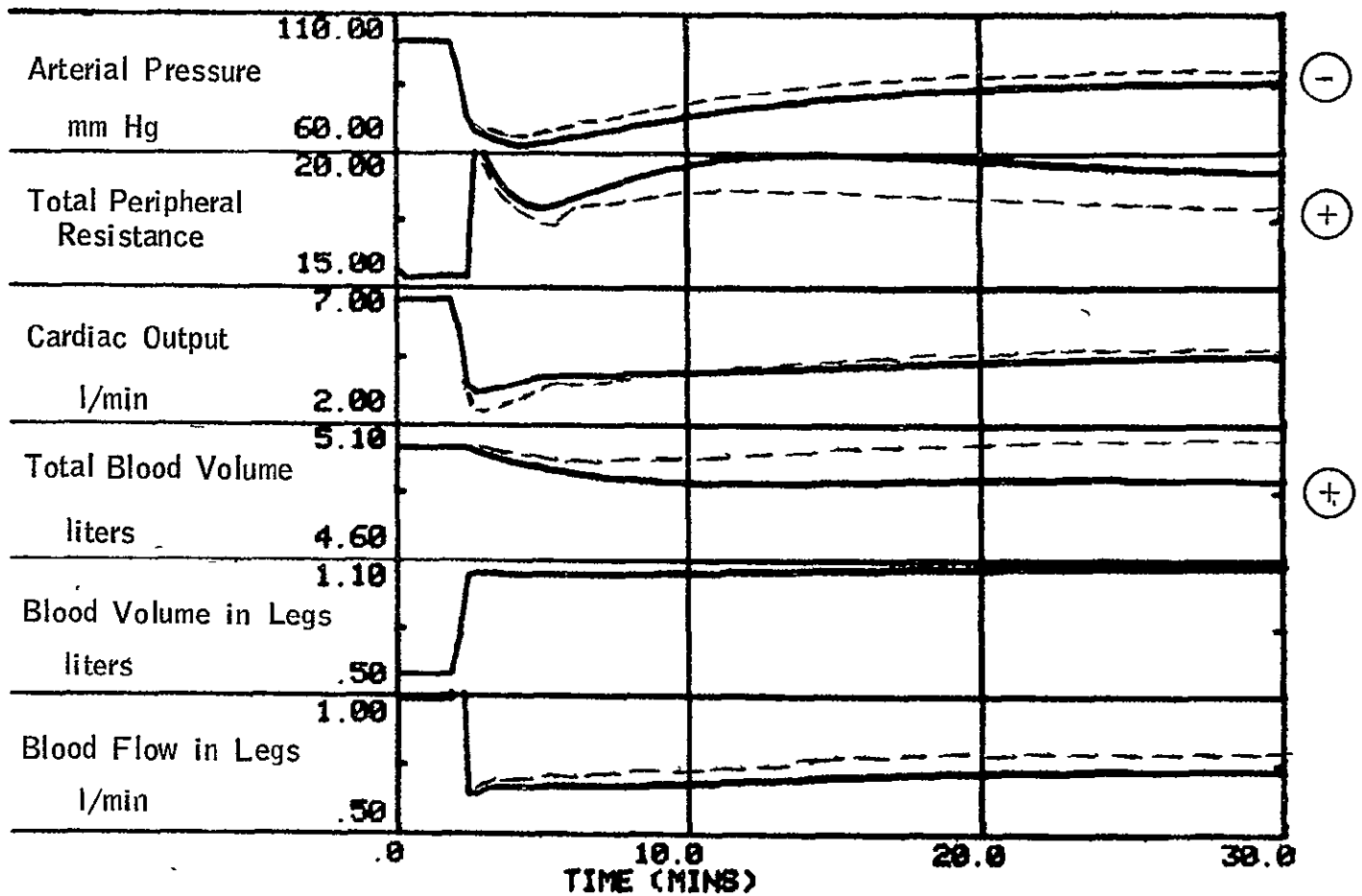REVERSE STRESS RELAXATION

FIGURE 2.4A

SIMULATED 90° TILT RESPONSE: EFFECT OF ENHANCED SPLANCHNIC
VENOCONSTRICTION

FIGURE 2.4B

Basic Model + Enhanced Venoconstriction

Response of Basic Model

⊕ Improved Response Due to Added Mechanism
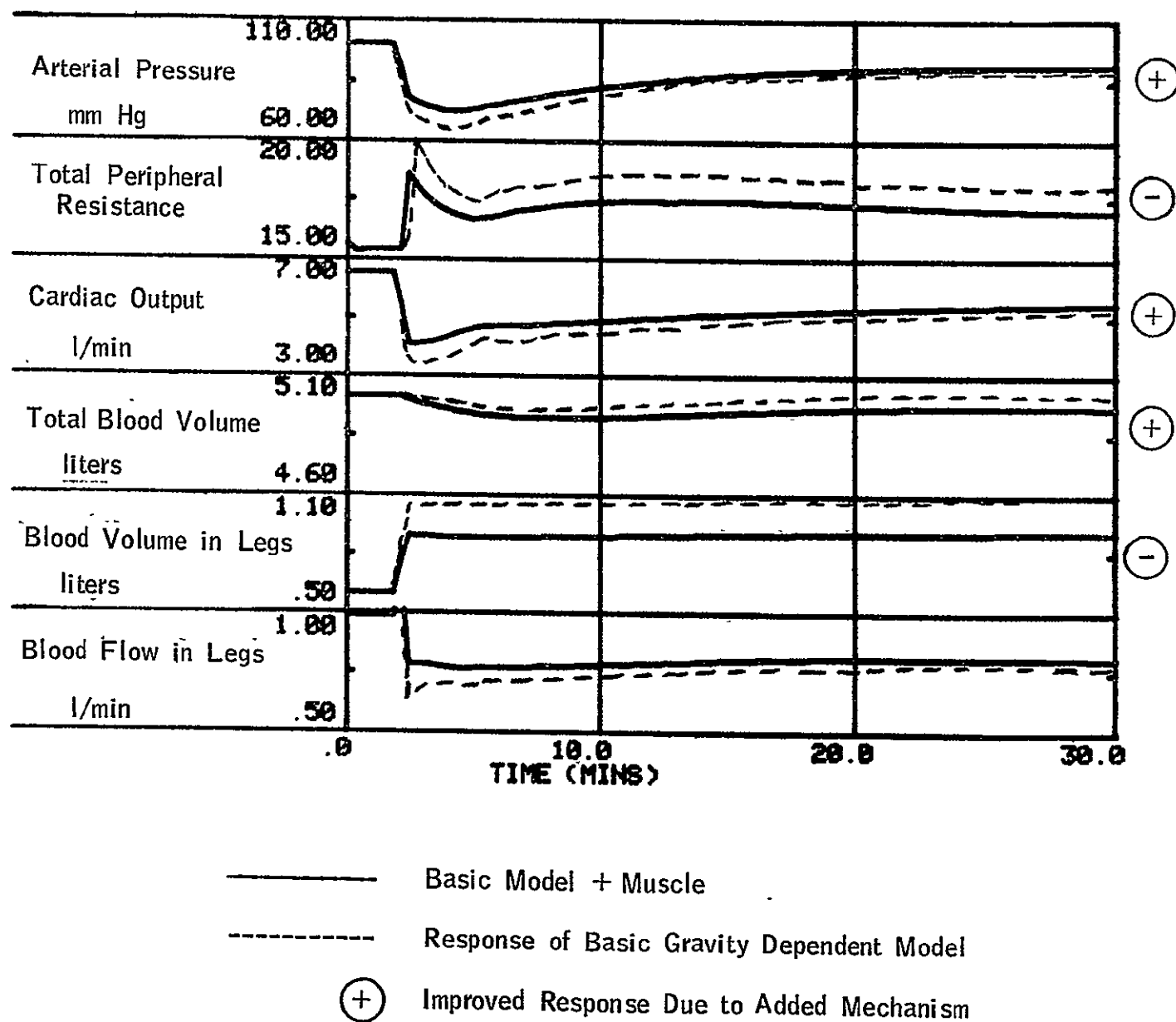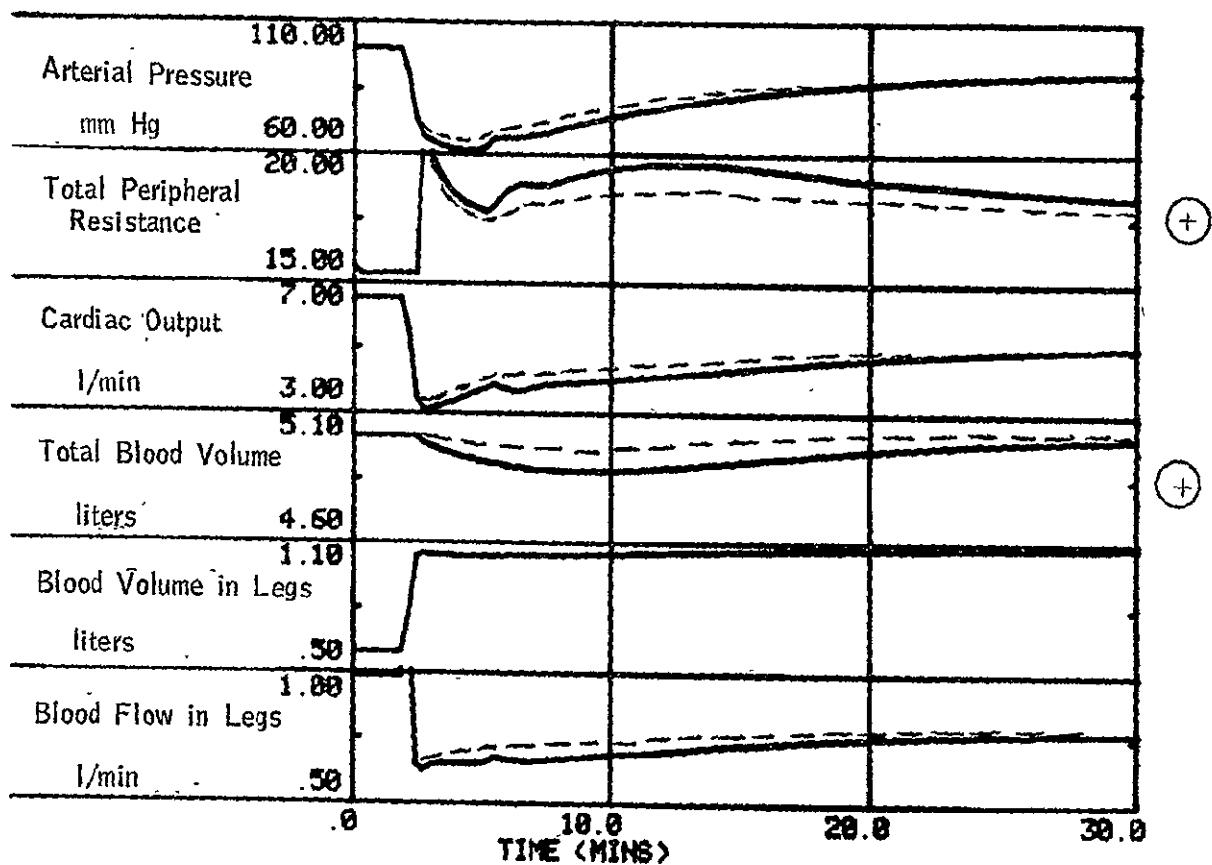
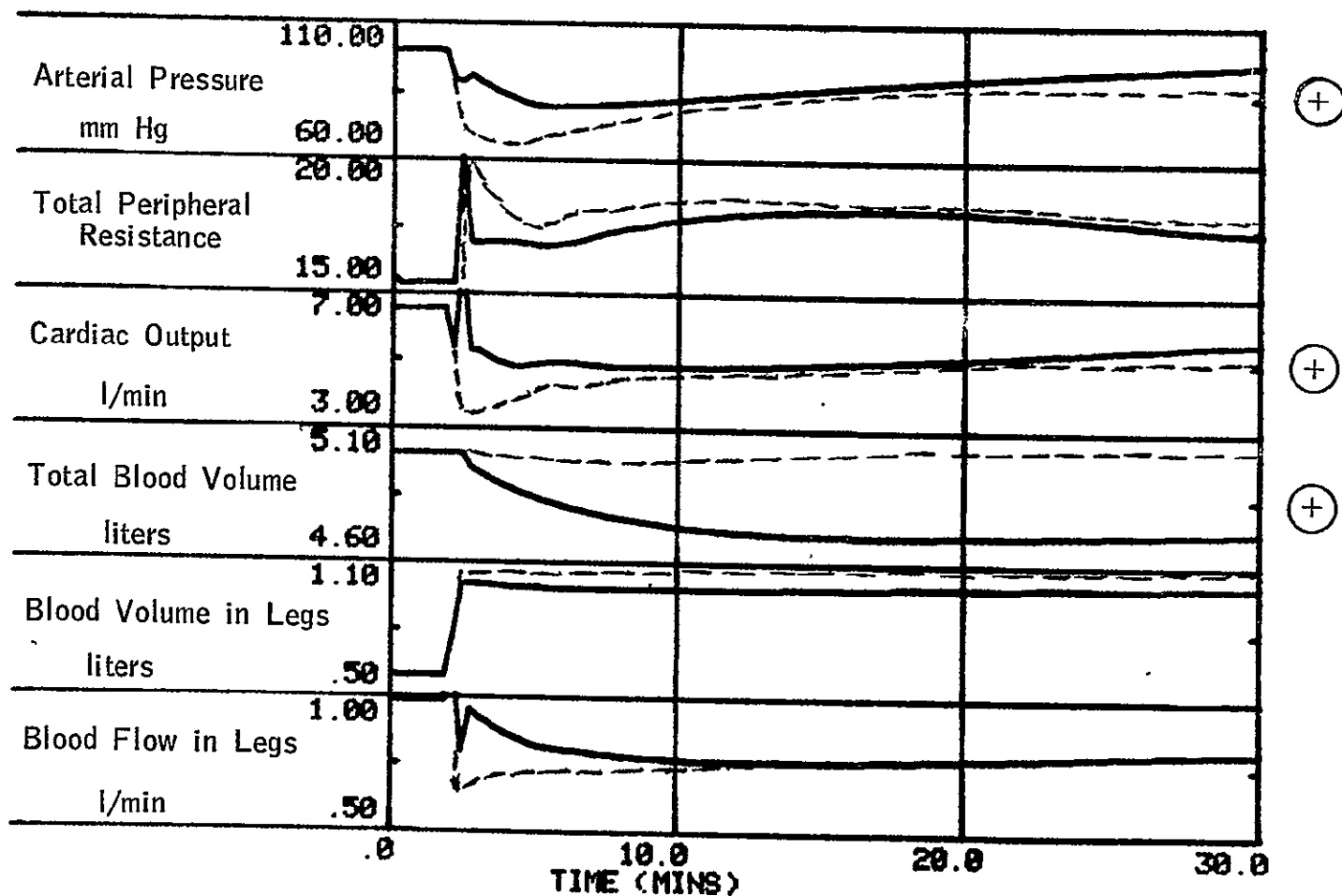# SIMULATED 90° TILT RESPONSE: EFFECT OF MUSCLE PUMP

FIGURE 2.4C

SIMULATED 90° TILT RESPONSE: EFFECT OF REDUCED CAPILLARY FILTRATION COEFFICIENT

——————— Basic Model + Reduced Filtration Coefficient

--------------- Response of Basic Gravity Dependent Model

(+) Improved Response Due to Added Mechanism

FIGURE 2.4D

SIMULATED 90° TILT RESPONSE: EFFECT OF COMBINATION OF FOUR
ORTHOSTATIC MECHANISMS
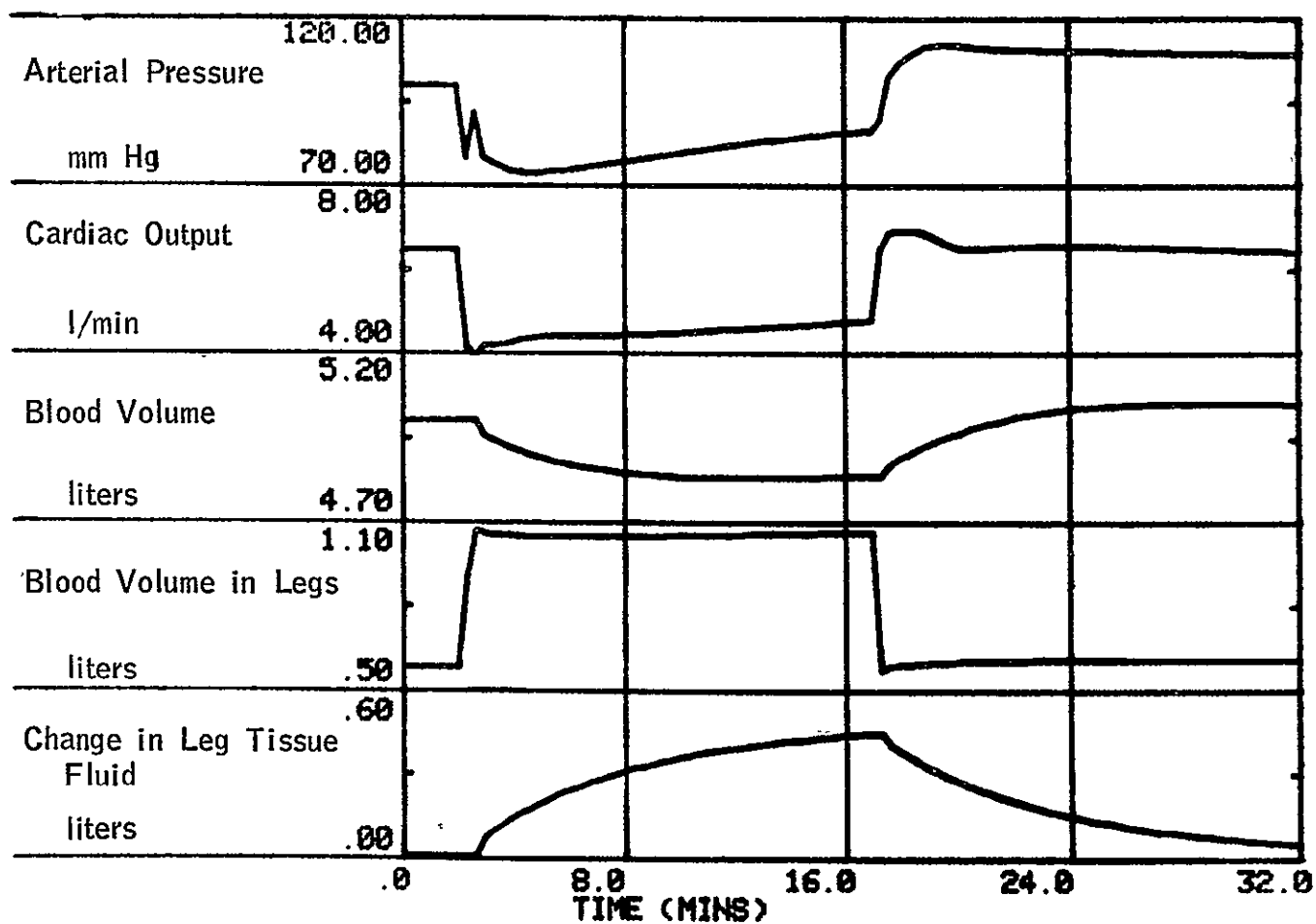

Mechanisms Added:
- Reverse Stress Relaxation
- Splanchnic Venoconstriction
- Reduced Filtration Coefficient
- Muscle Contraction Effect

---------- Response of Basic Gravity Dependent Model

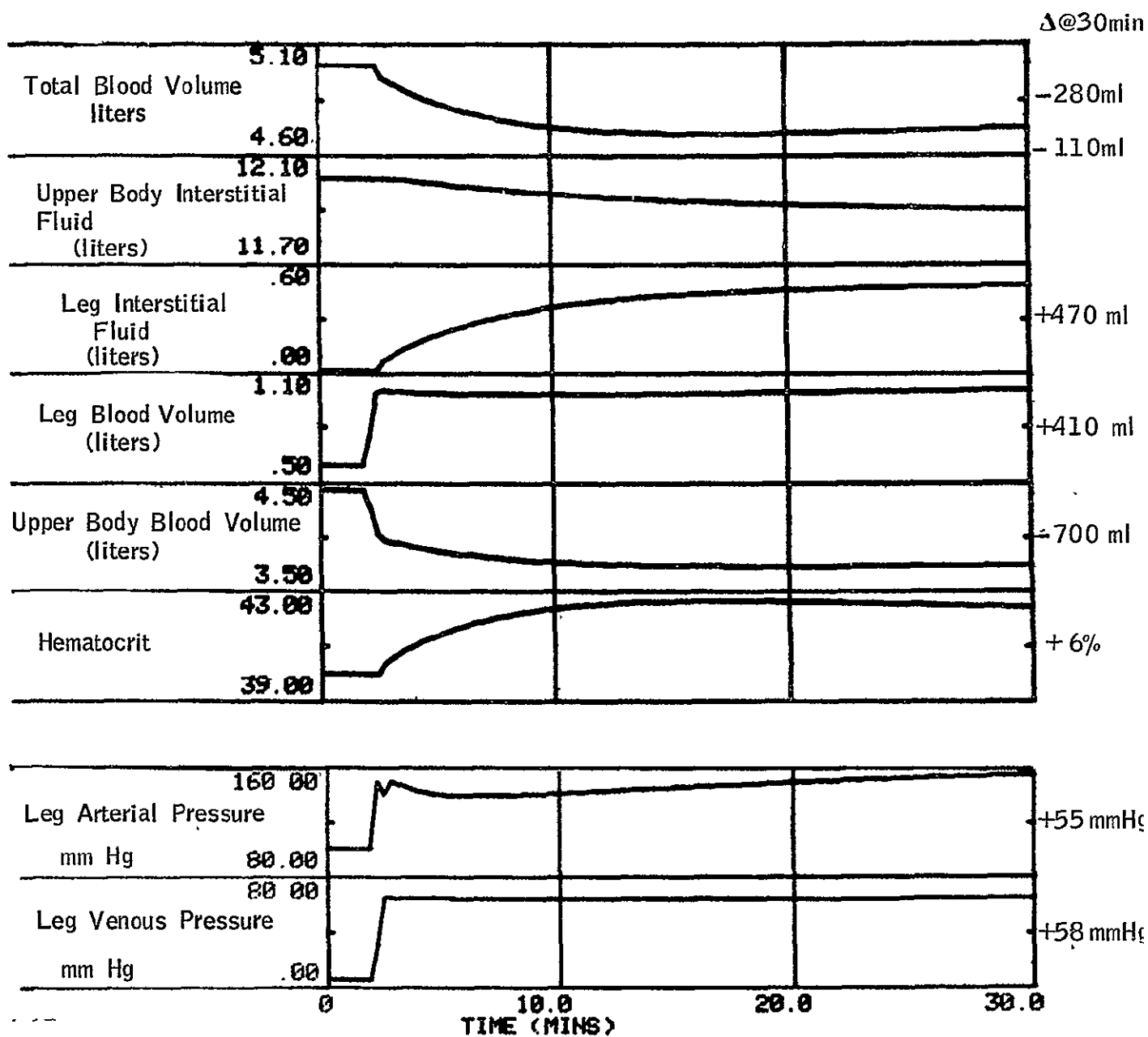(+) Improved Response Due to Added Mechanism

