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STUDY REPORT

ON

COMBINING DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS WITH SUBSYSTEM AND WHOLE-BODY SIMULATION

June 30, 1975

Prepared by

S. Furukawa, M. D.

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1.0 BACKGROUND AND INTRODUCTION

Since the inception of this project, many existing mathematical models of major physiological subsystems have been identified and simulation models have been developed, modified, and validated. Several new models have also been developed and tested in this program. This contract encompasses the first version of the whole-body algorithm which integrates these subsystem models to study major physiological interactions. Recent modeling activity has been to assemble, develop, and integrate physiological models and to collect pertinent literature from the last few years. One natural evolution from this point is the consideration of possible applications of simulation models in diagnosis and therapeutics.

This report presents the highlights of current development of models for clinical applications and results of related research studies. Since the major emphasis of this contract has been development, assembly, and integration of simulation models of various physiological subsystems, the application of these models for diagnostic and therapeutic problems is in a very early stage. A few clinical areas, however, have been studied and are discussed in the following sections.

2.0 CURRENT APPLICATIONS OF SIMULATION MODELS FOR CLINICAL RESEARCH

In reviewing applicable literature, it is clear that various physiopathological states have been studied by many investigators, but their selection of subjects, healthy or ill, are random and, of course, are limited to the specific regulation/control responses in one or a few body subsystems of interest to the investigation. The application of models to the circulatory system was selected here.

2.1 CIRCULATORY MODELS FOR CLINICAL RESEARCH

2.1.1 Tilt Model Simulation of Orthostatic Intolerance with Hemorrhage

Despite extensive research, the causes of many common disturbances of the human circulation remain obscure. The events leading to changes in blood pressure are not completely understood even for simple changes in posture. Recent space flights of long duration causing extended exposure to a weightless environment, and the resultant orthostatic fall in blood pressure upon reentry have renewed interest in gaining a better understanding of the underlying mechanisms of this phenomenon. The same orthostatic intolerance has been observed on first standing after prolonged bed rest. Computer simulation of the circulation and its controls permits a more rigorous analysis of these mechanisms.

The force of gravity causes blood to pool in the lower body (Gauer (1963(b)) which causes a transient fall in pressure to be sensed at the baroreceptors in the carotid artery and the aortic arch. When the pressure falls at the baroreceptor, the sensory nerves will decrease firing and there will be increased stimulation of the sympathetic fibers with decreased stimulation of the vagal fibers. This autonomic activity will produce vasoconstriction, increased heart rate, an increase in

stroke volume, and an increase in peripheral resistance (see Figure 1). The increased arteriolar resistance acts to restore arterial pressure as discussed by Henry (1955) and thus, a new steady-state is reached. Sjostrand (1952) indicates that stroke volume is dependent on cardiac filling, which responds to the decrease in central blood volume because of the legward shift due to gravity, and to a lesser extent on autonomic activity. The stroke volume is decreased due to the reduced central blood volume more than the heart rate is increased by the autonomics and the result is a decrease in blood pressure. It can be seen that without the autonomic reflex actions to restore cardiac output and increase peripheral resistance and thus restore arterial pressure through the baroreceptor feedback loop, the system would become unstable and one would probably faint every time the upright posture was assumed. All of these essential compensations depend on actions of the autonomic nervous system, which responds to the depletion of central blood volume and to a transient fall in arterial pressure. The model's response to a change in posture from supine to upright (see Figures 2 through 4 for normal blood volume) resembles the behavior of the human system as shown in Table 1.

It has been observed that there is a moderate decrease in total blood volume after extended exposure to a weightless environment or prolonged bed rest (Berry (1967), Gauer (1963), and Waterfield (1931) . This may be due to increased capillary filtration out of the central blood volume due to the increased pre-capillary pressure as a result of the headward migration of blood which occurs with the removal of the gravity force in the lower body and an observed reduction in red cell mass. The orthostatic intolerance which results after such exposure can then be simulated by a reduction in total blood volume (slow hemorrhage). The model's response to an upright tilt after a one

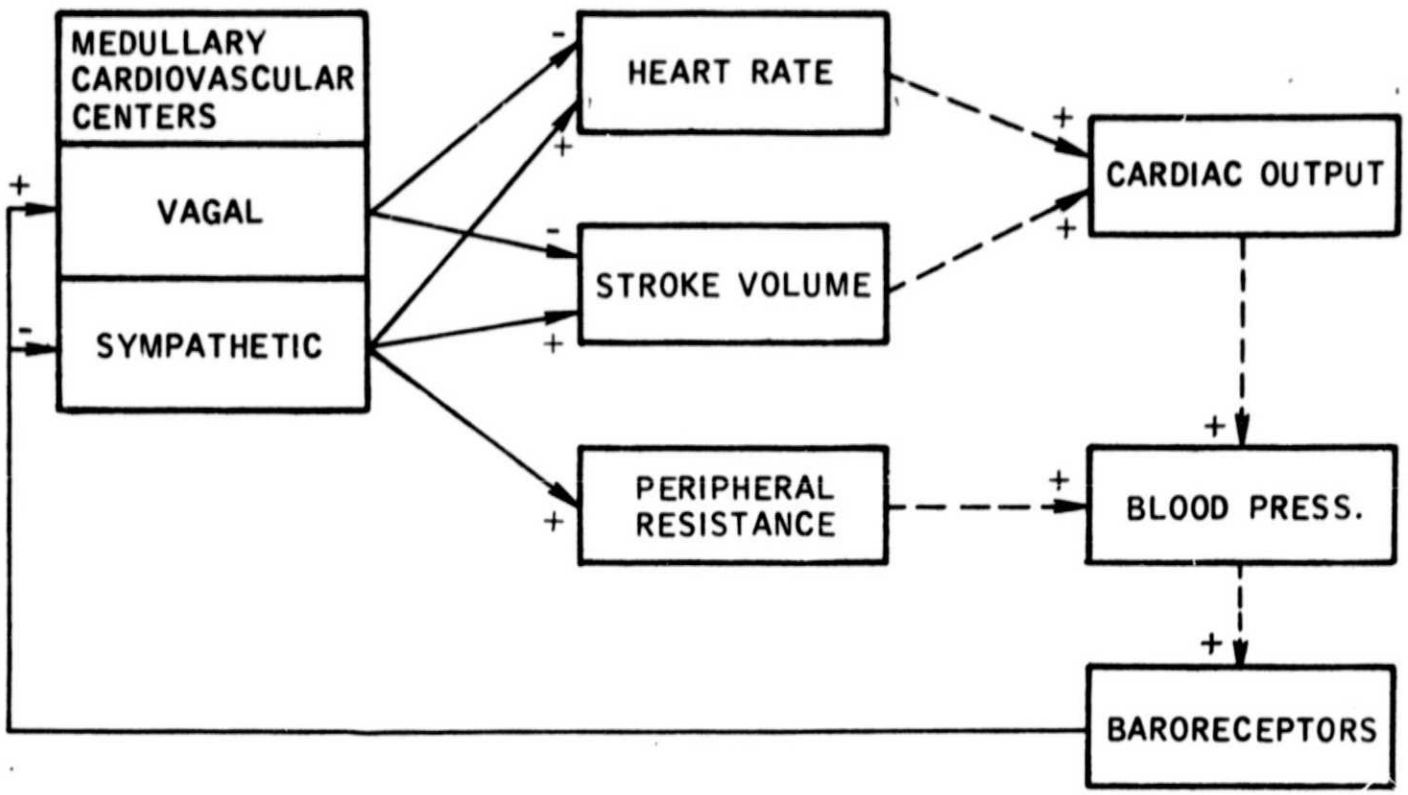


FIGURE 1. BLOCK DIAGRAM REPRESENTING BARORECEPTOR AND AUTONOMIC RESPONSE TO A CHANGE IN BLOOD PRESSURE

TABLE 1. TILT MODEL SIMULATION RESULTS COMPARED TO EXPERIMENTAL DATA FOR PASSIVE UPRIGHT TILT BEFORE AND AFTER ONE LITER HEMORRHAGE

	SUPINE-NORMAL B.V.		CHANGE AFTER 90° TILT (NOR. B.V.)		SUPINE - AFTER ONE LITER HEMORRHAGE	
	MODEL RESULTS	EXPERIMENT DATA*	MODEL RESULTS	EXPERIMENT DATA*	MODEL RESULTS	EXPERIMENT DATA*
MEAN ARTERIAL PRESSURE (mm Hg)	87	100	+5.0	-5 TO +5	79	85 TO 100
CARDIAC OUTPUT (liters/min)	6.6	5.86	-.4	-.86	5.5	4.5 TO 6.0
HEART RATE (beats/min)	63	64	+12.5	+16.0	71	65 TO 90
STROKE VOLUME (ml)	106	92	-23	-28	78	60 TO 90
LOWER BODY BLOOD VOL (ml)	500**	1400	+380**	+700	470	-
TOTAL BLOOD VOLUME (liters)	5.0	5.7	0	0	4.0	4.7

* EXPERIMENTAL DATA FROM REFERENCES Gauer (1963) Weissler (1957), Wright (1965), Shenkin (1944), and Warren (1945).

