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Essential Hypertension: An Approach to Clinical Data by the Use of Models

NGUYEN PHONG CHAU, MICHEL E. SAFAR, M.D.,
GERARD M. LONDON, M.D., AND YVES A. WEISS, M.D.

SUMMARY A new approach, based on animal circulatory models, was proposed for the study of clinical data in hypertension. Clinical data were identified with steady states in models. From the study of models, possible impairments, susceptible to account for the observed deviations of steady states in men, were analyzed. To be specific, the 1967-Guyton-Coleman model was confronted with a set of data on essential hypertension. The approach afforded a physiological interpretation for statistical results performed on clinical data. (*Hypertension* 1: 86-97, 1979)

KEY WORDS • essential hypertension • model approach • steady state • clinical data • 1967-Guyton-Coleman circulatory model • function blocks

SEVERAL global models have been proposed for the understanding of hemodynamics and hypertension.¹⁻³ The model building method required definitions of the hemodynamic system under study, physical bases underlying their behaviors and descriptions of these behaviors by mathematical relationships. Some of the complex interactions between the components of the system were lumped into the so-called "function blocks" which were obtained directly by experimentation on animals. The mathematical relationships were generally a set of differential equations, with time as an independent variable, together with a set of algebraic equations that defined the components of the system or described the function blocks.

From the mathematical viewpoint, any circulatory system is an open and stable system. In the absence of perturbation, the system remains indefinitely at a steady state. Under the effect of a perturbation, the system undergoes a transient state. Perturbations to the system can be classified into three types: 1) A shock (i.e., a sudden change of initial conditions)

brings the system abruptly out of its steady state. Then because of stability, the system will return to its initial steady state; 2) An infusion (i.e., a sustained change of input to the system) moves the system toward a new steady state compatible with the new input level. If infusion ceases, the system will return to its initial steady state; and 3) An impairment (that is, an irreversible change of a regulation function) also moves the system toward a new steady state compatible with the impaired regulation function.

In most studies of animal hypertension (except those of spontaneously hypertensive rats), each of the above perturbations was provoked and the resulting hemodynamics were followed as functions of time. In that manner, possible causes of hypertension could be localized. This method was used extensively by Guyton and collaborators.¹⁻⁴

The above method cannot be applied to man. In man, only a limited number of physiological components are measurable. Only some of them can be artificially changed — over a narrow range — and the consequences of these changes followed with time. Perturbations capable of producing sustained hypertension cannot be realized. However, in man, the measurements can be performed in a great number of individuals, mostly patients for whom the measures are required for clinical investigations. Human studies of hypertension have been mainly based upon these measures.

It is important to realize that clinical data are of a different nature, compared to those of animal ex-

From the UER of Saint-Quentin, University of Picardie and the Hemodynamic Laboratory of the Arterial Hypertension Research Center, Hopital Broussais, France.

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Address for reprints: Nguyen Phong Chau, UER de Saint-Quentin, 48 bld. Raspail, 02100 St-Quentin, France.

perimentation. For example, the published data⁶ selected from a study of essential hypertension were obtained under the following conditions. The patients were in equilibrated sodium balance for several days. They were either untreated or had therapy discontinued for several weeks. There was no reason to believe that any patient had had an acute perturbation or damage just before hospitalization. The measurements were performed with the patients at rest. For all of these reasons, it is clear that only specific steady states of the patients have been determined. As a consequence, any set of data on normotensive and hypertensive patients, obtained in comparable conditions as above, consisted of different steady states of different individuals with different degrees of pathology.

Clinical data were submitted to statistical analyses. When a group of normotensive individuals was compared with a group of hypertensive patients, mean levels of (and correlations between) some variables were different.⁶ These differences pointed out clearly that hemodynamic regulation in the two groups were not the same. However physiological interpretation of such a result was not easy.

The purpose of this article is to clarify the connection between the two methods of hypertension study recalled above: 1) The animal method, in which hemodynamics, acutely perturbed, were followed as functions of time; and 2) The human method, in which hemodynamic steady states of different individuals (clinical data) were submitted to statistical analyses.

To be specific, we considered the 1967-Guyton-Coleman circulatory model.¹ This model, of moderate complexity, contained the most important mechanisms of blood pressure control. As an example of human study, we considered a recently published set of data⁶ on cardiac output, heart rate and blood volume in essential hypertension.

In this paper, we discuss our findings in three parts. In Part I, the 1967-Guyton-Coleman model, selected to interpret our data, is reviewed. Steady states and deviations of steady states of this model are carefully examined. In Part II, statistical methods are discussed. A published set of data⁶ are re-analyzed in view of applications in Part III. Parts I and II afforded materials for a comparison study, performed in Part III. It is shown how a model might furnish a physiological interpretation for the statistical results obtained on clinical data.

Part I. The 1967-Guyton-Coleman Model and its Application to Hypertension

The 1967-Guyton-Coleman model¹ is well known and will be reviewed briefly below.

Block 1 (fig. 1) is the classical arterial pressure (AP)-urinary output (UO) renal function. Time-integration (block 3) of water and salt intake (I) minus urinary output (block 2) gives extracellular fluid volume (ECFV) which is in equilibrium with blood volume (BV) following the experimental curve of

block 4. Block 5 defines the basal systemic filling pressure, called mean systemic pressure (MSP), from blood volume. This pressure, after accounting for the autonomic effect (block 29), minus the right atrial pressure (RAP) (block 6), gives the effective pressure which develops cardiac output (CO) by overcoming the resistance to venous return (RVR) (block 7). Cardiac output times total peripheral resistance (TPR) (block 8) gives arterial pressure which is used in block 1. Now TPR is the sum of two parts: one part is a constant venous resistance (VRES), the other is a variable arterial pressure (AR) which is subjected to the control of the autonomic system (block 28). The uncontrolled part of this resistance (AR(b)) is inversely proportional (with coefficient k_1 , which might be called the "resistivity coefficient") to a variable index of vasculature (VAS) introduced to quantify the whole vascular network. The VAS is considered as an integral result (blocks 10 and 11) of two dynamic processes: a first-order destruction process with rate constant k_2 , and a creation process, depicted by block 9. Resistance to venous return is an algebraic combination of VRES and AR (block 15). Autonomic control, stimulated by the AP-level, is quantified by a baro-chemo coefficient (BC) (block 20). This coefficient acts partly through chemoreceptors (block 22) and partly through baroreceptors (block 21) on mean systemic pressure (block 29) and on arterial pressure (block 28). Notice that the baroreceptor is an adapted system, with the feedback loop 23-24-25. Finally, right atrial pressure is defined via the Starling curve (block 16), which is determined from normal cardiac output (CO_n). To reconstruct CO_n , cardiac output, after multiplication by a constant k_4 , which characterizes the "heart strength" (modifications of k_4 simulates cardiac deficiency) is divided by a "cardiac multiplier" (CM). Cardiac multiplier is simply a product of autonomic multiplier (AUM) and the arterial pressure multiplier (APM), which is also stimulated by arterial pressure (block 18).

