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Mechanisms and Quantitative Assessment of Drug Effects on Cardiac Output with a New Model of the Circulation*

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I. Introduction

OVER the past 50 years, information on the physiology and pharmacology of the cardiovascular system has increased to such a vast extent that it has become impossible for one person to become fully conversant with all areas. Studies are dissecting the mechanisms of actions

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of cardiovascular drugs in greater and greater detail down to the molecular level. In addition to this detailed analysis and in spite of the difficulty, it seems important that we also synthesise this knowledge and formulate overall concepts of the effects of drugs on the cardiovascular system. This review is an attempt to do this quantitatively.

Cardiac output is perhaps the single most important cardiovascular parameter since it summarises the overall blood flow round the body. Under steady state conditions, cardiac output equals venous return, pulmonary blood flow, and the sum of the individual organ flows and, as such, it is influenced by all parts of the cardiovascular system. The term "drug effect" is used to denote any consequence of the administration of a drug on the cardiovascular system, while the term "drug action" is reserved for the direct site of action of the drug. An understanding of the effects of any drug on cardiac output involves a synthesis of the actions of the drug and the physiological interrelationships within the cardiovascular system.

Control of cardiac output is frequently discussed in terms of preload, afterload, cardiac contractility, and rate. The first three of these terms are difficult to define precisely, and this type of analysis is perhaps less useful to the pharmacologist than to the physiologist or cardiologist, since drugs do not act directly on preload or afterload and the indirect effects may be subtle. For example, when small doses of epinephrine are infused intravenously into anaesthetised cats, the marked increases in cardiac output are associated with little change in right atrial pressure and arterial pressure (117) and it might be concluded that the increase in cardiac output was secondary to cardiac stimulation. However, the effects of cardiac stimulation produced by stimulation of the stellate ganglion (13, 277) are quite different since right atrial pressure falls and arterial pressure increases. It is therefore apparent that the responses to epinephrine involve much more than cardiac stimulation and that unchanged right atrial and arterial pressures do not indicate an absence of effects on the peripheral vascular bed. The problem with analysis in terms of preload and afterload arises from the fact that while preload and afterload undoubtedly affect cardiac output, cardiac output itself affects preload and afterload. When cardiac output is increased by cardiac stimulation preload falls and afterload increases, as is clearly shown by the responses to stellate ganglion stimulation mentioned above. At this point it becomes very difficult to separate cause and effect. Within the circulation, every parameter interacts with every other parameter to a greater or lesser degree, and while we can attempt to describe these interactions clearly and precisely, considerations of cause and effect are probably invalid (112, 198). Certainly mathematical equations can describe relationships but there is no mathematical expression for cause and effect.

Analysis of the mechanisms of action of drugs on the cardiac output must therefore be considered in three distinct stages: 1) The *primary actions* of the drugs on the cardiovascular system must be elucidated. These primary actions can be studied in vivo or in vitro. 2) Then the *secondary interactions* within the circulation that occur as a result of the primary actions must be delineated. 3) Then the modifications to both the primary actions and the secondary interactions that occur due to the presence of *intrinsic modulating mechanisms* must be described. These modulating mechanisms may be local (myogenic and metabolic), hormonal, and reflex. Drugs may modify cardiac output by their effects on these intrinsic modulating mechanisms as well as by primary cardiovascular actions, for example, attenuation of the baroreceptor reflex by sympathetic blocking agents.

The purpose of this review is to consider each of these three aspects and to review progress in each area. If we claim to understand the effects of any drug on cardiac output, we should be able to express the actions and relationships quantitatively in precise terms. Models of the circulation that describe quantitative relationships play an important role in demonstrating the extent of our understanding and in highlighting areas that require further study. As Sagawa (274) stated, "the more quantitative the model is, the more exact becomes the deduction and the testing." Therefore, a second purpose of this review is to demonstrate the value of such models for research as well as for teaching. Although Braunwald (20) suggested the importance of this approach in 1971, and Sagawa (274) wrote an excellent review on available models in 1973, progress has not been rapid and it will become apparent that we cannot yet produce a complete analysis for any drug. Knowledge of the primary sites of action of drugs is limited, often for technical reasons, while knowledge of the secondary interactions and intrinsic modulation is limited by the inadequacy of our concepts of cardiovascular function. However, I hope this review will demonstrate the usefulness of this synthetic approach and stimulate further work to improve the breadth and accuracy of the analysis. The bibliography is intended to be illustrative rather than comprehensive and where reviews are available the individual papers are not cited. Many hundreds of scientists have worked on cardiac output and contributed to the concepts discussed and it was not possible to cite all their papers individually.

II. Overall Concept of the Circulation

A. General Considerations

Although many of the areas considered in this section may appear to be basic elementary physiology, unworthy of repetition in a research review, they form the basic premises of much of our thinking about the circulation and hence should be carefully considered.

Drugs do not act on pressures, volumes, or flows within the circulation. They act directly only on smooth muscle

and cardiac muscle and, in a few cases, on noncontractile elements to alter, for example, heart rate or blood viscosity. Smooth muscle is distributed throughout the vascular system and at each point it influences vessel diameter. This in turn influences the resistance to the flow of blood through the vessel and the volume of blood contained within the vessel. To describe this system, the concepts of parallel and series-coupled sections of the vascular bed have been developed (84, 85, 215). The various organs are generally coupled in parallel while, within each organ, specialised sections coupled in series can be delineated. These ideas lead directly to the concept of compartments in the vascular system, each containing a finite volume of blood at a finite pressure and separated from each other by resistances. Clearly, the smaller the number of compartments, the more easily the system is described. Hence a frequently used model (112, 198, 264) involves four compartments—arterial, capillary, venous, and cardiopulmonary—as shown in figure 1. Each compartment is considered to be separated by a section with smooth muscle that primarily varies resistance to flow between compartments. Some compartments have smooth muscle that varies the compliance of the compartmental walls. Unfortunately, although it is the activity of the vessel smooth muscle that causes variations in flows, pressures, and volumes in the compartments, this smooth muscle activity cannot be measured independently except in some preparations in vitro. Thus we are forced to the circular argument of determining the resistances and compliances from the flows, pressures, and volumes, and then using these resistance and compliance changes to explain the variations in flows, pressures, and volumes. There seems to be no way to avoid these circular arguments until it becomes possible to measure the direct actions of a drug on the smooth muscle in vitro and then to calculate the effect on in vivo resistance or compliance.

Resistance to flow is usually expressed as pressure drop divided by flow or as its reciprocal, conductance. Although there are situations where the use of resistance may be inappropriate and misleading (295), it is a generally accepted measurement and will be used throughout this review. The pressure-flow curves for most vascular beds are not linear due to intrinsic mechanisms that are regulatory myogenic and metabolic processes or mechanical consequences of vessel structure (85, 108). For example, resistance varies with transmural pressure probably due to a myogenic mechanism (pressure-induced autoregulation) in the liver (126), intestine (162, 163), kidney (282), and especially in the brain (252). However, the assumption of linearity of the pressure-flow curve in an organ may not be a serious error when drug effects are being considered since it seems likely that the direct actions of the drug on the vasculature tend to limit the operation of the autoregulatory processes and therefore cause the curve to become more nearly linear (108). Further, the calculation of resistance involves the assumption of constant blood viscosity. Hence a change in resistance after infusion of saline or of a drug that alters viscosity may be erroneously interpreted as a change in the smooth muscle activity. Vessel elements other than smooth muscle may also affect resistance, for example, endothelial swelling.

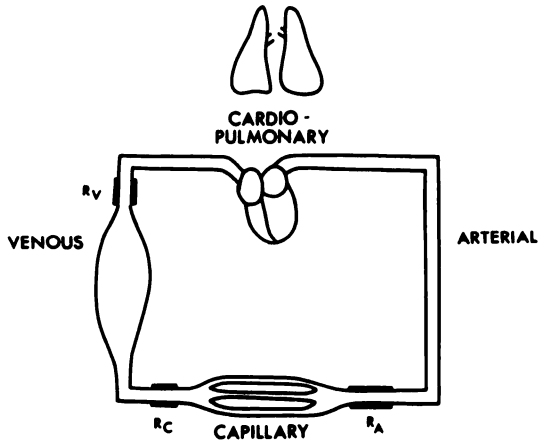

FIG. 1. The simple four compartment model of the circulation. R_A, R_C, and R_V are arteriolar, postcapillary, and venous resistances respectively.

The stiffness of the walls of a compartment is usually expressed as compliance. Compliance may be calculated either as the total compartment volume divided by the pressure, or as the change in volume divided by the corresponding change in pressure. The values obtained by these two methods are not necessarily the same since the pressure-volume curve is often nonlinear and the vascular system may contain a finite volume of blood at zero pressure. In this review, compliance is defined as the total compartment volume divided by the transmural pressure. As with resistance, changes in compliance may involve vessel elements other than smooth muscle, for example collagen and elastin may alter venous compliance and the pericardium may alter ventricular compliance (discussed later).

When resistances or compliances in series or parallel are considered, the analogue of an electrical direct current circuit is often used. This analogue is particularly useful when resistance networks are considered, and figure 2 illustrates the analogue of four vascular beds in parallel each with arteriolar, postcapillary, and venous resistances. This analogue demonstrates that pooling resistances between beds for arteriolar, postcapillary, and venous resistances, as was done in the simple model in figure 1, is invalid unless the capillary and venous pressures are identical in all organs. This limitation of the simple model has not been generally appreciated. Thus the model in figure 1 would predict that a drug that dilated arterioles in the kidney would have the same effects on cardiac output and arterial pressure as a drug that produced the same degree of vasodilatation in the splanchnic bed. This conclusion is incorrect since vasodilatation in the kidney raises renal venous pressure but causes little change in blood volume distribution since

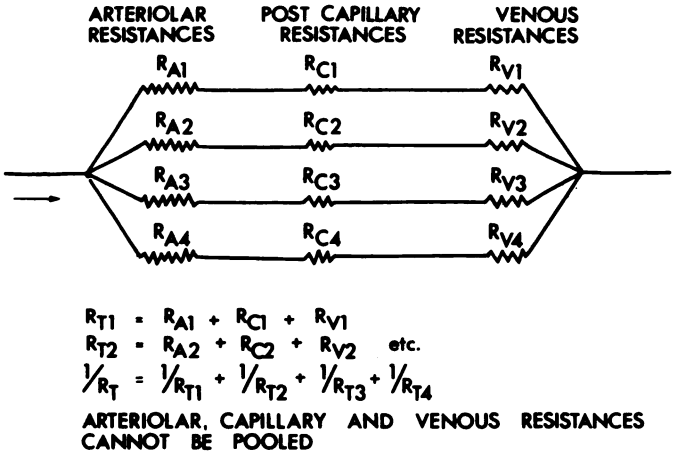

FIG. 2. The electrical analogue of the arteriolar (R_A), postcapillary (R_C), and venous (R_V) resistances in four vascular beds connected in parallel, to demonstrate that Ohm's law cannot be used to obtain pooled arteriolar, postcapillary, and venous resistances. Total vascular resistance (R_T) is obtained by summing the series resistances in each bed and then using reciprocals to sum the resistances of the individual beds.

renal venous compliance is small. On the other hand, vasodilatation in the splanchnic bed raises portal pressure and causes marked changes in blood volume distribution since splanchnic venous compliance is large. Therefore, a satisfactory model of the circulation requires separation of at least the major peripheral vascular beds, and pooled values for the series-coupled resistances cannot be used. Although the electrical analogue for circulatory resistances appears to be valid, it is inappropriate when used to model compliances. In a direct current electrical circuit, insertion of a capacitor in series causes current flow to stop, while in parallel current flow is unaltered after the capacitor is charged. Both situations clearly do not apply to the circulation.

Even greater limitations in the model shown in figure 1 arise in relation to the cardiopulmonary compartment. This is generally considered as a whole and right atrial pressure is related to cardiac output or stroke work (112, 198, 264). Hence the many intricate cardiovascular relationships in this compartment cannot be described.

Thus, rather regretfully, I have to conclude that the simple model shown in figure 1 is not appropriate for the analysis of drug effects on the circulation. We need a model that separates the major components of the peripheral vascular bed and that allows separation of the heart into four pumps separated by pulmonary arterial and venous compartments. Such a model is shown in figure 3 and this model will be used as the basis for discussion in this review.

B. Cardiovascular Parameters

The first stage in a discussion of the effects of drugs on cardiac output is to define clearly the sites of actions of these drugs. For example, it is confusing to denote a drug as hypotensive or hypertensive. Drugs do not act on arterial pressure directly; they modify certain parameters in the circulation that in turn may alter arterial pressure in various ways depending on the circumstances. It is well known that epinephrine produces clear and well-defined actions on the circulation that may in some circumstances raise arterial pressure and in others, produce a fall or no change. Thus we can divide the parameters of the cardiovascular system into two groups—*semi-independent variables*, which can be modified by factors external to the cardiovascular system, and *dependent variables*, which are determined solely within the circulation and which cannot be directly modified by external factors (112). These variables are listed in table 1. The derivation of the values for these variables is discussed later.

1. Semi-independent Variables. The major variables that can be modified by factors outside the circulation are resistances, compliances, cardiac contractility and rate, and total blood volume. However these variables are not completely independent, that is, they can be modified by changes within the circulation as well as by factors outside the circulation. Three examples may be considered. Blood volume is decreased after an investigator causes a hemorrhage but the subsequent changes in capillary pressure result in reabsorption of extracellular fluid, thus partly restoring the blood volume. In the splanchnic circulation, sympathetic nerve stimulation or norepinephrine infusions may increase arteriolar resistance but subsequent autoregulatory changes within the vascular bed may restore resistance towards its control level (114). Norepinephrine infusions increase skeletal muscle resistance but the increase in arterial pressure, through the arterial baroreceptor reflex, may reduce sympathetic tone and hence reduce the apparent action of the norepinephrine. Thus these variables, although susceptible to external control, are not totally determined by external factors. To emphasise this, I have called them "semi-independent variables." They can be considered as made up of three components:

A. BASAL COMPONENT. At present this basal component is considered to include all the factors that are operative

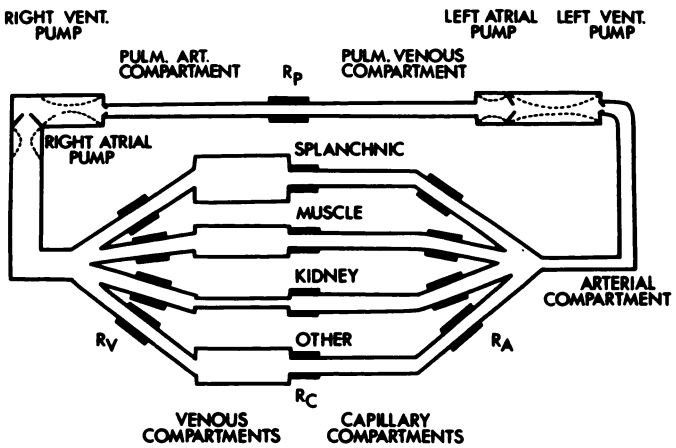

FIG. 3. The model of the circulation used in this review with four peripheral vascular beds and four separate cardiac pumps. R_A, arteriolar resistance; R_C, postcapillary resistance; R_V, venous resistance; and R_P, pulmonary resistance.

TABLE 1

The control values for the semi-independent variables on which drugs act (initialised) and the dependent variables determined solely within the circulation (calculated by the model) for the anaesthetised cat, the anaesthetised dog, and man.

	Cat	Dog	Man
Semi-independent Variables			
Blood volume, ml/kg	52	80	80
Compliances, ml/kg/mm Hg			
Arterial	0.04	0.06	0.06
Capillary	0.13	0.20	0.20
Splanchnic venous	2.60	4.00	4.00
Muscle venous	1.00	1.50	1.50
Kidney venous	0.05	0.08	0.08
Other venous	0.80	1.20	1.20
Pulmonary arterial	0.08	0.12	0.12
Pulmonary venous	1.00	1.50	1.50
Right ventricular diastolic	0.25	0.38	0.38
Left ventricular diastolic	0.13	0.20	0.20
Resistances, mm Hg.kg.min/ml			
Splanchnic arterial	2.60	2.60	2.60
Muscle arterial	3.00	3.00	3.00
Kidney arterial	3.60	3.60	3.60
Other arterial	3.00	3.00	3.00
Splanchnic postcapillary	0.32	0.32	0.32
Muscle postcapillary	0.36	0.36	0.36
Kidney postcapillary	0.43	0.43	0.43
Other postcapillary	0.36	0.36	0.36
Splanchnic venous	0.18	0.18	0.18
Muscle venous	0.20	0.20	0.20
Kidney venous	0.24	0.24	0.24
Other venous	0.20	0.20	0.20
Pulmonary	0.07	0.07	0.07
Heart			
Rate/min	180	120	75
Right ventricular contractility, mm Hg.kg/ml	50	22	20
Left ventricular contractility, mm Hg.kg/ml	350	140	100
Atrial contractility	1	1	1
Thoracic pressure mean, mm Hg	−2.0	−2.0	−2.0
Baroreflex parameters			
Set point, mm Hg	120	100	80
Resistance factor*	0.004	0.004	0.004
Heart rate factor*	0.4	0.4	0.4
Venous compliance factor*	0.01	0.01	0.01
Dependent Variables			
Total peripheral resistance	0.91	0.86	0.88
Flows, ml/kg/min			
Cardiac output	131	121	93
Splanchnic flow	38	35	27
Muscle flow	33	31	24
Kidney flow	28	25	20
Other flow	33	31	24
Stroke volume	0.72	1.00	1.20
Pressures, mm Hg			
Arterial mean	120	105	84
Systolic/diastolic	132/114	116/100	98/78
Splanchnic capillary	20	19	16
Muscle capillary	19	19	16
Kidney capillary	19	18	16
Other capillary	19	18	16
Splanchnic venous	7.7	7.6	7.3
Muscle venous	7.6	7.5	7.2
Kidney venous	7.6	7.5	7.2
Other venous	7.6	7.5	7.2
Right atrial mean	1.0	1.3	2.5
Right ventricular end diastolic	3.0	3.3	4.5
Pulmonary arterial mean	14	14	14
Systolic/diastolic	20/12	20/12	21/11
Left atrial mean	5.3	5.8	7.8
Left ventricular end diastolic	7.3	7.8	9.8
Volumes, ml/kg			
Arterial	4.8	6.5	5.2
Capillary	2.5	3.7	3.1
Total venous	34.0	52.0	50.0
Splanchnic	20.0	31.0	29.0
Muscle	7.5	12.0	11.0
Kidney	0.4	0.6	0.6
Other	6.0	9.3	8.9
Pulmonary arterial	1.2	1.8	1.8
Pulmonary venous	7.3	12.0	15.0
Right ventricular end diastolic	1.2	2.0	2.4
Right ventricular end systolic	0.5	1.0	1.2
Left ventricular end diastolic	1.2	2.0	2.3
Left ventricular end systolic	0.5	1.0	1.1

* These values are the constants k, m, and n in equations 14–16.

in the control, predrug situation. Ultimately it should be broken down into a true basal anatomical component plus intrinsic and extrinsic factors that may be operative in a particular situation, for example, disease-related factors, effects of anaesthesia and surgery in experimental situations, postural factors, etc.

B. EXTERNAL COMPONENT. This component is the external factor being studied—in our case it is the direct action of a drug. These direct actions can be examined either in vitro or in vivo. In vitro studies have the advantages of the absence of most intrinsic modulating mechanisms and often allow more precise control over the conditions of the experiment. However, some sites (e.g. arterioles) are difficult to study in vitro. Also it may be difficult to relate in vitro drug concentrations to in vivo drug dosage although the rapid accumulation of pharmacokinetic data is overcoming this problem. In vivo studies are often complex and the changes measured are the result of the direct actions of the drug plus the intrinsic modulatory mechanisms. This makes it difficult to quantify the direct actions. In addition, the manipulations to an animal such as anaesthesia, surgery, and insertion of measuring devices may modify drug action. It is beyond the scope of this review to discuss all these difficulties of determining the direct actions of a drug but they will be familiar to many readers.

C. INTERNAL COMPONENT. This internal component is due to changes in modulatory influences of intrinsic factors and reflexes that are altered after the action of the drug occurs.

Thus, in the case of arteriolar resistance in skeletal muscle, the basal component is the resistance before the drug is given; the external component is the change in resistance directly due to the action of the drug; and the internal component is subsequent changes in the resistance due to altered myogenic or metabolic factors and changes in sympathetic nervous activity due either to reflex consequences of the drug effects or to other actions

of the drug on the nervous system (e.g. adrenergic blocking action).

2. Dependent Variables. Cardiac output, and the pressures, flows, and volumes in each compartment are variables determined wholly within the circulation and hence they must be derived wholly from the semi-independent variables. The equations that describe these relationships will now be discussed.