FIGURE 2.4E

SIMULATED 90° TILT RESPONSE AND RECOVERY
WITH ENHANCED REVERSE STRESS
RELAXATION AND VENOCONSTRICTION

FIGURE 2.5

These changes have resulted in an overall improvement of the tilt response which is reflected not only in the few circulatory variables shown in these figures, but in most all variables which were monitored during these series of simulations. Figures 2.6A to 2.6D illustrate the response of a wider range of model variables that were obtained during a run incorporating the four additional orthostatic mechanisms. The general agreement with experimental observation of these many physiological parameters in response to a qualitatively new type of short term stress for this ("long term") model attests to the basic soundness of the original Guyton formulation and the new modifications. While other computer models have been able to simulate a tilt response with greater fidelity with regard to circulatory flows and pressure (especially during the first 10 minutes following tilt), they did not include the wider range of physiological subsystems of the Guyton model (Croston & Fitzjerrell, 1974; Boyers, et al, 1972; Snyder & Rideout, 1969). Thus, the responses shown here are representative of the circulatory, fluid, renal, autonomic, and endocrine responses to tilting that have been described by many investigators each observing only a portion of these physiological reactions. The following section is a more detailed discussion of these responses shown in Figures 2.6A – 2.6D and includes literature citations that support each observation.
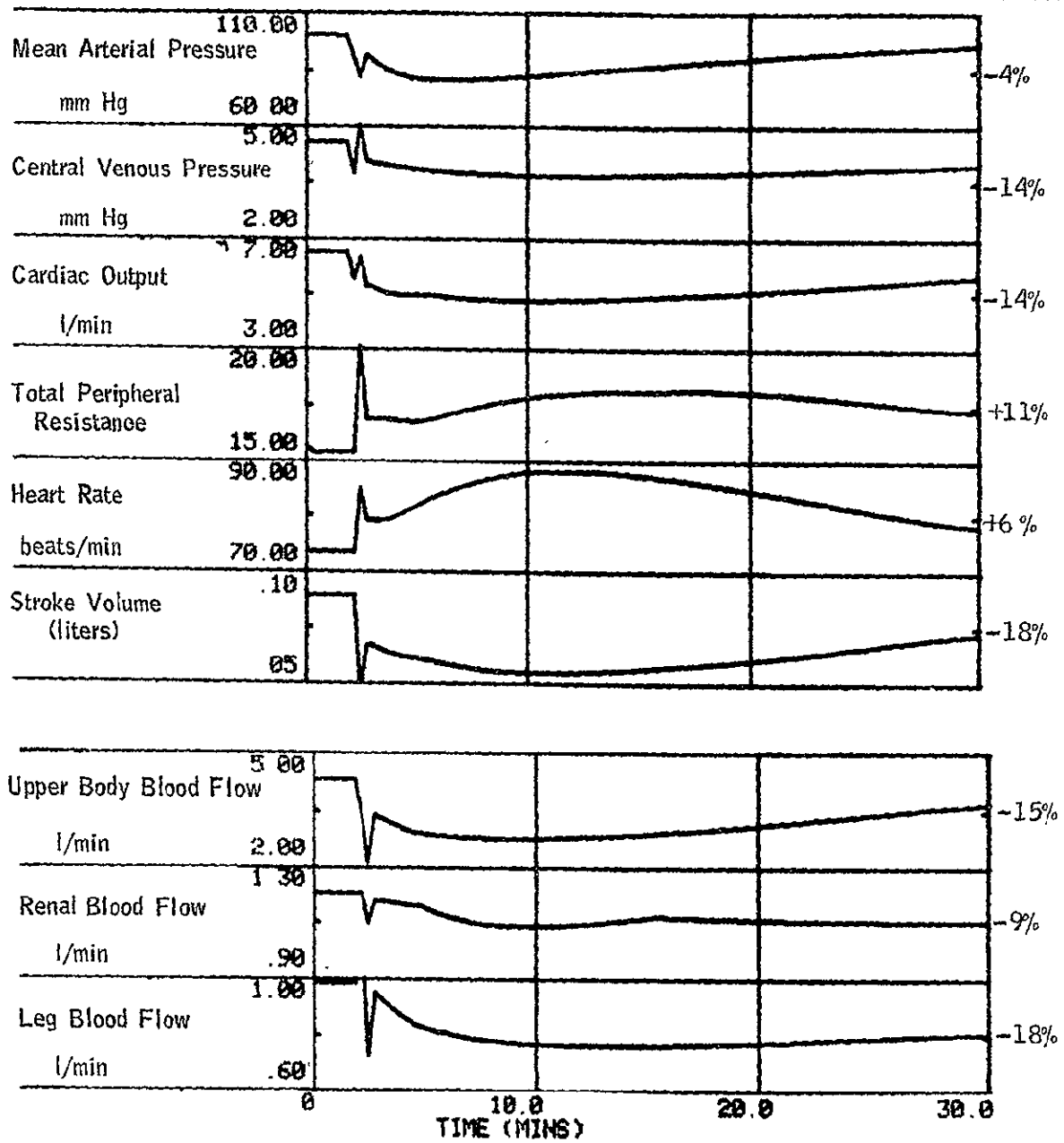
Fluid Volume Shifts   (Figure 2.6A)

The vertical orientation greatly increases the pressures in the legs due to the long hydrostatic column of blood. Inasmuch as both arterial and venous pressures are increased to the same extent there is no change in the driving force to flow. However, these high pressures do cause distention and about 400 to 600 ml of blood rapidly pools in the leg vessels, primarily in the veins (Rushmer, 1970; Sjostrand, 1953). (A slight muscle contraction effect has reduced the leg circulatory pressures and pooled fluid by about 15%). (Guyton, et al, 1973)).

SIMULATED 90° TILT RESPONSE WITH ADDED ORTHOSTATIC MECHANISMS:
FLUID SHIFTS AND LEG BLOOD PRESSURES

FIGURE 2.6A
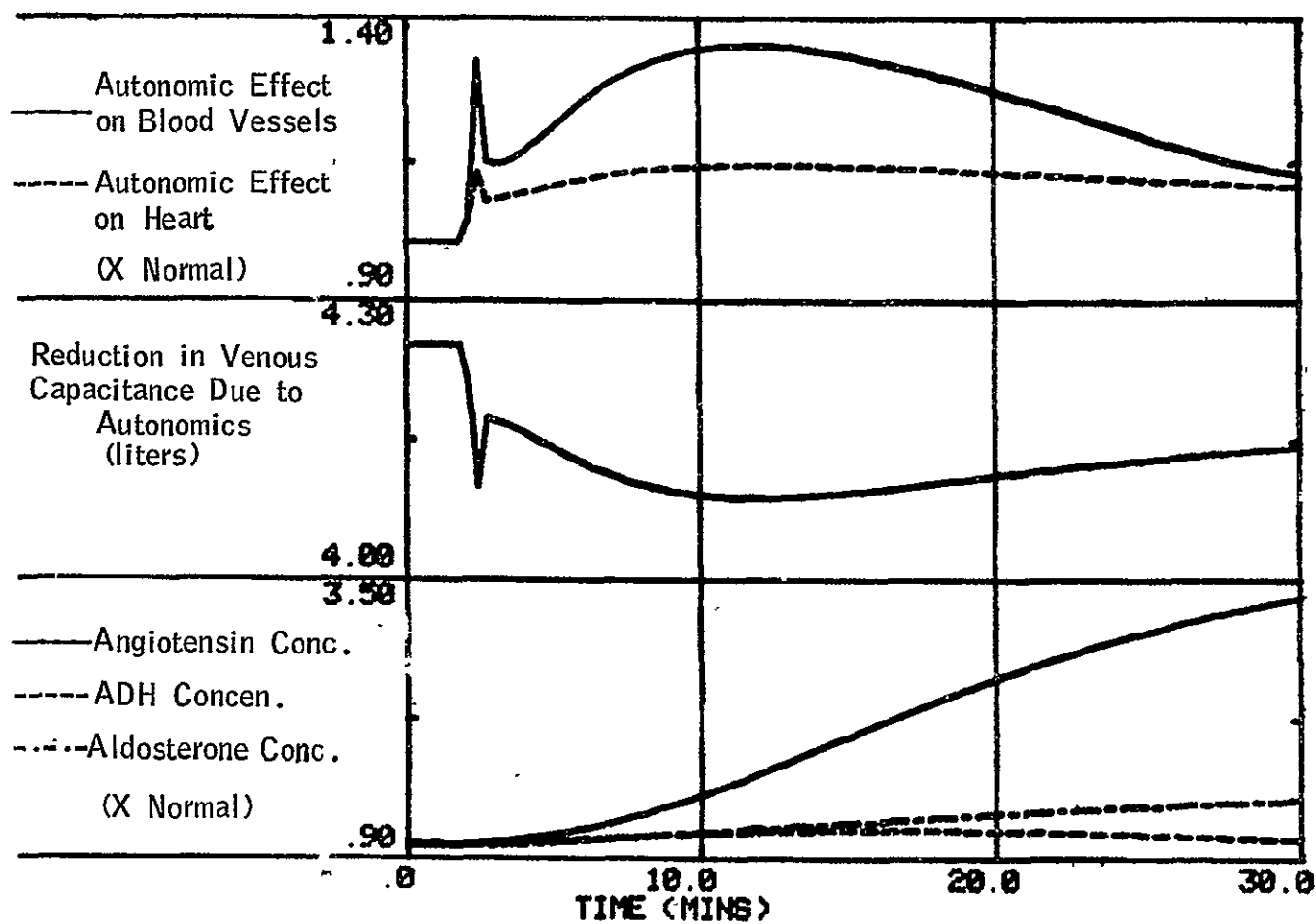
SIMULATED 90⁰ TILT RESPONSE WITH ADDED ORTHOSTATIC MECHANISMS:
MAJOR CIRCULATORY PARAMETERS

FIGURE 2.6B

SIMULATED 90° TILT RESPONSE WITH ADDED ORTHOSTATIC MECHANISMS:
UPPER BODY CAPILLARY FILTRATION PARAMETERS

FIGURE 2.6C

SIMULATED 90° TILT RESPONSE WITH ADDED ORTHOSTATIC MECHANISMS:
AUTONOMIC AND HORMONAL RESPONSES

FIGURE 2.6D

The accompanying increase in leg capillary pressures creates a driving force for filtration. At the end of 30 minutes, approximately 500 ml plasma has left the circulation and entered the leg interstitial compartment (Henry, 1955), while about 200 ml has entered the circulation through absorption from the upper body capillaries. This results in a net reduction in total blood volume of approximately 300 ml (Fawcett & Wynn, 1960; Hellenbraut & Franseen, 1943). Since this represents plasma changes only, the hematocrit increases accordingly (Tan, et al, 1973). The net deficit of fluid in the upper body (effective central blood volume) is approximately 700 ml: 400 ml of this due to limb pooling and 300 ml plasma loss due to net extravascular filtration . (Henry, 1975; Wood & Eckstein, 1957).

Major Circulatory and Cardiac Changes - Figure 2. 6B

At the end of the 30 minutes of simulated tilting the arterial pressures have returned to near normal while venous pressure is relatively depressed. The magnitude of these changes including the initial reduction in pressure are appropriate, but are known to occur more rapidly. Cardiac output is decreased by 15% due primarily to a reduction in stroke volume and in spite of an increase in heart rate (Rushmer, 1970; Weissler, et al, 1957; Tuckman and Shillingford, 1966).

The reduction in stroke volume is a result of a decreased venous return because of the large reduction in central blood volume while the heart rate changes reflect increased autonomic stimulation. Total peripheral resistance increases sharply at first (Tarazi, et al, 1970) as a result of intense autonomic-baroreceptor activity (Brigden, et al, 1950) which is later augmented by angiotensin release and attenuated by auto-regulatory effects. Blood flows to the three major tissue segments represented in the model (renal flow, leg muscle flow and non-muscle, non-renal flow) all decrease due to the general decrease in cardiac output as well as vasoconstriction (Rushmer, 1970; Culbertson, et al, 1951; King, et al,

1954).   The renal and leg flows appear to be more stable at their lower level than the splanchnic flow which tends to return toward normal.

Capillary Filtration - Figure 2. 6C

The filtration of nearly 500 ml plasma into the leg interstitium is basically completed within 20-30 minutes. (Tarazi, et al, 1970). The driving force for this event is an increase in leg capillary pressure of nearly 60 mm Hg - equivalent to the hydrostatic column from the heart to the midpoint of the legs.   This is opposed by the leg tissue pressure which increases gradually as fluid enters the interstitial spaces (Mellander, 1971).

While leg filtration is occurring the capillaries in the upper body are undergoing a more complex process.   At the beginning of the tilt response the fall in capillary pressure and the rise in colloidal oncotic pressure favors the absorption of fluid from the extravascular space into the bloodstream.   While colloidal pressures continue to rise the pre/post capillary resistance ratio decreases (due to a rise in venule resistance which gradually develops maximum intensity after a rapid arteriolar constriction) (Wood, et al, 1957). which causes capillary pressure to rise until it becomes greater than the oncotic pressure.   At this point (about 15 minutes following tilt) absorption of fluid stops and plasma filtration into the interstitium begins.   It has previously been demonstrated that adjustments in the pre/post capillary resistance following moderate hemorrhage lead to essentially the same dynamic behavior in capillary filtration as shown here (Mellander, 1971).   Opposite changes have been suggested during infusions (Leonard & Abbrecht, 1974).   However, no documentation exists to confirm whether this occurs during tilt.   Thus, the fall in blood volume due to extravasation of fluid from the legs is partially compensated by intravasation of fluid from the tissues of the upper body similar to the effect suggested during LBNP studies (Foux, et al, 1976).

Neural and Humoral Orthostatic Protective Mechanisms – Figure 2.6D

Several previously discussed mechanisms were added to the model during these simulations. However, these basically represented improvements to the orthostatic effects which were already present in the model. Several of the major neural and humoral reflex pathways which are activated during the tilt response are shown in Figure 2.6D. The autonomic influences include these that produce: a) vasoconstriction, b) cardio-acceleration and contractility, and c) reduction in venous capacitance (Guyton, et al, 1973). The humoral mechanisms are seen to be slower acting and include: a) angiotensin release which produces vasoconstriction (Oparil, et al, 1970), b) aldosterone release which inhibits sodium and water excretion (Gowenlock, et al, 1970), and c) ADH release which decreases urinary output and preserves body fluid volumes (Goetz, et al, 1975). All of these mechanisms are mediated in the model by reflex pathways originating at pressoreceptors in cardiopulmonary, arterial or renal areas. The realistic dynamic behavior of these reflexes should be noted; autonomic reflexes are fully operative within a few minutes while hormonal responses are slower acting.

3. 0   OTHER MODIFICATIONS AND IMPROVEMENTS

The primary emphasis in this report is upon the modifications to the
model to provide separate leg compartments, to add gravity dependency,
and to simulate bed rest.   However, other modifications and improve-
ments were included concurrently with this work, although not directly
related to it, because a major activity such as this provided an opportunity
to document updated areas of the model associated with other tasks.
Updated user's guides for the stand-alone model and Whole-Body Algorithm
will be provided which will include all these changes.   These modifications
required renaming many of the parameters and variables in the original
model and several cosmetic changes were included for ease of program
understanding.   These changes will also be reflected in the updated
user's guides.   Figure 3.1 shows the major blocks in the model which
were modified during this study.

Modified Red Blood Cell Production Algorithm

A new algorithm for red cell regulation has been implemented in the
recompartmentalized Guyton model.   This new block was based on the
erythropoiesis regulatory simulation model previously developed by GE
(TIR 782-MED-4012 & 6004).   This model was shown to be superior representa-
tion of the physiological system than the blood cell subroutine in the original
Guyton model, especially with respect to its ability to simulate hemopoietic
responses to hypoxia, red cell infusion and bed rest.   A detailed description
of this algorithm, as it appears in the modified Guyton model, is presented
in the Appendix.

The new red blood cell algorithm is based on a kidney sensor of
oxygen partial pressure located in tissue of constant metabolic rate and
perfused with venous capillary blood, flowing at a constant rate.   These
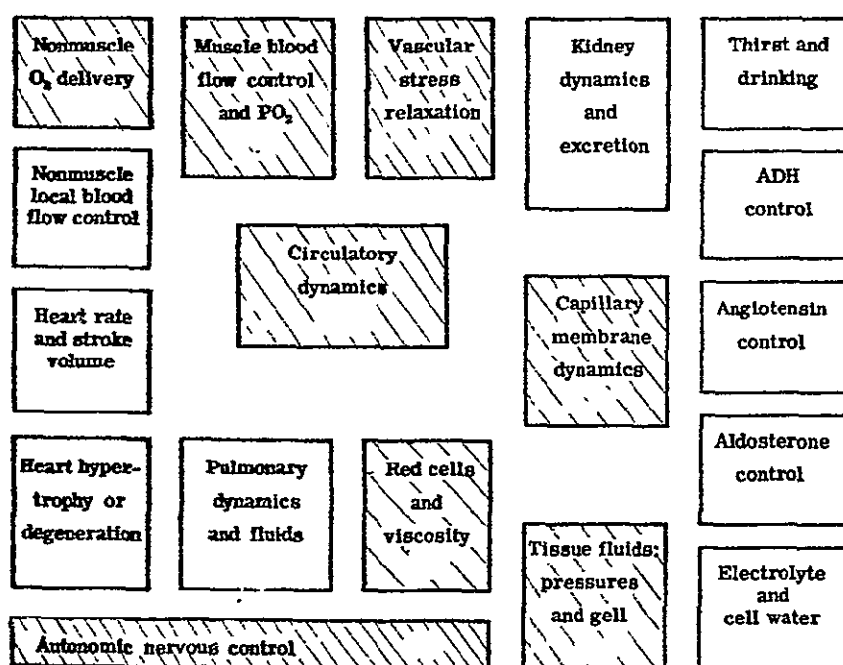restrictions permit erythropoiesis to be responsive primarily to changes

FIGURE 3.1

GUYTON MODEL SHOWING SUBSYSTEMS MODIFIED
(SHADED) IN THIS STUDY

in hematocrit, arterial oxygen partial pressure, shifts of oxy-hemo-globin dissociation and disturbances in oxygen carrying capacity of hemo-globin. It is not sensitive to changes in blood flow nor changes in total body metabolic rate.

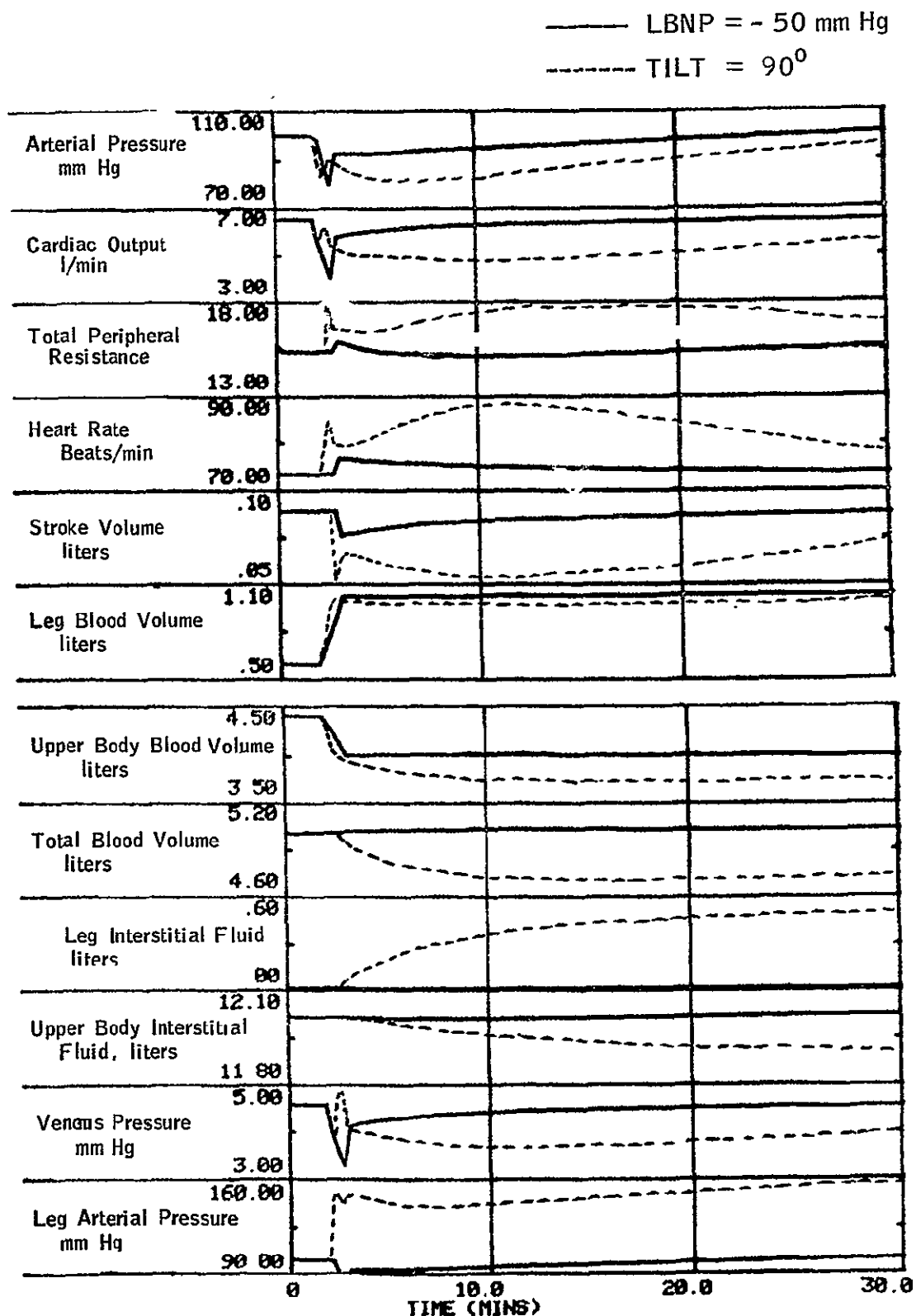## Simulation of Lower Body Negative Pressure (LBNP)

During LBNP in the supine human, the negative pressure surround-ing the legs creates a driving force for blood to be virtually sucked into the legs (primarily into veins) from the upper body. The degree of blood displacement can be up to a liter depending on the suction applied (Wolthuis, et al, 1974). Simulation of LBNP with another circulatory model has been previously accomplished by applying a negative pressure external to the leg vessels thereby increasing transmural pressure by the applied amount (Croston & Fitzjerrell, 1974). The model used was a closed circulatory system with constant blood volume. The present form of the Guyton model will permit fluid transfer by capillary filtration into and out of the leg and upper body tissue fluid compartments. More importantly, it is now possible to impose LBNP not only across the leg vessels, but also across the "walls" of the interstitial compartment of the legs thereby inducing plasma filling of that space. A slow component of the rise in leg volume during LBNP (following an initial rapid increase) has been frequently taken to represent fluid diffusion into the tissues (Foux, et al, 1976). It is also possible that part of this gradual swelling can be attributed to increased congestion in the blood vessels. To our knowledge, quantitative data are not available regarding the dynamic distribution of fluid pooling between leg vasculature and tissue space, or concerning net changes in blood volume which arise from net filtration from the legs and a possible intravasation of fluid from the capillaries in the upper body.