The above description of the Guyton-Coleman model, necessary for subsequent discussions, was reduced to the minimum. Detailed physiological descriptions of the model can be found in the literature.¹⁻⁴ Abbreviations for the main variables are depicted in table 1.

The Linearized Guyton-Coleman Model

To apply the Guyton-Coleman model to human hypertension, it is sufficient to study the model near its normal steady state. In our data (see Part II), averaged mean arterial pressure (fig. 4) ranged from 86 mm Hg to 147 mm Hg. Between these pressure ranges, only the linear portions of the function blocks (fig. 1) were concerned. As a result, we can suppose that all the function blocks were linear. Table 2 depicts the linearized function blocks with conventional notations. Two minor modifications were added to the model: 1) The baro-chemo components of AUM were written as α and $1-\alpha$, instead of $\frac{1}{4}$ and $\frac{3}{4}$;

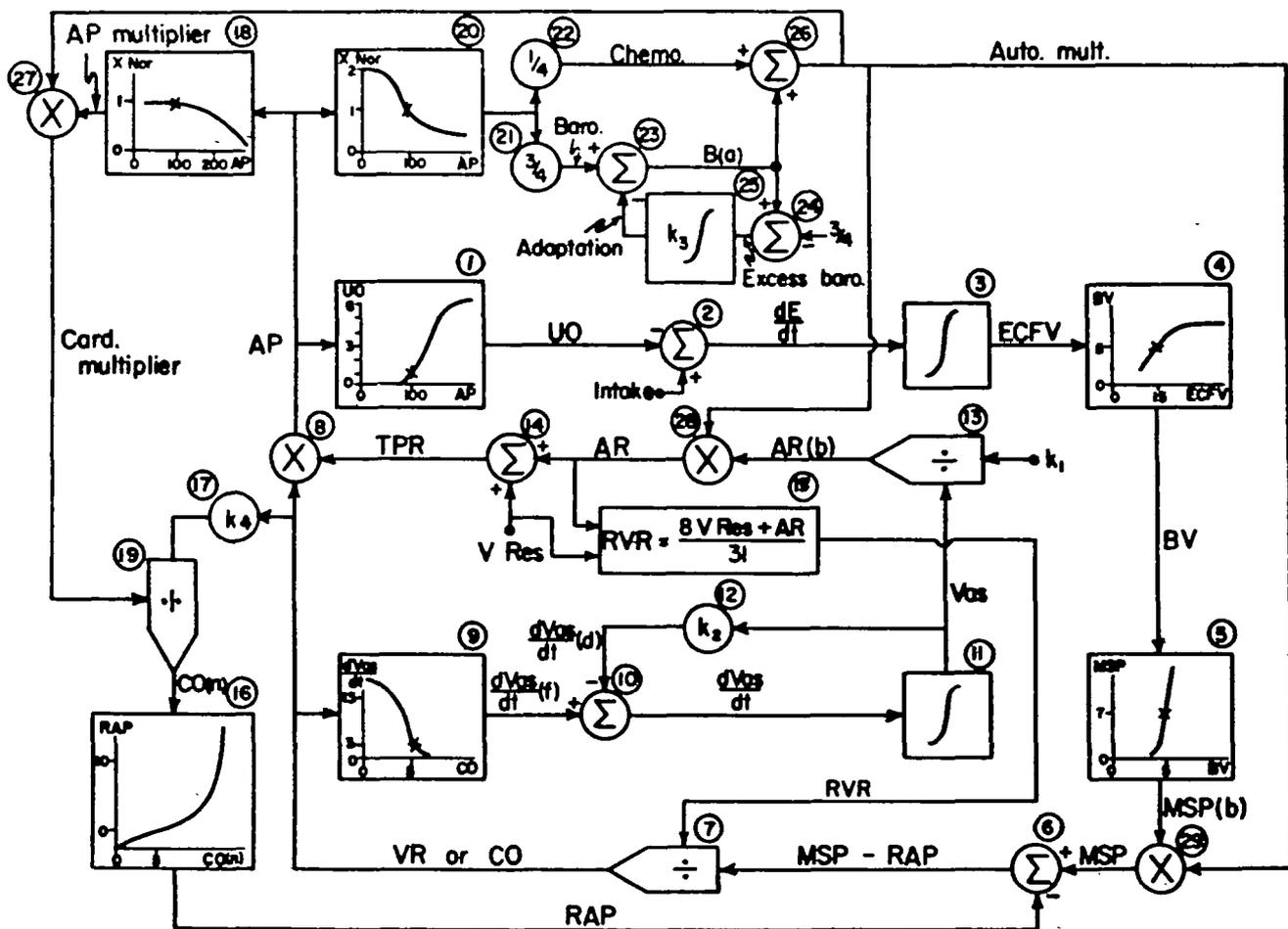


FIGURE 1. Structure of the 1967-Guyton-Coleman model (reproduced from Guyton AC, Coleman TG: Long-term regulation of the circulation: Interrelationships with body fluid volumes. In *Physical Bases of Circulatory Transport: Regulation and Exchange*, edited by Reeve EB, Guyton AC. Philadelphia, W B Saunders, 1967, with permission of the authors and the publisher).

and 2) The relation $RVR = (8 VRES + AR)/31$ was replaced by $RVR = \beta VRES + \gamma AR$ ($\beta, \gamma =$ constants). Later on, simulations were performed, with α close to $1/4$, β close to $8/31$ and γ close to $1/31$, to understand the influences of these coefficients on the behavior of the global system.

The linearized Guyton-Coleman model was governed by three differential equations, eight linear function blocks and a set of relationships defining the physiological components of the system. All the equations are detailed in the Appendix. To simplify the terminology, the components like AP and BV (which are functions of time) were called variables, and the constants, like a_1 and b_1 , were called coefficients of the system.

Steady State of the Model

It is well known that the Guyton-Coleman model is *stable*. If the input (I) to the system is constant, from any initial condition, each variable will tend, as $t \rightarrow \infty$, to a constant steady state. Steady-state levels can be determined by equating to zero the derivatives of

equations 1a, 2a and 3a in the Appendix. By solving the relations obtained, one derives, for example:

$$AP(t \rightarrow \infty) = \frac{(I - b_1)}{a_1} \tag{1}$$

This relation shows that steady-state pressure levels depend on the absorption rate of water and salt (coefficient I), on the renal function curve (coefficients a_1, b_1) and solely on these coefficients. Steady-state values for the other variables can be easily calculated. The results can be written as follows:

$$AUM_{\infty} = AUM_{\infty}(I, a_1, b_1, a_7, b_7), \tag{2}$$

$$VAS_{\infty} = VAS_{\infty}(I, a_1, b_1, a_7, b_7, a_4, b_4, k_1, k_2), \tag{3}$$

$$TPR_{\infty} = TPR_{\infty}(I, a_1, b_1, a_7, b_7, a_4, b_4, k_1, k_2), \tag{4}$$

$$CO_{\infty} = CO_{\infty}(I, a_1, b_1, a_7, b_7, a_4, b_4, k_1, k_2), \tag{5}$$

$$BV_{\infty} = BV_{\infty}(I, a_1, b_1, a_7, b_7, VRES, k_4, a_4, b_4, k_1, k_2, a_3, b_3, a_5, b_5, a_6, b_6, \beta, \gamma). \tag{6}$$

In the above equations, all the coefficients on which depend the steady-state levels were listed. Expressions for the second members are not simple and were not reproduced.