** MODEL LOWER BODY VOLUME INCLUDES ONLY THE LEGS

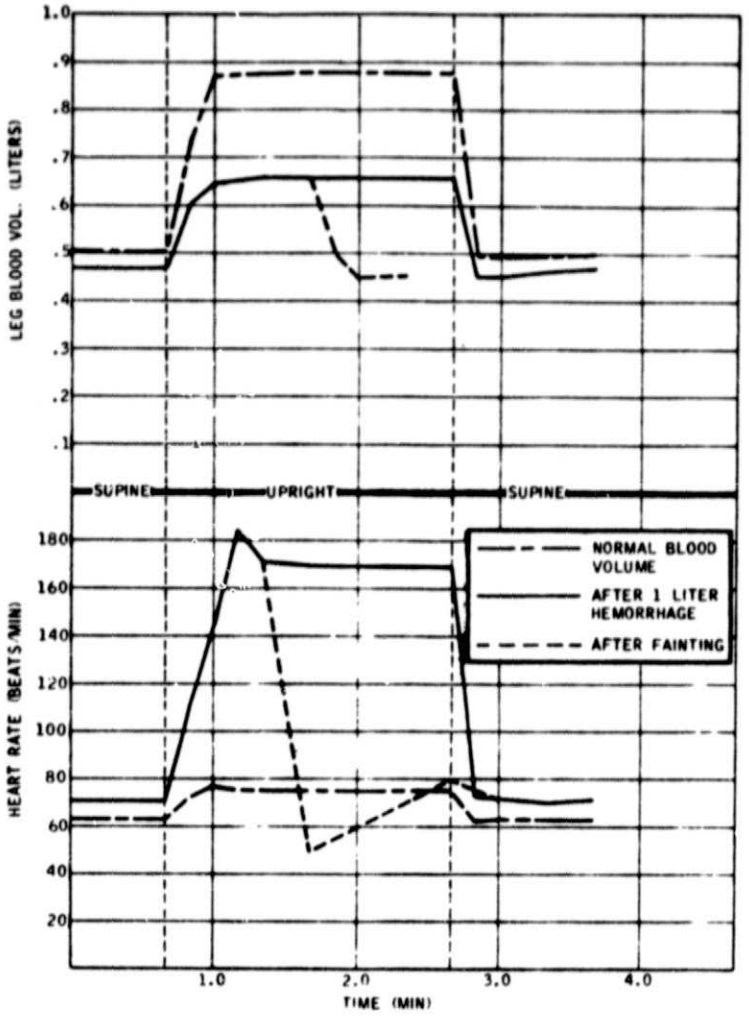


FIGURE 2. TILT MODEL OUTPUT OF LEG BLOOD VOLUME AND HEART RATE FOR UPRIGHT TILT SIMULATION BEFORE AND AFTER ONE LITER HEMORRHAGE

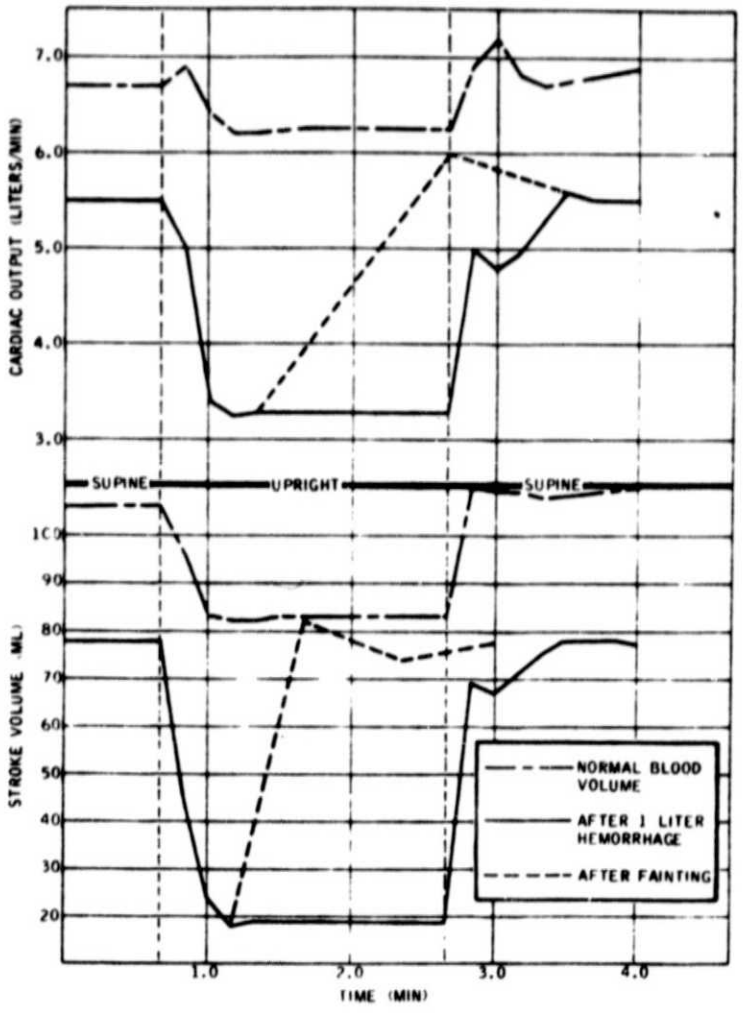


FIGURE 3. TILT MODEL OUTPUT OF CARDIAC OUTPUT AND STROKE VOLUME FOR UPRIGHT TILT SIMULATION BEFORE AND AFTER ONE LITER HEMORRHAGE

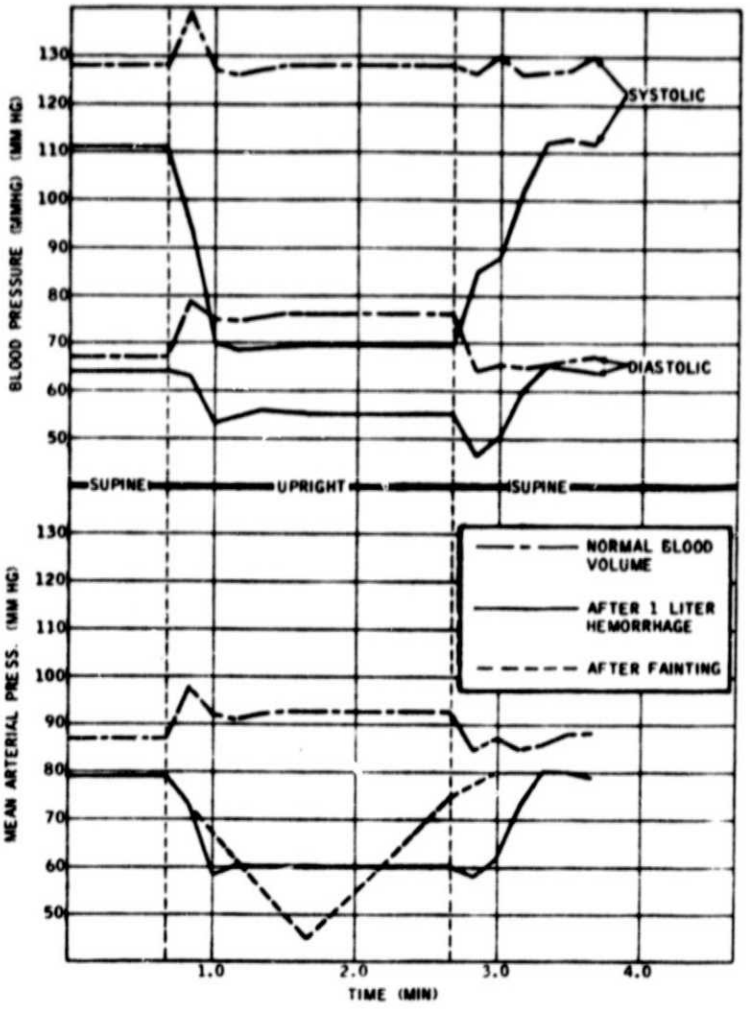


FIGURE 4. TILT MODEL MODEL OUTPUT OF BLOOD PRESSURE AND MEAN ARTERIAL PRESSURE FOR UPRIGHT TILT SIMULATION BEFORE AND AFTER ONE LITER HEMORRHAGE

liter blood loss is compared to the normal blood volume case in Figures 2 through 4. After removal of one liter of blood, the central and peripheral compartments are depleted proportional to their compliances. In the supine position (compare pre-tilt values) after this blood loss, the autonomic reflexes are able to maintain arterial pressure while venous return and cardiac output are moderately reduced (see Table 1). The system shows good stability so long as the recumbent posture is maintained. If the subject attempts to stand after the loss of one liter of blood, central blood volume becomes critically depleted (note the drastic reduction in stroke volume) and the blood pressure becomes dangerously low. This condition is often more than can be compensated for by the autonomics, and vasodepressor syncope (Weissler (1957)) results. These results agree with the observations of Shenkin (1944) in men who lost one liter of blood. Half of the subjects maintained a stable cardiac output and arterial pressure after loss of one liter of blood. Other subjects showed effects ranging from quickening pulse to premonitory symptoms of fainting.

The model can also be used to examine more complex circulatory reactions to stress and various changes in autonomic control (such as changes in contractility of the heart, increased baroreceptor sensitivity, increased peripheral resistance response, changes in venous tone, and combinations of the above).

2.1.2 Long Term Circulatory Regulation

Most of the basic circulatory models used in experimental applications have utilized a basic closed-loop flow system with no leaks in order to describe various facets of circulatory function. This kind of approach can be justified when the challenge being simulated is acute (1-15 min.), but when longer duration simulations are required, a large

number of other regulatory mechanisms must be included in order to describe overall circulatory control, even in a crude way. An initial attempt to model the major components involved in long term circulatory regulation has been made by Guyton, et al(1972), and this analysis has proved to be so useful in such a variety of different situations that the significant features of this long term model will be presented here.

Detailed flow charts and model explanations are available (Guyton et al (1972), Guyton et al (1973), White (1973), White (1974)) and will not be repeated. The systemic circulation is represented by the five-compartment model shown in Figure 5. In this figure, the abbreviations used are arterial volume (VAS); venous volume (VVS); right atrial volume (VRA); pulmonary arterial volume (VPA); pulmonary venous and left atrial volume (VLA); pulmonary vascular resistance (RPT); non-muscle, non-renal vascular resistance (RSN); muscle vascular resistance (RSM); renal resistance (RR); and large vein resistance (RVG). This model is similar to that pictured in Figure 6 except that parallel capacitive beds are not considered, but parallel flows are included. The model utilizes similar basic cardiac function curves as well, but includes the effects of autonomic stimulation, arterial pressure afterload, and cardiac hypertrophy or degeneration on the pumping ability of the heart. The unstressed volumes of each capacitive region are controlled by the level of angiotensin II in the blood, the level of autonomic stimulation, and by the pressure in the region (through stress relaxation). The flow resistances are controlled by a combination of local effects and hormonal effects. The oxygen transport features of the circulation are present and hematocrit and red cell control are considered. This circulation is not closed, but "leaks" through the capillaries, "excretes" through the kidneys, and "drinks" directly into the blood. The blood, composed of plasma (with dissolved proteins and