Accordingly, LBNP simulation was performed by two methods:
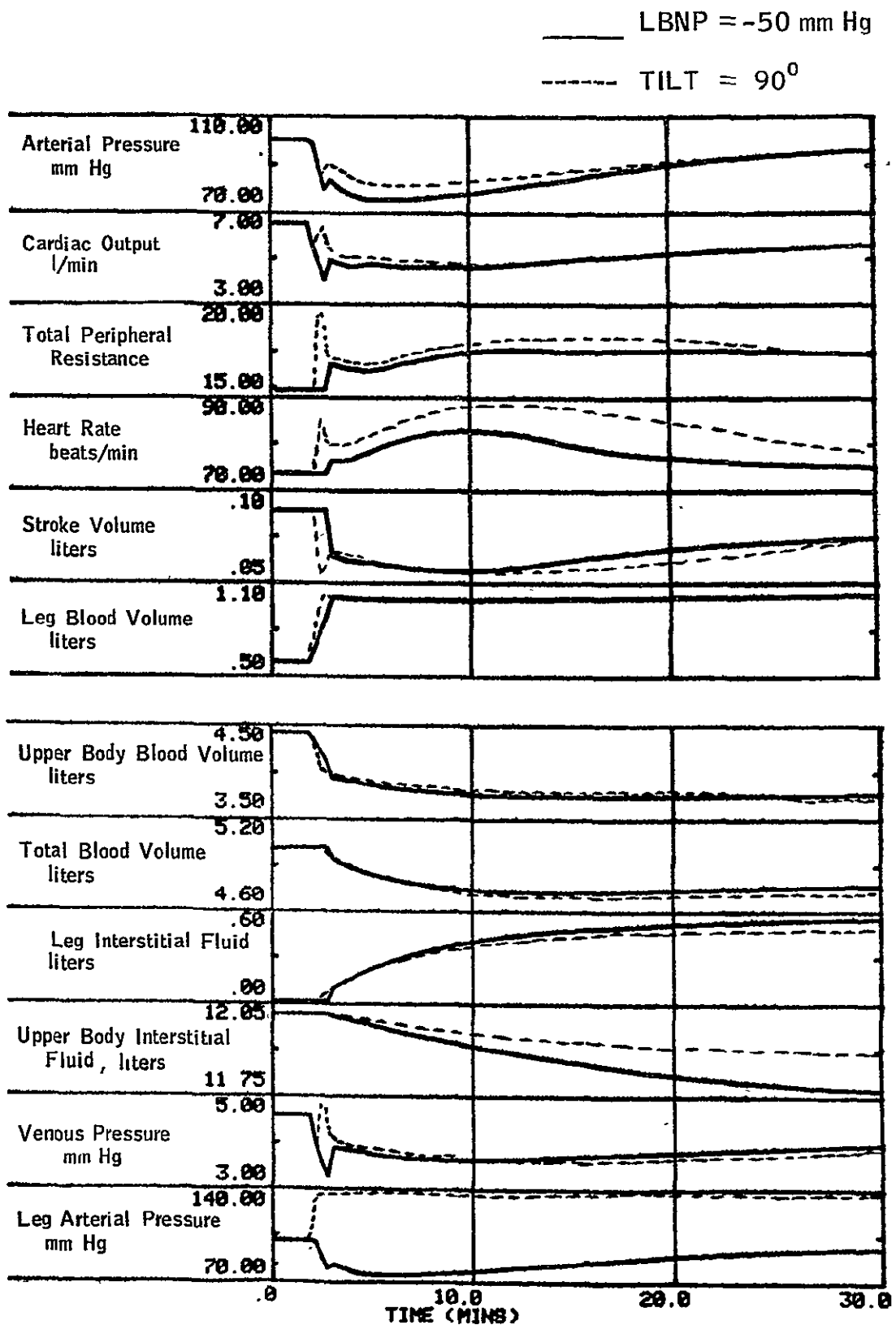a) application of LBNP to the leg vessels only, and b) application of

LBNP to the leg vessels and leg interstitial fluid compartment. In the second of these the same degree of LBNP was used for both external pressures although it can be argued that the effective pressures may be transmitted differently through the tissues and the vasculature. The results of these two types of LBNP simulation are shown in Figures 3.2 and 3.3. In each case they are compared to the 90° tilt simulation that is described earlier in this report. For simplicity, the same orthostatic mechanisms that were used for the tilt study were introduced during LBNP.

The fundamental difference between the two methods is the amount of fluid accumulated in the legs. LBNP applied to vessels and tissues accumulates nearly twice as much fluid in the legs as when applied only to the vessels. This larger accumulation of fluid in the legs creates a larger depletion of upper body blood volume (because tissue fluid came from plasma filtrate) and a net decrease in total blood volume. With LBNP applied to only the leg vessels the total blood volume actually rises slightly. In both cases there is inward filtration occurring from the upper body capillaries. The difference in the degree of blood reduction in the upper body between the two methods is solely responsible for the differences in response of other circulatory indices (i.e., pressures, flows, resistance, heart rate, and stroke volume). Thus, with the larger volume shift, blood pressures, cardiac output, and stroke volume are reduced further and increases in heart rate and peripheral resistance are enhanced. Although the dynamic behavior of the simulation suffers from the same inadequacies as was noted in the tilt response, the values of these indices at 30 minutes all agree in direction with those noted by observers of LBNP in man (Wolthuis, et al, 1974). In general, some combination of the two sets of responses would also result in appropriate magnitudes of change. As can be noted, the tilt response is closer in agreement with the LBNP simulation involving the larger fluid changes.

SIMULATION OF LOWER BODY NEGATIVE PRESSURE

WITH PRESSURE EFFECT ON LEG VESSELS ONLY

FIGURE 3.2

SIMULATION OF LOWER BODY NEGATIVE-PRESSURE

WITH PRESSURE EFFECT ON LEG VESSELS AND LEG INTERSTITIAL COMPARTMENT

FIGURE 3.3

The differences between LBNP and tilt simulations, in Figure 3.2 where total blood volume is essentially constant, previously reported by this laboratory using the closed circulatory system model (Croston and Fitzjerrell, 1974). There was no attempt during the present study to optimize the LBNP response. So, as a preliminary study, it can be concluded that the revised model performed rather well.

4. 0   COMPARISONS OF MODEL BEFORE AND AFTER MODIFICATION

Part of the process of validating a model after major modification is to compare the values of major parameters (such as volumes, pressures, flows, etc.) before and after modification to determine the impact of these changes on the overall physiological representation. These values are shown in Table 4.1. Another important part of this process is to examine not only the model output for simulations to which the modifications were addressed, but also for any other simulations that the model is capable of performing which may have been altered by the changes. Figures 4.1 and 4.2 show comparisons of important model outputs before and after modification for simulations which were altered by the modification. As can be seen from the figures, the modifications did not cause serious alterations in these simulations and the output of the modified model was at least as good, if not better, than prior to modification.

TABLE 4.1

STEADY-STATE VALUES OF MAJOR PHYSIOLOGICAL PARAMETERS IN GUYTON MODEL

COMPARISON OF PARAMETERS BEFORE AND AFTER MODIFICATION

	Blood Volumes (liters)	
	Before Modification	Modified Guyton
Rt. Heart	0.102	0.109
Pulmonary	0.395	0.413
Lft. Heart	0.409	0.431
Total Cardio-pulmonary	0.906	0.953
Upper Artery	N/A	0.714
Leg Artery	N/A	0.146
Total Artery	.853	.870
Upper Veins	N/A	2.750
Leg Veins	N/A	.440
Total Veins	3.304	3.190
Total Stressed Volume	0.821	0.877
Total Unstressed Volume	4.241	4.126
Total Upper Body Volume	N/A	4.417
Total Leg Volume	N/A	.586
Total Blood Volume	5.062	5.003
	Pressures (mm Hg)	
Upper Arterial	101.3	100.1
Leg Arterial	N/A	99.3
Upper Venous	4.39	4.55
Leg Venous	N/A	4.89
Rt. Heart	0.43	0 63
Pulmonary	18.54	18.87
Lft. Heart	0.86	0.970

Compliances

	Before Modification	Modified Guyton	
Upper Arteries	N/A	.00265	
Leg Arteries	N/A	.00112	
Total Arteries	.00355	.00377	
Upper Veins	N/A	.07905	
Leg Veins	N/A	.00772	
Total Veins	.0825	.08677	

Blood Flows (liters/min)

Cardiac Output	6.35	6.47	
Renal	1.19	1.20	
Leg (Muscle)	2.18	0.98	*
Non-Renal, Non-Muscle	2.99	4.30	*

Flow Resistances

Total Peripheral	15.87	15.60	
Renal	85.23	83.39	
Leg (Muscle)	44.49	96.31	*
Non-Renal, Non-Muscle	32.43	22.20	*
Large Veins	0.62	0.60	
Leg Arteries (fixed)	N/A	0.95	
Leg Veins (fixed)	N/A	0.35	
Pulmonary	2.78	2.76	

Body Fluid Volumes (liters)

Blood	5.062	5.003
Plasma	3.017	3.007
Red Cell	2.046	1.999
Interstitial, Total	12.156	12.013
– Free fluid	0.568	0.545
– Gel	11.589	11.467
Extracellular	15.187	15.042
Intracellular	24.995	24.996
Total Body Water	40.180	40.033

Miscellaneous

	Before Modification	Modified Guyton
Metabolic Rates, Total	314	310
– Non-muscle, non-renal	180	252
– Leg (muscle)	134	58
Plasma Sodium Concentration	142.0	142.0
Plasma Potassium Conc.	5.00	5.00
Plasma Protein Conc.	70.1	70.1
Hematocrit	40.42	39.95
Normalized Hormones Conc.		
– Angiotensin	1.022	1.004
– ADH	1.001	1.001
– Aldosterone	1.000	1.000
Autoregulatory Effect		
– Muscle	0.454	.979
– Non-muscle, non-renal	0.886	1.032
Stroke Volume	0.087	.088
Heart Rate	72.9	73.3

Previous Model Version Without Leg Compartments   New Model Version With Leg Compartments
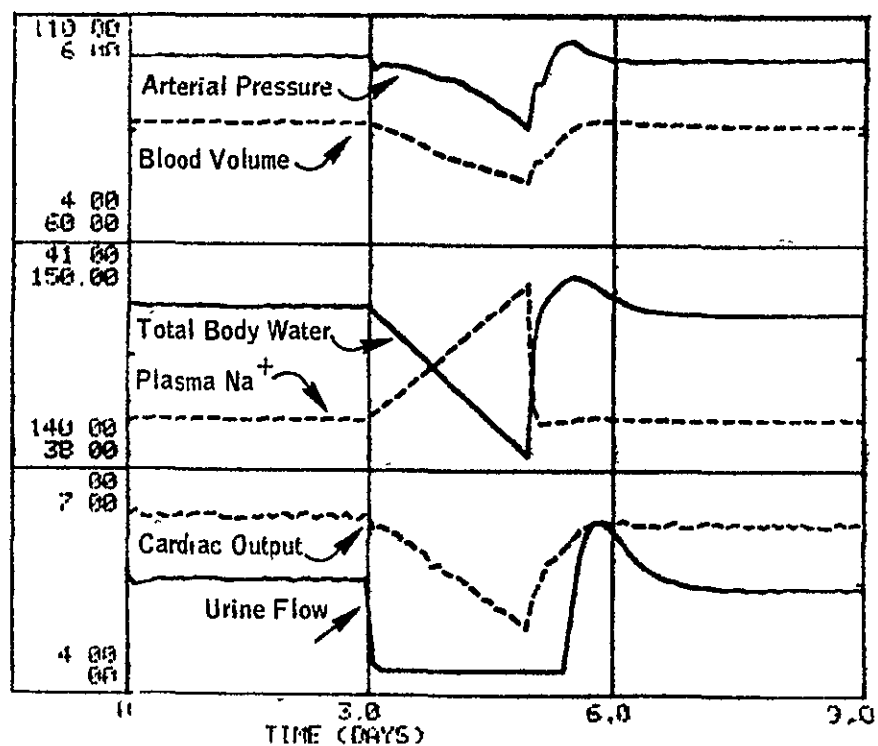

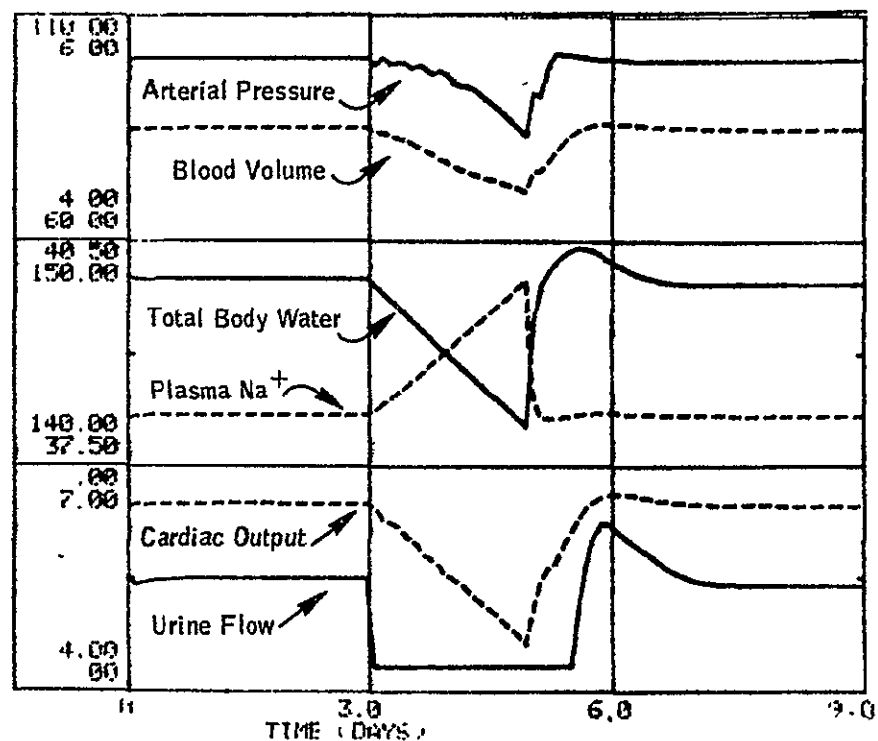Stress: @Day 2 Apply Goldblatt Clamp on Renal Artery

GOLDBLATT HYPERTENSION SIMULATION:

COMPARISON BETWEEN PREVIOUS AND CURRENT VERSIONS OF GUYTON MODEL

FIGURE 4.1

Previous Model Version Without Leg Compartments

New Model Version With Leg Compartments

Arterial Pressure

Blood Volume

Total Body Water

Plasma Na+

Cardiac Output

Urine Flow

TIME (DAYS)

Stress: @ Day 0 Begin evaporative water loss = 720 ml/day
@ Day 3 Cut off water and salt intake
@ Day 5 Allow ad libum intake

DEHYDRATION AND RECOVERY SIMULATION:

COMPARISON BETWEEN PREVIOUS AND CURRENT VERSIONS OF GUYTON MODEL

FIGURE 4.2

5. 0   MODIFICATIONS FOR BED REST SIMULATION

One objective of this study report is to set forth and test the hypo-
theses which have been suggested to explain the long term changes which
occur in the cardiovascular and fluid compartments during prolonged bed
rest.   The modified model described above was used to implement and
test the hypotheses separately and in combination as required. Although
this method cannot be expected to provide a precise, unique and irrefutable
description of the physiological processes at work during the bed rest
stress; it does allow the systematic study of the magnitudes and directions
of changes for each hypothesis separately and in combination.   These
studies may then be used to assess the "reasonableness" of the various
hypotheses and give some insight into the types of measurements which
must be made to ultimately verify them by experimentation.

An additional, if not equally important benefit of this study, is to
provide a model which can be used effectively to compare bed rest quan-
titatively with zero-g to assess its suitability as an analogous stress.

5. 1   PHYSIOLOGICAL ASPECTS OF BED REST

In bed rest, as in zero-g, there are many adaptive processes within
the human physiological system which occur simultaneously following the
initial stimulus of adapting the passive supine posture.   One of the major
functional systems affected by bed rest or zero-g is the cardiovascular
system.   Since standing involves the addition of hydrostatic forces along
the long axis of the body, these pressures affect the distribution of body
fluids.   The internal hydrostatic pressures are a function of the angle that
the body's long axis makes with the horizontal and the distance from a
pivotol or reference point.   This hydrostatic indifference point has been
measured to be slightly below the diaphragm in erect human beings
(Gauer and Thron, 1965).   These hydrostatic pressures which may reach

90 mm Hg in the foot (Guyton, 1973),will cause pooling of blood in the capacitance vessels of the lower body and when summed with the hydro-dynamic pressures of the circulatory system can give rise to capillary pressures as high as 160 mm Hg and if unrelieved could cause extra-vasation of fluid from plasma volume into the interstitium. This redis-tribution of body fluids affects the cerebral blood pressure, circulation, and perfusion which operate at low pressure in the circulatory system when erect. The ultimate consequences of these events if uncompensated would cause syncope. During bed rest, the adaptation of the physiological mechanisms of the cardiovascular system which counteract these hydro-static forces imposed by gravity causes orthostatic intolerance or loss of the ability to stand and function in the erect position. Other observed effects of bed rest which may be due in part to the removal of hydrostatic gradients will be discussed later in this section.

Another major factor imposed by bed rest is the lowering of meta-bolic activity or hypodynamia. The disuse of muscle groups used for opposing gravity can lead to loss of muscle tissue and other changes of a catabolic nature. (Dietrich, Saltin, 1956).

There are relatively few review articles or textbooks which deal with all aspects of bed rest on the human physiological system, or which attempt to range across the many major studies which have been conduc-ted in recent years (Johnson, 1975;Vogt, 1967;Taylor, 1949;Greenleaf,1976). One possible explanation for this fact is that differences in scope and meth-odology, especially as regards the degree and duration of immobilization, make quantitative comparisons between studies difficult or impossible.

The study which was used as a baseline for these simulations is the NASA 28-day bed rest (BR-2) conducted at the Baylor College of Medicine (Johnson, 1976). The similarities between the BR-2 Bed Rest Study and Skylab, including diet and acute stress testing with bicycle ergometry and LBNP, make the study attractive for further comparisons

between zero-g and bed rest stresses. The 28-day study data were augmented with other data from the literature to provide better understanding of model response or to add perspective.

Changes in plasma volume appears to be one of the most studied (Vogt, 1967) of the many physiological changes which occur as a result of bed rest. Some investigators have speculated that plasma volume decreases are a major factor in producing the orthostatic intolerance seen after bed rest and zero-g. Hoffler (1977), has shown a significant correlation between plasma volume and heart rate during maximum LBNP. The plasma volume changes shown in Figure 5.1 illustrate the changes observed in NASA-sponsored bed rest studies. The average decreases in plasma volume are 14.6% during BR-2 and 6.7% in the Hyatt Study (absolute magnitudes 486 and 203 ml, respectively).

The cause for loss of plasma volume appears to be the headward shift of blood from the legs to the thorax. In bed rest, this excess blood volume is believed to be subsequently removed from the circulation through a diuresis. The physiological mechanisms responsible for the diuresis are a response to elevated arterial pressure including renal arterial pressure (Guyton, 1975) or possibly mediated by volume (stretch) receptors located in the left atria and great veins (Gauer, 1971).

Total body water (TBW) increased by .4 liters during the 28-day BR-2 study, as measured between the first day in bed (BR + 0) and the last day in Bed (BR + 27). These measured changes occurred in spite of a decrease in extracellular fluid volume and indicate an apparent increase in intracellular fluid (ICF) volume. Biostereometric data suggest that these increases in intracellular fluid occurred in the abdominal region (Herron, 1976). Intracellular increase were not found in the 14-day BR-1 study and intracellular decreases were indicated in the 28-day study of Hyatt. The differences in ICF and TBW changes between studies must be attributed to factors other than the removal of hydrostatic gradients

X-28 Day
⊗-14 Day
X-Hyatt

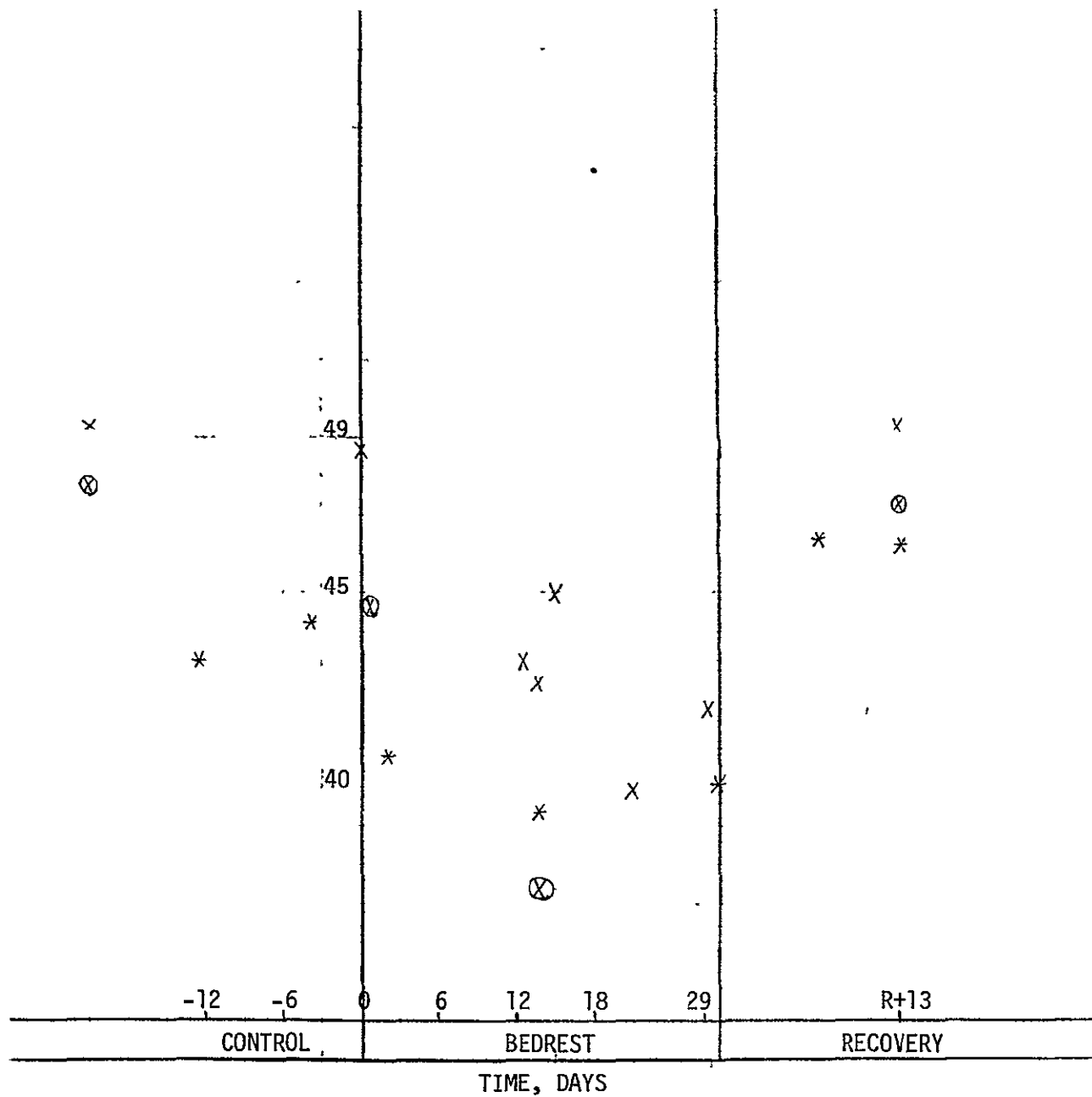Normalized Plasma
Volume (ML/Kg)

FIGURE 5.1

PLASMA VOLUME MEASUREMENTS DURING
28-DAYS BED REST

in the long axis of the body. Therefore, in order to accurately simulate changes in total body water and intracellular fluid volumes during bed rest, these differences must be more accurately described. Extracellular and interstitial volume measurements offer some additional insight into fluid volume changes. As shown in Figure 5.2, the 28-day (BR-2) study shows no change in interstitial fluid volume at the end of the bed rest period indicating that the modest and not statistically significant decrease in extracellular volume was all due to plasma volume changes. The Hyatt study and the 14-day study show very modest losses in interstitial fluid volume as well as plasma volume. The differences in these studies regarding total body water losses render the comparison in these measurements difficult at best.

The changes in leg volumes which occur during prolonged bed rest. are perhaps as universal a finding as plasma volume changes. The magnitudes of these volume changes were measured during the course of the 28-day study by Hoffler as shown in Figure 5.3. Hoffler's measurements indicate that the leg volume change during bed rest* was approximately 600 ml. Since it seems unlikely that intravascular volume decreases in the legs could account for a change of this magnitude after the initial shift of several hundred ml due to the removal of the gravity gradient, it must be assumed that much of this decrease was extravascular.