Normal Steady State

Table 3 depicts a set of normal levels in man. These levels were based on mean values calculated from the data on a group of normotensive patients reported in Part II (first group of 40 patients, classified by increasing mean arterial pressure). Table 3 lists also a set of normal values of the coefficients. The latter were borrowed from Coleman (personal communication) after minor modifications (when necessary) to account for the normal levels which were chosen.

Acute Change of a Coefficient: Transient State

With the system at its normal steady state, if at least one of the coefficients is suddenly modified from its normal value, the system will undergo a transient movement to reach, at $t \rightarrow \infty$, a new steady state defined by the new set of coefficients. A typical example can be seen in figure 2.⁴ After removal of 70% of the renal mass, the infusion rate was doubled from normal during 2 weeks (this corresponded to changes of a_1 , b_1 and I). The curves on the left (fig. 2) depict results from measurements in a series of six dogs, those on the right depict the results of a computer simulation of the Guyton-Coleman model. Figure 2 shows that the model, as simple as it was, was quite sufficient to predict the available data and it did the prediction quite well. Note that, at the new steady state, resistance and pressure were elevated while heart rate, cardiac output and stroke volume were close to normal.

Abnormal Steady States: Contribution of Each Coefficient to an Abnormal Steady State

Suppose that the Guyton-Coleman is in an abnormal steady state, for example with $AP = 140$ mm Hg and $CO = 8$ liters. From equations 1-6, one concludes that at least one of the coefficients $I, a_1, b_1, a_7, b_7, a_4, b_4, k_1, k_2$ is abnormal. However such information is only qualitative. To evaluate the quantitative contribution of each coefficient to an abnormal steady state, we proceed as follows.

Consider a particular coefficient, for example b_1 , and a particular variable, for example CO . Suppose that b_1 is doubled from its normal value (that is, from -4.4 to -8.8). Then the percentage of change of cardiac output from its normal value is:

$$100 \times \frac{CO(I, a_1, 2b_1, a_7, \dots) - CO(I, a_1, b_1, a_7, \dots)}{CO(I, a_1, b_1, a_7, \dots)} = 5.76.$$

The fact that b_1 is doubled means that the UO-AP renal curve is reset to the right (fig. 3). As a consequence, at the same pressure \bar{OP} , the urinary output is reduced from \bar{OA} to \bar{OA}' . This modification might account, for example, for a reduction of the number of

TABLE 1. *Abbreviations for the Main Variables Used in the Guyton-Coleman Model (Units are Given in Parentheses)*

AP = arterial pressure (mm Hg)
UO = urinary output (ml/min)
ECFV = extracellular fluid volume (liter)
BV = blood volume (liter)
MSP = mean systemic pressure (mm Hg)
AUM = autonomic multiplier (normalized unit)
CO = cardiac output (liter/min)
VAS = index of vasculature (normalized unit)
TPR = total peripheral resistance (mm Hg·min/ml)
RVR = resistance to venous return (mm Hg·min/ml)
VRES = venous resistance (mm Hg·min/ml)
RAP = right atrial pressure (mm Hg)
APM = arterial pressure multiplier (normalized unit)
BC = baro-chemo coefficient
AR = arterial resistance

TABLE 2. *Linearized Function Blocks in Guyton-Coleman Model*

$UO = a_1 AP + b_1$	$BV = a_2 ECFV + b_2$
$MSP_b = a_3 BV + b_3$	$\frac{dVAS}{dt} = a_4 CO + b_4$
$RAP = a_5 CO_r + b_5$	$APM = a_6 AP + b_6$
$BC = a_7 AP + b_7$	$RVR = \beta VRES + \gamma AR$

Abbreviations: see table 1.

TABLE 3. *Normal Levels of the Variables and Normal Values of the Coefficients*

$UO = 1$ ml/min	$ECFV = 15$ liters
$VAS = 1$ normalized unit	$BV = 5.25$ liters
$TPR = 0.01323$ mm Hg·min/ml	$AR = 0.10569$ mm Hg·min/ml
$MSP = 7$ mm Hg	$AP = 90$ mm Hg
$AUM = 1$ normalized unit	$CO = 6.8$ liter
$I = 1$ ml/min	
$a_1 = 0.06$	$b_1 = -4.4$
$a_2 = 0.35$	$b_2 = 0$
$a_3 = 9.52$	$b_3 = -42.98$
$a_4 = -0.59$	$b_4 = 4.4152$
$a_5 = 0.45$	$b_5 = -3.06$
$a_6 = -0.002$	$b_6 = 1.18$
$a_7 = -0.005$	$b_7 = 1.45$
$k_1 = 0.010569$	$k_2 = 0.4052$
$k_3 = 0.2304$	$k_4 = 1$
$\alpha = 0.75$	$\beta = 8/31$
$\gamma = 1/31$	$VRES = 0.002686$

Abbreviations: see table 1.