C. Equations that Describe the Circulation

Major steps forward in attempts to describe the interaction of variables within the circulation were made by the systems analysis proposed by Guyton et al. (132, 133) and the extensive discussion of the limitations of available models by Sagawa (274). Although this work had a major impact on circulatory physiology, two factors limited its usefulness. Guyton's analysis was based on the concept of mean circulatory pressure—the equilibrium pressure developed throughout the circulation when cardiac output is zero. Although this is theoretically sound, the circulation is never at rest; this mean circulatory pressure cannot be measured in man and although it can be estimated within a few seconds in dogs, smooth muscle activity has at least begun to change within these few seconds and repeated episodes of ventricular fibrillation cannot improve the state of the preparation. In addition, the precise equations used to describe the relationships were not discussed and the analysis was presented only as a flow chart. For these reasons, this systems analysis has not had a great impact on the interpretation of mechanisms of drug effects on the circulation. However, Levy (198) has recently summarised the three basic sets of equations that describe the equilibrium condition of the circulation. These sets of equations may be called the resistance equations, the compliance equations, and the cardiac equations.

1. Resistance Equations. The basic resistance equation states that the pressure-drop between compartments is a function of the flow and the resistance to flow between the compartments:

$$P_1 - P_2 = Q.R \quad (1)$$

where P_1 and P_2 are the pressures in the compartments on either side of the resistance R and Q is the flow. This well known equation is derived from Pouseille's law (85) and is analogous to Ohm's law. The resistance is primarily determined by the composite radius of the vessels, although changes in viscosity of the blood will also alter resistance. As demonstrated in figure 2, it is necessary to consider each vascular bed separately. Within each bed, the arteriolar, postcapillary, and venous resistances are in series and can be added to obtain the total resistance in that bed:

$$R_{Ti} = R_{Ai} + R_{Ci} + R_{Vi} \quad (2)$$

where R_{Ti} is total resistance in the individual bed and R_{Ai}, R_{Ci}, and R_{Vi} are the arteriolar, postcapillary, and venous resistances respectively. The total vascular resistance (R_T) of all the peripheral vascular beds is then given by the sum of resistances in parallel:

$$1/R_T = 1/R_{Ti} + 1/R_{Ti} + 1/R_{Ti}\ldots \quad (3)$$

Thus these equations determine the pressures in all compartments of the circulation *relative* to the pressures in adjacent compartments. They do not determine the absolute transmural pressure in any compartment. This is determined by the compliance equations.

2. Compliance Equations. Within each compartment, transmural pressure is a function of the blood volume in the compartment and the compliance of its walls:

$$P = V/C \quad (4)$$

where P is transmural pressure, V is volume, and C is compliance in a particular compartment. This equation assumes a linear relation between volume and pressure, with the volume decreasing to zero when pressure is zero. Other models have assumed a finite volume of blood in the circulation at zero pressure. However, this volume cannot be measured and it changes when venous smooth muscle activity changes; it is therefore very difficult to handle equations of this type. In addition, the shapes, slopes, and intercepts of pressure-volume curves obtained with currently available methods are so variable that it is not yet possible to formulate accurate equations. Therefore, the simplest possible equation was used in this analysis.

When both the resistance and compliance equations for all the compartments are simultaneously satisfied, the pressures and volumes throughout the circulation are described. Since the resistance equation (equation 1) involves flow, the third set of equations, the cardiac equations, are also required before a solution can be attempted.

3. Cardiac Equations. These equations relate the function of the heart to its input and output parameters and this set of equations is clearly the most complex and controversial. Equations used in the simple models of the circulation are unsatisfactory since the equation relates cardiac output or stroke work to right atrial pressure (112, 132, 133, 198). These curves incorporate a relationship between preload (expressed as right atrial pressure) and cardiac output but different curves must be used for different afterloads, heart rates, and contractility changes, and interactions between the ventricles cannot be described. This review will attempt to formulate a more complete set of equations and it is hoped that the problems encountered and the approximations made will stimulate readers to improve this analysis.

A. PRELOAD. Preload is defined as the degree of stretch of the actin-myosin elements prior to contraction and, in general, it is directly related to end-diastolic ventricular volume. The equations that determine this volume link the resistance and capacitance equations to the cardiac equations on the input side of each ventricle. End-dia-

stolic ventricular pressure is greater than mean atrial pressure due to the gradual filling of the ventricle during diastole and to the final rise in ventricular pressure due to atrial contraction. A precise relationship has not yet been formulated but I have assumed the following relationship:

$$P_{ED} = P_{AT} + k.F_{AT} \quad (5)$$

where P_{ED} is end-diastolic ventricular pressure, P_{AT} is mean atrial pressure, k is a constant, and F_{AT} is an arbitrary measure of atrial contractility (normal = 1). This equation assumes that end-diastolic pressure is greater than mean atrial pressure by a constant amount that is dependent on atrial contractility but is independent of the mean atrial pressure. This seems reasonable since as the atria become distended, their force of contraction increases due to Starling's law (342) but their ability to generate pressure may become limited due to LaPlace's law (109). Atrial contractility must be considered as a separate factor independent from ventricular contractility since vagal stimulation, by depressing atrial contractility, changes the relationship between mean atrial pressure and stroke work but not the relationship between end-diastolic pressure and stroke work (277). It is not clear whether contractility of the right and left atria can vary independently but for the present I have assumed the same contractility for both atria.

The relationship between left ventricular end-diastolic volume and pressure is determined by the ventricular diastolic compliance.

$$V_{ED} = P_{ED}.C_{DV} \quad (6)$$

where V_{ED} is end-diastolic ventricular volume, P_{ED} is end-diastolic ventricular pressure, and C_{DV} is diastolic ventricular compliance. This equation produces a linear relationship and this appears to occur over the normal physiological range (97, 200). However, as end-diastolic pressure increases, the ability of the ventricle to expand is limited by the pericardium. Opening the pericardium increases ventricular diastolic compliance (24, 97, 221). In modelling these relationships, we could either use the simple equation (equation 6) and apply an empirical correction at high end-diastolic pressures or we could use a complex equation describing the whole curve. We chose the former approach and the program was arranged to progressively decrease diastolic ventricular compliances as left and right end diastolic pressures exceeded 8 and 3 mm Hg, respectively. These values were chosen to put the control values for the left ventricle near the bend in its pressure-volume curve at heart rates similar to those found in conscious animals, while the values fell considerably below the bend at heart rates found in anaesthetized animals (24). There are also complex relationships between the two sides of the heart (24, 73, 200, 313, 334) and five possible mechanisms for a change in ventricular diastolic compliance have been reviewed by Glantz and Parmley (97). Direct mechanical coupling between the two ventricles is an important mechanism for producing changes in the left ventricular diastolic pressure-volume relationship and the effects are large enough to be physiologically significant. In addition, during systole, contraction of the right ventricle is influenced by the characteristics of left ventricular systole (72). However, it is difficult to formulate equations modelling these reciprocal relationships at the present time.

B. CONTRACTILITY AND AFTERLOAD. Recent excellent reviews by Katz (168), Braunwald, Sonnenblick, and Ross (24), and Parmley and Talbot (240) have summarised current knowledge on the mechanism of contraction in the normal heart. We have to formulate a relationship between end-diastolic ventricular volume and stroke volume and this relationship involves the concepts of contractility and afterload. The Frank-Starling relationship or heterometric autoregulation (277) has usually been used in previous models (112, 133, 264). This relationship states that within limits stroke work is related to the end-diastolic length of the muscle fibres. This relationship (the ventricular function curve) is not linear and the precise algebraic expression must be determined from experimental data for the species being modelled.

$$\text{Stroke work} = SV.P = f(V_{ED}) \quad (7)$$

where SV is stroke volume, P is mean aortic pressure during ejection, and $f(V_{ED})$ indicates a nonlinear function of end-diastolic ventricular volume. A change in this relationship is frequently used as a definition of cardiac contractility (22). Shifting of the curve to the left and upwards is taken as a positive inotropic effect while a right and downward shift is taken as a negative inotropic effect. However, stroke work varies with afterload (22, 86, 205, 290) and Sarnoff and his coworkers (277) analysed the additional stroke work done by the left ventricle when end-diastolic pressure was increased by increasing aortic pressure as opposed to increasing stroke volume (pressure-induced homeometric autoregulation). Therefore, the position of the ventricular function curve is not a valid measure of contractility.

We have tried to incorporate a variety of equations similar to equation 7 into our model to derive stroke volume, end-systolic volume, and end-systolic pressure. However, we have never been able to derive values that satisfy the requirement demonstrated by Suga, Sagawa, and their colleagues (275, 276, 302–305) and by Ross and his colleagues (206, 312) that there is a constant relationship between end-systolic pressure and end-systolic volume independent of preload and afterload. Thus when data derived from these models were plotted in the form of pressure-volume loops (22, 275), there was no obvious relationship between end-systolic pressure and end-systolic volume when end-diastolic volume was varied over a considerable range.

Afterload is closely related to intramyocardial systolic tension (20, 290) but the precise definition of afterload in the intact animal is controversial. A complete discussion

of afterload and aortic impedance is outside the scope of this review. Some aspects have been discussed in the following reviews (29, 74, 232, 333), but none of these approaches has, as yet, led to an equation that could be used to quantify cardiac function in terms of an improved ventricular function curve. We therefore turned to the approach developed by Suga, Sagawa, and their coworkers (274–276, 302–305). This approach is based on experimental data obtained both in vivo and in vitro, which demonstrates that when a final tension is specified, the heart muscle shortened to the same final length, independent of preload and aortic impedance. The term "afterload" as used in this review is defined as end-systolic ventricular pressure.

Stroke volume is the difference between end-diastolic volume and end-systolic volume:

$$SV = V_{ED} - V_{ES} \quad (8)$$

where SV is stroke volume and V_{ED} and V_{ES} are the end-diastolic and the end-systolic ventricular volumes, respectively. Suga and Sagawa demonstrated that end-systolic ventricular pressure and volume are related:

$$P_{ES} = E_{max}.(V_{ES} - V_D) \quad (9)$$

where P_{ES} is end-systolic ventricular pressure, V_{ES} is end-systolic ventricular volume, V_D is the dead volume (ventricular volume when P_{ES} is zero), and E_{max} is the maximal volume elastance of the contracting ventricle in mm Hg/ml. When equations 8 and 9 are combined,

$$SV = V_{ED} - V_D - P_{ES}/E_{max} \quad (10)$$

Since systolic pressure is itself related to stroke volume, this equation cannot be resolved and some approximations are necessary. By using equation 1 and, since right atrial pressure is low, mean arterial pressure can be considered as cardiac output (or stroke volume times heart rate) times total peripheral resistance. Pulse pressure is stroke volume divided by arterial compliance and systolic aortic pressure is approximately mean pressure plus two-thirds of pulse pressure. Thus

$$P_S = SV.HR.R_T + 0.67.SV/C_A \quad (11)$$

where P_S is systolic aortic pressure, SV is stroke volume, HR is heart rate, R_T is total peripheral resistance, and C_A is arterial compliance. This equation incorporates the two major factors in overall aortic impedance as defined by Braunwald (22), that is, peripheral resistance and arterial wall compliance.

If we assume that end-systolic ventricular pressure approximates systolic aortic pressure, then by combining equations 10 and 11

$$SV = V_{ED} - V_D - [SV.(HR.R_T + .67/C_A)]/E_{max} \quad (12)$$

and this resolves to

$$SV = (V_{ED} - V_D)/[1 + (HR.R_T + .67/C_A)/E_{max} \quad (13)$$

This equation can be solved in a reiterative computer program (see below). Volume elastance (E_{max}) is a measure of contractility (128, 206, 275, 302–305). E_{max} is constant over the physiological range (276) but it seems reasonable that it must decrease at very high values of end-systolic pressure, as is usually shown in hand-drawn figures (22, 24, 128). In modelling these relationships, we therefore used a single value for E_{max} for each ventricle with an empirical correction decreasing E_{max} at high end-systolic ventricular pressures. E_{max} was decreased progressively at end-systolic ventricular pressures above 160 mm Hg for the left ventricle and above 30 mm Hg for the right ventricle. When contractility is decreased, these ventricular pressures at which E_{max} begins to fall off were reduced proportionally.

Provided that V_D (the end-systolic ventricular volume when end-systolic pressure is zero) is small, volume elastance is pressure divided by volume, its reciprocal is compliance as used in this review, and the reciprocal of E_{max} is systolic ventricular compliance. Therefore, this model views ventricular contraction as a change in ventricular compliance. The end-diastolic compliance defines the resting pressure/volume relationship at the start of contraction and the systolic ventricular volume elastance defines the pressure/volume relationship at the end of contraction. Depending on the relative diastolic and systolic pressures, a certain volume of blood will leave the heart because of this decrease in compliance during contraction. It can be seen that this effect, although on a totally different time scale, is similar to a decrease in venous compliance that causes a rise in pressure in the capacitance vessels, a decrease in their blood content, or a combination of the two.

When these equations are incorporated into the model, we not only obtain the constant end-systolic pressure-volume relationship but we can plot ventricular function curves relating stroke work or cardiac output to end-diastolic volume or pressure (see section V G). Thus an analysis based on the end-systolic pressure-volume relationship leads to data compatible with the normal ventricular function curve while an analysis based on the function curve does not give rise to constant end-systolic pressure-volume relationships. We are unable to explain this at present. When we model the experiments described by Sarnoff et al. (277), where end-diastolic volume is increased either by increasing stroke volume at constant aortic pressure, or by increasing aortic pressure at constant stroke volume, the area inside the pressure-volume loop (stroke work) is greater for the second case compared to the first. Thus the model shows pressure-induced homeometric autoregulation as defined by Sarnoff et al. (for diagram see section V G). Rate-induced homeometric autoregulation (277) is not incorporated in the equations but Johnson (160) states that steady state contractility appears to be substantially independent of heart rate since long-term force-interval relationships tend to neutralise short-term ones.

These series of equations, although at best approxi-

mations, allow the heart to be considered as four separate interacting pumps and they allow modelling of the following parameters: (a) changes in atrial contractility; (b) changes in diastolic ventricular compliance; (c) changes in contractility and heart rate; (d) pressure-volume loops for both ventricles; (e) the relationship between end-diastolic volume or pressure and stroke work, stroke volume or cardiac output; (f) effects of peripheral resistance and arterial compliance on cardiac function.

We now have three sets of equations—resistance, compliance, and cardiac—that describe the interactions within the cardiovascular system. When they are simultaneously solved, we have a description of the cardiovascular system at equilibrium, given the input parameters for the semi-independent variables. As yet the system has no intrinsic modulation (reflexes, etc.).

4. Intrinsic Modulation. The direct actions of a drug and the resulting secondary interactions within the circulation result, in turn, in activation or inhibition of a variety of intrinsic mechanisms and reflexes. This modulation further alters the cardiovascular system, usually in the direction of reducing the effects produced by the drug. The reflex effects are brought about by the action of the autonomic nerves or hormones on the semi-independent variables. Thus, a complete description of the consequences of drug action must include this secondary modulation.

In spite of very extensive study of many cardiovascular intrinsic mechanisms and reflexes, the information necessary to incorporate this modulation quantitatively into a model of the circulation is not available. For example, we were unable to answer the question, "If phenylephrine raises arterial pressure by 50 mm Hg by a direct action on arterioles, how much will the pressure rise in the presence of the arterial baroreceptor reflex?" Experiments (116) demonstrated that, in the anaesthetised cat, the baroreceptor reflex reduced drug effects on arterial pressure to about one-third over a wide range of responses and that effects on heart rate were small probably due to anaesthesia. Thus, equations were derived describing the effects of the baroreceptor reflex on peripheral resistance, heart rate, and venous compliance in anaesthetised cats:

$$R_T' = R_T - k.(P_A - P_S) \quad (14)$$

$$HR' = HR - m.(P_A - P_S - 10) \quad (15)$$

$$C_V' = C_V + n.(P_A - P_S) \quad (16)$$

where R_T', HR', and C_V' are the total peripheral resistance, heart rate, and venous compliance respectively after operation of the baroreceptor reflex and R_T, HR, and C_V are the same parameters in the absence of the reflex, P_A is the arterial pressure in the absence of the reflex, P_S is the set point of the reflex, and k, m, and n are constants.

These equations were used to incorporate the baroreceptor reflex into the model but the problem arises of how to distribute the effects over the four different vascular beds. The changes in arterial pressure induced by the drug cause myogenic responses in the vascular beds and, as the baroreceptor reflex restores arterial pressure approximately two-thirds of the way back towards the control level (116), these myogenic effects are reduced also. Thus it becomes difficult to separate those vascular beds where sympathetic tone is changed from those where myogenic tone is changed. Although the predominant effect of the reflex may be on skeletal muscle arterioles, the myogenic changes are greater in other beds, and the net result is that flow does not change very much in any vascular bed (176). We have therefore distributed the change in arteriolar resistance across all the vascular beds. The distribution of the capacitance effects of the baroreceptor reflex is also not well established (176) and there may be species differences (116). We have therefore distributed these changes across all the vascular beds also. The baroreceptor reflex produces modest changes in cardiac contractility (304) but we have not yet incorporated this effect into the model.

As yet we have been unable to incorporate any other intrinsic, hormonal (angiotensin, vasopressin, and catecholamines), or reflex-modulating mechanisms into equations. Cardiopulmonary reflexes are important (47, 63, 346) but the lack of quantitative data clearly illustrates how little we know of the quantitative interactions of these reflexes in the intact animal or man (62). However the effects of endogenous angiotensin can be incorporated into the overall effects of a drug that releases renin by adding the direct actions of a small dose of exogenous angiotensin to the direct actions of the drug (see section IV).

5. Solving the Equations. The equations can be easily solved with a small computer program written in BASIC. The flow chart for the program is shown in figure 4 and the program in BASIC-11 (Digital Equipment Corp.) is given in full in the APPENDIX. The program is initialised for the species selected with the values for the semi-independent variables that are given in table 1. In the first run through the calculations (I = 1 in fig. 4), these values are used to calculate the values for the dependent variables. The program initially assumes that 18% of the total blood volume is in the lungs and it solves the equations from this starting point. After the first iteration, the sum of the calculated volumes of blood in the various compartments is compared with the initialised value for total blood volume. If these values differ, the volume of blood in the lungs is changed proportionally and the equations are solved again. This sequence is reiterated until the calculated blood volume is within 1% of the initialised total blood volume and at this point all the equations are solved to within 1%. The calculated values for the dependent variables are then used to change the values of the semi-independent variables as a result of the intrinsic modulating mechanisms. These modified values are then used to recalculate the values

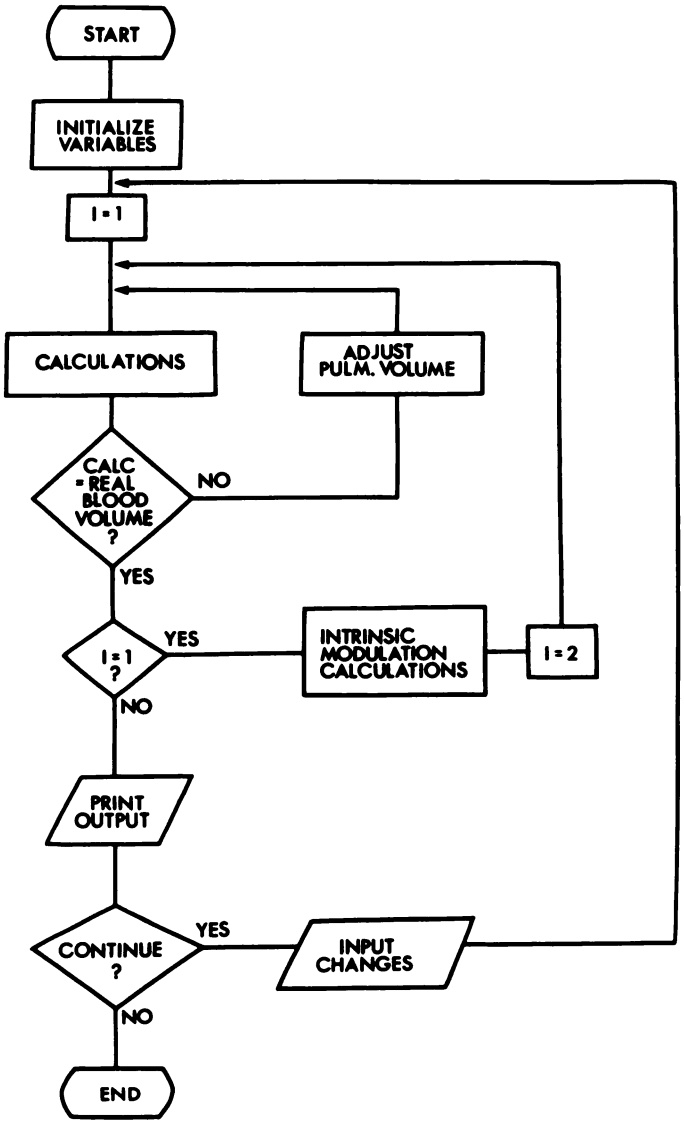

FIG. 4. Flow chart for the computer program that solves the equations.

of the dependent variables (I = 2 in fig. 4). The program then prints out the values for the 76 cardiovascular parameters incorporated into it. These values represent the control values for the species selected. The user then inputs changes in the semi-independent variables to mimic as many experimental situations (doses, drugs, or combinations of drugs) as he requires. The program then calculates and prints the values of the 76 cardiovascular parameters for each experimental situation. Dose-response curves from sequential runs have to be plotted by a separate program or by hand.