In order to approximate the amount of fluid contributed from each compartment, tilt table data taken before and after bed rest was examined. As a result of 28-days bed rest, Hyatt (Hypogravic and Hypodynamic) shows a difference in response to 70° tilt during the first minute of approximately 1.8 ml/100 ml leg volume. These data are interpreted to represent the

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* Measurements of fluid volume changes are assumed to be made from 30 to 60 minutes after assuming the supine resting state after other significant changes related to removal of gravity gradient have occurred.
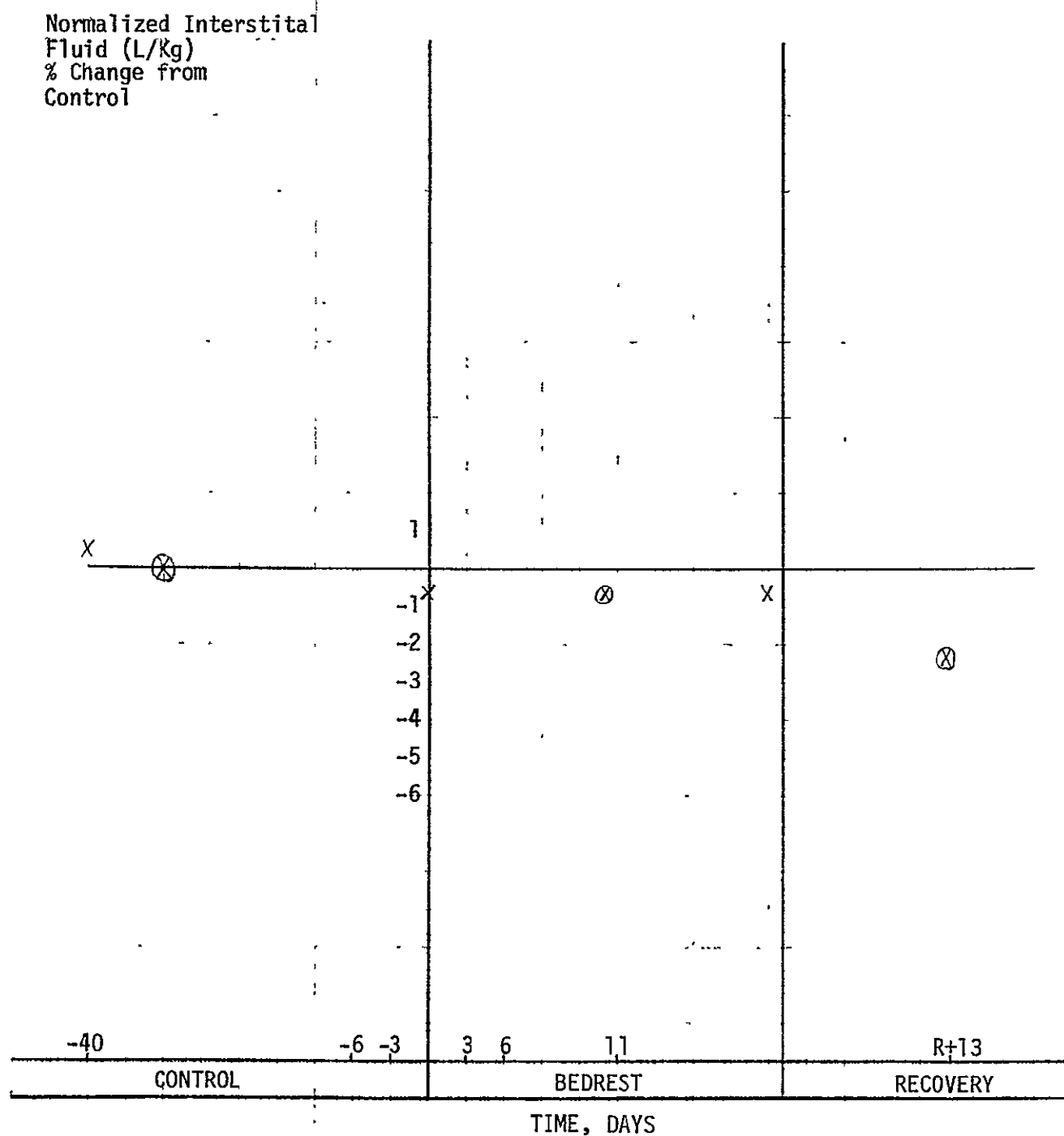
X-28 Day
⊗-14 Day·

FIGURE 5.2

INTERSTITIAL FLUID VOLUME AS MEASURED
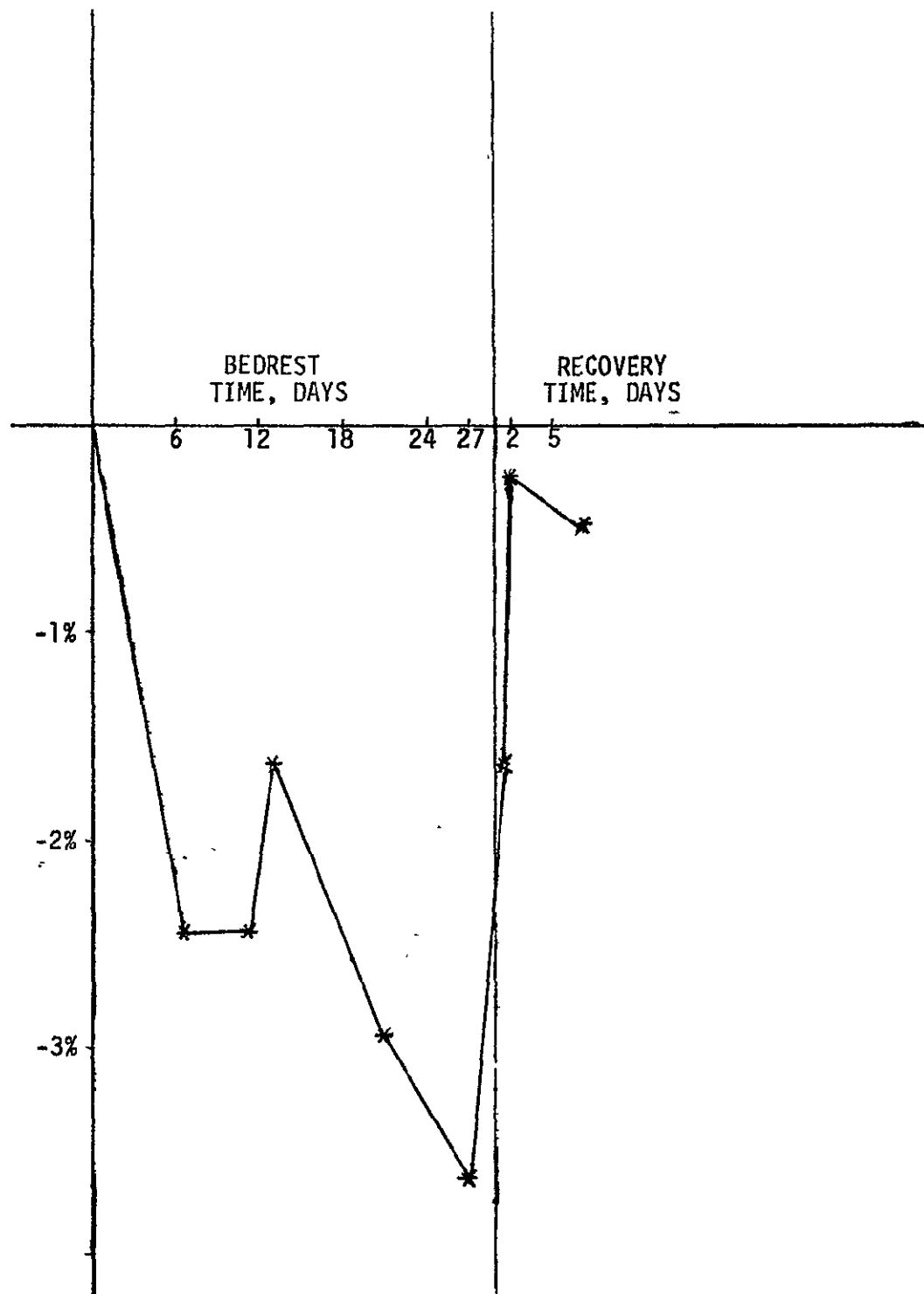IN TWO NASA BED REST STUDIES

LEFT LEG VOLUME 28-DAY BEDREST

FIGURE 5.3

LEG VOLUME CHANGES MEASURED DURING

28 DAYS OF BED TEST (BR-2)

difference in filling volume of the leg veins before venous stress relaxation or fluid transudation. This interpretation is strengthened by the observation that this approximate difference is maintained for the duration of the 20 minute tilt. This could also suggest that venous compliance and rate of fluid filtration from the capillaries had not been significantly changed during the course of the bed rest. However, this procedure is only intended to be a method of approximating changes in leg vascular volume. If we assume that the legs contain about 1.6 liters of volume, this difference amounts to about 280 ml of blood volume. The difference between the vascular change and the total leg volume change during bed rest is assumed to be the extravascular volume changes which would be approximately 320 ml. This loss would be divided between interstitial fluid and intracellular fluid losses. There is no direct evidence to date which would give a clear indication of the time course of the changes in these two compartments. The approach used for modeling these processes is to test the prevailing hypotheses and examine the possible mechanisms and the "reasonableness" of each by comparison with experimental data.

5.2   TESTING HYPOTHESES AND FORMULATION OF MECHANISMS IN THE MODEL

The model of Guyton (1972) was modified, as explained earlier in this report, to incorporate a fluid volume compartment which represents the legs. Postural changes or stresses such as tilt and LBNP which became possible with the addition of the leg compartments are also discussed in an earlier section. These simulations which include aspects of the control mechanisms which allow us to function in the erect posture may have some significance also in improving the bed rest simulation as will be discussed later in this report.

Initial Stimulus of Bed Rest

In order to simulate the fluid shifts associated with bed rest, one must consider the effects of assuming the supine position which begin immediately, and determine the long term significance of the changes, if any. As demonstrated in tilt studies, approximately 400 to 400 ml of blood is pooled in the leg veins from a 90° tilt. In going from erect to supine, an equal volume is shifted into the great veins, heart, and pulmonary circulation. This relative hypovolemia as discussed earlier . is relieved through a reduction in plasma volume. Red cell mass, however, does not change leaving an increased hematocrit. In order to simulate the long term consequences of these events , an arbitrary point was established when the plasma volume of the shifted blood had been removed from the circulation. In order to keep the model from being subjected to a step decrease in blood volume, the effect was simulated keeping blood volume constant. For 500 ml of blood shifted 200 ml would be red cells, so RCM was increased by 200 ml and plasma volume decreased by the same amount. The effect of this stimulus on arterial pressure, leg volume, hematocrit, and plasma volume are shown in Figure 5. 4. The arterial pressure response is due principally to viscosity changes due to increased hematocrit. Leg volume decreases are thought to be caused by increased plasma oncotic pressure. Total body water and extracellular fluid are effected by the primary decrease in plasma volume and extra-vascular effects of increased plasma oncotic pressure. Note that the transient nature of this stimulus allows all the above parameters to return to near their initial values by the end of 28 days.

Another aspect of the initial stimulus which was tested for its long term effect is the reabsorption of fluid that had filtered out of the vasculature and into leg tissues during the ambulatory phase prior to bed rest.
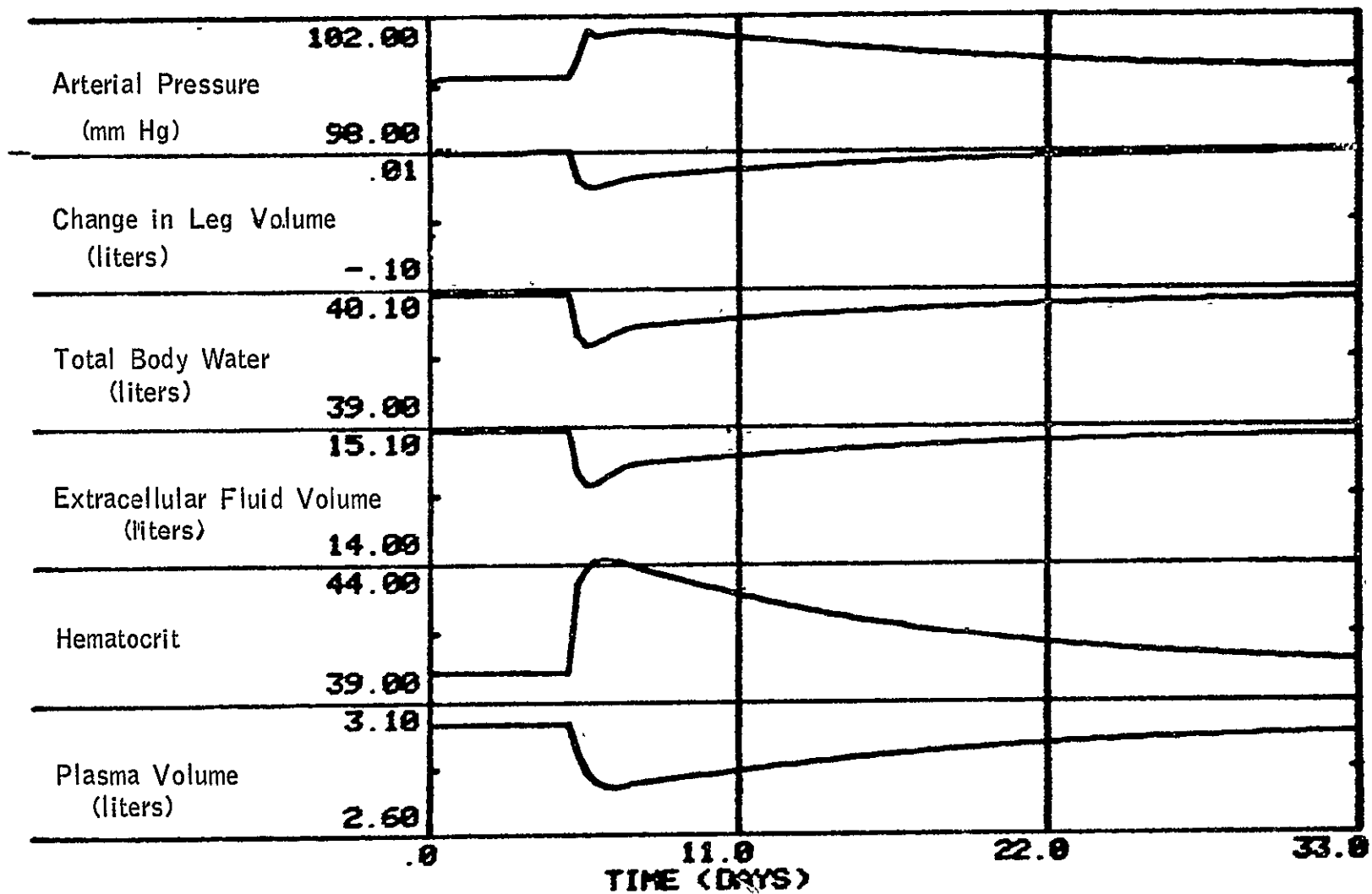
FIGURE 5.4

THE EFFECTS OF A STEP INCREASE IN RCM AND A
DECREASE IN VP OF 200 ml

In the model the volume of this fluid compartment is controlled by capillary dynamics and a set point and compliance term which approximates the pressure volume response of the tissue. Although gravity terms were added to this model, they are initialized in the supine resting position. This was necessitated by the difficulty in defining average ambulatory initial conditions which would be much more complex than a simple tilt case and in the man would depend somewhat on the history of his activity (e.g., standing, walking, sitting, etc.). So, in a model which maintains a supine steady-state, the removal of gravity terms would have no effect at all. In order to investigate the dynamics of fluid reabsorption from the leg tissues, a change in the set point for volume was used. This change is then sensed as an excess fluid volume in the legs and creates a tissue pressure which alters the capillary fluid dynamics. The effects of a set point change of 500 ml on arterial pressure, plasma volume, blood volume, total body water, extracellular fluid volume, and change in leg volume are shown in Figures 5.5 and 5.6. Figure 5.5 shows the changes which occur within 1 hour of the stimulus. The first two mintes are baseline conditions. These short term effects on arterial pressure are almost gone by the end of the first hour. As shown in Figure 5.6, plasma volume will return to normal by the end of the second day. The total body water and extracellular fluid volume have just noticeably begun to change within an hour, but the entire leg fluid volume given up will be eliminated from the body by the end of the second day.

Long Term Fluid Shifts from the Legs

One of the important objectives of this effort was to create the ability to simulate the prolonged dehydration effects of bed rest and weightlessness in the legs. A preliminary study of bed rest simulation with the original Guyton model (adapted for the Whole-Body Algorithm) indicated that many of the circulatory, renal, fluid and electrolyte responses could
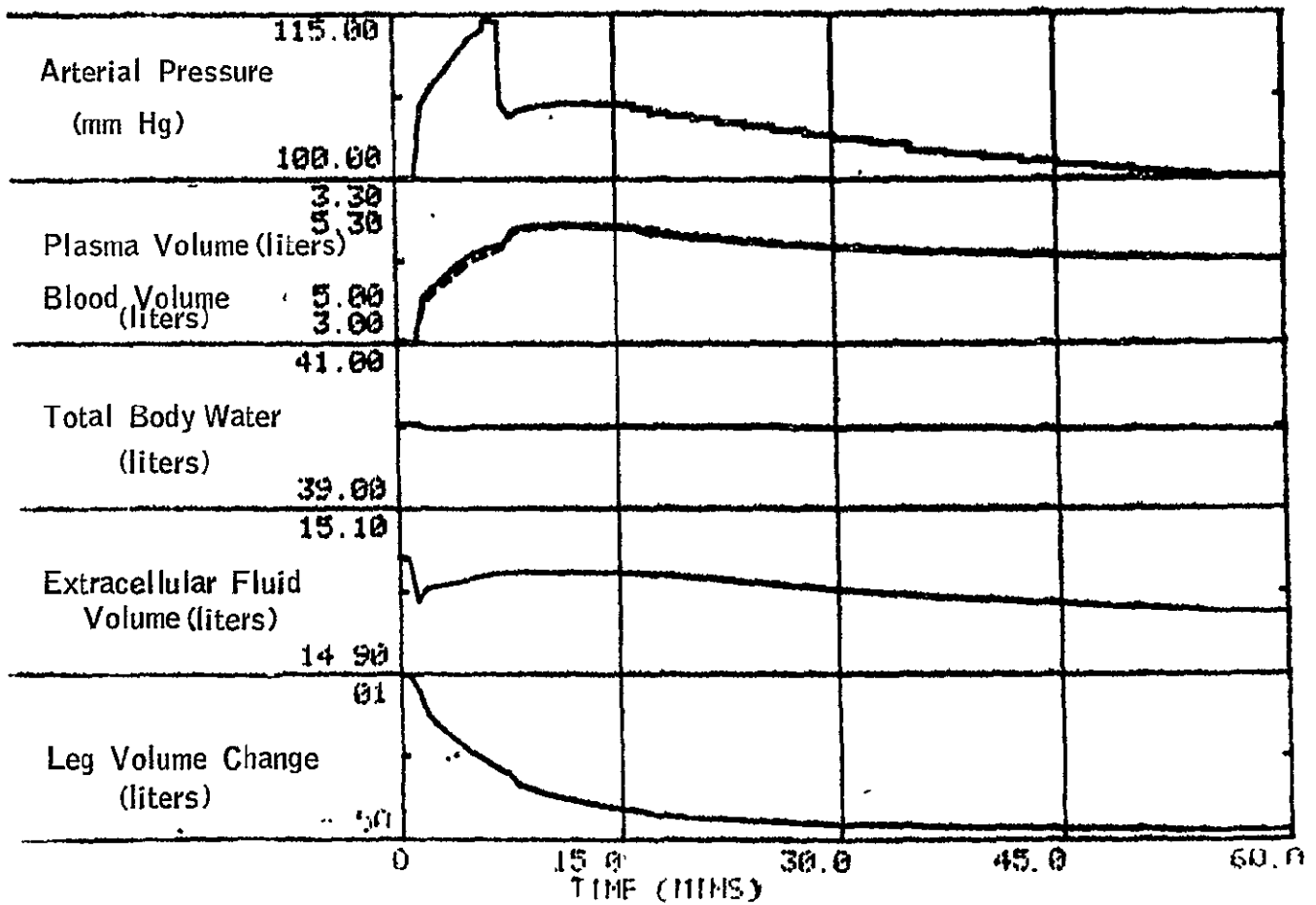
FIGURE 5.5

A STEP DECREASE IN LEG TISSUE VOLUME
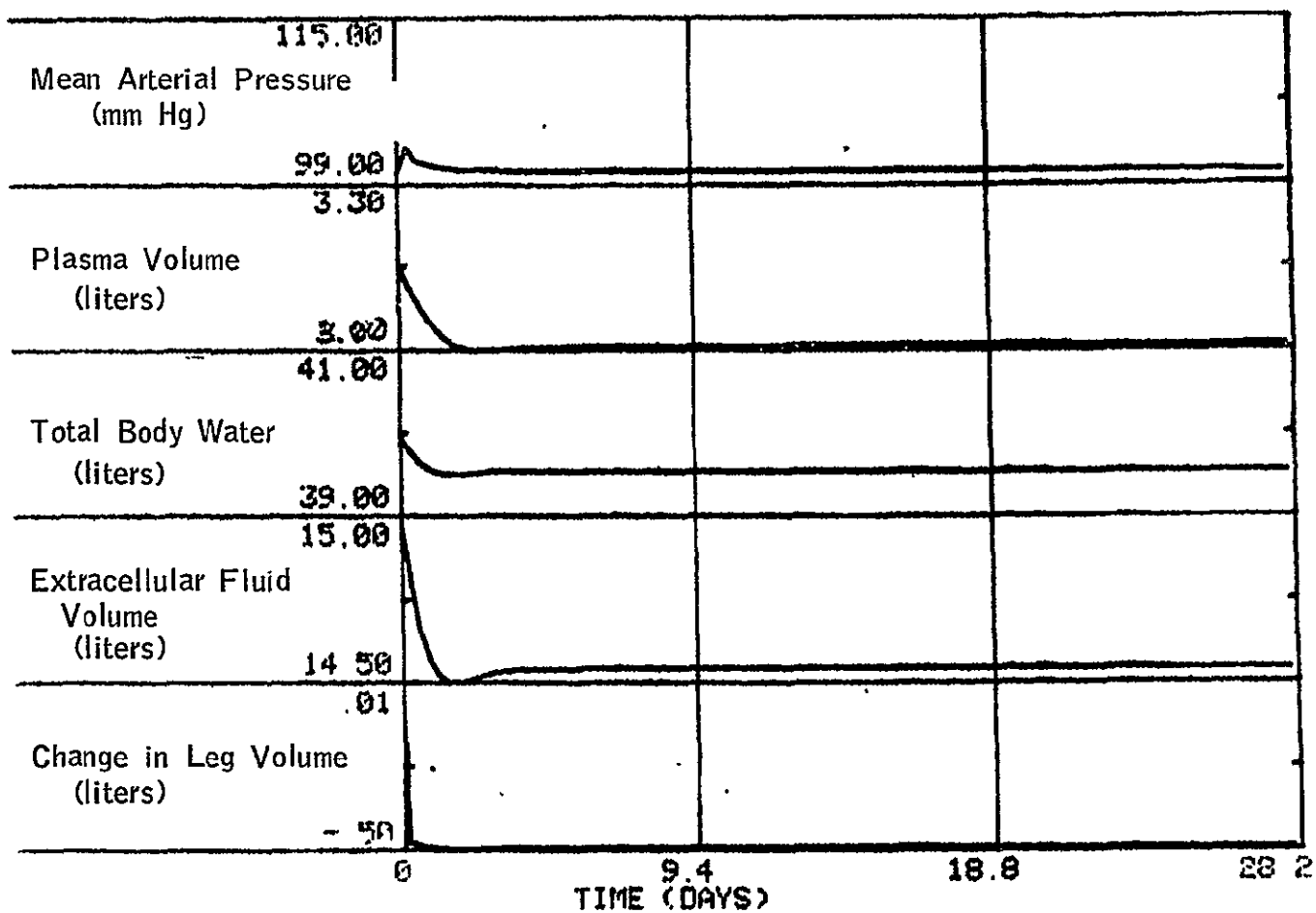SET POINT OF 500 ml

FIGURE 5.6

A STEP DECREASE IN LEG TISSUE VOLUME SET POINT

be in part explained by an acute expansion of the stressed blood volume (Fitzjerrell, et al, 1975). However, the resulting reduction in body fluids was confined to the losses in blood volume. It was suggested that a more realistic simulation should entail changes in interstitial and intracellular fluids, a portion of this decreasing rapidly at the onset of bed rest and a significant volume being depleted more gradually. This latter effect represents dehydration of the legs. One major purpose of this type of simulation would be to determine if this long term effect could account for the changes observed during the cardiovascular and metabolic stress tests performed periodically throughout the experiment.