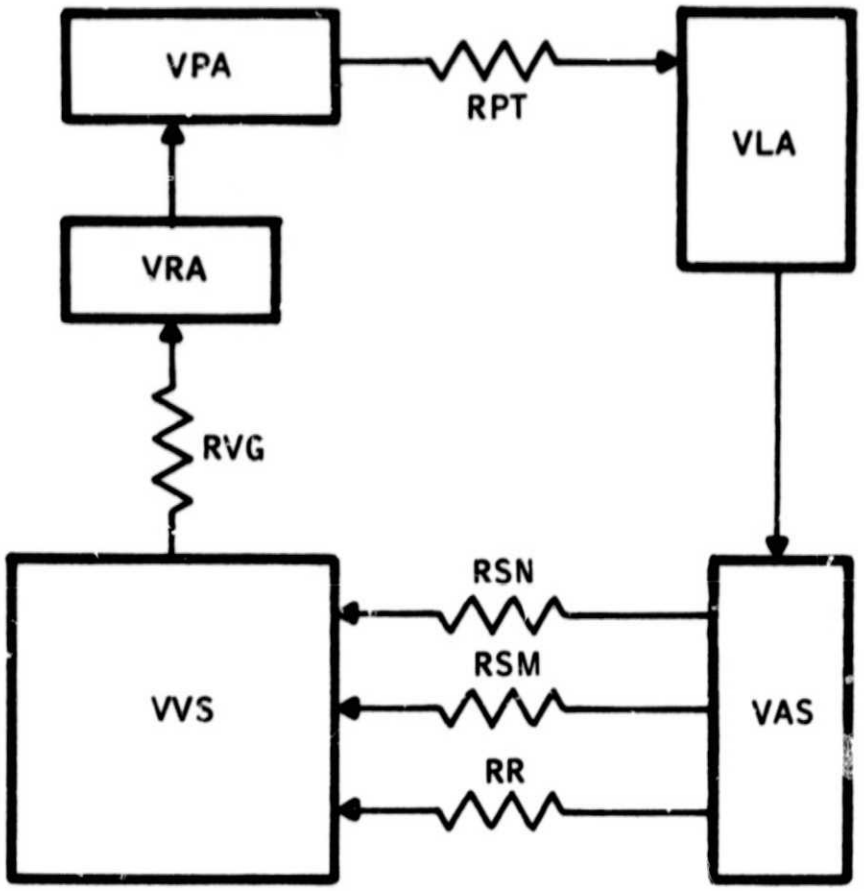


FIGURE 5. SYSTEMIC CIRCULATION MODEL CONTAINED IN LONG TERM CIRCULATORY MODEL

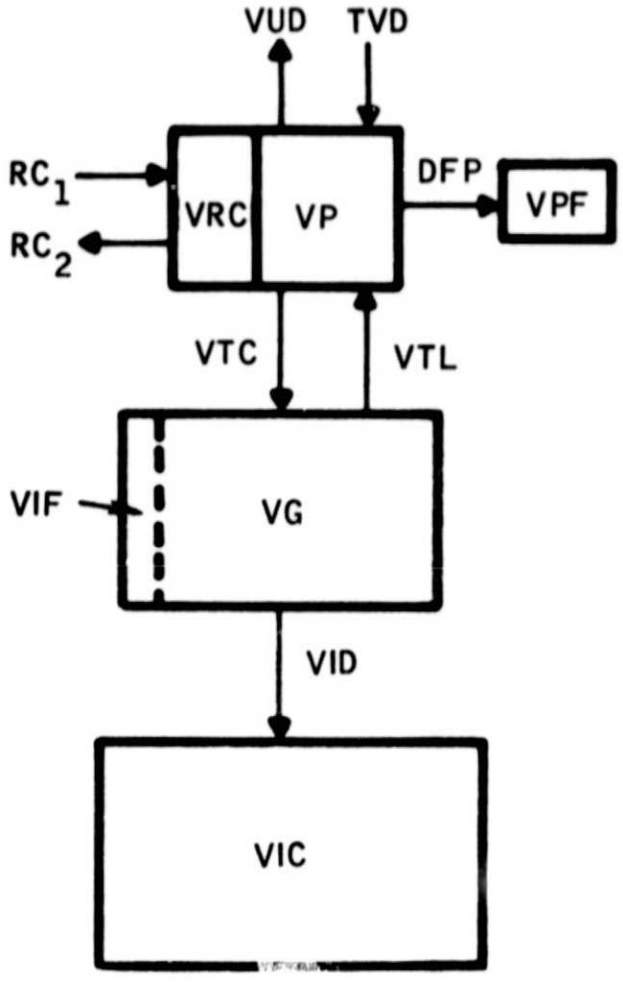


FIGURE 6. FLUID CONTAINING RESERVOIRS OF LONG TERM MODEL. FROM WHITE & CROSTON (1974).

electrolytes) and red cells, thus serves as a filterable fluid and Figure 6 illustrates the fluid containing reservoirs of the model. The symbols on this figure represent plasma volume (VP), red cell volume (VRC), interstitial gel volume (VG), free interstitial fluid volume (VIF), cell fluid volume (VIC), pulmonary fluid volume (VPF), water intake rate (TVD), urinary output rate (VUD), red cell production rate (RC1), red cell destruction rate (RC2), rate of capillary filtration (VTC), lymph flow rate (VTL), and the rate of fluid flow into the cells (VID). The capillary filtration rate is determined from a whole-body version of Starling's relationship which states that net filtration pressure is equal to capillary pressure, plus tissue colloid osmotic pressure, minus interstitial fluid pressure, and minus plasma colloid osmotic pressure. Protein is produced and lost by the body and is distributed between the interstitial space and the plasma.

Although the above description is far from complete, even for the present rather crude model, it illustrates the variety of component systems necessary for long term circulatory control. In fact, at least eight major pressure control mechanisms are present in this model. These are the baroreceptor mechanism, the chemoreceptor mechanism, the central nervous system ischemic response mechanism, the mechanism of stress-relaxation, the capillary fluid shift mechanism, the renin-angiotensin mechanism, the renal-body fluid control mechanism, and the aldosterone control mechanism. One way of characterizing the effects of these different control system of arterial pressure is through the feedback gains which occur as a result of a given pressure disturbance. Figure 7 illustrates a preliminary attempt at such a characterization (Guyton et al (1972b)), The solid portions of these curves are based on experimental results, while the dashed portions are extrapolations and are somewhat hypothetical. Note that the gains fall into three general categories. First, the three nervous control mechanisms act very quickly (within seconds on the

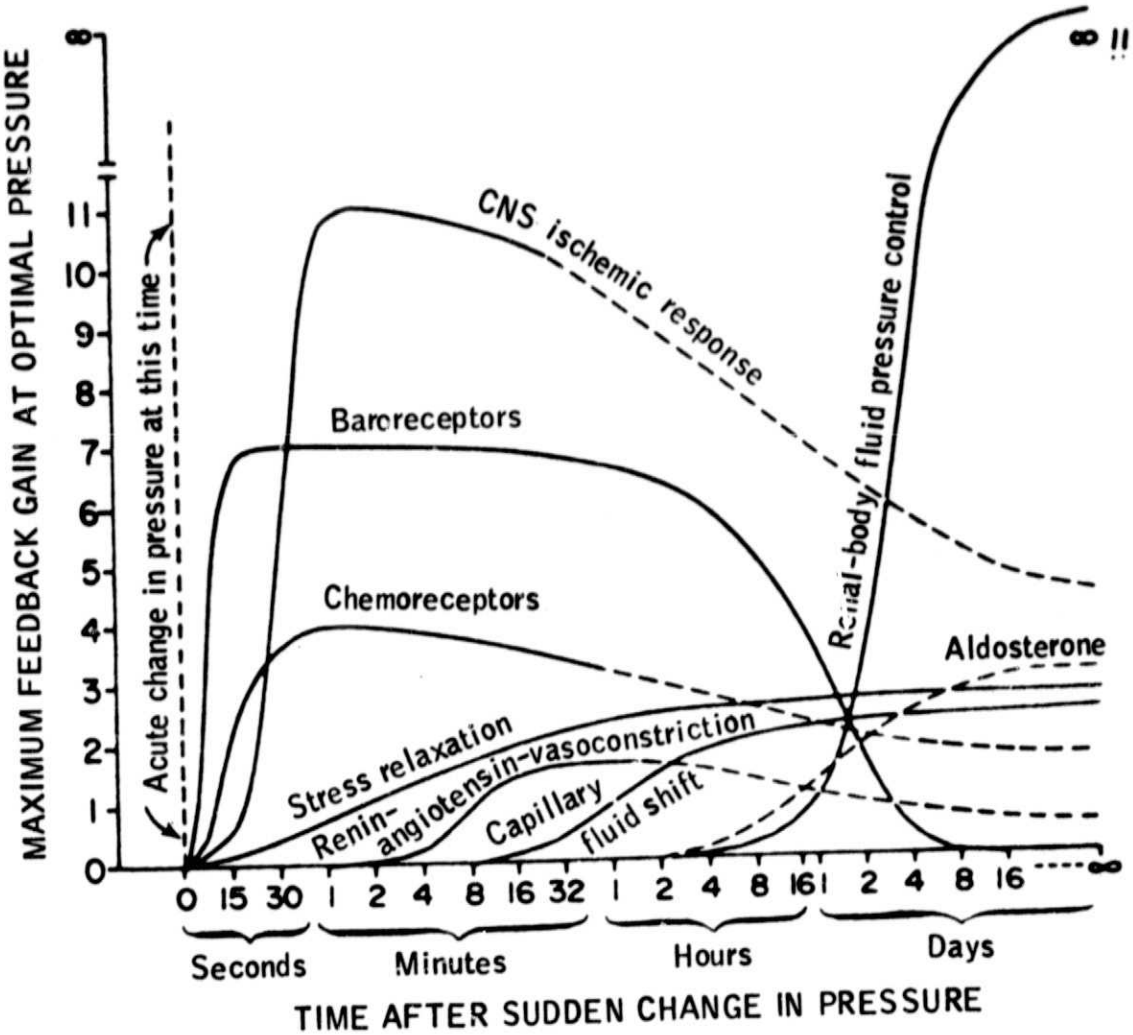


FIGURE 7. FEEDBACK GAINS OF SOME PRESSURE REGULATORY MECHANISMS. FROM GUYTON et al (1972b)

essentially logarithmic abscissa). Then several mechanisms (stress-relaxation, renin-angiotensin, and fluid shift) begin to act only after a few minutes and reach full development within a few hours. Finally, the renal-body fluid mechanism and the aldosterone control mechanism require hours to days to affect arterial pressure maximally. A remark is in order on the nature of the gains quoted in Figure 7. Each of these represent a single system result; i.e., all systems except the one in question are presumably not responding to the stimulus. Thus, gains listed are only indicative of (not a measure of) expected in vivo responses. For example, the infinite gain characteristic of the renal-body fluid system (which implies an integral controller with a physiologically fixed set point) only occurs if fluid intake (net drinking) is absolutely normal and if the renal function curve, which relates arterial pressure to urinary output rate, remains absolutely normal. If such is not the case, the gain may be high, but is not infinite. In spite of the somewhat hypothetical nature of the gain curves, they are useful as a means of categorizing both the relative speed and effectiveness of the pressure regulating mechanisms of the body.