There are two major differences between this model and previous models (133, 274). First, only the semi-independent variables can be changed by the user. Since drugs act only on these variables, this model is particularly useful to pharmacologists. Physiological experiments where arterial pressure, venous outflow, or cardiac output are artificially held constant by the investigator require the addition of artificial compartments to the model shown in figure 3 and therefore require modifications to the equations. Similarly, postural changes and pathological conditions such as valvular heart disease can only be analysed after appropriate modifications to the model and the equations. Modifications to model right-heart bypass experiments are discussed in section III E. Secondly, the model does not incorporate time at any point. The circulation is considered to be at equilibrium at the time the equations are solved. Therefore if the effects of a drug change with time, the model must be rerun with appropriately changed input values for each time selected by the investigator. It is not possible to study effects of a bolus injection of a short-acting drug such as epinephrine with this model since drug actions and intrinsic modulations are interacting with complex time courses and the circulation is never at equilibrium.

6. Modelling Different Species. To use the model, values have to be assigned to the constants in the various equations and to the basal components of the semi-independent variables (table 1). These values were taken initially from our own work on the anaesthetised cat. However, many cardiovascular scientists are more interested in the anaesthetised dog or in man and it was of interest to examine the extent of the changes required to model these other species. In fact few changes were needed, which illustrates the close similarity of the cardiovascular systems in these species. Blood volume was increased from 52 ml/kg of body weight for the cat (122) to 80 ml/kg of body weight for the dog and man (4). To compensate for this, all compliances were increased by the factor 80/52. Heart rate was reduced from 180/min for the anaesthetised cat, to 120/min for the anaesthetised dog, and to 75/min for man. Since our anaesthetised and surgically prepared cats have a high degree of cardiac sympathetic tone as demonstrated by the substantial reductions in heart rate and cardiac output after beta-blockers, we reduced ventricular contractility (E_{max}) for both ventricles for the dog and for man. Finally, the set point of the baroreceptor reflex was reduced to correspond to the usual mean arterial pressure (120 mm Hg for cat, 100 mm Hg for dog, and 80 mm Hg for man). Leaving the baroreceptor heart rate factor (equation 15) unchanged gives a proportionally larger baroreflex heart rate change in man. This seemed reasonable since the heart rate changes are depressed in anaesthetised cats (116). All other semi-independent variables were the same for all three species.

These initialising control values for the semi-independent variables and the resulting calculated control values for the dependent variables for all three species are shown in table 1. All values are given per kilogram of body weight. No attempt has been made to cite references showing that these values are "normal." In all species, there is considerable individual variation and no single set of values for the semi-independent variables will precisely model all experimental data in the literature. It should be remembered that these are only initial

starting values. If an investigator wishes to model a particular data set, he can input the appropriate values for the semi-independent variables to match the control data set before he begins modelling the experimental situation. Thus only the relationships between variables are preset by the computer program and the values for the variables can be changed to match the variability seen under different experimental conditions.

D. Summary of Overall Concepts of the Circulation

In this first section of the review, I have argued that the analysis of the mechanisms of drug action on cardiac output involves three stages—identification of the primary actions of the drug, delineation of the resulting secondary interactions within the cardiovascular system, and then delineation of the consequences of intrinsic modulation of the responses. The ultimate aim is to describe precise relationships between all the cardiovascular variables and to calculate the new equilibrium conditions in the presence of the drug. Cardiovascular parameters were divided into those on which drugs may act (semi-independent variables) and those which are wholly determined within the circulation (dependent variables) and a series of equations based on the model shown in figure 3 were proposed to describe the relationships between these parameters. This model represents a way of integrating the known direct actions of drugs, determined in vitro or in vivo, to demonstrate or predict the resultant effects on cardiac output. When the model fails to correctly demonstrate the observed effects of a drug, there are three possible reasons: 1) the direct effects of the drug (as input to the model) are incorrect; 2) the cardiovascular relationships described by the model are incorrect; 3) the constants and/or basal values are incorrect. Thus the model demonstrates how well our knowledge of the circulation fits together and when it fails, it demonstrates areas that require further study.

The next section of this review discusses the predicted effects on cardiac output of changes in each of the semi-independent variables on which drugs might act, while the later sections examine how far the known effects of certain groups of drugs agree with these predictions.

III. Effects of Semi-independent Variables on Cardiac Output

Before dealing with the complex multiple actions of real drugs, it is useful to examine the relative effects on cardiac output of each semi-independent variable. Since no drug has one single action, this analysis is necessarily theoretical. The data shown are for the model of the human. Data for the models of the anaesthetised cat and dog are very similar.

A. Blood Volume and Compliances

Figure 5 shows the effects on cardiac output, arterial pressure, and left atrial pressure that occur when blood volume and the various compliances are decreased to

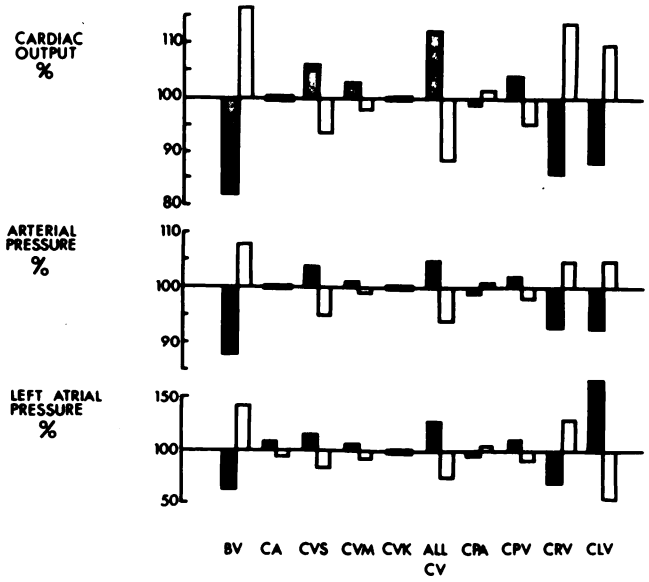

FIG. 5. The effects of changing blood volume and each compliance to 67% (cross-hatched bars) and 150% (open bars) of the control values (table 1) on cardiac output, mean arterial pressure, and mean left atrial pressure, expressed as percent of control. BV, blood volume; CA, arterial compliance; CVS, splanchnic venous compliance; CVM, muscle venous compliance; CVK, kidney venous compliance; ALL CV, all systemic venous compliances; CPA, pulmonary arterial compliance; CPV, pulmonary venous compliance; CRV, right ventricular diastolic compliance; and CLV, left ventricular diastolic compliance.

67% or increased to 150% of the normal control values given in table 1. As expected, changes in blood volume produce major effects on cardiac output. An increase in blood volume increases the pressure and volume in all compartments of the circulation but the model predicts that a major portion (50%) of the blood volume added or removed will be pooled in, or mobilised from, the splanchnic bed. These predicted values are somewhat smaller than the experimentally observed values (66%) in cats and dogs (26, 122).

Arterial and pulmonary arterial compliances have only small effects on cardiac output due to two opposing effects. For example, when either of these compliances is decreased, blood volume is redistributed towards the venous system and atria tending to increase cardiac output, while the increased pulmonary or aortic systolic pressures tend to reduce cardiac output.

Changes in venous compliance in peripheral vascular beds have effects on cardiac output that vary from significant (splanchnic) to negligible (kidney) depending on the organ blood content. Since one-third of the total blood volume is contained in the splanchnic bed (122), it is not surprising that changes in this venous compliance will mobilise or pool substantial volumes of blood and hence have significant effects on cardiac output. About half of the effect of a change in total systemic venous compliance is due to the splanchnic bed. It should be noted that the effects of a change in venous compliance may be modified if venous resistance also changes. This is discussed later. Since venous smooth muscle has little

basal tone (84, 99), a drug-induced increase in venous compliance usually involves reduction of sympathetic tone on the veins. Changes in pulmonary venous compliance produce directionally similar changes in cardiac output to those produced by changes in peripheral venous compliance and the effects are quantitatively similar to those in skeletal muscle. Thus when we are considering the effects of venous compliance on cardiac output, the effects in the splanchnic bed are most important, changes in the pulmonary and skeletal muscle beds are quite important, and changes in the renal bed are unimportant.

Changes in right and left ventricular diastolic compliances exert major effects on cardiac output. A decrease in ventricular diastolic compliances reduces cardiac output—as for example in experimental cardiac tamponade, while an increase will increase cardiac output—as for example by opening the pericardium. The effects of decreased left ventricular compliance are as large as those of an equivalent percentage reduction in contractility (see below and fig. 7). In some patients with heart failure, the reduced cardiac output may be due to decreased diastolic ventricular compliance as well as, or instead of, reduced contractility, especially when fibrosis or hypertrophy stiffens the ventricular wall. However, as discussed later, the effects on ventricular end-diastolic volume are quite different. It is not clear yet whether drugs can produce genuine changes in ventricular diastolic compliance. Although some drugs cause apparent changes in left ventricular diastolic compliance, these effects may be indirect consequences of pressure changes in the right ventricle (97, 201, 202).

B. Resistances

Figure 6 shows the effects on cardiac output, arterial pressure, and left atrial pressure that occur when the various resistances are decreased to 67% or increased to 150% of the normal control values given in table 1. In the normal animal (117) or man, changes in arteriolar resistance in individual beds have quite small effects on cardiac output. The change in cardiac output is predominantly due to the change in arterial pressure and hence afterload (end-systolic ventricular pressure). However, venous pressure is also changed. In the kidney this has little effect because renal venous compliance is very small (table 1), but in the splanchnic bed, where venous compliance is much larger (table 1), it results in a redistribution of the blood volume, which opposes the change in cardiac output. Thus splanchnic vasoconstriction has less effect on cardiac output than renal vasoconstriction of an equivalent degree.

Postcapillary resistance has little direct effect on cardiac output and its major function is in control of capillary pressure (85, 215). This may indirectly influence cardiac output through the effects of capillary pressure on blood volume but that aspect is not included in the model. Changes in venous resistances have significant

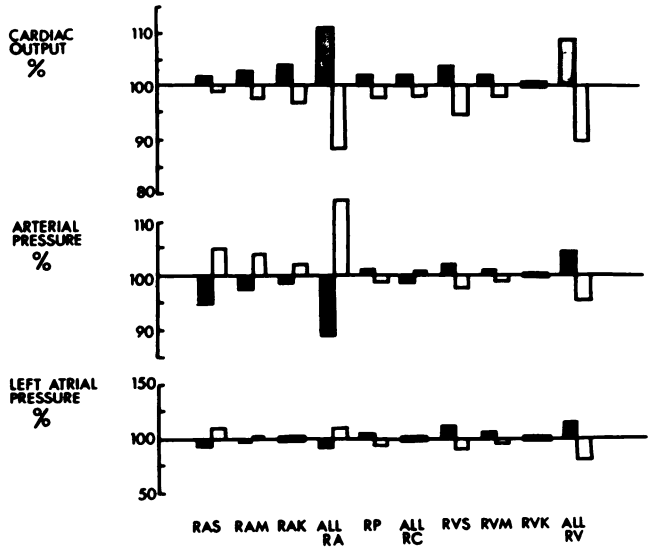

FIG. 6. The effects of changing each resistance to 67% (cross-hatched bars) and 150% (open bars) of the control values (table 1) on cardiac output, mean arterial pressure, and mean left atrial pressure, expressed as percent of control. RAS, splanchnic arteriolar resistance; RAM, muscle arteriolar resistance; RAK, kidney arteriolar resistance; ALL RA, all arteriolar resistances; RP, pulmonary resistance; ALL RC, all postcapillary resistances; RVS, splanchnic venous resistance; RVM, muscle venous resistance; RVK, kidney venous resistance; and ALL RV, all venous resistances.

effects on cardiac output. By increasing the pressure drop between the capacitance vessels and the right atrium, an increase in venous resistance decreases preload and hence cardiac output. A combination of an increase in venous resistance and a decrease in venous compliance results in little change in cardiac output. These effects have important implications in the analysis of drug effects on the venous system. Venoconstriction might increase, decrease, or have little effect on cardiac output depending on the relative effects on venous compliance and venous resistance. These aspects will be discussed further in section III E and section IV.

C. Heart Rate and Contractility

Figure 7 shows the effects on cardiac output, arterial pressure, and left atrial pressure that occur when heart rate and ventricular and atrial contractilities are decreased to 67% or increased to 150% of the normal control values given in table 1. Heart rate changes of this magnitude produce rather large changes in cardiac output, as do changes in total cardiac contractility. Changes in only right or only left ventricular contractility cause quite small changes in cardiac output because the effects of the localised contractility changes are opposed by compensatory changes in preload and afterload.

Thoracic pressure, due to its effects in modifying transmural intrathoracic pressures, exerts moderate effects on cardiac output. Decreasing intrathoracic pressure towards zero (opening the chest) causes the expected decrease in cardiac output.

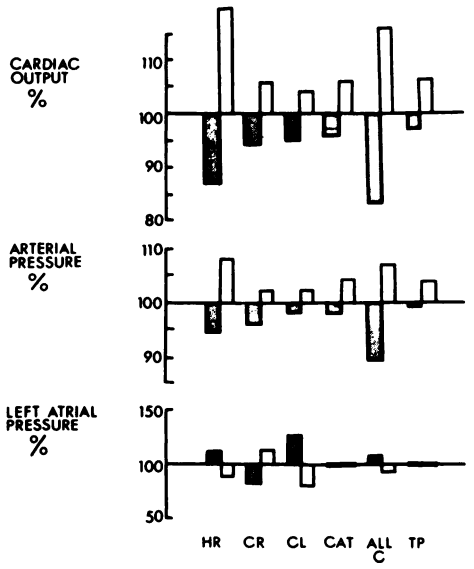

FIG. 7. The effects of changing cardiac rate and contractility to 67% (cross-hatched bars) and 150% (open bars) of the control values (table 1) on cardiac output, mean arterial pressure, and mean left atrial pressure, expressed as percent of control. HR, heart rate; CR, right ventricular contractility (E_{max}); CL, left ventricular contractility; CAT, atrial contractility; ALL C, right and left ventricular and atrial contractilities; TP, intrathoracic pressure.

D. Summary and Discussion

Changing the value of any semi-independent variable to 67% or 150% of its control value changed cardiac output by at most 15% and the effects in the intact animal or man would undoubtedly be smaller still due to the many other intrinsic modulating mechanisms not incorporated in the model. A change in one semi-independent variable causes compensating changes in other variables that influence cardiac output. It can be seen in Figures 5 to 7 that in every case where the semi-independent variable altered the vascular system, preload (as indicated by left atrial pressure) and afterload (as indicated by arterial pressure) changed in the same direction thus producing opposing effects on cardiac output. When the semi-independent variable altered cardiac activity, preload and afterload changed so that both opposed the change in cardiac output. Thus the interaction of cardiac function, preload, and afterload results in a high degree of stability in cardiac output.

It follows therefore that if a drug has secondary actions that prevent these compensatory adjustments, its effects on cardiac output will be much greater. In particular, the combination of cardiac stimulation (150% control), decreased venous compliance (67% control), and decreased arteriolar resistance (67% control) produces a large increase in cardiac output (170% control). The decreased venous compliance reduces the fall in preload and the decreased arteriolar resistance reduces the increase in afterload that normally follow cardiac stimulation alone. These combined effects resemble the effects of epinephrine (see section IV A). Thus, simultaneous changes in several semi-independent variables that change cardiac output in the same direction produce larger changes in cardiac output than the sum of their individual effects. Conversely, simultaneous changes in several semi-independent variables that change cardiac output in opposite directions, tend to neutralise one another, resulting in no change in cardiac output. The decrease in cardiac output produced by an increase in peripheral arteriolar resistance can be neutralised by a simultaneous decrease in venous compliance as demonstrated in anaesthetised cats (115). Responses to other combinations will be discussed where appropriate in section IV, which deals with the actions of some common drugs.

E. "Unstressed Volume," "Total Systemic Compliance," and Techniques to Study the Venous System

Before going on to the effects of individual drugs, it is convenient at this point to briefly assess some commonly used techniques to examine the actions of drugs on the venous system.

The venous return long-circuit technique involves diverting the total venous return to an extracorporeal reservoir through an outflow pipe, the height of which can be changed to alter venous pressure. From the reservoir, the blood is returned with a pump to the right atrium, the pulmonary artery (right heart bypass), or into a systemic artery (total cardiopulmonary bypass). In all cases, cardiac output is controlled by the pump and held constant. Two types of measurement are made: the change in reservoir volume when a drug is given—this is called the change in "unstressed volume"; and the change in reservoir volume when the outflow pipe is raised or lowered by a defined amount—this is calculated as reservoir volume change divided by the venous pressure change and called the "total systemic compliance." Changes in "unstressed volume" and "total systemic compliance" are usually interpreted as effects of the drug on the venous system (23, 129, 152, 166, 222, 249, 260, 271, 285).

Based on our own earlier experience with similar techniques, it seemed unlikely that a change in reservoir volume ("unstressed volume") would be caused only by a drug action on the venous system. Cardiac and arteriolar resistance changes cause large changes in venous pressure and we expected that these effects would alter reservoir volume. Stated in another way, if the drug would have produced a change in cardiac output *by any means* in the intact circulation, then maintenance of an artificially constant cardiac output would require infusion or removal of blood. To test this hypothesis, we modified the model to allow cardiac output and central venous pressure to be fixed input values. The discrepancy between the calculated blood volume and the real blood volume then became the change in "unstressed volume." The model confirmed the above hypothesis. Changes in resistances, heart rate, and contractility, as well as in venous compliances, all produced large changes in "un-

stressed volume." Thus, measurement of "unstressed volume" during constant cardiac output proves only that a drug alters some cardiovascular parameters—it cannot be used to determine which parameters.

Measurement of total systemic compliance involves application of a known pressure to the capacitance vessels through the venous resistances. This measurement was not altered in the model when cardiac function or arteriolar resistances were altered but it was sensitive to changes in venous compliance. The change in total systemic compliance was quantitatively related to the change in venous compliance but changes in the muscle or splanchnic beds could not be distinguished. Thus, in this type of preparation, only the total systemic compliance can be used as an index of drug effects on overall venous compliance.

In addition, the use of extracorporeal circuits may modify the drug effects. The problems of arterial long-circuits have been discussed previously (82, 126) and even venous long-circuits with the associated surgery may cause moderate or marked degrees of outflow block in the canine liver (126). Studies on splanchnic venous resistance that use extracorporeal circuits in dogs (272, 273) must be interpreted with considerable caution especially if there is any indication of an abnormally high portal venous pressure. In anaesthetised cats in my laboratory, the effects of drugs on cardiac output have always been substantially smaller in preparations involving an extracorporeal circuit compared with those in cats without such a circuit (127).

Plethysmography represents an alternative technique for measurement of regional blood volume. It was used extensively for skeletal muscle and intestine by Folkow's group—see review by Mellander and Johannson (215)—and for the liver and spleen in my laboratory (126). It avoids the problems of the long-circuit technique but only one organ can be studied in each experiment. The advantages and disadvantages of plethysmography, particularly as applied to the liver, were reviewed recently (113). In most vascular beds, calculation of venous compliance is difficult since the pressure within the capacitance vessels (venules) is difficult to measure. This problem is largely overcome in the liver since intrahepatic pressure is very close to portal pressure, which is easily measured (113).

There have been many studies on the effects of drugs on human cutaneous veins (see references under individual drugs). A major problem in these studies is that these large veins form a part of specialised temperature-control mechanisms. Their responses may not be representative of those in small venules in deep organs. In addition, the responses are usually studied under abnormally high venous pressures (25 mm Hg) and the drugs are administered by local infusion. Their concentrations may not be similar to those reaching the veins after a drug has passed through the tissues. It seems readily conceivable that some short-acting drugs may produce marked venous responses in vitro or by local infusion and yet have no venous actions in vivo due to rapid clearance by the tissues. This aspect is discussed in more detail in relation to individual drugs.

In summary, our techniques for studying the venous system have severe limitations. Since it is now clear that the venous system plays a major role in cardiovascular responses to drugs, as proved throughout this review, we should pay much more attention to development of precise, valid, and reproducible techniques for measurement of venous compliance and venous resistance.