The mechanisms responsible for leg dehydration during bed rest or zero-g have never been conclusively identified, but the model, as it is presently conceived contains elements which can be employed to test various hypotheses. These elements include:

a) External pressure biases on the leg blood vessels and on the leg tissue compartments: an increase in this parameter will drive fluid out of the legs.

b) Compliance of the leg blood vessels: a decrease in this parameter will increase leg blood pressure and decrease stressed volume

c) Angle of tilt: negative values will simulate head-down tilt and pool blood from the legs into the upper body.

d) Amount of hyaluronic acid in the interstitium: a decrease in this parameter will decrease the amount of gel which contains the largest portion of interstitial fluid. Gel is not explicitly represented in the leg interstitium, but removing it from the upper body would still result in realistic dynamic behavior of interstitial dehydration.

e) Cellular permeability of potassium: An increase in this
parameter will allow potassium to leak across the cell mem-
brane and water will follow. While the legs do not presently
contain a separate intracellular fluid space, this mechanism
will effectively produce a net decrease of intracellular fluid
which would be attributed to the legs.

Table 5.1 indicates the hypotheses for long term fluid shifts from
the legs employing some of the elements listed above which were imple-
mented and tested in the model.

The first hypothesis is based upon the observation that bed rest
subjects are not as active as when they are ambulatory. This inactivity
which results in disuse atrophy of antigravity muscles should also lower
the oxygen demand of the resting muscles. The blood flow through these
inactive muscles would not be as great due to autoregulation of flow and
an increase to arteriole resistance or decrease in the number of open
capillaries would be expected as shown in schematic hypothesis chart in
Figure 5.7. This could cause an effective lowering of capillary pressure
with an increase of fluid reabsorption as predicted by the Starling forces.
Values for average oxygen consumption were not available from the BR-1
28-day bed rest. However, (Dietrich, et al,1948) in their study of
subjects immobilized with plaster hip casts showed a 7% decrease in
basal metabolic rate.

Figure 5.8 shows the model's response to lowering the resting
muscle oxygen demand by 7% of the total metabolic rate $\cong$ 22 meg O_2/min
in a stepwise manner. The existing oxygen demand of the muscles in
the Guyton model was 58 meq O_2/min. This relatively high value for
resting muscle was being used to match initial conditions of the short
term cardiovascular model for exercise which was for subjects in the
resting seated position anticipating exercise. As shown in the Figure,
the response of the model is one of increased peripheral resistance with

HYPOTHESIS FOR LONG TERM FLUID SHIFTS FROM LEGS

Fluid Compartment	Description
Interstitial	#1 Decreased Oxygen Demand Increases Resistance to Flow in the Leg Muscles. Capillary Pressure Decreases and Starling's Forces Favor Increased Fluid Reabsorption.
Intercellular & Vascular	#2 Decreased Activity Leads to Muscle Atrophy and Loss of Cellular Fluids and Electrolytes with Concomitant Loss of Vascularization.
Vascular	#3 Vascular Emptying Leads to Reverse Stress Relaxation in the Leg Veins Until Pressure is Restored Thereby Further Emptying the Veins
Intercellular	#4 Increased Cortisol Causes an Increase in the Permeability of the Cell Membrane to Potassium. As the Potassium Leaves the Cell, Water Will Follow.
Interstitial (Not Tested)	#5 Decreased Hydrostatic Gradients Enhance the Effectiveness of the Muscle Contraction and Negative Thoracic Pressures to Increase Lymphatic Flow. Increased Lymph Flow Removes Protein Which Leaks into the Tissue Space, Reducing the Oncotic Pressure in the Tissue Compartment Thereby Keeping the Tissues Dryer.

TABLE 5.1

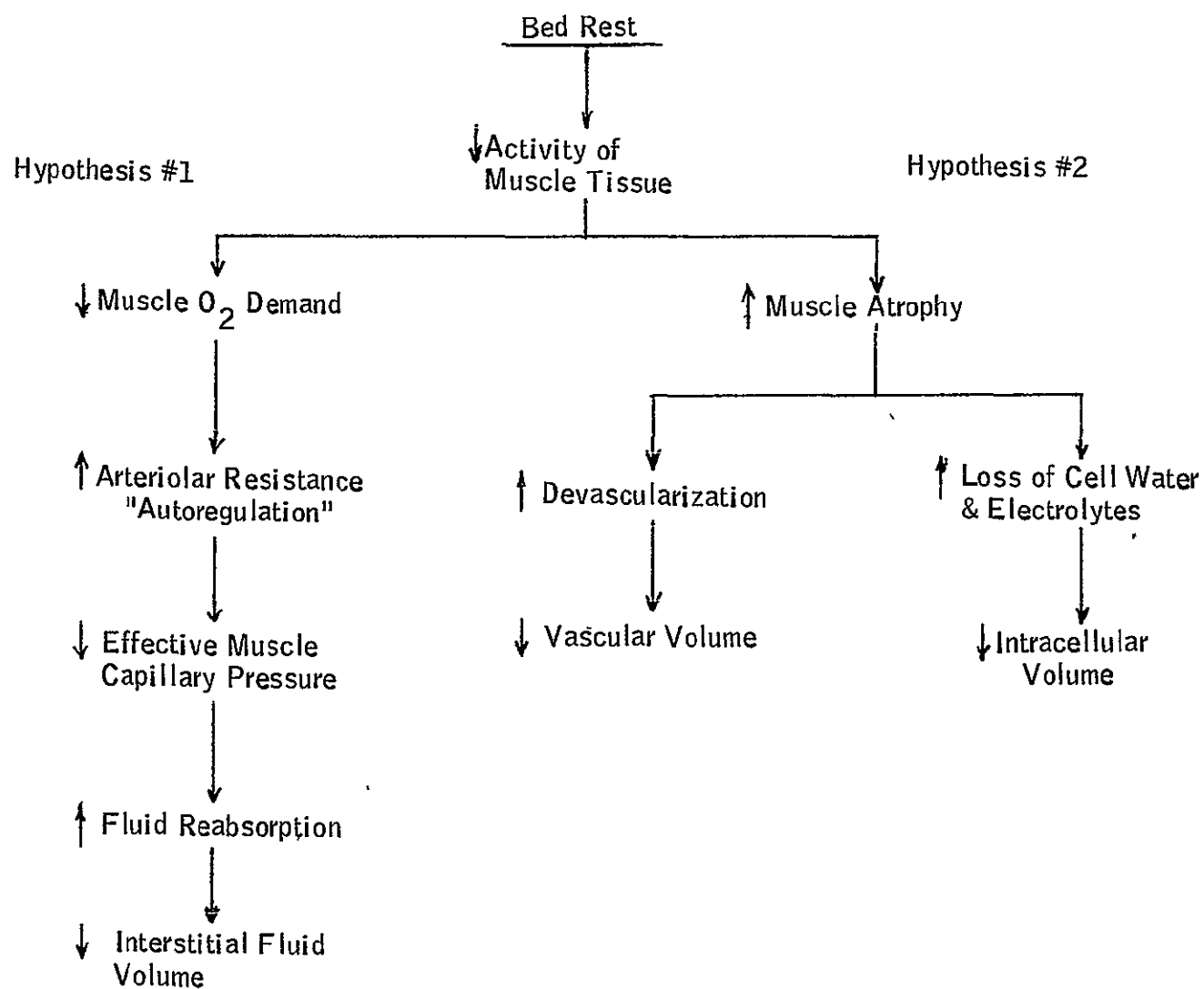HYPOTHESES TESTED FOR LONG TERM
CHANGES IN LEG VOLUME

FIGURE 5.7

HYPOTHESES FOR LEG VOLUME LOSS DUE
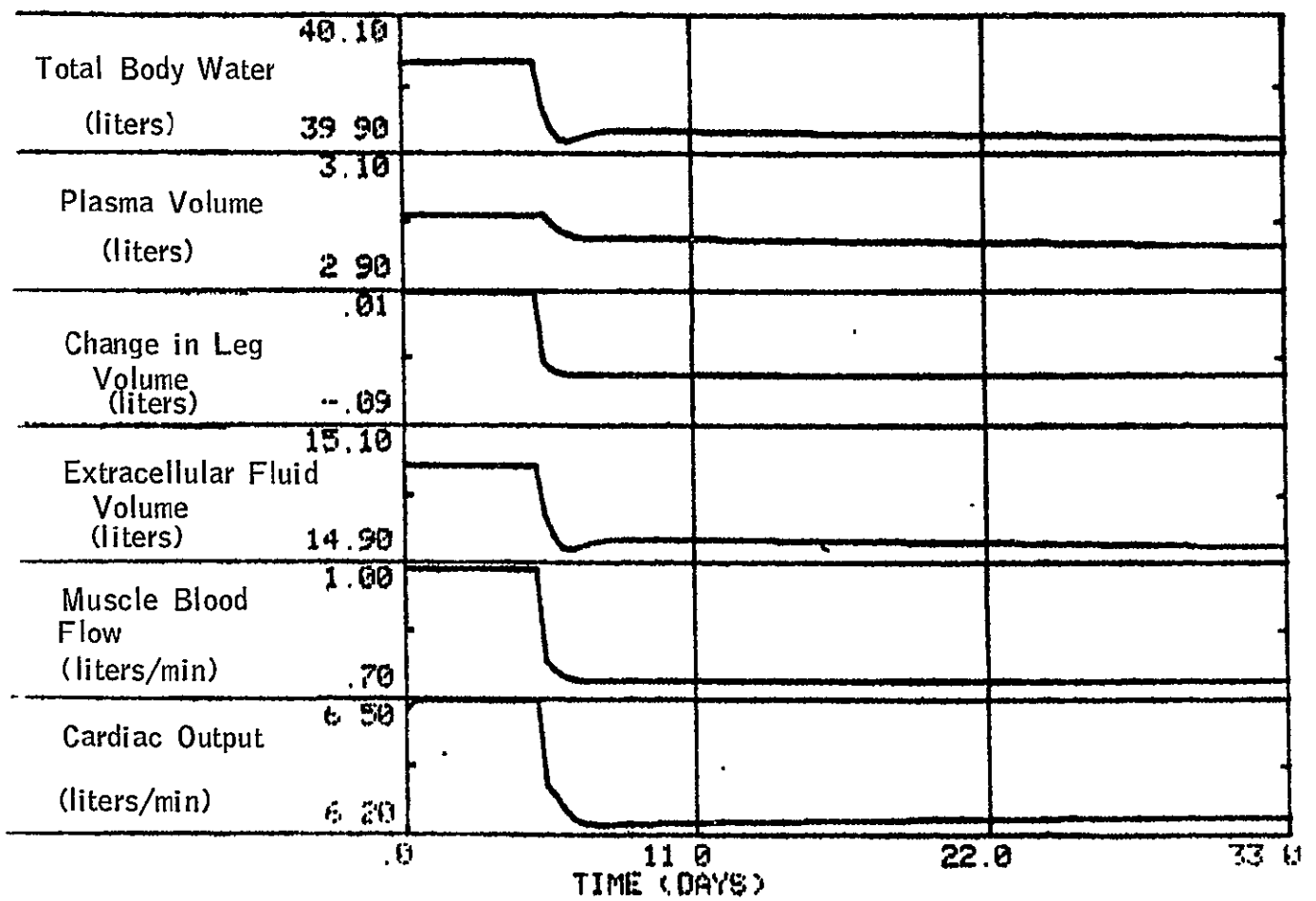PRIMARILY TO INACTIVITY OF MUSCLE

FIGURE 5.8

EFFECT OF REDUCED OXYGEN DEMAND IN MUSCLES

associated decrease of cardiac output and muscle blood flow. The loss
of leg volume is approximately 63 ml which comes from the interstitium
This fluid is given up as loss of body water.

Modest decreases in plasma volume probably reflect the increased
arterial pressure which along with all the interstitial losses account
for the loss in total body water. The stepwise manner in which the change
in oxygen consumption is entered is not physiologically correct, but
rather is used only as a means of testing model response.

Figure 5.9 shows the effect of a decrease in resting oxygen con-
sumption of muscle of approximately 7% of the total metabolic rate decreas-
ing linearly over 28 days. Note the leg volume losses reach about the same
-65 ml as in the stepwise decrease without an obvious rise in mean arterial
pressure.

Measurements of maximum calf girth are thought to more nearly
represent a measure of muscle mass loss than the total leg volume meas-
urements. Zero-g measurements made during the 84-day SL-4 mission
show that the losses in maximum calf girth are approximately exponential
showing about 80% of the total decrement of 1.1 liters (14.6%) accruing
within the first five days inflight with a gradual flattening out toward the
end of the mission, but not showing a clear leveling off at 84 days. Calf
circumference measurements from the 28-day BR-2 study, taken on the
first day of recovery, showed a 3.7% decrease in calf size compared to
pre- bed rest which returned to -2% by R+1 and remained. The data do
not allow an assessment of the time course of this change during bed rest.
However, a first order loss of muscle mass with attendant devasculariza-
tion and decrease in resting oxygen demand may be more appropriate
than either a step function or a completely linear rate of change, for both
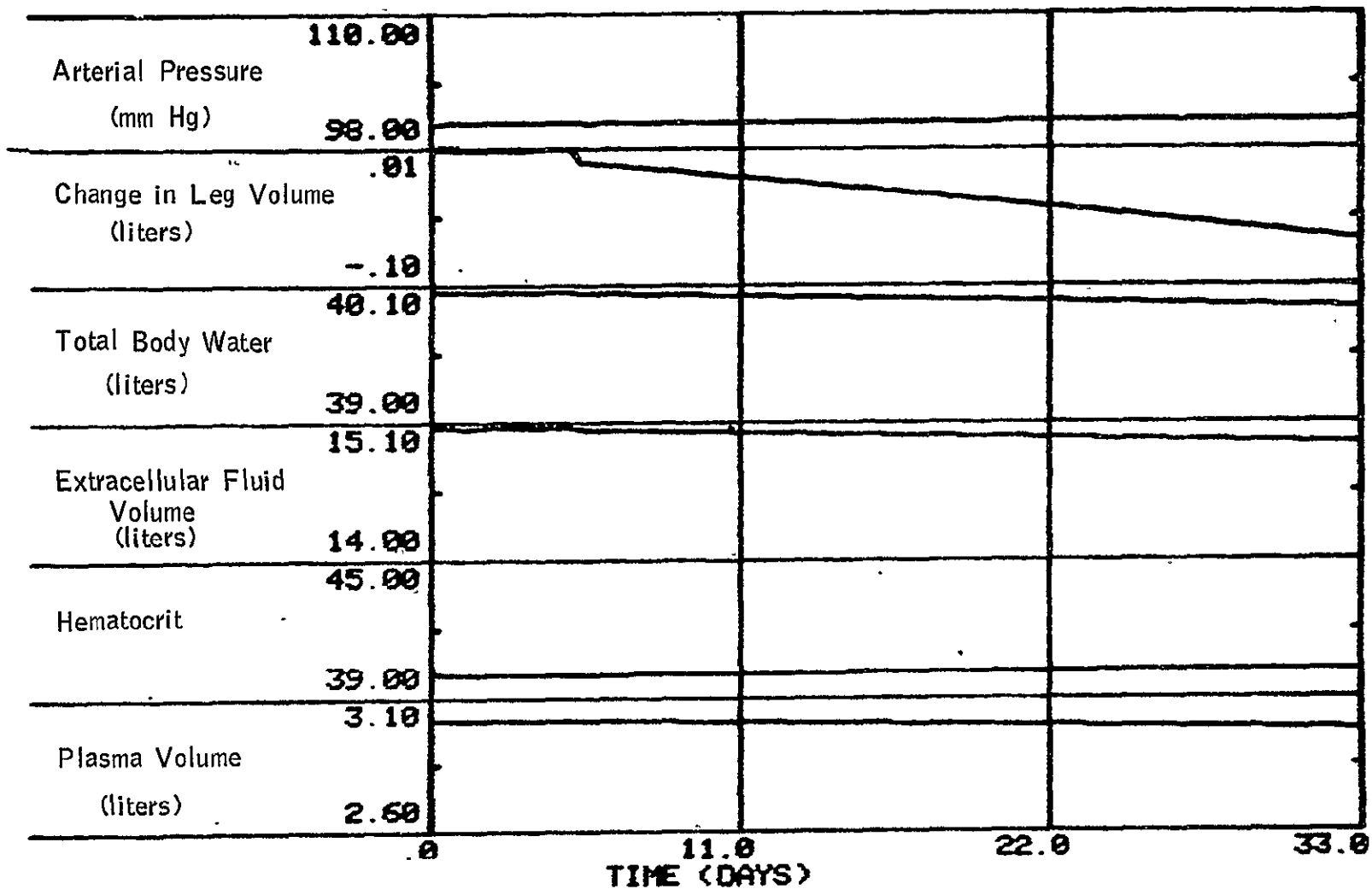bed rest and zero-g.

FIGURE 5.9

DECREASE IN MUSCLE OXYGEN DEMAND
WHICH OCCURS LINEARLY WITH 28 DAYS

The second hypothesis tested was that muscle atrophy due to disuse was responsible for the long term changes in leg volume. This hypothesis, which is illustrated in Figure 5.7, shows that muscle tissue losses largely due to inactivity would decrease both intercellular volume and the volume of blood normally associated with the lost tissue. The subjects of the 28-day BR-2 study have a blood volume to lean body mass (LBM) ratio of 89 ml/Kg during the control period. A correlation between LBM and blood volume in adults has been demonstrated by Sjostrand (1953). In order to estimate extravascular losses in the leg we can take the measured leg losses of approximately 600 ml and subtract the 280 ml of decreased vascular volume estimated in the tilt study of Hyatt, to arrive at a difference of approximately 320 ml as mentioned earlier. Another gross estimate of leg tissue loss would be to use the information that 46% of the decrease in maximum calf circumference returned by the end of the first recovery day and then remained constant. If the remaining 54% represents muscle loss and devascularization and further if this proportion is constant for the total leg loss, then 329 ml of loss were from extra-vascular sources. Using the LBM to blood volume ratio, 29 ml of blood would have been lost to devascularization. In the model the leg extra-vascular compartment is affected by capillary exchange parameters and a volume set point. The model does not presently include separate cellular com-partments and interstitial gel. Therefore, the only parameter presently in the model which could be used to simulate the loss of tissue volume is the leg tissue volume set point. Without sufficient information of the time course of changes the simulation is performed exactly the same as shown earlier in Figures 5.8 and 5.9. In addition to that stimulus, the amount of devascularization would be subtracted from the unstressed volume of the leg veins, in this case 30 ml would be removed. This type of change is modeled like the reverse stress relaxation described in the next hypothesis, only the time course of change would ultimately

be different. However, muscle atrophy and devascularization will be discussed later in this section in conjunction with other simulations of bed rest.

The third hypothesis tested is based on the knowledge that veins act as viscoelastic materials. That is, when subjected to a mechanical strain, part of the strain is immediately reversible (i. e. , the elastic part), and part of the strain is not immediately reversible (i. e. , plastic deformation, creep, or stress relaxation). In the veins, the amount of elastic stretch is measured by the compliance which describes the relationship between pressure changes and volume changes. The filling volume of the venous compartment (Vo) is the volume which can be filled before pressure changes are caused. This volume is a function of the pressure history of the vessel and the stress relaxation characteristics of that vessel. During ambulatory periods the leg veins are often distended and a certain amount of stress relaxation occurs as a result. During bed rest, however, the leg veins are not distended and the reverse process occurs, or reverse stress relaxation, which decreases the filling volume of the leg veins until transmural pressures across the vein reach some steady-state condition. The effects of bed test on fluid volume changes, based on this hypothesis, are shown in Figure 5. 10. As the transmural pressures are increased during reverse stress relaxation, additional blood would leave the leg vascular compartment in the same manner as the initial transient headward shift of blood.