Simulation of more pathological states and some therapeutic examples are illustrated in the following. Figures 8 - 13 illustrate typical experiments simulated with this model. These figures show the diversity of simulations which this large, though simple, model is capable of performing. Figure 8 illustrates the results obtained by a 2-liter infusion of isotonic saline into an effectively nephrectomized subject (infusion rate = 67 ml/min.). Figure 9 pictures the development of hypertension in a renal deficient subject during salt loading. Figure 10 shows a simulation of Goldblatt hypertension following a renal arterial clamp. Figure 11 illustrates the effects of plasma protein deficiency (hypoproteinemia) on circulatory function. Figure 12 shows the simulation of circulatory changes following opening and subsequent closing of a massive arteriovenous fistula. Figure 13 pictures the development of (bilateral)

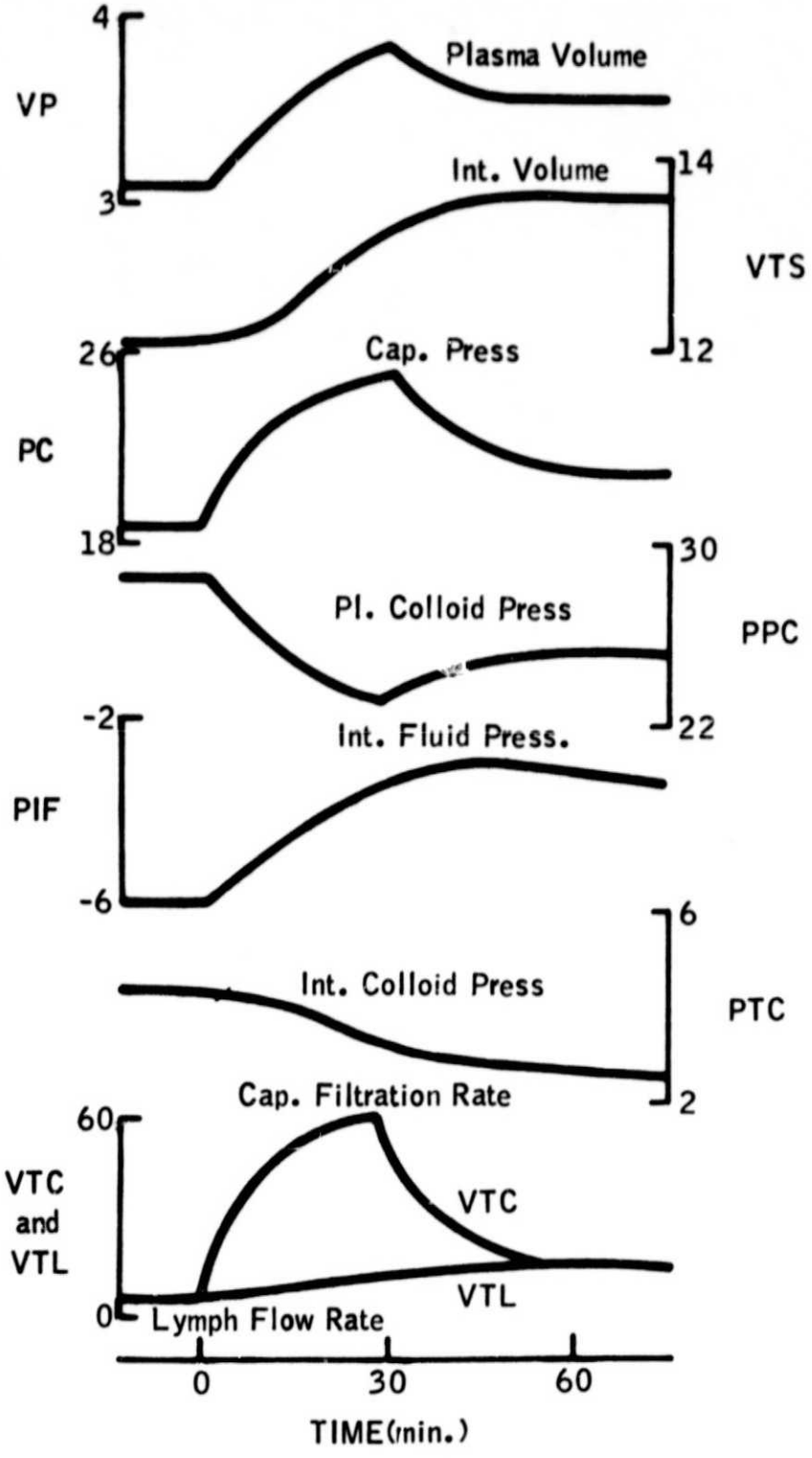


FIGURE 8. ISOTONIC SALINE TRANSFUSION SIMULATION FROM WHITE & CROSTON (1974).

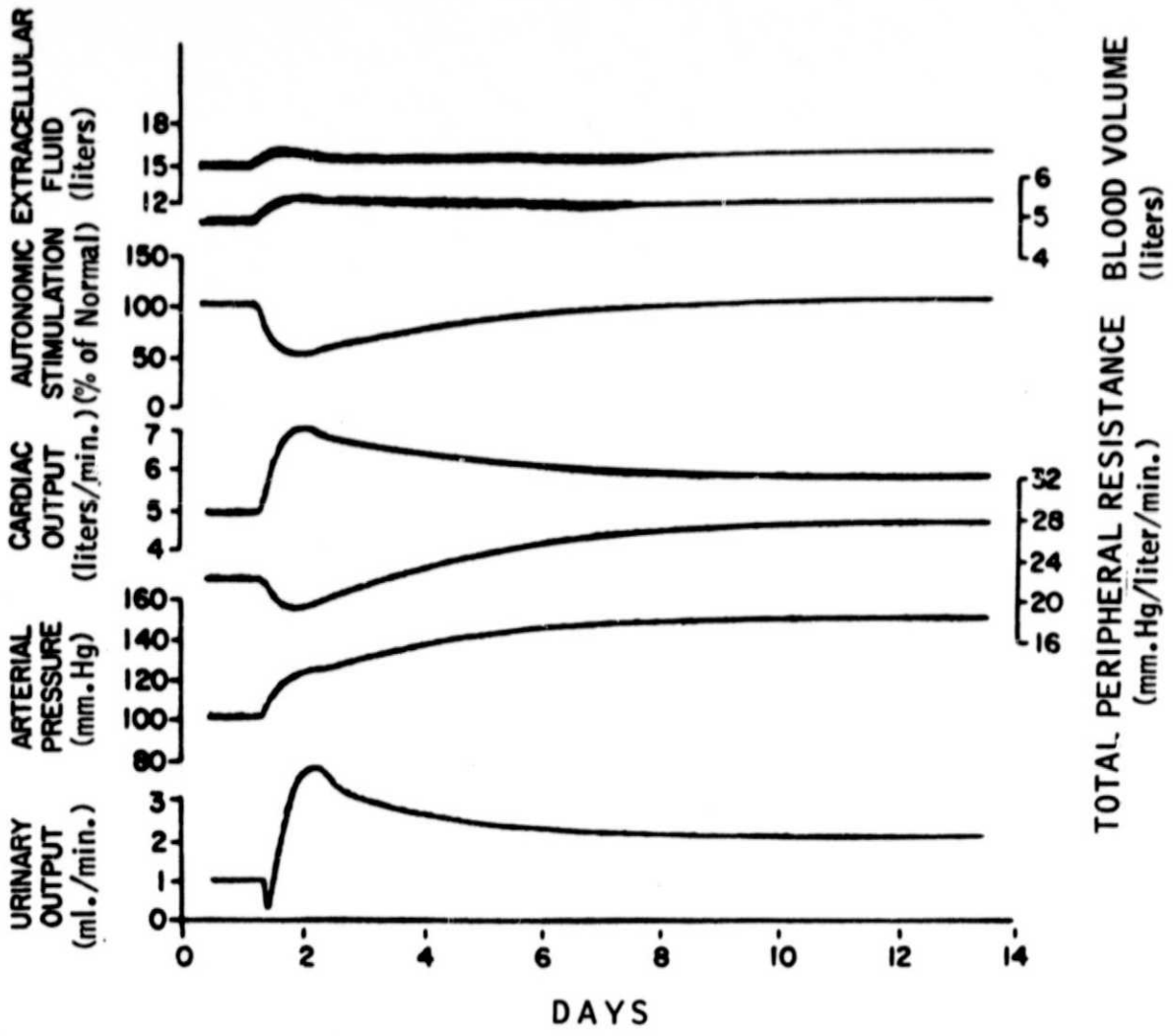


FIGURE 9. SIMULATION OF HYPERTENSION DEVELOPING DURING SALT LOADING OF RENAL DEFICIENT SUBJECT. FROM GUYTON et al (1972).

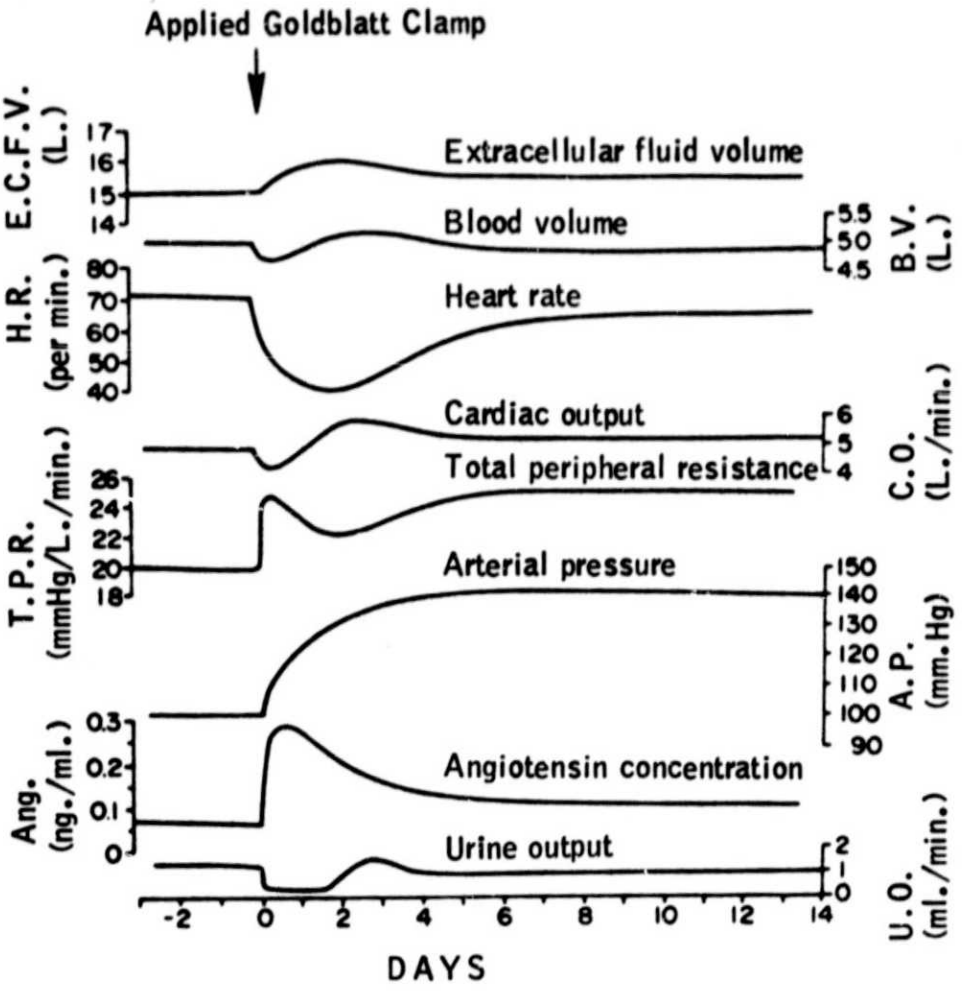


FIGURE 10. SIMULATION OF GOLDBLATT HYPERTENSION. FROM GUYTON et al (1973b).