IV. Effects of Some Common Drugs on Cardiac Output

There is clearly a limit to the number of drugs that can be reviewed but at the present time the number of drugs that can be reasonably analysed is quite small. For many drugs the information about the direct actions is so limited that the analysis becomes little more than guesswork. One problem is that drugs that have important clinical uses frequently have rather long plasma half-lives. These drugs are difficult to study in anaesthetised animals since only one drug can be examined per experiment. The in vitro actions cannot yet be extrapolated to the intact animal since the pharmacokinetic data are often not available; not only is it difficult to relate molar drug concentrations in an isolated organ bath to in vivo dosage, but metabolic clearance must be considered. For example, many substances are rapidly cleared during one passage through the tissues (322) and the concentration of these agents reaching the venous bed may be much lower than the concentration reaching the heart and arterioles when the drugs are given intravenously. Even drugs with a longer half-life may not reach the venous bed in certain organs. For example, prazosin causes alpha-1-receptor block in the mesenteric veins (241) but has no significant effect on the hepatic veins (111). This difference may be due to almost complete removal of prazosin from the blood by the hepatic parenchyma. Thus, some drugs may not reach the venous system in significant concentrations in vivo. We have more data from studies in anaesthetised animals for drugs with short half-lives and the sympathomimetic amines and angiotensin have been studied extensively. Although some of these agents have few clinical uses, they are endogenous substances that are released by many other drugs that affect cardiac output. Another area of considerable interest is the actions of vasodilator drugs in relation to treatment of cardiac failure. These drugs will therefore be discussed in some detail.

A. Epinephrine, Norepinephrine, Isoproterenol, and Phenylephrine

The pharmacological actions of the sympathomimetic amines have been reviewed (3, 8, 69, 336, 345). Four sympathomimetics were chosen for review since there are extensive data available and they represent the spec-

trum of action of this group of drugs. Dopamine and dobutamine are considered separately. Tables 2 and 3 are attempts to tabulate the quantitative direct actions of three doses of each of these amines on the semi-independent variables when each drug is infused i.v. over a few minutes. Since the control values varied widely in different preparations, the changes are expressed as percentages of control. These dose ranges are within the rates of norepinephrine and epinephrine that can be secreted by the adrenal medulla (33). In the dose ranges considered, phenylephrine stimulates alpha-1 receptors (296, 336, 340), while isoproterenol stimulates beta-receptors nonselectively. Epinephrine and norepinephrine stimulate both alpha and beta-receptors but the balance varies in different organs and under different conditions.

TABLE 2

Actions of epinephrine and norepinephrine on the semi-independent variables expressed as per cent of control value.

Dose	Epinephrine			Norepinephrine		
	0.25	0.5	2.0	0.25	0.5	2.0
	μg/kg/min			*μg/kg/min*		
Blood volume	100	100	100	100	100	100
Arterial compliance	100	100	100	?	?	?
Splanchnic venous compliance	60	40	30	70	50	40
Muscle venous compliance	90	80	70	90	80	70
Other venous compliance	?	?	?	?	?	?
Pulmonary artery compliance	?	?	?	?	?	?
Pulmonary venous compliance	?	?	?	?	?	?
Ventricular diastolic compliance	?	?	?	?	?	?
Splanchnic arteriolar resistance	50	60	80	130	150	200
Muscle arteriolar resistance	50	70	100	160	250	400
Renal arteriolar resistance	150	200	250	160	250	400
Other arteriolar resistance	100	100	100	130	150	200
Splanchnic venous resistance	100	100	100	120	130	150
Muscle venous resistance	100	100	100	150	200	300
Pulmonary resistance	?	?	?	100	100	100
Heart rate	120	130	140	120	130	140
Right ventricular contractility	120	130	140	120	130	140
Left ventricular contractility	120	130	140	120	130	140
Atrial contractility	120	130	140	120	130	140
Thoracic pressure	?	?	?	?	?	?

TABLE 3

Actions of isoproterenol and phenylephrine on the semi-independent variables expressed as per cent of control value.

Dose	Isoproterenol			Phenylephrine		
	0.25	0.5	2.0	2	4	16
	μg/kg/min			*μg/kg/min*		
Blood volume	100	100	100	100	100	100
Arterial compliance	?	?	?	?	?	?
Splanchnic venous compliance	70	65	60	90	80	70
Muscle venous compliance	100	100	100	95	90	80
Other venous compliance	100	100	100	?	?	?
Pulmonary artery compliance	?	?	?	?	?	?
Pulmonary venous compliance	?	?	?	?	?	?
Ventricular diastolic compliance	?	?	?	?	?	?
Splanchnic arteriolar resistance	60	40	30	120	135	170
Muscle arteriolar resistance	80	50	40	140	160	200
Renal arteriolar resistance	90	80	60	150	175	220
Other arteriolar resistance	80	50	40	120	135	170
Splanchnic venous resistance	?	?	?	?	?	?
Muscle venous resistance	?	?	?	?	?	?
Pulmonary resistance	100	100	100	100	100	100
Heart rate	120	130	140	100	100	100
Right ventricular contractility	140	150	160	100	100	100
Left ventricular contractility	140	150	160	100	100	100
Atrial contractility	140	150	160	100	100	100
Thoracic pressure	?	?	?	?	?	?

Blood volume is probably unchanged by these short infusions and low doses (336), although longer infusions of epinephrine and norepinephrine may decrease plasma volume secondary to elevated capillary pressure (43, 177, 345). Few data are available on the actions on arterial compliance. In a recent study, arterial compliances in dogs were not significantly different before and during infusions of moderate doses of epinephrine (285). Data for the other amines are not available.

There is no doubt that epinephrine markedly reduces total systemic venous compliance but quantitative measurements in individual vascular beds are few. Measurements of "unstressed volume" (23, 152, 166, 260, 273) have been shown to be invalid as an index of venous compliance changes (section III E) but total systemic compliance is decreased by epinephrine (222, 285). Epinephrine, norepinephrine, and phenylephrine decrease splanchnic venous compliance. There is a marked contraction of the spleen (56, 125) in cats and dogs but splenic volume changes are unimportant in man (10, 56). Isolated mesenteric and portal veins strips are contracted (294, 306). Hepatic venous compliance is markedly reduced and these changes have been measured quantitatively (117, 118). These agents also decrease skeletal muscle venous compliance (70, 83, 99, 157, 214, 216, 294, 306, 345). In studies of pressure-volume responses in the human forearm (43, 70), norepinephrine produced a substantial decrease in venous compliance while epinephrine responses were slightly smaller. However, the effects were most marked at high venous pressures and were quite small at pressures within the normal range. Cutaneous veins in the human hand are contracted (50, 226). Phenylephrine is much less potent than norepinephrine and epinephrine (70, 345) and this is reflected in the doses in table 4. Quantitative comparisons of these beds are not available in the same preparation. However, if all venous compliances were decreased equally during i.v. infusions of these agents, there would be large increases in venous pressures but little redistribution of blood volume. Since we consistently observe a marked decrease in splanchnic blood volume (117, 118), this suggests that the decrease in splanchnic venous compliance is considerably greater than the decrease in venous compliance elsewhere.

Isoproterenol in small to moderate doses has little effect or causes weak relaxation of venous smooth muscle, in isolated organs (306, 310), vein segments in vivo (50), and during short intra-arterial infusions (56, 118, 125, 165). It did not modify the responses to sympathetic nerve stimulation in the hepatic venous bed (111). However, in the human hand isoproterenol relaxes venous

TABLE 4

Actions of dopamine and dobutamine on the semi-independent variables expressed as per cent of control value.

Dose	Dopamine			Dobutamine		
	10	20	80	4	8	32
	μg/kg/min			μg/kg/min		
Blood volume	100	100	100	100	100	100
Arterial compliance	?	?	?	?	?	?
Splanchnic venous compliance	70	50	40	?	?	?
Muscle venous compliance	90	80	70	?	?	?
Other venous compliance	?	?	?	?	?	?
Pulmonary artery compliance	?	?	?	?	?	?
Pulmonary venous compliance	?	?	?	?	?	?
Ventricular diastolic compliance	?	?	?	?	?	?
Splanchnic arteriolar resistance	60	80	100	100	100	100
Muscle arteriolar resistance	100	100	140	80	70	60
Renal arteriolar resistance	50	70	80	100	100	100
Other arteriolar resistance	?	?	?	?	?	?
Splanchnic venous resistance	100	100	100	?	?	?
Muscle venous resistance	?	?	?	?	?	?
Pulmonary resistance	100	100	100	100	100	100
Heart rate	100	105	120	105	110	130
Right ventricular contractility	120	130	140	120	130	140
Left ventricular contractility	120	130	140	120	130	140
Atrial contractility	120	130	140	120	130	140
Thoracic pressure	?	?	?	?	?	?

smooth muscle preconstricted by norepinephrine (50). These observations are consistent with the concept that venous smooth muscle has little myogenic (basal) tone (84) but some venous smooth muscle may have beta-receptors that produce relaxation in the presence of an extrinsic constricting influence. However, during i.v. infusions, isoproterenol causes a pronounced decrease in hepatic venous compliance (111, 117) and some decrease in splenic volume due to interference with the intrasplenic mechanisms for concentrating red cells (110). The effect on hepatic venous compliance is mediated indirectly but the hepatic sympathetic nerves are not essential for the effect (111). It seems most likely that it is due to angiotensin formed through the action of isoproterenol directly on the beta-receptors of the kidney (6, 161, 169). These secondary effects of isoproterenol on splanchnic venous compliance require further investigation. Isoproterenol has not been reported to have any effects on venous compliance in other organs.

Although epinephrine increases pulmonary arterial and venous pressures, it also increases pulmonary blood volume (336). This redistribution of blood volume results from the decrease in systemic venous compliance and it suggests that any decrease in pulmonary venous compliance is smaller than the decrease in systemic venous compliance. In vitro, epinephrine contracts pulmonary vein strips from dog and human (288) and norepinephrine reduces the diameter of pulmonary arteries and veins and decreases blood volume in isolated dog lung perfused at constant flow (14, 149). Thus these agents may decrease pulmonary venous compliance but quantitative data are not available.

Quantitative effects of epinephrine on arteriolar resistances are variable but the general pattern is clear. In the splanchnic bed, low doses caused vasodilatation in man, cat, and baboon (15, 56, 77, 119, 120, 125, 126, 171, 187, 279, 336), but perhaps not in the dog (144, 307). Larger doses cause lessening vasodilatation and eventually vasoconstriction. A similar response occurs in skeletal muscle (3, 12, 28, 185, 214, 336) but the vasodilatation is less well sustained (67, 337). Although I am not aware of a definitive study, i.v. infusions of small doses of epinephrine appear to produce greater vasodilatation in skeletal muscle than intra-arterial infusions of appropriately smaller doses (337). This may be due to the significant rise in plasma K^+ secondary to the release of K^+ from the liver (126), since increased plasma K^+ dilates skeletal muscle arterioles (178, 179). Epinephrine increases renal vascular resistance (8, 107, 336) and cutaneous vascular resistance (288, 336); cerebral vascular resistance is unchanged (8, 175), while coronary vascular resistance is decreased (8, 336). Summarising the effects of epinephrine, splanchnic and skeletal muscle arteriolar resistances are reduced by low doses and reversed to an increase by progressively increasing doses; renal arteriolar resistance is increased, and there is probably little change in the combined arteriolar resistances of the remaining beds.

Norepinephrine increases arteriolar resistances in all vascular beds (69, 153) except the heart. There is vasoconstriction in the splanchnic (15, 56, 77, 125, 144, 171, 187, 279, 307), skeletal muscle (28, 83, 98, 157, 185, 214, 216, 317, 337), renal (107, 289), and cerebral (8, 175) beds. In the splanchnic circulation, escape from the vasoconstrictor effects of infused norepinephrine has been demonstrated in the intestine (66) and liver (121) but the mechanism of this escape is controversial (114, 121, 124, 131, 261). Although the predominant action in skeletal muscle is vasoconstriction, i.v. infusions may sometimes cause vasodilatation by an indirect mechanism (3, 337) and it seems likely that the mechanism is similar to that for epinephrine. The actions of phenylephrine are similar to norepinephrine but larger doses are required to produce the same degrees of vasoconstriction (8, 28, 172, 185, 254, 345). Isoproterenol reduces arteriolar resistance in all vascular beds but the vasodilatation appears to be greatest in the splanchnic region and least in the kidney (3, 8, 34, 56, 144, 153, 185, 255, 279, 307).

There are few data on the effects of these drugs on venous resistances. In the splanchnic bed, venous resistance is unchanged by low doses of epinephrine (127, 187). We have no published data on norepinephrine but norepinephrine and splanchnic nerve stimulation increased splanchnic venous resistances calculated from our earlier experiments (113, 118, 121). Rutlen et al. (272, 273) concluded that isoproterenol and norepinephrine reduced hepatic venous resistance. However, their experiments were carried out in a pump-perfused dog liver system. This type of preparation is notorious for developing elevated hepatic venous resistance due to release of endogenous histamine (126) and the high portal pressures they reported strongly suggest the presence of

outflow block. Catecholamines are effective physiological antagonists of histamine and would be expected to reduce hepatic venous resistance under these conditions. Although the displacement of blood by isoproterenol into an extracorporeal reservoir during constant cardiac input in dogs has been interpreted as due to decreased venous resistance (152), there were no actual measurements of venous resistance and many factors alter "unstressed volume" (see section III E). In canine skeletal muscle, venous resistance was unchanged by epinephrine but increased threefold during intra-arterial norepinephrine infusions (134).

Pulmonary vascular resistance is increased by norepinephrine, epinephrine, and phenylephrine (8, 9, 317) and decreased by isoproterenol (9). However pulmonary vascular resistance changes with blood flow (the pressure/flow curve is not linear) and these effects may not be direct actions of the drugs on the lung vessels (9). In lungs perfused at constant flow, the drugs increased pulmonary resistance but large doses were required (9, 14, 149). Infusions of small doses of norepinephrine into the pulmonary artery of humans resulted in no changes in pulmonary vascular resistance (87, 136).

Epinephrine increases heart rate (8, 31, 77, 336) and atrial (16) and ventricular (8, 31, 103, 143, 336) contractilities. Norepinephrine is similar (16, 65, 69, 103, 303) and isoproterenol is more potent (150, 208, 276, 303). Phenylephrine has no direct effects on heart rate or contractility in moderate doses although in large doses it produces an inotropic effect due to stimulation of alpha-receptors (8, 329, 345).

In summary, epinephrine, by a combination of actions on alpha- and beta-receptors, produces decreased venous compliance, cardiac stimulation, and an overall decrease in arteriolar resistance. Isoproterenol, by its direct actions on beta-receptors and an indirect effect on venous compliance, produces qualitatively the same effects. Norepinephrine produces decreased venous compliance and cardiac stimulation but its overall effect on arteriolar resistance is strongly vasoconstrictor. Phenylephrine is similar to norepinephrine except that it lacks cardiac stimulant actions.

Figure 8 shows the effects of epinephrine on some major dependent variables modelled for the human from the direct actions discussed above and listed in table 2. It can be seen that, due to the combination of decreased venous compliance, decreased peripheral resistance, and cardiac stimulation, epinephrine causes a marked increase in cardiac output with little change in atrial pressures and a small rise in arterial and pulmonary pressures. There is a redistribution of blood flow and a redistribution of the blood volume. Heart rate increases but this increase falls off with larger doses as hypertension stimulates the baroreceptors. These effects predicted by the model agree closely with the effects reported in the literature cited above when some allowance is made for the variability of the control values in the different preparations.

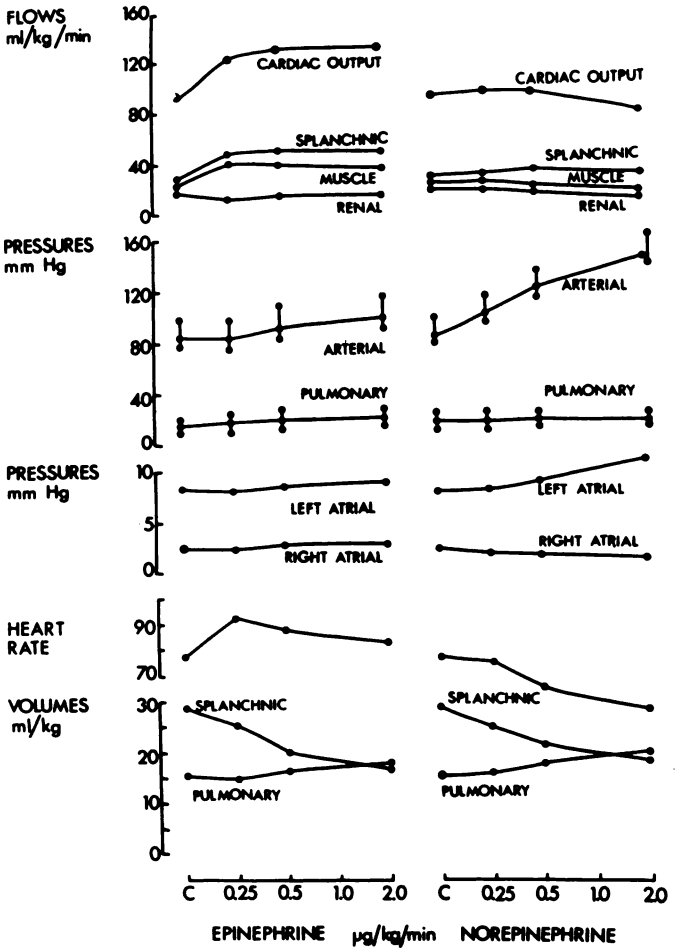

FIG. 8. The effects on some dependent variables of infusions of epinephrine and norepinephrine modelled for the human from the direct actions of the drugs shown in table 2.

Figure 8 shows the effects of norepinephrine modelled in the same way. Even though the decreased venous compliance and cardiac stimulation are similar to those caused by epinephrine, norepinephrine in small doses causes little change in cardiac output due to the large increase in left ventricular afterload due to peripheral vasoconstriction. This large increase in afterload causes a compensatory increase in left atrial pressure and hence in pulmonary blood volume; large doses of norepinephrine can cause acute pulmonary edema. Since right ventricular afterload increases to a much smaller extent, right ventricular preload decreases due to cardiac stimulation. The result is a marked redistribution of blood volume into the pulmonary circulation.

Figure 9 shows the effects of isoproterenol modelled in the same way. These effects are similar to those of epinephrine except that the increases in heart rate and cardiac output are larger due to the greater decline in total peripheral resistance. Arterial pressure falls only slightly because the large decrease in total peripheral resistance is balanced by the large increase in cardiac output. All blood flows increase, especially splanchnic, but there is little change in the distribution of blood volume. The splanchnic venoconstriction discussed

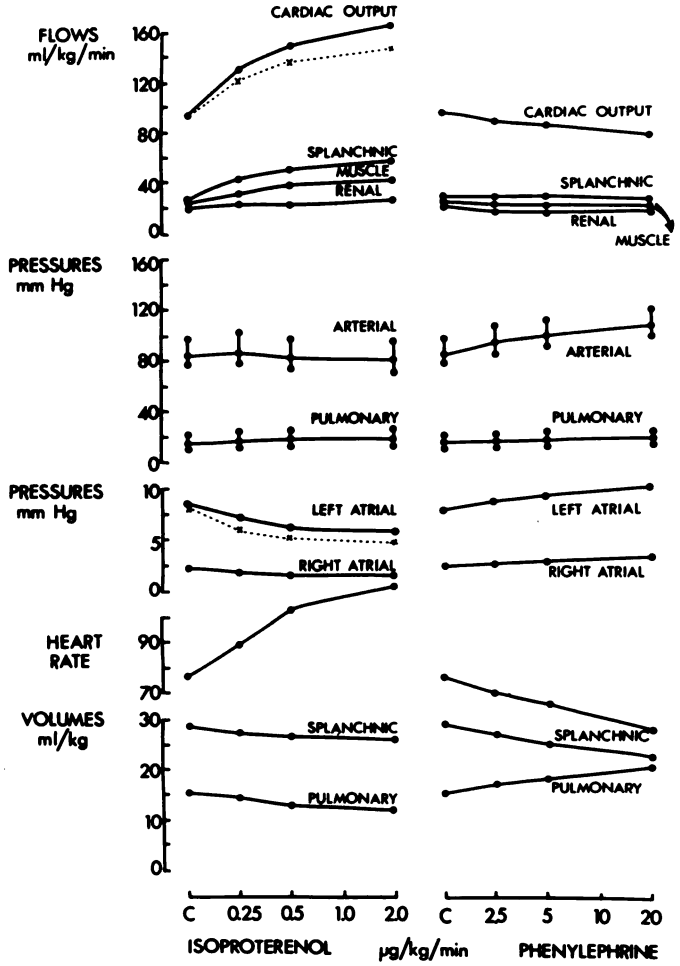

FIG. 9. The effects on some dependent variables of infusions of isoproterenol and phenylephrine modelled for the human from the direct actions of the drugs shown in table 3. The dotted lines show the effects of isoproterenol on cardiac output and left atrial pressure when the indirect splanchnic venoconstrictor action is not included.

above helps to maintain ventricular preload and sustains even higher cardiac outputs.