Since the leg veins of the modified Guyton model do not have an inherent function for reverse stress relaxation, the unstressed volume of the leg veins was changed directly. Figure 5. 11 illustrates the effect of reverse stress relaxation input to the model as a ramp function over 28 days. The total magnitude of stress relaxation was 280 ml which was estimated in previous calculations as the change in leg vasculature volume during 28 days of bed rest. Note the decrease in plasma volume of approximately the same magnitude (280 ml).
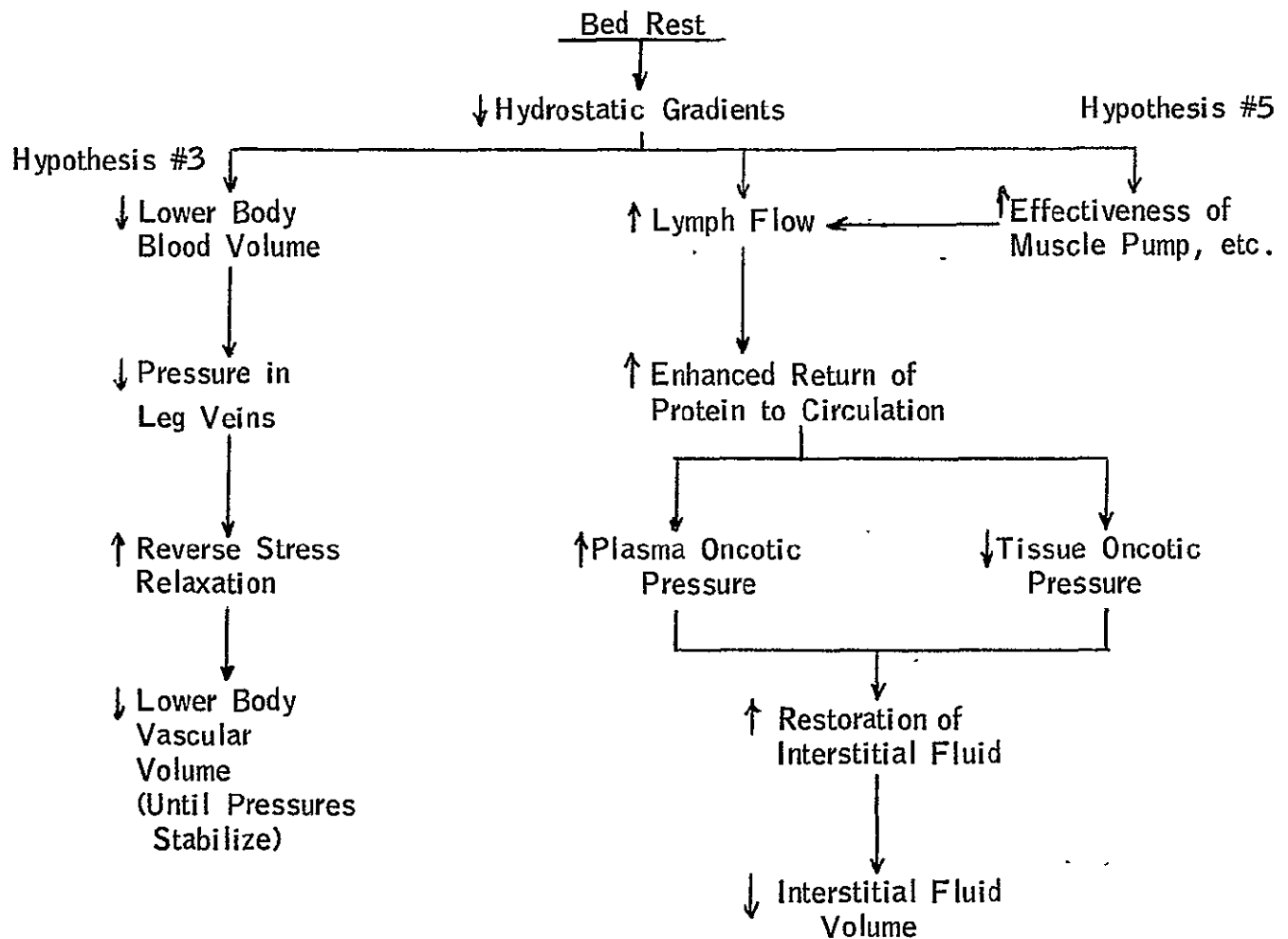
FIGURE 5.10

HYPOTHESES FOR EXPLAINING FLUID VOLUME CHANGES
DURING BED REST BASED PRIMARILY ON REMOVAL
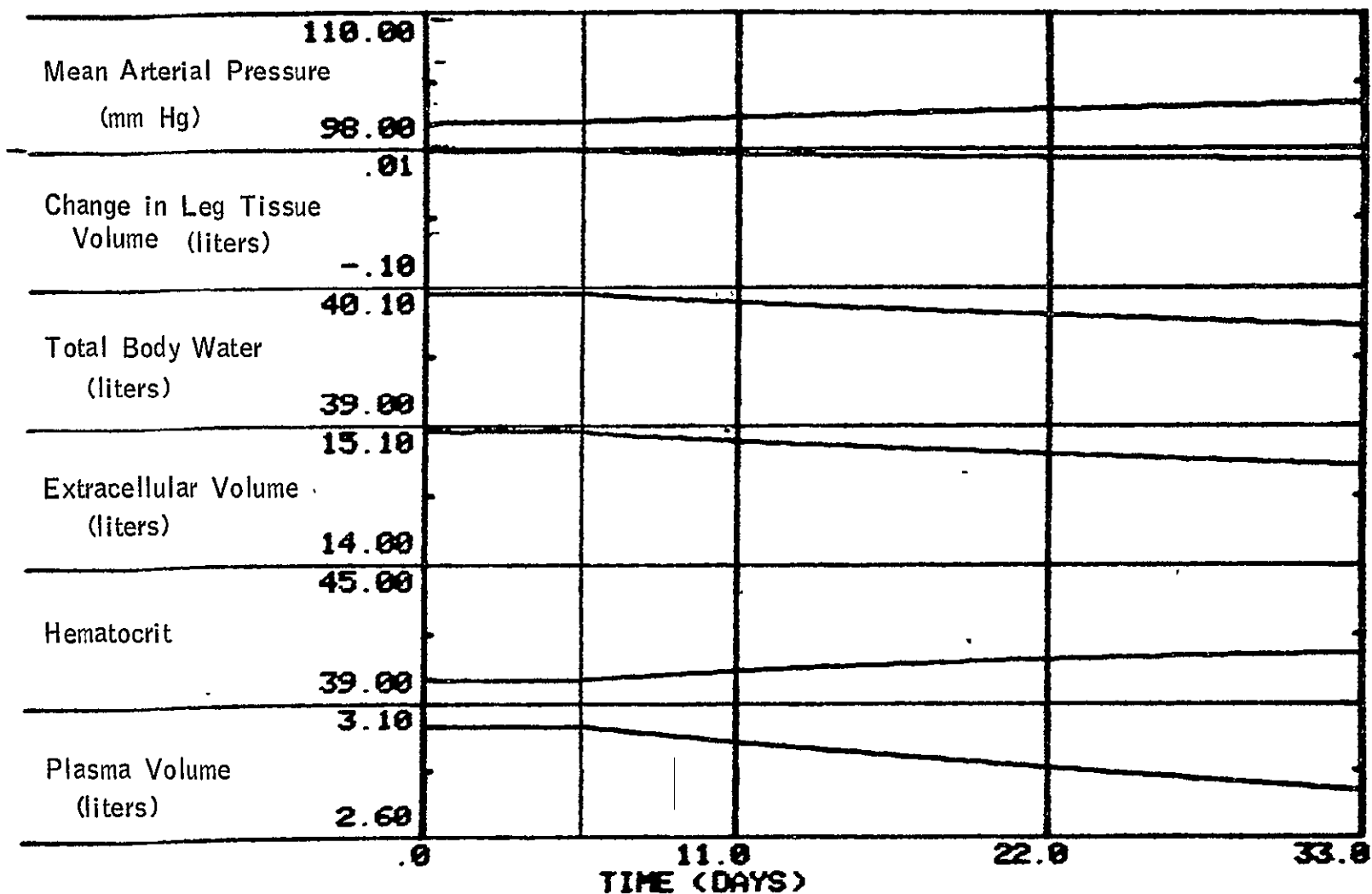OF HYDROSTATIC GRADIENTS

FIGURE 5.11

REVERSE STRESS RELAXATION IN LEG VEINS (280 ml)
INPUT AS A RAMP FUNCTION OVER 28 DAYS

With proper data on the dynamics of venous stress relaxation in the leg veins and a good estimate of the strain history encountered during ambulatory periods, the fidelity and usefulness of this mechanism in explaining the effects of weightlessness will be enhanced greatly.

The fourth hypothesis to be tested was based on the observations by Leach (1976) of increased urinary cortisol during bed rest and zero-g. This hypothesis is illustrated schematically in Figure 5.12. The effect of the elevated cortisol would be to increase cell membrane permeability to potassium and allowing potassium to leave the intercellular compartment taking fluid along with it. The kidneys would then act to remove potassium from the body with a kaliuresis and associated fluid loss.

(The model of Guyton does not have a function for corticol production, effects, or clearance. Therefore, in order to simulate the aforementioned effects of cortisol, the permeability of the cell membrane to potassium was arbitrarily changed by 10%. The simulated effects upon certain fluid parameters (TBW, plasma volume, potassium excretion, ECF, inter- cellular potassium, and extracellular potassium) are shown in Figure 5.13. The transient increase in TBW is caused by excessive drinking which expands plasma volume by about 100 ml. This mechanism could be useful in explaining the Kaliuresis observed during bed rest, but must be inter- preted with extracellular fluid volume changes in mind and in the light of increased information regarding the relationship between cortisol activity and increased cell membrane permeability.

The fifth hypothesis considered is illustrated in Figure 5.10 which shows that the removal of hydrostatic forces during bed rest should enhance the return of lymph from the legs. Although there is some spec- ulation about the ability of lymph to actively pump interstitial fluid back toward the central venous compartment and therefore back into the circu- lation, lymph flow is largely dependent on muscle pumping and the negative thoracic pressures to function in the erect ambulatory model. Without
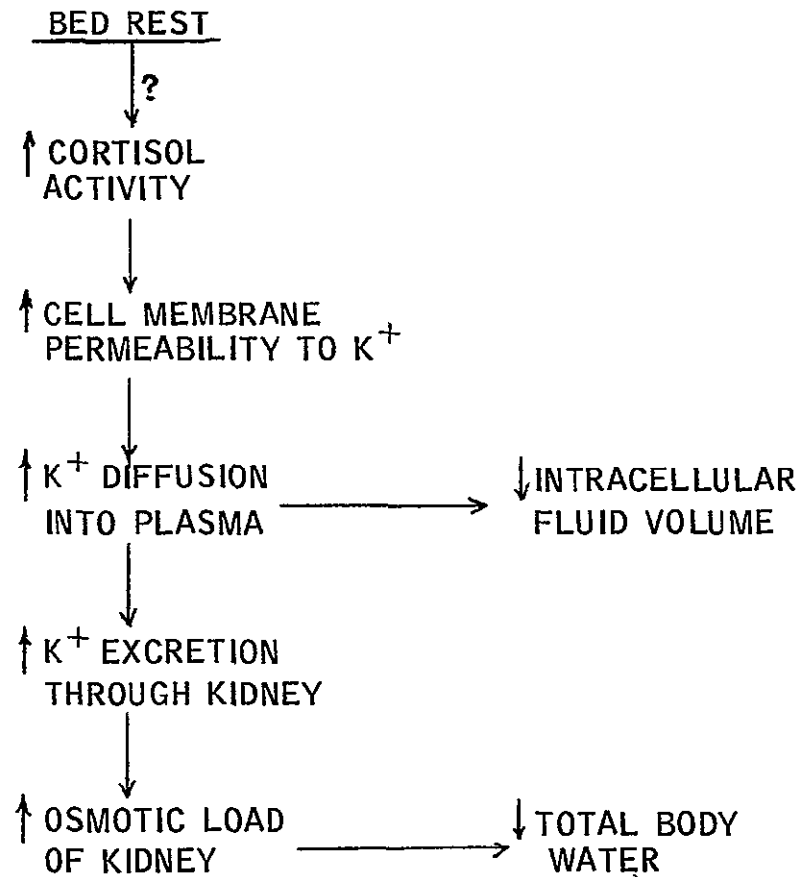
FIGURE 5.12

HYPOTHESIS FOR EXPLAINING FLUID VOLUME CHANGES
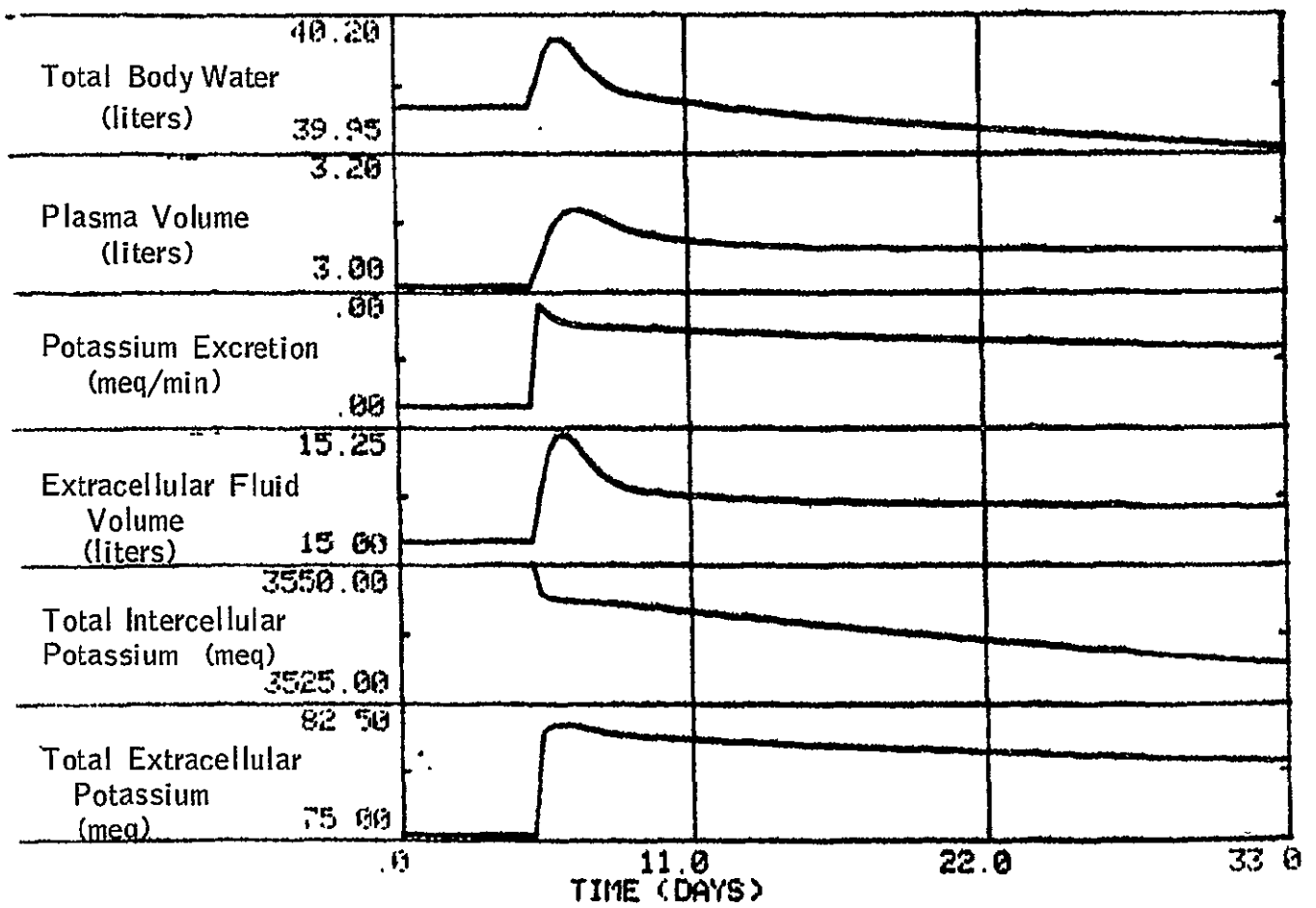DURING BED REST BASED ON OBSERVED CHANGES
IN URINARY CORTISOL

FIGURE 5.13

EFFECT OF A 10% INCREASE IN CELL MEMBRANE
PERMEABILITY TO POTASSIUM

lymphatic return of fluid filtered out of the capillaries, one would become edematous and life processes could not continue for more than a few hours (Guyton, 1973). The terminal lymphatics serve as the mechanism by which plasma proteins which leak into the interstitium are eventually returned to the circulation. Otherwise those proteins would be trapped outside the capillary membrane, which is highly impermeable to large proteins, until finally they exert an oncotic pressure which must be balanced with a tissue hydrostatic pressure causing edema. During bed rest, while hydrostatic forces are reduced along the long axis of the body, the leg tissues would have a lymphatic return which on the average might be at an elevated rate thereby more effectively removing tissue fluid and proteins. If the proteins are returned to the circulation more effectively, then, conceivably, tissue oncotic pressure would be lower and plasma protein concentration would be higher. This change in the balance of Starling's forces would keep the interstitial fluid "drier" and conceivably affect tissue gel hydration.

This hypothesis was tested in the model, but only to a very limited extent. Since the leg compartments do not contain a representation of tissue gel, rate of protein leakage, and lymphatics, a direct pump of fluid was put between the leg tissues and the central blood compartment. The flow rate was set equal to the existing lymphatics flow rate in the upper part of the body to see if capillary filtration into the tissue would balance it. No changes in leg tissue volume were observed until the lymphatic flow rate was increased an unusual 25 times normal flow rate in the thoracic duct. Although there is presently no data from bed rest to support or refute this hypothesis, it is worth consideration and may deserve further study and model refinement. If the tissue protein and gel dynamics were added to the leg tissue compartment, perhaps a noticeable effect could be seen.

Combined Hypotheses and Further Refinements

A simplified schematic of the all various hypotheses thus far examined in the model are shown in Figure 5.14. Various combinations of the long term hypotheses and the initial stimulus were simulated using the model. Figure 5.15 shows a combination of the step increase in hematocrit, release of 500 ml of leg extravascular fluid volume, decrease in muscle oxygen demand (22 meq/min) in a linear fashion over 28 days, and 280 ml of reverse stress relaxation in a linear fashion for 28 days. The use of a step increase in hematocrit, as explained earlier in this section under the discussion on initial stimulus of bed rest, is based upon the assumption that upon assuming the supine position pooled blood in the legs shifts headward, plasma filters out of the vasculature, and results in an elevated hematocrit. The remaining inputs are associated with the hypotheses discussed above. The model output agrees remarkably well in many respects with the data from bed rest studies despite lack of refinement in stimulating the model. Leg volume decreased 600 ml and plasma volume decreased 10% (300 ml) from control values.

Pooled blood in the legs as a result of standing is not available for transfer to the upper body since the model is initialized in the supine position. The increased hematocrit (since hematocrit is calculated based on plasma volume and red cell volume) is simulated by decreasing plasma volume and increasing the red cell mass in equal amounts thus keeping blood volume constant. This provides the stimulus for reduced production of red cells, but does not give the proper blood volume response since the plasma filtration resulting from the headward shift would result in a corresponding reduction in total blood volume.

Another approach for simulating this initial event, short of initializing the model in the standing ambulatory mode and tilting down to the
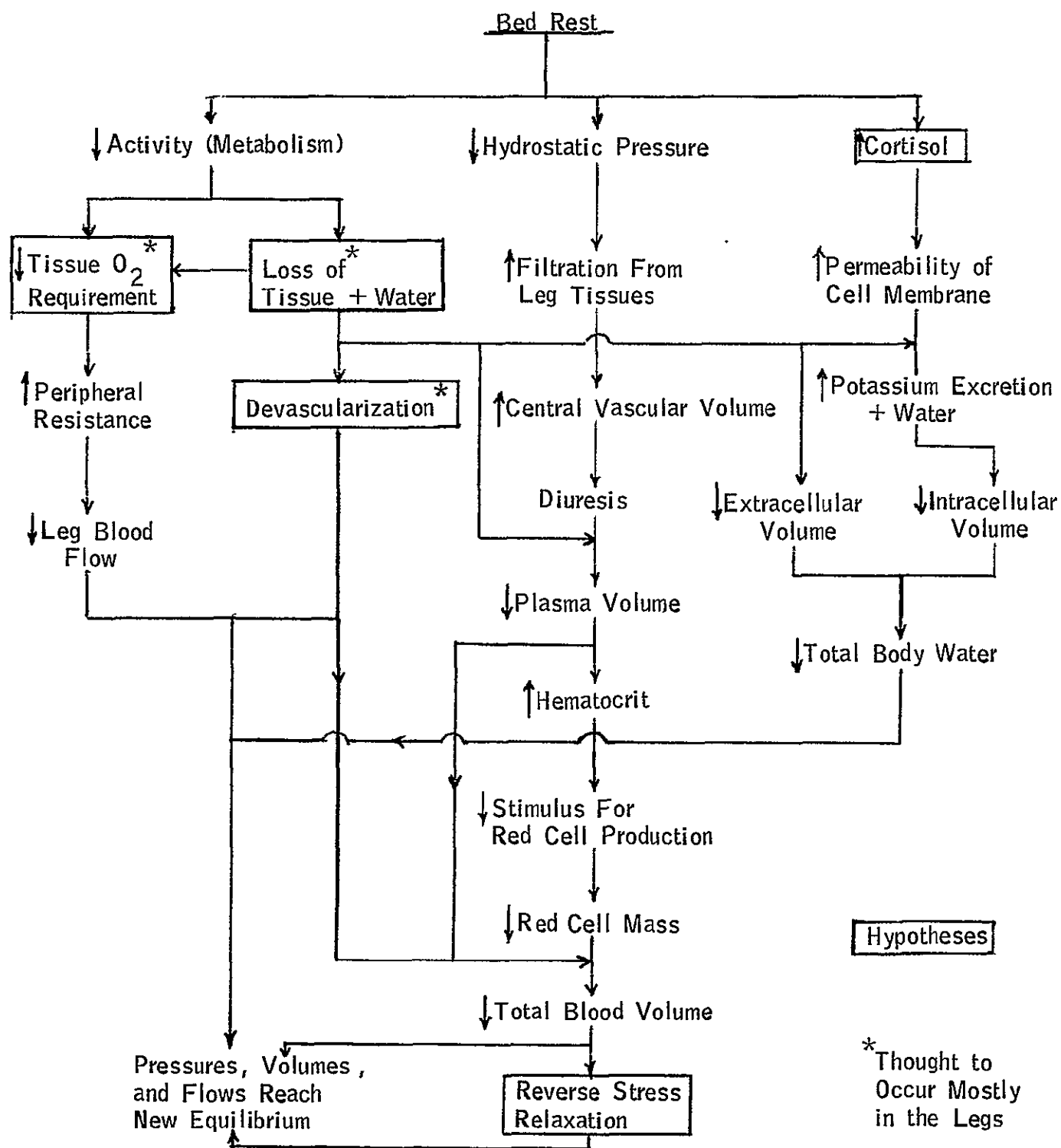
FIGURE 5.14

COMBINED BED REST HYPOTHESES

FIGURE 5.15

MODEL RESULTS FOR COMBINED LONG TERM HYPOTHESES
AND INITIAL STIMULI FOR BED REST

supine, was considered. In this approach, the leg blood volume and intracellular fluid are assumed to be increased due to pooling from having been erect and these compartments are "preloaded" with this extra volume in the supine model. "Release" of these volume excesses, then, provides the initial stimulus to set off the chain of events of head-ward blood shift, plasma filtration (diuresis), increased hematocrit, and decreased total blood volume which are hypothesized. Figure 5.16 shows the model response of selected variables for a 28-day bed rest simulation using this initial stimulus and the same combination of hypo-theses as assumed for Figure 5.15. This simulation appears to provide a more satisfactory representation of the events believed to occur in both the intermediate and long term observations of bed rest. This simulation is used in the following section to compare the model simulation with experimental data for bed rest.