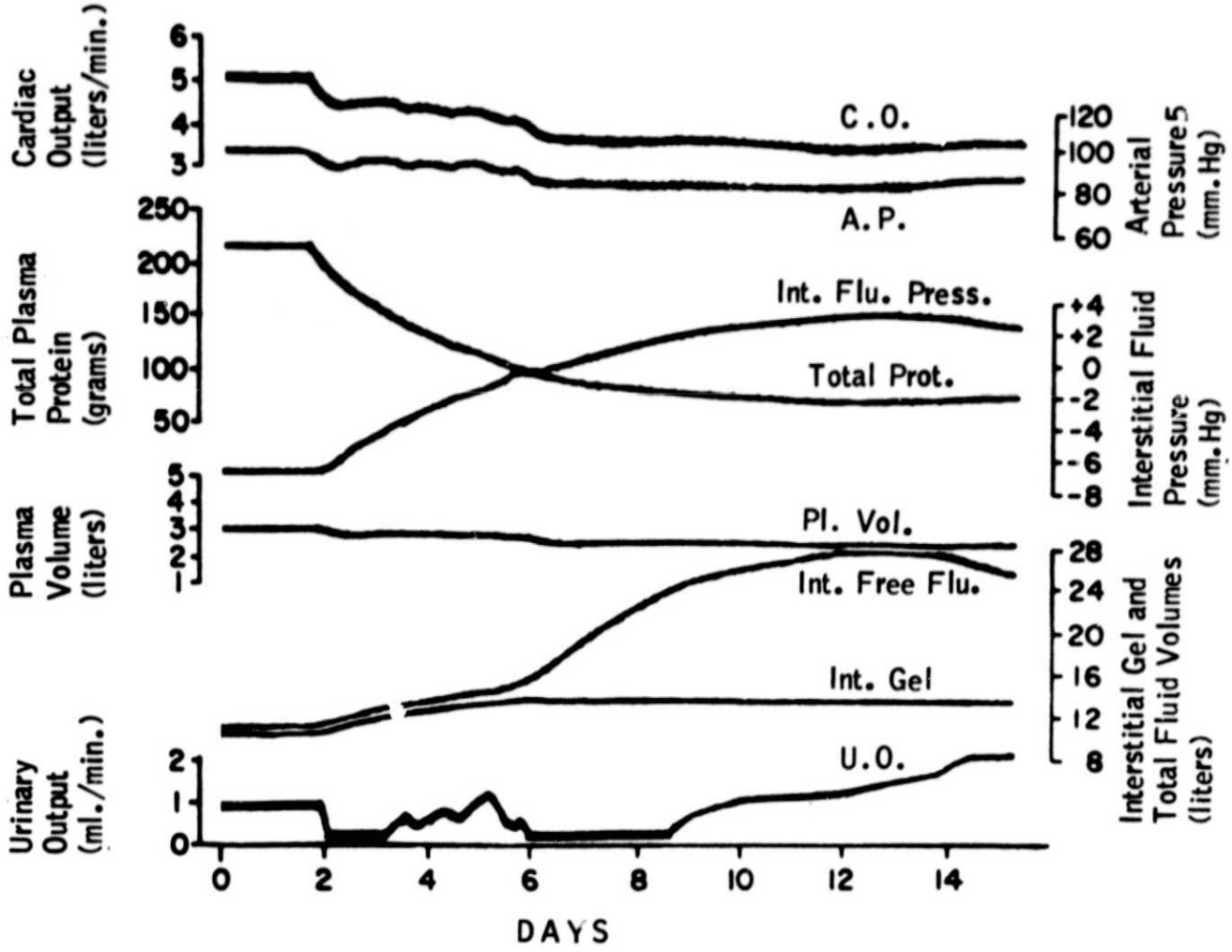


FIGURE 11. SIMULATION OF THE CIRCULATORY EFFECTS OF PROGRESSIVE HYPOPROTEINEMIA. FROM GUYTON et al (1972).

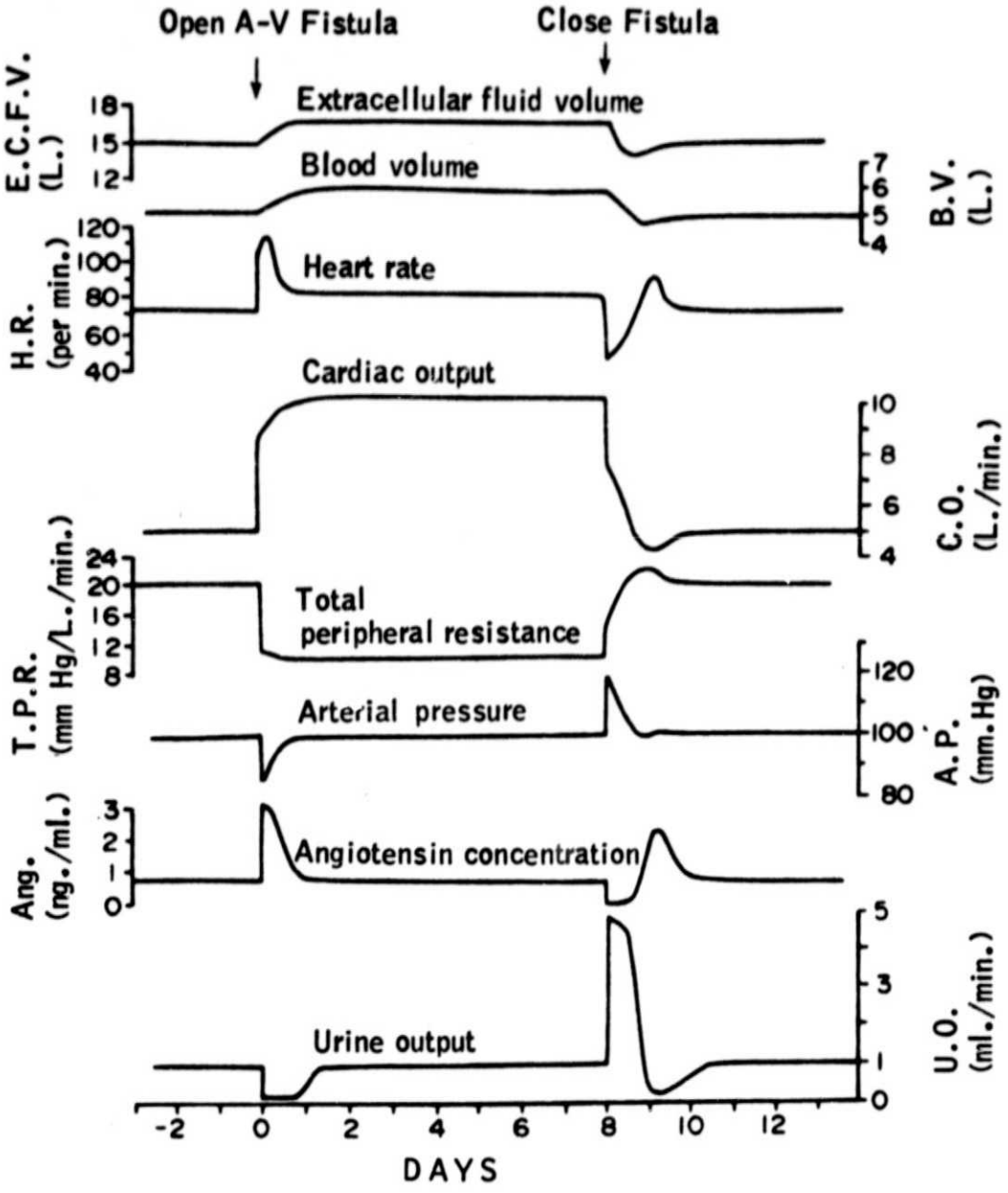


FIGURE 12. SIMULATION OF CIRCULATORY FUNCTION FOLLOWING OPENING AND SUBSEQUENT CLOSING OF A-V FISTULA. FROM GUYTON et al (1973).