Figure 9 also shows the effects of phenylephrine modelled in the same way. Phenylephrine is similar to norepinephrine except that it does not stimulate the heart. Cardiac output decreases as arterial pressure increases but is sustained to some degree by the decrease in venous compliance. As with norepinephrine there is a redistribution of blood volume into the lungs. Heart rate decreases due to the unopposed action of the baroreceptor reflex.

The effects of these sympathomimetic amines as predicted by the model agree well with the effects reported in the cited literature. Although there are some question marks in tables 2 and 3, and although many readers may question some of the specific numbers, on the whole the available data on these drugs are reasonably consistent and form a coherent picture of their actions and effects.

B. Dopamine and Dobutamine

The cardiovascular effects of dopamine have been reviewed by Goldberg et al. (102, 104) and by others (3, 278, 336). The effects result from complex interactions of the drug with alpha-receptors, beta-receptors, specific dopaminergic receptors in the renal and mesenteric arterioles, and variable norepinephrine-releasing effects on sympathetic terminals. The overall pattern of response resembles that of epinephrine but there are important differences: the renal and mesenteric vascular beds are dilated by small doses of dopamine, in contrast to the muscle and mesenteric vasodilatation by epinephrine; dopamine increases heart rate to a smaller extent relative to its other actions than does epinephrine, and dopamine is less potent than epinephrine. Table 4 shows an attempt to quantify the actions of dopamine as discussed below and these effects can be compared to epinephrine and other catecholamines (tables 2 and 3).

Like epinephrine, dopamine is a powerful venoconstrictor and the evidence for this was discussed by Goldberg (102). We found a marked decrease in hepatic venous compliance in anaesthetised cats (117).

In small doses, dopamine selectively reduced vascular resistances in the renal and mesenteric beds (7, 144, 211, 262) and, as the dose was increased, this reversed to a vasoconstriction (102, 242, 278). The effects on skeletal muscle vascular resistance are controversial—intra-arterial infusions produce vasoconstriction while i.v. infusions may produce vasoconstriction, vasodilatation, or little effect (102, 257, 262, 337). This variability is a consequence of the complex alpha, beta, and central mechanisms that are involved (102). In any event, the overall effects on skeletal muscle vascular resistance appear to be small. Dopamine had insignificant effects on splanchnic venous resistance (127) and effects on pulmonary resistance were variable and small (102, 104, 327).

Dopamine is considerably less potent than epinephrine and norepinephrine in producing an increase in cardiac contractility and its chonotropic effect is even weaker, especially in lower doses. This has been explained on the basis of a greater norepinephrine-releasing action in ventricular muscle than in the sinoatrial node (102, 204, 318).

Dobutamine is one of the most specific of the sympathomimetic amines and it was designed to produce an inotropic effect with minimal chronotropic, arrhythmogenic, and vascular side effects (318). Its effects have been reviewed (104, 291, 336). It generally produces a small decrease in total peripheral vascular resistance (17, 104, 159, 195, 291, 319) with no significant change in pulmonary vascular resistance (17, 195). It has negligible effects on the renal and mesenteric beds but decreases femoral vascular resistance (257). This does not reverse to a constriction as the dose increases (257). Although its actions on venous compliances and venous resistances have not been reported, it seems likely any effects would be small. For the dose ranges considered, it has greater effects on heart rate than dopamine (257) but less than isoproterenol (143, 204) and it increases myocardial contractility (143, 204). The quantitative actions of dobutamine as assessed from this literature are shown in table 4.

Figure 10 shows the effects of dopamine and dobutam-

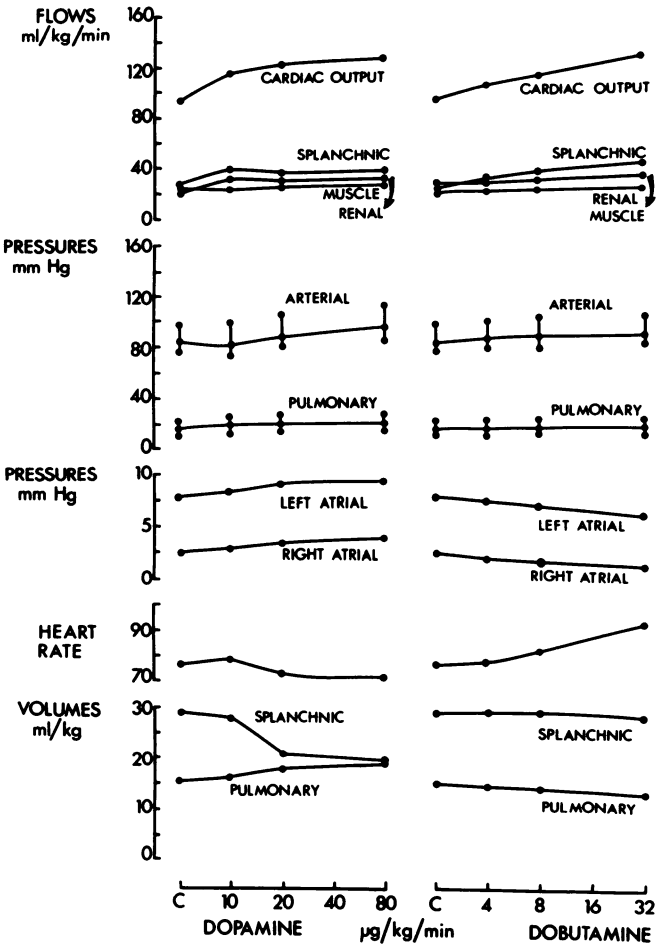

FIG. 10. The effects on some dependent variables of infusions of dopamine and dobutamine modelled for the human from the direct actions of the drugs shown in table 4.

ine on some dependent variables modelled for the human from the direct actions shown in table 4. Both drugs increase cardiac output and peripheral blood flows. Dopamine has a small biphasic effect on arterial pressure, decreasing it slightly with small doses and increasing it with large doses. Dobutamine causes a small increase in arterial pressure. Dopamine increases both left and right atrial pressures, in spite of cardiac stimulation, due to its marked venoconstrictor action. Dobutamine decreases atrial pressures due to cardiac stimulation in the absence of any actions on venous compliance. Dopamine has little effect on heart rate while dobutamine in large doses increases it. Dopamine redistributes the blood volume towards the lungs while dobutamine has little effect on the distribution of blood volume. These effects agree reasonably well with those described in the literature cited.

C. Angiotensin and Vasopressin

These endogenous polypeptides have marked effects on the cardiovascular system and, although the overall effects on cardiac output are small, it is interesting to review why this should be. The actions of angiotensin (64, 253, 345) and vasopressin (140, 228) have been reviewed. An important component of the actions of angiotensin is mediated through the sympathetic nervous system by both peripheral and central mechanisms (64, 93, 253, 309, 345). Although there is evidence that these interactions play only a small role in the overall cardiovascular responses to short i.v. infusions of angiotensin (64, 338), they may account for some of the variability in responses to angiotensin reported in the literature. Because of this variability, the quantitative effects of angiotensin compiled in table 5 must be interpreted with caution.

Although angiotensin contracts aortic smooth muscle in vitro (253), the effects of angiotensin and vasopressin on arterial compliances in vivo are unknown. Angiotensin has weak effects on venous smooth muscle in vitro (306), it has no effect on occluded femoral vein segments (260), and its effect on skeletal muscle blood volume and human hand veins are much smaller than the effects of norepinephrine (43, 50, 83, 157). Thus angiotensin appears to have little or no effect on skeletal muscle venous compliance (345). However, it does decrease venous compliance in the splenic and hepatic components of the splanchnic bed in cats (56, 118, 125–127). This is a significant effect with small doses of angiotensin. Effects on pulmonary compliances are negligible (149). Although angiotensin may decrease left ventricular diastolic compliance (234), this effect is probably the consequence of the rise in end-diastolic pressure and the shape of the ventricular pressure-volume curve (see earlier in this review). Thus the effects of angiotensin on compliances appear to be confined to the splanchnic bed. Vasopressin has no known effects on any venous smooth muscles. It has no effect on isolated vein strips (167, 228, 306), the spleen (125), or hepatic venous compliance (118) and it does not contract human hand veins (50).

TABLE 5

Actions of angiotensin and vasopressin on the semi-independent variables expressed as per cent of control value.

Dose	Angiotensin			Vasopressin		
	0.05	0.1	0.4	10	20	80
	μg/kg/min			*mU/kg/min*		
Blood volume	100	100	100	100	100	100
Arterial compliance	?	?	?	?	?	?
Splanchnic venous compliance	80	70	60	100	100	100
Muscle venous compliance	100	100	100	100	100	100
Other venous compliance	100	100	100	100	100	100
Pulmonary artery compliance	?	?	?	?	?	?
Pulmonary venous compliance	?	?	?	?	?	?
Ventricular diastolic compliance	?	?	?	?	?	?
Splanchnic arteriolar resistance	160	200	250	200	300	400
Muscle arteriolar resistance	140	180	220	100	100	100
Renal arteriolar resistance	170	220	300	100	100	100
Other arteriolar resistance	150	190	220	110	130	160
Splanchnic venous resistance	105	115	125	100	100	100
Muscle venous resistance	?	?	?	?	?	?
Pulmonary resistance	110	120	140	105	110	115
Heart rate	100	100	100	90	85	80
Right ventricular contractility	100	100	100	100	100	100
Left ventricular contractility	100	100	100	100	100	100
Atrial contractility	100	100	100	100	100	100
Thoracic pressure	?	?	?	?	?	?

Angiotensin causes an overall increase in arteriolar resistance and is 10 to 40 times more potent than norepinephrine (64, 345). Its vasoconstrictor effect is greatest in the kidney (64, 345) and splanchnic area (30, 42, 56, 64, 118, 125, 126, 254, 280, 345), moderate in skin, and least in skeletal muscle (64, 83, 157, 345). In contrast, vasopressin produces a marked vasoconstriction in the splanchnic region—intestine and spleen, but not hepatic artery (42, 56, 66, 118, 125, 126, 137, 140, 170, 188)—but it has little effect on other vascular beds except the coronary bed and skin (228), which are constricted by larger doses. Effects on the renal vascular bed are very variable between different preparations (228).

Of the venous resistances, only the splanchnic bed has been studied. Angiotensin increases splanchnic venous resistance about 25% (188, 280). Vasopressin probably has little effect although decreases (126) and increases (137) have been reported. Pulmonary resistance is unchanged or increased somewhat by angiotensin (149, 260). Early reports on the effects of vasopressin on pulmonary resistance were confused (228) but this substance may cause an increase since pulmonary arterial pressure increases without an increase in pulmonary blood flow (140).

Direct effects of angiotensin on heart rate and contractility have been controversial but, in small doses, the effects, if any, appear to be small (31, 64, 65, 254, 345). However, there may be a postinfusion depression of contractility (65). Vasopressin has no significant direct effects on contractility in moderate doses (140, 228) but it appears to have a direct negative chronotropic action on the heart (223, 251).

Figure 11 shows the effects of angiotensin on the major dependent variables modelled in the human from the direct actions shown in table 5. The intense vasoconstrictor action of angiotensin increases arterial pressure and afterload. Atrial pressures increase, but in the absence of cardiac stimulation, the overall effect is a decrease in cardiac output and peripheral blood flows. Blood volume is redistributed towards the lungs. Comparison of Figures 9 and 11 shows the similarities in the actions of angiotensin and phenylephrine although angiotensin is much more potent. These effects of angiotensin play an important role as secondary modulations of the effects of other drugs on cardiac output and this aspect will be discussed later in more detail. Pharmacological alteration of renin release has been reviewed recently (169).

Figure 11 also shows the effects of vasopressin. It is a selective splanchnic arteriolar constrictor and this accounts for its therapeutic use in portal hypertension (53, 164). It causes a modest decrease in cardiac output. Since it has little effect on other major vascular beds apart from the splanchnic, its effect on arterial pressure is modest in low doses and does not increase further as the dose is increased. Splanchnic blood volume decreases due to the decrease in portal venous pressure caused by splanchnic arteriolar constriction, and blood volume is redistributed away from the splanchnic bed.

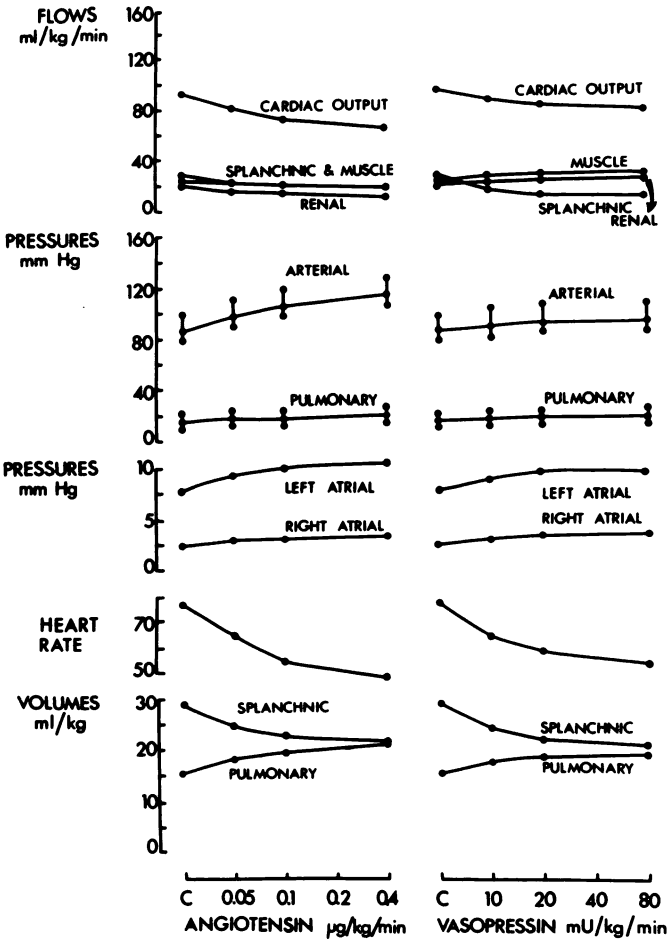

FIG. 11. The effects on some dependent variables of infusions of angiotensin and vasopressin modelled for the human from the direct actions of the drugs shown in table 5.

These effects of angiotensin and vasopressin agree well with the effects reported in the literature cited and the actions and effects of these agents form a coherent and reasonably complete picture.

D. Sodium Nitroprusside

The effects of this drug on the cardiovascular system have been reviewed (18, 239, 315, 320, 324). There are no data on its effects on arterial or pulmonary arterial compliances. Its actions on venous compliance are controversial. In the splanchnic bed, nitroprusside does not modify norepinephrine-induced contractions of rat portal vein strips (158) and in anaesthetised cats, it had no significant effect (117) or produced a small increase (111) in hepatic venous compliance. It did not modify the effects of hepatic nerve stimulation on hepatic venous compliance except in very large doses (111). Although it modifies "unstressed volume" in dogs (271), these effects cannot be taken as an indication of changes in venous compliance (see section III E). In these experiments, total systemic compliance remained unchanged after nitroprusside suggesting that nitroprusside did not increase venous compliance although it may relax the spleen in dogs (271). However, locally infused nitroprusside relaxed dorsal human hand veins preconstricted by norepineph-

rine (49, 258) and it relaxed bull metacarpal veins preconstricted with norepinephrine in vitro (100). Forearm venous tone was reduced in patients with congestive heart failure (207, 220). Thus nitroprusside increases muscle venous compliance when applied locally but since it is very rapidly removed from the circulation, the venules may not be exposed to comparable concentrations when the drug is administered systemically. It is commonly stated that nitroprusside relaxes the venous system (see reviews cited above). This view is largely based on the fact that nitroprusside reduces preload but sections III and V demonstrate that many factors besides venous compliance may alter preload. Nitroprusside in higher concentrations reaches the pulmonary veins and pulmonary venous compliance may be increased to a small extent (287). Others have also found that pulmonary blood volume decreased less than expected from the fall in pulmonary wedge pressure, which suggests an increased pulmonary compliance (231).

Nitroprusside increased left ventricular diastolic compliance in patients with congestive heart failure (25). However, it is not clear whether this represented a direct effect of the drug on the left ventricle or whether it was secondary to interactions with the right side of the heart (25). One study suggested that left ventricular diastolic compliance is unchanged in the normal heart by nitroprusside (238).

Nitroprusside reduces peripheral vascular resistance (217, 235, 263, 265, 301, 320). The decreases in regional vascular resistances are relatively uniform across the vascular beds (76, 94, 238, 263, 331). Decreases in renal vascular resistance have been reported to be smaller (94, 238) or larger (331) than average. The arteriolar vasodilatation may be smaller in skeletal muscle (331) but this was not apparent in another study (263). Coronary vessels are dilated (238, 243, 263, 265) and the hepatic artery dilates partly by a direct effect and partly by a myogenic effect secondary to decreased portal venous pressure (94). One study reported that mesenteric vascular resistance increased (331) and one that iliac resistance increased (238); it seems likely that these effects were secondary to endogenous production of angiotensin (see below).

Splanchnic venous resistance has been reported to decrease slightly in dogs (94) but we found no change in cats (127). Skeletal muscle venous resistance has not been studied. Pulmonary vascular resistance has been reported to be unchanged (76, 235) or to be substantially reduced (115, 265, 287). This variability may be dependent on the degree of preexisting tone since nitroprusside had no significant effect on pulmonary resistance in anaesthetised dogs breathing air but decreased the enhanced resistance in dogs breathing 5% oxygen (61, 235), or with regional atelectasis (48). Alternatively a direct relaxant effect on the pulmonary arterioles may be opposed by endogenous production of angiotensin.

Nitroprusside has no direct effects on the heart (36, 100, 243, 263), and left ventricular contractility, measured as systolic volume elastance, was unchanged during nitroprusside infusions in man (217).

During nitroprusside infusions, there is moderate reflex activation of the renin-angiotensin system (169, 320) and the rebound hypertension seen for about 30 minutes after cessation of nitroprusside infusions may be due to the much longer half-life of renin compared to nitroprusside (54, 60, 238). If the actions of this angiotensin are significant, then the effects of nitroprusside will be reduced (combining the actions in table 6 with the smallest dose of angiotensin in table 5).

Figure 12 shows the effects of sodium nitroprusside on the major dependent variables modelled for the human from the direct actions shown in table 6. Of the drugs considered so far, the effects predicted for nitroprusside show some divergence from the effects reported in the cited literature. Cardiac output is predicted to increase whereas it has been observed to increase (265, 301) or to remain unchanged with small doses (301, 311) and to decrease with larger doses (88, 239). Substantial increases in heart rate have been reported (88, 265, 311) but are sometimes absent (301). Changes in heart rate and cardiac output are smaller in conscious than in anaesthetised humans (301). Further studies on its venous actions are clearly necessary.

TABLE 6

Actions of nitroprusside and hydralazine on the semi-independent variables expressed as per cent of control values.

Dose	Nitroprusside			Hydralazine		
	2	4	16	0.5	1	4
	μg/kg/min			*mg/kg*		
Blood volume	100	100	100	100	100	100
Arterial compliance	?	?	?	?	?	?
Splanchnic venous compliance	100	100	130	75	75	75
Muscle venous compliance	120	140	180	100	100	100
Other venous compliance	?	?	?	?	?	?
Pulmonary artery compliance	?	?	?	?	?	?
Pulmonary venous compliance	105	110	140	?	?	?
Ventricular diastolic compliance	?	?	?	?	?	?
Splanchnic arteriolar resistance	80	60	20	75	60	40
Muscle arteriolar resistance	80	60	20	90	80	50
Renal arteriolar resistance	80	60	20	75	60	40
Other arteriolar resistance	80	60	20	75	60	40
Splanchnic venous resistance	100	100	100	?	?	?
Muscle venous resistance	?	?	?	?	?	?
Pulmonary resistance	90	80	40	80	65	50
Heart rate	100	100	100	110	120	130
Right ventricular contractility	100	100	100	110	120	130
Left ventricular contractility	100	100	100	110	120	130
Atrial contractility	100	100	100	110	120	130
Thoracic pressure	?	?	?	?	?	?