FIGURE 5.16

MODEL OUTPUTS RESULTING FROM A FIRST ORDER DECREASE
IN FILLING VOLUME OF LEG VEINS AND DECREASES
IN OXYGEN DEMAND IN MUSCLE TISSUE AND
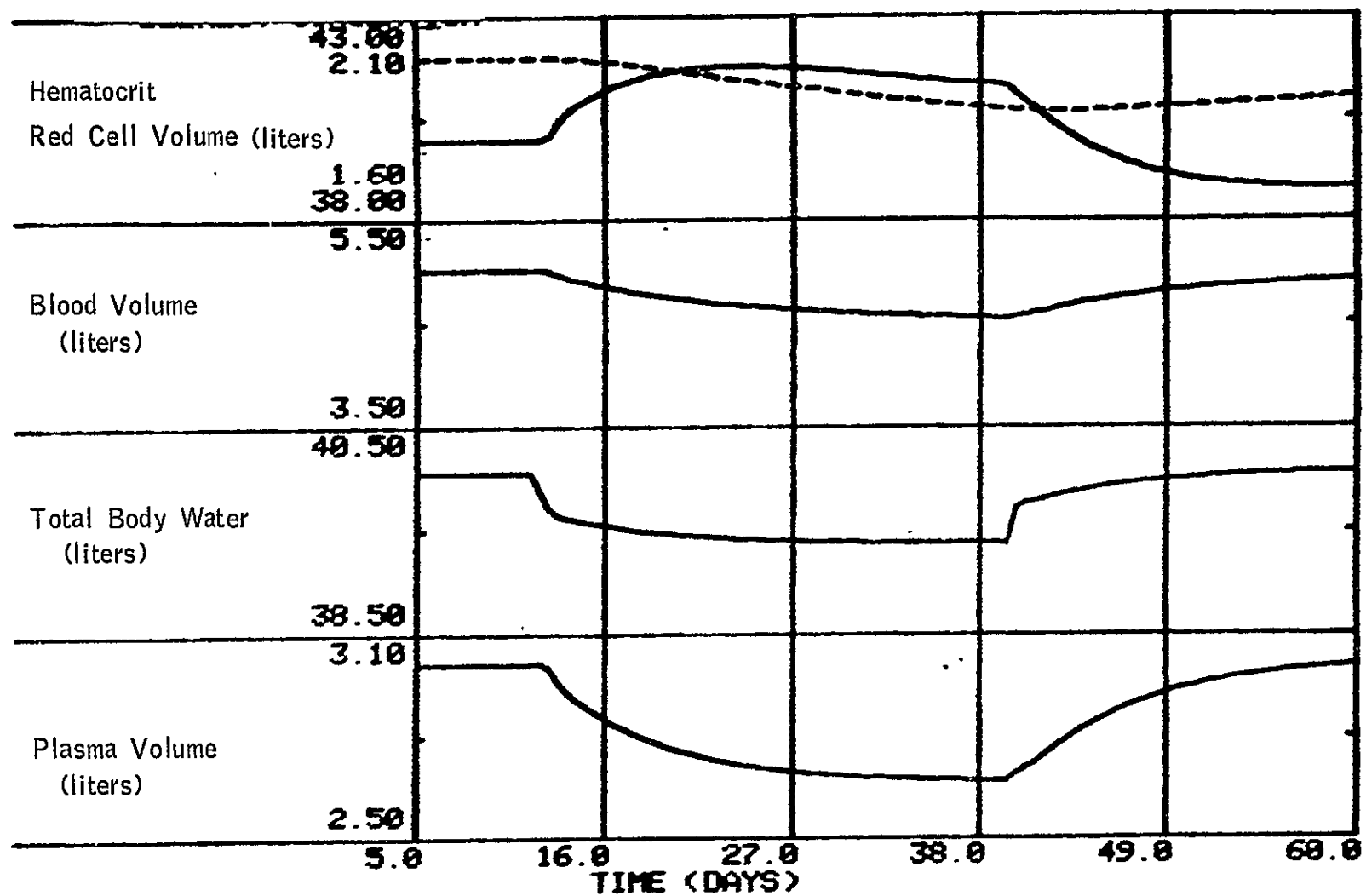RELEASE OF EXTRAVASCULAR FLUID

6.0   BED REST SIMULATION COMPARED WITH EXPERIMENTAL DATA

Model results were compared to experimental data in order to refine hypotheses which have been suggested to explain fluid volume changes associated with bed rest. This comparison yields information regarding the magnitude of hypothesized changes, and the ability of the model to predict the time course of effects. Figure 6.1 shows plasma volume changes in the simulation model compared to data from three experimental studies. Model inputs for this run were described in Section 5 and consist of forcing 400 ml of blood into the upper body from leg veins, decreasing resting oxygen demand in muscle tissue, releasing 300 ml extravascular fluid volume which was preloaded during ambulation and 30 ml of devascularization. This figure shows that the first order approximation for decrease in venous volume produces results which compare favorably in time course and magnitude for all three studies used.

This assumption for the initial stress requires that the greatest effect of relative hypovolemia occur at the onset of bed rest with 63% of the stimulus occurring within the first 3.7 days. The two 28-day studies shown vary considerably in the total decrement of plasma volume with the model predicting somewhat less than the BR-2 study, but greater than the study of Hyatt, et al (1970).

Figure 6.1 shows that the recovery of the model is slower than indicated by the data and shows only a slight tendency to overshoot the control level as compared to the data. All three studies used show an overshoot by the second week of recovery and two of these show overshoots of over 5%. The factors in the model responsible for even the slight overshoot, which occurs by 20 days of recovery, should be investigated further for possible explanation of this phenomenon.

Figure 6.2 shows the model output of leg volume versus data from the 28-day BR-2 study. Several factors prevent precise comparison
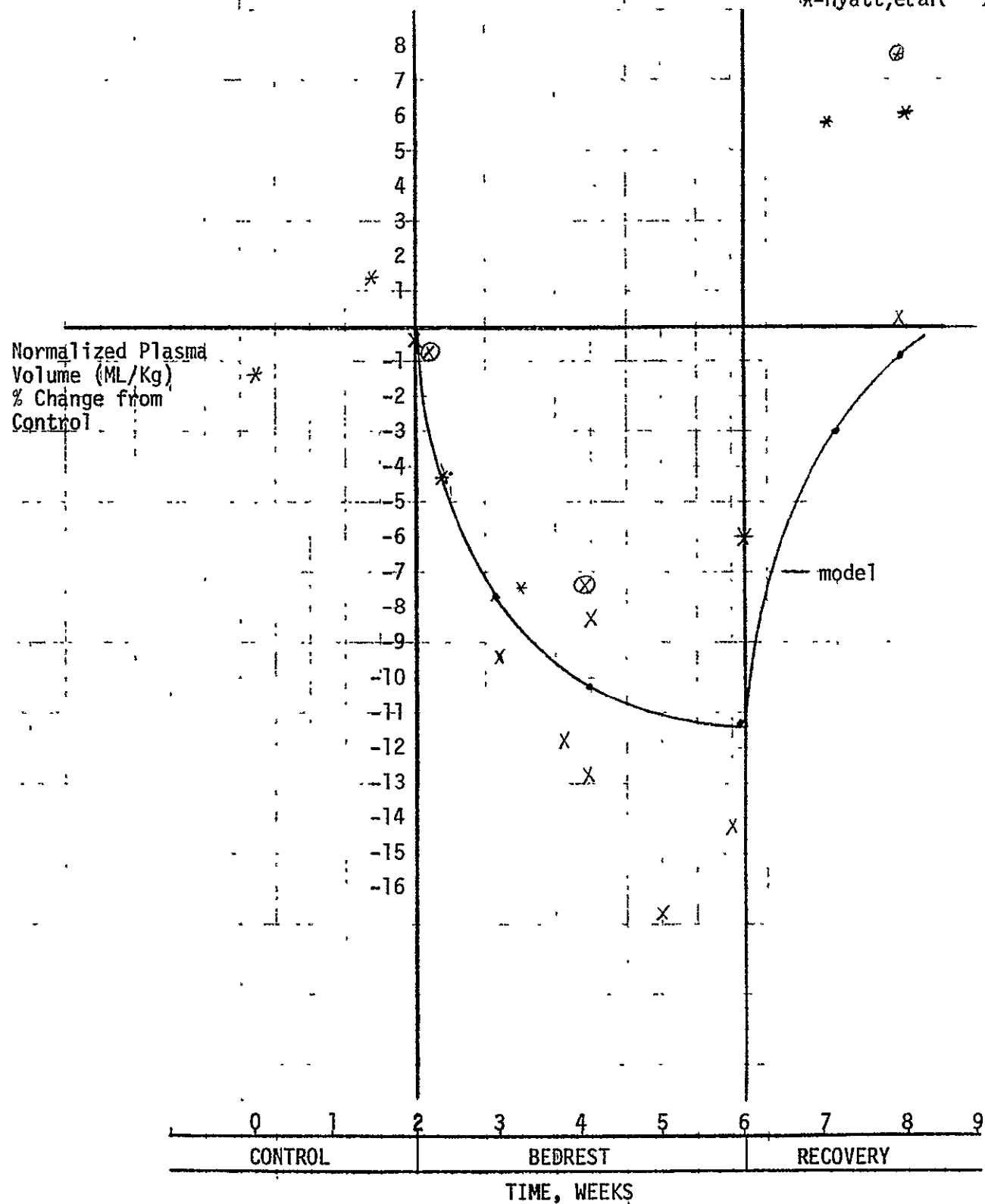
FIGURE 6.1

COMPARISON OF PLASMA VOLUME CHANGES DURING
BED REST, MODEL VS. DATA

LEFT LEG VOLUME 28 DAY BEDREST
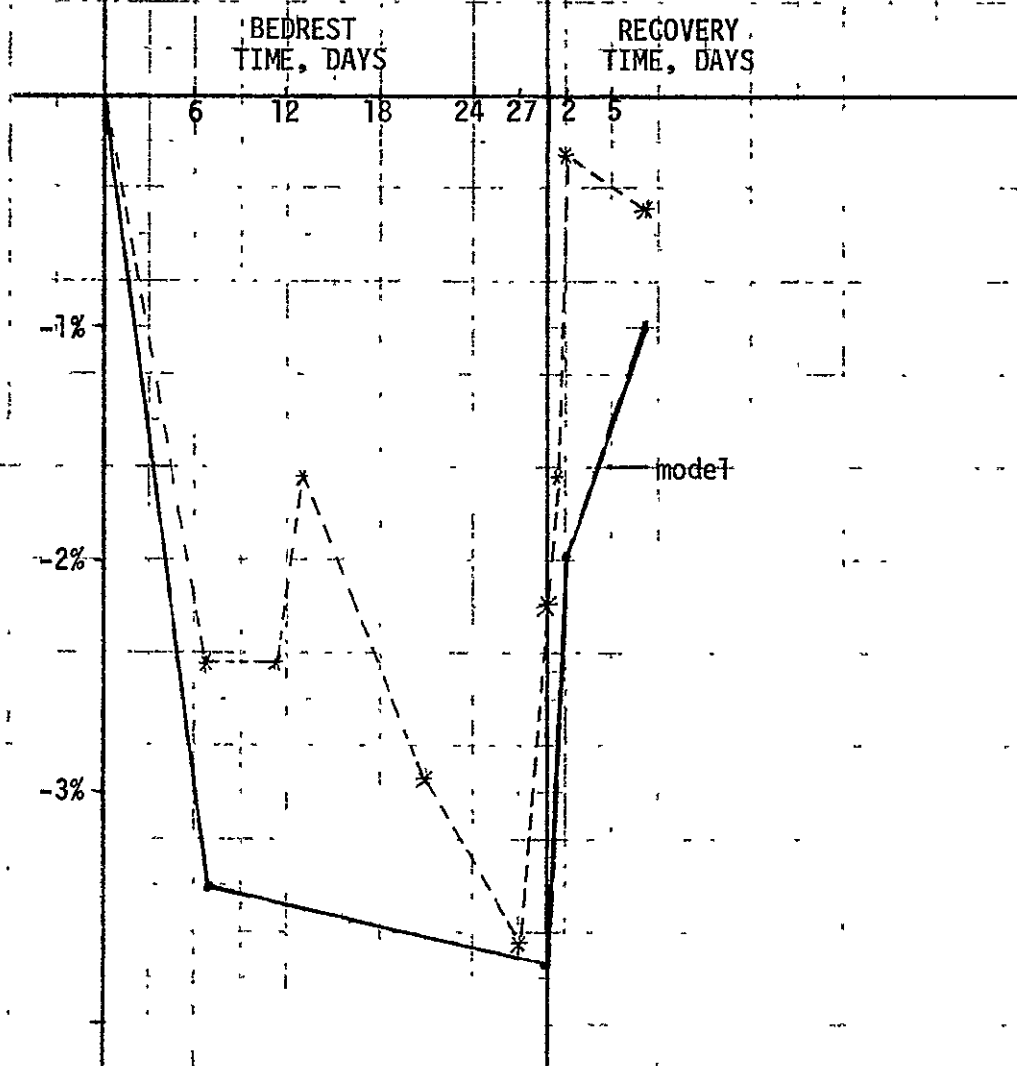
FIGURE 6.2

COMPARISON OF LEG VOLUME CHANGES
DURING BED REST, MODEL VS. DATA

between model and experimental response. The data shown represents changes in total leg volume including those due to decrements in fluid volume (intravascular and extravascular) as well as solid tissue. The model response, on the other hand, takes into account only those changes due to leg intravascular and interstitial fluid shifts. The spike in the data at the end of two weeks of bed rest coincides with the LBNP + saline ingestion crossover study, a factor not accounted for in these simulations.

The rapid initial decline of the simulation was due to an intravasation of 300 ml of leg tissue fluid, while the continuing slower decrease is a result of the decreased O_2 demand and the devascularization mechanism. Changes in tissue volume as a result of muscle atrophy could not be measured during the bed rest study and were not considered in the simulation. However, this factor could alter the time course of the response. Recovery results indicate that the model recovers leg volume less quickly than the human subjects. All forcing functions used to create the changes were made symmetrical for either decreases or increases in fluid volumes. It has been suggested that this may not be the case in the real system (Guyton, et al, 1975).

Figure 6.3 shows a comparison of the ECF differences between the simulation and the experimental data from the 28-day bed rest study (BR-2), the 1 + day Bed Rest Study (BR-1), and the 28-day Bed Rest Study of Hyatt (1970). The model's response of ECF coupled with the leg volume response shown previously suggest that the extravascular volume of the legs is decreased too quickly and perhaps less than the 300 ml used for this simulation might be more appropriate.

Not enough experimental data is shown immediately after recovery to evaluate the recovery response. The notation of extrapolated and 30-minute values on the BR-2 study indicate two techniques which were used to interpret the isotopic diffusion data (Johnson, 1976).
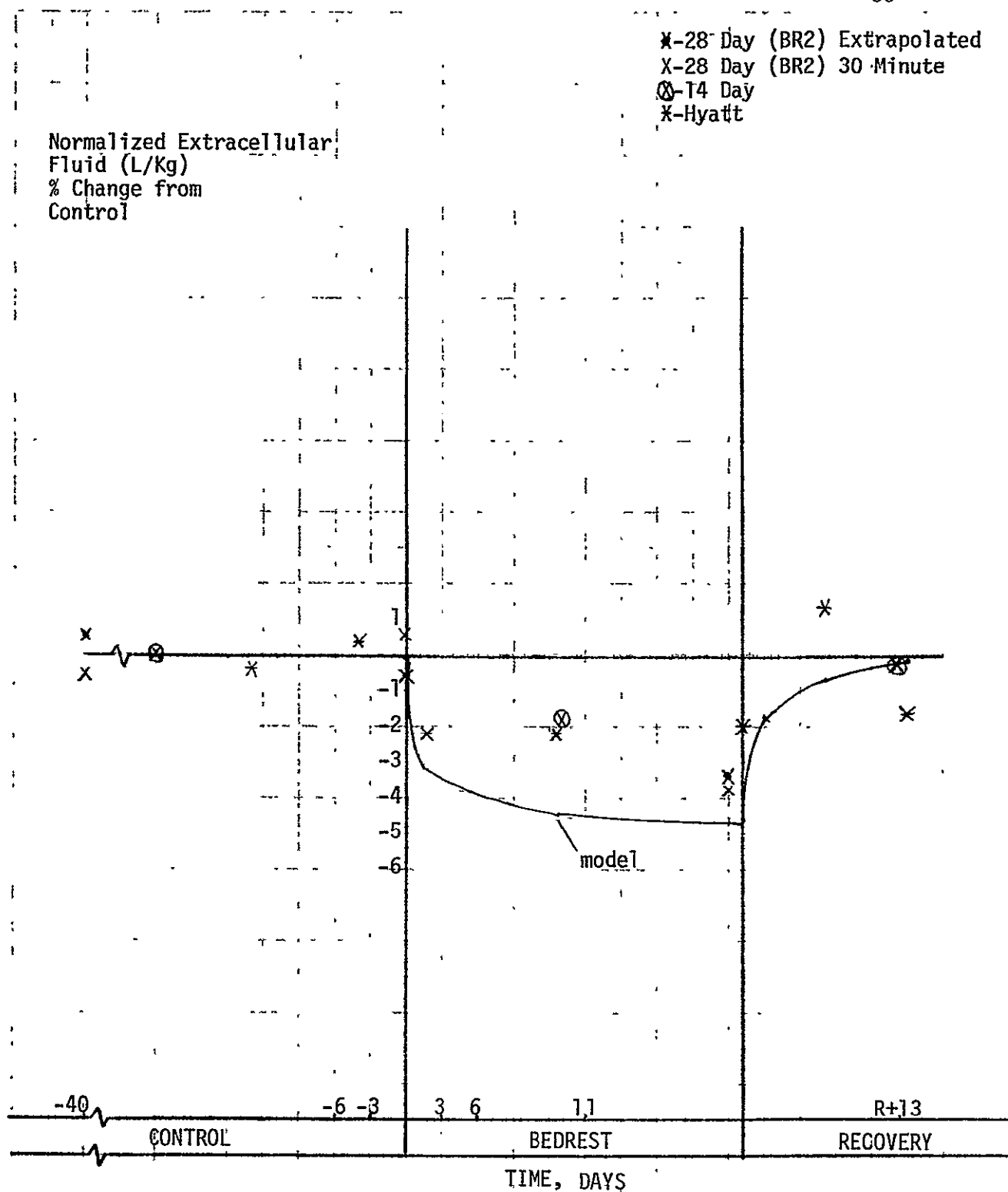
FIGURE 6.3

COMPARISON OF EXTRACELLULAR FLUID VOLUME CHANGES
DURING BED REST MODEL VS. DATA

Figure 6.4 shows the total body water (TBW) response of the simulation compared to data from three experimental studies. As discussed earlier in Section 5, the TBW changes include the net changes in both the extracellular fluid (ECF) and the intracellular fluid (ICF) compartments.

The model shows a reasonable comparison to two studies at day 14. At the end of 28 days there is disagreement between the two studies as to whether TBW is slightly higher or several percent below control; the simulation indicates a rapid and then a gradual decline in TBW throughout the remainder of bed rest. The changes in the model's TBW are a result almost entirely of changes in extracellular volume in the leg compartments. Although data are lacking in this regard, it is possible that during these bed rest studies, the changes in TBW could be explained by a decrease in extracellular volume offset somewhat by an increase in intracellular volume. It can be surmised that if intracellular increases had occurred during bed rest, the notable overshoot in TBW during recovery which occurs in both studies would have been much more pronounced in the model when extracellular refilling occurs.

The results of the simulation also show good agreement in other areas of experimental observations showing a 6.7% decrease in red cell mass which is compared to the observed value of 6% decrease at the end of bed rest as measured by Kimzey (1976). This favorable comparison indicates the soundness of the improved erythropoiesis algorithm which has been recently inserted in the model. (Leonard, 1975).

The responses of the cardiovascular indices also compare well to some studies, but in general not so well with the BR-2 study. One factor which deserves further attention is resting heart rate. An increased resting heart rate has been a consistent finding in almost every bed rest study to date. Yet, without additional changes to the autonomic elements,
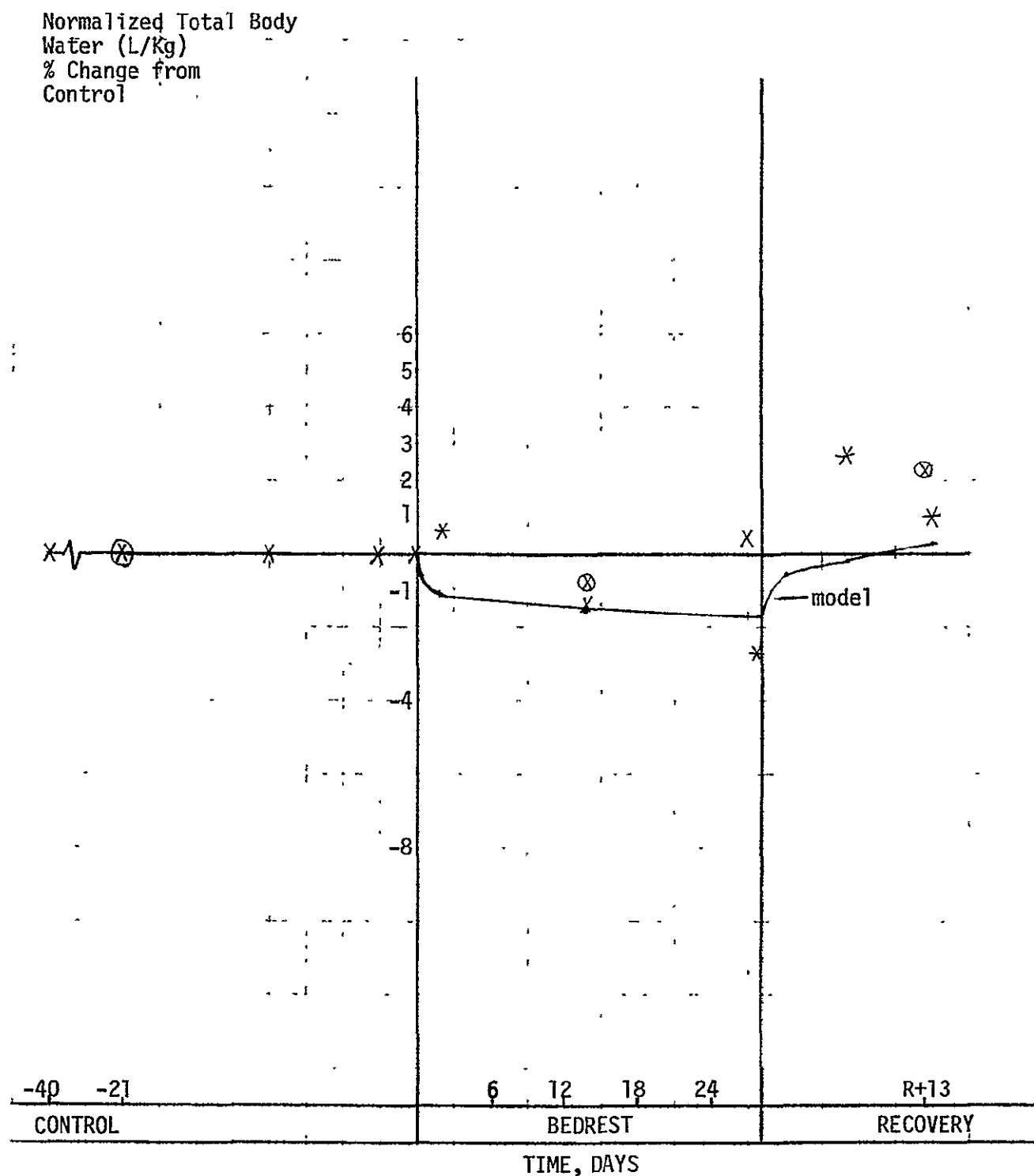
FIGURE 6.4

COMPARISON OF TOTAL BODY WATER CHANGES DURING
BED REST AND RECOVERY, MODEL VS. DATA

the Guyton model predicts practically no change in resting heart rate for 28 days of bed rest. An empirical algorithm is applied to the heart rate function to provide realistic heart rate and stroke volume response for bed rest simulation. The mechanisms which are responsible for this effect are not known. However, the suggestion and study of possible mechanisms for this phenomenon is an important area of future study. A related area which would be effected by such changes would be the stroke volume.

Other hemodynamic parameters which showed a change at the end of 4 weeks simulated bed rest are a 4.15% decrease in cardiac output, a 2.5% increase in arterial pressure, and a 7.1% increase in total peripheral resistance. These values show reasonably good correspondence to studies by others (Saltin, 1968; Stevens, 1966; Birkhead, 1963; Valbona, 1965, and Taylor, 1949).

In conclusion, the primary stimulus of a decrease in leg venous volume which forces blood headward seems to be quite effective in producing the type of changes seen in plasma volume during bed rest. The magnitude of 400 ml shifted and a time constant of slightly less than 4 days gives good correspondence to experimentally observed losses in plasma volume. The extravascular fluid from the legs, originally estimated to be around 300 ml leaves the tissue too quickly at present and may be too much volume. Mechanisms will be investigated and included which will increase the fidelity of the response in that area. A decrease in resting oxygen demand of muscle seems warranted, and has positive effects on leg volume changes and hemodynamic parameters. The role of intra-cellular changes in creating an overshoot in TBW during recovery should be investigated, an an explanation of the observed overshoot in plasma volume refill should be investigated.

In spite of the crude approximations which were made, reasonable results have been obtained in simulating the fluid shifts of bed rest. With the suggested refinements discussed throughout Sections 5 and 6, the role of the changes can now be related to the acute stresses of exercise and LBNP as a result of bed rest. Furthermore, the utility of bed rest as an analog to zero-g can be developed on the basis of this and future studies.