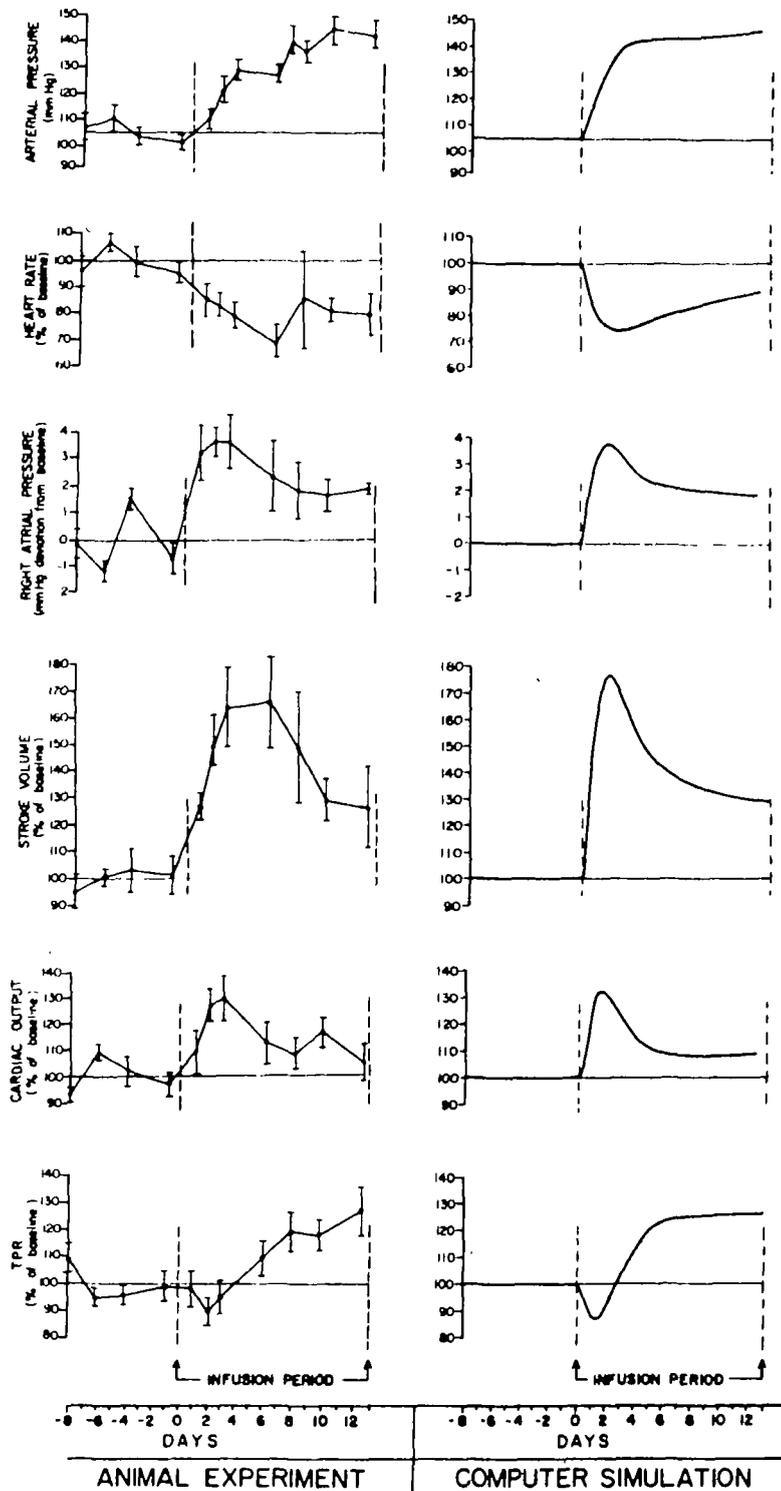


FIGURE 2. Left: Transient changes of different variables in a series of six dogs in which 70% of the renal mass had been removed and intravenous infusion of saline at a rate of 2 to 3 liters per day was given for 13 days. Right: Computer simulation of the same experiment as that seen on the left in dogs. Note that the changes in all the variables are essentially the same as those found in the animals. (Heart rate is calculated in the simulation to change in proportion to changes in the autonomic multiplier.) The simulation was performed in a version of the 1967-Guyton-Coleman model. (Reproduced from Guyton AC, Coleman TG, Cowley AW Jr, Norman RA, Manning RD, Liard JF: Relationships of fluid and electrolytes to arterial pressures control and hypertension: quantitative analysis of an infinite gain feed-back system. In: Hypertension: Mechanism and Management, edited by Onesti G, Kim KE, Moyer JH. New York, Grune and Stratton, 1973, with permission from the authors and the publisher.)

active nephrons. An analog calculation of the total peripheral resistance gives:

$$100 \times \frac{\text{TPR}(I, a_1, 2b_1, a_7, \dots) - \text{TPR}(I, a_1, b_1, a_7, \dots)}{\text{TPR}(I, a_1, b_1, a_7, \dots)} = 72.4.$$

One concludes that the above impairment of the renal function leads the system to a new steady state with higher cardiac output (+6%), and higher resistance (+72.4%). The effect of the impairment is $72.4/5.76 = 12.6$ more important on the levels of resistance than on those of cardiac output.

The calculations can be performed on all the other variables. Table 4 depicts the percent of changes from normal values of seven variables, when each of the coefficients is doubled from its normal value. It is seen from Table 4 that:

1. A change of the renal function (coef. a_1, b_1) has tremendous effects on AP, TPR and vasculature (VAS), but relatively small effects on fluid volumes, CO and autonomic control. The coefficients a_1 and b_1 act on pressure, volumes and cardiac output in the same direction.

2. A change of the autonomic system (coef. a_7, b_7) has relatively small effects on volume, resistance and cardiac output.

3. A change in the rate of creation of vasculature (coef. a_4, b_4), in the rate of destruction of vasculature (coef. k_2) or in the resistivity of the vascular bed (coef. k_1) has comparable effects, but in the opposite direction, on TPR and CO. Their effects on fluid volumes are comparatively small.

4. Blood volume depends on 19 coefficients of the system. However, except for two groups, doubling each of the coefficients changes blood volume only 5% to 10%. The two exceptional groups are: the coefficients a_2, b_2 , which define the partition of blood and extracellular fluid volumes; and the coefficients a_3, b_3 , which characterize the capacitance of the vascular bed.

5. The coefficients α (partition of the autonomic control into baro and chemo components) and k_3 (adaptation of the baro-chemo system) have no effect on the steady state of the system.

Table 4 was of fundamental importance in the discussions of clinical data, as is shown in Part III below.

Part II: Analysis of Human Data in Essential Hypertension

This part discusses a set of clinical data which were reported previously.⁵ The data were submitted to statistical analyses, using the same "smoothing technique."⁶ However, to compare the results with the Guyton theory, mean arterial pressure, instead of diastolic arterial pressure, has been used as the "classifying variable" (see definition below).

Material and Methods

We studied 196 male normotensive and hypertensive adults. To minimize the role of age in the study, only individuals aged 20 to 40 years were included.

The patients were either untreated or had discontinued therapy for at least 4 weeks before the study. During hospitalization for 6 days, dietary sodium was 110 mmoles/day. A steady state of sodium balance was established on the basis of body weight, sodium intake and urinary output. All the patients were diagnosed as having essential hypertension. After overnight fasting, the patients were brought to the hemodynamic laboratory without premedication. Intra-arterial pressure was measured through a thin-walled needle inserted into a brachial artery. Cardiac output was determined with a Waters cuvette, and an indocyanine green densitometer. Mean arterial pressure was measured with an electronic integrator. Blood volume was determined by radioiodinated albumin. The protocol was approved by the Institut National de la Santé et de la Recherche Médicale (INSERM). Consent was obtained from the patients after a detailed description of the procedure. Full details of materials and methods have been reported previously.⁵