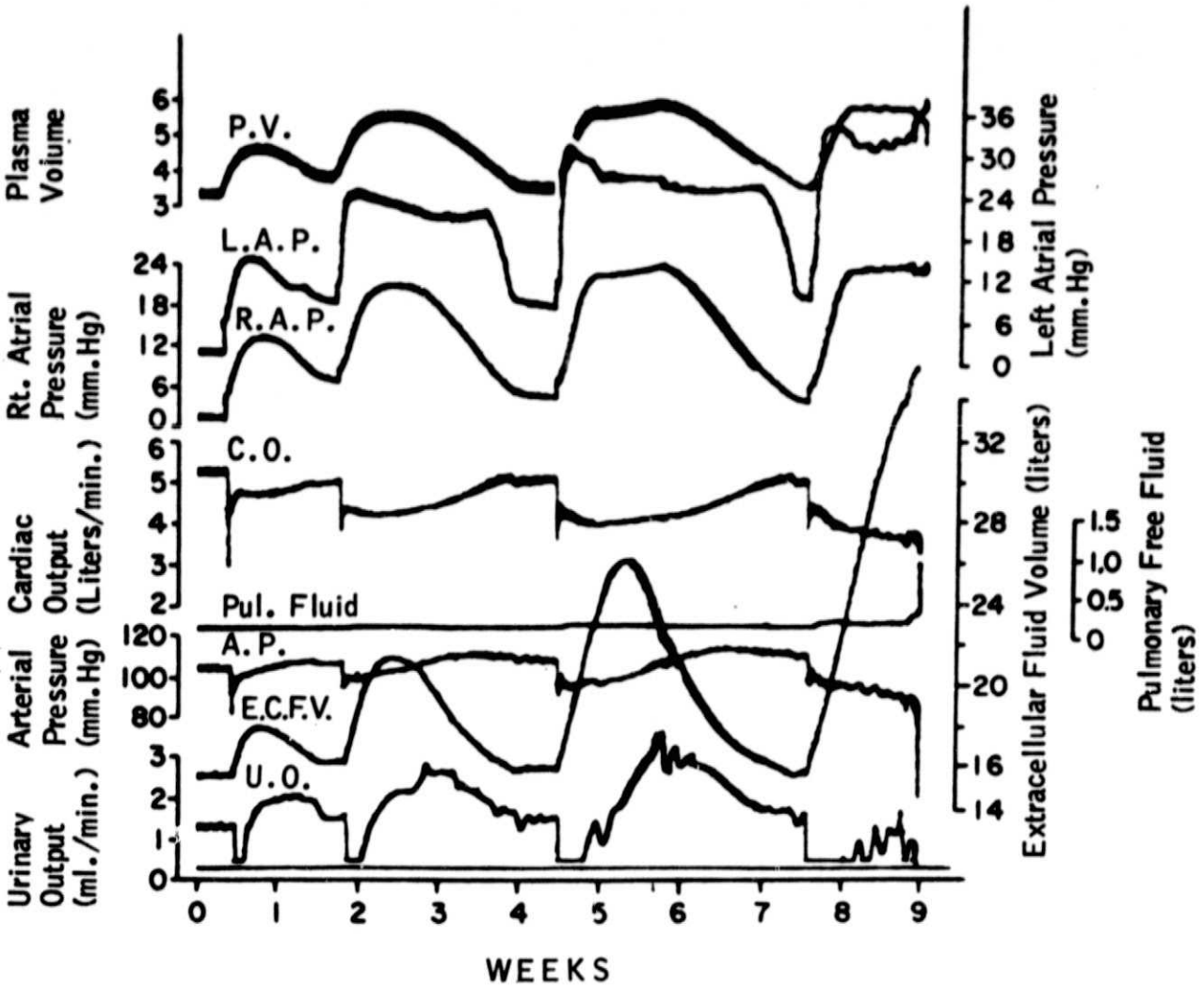


FIGURE 13. SIMULATION OF CIRCULATORY DYNAMICS FOLLOWING PROGRESSIVE BILATERAL HEART FAILURE. FROM GUYTON et al (1972).

congestive heart failure. Each of these simulations is realistic in the sense that average experimental results compare quite well with the representation predicted by the model.

For the saline infusion simulation, Figure 8 , the variables shown are (top to bottom) plasma volume (VP), interstitial volume (VTS), capillary pressure (PC), plasma colloid osmotic pressure (PPC), interstitial fluid pressure (PIF), interstitial colloid osmotic pressure (PTC), capillary filtration rate (VTC), and lymph flow rate (VTL). The infusion began at time zero and ended at 30 minutes (Input: not shown in Figure 8). Note that capillary filtration increases markedly as the transfusion begins and that lymph return increases more slowly resulting in an outward flow of fluid from the plasma. At the conclusion of the infusion capillary filtration fell rapidly to equal lymph flow and only 265 ml of fluid was transferred to the interstitial space before equilibrium was obtained. In the new steady-state the infused saline was thus distributed in the ratio of about 1:3 between the plasma and interstitial space. If the infusion had been large enough for the "safety factor for edema" to be exceeded on the other hand, almost all of the infused fluid, beyond a certain point, would have entered the interstitial space. This experiment indicates quite clearly the dynamic nature of fluid shift mechanisms and demonstrates the suitability of the model for studying such problems.

Prior to the simulation shown in Figure 9 (about 10 days simulation), the model subject had its effective renal mass reduced to 30 percent of normal (a formulation of analogous pathological state) modifying circulatory variables in the model. A new steady-state developed which was not very different from the normal steady-state as long as the diet was kept normal. At the break in the curves intake of salt was increased to five times normal (Input: not shown in Figure 9), and the simulation pictures the classical development of salt-induced, renoprival hypertension. Note

in particular the initial rise in cardiac output that leads to an increasing arterial pressure, in spite of a slight fall in total peripheral resistance, and the subsequent rising peripheral resistance enhancing and then maintaining an increased mean pressure in spite of cardiac output returning to near normal. Such a simulation illustrates the danger of drawing conclusions about what happens in a situation by examining the steady-state only.

The simulation of Figure 10 illustrates the sequence of events following application of a Goldblatt clamp causing sudden renal artery constriction in both kidneys (input). Note especially the biphasic behavior of both the cardiac output and peripheral resistance curves. The initial large peripheral resistance response is due to the greatly increased angiotensin secretion, while the final state is primarily due to reduced capacitance of the circulation and somewhat increased fluid retention.

The effects on the circulation of progressive depletion of plasma protein (hypoproteinemia) are shown in Figure 11. At the initial break in the curves the plasma was made to lose protein as shown by the third curve from the top (input). This loss decreased the plasma colloid osmotic pressure, causing fluid to migrate into the interstitial space. The resultant decrease in plasma volume reduced cardiac output and arterial pressure slightly. When interstitial pressure rose to about atmospheric pressure (at about the 6-day mark) the interstitial volume began to increase drastically and pitting edema began to develop with most of the fluid in the interstitial spaces being in the free (non-gel) form. At about the twelfth day the loss of protein was reduced slightly and this had the effect of shifting the capillary flow enough to cause a high urinary output and some reduction of the level of edema.

Figure 12 shows the sequence of events taking place following the opening and later closing of a large arterio-venous fistula. At the

opening of the fistula (input), peripheral resistance fell dramatically to about one-half of normal. This was followed by a rise in cardiac output (due to enhanced venous return) and a fall in mean pressure. The falling arterial pressure elicited an autonomic response which increased heart rate, and the lower renal arterial pressure led to an increase in renin secretion and angiotensin formation. The ultimate effect of the fall in pressure then was to decrease urine output and increase drinking leading to an increase in extracellular (and blood) volume. This increase returned pressure to normal and a steady-state developed with 50 percent normal peripheral resistance, twice normal cardiac output and normal values for most other variables with the exception of fluid volumes. Closing of the fistula (removal of input) led to essentially opposite effects.

Figure 13 pictures the effects of repeated reduction in ventricular pumping ability of both sides of the heart. Shown are (top to bottom) plasma volume (PV), left atrial pressure (LAP), right atrial pressure (RAP), cardiac output (CO), free fluid volume in the lungs (Pul. fluid), arterial pressure (A.P.), extracellular fluid volume (E.C.F.V.), and urinary output (U.O.). At the first break in the curves, the pumping ability of both ventricles was reduced to 0.3 normal and at each subsequent break in the curves this pumping ability was further reduced by about 10 percent of the value just prior to the break (inputs: not shown in Figure 13). After each reduction a marked decrease in cardiac output and arterial pressure occurred, but these returned toward normal rapidly. Urinary output decreased and extracellular volume then increased rapidly and the atrial pressures increased. After a day or so all variables tended to return to normal, but with each subsequent attack the transients became more severe until finally recovery became insufficient (Note: a steady increment of magnitude of responses of these variables, especially extracellular fluid volume and a poor response of urinary output in 8-9th day episode.) At this point pulmonary edema became severe (due to the high left atrial pressure) and death resulted as the oxygen saturation of the blood (not shown), decreased below 50 percent.

2.2 CURRENT CAPABILITIES

Examples shown here clearly depict the following capabilities of existing simulation models:

1. The ability to simulate analogous pathological states and effects of abnormal environmental stressors by manipulation of system variables and changing inputs in various sequences.

2. The ability to simulate time courses of responses of controlled variables caused by the altered inputs and their relationships.

3. The ability to simulate physiological responses of treatment such as isotonic saline transfusion as shown in Figure 8.

4. Since the ability of changing inputs during a course of simulation exists, e.g., opening and closing of A-V fistula in Figure 12, it is possible to simulate effectiveness of a treatment, as well as to simulate effects of complication superimposed on an existing pathological state.

5. Since sequence and magnitude of input representing a treatment can be manipulated, it is possible to compare the effectiveness of various treatments/countermeasures for a given pathological state.

Current capability to manipulate input to the whole-body simulation model and the supportive data analysis system can have almost unlimited potential in its clinical and therapeutic research applications. The use of simulation models in concert with studies like those mentioned above with their ease of manipulation of inputs, the availability of various output that is difficult to obtain experimentally, and the computation of related system parameters would certainly provide a powerful tool in the research of dynamic pathology as well as in the search of therapeutic means (inputs/countermeasures) and for aid in prognostication of

outcome. For example, parameters obtainable from non-invasive measurement form only 3 - 4 percent of total parameters (8 parameters out of total 207 physiological important parameters) in Guyton's integrated model. Development of the capability to select and display invasive parameters desired, capability of manipulating inputs, and the computation of parameters corresponding to both non-invasive and invasive measurements from subjects when applied to the current system would open a way in which models could yield a non-invasive measurement tool which may be useful for evaluation of patients who could not tolerate invasive procedures.

In summary, results of this study have exhibited that existing simulation models have some capability in clinical applications with the few examples presented. However, this work is in an early stage. Broad, sometimes unforeseeable, applications of models to clinical, therapeutic, and countermeasure research for NASA's future needs represents a new and largely undefined area of research.

3.0 FEASIBILITY OF APPLYING THE SIMULATION MODEL IN DIAGNOSTIC AND THERAPEUTIC RESEARCH PROBLEMS

A preliminary investigation indicates that the feasibility of applying current simulation models in diagnostic research requires further basic study. Other types of models, such as stochastic models, probably have greater applicability to clinical diagnosis. However, since the contract work to date has considered only simulation models of major body subsystems, this report considers only applications of this type of model. A few areas of possible application are noteworthy because of their theoretical applicability even if their practicality remains in question. These areas include utilization of sensitivity coefficient analysis methods, particularly stability analysis, and inverse sensitivity analysis using current simulation models. Applications in therapeutic research appear to provide the most fruitful area for future studies and some of these ideas are discussed in this section.

3.1 SIMULATION MODEL APPLICATIONS IN CLINICAL DIAGNOSIS

Analysis of the stability of biological systems becomes a useful aid to clinical diagnosis if stability can be measured and recognized quantitatively for major body subsystems. Examples of such needs are assessment of crew health status and recognition of a change in pathological state (e.g., recorded as the daily progress report of a patient in clinical medicine).