7.0   CONCLUSIONS AND RECOMMENDATIONS

The performance of this study has produced several end products
and its conclusion suggests a completed study, which indeed it is. How-
ever, this is not be be interpreted as an exhaustion of the subject, for it
is only an initial step in the difficult process of understanding and anal-
yzing the many adaptive physiological changes that are known to occur in
the human system under the stresses considered in this study. The next
step planned for this program is to simulate the response to weightlessness
and to compare these responses to the simulation of bed rest performed
as a part of this study. This does not imply that there are not other
modifications, improvements, or validation studies which should be per-
formed, for indeed there are many. The conclusion of this study pre-
sents an opportune time for documenting recommendations for future work
in this area and this section attempts to point out these recommendations
and to discuss them in some detail.

7.1   RECOMMENDATIONS FOR IMPROVING THE CAPABILITY OF THE
        MODIFIED GUYTON MODEL

The gravity dependent capability of the modified Guyton model now
allows a large group of simulations which were heretofore impossible.
The addition of leg compartments also makes it possible to distinguish
between upper and lower body pressures, flows, and volumes in either
supine or erect positions. The ability to apply differential stresses to
these different segments is also present. Some of these simulations
represent stresses whose experimental responses are well documented.
Other are more scantily represented in the literature, but are of impor-
tance to the physiology of space flight and weightlessness. In the time
available during the present effort only a small portion of the stresses
listed below were studied with the model.

- Head-down tilt
- Head-up tilt
- Standing: short term and long term
- Vasovagal Syncope
- LBNP
- Erect Exercise
- Acceleration (centrifugation): $+G_z$ and $-G_z$
- Comparison of hemorrhage in erect and supine positions
- Comparison of erect and supine exercise
- Comparison of LBNP, standing and tilt responses
- Bed rest: short term and long term, including the effects of bed rest on LBNP, tilt and exercise responses
- Weightlessness: short term and long term, including: a) effects on LBNP and exercise response, and b) effects of counter-measures on deconditioning.

Each of these stresses may be studied with the model with respect to the responses of many physiological subsystems including the circulatory, body fluids, renal, endocrine and autonomic systems. In particular, it is possible to simulate a large variety of fluid shifts which have long been thought to be intimately involved in producing long term effects observed in bed rest and weightlessness (See Figure 7.1). Studies of changes in orthostatic tolerance and cardiovascular deconditioning due to bed rest and weightlessness involve the use of the Whole-Body Algorithm with the short term stresses of LBNP, tilt, and exercise simulated before and after the long term simulation of bed rest or weightlessness (Fitzjerrell, et al, 1975). These short term stresses will be important points of comparison between bed rest and zero-g which is the subject of a simulation study to be conducted in the near future.
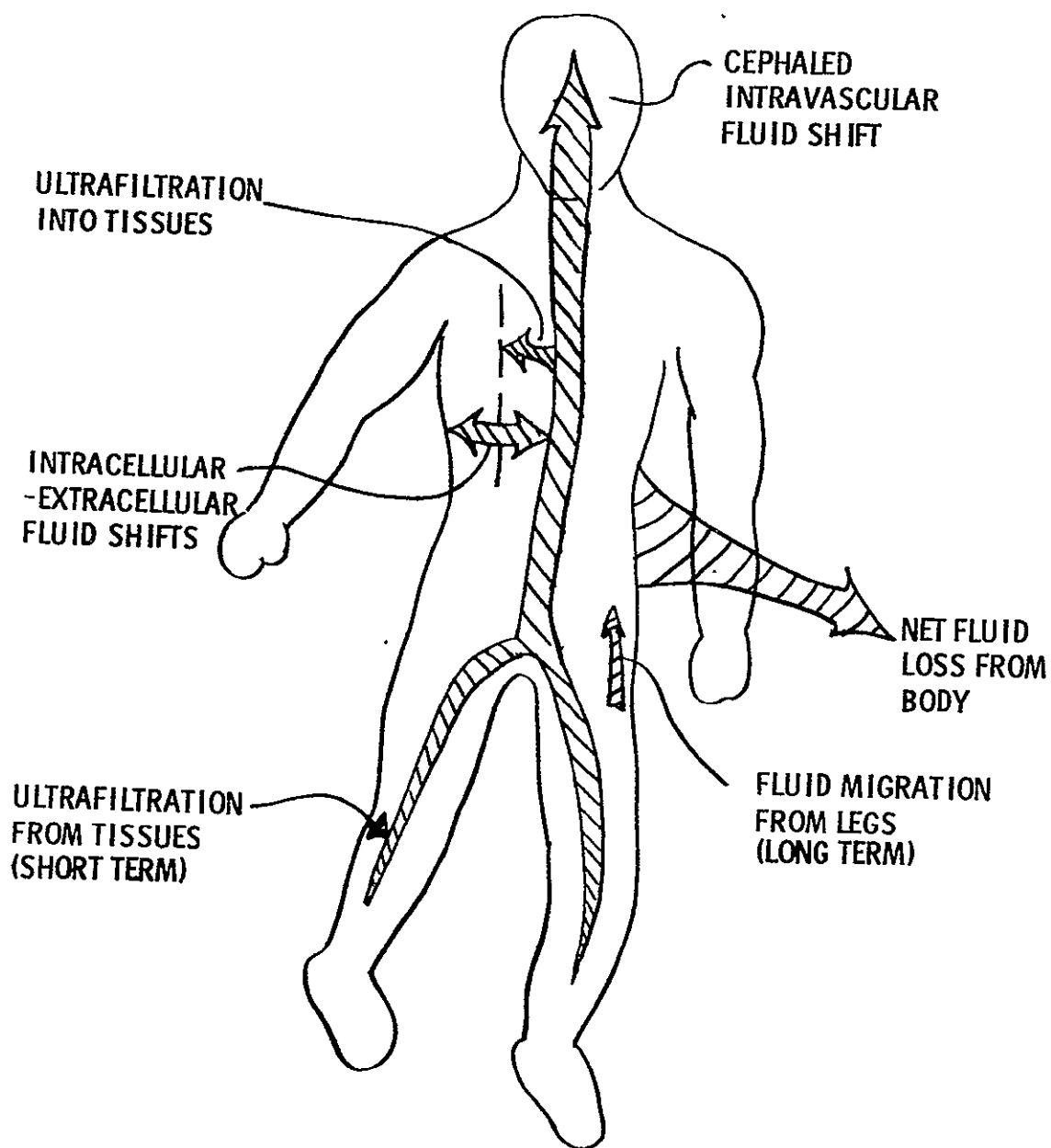
FIGURE 7.1

TYPES OF FLUID SHIFTS DURING WEIGHTLESSNESS SIMULATED
BY MODIFIED CIRCULATORY, FLUID & ELECTROLYTE MODEL

As we discovered in developing the whole-body algorithm, the more versatile the model becomes, the more difficult it becomes to validate. This arises out of the fact that validation of multiple stresses and responses entail careful assemblege of data from many different laboratories. While this poses some disadvantage it also emphasizes one of the primary benefits of this systems analysis approach: a quantitative model can become a framework into which many diverse kinds of experimental observations can be inserted — if the framework is sound, the responses to different stresses, acting singly, in sequence, or in combination, will all be appropriate.

7.2   RECOMMENDATIONS FOR FUTURE MODEL IMPROVEMENTS

There is little doubt that more realistic simulations of changes in or removal of orthostatic forces can be obtained with the gravity dependent Guyton model. Blood pressures and flows should stabilize at new levels within several minutes according to most studies. It is far easier to accomplish this in a model concerned only with a closed circulatory system, (Croston & Fitzjerrell, 1973) or with a minimum number of control elements (Snyder & Rideout, 1969). However, the Guyton model contains a circulatory system open to fluid transfer with adjoining compartments as well as with the external environment. In addition, it contains a large number of central and local control elements, both active and passive in nature which often oppose one another with effects that develop in periods of seconds to weeks (Guyton, et al, 1972). For the simulation of postural changes, a true steady-state in such a model cannot occur in a matter of 30 minutes and it is not likely that it ever occurs in man. Unfortunately, most data obtained during postural studies gives the erroneous impression that steady-state can be achieved rather quickly. Studies performed in the supine position during bed rest for

many weeks or in the erect posture for prolonged periods refute this notion. Thus, more realistic simulations will involve not only consideration of many complex factors of physiological regulation, but also a more complete description of the dynamic changes that occur in humans during both short term and long term orthostatic stress.

During the design and validation stages of the current study, it became apparent that the original model lacked many of the known or postulated mechanisms which become operative during postural change. Not all of these would be expected to produce greater orthostatic tolerance, but they could lead to a more faithful simulation and increased model flexibility for simulating other stresses such as bed rest. If bed rest can be considered a removal or attenuation of the effects necessary for activity in the erect position, it would be prudent to include into future models, capable of bed rest simulation, those elements for maintaining "normal, healthy" ambulatory function. This task is by no means easy and the recommendations discussed below are only a beginning in this direction.

Several of the more obvious elements have been already incorporated into this modified version. These include:

a)   a leg tissue compartment that can normally receive about a half liter of plasma during standing,

b)   a muscle contracting effect that decreases transmural pressure and decreases leg fluid pooling,

c)   valves in the leg veins that allows flow to move only toward the heart,

d)   passive distention effect at the leg veins affecting postcapillary resistance and decreasing leg filtration.

e)   autonomic and angiotensin effects on leg arteriolar resistance
     which limits flow to the legs, raises arterial pressure, and
     decreases capillary filtration.

These mechanisms have been previously discussed in this report.   In
addition, there are other suggested areas for model improvements
worthy of consideration.

Factors Affecting Venous Capacitance

It is clear that a more faithful simulation of tilt requires a greater
degree of compensatory venous return than was seen in these studies.
Venous return can be enhanced in the model or in man most effec-
tively by reducing capacitance of the central veins and perhaps leg
veins. (Increasing the effects on cardiac contractility or acceleration
have not been considered thus far in our studies, although this should be
reviewed at some later time). The mechanisms which are involved in
these changes arise from centrally mediated high pressure and low pres-
sure baroreceptors in the upper body, from vasoconstricting hormones,
and from local effects such as reverse stress relaxation and passive
elastic recoil. Contraction of the leg and abdominal musculature, con-
sidered also to be important compensatory reflexes to orthostatic pooling,
are probably mediated via central and local mechanoreceptors (Guyton,
1973; Hellenbrant and Franseen, 1943). Unfortunately, the relative con-
tribution of these various afferent and efferent pathways to reflex changes
in venous return and other orthostatic protective elements are not quan-
titatively known.

Observations on the behavior of the capacitance vessels in the
human have been restricted to the limbs, but even here inconsistent
results have been found during tilt studies (Shepherd & Van Houtte, 1975).
It is not possible at present to determine whether changes in splanchnic

C -2

blood volume are induced actively or passively, although this generally

is considered to be an important fluid source during acute hypovolemia

(Rowell, 1974).   Boyers, et al (1972), using a model for tilt simu-

lation, found it necessary to employ a low-pressure autonomic input

sensitive to central blood volume or pressure which acts, in part, on the

veins to enhance venous return.   Evidence for this effect is not yet strong

(Zollan, et al, 1972).   The current version of the Guyton model does not

include low pressure autonomic effects other than those used to influence

ADH release.   The tilt studies presented here have suggested a lack of

sufficient venous regulation during an orthostatic stress.   (This was also

noted by White in an early attempt to simulate postural changes with the

Guyton model (Croston, et al, 1974)).   Perhaps a new autonomic reflex

pathway, mediated by low pressure receptors which influence venous

resistance and capacitance, can be postulated and incorporated for future

evaluation.

Stress Relaxation of Veins

In the erect position, reverse stress relaxation takes place in the

large veins of the model following decrements of central blood volume.

This may occur more rapidly and intensively than heretofore suspected

according to recent evidence from Guyton's laboratory and others.

(Shoukas & Sagawa, 1973; Dress & Rothe, 1974).   Such an effect greatly

enhanced the present tilt responses.   Quantitative studies on the com-

pensatory effects of stress relaxation and stress relaxation recovery

following blood volume changes are meager (Guyton, et al, 1973).   It is

important to ascertain where in the circulation it occurs.   If stress

relaxation has an influence on the smaller leg veins it would act in a

direction to gradually increase blood pooling, as is known to occur during

standing.   In the present version of the model, the leg vein capacitance

is affected only by a small autonomic influence and not by stress relaxation. An updated algorithm for stress relaxation includ- ing these rapid effects is presently being considered for insertion into the model.

Pre- and Post-Capillary Resistance

Previous simulations with the Guyton model have led us to suggest that autoregulation effects (a mechanism which adjusts precapillary resistance to meet local oxygen demands) may be too strong and rapid in dampening peripheral resistance changes follow- ing intravascular fluid shifts either headward or feetward as occurs during postural changes. More recent studies on our part indicate that a more powerful influence on postcapillary resistance may be required rather than an attenuation of autoregulation. Evidence for this hypothesis is only suggestive. Nevertheless, it is important to note that venous capacitance and venous resistance changes are theoretically independent in the model, but not necessarily in the human vasculature. Thus, any changes in the model which effect autonomic influence on capacitance, such as discussed above, should also be considered for their influence on postcapillary resistance also. In addition, it is important to consider that under various conditions there may be a dissociation in the reflex changes of the (arterial) resistance and (venous) capacitance vessels due to competing control elements or perhaps redistribution of efferent autonomic signals. (Epstein, et al, 1968; Mellander, 1971). This was observed in the tilt response of this study where pre-post capillary resistance adjustments reversed the direction of inward filtration after a short

interval in accord with the experimental studies. More direct evidence of the direction of capillary filtration during tilt and LBNP is required; however, before these simulations can be accepted. (Foux, et al, 1976). The role of pre-/post capillary resistance takes on new importance in the Guyton model now that there are two distinct capillary beds. These elements have been implicated in the regulation of regional blood flow, number of patent capillaries, nutritional exchanges, plasma volume, and venous return.

Improved Leg Circulatory Elements

While the degree of fluid pooling in the legs appears to have been adequately simulated by the current model it should be realized that this is a preliminary study and that many factors which control fluid pooling, filtration and blood flow in the legs have not been included (Rushmer, 1970). Fluid pooling in legs during standing is known to be reduced by the leg muscle pump, venous valves, autonomic vasoconstriction and humoral (angiotensin) mechanisms as well as by a buildup of fluid pressure in the interstitium (Guyton, et al, 1973). All these effects have been included to some extent in the model. However, their mathematical representation was only estimated; quantitative data were mostly lacking. In addition, there is evidence for the presence of other major effects not presently included such as: a) catecholamine influence (Sundin, 1956), b) postural sway (Hellenbraut & Franseen, 1943), and c) myogenic vasoconstriction (Mellander, 1971). This latter effect acts in the face of high transmural pressures to increase pre-capillary resistance, induce sphincter closure and reduce filtration

area. Several other effects are detrimental to orthostatic tolerance
such as stress relaxation and passive distention of arteries and veins.
If long term studies are desired all these effects may be required. For
example, it has been suggested that postural sway and the venous pump
are responsible for maintaining orthostatic tolerance during prolonged
standing or minimal upright activity. This occurs by reducing fluid pool-
ing and leg venous pressures to very low values. However, this creates
the potential for a tremendous pressure gradient for flow between leg
arteries (which do not receive the full benefit of these effects) and veins
and would otherwise lead to a large drop in cardiac output (Rushmer,
1970). That this does not occur may be due to a locally produced vaso-
constriction, enhanced autonomic effects, chemical effects, or mechan-
isms not currently in the model. This effect must be strong enough to
compete with the powerful autoregulatory effects that attempt to maintain
flow. It is unfortunate that many of these effects which are only seen
during prolonged standing have not been more thoroughly investigated.
Most studies to date in the erect position are made on subjects during
passive tilt. An improvement in the leg muscle elements would do more
than enhance the tilt response. Because of the large mass of the skeletal
muscles, passive and active fluid mobilization, especially when reinforced
by the mechanical effect of muscle contraction, provides the potential
for large changes in capacity within the entire circulation during a wide
variety of stress conditions.

Leg Interstitial Compartment

· The leg interstitial compartment was modeled quite simply as a
water reservoir with a linear compliance. For the present effort this
appears to be adequate. However, absent from this formulation is a
lymphatic system, a tissue gel, colloids and a nonlinear compliance, all
of which are important elements of the upper bodh tissue fluid compart-
ment (Guyton, et al, 1971). Data are not available to model a completely

realistic distributed parameter interstitial compartment system. However, certain of the above elements, such as lymph ducts and colloids, can be introduced, if desired, for testing hypotheses regarding leg dehydration during prolonged bed rest.

Improvements in Endocrine Systems

This recommendation concerns improving the endocrine system of the Guyton model. The response to tilt of ADH, angiotensin, and aldosterone was in good agreement with available data. However, there are areas which can be immediately addressed that might improve responses to tilt and other stresses. First, it was noted that during the off transient to tilt, angiotensin did not fall as rapidly as it does in the tilt recovery of man (Oparil, et al, 1970). This was believed to be due, in part, to the arterial pressure response which was unrealistically low for a short period and, in part perhaps, to an inadequate description of the renal pressoreceptor releasing site of renin. Several model descriptions have recently become available that would assist in improving this response (Leutscher, et al, 1973; Blaime, et al, 1972). Secondly, the aldosterone algorithm of the Guyton model has been recently revised (R. White, private communication), and it is suggested that if feasible, it be incorporated into the NASA/GE gravity dependent model. Finally, data has recently appeared which may allow a revision of the ADH algorithm. This concerns the ADH response to immersion and a quantitative description of the relative influence of blood volume and osmolarity on ADH concentration (Epstein, et al, 1975; Dunn, et al, 1973). Unfortunately, there is still much conflict in the literature regarding the regulation and physiological role of ADH during postural changes both during short term and prolonged studies (Kimura, et al, 1976). It may be possible to reconcile some of these points with an integrated model.

Response to Hemorrhage

Simulations of hemorrhage have previously been performed by the authors using the original supine version of the Guyton model with generally disappointing results (unpublished observations). While short term fluid shifts appeared appropriate, gross indices of circulatory competency such as blood pressure and cardiac output suggested the lack of sufficient reflex compensation. Simulations of short term dehydration producing similar changes in plasma volume over longer periods of time confirmed that point of view. Attempts to improve these results with a revised stress relaxation formulation were only partially successful. In the present study, hemorrhage was again simulated with results that were somewhat more realistic in the erect but not the supine positions.

In supine man, as opposed to the model, moderate hemorrhage does not reduce mean arterial pressure or cardiac output significantly. Although the protective mechanisms involved in this reaction are not clearly understood, it is believed that low pressure pressoreceptors are involved (Shepherd & Van Houtte, 1975). These sensors located in the venous circulation would be expected to first detect small changes in blood volume. The previously discussed recommendations of adding a low pressure autonomic influence and an improved stress relaxation element to the model in order to improve the tilt response would undoubtedly aid in the hemorrhages of the thoracic volume. Until the relative importance of high versus low pressure baroreceptor influence in these conditions is more clearly defined, any proposed mechanism should be considered as only suggestive.

While these changes would lead to improvements in the short term response, recent studies of the hemorrhage reaction present data for the longer term endocrine control over intracellular-extracellular fluid shifts which would be suitable for mathematical description in the current model (Pirkle and Gann, 1975).

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APPENDIX

DESCRIPTION OF MODIFIED RED BLOOD CELL PRODUCTION ALGORITHM

The mathematical description of this algorithm in FORTRAN notation is presented on the following page as it appears in the modified Guyton model.

Line 1:   Calculation of renal vein oxygen saturation (OVR) based on a delayed approach to its equilibrium value. The product 1.2*OVA represents renal blood flow (assumed constant at 1.2 liters/min) times the volume of oxygen per liter (OVA) and is the rate of oxygen delivery to the renal vein tissue cells. These cells are the assumed site for erythropoietin release governing red cell production in the bone marrow. Subtracting the rate of oxygen delivery to the tissues (DOR) gives the rate of oxygen delivery to the veins. Dividing this by a term representing the rate of arterial oxygen delivery to the tissues (HM*6.0) gives a ratio of oxygen in veins to maximum oxygen capacity of blood which is the fractional oxygen saturation of hemoglobin after equilibrium has been established. The other terms in the equation are delay mechanisms with the constant Z7 controlling the time constant.

Line 2:   Renal vein oxygen partial pressure (RPO) is obtained from the fractional oxygen saturation of venous blood (OVR) using a function POX which is an accurate description of the standard oxy-hemoglobin saturation curve.

Lines 3-4:   Calculation of the diffusion resistance of oxygen from venous capillaries to cells (ROR) assuming that a far greater number of capillaries open up and the resistance decreases as the renal tissue pO_2 (TPO) falls below normal.

Line 5:   Calculation of the rate of delivery of oxygen from renal capillaries to renal tissue cells (DOR) by multiplying the partial oxygen pressure difference between oxygen in tissue capillaries (RPO) and pressure of oxygen in the tissue cells (TPO) times a constant (PPZ) and dividing by the resistance for diffusion of oxygen (RPO).

Line 6:   Calculation of the actual total quantity of oxygen accumulated in the renal cells (QOR) by integration of the rate of accumulation of oxygen in the tissue cells. This rate is determined by subtracting the rate of utilization of oxygen in the cells (assumed constant at 20 ml 0_2/min) from the rate of delivery of oxygen to cells (DOR).

Line 7:   Calculation of tissue cell pO_2 (TPO) from quantity of oxygen accumulated in the cells (QOR) by multiplying QOR times an effective solubility coefficient.

Line 8-14:   Red cell production (RC1) is determined by the product of tissue oxygen partial pressure (TPO) subtracted from a set point (at which no red cell production occurs) times a gain constant (POY). Normal red cell production occurs at a value of TPO of 20 mm Hg. The function curve relating RC1 and TPO is nonlinear. For values of TPO greater than normal lines 12-13 are used, and for values of TPO less than normal lines 9-10 are used.

Line 15:   Calculation of maximum red cell production (RMX) based on the fact that this value is approximately six times normal.

Lines 16-17:   Red cell production is restricted to values above zero and below RMX.

Line 18:   Calculation of red cell destruction (RC2) based on law of mass action which assumes rate of disappearance is a product of red cell mass (VRC) times a clearance constant (RKC).

Lines 19-20:   Production rate (PRC) and destruction rate (DRC) of red cells are converted to ml/day to aid printout interpretation.

Line 21:   Calculation of net rate of red cell production (RCD) by subtracting the rate of destruction (RC2) from the rate of production (RC1) and adding or subtracting gain or loss rates due to blood infusion or hemorrhage (RC1).

Line 22:   Calculation of red cell mass (VRC) by integrating the net rate of red cell production (RCD).

NEW FORTRAN ALGORITHM FOR RED BLOOD CELL PRODUCTION

```
Line No.    C
            C    P02 at Renal Detector for RBC Production
            C
  1         OVR=OVR+((1.2*OVA-DOR)/(HM*6.0) - OVR)/Z7
  2         CALL POX(OVR,RPO)
  3         ROR=TPO**3.
  4         IF(ROR  .LT.  50  ) ROR=50.
  5         DOR=(RPO-TPO)*PPZ/ROR
  6         QOR=QOR+ (DOR-20.)*(1.-EXP(-1/24))
  7         TPO=QOR*.0625
            C
            C    Red Blood Cells
            C
  8         IF(TPO .GT. 20.) GO TO 172
  9         PO2=21.6-TPO
 10         RC1=POY*PO2
 11         GO TO 174
 12   172   PO2=2C.42-TPO
 13         RC1=3.6381 E-05*PO2
 14   174   CONTINUE
 15         RMX=6.*(21.6-20.)*POY
 16         IF(RC1 .GT. RMX)  RC1=RMX
 17         IF(RC) .LT.  0.0)  RC1 = 0.0
 18         RC2=RKC*VRC
 19         VV1=RC1*1000.*1440.
 20         VV2=RC2*1000.*1440.

 21         RCD=RC1-RC2+RC1
 22         VRC=VRC + RCD*1
            C
```