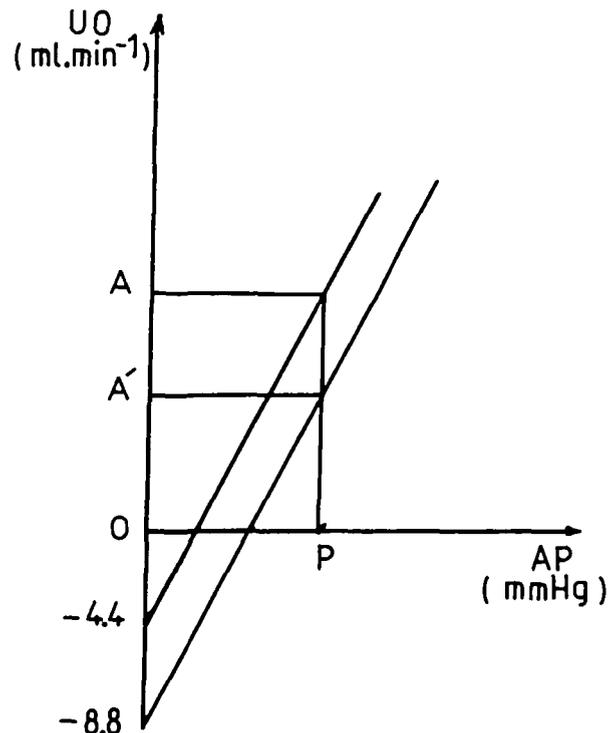


FIGURE 3. Two urinary output-arterial pressure curves, with intercepts $b_1 = -4.4$ and $b_2 = -8.8$.

TABLE 4. Percent of Changes of the Variables from Normal Steady States when Each of the Coefficients is Doubled from Normal Value (b_1 is changed from 0 to 1).

Coef- ECFV ficient	BV*	VAS	TPR	AP	CO	AUM
I	2.3	-18.7	16.3	18.5	1.9	-2.1
a_1	-5.9	126.9	-42.7	-50	-12.8	5.6
b_1	9.5	-52.4	72.4	81.5	5.3	-9.2
a_7	2.8	-10.1	-1	0	1.0	-11.2
b_7	-5.2	31	3.2	0	-3.1	36.2
a_4	-6.8	-53	89.9	0	-47.3	0
b_4	13.5	155.3	-48.6	0	94.5	0
k_2	-1.1	-9.9	8.8	0	-8.1	0
k_1	-1.1	80.2	8.8	0	-8.1	0
VRES	7.6	27.6	2.8	0	-2.8	0
a_2	-50.0	0	0	0	0	0
b_2	-86.0	0	0	0	0	0
a_6	1.3	0	0	0	0	0
b_6	-3.3	0	0	0	0	0
a_5	6.1	0	0	0	0	0
b_5	-6.1	0	0	0	0	0
k_4	6.1	0	0	0	0	0
β	9.4	0	0	0	0	0
γ	4.6	0	0	0	0	0
a_3	50	0	0	0	0	0
b_3	-19	0	0	0	0	0
α	0	0	0	0	0	0
k_3	0	0	0	0	0	0

*Values for the ECFV and BV columns are identical except for lines a_2 , b_2 .

Abbreviations and units: see table 1.

Analysis of the Data

To investigate how the hemodynamic pattern changes with hypertension, a mathematical technique, described below, has been used.

Geometric Analysis

Consider a population of N individuals and an arbitrary hemodynamic variable X . Let us classify the N subjects by increasing X levels, denote the classified subjects by an index i ($i = 1, 2, \dots, N$) and form subgroups of n subjects from the total population as follows:

Subgroup 1 = individuals 1,2, ..., n

Subgroup 2 = individuals 2,3, ..., $n+1$

...

Subgroup $N-n+1$ = individuals $N-n+1$,
 $N-n+2$, ..., N .

In each subgroup, mean values of hemodynamic variables and correlations between them can be calculated.⁸ The results describe the characteristics of

the subgroup. As two adjacent subgroups differ only by one individual, from one group to the next, mean values, correlation and regression coefficients change very slowly. Such variations depict a smooth picture of the changes in the hemodynamic pattern accompanying the increase of the variable X . This technique might be useful in a primary exploration of the data.

Statistical Analysis

To assert statistical meaning to the geometric findings, distinct subgroups of patients can be considered (see Results section). In these subgroups, difference of mean values can be assessed by the t test or by a variance analysis, and difference of correlation can be tested via the Fischer z -transform: $z = 0.5 \ln \left(\frac{1+r}{1-r} \right)$, where r = correlation coefficient, which is approximately normally distributed.⁹

Calculations and Plots of Figures

Calculations and plots of figures were performed with the aid of a CDC 6600 computer.

Results

Geometric Analysis

Mean arterial pressure has been chosen as variable X to classify the patients. From the 196 patients, we composed 157 subgroups of 40 patients, each subgroup differing from the following by one individual. Obviously the smoothness of the curves obtained depends on the number of individuals in each subgroup. The higher the number, the smoother the curves. However, the number must not be too large, otherwise details in the changes of the variables might be lost.

Mean Values. The results were visualized (fig. 4) by plotting, from Subgroup 1 to Subgroup 157, mean values of heart rate (\overline{HR}), blood volume (\overline{BV}) and cardiac output (\overline{CO}) against mean values of mean arterial pressure (\overline{MAP}). In figures 4 and 5, the successive points were joined linearly. Figure 4 shows that heart rate sharply increases for \overline{MAP} between 85 mm Hg and 95 mm Hg, and remains elevated at higher pressures. Cardiac output has an increasing phase for mean pressure between 85 mm Hg and 110 mm Hg, and a decreasing phase for mean pressure between 130 mm Hg and 147 mm Hg. Over the whole range of pressure, blood volume remains unchanged.

Correlations. The results were visualized by plotting, from Subgroup 1 to Subgroup 157, the correlation coefficients of the cardiac output-heart rate and of the cardiac output-blood volume relationships against mean values of mean arterial pressure. Figure 5 shows that the correlation \overline{CO} - \overline{HR} is significant only in the normotensive ranges, while the correlation \overline{CO} - \overline{BV} is significant only in the hypertensive ranges.