E. Hydralazine

The effects of hydralazine have been reviewed (18, 35, 182, 184, 207, 311). These effects have caused considerable confusion. Although it was initially believed that hydralazine had predominantly central actions (224), it later became accepted as a direct smooth muscle relaxant and its cardiac effects were considered to be reflex consequences of the hypotension produced by arteriolar vasodilatation (1, 92, 184, 300). At that time there were

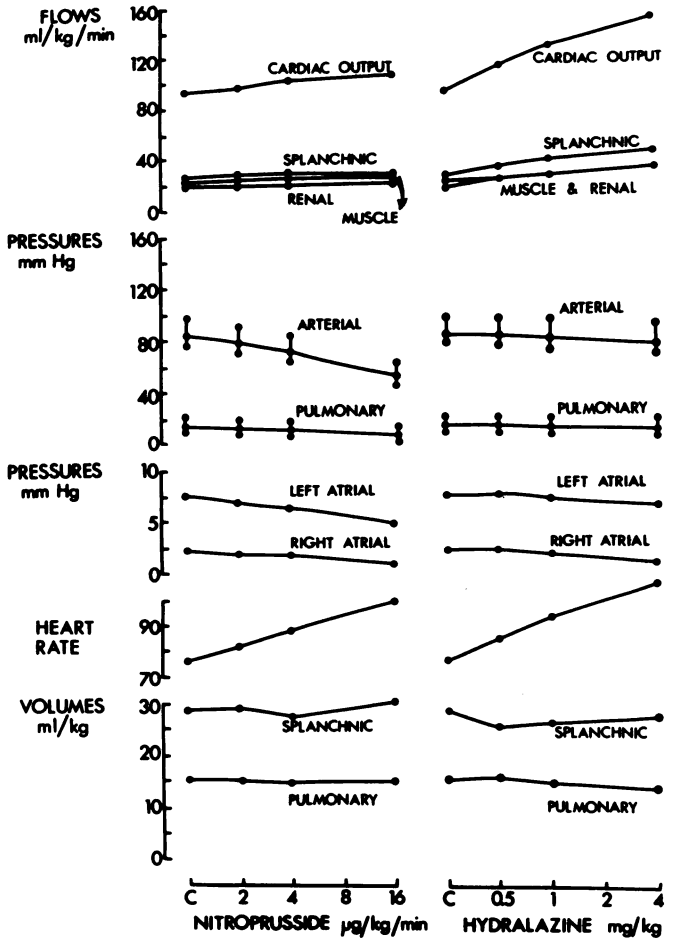

FIG. 12. The effects on some dependent variables of infusion of nitroprusside and injections of hydralazine modelled for the human from the direct actions of the drugs shown in table 6.

few other arteriolar vasodilators with which it could be compared. It now seems clear that it has additional actions on the sympathetic nervous system that are substantially greater than the reflex consequences of hypotension. Increases in heart rate and cardiac output have been seen before any hypotension develops (75, 117, 292). These sympathetically mediated effects appear to be confined to beta-receptor stimulation and include cardiac stimulation (194), mesenteric vasodilatation (92), and renin release (169, 245, 246, 321). They are reduced or blocked by beta-blockers (57, 245, 246, 344). The actions on renin release are not due to a direct action of hydralazine on beta-receptors (169, 321) and the mechanism of the activation of the renal sympathetic nerves is not clear at present. In the heart, hydralazine may have a direct inotropic action in vitro (256) and in vivo (173). These effects represent important components of the actions of hydralazine on the semi-independent variables. Prostaglandins have also been implicated in the effects of hydralazine (32, 138, 268) and it is clear that the classification of this drug as a smooth muscle relaxant acting predominantly on arterioles (18) is an oversimplification.

It is generally agreed that hydralazine has little direct effect on venous compliance (18, 182). However, like isoproterenol, hydralazine causes an indirect decrease in hepatic venous compliance that can be considered as part of the beta-agonist-mimetic effect of hydralazine (117). As discussed in relation to isoproterenol, this decreased hepatic venous compliance could be a consequence of angiotensin formation but at present its mechanism is unknown. These observations provide direct confirmation of the previously postulated venoconstrictor action of hydralazine (292). Hydralazine has little action on skeletal muscle venous compliance (1).

Systemic and pulmonary vascular resistances are decreased by hydralazine (35, 182, 269). The vascular resistances in coronary, cerebral, splanchnic, and renal beds are decreased more than those in skin and muscle (35, 92, 292). The arteriolar vasodilatation in the renal bed, but not that in the other beds, was antagonised by prostaglandin-synthetase inhibitors (292). Hydralazine was reported to decrease the pulmonary vasoconstrictor effects of hypoxia and this effect also was prevented by indomethacin pretreatment (268). However, these experiments are puzzling since cardiac output, arterial pressure, and systemic vascular resistance were not significantly altered by hydralazine. Hydralazine produced a marked decrease in pulmonary vascular resistance in patients with primary pulmonary hypertension (269).

Hydralazine increases heart rate markedly (75, 173, 292) and produces a positive inotropic effect in vitro and in vivo (173, 207, 256), although others were unable to demonstrate any effect in vitro (183). These cardiac effects are not simply reflex consequences of hypotension (see above) and they are mediated through beta-receptors since they are blocked by beta-blockers (173, 182).

Table 6 summarises the quantitative effects of hydralazine as assessed from the literature cited above. Figure 12 shows the effects of hydralazine on the major dependent variables modelled for the human from the data in table 6. Hydralazine causes a large increase in cardiac output and its effects resemble those of isoproterenol except for the greater increase in renal blood flow caused by hydralazine. This picture resembles the effects of hydralazine reported in the cited literature. Although we therefore have a coherent picture of the actions and effects of hydralazine, the mechanisms of these effects, especially those mimicking the beta-agonists, are far from clear. After propranolol, hydralazine resembles diazoxide (see below) and behaves as a direct arteriolar vasodilator.

F. Diazoxide

The actions of diazoxide have not been extensively studied but it is generally agreed to cause arteriolar vasodilatation with little effect on the venous system and heart (11, 18, 267). It had no significant effects on human forearm veins, dog saphenous veins, or isolated rabbit mesenteric veins (314) and we found no significant change in hepatic venous compliance in anaesthetised

cats (117). In hypertensive patients, no significant changes in venous distensibility were found (11).

Peripheral vascular resistance is reduced (229, 250, 266, 267, 343) but the pattern of the reduction in different vascular beds has not been studied. I have therefore assumed a uniform decrease in vascular resistance. Pulmonary vascular resistance was markedly reduced in a patient with primary pulmonary hypertension (180) but effects on pulmonary vascular resistance in normal humans are unknown. Diazoxide increased heart rate and this effect was not dose-related or blocked by beta-blockers (225, 293); its mechanism is unknown. Diazoxide increases plasma renin levels by increased renal sympathetic activity (169) and its direct actions may be partly offset by angiotensin production.

As far as is possible from these limited data, the direct actions of diazoxide are summarised in table 7. Figure 13 shows the effects of diazoxide on the major dependent variables modelled for the human from the data in table 7. It causes a modest increase in cardiac output (267, 311, 343) and decrease in arterial pressure with an increase in heart rate and no redistribution of blood flow or blood volume. These effects resemble the limited data available in the cited literature. Thus diazoxide represents the effects of an arteriolar vasodilator without significant other cardiovascular actions.

G. Nitroglycerin and Isosorbide Dinitrate

The effects of nitroglycerin and other nitrites have been reviewed (35, 46, 207, 230, 332). The overall effects are not dramatic largely because the direct actions are offset by reflex compensatory mechanisms and there is wide variation in different patients (79). Although it has been suggested that arterial and pulmonary arterial compliances are increased (79), no direct measurements have been reported. Venous compliances are increased in the splanchnic and muscle beds. In the liver, isosorbide dinitrate increased basal splanchnic venous compliance but did not alter the decreased compliance during hepatic nerve stimulation (111). In cats, nitroglycerin and sodium nitrite increased hindquarter blood volume during constant blood flow (165) and in dogs, femoral vein diameter increased in spite of a slight fall in venous pressure after administration of nitroglycerin and isosorbide dinitrate (146). Venous tone was reduced in the human forearm (209).

Small doses of nitroglycerin have no significant effects on total peripheral resistance while larger doses decrease it slightly (207, 230, 332). Forearm vascular resistance may be decreased or unchanged (35, 207, 209, 220). Rapid administration may cause larger initial decreases in resistance that are not sustained (111, 147). Pulmonary vascular resistance is reported to be consistently reduced (230). Nitroglycerin has no significant direct effects on heart rate or contractility (230).

These direct actions of nitroglycerin are summarised in table 7. Figure 13 shows the effects of nitroglycerin on

TABLE 7

Actions of diazoxide and nitroglycerin on the semi-independent variables expressed as per cent of control values.

Dose	Diazoxide			Nitroglycerin		
	1	2	8	10	20	80
	mg/kg			*μg/kg/min*		
Blood volume	100	100	100	100	100	100
Arterial compliance	?	?	?	?	?	?
Splanchnic venous compliance	100	100	100	125	140	160
Muscle venous compliance	100	100	100	125	140	160
Other venous compliance	100	100	100	?	?	?
Pulmonary artery compliance	?	?	?	?	?	?
Pulmonary venous compliance	?	?	?	?	?	?
Ventricular diastolic compliance	?	?	?	?	?	?
Splanchnic arteriolar resistance	80	65	50	100	95	90
Muscle arteriolar resistance	80	65	50	100	90	70
Renal arteriolar resistance	80	65	50	100	95	90
Other arteriolar resistance	80	65	50	100	90	70
Splanchnic venous resistance	?	?	?	?	?	?
Muscle venous resistance	?	?	?	?	?	?
Pulmonary resistance	?	?	?	90	80	70
Heart rate	110	110	110	100	100	100
Right ventricular contractility	100	100	100	100	100	100
Left ventricular contractility	100	100	100	100	100	100
Atrial contractility	100	100	100	100	100	100
Thoracic pressure	?	?	?	?	?	?

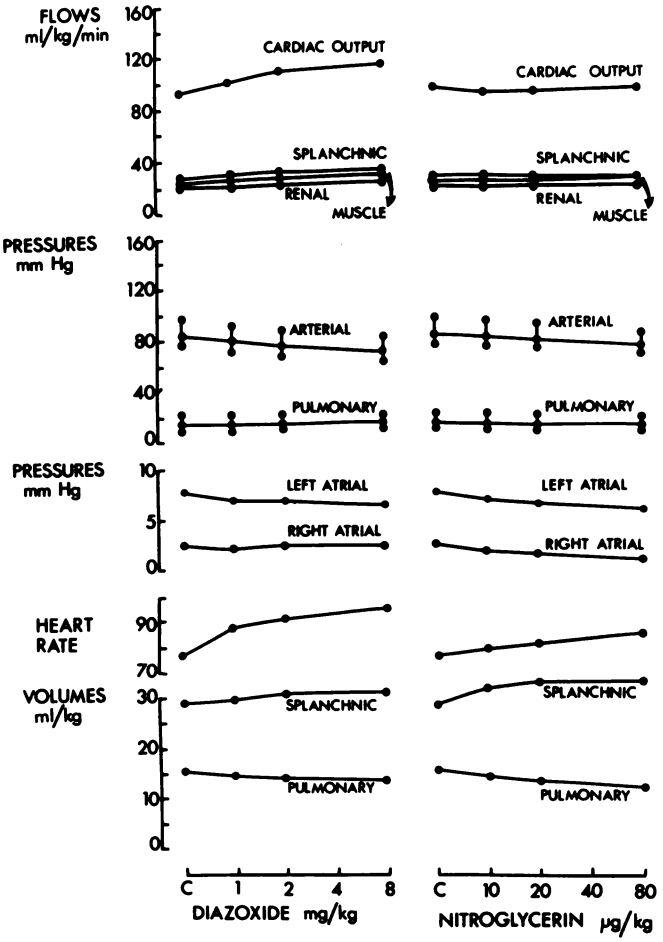

FIG. 13. The effects on some dependent variables of injections of diazoxide and nitroglycerin modelled for the human from the direct actions shown in table 7.

the major dependent variables modelled for the human from the data in table 7. There is a modest fall in cardiac output and arterial pressure (52, 79, 106, 341), decreases in right and left atrial pressures (332), and a redistribution of blood volume from the lungs to the systemic venous bed although, in some reports, nitroglycerin increased cardiac output especially during the early phase when total peripheral resistance was reduced (147, 335). Ventricular systolic and diastolic volumes decrease (332, 341). These effects resemble those reported in the cited literature.

H. Nifedipine

The agents that selectively inhibit membrane transport of calcium (40, 71) were used initially in the management of arrhythmias and angina (286, 347). Verapamil in doses that lower arterial pressure in hypertensive patients has undesirable effects on atrioventricular conduction in the heart (191) but recently nifedipine has been shown to be useful in heart failure (181, 210, 248) and hypertension (193, 233) and diltiazem is being studied (189). Relatively little data on the detailed pharmacological actions in normal animals and man are available (71).

Although indirect evidence suggests that nifedipine has little effect on veins (193), no direct studies on venous compliance in vivo have been reported. It relaxed rat portal vein strips constricted with norepinephrine in vitro (158) but local infusion did not relax human hand veins preconstricted by norepinephrine (259). Nifedipine decreased systemic and pulmonary vascular resistances (233, 248, 347) and it decreased forearm vascular resistance (192, 193, 259). In normal dogs and those subjected to coronary occlusion, it decreased systemic vascular resistance and increased cardiac output (139, 141, 339). Diltiazem, the newest member of the group, produced vasodilatation in coronary, cerebral, and hepatic vascular beds and it had only small effects on renal, gastrointestinal, skin, and muscle beds in conscious rats. This vasodilator action resulted in an increase in cardiac output (81, 347). In dogs, hepatic, mesenteric, femoral, and renal resistances were decreased (154, 155, 330). Although these agents have negative inotropic effects on isolated cardiac muscle (139, 286), this is not evident in usual doses in vivo (71, 139, 347). Nifedipine increases heart rate and this is assumed to be a reflex consequence of hypotension (193). Overall effects of nifedipine on arterial pressure were insignificant in normal humans but a significant decrease occurred in hypertensive patients (192, 233). Diltiazem decreased cardiac output and had variable effects on arterial pressure in patients with angina (189) but it produced small increases in cardiac output in dogs (151).

These data are not yet sufficient to allow quantitative analysis of nifedipine. Some studies show that the calcium antagonists block the actions of norepinephrine (40, 330) and we have no quantitative data on what proportion of the in vivo effects should be considered as direct actions or as sympathetic blocking actions. From the evidence above, nifedipine resembles diazoxide but without the small direct effect on heart rate.

I. Summary

This section has reviewed the direct actions of some common drugs that have been studied sufficiently to allow analysis. The model described in section II was then used to predict the effects of these direct actions on cardiac output and other dependent variables. Although the direct actions of these drugs on many variables, notably arterial and pulmonary compliances and ventricular diastolic compliances, remain unknown, the major actions of these drugs are consistent with the observed effects on cardiac output, regional flows, pressures, and volumes. The known direct actions of nitroprusside may not yet completely explain its effect on cardiac output, the mechanisms of the sympathetic effects of hydralazine are not clear, and we have insufficient quantitative data to analyse the newer calcium antagonists such as nifedipine and diltiazem.

V. Vasodilators and Heart Failure

Vasodilators now play an important role in the therapy of heart failure and many articles have been written reviewing the hemodynamic changes in heart failure, before and after administration of the vasodilators (5, 35, 45, 88, 104, 190, 207, 236, 278, 283, 291). A bibliography was compiled by Cohn (44). Although "afterload reduction" plays a major role in the therapeutic effectiveness of these agents, in some patients there may be increased cardiac output with rather small decreases in arterial pressure. It must be remembered in analysing these reports that preload (end-diastolic ventricular volume) and afterload (end-systolic ventricular pressure) are not independent variables that control cardiac output. As noted in the INTRODUCTION, they are themselves influenced by cardiac output. Therefore it seems more reasonable to approach the mechanism of the therapeutic effects of these drugs in terms of the direct actions of the drugs on the semi-independent variables—compliances, resistances, and cardiac function. Changes in preload and afterload are then consequences of the drug actions rather than causes of the changes in cardiac output.

There seems to be considerable uncertainty in these reports on whether we can explain the hemodynamic changes in heart failure and the effects of vasodilators on the basis of the physiological principles and pharmacological actions developed from normal animals and man as described earlier in this review, or whether we have to invoke altered hemodynamics and drug effects that do not occur in normal animals and man. In other words, can we predict the hemodynamic changes in heart failure and the effects of the vasodilators from the normal physiology and pharmacology or is it only possible to study these hemodynamic changes in patients with heart fail-

ure? This is clearly an important question for basic pharmacologists who study drug actions in normal animals. In this section of the review, a model for heart failure based on the physiological principles in section II is developed and the consequences of superimposing the direct actions of the vasodilators as described in section IV are examined. The predicted effects are then compared with the clinical reports of the effects of vasodilators in heart failure.

A. Heart Failure

Clinical and physiological aspects of heart failure have been reviewed (21, 101, 168) and are also discussed extensively in the reviews on vasodilators in heart failure cited above. Depending on the various etiologies and the duration of development of failure, the clinical manifestations show marked variability and it is not possible to consider in detail here all these variations and their mechanisms. In essence, there is a reduction in myocardial contractility and I have assumed that this failure is occurring in all parts of the myocardium. There is a compensatory expansion of blood volume. Superimposed on these changes there may be increased sympathetic activity with elevated plasma norepinephrine levels (in spite of tissue norepinephrine depletion), and/or elevated plasma angiotensin levels (27, 95, 218, 298). These effects have been modelled to show four degrees of severity of heart failure by combining the following changes: 1) a reduction in contractility to 50% of normal, an increase in blood volume to 105% of normal, combined with the actions of norepinephrine (0.13 μg/kg/min) and angiotensin (0.025 μg/kg/min) from section IV; 2) a reduction in contractility to 40% of normal, an increase in blood volume to 110% of normal, combined with the actions of norepinephrine (0.25 μg/kg/min) and angiotensin (0.05 μg/kg/min) from section IV; 3) a reduction in contractility to 30% of normal, an increase in blood volume to 115% of normal, combined with the actions of norepinephrine (0.37 μg/kg/min) and angiotensin (0.075 μg/kg/min) from section IV; 4) a reduction in contractility to 20% of normal, an increase in blood volume to 120% of normal, combined with the actions of norepinephrine (0.5 μg/kg/min) and angiotensin (0.1 μg/kg/min) from section IV.

The results are shown in figure 14. Decreases in contractility without the hormonal effects cause marked falls in cardiac output and arterial pressure with modest increases in atrial pressures and heart rate. Superimposed norepinephrine prevents the fall in arterial pressure and improves cardiac output slightly but at the expense of larger increases in heart rate, left atrial pressure, and pulmonary blood volume. Angiotensin without norepinephrine (not shown in figure 14) causes similar effects except that since it does not stimulate the heart, cardiac output falls further and heart rate increases less. The overall combination of decreased contractility, norepinephrine, and angiotensin maintains or raises arterial pressure, markedly reduces cardiac output, and increases

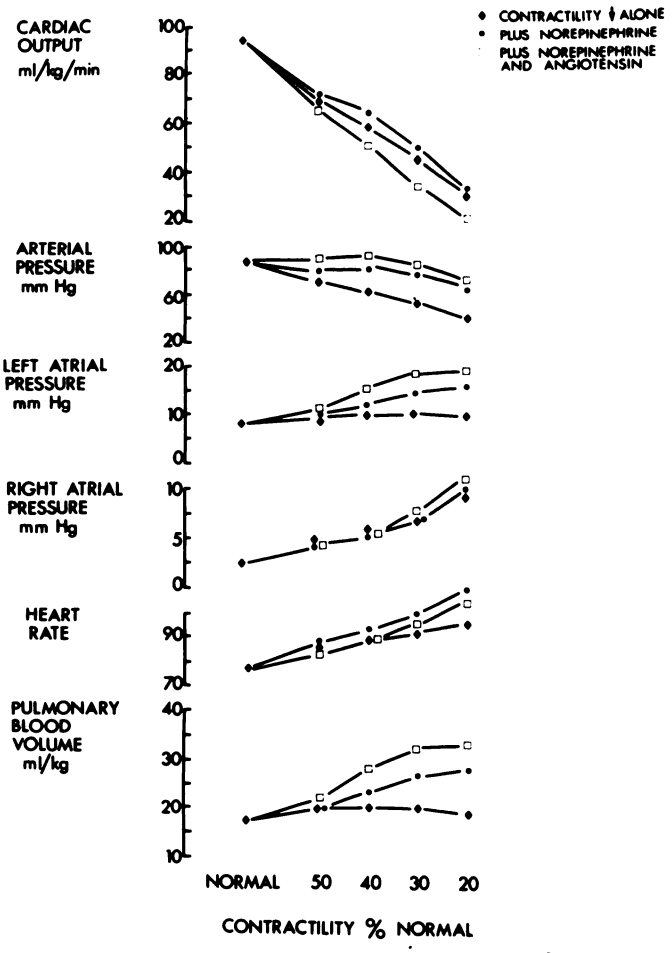

FIG. 14. The effects on some dependent variables of heart failure modelled for the human by reducing contractility combined with small increases in blood volume and the actions of small doses of norepinephrine and angiotensin (see text for doses).

atrial pressures, heart rate, and pulmonary blood volume. These changes resemble the effects seen in clinical congestive heart failure.