Theoretically, the stability of a dynamic system has an inverse relationship with sensitivity in a negative feedback system. In general, sensitivity to disturbing factors can be reduced by an increase in feedback gain. On the other hand, the onset of instability occurs as a consequence of this gain increase. Thus, systems with high gain may

have low sensitivity to external perturbations. Most biological systems are normally stable and they exhibit low sensitivity. Whether or not they are working somewhere near the stability limit via high gain factors is not known, but should be studied on a case-by-case basis (Jones, 1973). Inherent instability is dependent upon the properties of the system and is not normally a function of the specific disturbance. If the system is inherently stable, all transients will ultimately disappear regardless of the disturbance causing them although biological systems have their own threshold to the disturbance. On the other hand, any disturbance to an unstable system will initiate oscillations that increase in amplitude with time. Instability can arise from either inherent features of the real system or from structural features of the mathematical model. Techniques of recognizing such instability of selected systems appears feasible utilizing sensitivity analysis methods which can reveal both types, those inherent to the real body system and those from the simulation model itself although it is not always possible to distinguish between the two.

In clinical diagnosis, whether the biological system is stable or unstable may not be important, but the degree of stability and its change may be the concern. An analysis of stability, thus, not only becomes an important measure of the competence of a model, but also becomes a useful aid in systematic diagnostic research when there is confidence in the mathematical simulation. Little work has been done on stability analysis of complex physiological systems of such a practical nature. Formal techniques for investigating stability in linear systems and for simple nonlinear systems have been reported (Jones, 1973; Rosen, 1970; Tomovic, 1963; and Tomovic, et al, 1972), but for the most part, studying large scale nonlinear models is a trial and error experience. Applications of the simulation model in this area, therefore, requires further study.

Inverse sensitivity analysis is another technique which appears to have a potential application in diagnostic research. If the problem of sensitivity analysis is expressed as determining the behavior of a model, given all the parameter variations, then the inverse problem would be to determine (or identify) the parameter variations capable of producing a given behavior of the real system. The problem of direct sensitivity can be solved satisfactorily if the sensitivity coefficients of the dynamic system are known. The method for finding inverse sensitivity is also based on a knowledge of the sensitivity coefficients. Unlike direct sensitivity analysis, inverse sensitivity analysis requires data measurements from the real system.

In essence, solving the inverse sensitivity problem is not unlike parameter estimation analysis. Analytic methods have been worked out for the linear system (Tomovic, 1963) while empirical methods must be used for nonlinear systems. With inverse sensitivity, one starts from the known perturbation of the transient state and seeks the set of parameter perturbations capable of causing them. This inverse problem may not have a unique solution. Uniqueness is dependent primarily on the number of parameters vs. the number of variables measured and the number of points in time at which measurements are made. Nevertheless, it would be valuable to know the various solutions possible since this would narrow down the range of search for the possible causes of observed pathological or undesirable states. If several different parameter perturbations could produce similar model results, it may be possible to accept the most reasonable based on physiological plausibility or alternatively this information could provide the basis for further experiments and diagnostic testings.

It should be noted that the clinical diagnostic procedures do not necessarily follow the procedure of a direct determination of inputs (causes) from the observed responses in the strict sense of a control

system. The clinical definition of "diagnosis" is also rather vague. Physicians use a treatment as a means of diagnosis in some cases. Inverse sensitivity analysis could, therefore, provide a more systematic approach to the diagnostic processes.

It is worth mentioning here that numerous studies have been reported on computer-aided medical diagnosis which are based on stochastic approaches. This area of investigation was not included as a part of this contract. A simple stochastic compterized diagnosis assistance program based on a diseases-symptom matrix to investigate and demonstrate the feasibility of this approach has been developed as a part of an independent research and development project. This program is currently capable of making differential diagnosis of 336 diseases from among 82 signs and symptoms.

3.2 THERAPEUTIC/COUNTERMEASURE RESEARCH

Applications of current simulation models in therapeutic/countermeasure research is feasible and may have applicability in broad areas of interest. An example of such interest was indicated in the recent Skylab Life Sciences Symposium. The need for developing countermeasures which were indicated by the Symposium include:

- Countermeasures for habitation space sickness in the first 5 days of space flight.
- Countermeasures for fluid redistribution or orthostatic intolerance (such as hypotensive/hypertensive suit) for Shuttle passenger population groups.
- Countermeasures for cardiovascular deconditioning.
- Countermeasures for the maintenance of muscular mass and functional integrity against their loss in space flight.

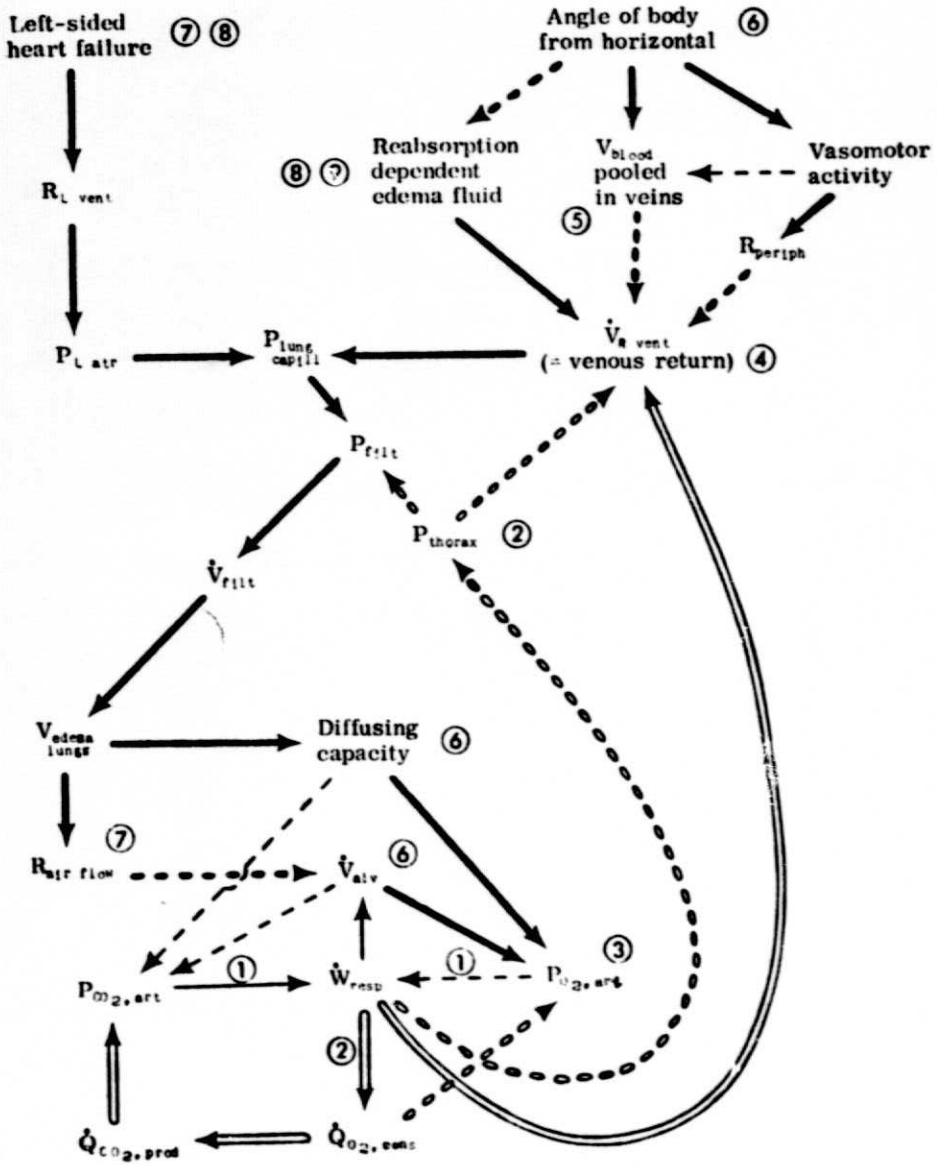
- o Countermeasures for inflight bone calcium loss.
- o Countermeasures for the erythropoietic inhibition/arrest in space.
- o Countermeasures for body weight loss in space.

Many areas of therapeutic research could be investigated with little or no modification to the current models. This section illustrates the feasibility of this application with a few examples.

D. C. Riggs (1970) describes therapeutic target points in his explanation of vicious circles using a case of paroxysmal nocturnal dyspnea due to acute pulmonary edema with a symbol-and-arrow diagram as shown in Figure 14. When a vicious circle underlies a pathological process, measurements of the open-loop gain would warn of impending disaster and would serve as a quantitative index of the effectiveness of treatment. Unfortunately, the variables in the positive feedback loop are often difficult to identify and even more difficult to measure accurately enough so that feedback equations describing the interrelations between two members of the loop could be written.

With left heart failure, acute episodes of pulmonary edema characteristically occur at night after the patient has gone to bed. Unless prompt treatment is given, a severe attack may be fatal presumably because the overall gain of the vicious circles equals or exceeds unity.

In Figure 14, the steps directly involved in the pathogenesis of pulmonary edema and the consequent anoxia have been identified by heavy arrows. In left heart failure, $R_{L_{vent}}$, the resistance of the left ventricle to the inflow of blood is increased, so that $P_{L_{atr}}$, the pressure in the left atrium is abnormally elevated, necessitating an elevation of $P_{lung\ capill}$ and hence of P_{filt}, the net transcapillary filtration pressure in the lungs, which causes movement of fluid from blood plasma into the alveoli. During the day, while the patient is "up and around", the force of gravity tends to limit venous return,



$R_{L\ vent}$: Resistance of the left ventricle to the inflow of blood

R_{periph}: Peripheral resistance

$P_{L\ atr}$: Pressure in the left atrium

$P_{Lung\ capill}$: Pressure in the lung capillaries

$V_{R\ vent}$: Output of the right heart (venous return)

P_{filt}: Net transcapillary filtration pressure in the lung

$R_{air\ flow}$: Resistance of air flow in the lungs

V_{alv}: Alveolar ventilation

$P_{O2,art}$: Partial pressure of O_2 in arterial blood

$\dot{V}_{filt}$: Rate of fluid transudation into the alveoli

$P_{CO2,art}$: Partial pressure of CO_2 in arterial blood

$\dot{W}_{resp}$: Rate of respiratory muscle work

$\dot{Q}_{O2,cons}$: Rate of O_2 consumption

$\dot{Q}_{CO2,prod}$: Rate of CO_2 production

FIGURE 14. ACUTE PULMONARY EDEMA (RIGGS, 1970)

($V_{R_{vent}}$, the output of the right heart) by pooling fluid in dependent parts of the body, and by vasoconstriction (mediated via the baroreceptors) which increases peripheral resistance, R_{periph}. (Venomotion, however, tends to maintain venous return by decreasing the volume of blood pooled in the veins). When the patient goes to bed, the angle which the long axis of the body makes with the horizontal is decreased towards zero; gravitational forces no longer hinder the return of blood to the heart, and cardiac output increases, particularly if there is any dependent edema which can be reabsorbed into the $P_{lung\ capill}$ and P_{filt}. As P_{filt} increases, V_{filt}, the rate of fluid transudation into the alveoli becomes more rapid and the volume of edema fluid in the lungs increases. Fluid accumulation increases the resistance to air flow into the alveoli (thus reducing $\dot{V}_{alv}$, the alveolar ventilation), and decreases the diffusing capacity of the lungs. Both effects reduce $p_{O2,art}$, the partial pressure of oxygen in arterial blood, and cause anoxia. Both effects also increase $p_{CO2,art}$, the partial pressure of carbon dioxide in arterial blood.