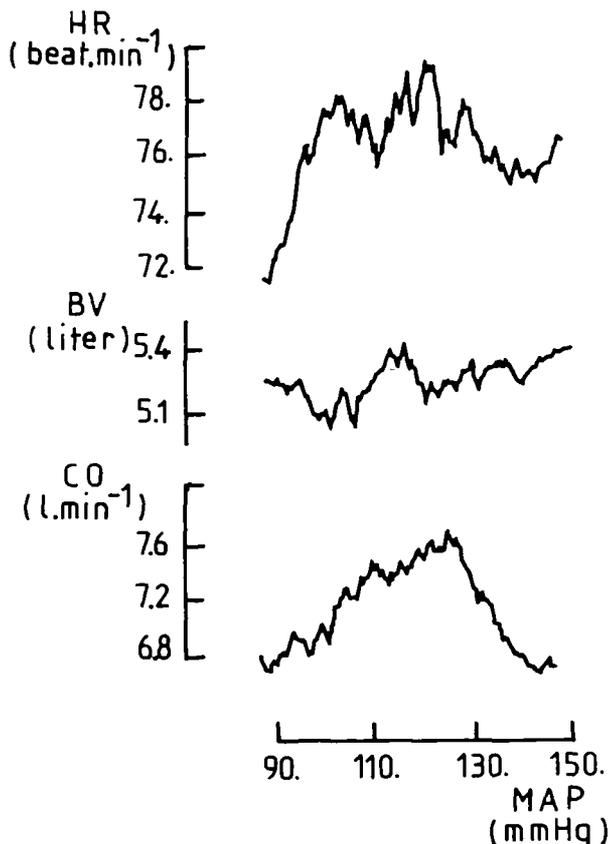


FIGURE 4. Mean values of heart rate, blood volume and cardiac output depicted against mean values of mean arterial pressure. The successive points were joined linearly.

Statistical Analysis

To ascertain statistical meaning to the above geometric findings, classical tests were performed in distinct subgroups isolated from the global population.

Mean Values. From the results of figure 4, the population was divided into two groups, A and B, to test the increase of heart rate from normotensive to hypertensive patients, and into three groups, C, D, and E, to test the changes in cardiac output. Table 5 shows that heart rate was significantly increased from Group A to Group B. Table 6 gives the mean values of heart rate CO and BV in Groups C, D and E. Table 7 depicts the results of a variance analysis, performed to test the equality of mean cardiac output in Groups C, D, and E.⁷ As the calculated F-value was higher than the F-value read from the table, mean values of cardiac output were not the same in the three groups. One concludes that cardiac output among the three groups was highest in Group D.

Correlations. To show the effectiveness of the changes in correlations, we considered the following groups:

Group F = patients numbered 1-93

Group G = patients numbered 134-196.

Table 8 shows that the correlation CO-HR was significant in Group F but not in Group G. In contrast, the correlation cardiac output-blood volume was significant in Group G but not in Group F. Furthermore, from Group F to Group G, the two correlations were significantly changed ($p < 0.05$)

Normalized Data

Normalized data, classified by increasing diastolic arterial pressure, have been discussed previously.⁸ Cardiac index (CI) had an increasing phase followed by a decreasing phase. Weight-normalized blood volume significantly decreased (this result reflected the well-known fact that body weight increases in hypertensive patients). The correlation CI-HR and CI-BV had the same pattern as in figure 5. Normalized data, classified by increasing mean arterial pressure, give essentially the same results.

Remarks

In the above tests, partitions of the total population into subgroups have been performed on the basis of figures 4 and 5. It is clear that equivalent results could be obtained if the partitions were slightly modified. However, the pressure levels adopted for the partitions were introduced exogenously to the tests. It would be important to determine by a test the pressure levels (together with confidence intervals for each) where the general pattern of the data (mean values or correlations) most significantly changes. This is a rather difficult problem. See a comment on this point in the Discussion.

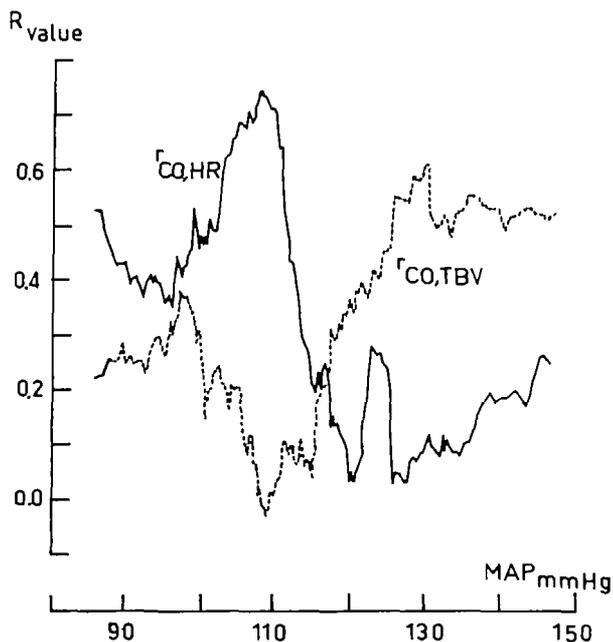


FIGURE 5. Correlation coefficients of the cardiac output-heart rate relationship and of the cardiac output-blood volume relationship depicted against mean values of mean arterial pressure. The successive points were joined linearly.

TABLE 5. *Test for the Increase of Heart Rate from Normotensives to Hypertensive Patients*

	Group A	Group B
Patient no.	1 to 40	41 to 196
Mean arterial pressure range (mm Hg)	63 to 95	96 to 174
Heart rate (beat/min)	72 ± 2	77 ± 1*
Cardiac output (liter/min)	6.79 ± 0.24	7.22 ± 0.12†
Blood volume (liter)	5.30 ± 0.12	5.29 ± 0.06†

**p* < 0.05.†*p* = not significant.TABLE 6. *Mean Values of Heart Rate, Cardiac Output, and Blood Volume in Groups C, D and E*

	Subgroup		
	C	D	E
Patient no.	1-93	94-150	151-196
Mean arterial pressure range (mm Hg)	63-110	111-130	131-174
Heart rate (beat/min)	75 ± 1	78 ± 2	77 ± 2
Cardiac output (liter/min)	6.99 ± 0.15	7.54 ± 0.20	6.87 ± 0.26
Blood volume (liter)	5.22 ± 0.07	5.34 ± 0.10	5.37 ± 0.13

TABLE 7. *Variance Analysis for Cardiac Output in Groups C, D and E*

Origin of variations	Sum of squares of deviations	Variance	Degree of freedom	Calculated F-value
Inter-groups	14.71	7.36	2	3.10
Residual	457.70	455.32	193	
Total	472.41		195	

TABLE 8. *Correlation Coefficients *r* Between Cardiac Output, Heart Rate and Blood Volumes in Two Distinct Groups, F and G*

	Group F	Group G
Patient no.	1-93	134-196
Mean arterial pressure range (mm Hg)	63-110	121-174
<i>r</i> (CO-HR)	0.56*	0.28
<i>r</i> (CO-BV)	0.18	0.50*

**P* < 0.001.

Abbreviations: see table 1.

Part III: Guyton-Coleman Model and Essential Hypertension

In this section an attempt was made to discuss the results of Part II in the framework of the Guyton-Coleman model. Clinical data were identified with steady-state levels in the model. Unnormalized data were used. Observed heart rate was identified with the model's autonomic multiplier, after multiplication by a constant factor, matching the normal heart rate to normal AUM (= 1). The latter identification was proposed by Guyton et al.⁴

Study of Mean Values

To account for the observed pattern of figure 4, we discussed the possible causes for the elevation of pressure, heart rate and cardiac output at moderate pressure, and the reasons for the decrease for cardiac output at elevated pressure. Table 4 is of fundamental importance in this discussion.