Many other variations are possible. The contractility of one ventricle can be decreased more than that of the other and this results in much greater venous congestion on the side of the heart that is failing more. In addition to contractility changes, decreases in ventricular diastolic compliances produce similar effects but without an increased end-diastolic ventricular volume (97). Thus the effects of myocardial infarction may be modelled either as decreased contractility, or decreased diastolic ventricular compliance, or a combination and such changes result in similar cardiac output decreases but a wide range of left ventricular end-diastolic volumes. It might be reasonable to model left ventricular infarction as decreased left ventricular contractility with a resultant decreased right ventricular diastolic compliance due to the effect of the pericardium as the left ventricle enlarges. Increased pulmonary resistance can also be incorporated to model clinical conditions where pulmonary vasoconstriction is part of the picture. This accentuates the right ventricular failure and increases right atrial and venous

pressures to a greater extent than shown in figure 14. Valvular defects cannot be modelled without changes to the compartmental system (fig. 3) on which the model is based.

It is clear that heart failure can be modeled in many different ways and the resulting cardiovascular changes, although basically similar, vary in detail sufficiently to explain the wide variety of measurements reported in the literature. However, to allow examination of the effects of some inotropic and vasodilator drugs in heart failure, I shall use the combination of reduced contractility to 30% of normal, increased blood volume to 115% of normal, combined with norepinephrine (0.37 μg/kg/min) and angiotensin (0.075 μg/kg/min) as the model for heart failure. The effects of combining these changes with the actions of some of the drugs discussed in section IV are shown in figure 15.

B. Alpha-Blockers and Converting Enzyme Inhibitors

The potential effects of an alpha-receptor blocker such as prazosin can be modelled by removing the vasoconstrictor effects of the norepinephrine that were incorporated into the heart failure model (298). The consequences of this are shown in figure 15. There is an increased cardiac output of about 40%, a modest decrease in arterial pressure, and a marked reduction in left atrial pressure and pulmonary blood volume. Similar changes have been reported in clinical studies (38, 207, 212, 213, 236, 237, 297) but heart rate often does not increase and may decrease. An alpha-receptor blocker such as phentolamine would be predicted to produce greater effects. The alpha-receptor-mediated vasoconstriction may be reversed to a beta-receptor-mediated vasodilatation (241) and cardiac stimulation may be increased due to removal of the inhibitory feed-back control of norepinephrine release since phentolamine blocks both alpha-1 and alpha-2 receptors, while prazosin blocks only alpha-1 receptors (296, 340). However, due to the deleterious effects of large doses, small doses of phentolamine are used clinically and produce effects similar to those for prazosin (36, 186, 207, 220, 281).

When angiotensin was added to the model of heart failure (fig. 14), it resulted in hemodynamic deterioration even though arterial pressure rose. Cardiac output decreased and atrial pressures and pulmonary blood volume increased. Converting enzyme inhibitors such as captopril prevent these effects by inhibiting the formation of this angiotensin. Figure 15 shows the effects of removing the angiotensin; these effects resemble the clinical responses to captopril reported in the literature (2, 55, 58, 68, 78, 197, 326). In a recent study in 11 patients, cardiac index increased to 124%, total peripheral resistance decreased to 69%, pulmonary resistance decreased to 62%, and arterial, pulmonary capillary wedge pressures and right atrial pressures fell (197). The decreases in pulmonary resistance and hence in right atrial pressures in these patients were somewhat larger than predicted by the model but nevertheless the agreement is good consid-

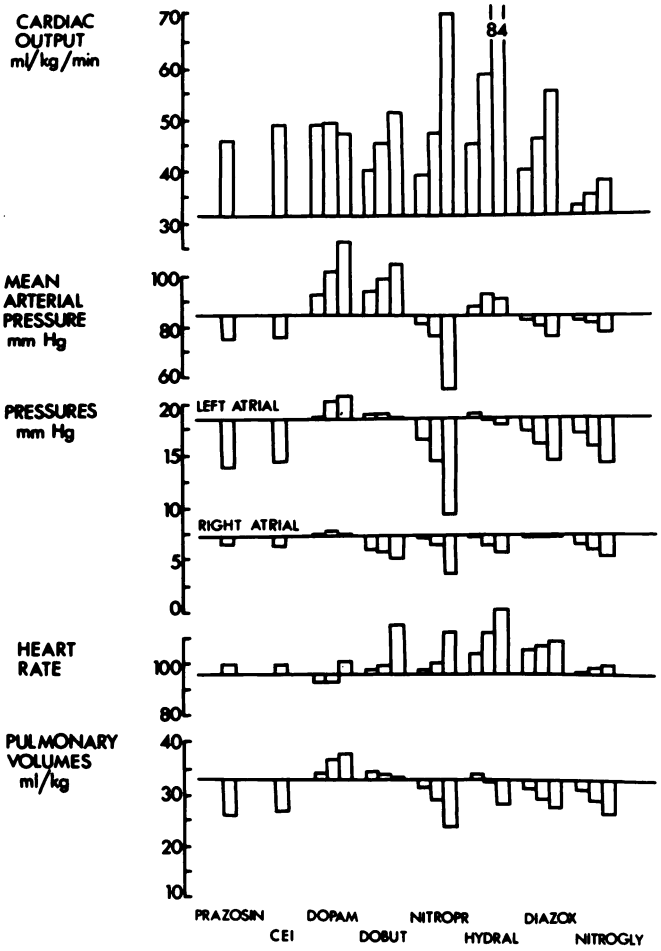

FIG. 15. The effects of various drugs in heart failure modelled for the human. Heart failure was modelled as contractility 30% of normal, blood volume 115% of normal, plus the actions of norepinephrine (0.37 μg/kg/min) and angiotensin (0.075 μg/kg/min). Prazosin was modelled by removing the vasoconstrictor actions of the norepinephrine, captopril by removing the angiotensin, and the remaining drugs by adding the direct actions of each of the three doses as analysed in section IV.

ering the variability of the disease. Others have commented that the large decrease in pulmonary resistance was greater than expected due to inhibition of angiotensin generation (326) but in some studies pulmonary arterial resistance was unchanged (78). As expected from the lack of effect of angiotensin on skeletal muscle venous compliance (section IV), converting enzyme inhibitors did not alter venous compliance in the calf muscles (78).

It is not yet clear whether the effects of converting enzyme inhibitors are solely due to reduction in plasma angiotensin II levels or whether other unknown actions are involved (135, 145, 148, 156, 316, 323, 325, 328). Restoration of the arterial pressure to the levels prior to administration of converting enzyme inhibitors by infusion of angiotensin required plasma angiotensin levels strikingly higher than those found prior to the converting enzyme inhibitor (145, 308). Various other actions involving endogenous kinins and prostaglandins have been suggested.

In summary, the effects of alpha-blockers and converting-enzyme inhibitors in heart failure can be explained

to a first approximation on the basis of removal of the alpha-receptor actions and reduction in plasma angiotensin levels respectively, but we cannot exclude the possibility of other subsidiary actions that may be important in certain patients.

C. Dopamine and Dobutamine

The effects of these agents in heart failure, predicted from their direct actions in normal animals and man (section IV) are shown in figure 15. Small doses of dopamine are clearly more beneficial than large doses (195) since they produce as large an increase in cardiac output without the deleterious effects of increased arterial pressure and heart rate. In small doses these beneficial effects of dopamine are due to a combination of vasodilatation and cardiac stimulation. However, the effect of improved cardiac function on preload is offset by the decreased venous compliances and atrial pressures do not fall. These predictions agree closely with the clinically observed effects of dopamine; cardiac index increased about 50% with increases or little change in arterial and pulmonary wedge pressures (174, 195, 199, 219, 227, 299).

The model predicts that dobutamine will increase cardiac output but, because it has little peripheral vasodilator effect, this in turn will result in an increase in arterial pressure. Although dobutamine may increase arterial pressure in patients with failure (45, 174), this does not occur in the majority of clinical studies. Usually dobutamine produces a small fall or no change in arterial pressure in spite of substantial increases in cardiac output (17, 105, 159, 195, 199, 299). It seems clear that in heart failure patients, dobutamine has a greater peripheral vasodilator action than predicted from the studies in normal animals and man (section IV) or in dogs with low cardiac output (318). Possibly the improved cardiovascular function results in reduction in plasma angiotensin or norepinephrine levels but this seems unlikely since dobutamine is reported to increase renin levels in these patients (174). This vasodilator action, combined with improved cardiac function but without decreased venous compliance, results in increased cardiac output, little change in arterial pressure, and decreased atrial pressures (104, 105, 159, 199, 291, 299). This suggests that dobutamine is superior to dopamine in patients with elevated left ventricular preload (195, 199).

The model predicts that dopamine will increase renal blood flow while dobutamine will not; dobutamine will increase muscle flow while dopamine will produce only a small increase. These effects have been observed (104, 195). However, the model predicts that dopamine will increase splanchnic flow but this was not seen (195).

D. Nitroprusside, Diazoxide, Nifedipine, and Salbutamol

Nitroprusside increases cardiac output primarily by decreasing peripheral resistance. The increased cardiac output in turn results in decreased preload. These effects may be enhanced by the small venodilator action (see section IV) as can be seen by comparing nitroprusside and diazoxide, which has no venodilator action (see figure 15). There is also a suggestion that nitroprusside may increase arterial compliance (244). There is a modest reduction in arterial pressure and an increase in heart rate. These effects are similar to those in clinical reports although the decreases in atrial pressures may be somewhat larger and the increases in heart rate are often smaller or absent (17, 36, 41, 88, 130, 186, 203, 212, 213, 217, 219, 220, 227, 237, 326). Since nitroprusside may cause a decrease in arterial oxygen saturation, which has been attributed to reduced pulmonary vascular resistance and development of ventilation/perfusion abnormalities (17, 48, 61, 326), it seems likely that in many patients, pulmonary resistance is elevated prior to treatment and that nitroprusside produces a substantial reduction (17, 326). This action would result in a substantial reduction in right ventricular afterload and in turn in a further improvement in cardiac output. If this effect is large, the improvement in cardiac output offsets the decreased peripheral resistance resulting in no change in arterial pressure. However, the effects on arterial oxygen saturation may be harmful.

The predicted effect of the middle dose of nitroprusside on the left ventricular pressure-volume loop is shown in figure 16. Left ventricular end-diastolic volume decreased about 10% while stoke volume increased 40%. This is similar to reported changes in patients (130, 217). As mentioned in section IV D, nitroprusside has been reported to increase left ventricular diastolic compliance in patients with congestive heart failure but it is not clear whether this is the direct action of the drug or a consequence of reduced right ventricular pressures (25).

If we assume that the overall effects of nifedipine resemble those of diazoxide (see section IV), then the predicted effects (see diazoxide in figure 15) resemble those reported in clinical studies in heart failure (71, 181, 210, 248). However, quantitative comparisons cannot yet be made. Minoxidil is similar (91). Salbutamol, a selective beta-2 receptor stimulant used in asthma, also has potentially useful effects (19, 59, 284), probably due primarily to its arteriolar vasodilator actions.

E. Hydralazine

As figure 15 shows, the combined vasodilator, cardiac stimulant, and venoconstrictor actions of hydralazine result in marked increases in cardiac output with modest changes in arterial pressure, atrial pressures, and pulmonary blood volume. As with dopamine, the decreased venous compliance prevented the fall in preload expected as a consequence of improved cardiac function. Heart rate increased markedly. These effects resemble those in clinical reports except that the predicted change in heart is not usually seen in patients (35, 37–39, 41, 80, 96, 142, 194, 196, 213, 247, 270). Whatever the mechanism of the tachycardia seen in normal or hypertensive animals and man (see section IV), it is much less prominent in failing hearts. When hydralazine is modelled without an increase

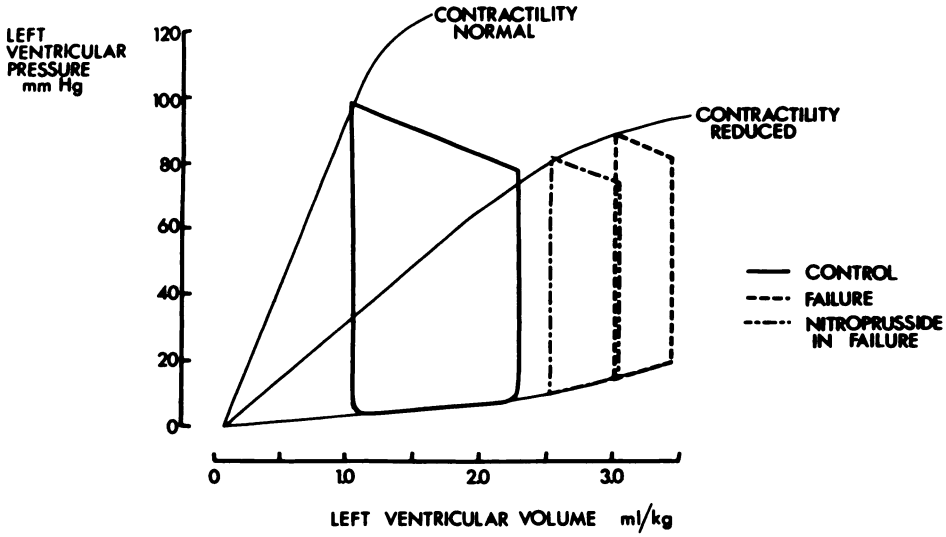

FIG. 16. Pressure-volume loops for the human left ventricle in the normal subject and in the patient with heart failure modelled as in figure 15 before and after treatment with nitroprusside (4 μg/kg/min).

in heart rate, the effects on cardiac output are only slightly reduced since stroke volume increases. In comparison with the other drugs, hydralazine more closely resembles the effects of dopamine than those of nitroprusside. The model predicts an increased renal blood flow. This has been observed (196) and could account for the reports of improved renal function (41, 247). In the model, left ventricular end-diastolic volume is unchanged by hydralazine and this also agrees with clinical reports (142).

F. Nitroglycerin

Nitroglycerin caused only a small increase in cardiac output with a modest decrease in arterial pressure. However, left and right atrial pressures and pulmonary blood volume decreased. Thus any beneficial effects of nitroglycerin would be expected to relate to relief of pulmonary congestion rather than to increased cardiac output. This is generally what has been reported (35, 51, 89, 186, 196, 220, 236, 332) although some reports show a larger increase in cardiac output especially if left ventricular filling pressures are very high before administration of nitroglycerin. The doses used in heart failure are often sufficient to cause a larger fall in systemic vascular resistance (89, 236) and therefore nitroglycerin as used in patients with heart failure falls between the models of nitroglycerin and nitroprusside. Also, as with nitroprusside, the pulmonary vascular resistance may be more elevated in the patients and more reduced by nitroglycerin than I have estimated in the model. The effects of nitroglycerin on ventricular diastolic compliance are potentially important (201, 202) and require further study.

G. Discussion

In general, the effects of these drugs, predicted from their actions in normal animals and man, agree remarkably well with the observations in patients with heart failure. The two major differences are in the general absence of tachycardia when arterial pressure is reduced or hydralazine is given to patients with heart failure and in the rather larger effects on pulmonary vascular resistance. A major point emphasised in this analysis is that decreased preload is an expected consequence of increased cardiac output. The finding of decreased preload does not necessarily indicate venodilatation but the absence of a decrease in preload with an increase in cardiac output does indicate venoconstriction. If venodilatation occurs, the fall in preload will be larger and the increase in cardiac output will be smaller.

Since many clinical reports discuss the effects of these drugs in heart failure in relation to the Starling function curve, it is worth discussing this more fully. Graphs of some of the data generated from the model are shown in figure 17. These curves were obtained by progressively increasing left ventricular end-diastolic volume by increasing total blood volume from 60% to 160% of normal. As end-diastolic volume increases, cardiac output and stroke work increase, giving the typical normal ventricular function curves (277). However, when this is repeated with a modest elevation in total peripheral resistance, cardiac output is reduced but stroke work is increased at any given left ventricular end-diastolic volume. When total peripheral resistance is lowered, cardiac output is increased but stroke work is reduced. Thus stroke work varies with total peripheral resistance at any given left ventricular end-diastolic volume and the model shows pressure-induced homeometric autoregulation (277) as discussed in section II. The end-systolic and end-diastolic ventricular pressure-volume relationships are not altered by the changes in total peripheral resistance. When similar curves are modelled for heart failure (contractility 30% plus norepinephrine and angiotensin as used earlier) and its treatment by nitroprusside, the reduction in total peripheral resistance by nitroprusside

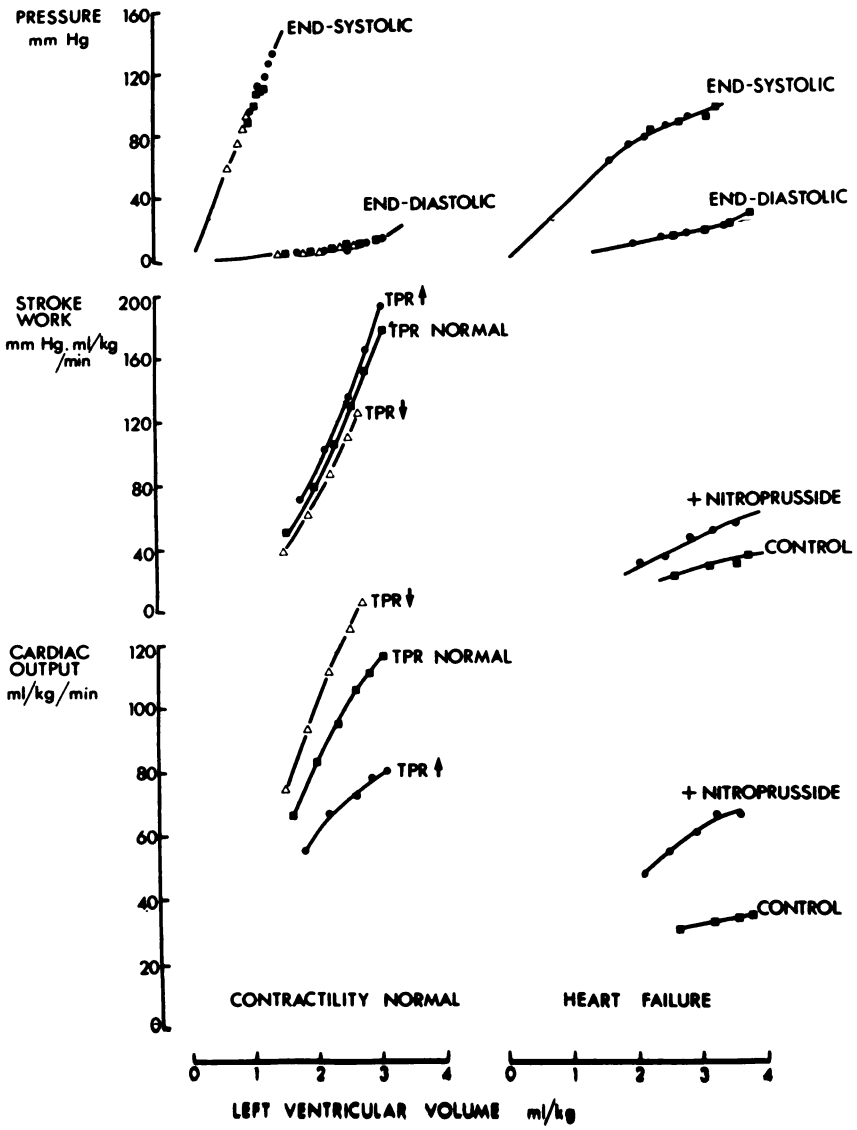

FIG. 17. Left ventricular end-systolic and end-diastolic pressure-volume relationships, and stroke work (mean arterial pressure times stroke volume) and cardiac output plotted against left ventricular end-diastolic volume, modelled for the human with normal contractility and normal, increased, and decreased total peripheral resistance (left panel), and in heart failure modelled as in figure 15 before and during nitroprusside infusion (right panel).

increases both cardiac output and stroke work at any given end-diastolic volume. Again the end-systolic and end-diastolic ventricular pressure-volume relationships are not altered by the change in total peripheral resistance. Thus it is clear that stroke work as well as cardiac output varies with changes in afterload and small shifts in the ventricular function curve cannot always be interpreted as changes in ventricular contractility (see section II C 3b).

It is not within the scope of this review to consider the relative merits of these drugs in the treatment of heart failure. Many factors are involved in this in addition to the pharmacological actions of the drugs and these have been discussed extensively in the reviews cited earlier. However, from the limited perspective of the pharmacological actions of these agents, their effects may be summarised: 1) inotropic agents will increase cardiac output and therefore decrease preload and increase afterload; 2) arteriolar vasodilators will decrease afterload and therefore increase cardiac output and decrease preload; 3) venodilation in combination with either of these will decrease preload further and therefore reduce the increase in cardiac output, while venoconstriction will tend to maintain preload and further increase the cardiac output; 4) the role of increased left ventricular diastolic compliance is potentially important and requires further study (201, 202). All the currently available drugs produce combinations of these effects and the choice of drug depends on whether the primary clinical objectives are to increase cardiac output or to decrease venous congestion, and how great a reduction in arterial pressure can be tolerated. In some cases the desired clinical objective may be best achieved by a combination of drugs (35, 45, 90, 219, 227).