Key portions of positive feedback loops are emphasized by thick, but unfilled arrows. All of these positive loops depend upon the ability of hypercapnia and hypoxia to increase $\dot{W}_{resp}$, the rate at which the muscles of respiration do work. The positive feedback loops which involve increased O_2 consumption and CO_2 production by the respiratory muscles were described in his model on the chemical control of breathing. In pulmonary edema, two other positive feedback paths establish additional vicious circles. First, the labored, gasping respiration (dyspnea) decreases the mean intrathoracic pressure. This decrease not only tends to promote return of blood to the heart, but also decreases the pressure within the alveoli, thereby increasing P_{filt}. Second, as is true of any kind of exercise, the increased work of the respiratory muscles will cause an increase in cardiac output via mechanisms which are still not entirely clear.

The preponderance of positive feedback in pulmonary edema causes a paradox. The rapidly worsening tissue anoxia would seem to demand measures to increase delivery of oxygen from the air to the lungs via increased lung ventilation, and from the lungs to the tissues via increased cardiac output; yet increased cardiac output and increased ventilatory efforts are two of the main factors accounting for the initiation and perpetuation of the pulmonary edema. In fact, as clinicians have long recognized, in pulmonary edema it is essential to interrupt the greater-than-unity-gain positive feedback loops even if we do so by depressing respiration and decreasing cardiac output.

The following list shows what therapeutic measures are available to reverse the rapidly progressive deterioration characteristic of untreated pulmonary edema. Each circled number in Figure 14 shows the point of attack of the correspondingly numbered therapeutic measure.

- To interrupt the vicious circles
  1. Morphine sulfate intravenously. Lowers $\dot{W}_{resp}$ by decreasing the sensitivity of the respiratory center to stimuli caused by hypercapnia and hypoxia.
  2. Assisted respiration. (Gas mixture is supplied at greater-than-atmospheric pressure during inspiration.) In part, substitutes exogenous for endogenous respiration work. Also raises mean intrathoracic pressure.
- To combat anoxia directly.
  3. Increasing the partial pressure of oxygen in the inspired air.
- To decrease venous return and cardiac output
  4. Bleeding (venesection).
  5. Pooling blood in limbs by applying tourniquets to obstruct venous outflow ("bloodless venesection").

6. Elevation of head of bed, or sitting posture, to promote gravitational pooling. This may also favor redistribution of fluid in the lungs so that at least the upper portions can be aerated, thus increasing diffusing capacity and decreasing resistance to air flow.

o To combat the heart failure.

7. Aminophylline slowly intravenously, for its positive inotropic effect on the heart, and to relax bronchiolar smooth muscle thus reducing $R_{\text{air flow}}$.

8. Digitalization with a rapidly-acting cardiac glycoside, to relieve the heart failure.

o Longer term preventive measures

9. Maintain digitalization with a suitable drug.

10. Administer diuretics if needed to prevent accumulation of dependent edema.

The above example suggests a method of applying a simulation model in therapeutic/countermeasure research which is: (1) the requirement to interpret effects of physical and chemical (including drugs) treatments to their biological effects which can be expressed by variables in the model, (2) their target points have to be identified, and (3) a simulation model for the above requires a program of the vicious circle with a regulation threshold model which controls inclusion or exclusion of the vicious circle.

Recently, interest has developed concerning whether or not the existing hypertensive anti-g suit successfully used for Skylab missions is adequate for the Shuttle passenger population. Clinical applications of hypertensive and hypotensive devices applied to the lower body have been reported by many researchers (e.g., by Wothuis, Bergman, and

Nicogossian, 1974). In addition to static hypertensive or hypotensive lower body devices, an external counterpulsation device (ECP) has been applied to combat against cardiogenic shock of myocardial infarction victims. (Birtwell, et al, 1969; Soroff, et al, 1969, 1971, and 1974). Counterpulsation raises the diastolic pressure and lowers the systolic pressure to assist circulation. It accomplishes this by synchronizing its pumping action with the heart's own action triggered by the R wave of electrocardiogram. The pumping pressure is exerted in the opposite way creating blood pressure of 80 over 120 mm Hg. The hemodynamic response should be noticeable within 45 minutes after the use of positive-negative pressure assist. By raising the diastolic pressure, myocardial and coronary perfusion is increased. The work of the heart is reduced by taking the pressure off the left ventricle thereby increasing its stroke volume. Improved perfusion oxygenation of the injured myocardium and providing a rest to the impaired left ventricle are the principal therapeutic aims of this approach. Soroff, et al (1969) also claims the evidence of the development of more and larger collateral myocardial vascularization. The authors report that there is no evidence of impairment of peripheral circulation or aggravation hemolysis and no reason to anticipate thromboembolism. The only contraindication for its use is in patients with aortic insufficiency.

The cardiovascular model for LBNP simulation is capable of simulting the effects of such devices with only minor changes. The evaluation of existing and proposed devices for Shuttle using the simulation model will not only reveal effects of such devices, but should also indicate the most effective approach before actual construction is required. This evaluation should consider inflight prophylactic devices as well as postflight therapeutic devices.

4.0 CONCLUSIONS AND RECOMMENDATIONS

The feasibility of applying subsystem and whole-body simulation models to diagnostic and therapeutic considerations has been studied, and examples of model applications are given in Section 2.0. It is concluded that simulation models can be applied to clinical and aerospace medicine areas, although this work is in a very early and preliminary stage. The results here indicate that there are many areas to be explored and models to be developed to produce practical applications to diagnostic and therapeutic problems in clinical research as well as aerospace medical operations.

Based on the preliminary study in this area, the following study tasks are recommended for a more in-depth and advanced research plan:

(a) Select applicable pathological states, or diseases, and injuries of interest to NASA aerospace operations.

(b) Survey and formulate known physiopathological mechanisms and interpretation of treatments into variables and target points for development of pathological simulation models including vicious circle models.

(c) Perform a system requirements analysis for the application of diagnostic and pathological simulation models to an integrated crew health monitoring system for the Shuttle era.

(d) Investigate the possible use of stochastic models in combination with the whole-body algorithm to provide a total system diagnostic and therapeutic model.

(e) Develop a model to simulate effects of lower body counterpressure devices.

(f) Perform simulations of constant LBNP effects on body fluid redistribution after orbital insertion.

(g) Survey past studies and investigate simulation of constant pressure hypertensive g-suit used during reentry and post-landing phases.

REFERENCES

Berry, C. A., D. O. Coons, A. D. Catterson, G. F. Kelly, 'Man's response to long-duration flight in the Gemini spacecraft', Gemini Mid-program Conference, NASA Special Publication, 121 (1967) pp. 235-260.

Birtwell, W. C., et al. Synchronous pressure assist-counterpulsation. Progr. Cardiovascular Dis., V. 11, pp. 323-337, January 1969.

Gauer, O. H., J. P. Henry, 'Circulatory basis of fluid volume control', Physiological Review, V. 43, (1963), pp. 423-481.

Gauer, O. H. H. L. Thorn, Handbook of Physiology Circulation II, Williams and Wilkins (Baltimore, 1963b), V. 67, pp. 2409-2439.

Guyton, A. C., T. G. Coleman, H. J. Granger, 'Circulation: overall regulation', Annual Review Physiology, V. 34, (1972), pp. 13-46.

Guyton, A. C., T. G. Coleman, A. W. Cowley, R. A. Norman, R. D. Manning, J. F. Liard, Hypertension: Mechanisms and Management, (edited by G. Onesti, K. E. Kim, and J. H. Moyer), Grune & Stratton, Inc. (New York, 1973b), pp. 25-36.

Guyton, A. C., A. W. Cowley, T. G. Coleman, Hypertension, (edited by J. Genest and E. Koiw), Springer-Verlag (Berlin, 1972b).

Guyton, A. C., C. E. Jones, T. G. Coleman, Circulatory Physiology: Cardiac Output and Its Regulation (2nd edition), W. B. Saunders (Philadelphia, 1973).

Henry, J. P., 'Orthostasis and the kidney', Wright Air Development Center Tech Report 55-478 (1955), pp. 4-14.

Jones, R. W. 'Principles of Biological Regulation, Academic Press, New York, (1973).

Riggs, D. C., 'Control Theory and Physiological Feedback Mechanisms, Williams and Wilkins, Baltimore, Md. (1970), pp. 500-503.

Rosen, R. 'Dynamic Systems Theory in Biology, Vol. I: Stability Theory and Its Applications', Wiley-Interscience, New York, (1970).

Shenkin, H. A., R. H. Cheney, S. R. Govons, J. D. Hardy, A. G. Fletcher, I. Starr, 'On the diagnosis of hemorrhage in man: a study of volunteers bled large amounts', American Journal Medical Sciences, 208-4 (1944) pp. 421-436.

REFERENCES (continued)

Sjostrand, R. ' The regulation of the blood distribution in man', Acta Physiol. Scandinavica, 26-4 (1952) pp. 312-327.

Soroff, H. S. and W. C. Birtwell, Assisted circulation: a progress report. Hosp. Practice, V. 6, pp. 139-140., Apr. 1971.

Soroff, H. S., et al. Physiological support of heart action. New England Journal Medicine, 280;296, March 1969.

Tomovic, R., 'Sensitivity Analysis of Dynamic Systems', Mc-Graw-Hill, New York, (1963).

Tomovic, R. and M. Vukobratovic, 'General Sensitivity Theory', American-Elsevier, New York (1972).

Waterfield, R. L., 'The effects of posture on the circulating blood volume', Journal of Physiology, 72-1, (1931), pp. 110-120.

Weissler, A. M., J. V. Warren, E. H. Estes, H. D. McIntosh, J. J. Leonard, 'Vasodepressor syncope-factors influencing cardiac output', Circulation, 15-6 (1957) pp. 875-882.

White, R. J., R. C. Croston, 'Human physiological problems in zero gravity: an attempt at understanding through systems analysis', Proceedings of the 1974 Summer Computer Simulation Conference, La Jolla: Simulation Councils, Inc. (1974) pp. 743-747.

Wolthuis, R. A., S. A. Bergman and A. E. Nicogossian., 'Physiological Effects of Locally Applied Reduced Pressure in Man. Physiological Review, V. 54, No. 3 (1974). pp. 566-595.