Elevation of Pressure

From table 4, it was seen that steady-state pressure increases only if the absorption rate increases and/or the renal function is impaired. Figure 6a depicts the first sequences of simulation, in which absorption was supposed normal but both a_1 and b_1 were supposed decreased. The final values of a_1 and b_1 were calculated to get a pressure of 150 mm Hg. The whole variations of a_1 and b_1 were then divided into 100 steps. In each step, steady-state values of AP, CO, AUM and BV were calculated. Finally, steady-state values of AUM, BV and CO were depicted against those of AP. In figures 6 and 7 the successive points were joined linearly. The simulated enfeeblement of the renal function resulted in a potent increase of mean arterial pressure, a decrease of autonomic control and an increase of blood volume and total peripheral resistance. In contrast, cardiac output remained almost constant. Except for the rise in pressure, these simulations *did not* match with figure 4.

Increase in Heart Rate

To account for the increases in heart rate and cardiac output at mild pressure, we propose, by a close examination of table 4, that: 1) the heart rate elevation was due to a decrease in a_7, b_7 (these modifications slightly decreased cardiac output); and 2) the rise in CO was due to a change in the rate of creation of vasculature.¹ Figure 6b depicts a second set of simulations in which the renal function (coef. a_1, b_1), the autonomic control (coef. a_7, b_7) and the rate of creation of vasculature were modified. Figure 6b shows that CO sharply increased, AUM increased and remained elevated, and BV and TPR both mildly increased.

Decrease in Cardiac Output

To account for the fall in cardiac output at high pressure, and based on table 4, we suggest that, at

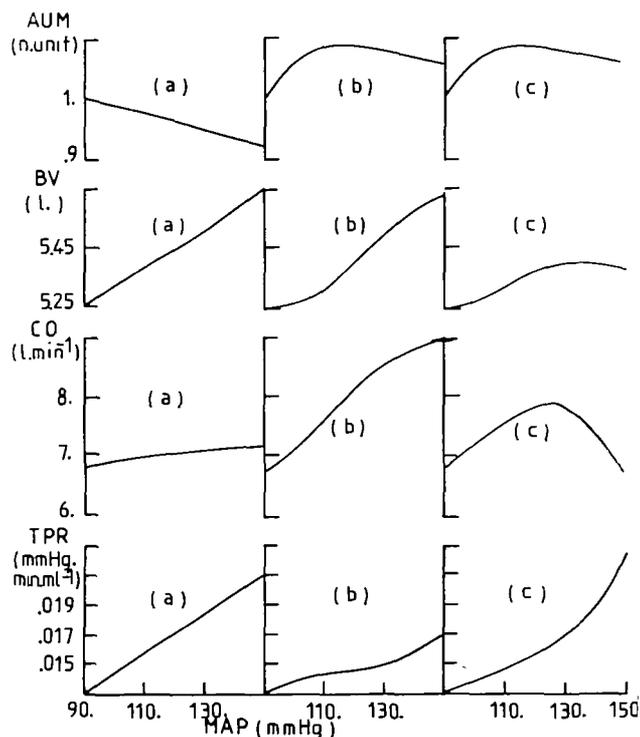


FIGURE 6. Steady-state values of autonomic multiplier, blood volume, cardiac output and total peripheral resistance depicted against steady-state values of arterial pressure, when the renal function was progressively impaired (curves a); when the renal function, the autonomic control and the vasculature were progressively impaired (curves b); and when the renal function, the autonomic control, the vasculature and the systemic resistivity coefficient were progressively impaired (curves c).

these pressure levels, the vasculature destruction process (coef. k_2) became important, and the resistivity of the vascular bed (coef. k_1) increased. Both processes decreased CO but greatly increased TPR. Figure 6c depicts the final simulations. The curves in figure 6c are quite comparable with the observations in figure 4.

Correlations

At moderate mean arterial pressure, CO and AUM vary in the same direction (fig. 6c). At high pressures cardiac output and blood volume vary in the same direction. These facts explain the results of the correlation study (fig. 5). One realizes that the interpretation of the existence or nonexistence of correlations is a difficult problem and the use of a model is indispensable for this interpretation.

Impairments

Variation of the coefficients accounting for the pattern of figure 6c are shown in figure 7. By displacing a vertical rule at any AP level (between 90 and 150 mm Hg, fig. 7) one may determine, at the intersec-

tions of the rule with the curves, the values of the coefficients contributing to define this pressure level. By the same method in figure 6c, one may read the corresponding values of AUM, BV, CO and TPR.

Note that in figures 6 and 7, arterial pressure has been used on the abscissa for the purpose of presentation. This did not mean that, in these figures, AP was an independent variable and the other variables or coefficients represented in ordinates were dependent variables.

Discussion

This article presents a new approach to clinical data based on animal models. The approach is illustrated by the application of the 1967-Guyton-Coleman circulatory model to essential hypertension.

1. The starting point of the article was the following fundamental remark: In most animal studies of hypertension, the hemodynamics, artificially and acutely impaired, were observed as functions of time.

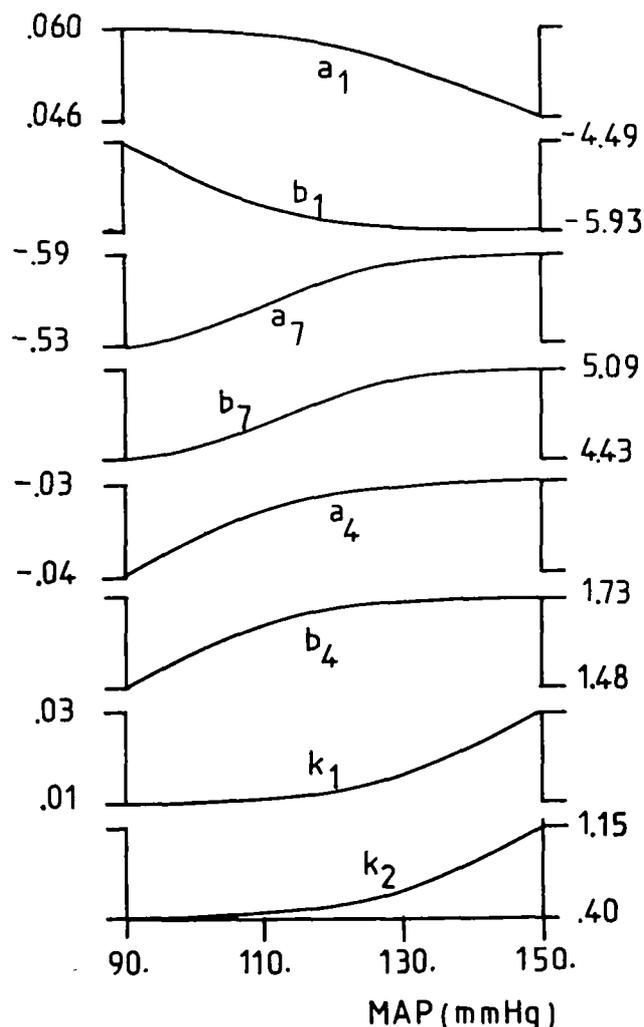


FIGURE 7. Variation of the regulation coefficients accounting for the pattern of figure 6c, depicted against steady state of arterial pressure.