VI. Summary

The primary purpose of this review is to attempt to synthesise cardiovascular physiology and pharmacology in such a way that the complex effects of drugs on cardiac output can be quantitatively explained on the basis of their direct actions on smooth muscle, cardiac muscle, or on intrinsic modulating mechanisms such as the baroreceptor reflex or endogenous production of angiotensin. Previous approaches to the analysis of cardiac output in terms of preload, afterload, and contractility have had the disadvantages that drugs do not act on preload and afterload directly, and although preload and afterload influence cardiac output, they are themselves influenced by cardiac output. Changes in preload and afterload are often the consequences rather than the causes of altered cardiac output.

In the analysis proposed, cardiovascular parameters are divided into two types: *semi-independent variables* (blood volume, compliances, resistances, cardiac rate, and contractilities) that represent the direct sites of drug action but which can also be modified by intrinsic modulating mechanisms such as reflexes and hormones, and *dependent variables* (pressures, flows, and volumes) that are determined within the circulation as consequences of the values of the semi-independent variables. The values of the dependent variables must therefore be calculated from the input values of the semi-independent variables and these calculated values must agree with experimental observations. Section II reviewed some physiological concepts of the circulation and developed simple equations that describe cardiovascular interrelationships and allow calculation of the dependent variables. This section thus developed a model of the circulation. This model differs from most previous models because it separates the variables as described and because contractility is not defined in terms of the ventricular function curve but in terms of ventricular end-systolic pressure-volume relationships as described by Sagawa, Suga, and coworkers (276). The relationships described by the equations were used for the anaesthetised cat and dog and for man, and species differences were discussed.

Section III analysed the effects of each semi-independent variable on cardiac output. Thus the relative importance of each potential site of drug action as a determinant of cardiac output was discussed. Major effects on cardiac output are produced by changes in blood volume, splanchnic venous compliance, ventricular diastolic compliance, arteriolar and venous resistances, and cardiac rate and contractility. However, the interaction of preload, afterload, and cardiac function result in a high degree of stability in cardiac output and multiple drug actions are generally required to produce significant changes in cardiac output. At the end of this section, certain techniques used to study the venous system were criticised.

In section IV, the direct actions of some common drugs were evaluated quantitatively from the literature and their secondary effects on the dependent variables were then predicted from these direct actions. There are sufficient data to allow this analysis for a few drugs only and the sympathomimetic amines (epinephrine, norepinephrine, isoproterenol, phenylephrine, dopamine, and dobutamine), angiotensin, vasopressin, sodium nitroprusside, hydralazine, diazoxide, nitroglycerin, and nifedipine were considered. Although the actions of these drugs on some important semi-independent variables, notably arterial, pulmonary, and ventricular diastolic compliances, are unknown, the major actions of these drugs are consistent with their observed effects on cardiac output, regional flows, pressures, and volumes.

Heart failure was considered in section V as a combination of reduced myocardial contractility, increased blood volume, plus the direct actions of small amounts of norepinephrine and angiotensin. The effects of this combination resemble those seen in patients with heart failure although other factors are discussed. When this model of heart failure is combined with the direct actions of the inotropic and vasodilator drugs as assessed in section IV, the clinical effects of therapy of heart failure with these agents can be explained although some quantitative discrepancies occur. The inadequacy of the ventricular function curve as an index of contractility and the problems of analysing cardiac output in terms of preload and afterload were discussed further.

Overall this analysis does synthesise physiological and pharmacological concepts and data into a coherent picture that is in agreement with a large body of experimental observations, and most of the variables that are of current interest to cardiovascular scientists are incorporated into the analysis. However, many aspects of both the relationships and the values assigned to the variables will be controversial and reports can be cited to support modified relationships and different values. However, the important consideration is whether this overall approach merits further consideration or whether better alternatives exist. Some merits of the approach are:

1. We are forced to take cognisance of all parts of the circulation and not just the part we are studying.

2. We are forced to a quantitative rather than a descriptive approach and, as Sagawa stated, "the more quantitative the model is, the more exact becomes the deduction and the testing" (274).

3. The approach clearly demonstrates areas that require further study as is demonstrated by the numerous question marks in tables 2–7. In particular, ventricular diastolic compliance has large effects on cardiac output and changes may play an important role in both disease and drug therapy. New techniques have opened the way to study this variable and important new information is likely to be published in the next few years.

4. As pharmacokinetic data become available, in vitro and in vivo studies can be integrated into a single body of knowledge and the potential in vivo effects of drug

actions discovered in vitro can be evaluated. At present many of the drug actions on the semi-independent variables cannot be measured independently and must be back-calculated from measurements of dependent variables. However, even in this situation, the analysis allows the fitting together of many pieces of the jigsaw puzzle.

Although it is possible to summarise the approach to the analysis of the effects of drugs on cardiac output, it is difficult to summarise the effects of the drugs themselves. All the drugs reviewed have different actions and their effects on cardiac output are quantitatively different. Nevertheless, it is clear that drugs that increase heart rate and contractility, reduce arteriolar resistances, and decrease venous compliances simultaneously will produce maximal increases in cardiac output.

Appendix

The computer program in BASIC-11 (Digital Equipment Corp.) was used throughout this review to calculate the values for the dependent variables from the initialised or input semi-independent variables. To run the program for the first time, answer the query "How many runs?" with a zero. This will give a print-out of the control values that includes the abbreviations for the variables that the user needs to answer the later queries. The first value printed out for each variable is the value in the absence of intrinsic modulation; the second value is with intrinsic modulation. To answer the query on line 190 with a "D," the user requires the additional file DRUG.MOD. This file contains the data from tables 2 to 7 and allows the user to model these drugs without typing in the changes through the keyboard. This file and a list of the variable names may be obtained from the author.

```
10 REM ***MOD10.BAS***
20 PRINT "MODEL OF CARDIOVASCULAR SYSTEM (version 10)" \ PRINT
30 DIM S(44,2),D(44,2),S$(44),S1$(44),S2$(44),D$(44),C(15,44),C$(15,44),T$(15)
40 FOR I=1 TO 44 \ READ S$(I),S1$(I),D$(I) \ NEXT I
50 PRINT "MODEL OF CAT (C), DOG (D) OR HUMAN (H) "; \ INPUT A$
60 IF A$⟨⟩"C" THEN IF A$⟨⟩"D" THEN IF A$⟨⟩"H" GO TO 50
70 PRINT "HOW MANY RUNS AFTER CONTROL RUN (max 15) "; \ INPUT N
80 PRINT "TITLE FOR DATA SET" \ LINPUT T$(0) \ T$(0)=T$(0)+ "– CONTROLS"
90 I3=0 \ J= 1 \ A=2 \ D=.12 \ G=.3 \ REM INITIALIZE
100 FOR I=1 TO 44 \ READ C(0,I) \ NEXT I \ IF A$="C" GO TO 140
110 FOR I=1 TO 13 \ C(0,I)=C(0,I)*80/52 \ NEXT I
120 IF A$="D" THEN C(0,34)=120 \ C(0,35)=22 \ C(0,36)=140 \ C(0,41)=100
130 IF A$="H" THEN C(0,34)=75 \ C(0,35)=20 \ C(0,36)=100 \ C(0,41)=80
140 F1=C(0,35) \ F2=C(0,36)
150 FOR I3=1 TO N \ PRINT "SHORT TITLE FOR RUN ";I3; \ INPUT T$(I3)
160 PRINT "CHANGES FROM CONTROL (0) OR RUN # "; \ INPUT N1
170 IF N1⟩=I3 THEN PRINT "IMPOSSIBLE " \ GO TO 160
180 FOR I=1 TO 44 \ C(I3,I)=C(N1,I) \ NEXT I
190 PRINT "CHANGES IN ABS. VALUES (A), AS % (P), OR DRUG (D) "; \ INPUT A3$
200 IF A3$⟨⟩"A" THEN IF A3$⟨⟩"P" THEN IF A3$⟨⟩"D" GO TO 190
210 IF A3$="D" GO TO 980
220 PRINT "ABBREV. OF VARIABLE TO BE CHANGED OR ⟨CR⟩ "; \ INPUT C$
230 IF C$="" GO TO 280 \ FOR I=1 TO 44 \ IF C$=S1$(I) GO TO 250
240 NEXT I \ PRINT "INCORRECT ABBREV. " \ GO TO 220
250 PRINT "NEW VALUE "; \ INPUT V \ C$(I3,I)="*"
260 IF A3$="A" THEN C(I3,I)=V \ GO TO 220
270 IF A3$="P" THEN C(I3,I)=C(I3,I)*V/100 \ GO TO 220
280 NEXT I3 \ OPEN "LP:" FOR OUTPUT AS FILE #2
290 FOR I3=0 TO N \ FOR I=1 TO 44 \ S(I,1)=C(I3,I) \ S2$(I)=C$(I3,I) \ NEXT I
300 S(16,J)=S(20,J)+S(24,1)+S(28,1) \ S(17,J)=S(21,J)+S(25,1)+S(29,1)
310 S(18,J)=S(22,J)+S(26,1)+S(30,1) \ S(19,J)=S(23,J)+S(27,1)+S(31,1)
320 S(15,J)=1/(1/S(16,J)+1/S(17,J)+1/S(18,J)+1/S(19,J))
330 S(5,J)=S(6,J)+S(7,J)+S(8,J)+S(9,J)
340 D(34,J)=.18*S(1,1) \ I2=0 \ REM VOLUME LOOP
350 D(23,J)=D(34,J)/S(11,1)+S(38,1) \ D(24,J)=D(23,J)+A*S(37,1)
360 C7=S(13,1) \ IF D(24,J)–S(38,1)⟩10 THEN C7=S(13,1)–S(13,1)*(D(24,J)–S(38,1)–10)/60
370 D(37,J)=(D(24,J)–S(38,1))*C7
```

```
380 D(7,J)=(D(37,J)−D) / (1+((S(34,J)*S(15,J)+.67/S(3,1))/S(36,1)))
390 D(38,J)=D(37,J)−D(7,J) \ D(2,J)=D(7,J)*S(34,J) \ D(21,J)=D(23,J)+D(2,J)*S(32,1)
400 D1(J)=D(21,J)−.33*D(7,J)/S(10,1) \ D(22,J)=D(21,J)+.67*D(7,J)/S(10,1)
410 IF D(22,J)⟨25 GO TO 430 \ P2=1 \ F5=S(35,1) \ Q=D(22,J)−25 \ IF Q⟩15 THEN Q=15
420 S(35,1)=S(35,1)−S(35,1)*.05*Q
430 D(35,J)=D(7,J)+D+D(22,J)/S(35,1) \ IF P2=1 THEN P2=0 \ S(35,1)=F5
440 D(36,J)=D(35,J)−D(7,J) \ C6=S(12,1) \ D(20,J)=D(35,J)/C6+S(38,1)
450 IF D(20,J)⟩3 THEN C6=S(12,1)−S(12,1)*(D(20,J)−3)/30 \ D(20,J)=D(35,J)/C6+S(38,1)
460 D(19,J)=D(20,J)−A*S(37,1) \ D(33,J)=D(21,J)*S(10,1) \ D(36,J)=D(35,J)−D(7,J)
470 D(9,J)=D(2,J)*S(15,J)+D(19,J) \ D(26,J)=D(9,J)*S(3,1)
480 D2(J)=D(9,J)−.33*D(7,J)/S(3,1) \ D(10,J)=D(9,J)+.67*D(7,J)/S(3,1)
490 IF P1=1 THEN P1=0 \ S(36,1)=F4 \ GO TO 530
500 IF D(10,J)⟨160*S(36,1)/F2 GO TO 530
510 P=D(10,J)−160*S(36,1)/F2 \ IF P⟩65 THEN P=65
520 F4=S(36,1) \ S(36,1)=S(36,1)−S(36,1)*5.00000E−03*P \ P1=1 \ GO TO 380
530 D(3,J)=(D(9,J)−D(19,J))/S(16,J) \ D(4,J)=(D(9,J)−D(19,J))/S(17,J)
540 D(5,J)=(D(9,J)−D(19,J))/S(18,J) \ D(6,J)=(D(9,J)−D(19,J))/S(19,J)
550 D(11,J)=D(9,J)−D(3,J)*S(20,J) \ D(12,J)=D(9,J)−D(4,J)*S(21,J)
560 D(13,J)=D(9,J)−D(5,J)*S(22,J) \ D(14,J)=D(9,J)−D(6,J)*S(23,J)
570 D(27,J)=S(4,1)/4*(D(11,J)+D(12,J)+D(13,J)+D(14,J))
580 D(15,J)=D(3,J)*S(28,1)+D(19,J) \ D(16,J)=D(4,J)*S(29,1)+D(19,J)
590 D(17,J)=D(5,J)*S(30,1)+D(19,J) \ D(18,J)=D(6,J)*S(31,1)+D(19,J)
600 D(29,J)=D(15,J)*S(6,J) \ D(30,J)=D(16,J)*S(7,J)
610 D(31,J)=D(17,J)*S(8,J) \ D(32,J)=D(18,J)*S(9,J)
620 D(28,J)=D(29,J)+D(30,J)+D(31,J)+D(32,J) \ I2=I2+1
630 IF I2⟩200 THEN PRINT "FAILED TO SOLVE WITH 200 ITERATIONS − RUN ";I3 \ GO TO 1320
640 B1=D(26,J)+D(27,J)+D(28,J)+D(33,J)+D(34,J)+D(35,J)+D(37,J) \ B=S(1,1)/B1
650 IF B⟨.995 THEN D(34,J)=D(34,J)+(B−1)*5 \ GO TO 350
660 IF B⟩1.005 THEN D(34,J)=D(34,J)+(B−1)*5 \ GO TO 350
670 IF J=2 GO TO 770 \ J=2 \ REM BAROREFLEX CALCULATION
680 G1=S(42,1)*(D(9,1)−S(41,1)) \ IF G1⟩G THEN G1=G
690 S(15,2)=S(15,1)−G1 \ S(34,2)=S(34,1)−S(43,1)*(D(9,1)−S(41,1)−10)
700 S(16,2)=S(16,1)*S(15,2)/S(15,1) \ S(20,2)=S(16,2)−S(24,1)−S(28,1)
710 S(17,2)=S(17,1)*S(15,2)/S(15,1) \ S(21,2)=S(17,2)−S(25,1)−S(29,1)
720 S(18,2)=S(18,1)*S(15,2)/S(15,1) \ S(22,2)=S(18,2)−S(26,1)−S(30,1)
730 S(19,2)=S(19,1)*S(15,2)/S(15,1) \ S(23,2)=S(19,2)−S(27,1)−S(31,1)
740 S(5,2)=S(5,1)+S(44,1)*(D(9,1)−S(41,1))
750 S(6,2)=S(6,1)*S(5,2)/S(5,1) \ S(7,2)=S(7,1)*S(5,2)/S(5,1)
760 S(8,2)=S(8,1)*S(5,2)/S(5,1) \ S(9,2)=S(9,1)*S(5,2)/S(5,1) \ GO TO 340
770 PRINT #2,TAB(5);"CIRCULATION OF "; \ REM PRINT OUTPUT
780 IF A$="C" THEN PRINT #2,"ANAESTHETIZED CAT ";
790 IF A$="D" THEN PRINT #2,"ANAESTHETIZED DOG ";
800 IF A$="H" THEN PRINT #2,"HUMAN ";
810 PRINT #2,"WITHOUT AND WITH BAROREFLEX"
820 PRINT #2,TAB(20);"Version 10      ";DAT$;"      ";CLK$,I2,F$ \ PRINT #2
830 PRINT #2,"RUN";I3;" "; T$(I3) \ PRINT #2
840 PRINT #2,"SEMI-INDEPENDENT VARIABLES";TAB(42);"DEPENDENT VARIABLES" \ PRINT #2
850 FOR I=1 TO 44 \ PRINT #2,S$(I);TAB(20);S1$(I);" ";S2$(I);TAB(26);
860 FOR J=1 TO 2 \ Z=S(I,J) \ GOSUB 920 \ PRINT #2,TAB(33); \ NEXT J
870 PRINT #2,TAB(42);D$(I);TAB(65); \ FOR J=1 TO 2
880 IF I=10 THEN PRINT #2,USING "###/###",D(10,J);D2(J); \ GO TO 910
890 IF I=22 THEN PRINT #2,USING "##/##",D(22,J);D1(J); \ GO TO 910
900 Z=D(I,J) \ GOSUB 920
910 PRINT #2,TAB(74); \ NEXT J \ PRINT #2 \ NEXT I \ PRINT #2,CHR$(12) \ GO TO 970
920 IF ABS(Z)⟩9.9 THEN PRINT #2,USING "###",Z; \ RETURN
930 IF ABS(Z)⟩.99 THEN PRINT #2,USING "###.#",Z; \ RETURN
940 IF ABS(Z)⟩.099 THEN PRINT #2,USING "###.##",Z; \ RETURN
```

```
950 IF Z=0 THEN PRINT #2,"          "; \ RETURN
960 PRINT #2,USING "###.###",Z; \ RETURN
970 J=1 \ NEXT I3 \ GO TO 1320
980 REM DRUG DATA INPUT
990 PRINT "ABBREV. OF DRUG: EPI NE ISO PE DOP DOB ANG VAS NTP HYD DIA NTG"
1000 INPUT M$ \ OPEN "PD1:DRUG.MOD" FOR INPUT AS FILE #5
1010 FOR K=1 TO 12 \ INPUT #5,M1$,M2$
1020 IF M1$=M$ THEN PRINT M2$ \ INPUT M3$
1030 FOR K1=1 TO 5 \ INPUT #5,M4$ \ FOR I=1 TO 44 \ INPUT #5,M
1040 IF M1$=M$ THEN IF M3$=M4$ THEN IF M<>100 THEN C$(I3,I)="*" \ C(I3,I)=C(I3,I)*M/100
1050 NEXT I \ IF M1$=M$ THEN IF M3$=M4$ THEN T$(I3)=T$(I3)+M4$ \ CLOSE #5 \ GO TO 280
1060 NEXT K1 \ NEXT K \ PRINT "NOT FOUND" \ CLOSE #5 \ GO TO 190
1070 DATA "BLOOD VOL. ml/kg", "BV","FLOWS ml/kg/min","COMPLIANCES ml/kg/min",""
1080 DATA "Cardiac output", "Arterial", "CA"," Splanchnic flow", "Capillary",""
1090 DATA " Muscle flow","Venous","", "Kidney flow"," Splanchnic","CVS"," Other flow"
1100 DATA " Muscle","CVM","Stroke volume"," Kidney","CVK","PRESSURES mm Hg"
1110 DATA " Rest","CVR","Arterial","Pulm. arterial","CPA"," Syst./diast.","Pulm. venous"
1120 DATA "CPV","Splanchnic capillary","Right ventric.","CRV","Muscle capillary"
1130 DATA "Left ventric.","CLV","Kidney capillary","RESISTANCES mm Hg.kg.min/ml",""
1140 DATA "Rest capillary","Total","","Splanchnic venous"," Splanch. total",""
1150 DATA "Muscle venous"," Muscle total","","Kidney venous"," Kidney total",""
1160 DATA "Rest venous"," Rest total","","Right atrial"," Splanchnic art."
1170 DATA "RAS","RV end diastolic"," Muscle art.","RAM","Pulmonary arterial"
1180 DATA " Kidney art.","RAK"," Syst./diast."," Rest art.","RAR","Left atrial"
1190 DATA " Splanc. postcap","RCS","LV end diastolic"," Muscle postcap","RCM"
1200 DATA "VOLUMES ml/kg"," Kidney postcap","RCK","Arterial"," Rest postcap"
1210 DATA "RCR","Capillary"," Splanc. venous","RVS","Venous"," Muscle venous"
1220 DATA "RVM"," Splanchnic"," Kidney venous","RVK"," Muscle"," Rest venous"
1230 DATA "RVR"," Kidney","Pulmonary","RP"," Rest","HEART","","Pulm. arterial"
1240 DATA "Heart rate / min","HR","Pulm. venous","Contractility RV","CR"
1250 DATA "RV end diastolic","                    LV","CL","RV end systolic"
1260 DATA "                atrial","CAT","LV end diastolic","Thor. press. mm Hg", "TP"
1270 DATA "LV end systolic","","","","","BAROREFLEX PARAMETERS","","","Set point"
1280 DATA "BSP","","Resist. factor","BRF","","Heart rate factor","BHF",""
1290 DATA "Ven. comp. factor","BVF",""
1300 DATA 52,0,.04,.13,4.45,2.6,1,.05,.8,.08,1,.25,.13,0,0,0,0,0,0,2.63,3,3.6,3,
1310 DATA .32,.36,.43,.36,.18,.2,.24,.2,.07,0,180,50,350,1,-2,0,0,120,.004,.4,.01
1320 END
```

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