In contrast, in most human studies, only steady states of hemodynamics were determined. Clinical data, in particular, are steady-state levels, and must be compared with steady states in animal models.

2. The 1967-Guyton-Coleman model has been used to interpret our data. Of course, a simpler model might be sufficient for the study of cardiac output, heart rate and blood volume. However, the Guyton-Coleman model was well known, has been repeatedly tested, and included the most important mechanisms of blood pressure control. Based on this model, table 4, which details the effects of different impairments on the global steady state, might be useful for other studies, independent of the data in this article. When extended to include the renin-angiotensin-aldosterone system, weight, and age, this model might be most useful to interpret the clinical data on hypertension available in the literature.

3. Human data can only be analyzed by statistical methods. A geometric screening technique has been proposed to explore the data and to point out the most important changes of hemodynamics from normotensive to hypertensive patients. The underlying statistical basis for this technique is the piecewise linear regression and correlation analysis. The geometric problem is to define a broken line (fig. 8) ABCD which best fit the data. Two statistical problems must be solved. First, to test the significance for a change of slope using the data over the whole population. Second, to determine the number and localize (with confidence intervals) the breakpoints. Much effort has been devoted to piecewise linear regression.⁸⁻¹⁰ However, in the referenced studies, the data were *a*

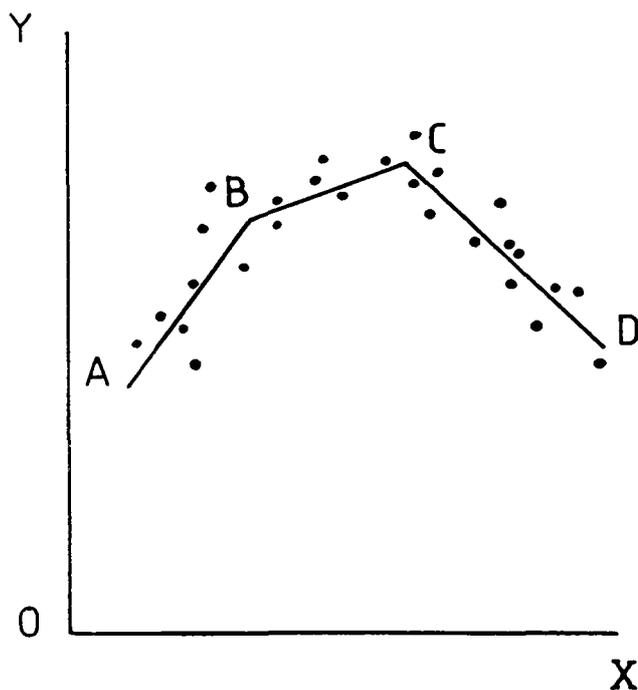


FIGURE 8. Piecewise regression line ABCD.

priori divided into subgroups, by considerations exogenous to the tests, so that the second problem above has not been completely solved.

4. Figure 6c was obtained by a careful study of table 4. This figure depicts a possible schema of multiple impairments leading to the multiparametric observations of fig. 4. Figure 6a and b, or other analog simulations might be useful for eventual animal experimentations, in which one might determine the steady states of hemodynamics resulting from progressive impairments of some control loop.

In conclusion, by considering the application of the Guyton-Coleman model to essential hypertension, we wanted to detail a new approach to clinical data by the use of models. This approach affords a rationale to the interpretation of statistical results performed on clinical data.

Appendix

From figure 1 and table 2, the following equations can be obtained:

$$\frac{dECFV}{dt} = I - UO \quad (1a)$$

$$UO = a_1 AP + b_1$$

$$BV = a_2 ECFV + b_2$$

$$MSP_b = a_3 BV + b_3$$

$$CO = 1000 (MSP - RAP) / RVR$$

$$RVR = \beta VRES + \gamma AR$$

$$\frac{dVAS}{dt} = -k_2 VAS + a_4 CO + b_4 \quad (2a)$$

$$AR_b = k_1 / VAS$$

$$AR = AUM \cdot AR_b$$

$$TPR = VRES + AR$$

$$AP = 1000 \cdot CO \cdot TPR$$

$$APM = a_6 AP + b_6$$

$$CO_n = k_4 CO / (AUM \cdot APM)$$

$$RAP = a_5 CO_n + b_5$$

$$BC = a_7 AP + b_7$$

$$AUM = (1 - \alpha) BC + B(a)$$

$$\frac{dZ}{dt} = -k_3 Z + \alpha k_3 (1 - BC) \quad (3a)$$

$$\text{where } Z = B(a) - \alpha BC.$$

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References

1. Guyton AC, Coleman TG: Long-term regulation of the circulation: Interrelationships with body fluid volumes. *In* Physical Bases of Circulatory Transport: Regulation and Exchange, edited by Reeve EB, Guyton AC. Philadelphia, WB Saunders, 1967, p 179
2. Guyton AC, Coleman TG: Quantitative analysis of the physiopathology of hypertension. *Circ Res* 24 (suppl I): 1-19, 1969
3. Guyton AC, Jones CE, Coleman TG: Circulatory Physiology: Cardiac Output and its Regulation. Philadelphia, WB Saunders, 1973
4. Guyton AC, Coleman TG, Cowley AW Jr, Norman RA, Manning RD, Liard JF: Relationships of fluid and electrolytes to arterial pressure control and hypertension: quantitative analysis of an infinite gain feed-back system. *In*: Hypertension: Mechanism and Management, edited by Onesti G, Kim KE, Moyer JH. New York, Grune and Stratton, 1973, p 25
5. Chau NP, Safar ME, Weiss YA, London GM, Simon ACh, Milliez PL: Relationships between cardiac output, heart rate and blood volume in essential hypertension. *Clin Sci Mol Med* 54: 175, 1978
6. Safar ME, Chau NP, London GM, Weiss YA, Milliez PL: Cardiac output control in essential hypertension. *Am J Cardiol* 38: 332, 1976
7. Schwartz D: Methodes Statistiques à l'Usage des Médecins et des Biologistes. Paris, Flammarion, 1963, p 181
8. Kastenbaum MA: A confidence interval on the abscissa of the point of intersection of two fitted linear regressions. *Biometrics* 15: 323, 1959
9. Quandt RE: The estimation of the parameters of a linear regression on systems obeying two separate regimens. *JASA*, 53: 873, 1958
10. Robison DE: Estimates for the point of intersection of two polynomial regressions. *JASA* 59: 214, 1964