CARDIOVASCULAR PHARMACOLOGY[1,2]

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In this review, the literature on the cardiovascular actions of some naturally occurring chemicals is summarized from the viewpoint of the physiologist. Emphasis is given the effects on the mechanical forces which determine cardiac output, resistance to blood flow, and capillary hydrostatic pressure. Where possible, direct effects are separated from indirect effects. The authors found the information to be inadequate in many areas and, in the interest of future research, these areas are noted.

Review of Mechanical Forces Which Determine Cardiac Output

Figure 1 shows that the minute output of the ventricle is immediately determined by the stroke volume and the frequency of contraction of the ventricle. The stroke volume is determined by arterial pressure, strength of the ventricle muscle,[4] and diastolic ventricular volume. The diastolic ventricular volume is in turn determined by the volume remaining in the ventricle at the end of systole, venous filling pressure, diastolic filling time, compliance of the ventricular wall during diastole, and resistance to blood flow through the atrioventricular valve. Hence, cardiac output is influenced by seven immediate and remote mechanical factors (frequency, arterial pressure, strength, filling pressure, filling time, ventricular compliance, and valvular resistance). Each factor can be influenced by a chemical agent. For more detail regarding the mechanical factors, see Grodins (1) and Grodins et al. (2).

Review of Factors Which Determine Resistance to Blood Flow, Capillary Hydrostatic Pressure, Capillary Flow Rate, and Blood Storage

The resistance to blood flow through the entire systemic vascular bed influences arterial pressure which in turn affects cardiac output (see above

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[4] Strength is defined as the ratio, stroke work/diastolic ventricular volume. The "stronger" ventricle performs more work at any given diastolic ventricular volume (initial fiber length). Thus, the force of ventricular contraction is influenced by two factors, diastolic ventricular volume and strength.

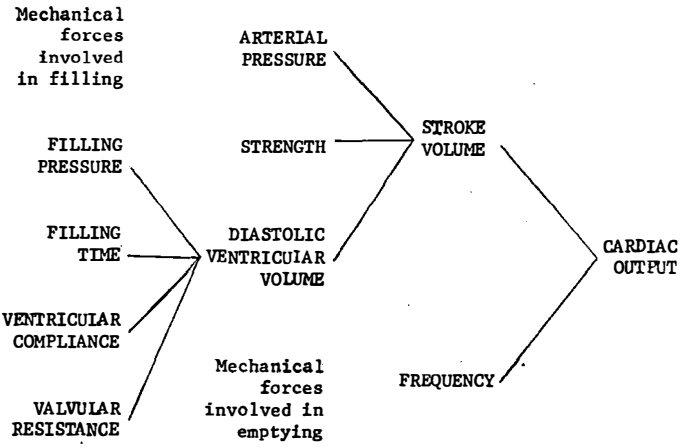

FIG. 1. Mechanical forces which determine the minute output of the ventricle.

and Figure 1). Each of the many parallel components in the systemic circuit receives only a fraction of the cardiac output. The distribution of the cardiac output among these competing systemic organs depends upon their respective resistances to blood flow. Figure 2 shows that the resistance is immediately determined by the geometric and viscous components of resistance. Vessel radius is the most important variable in the geometric component of resistance. Radius is influenced by the contractile state of vascular smooth muscle, transmural pressure, and morphological changes in the vessel wall. The viscous component of resistance is influenced by the concentration, size, shape, and aggregation of blood cells. A chemical may affect

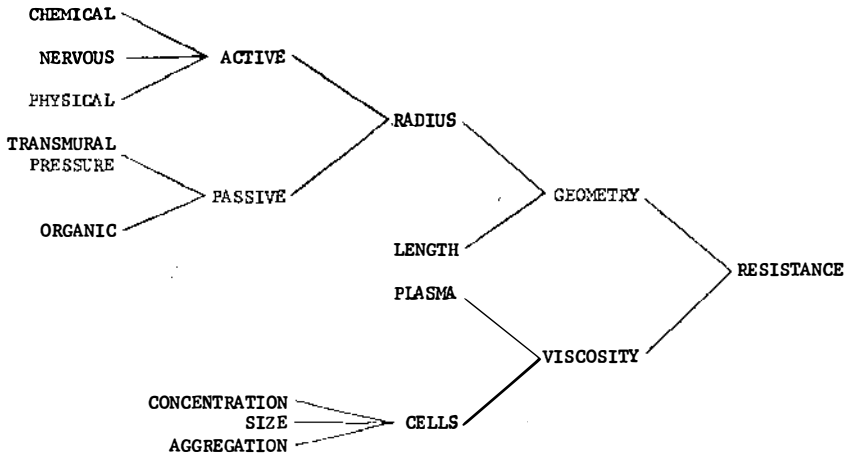

FIG. 2. Factors which determine the resistance to blood flow.

resistance by altering the contractile state of vascular smooth muscle, transmural pressure, morphology of the wall (for example, changes in the water content), and the concentration, size, shape, and aggregation of blood cells.

In many vascular beds, the entering blood is distributed between the capillaries and arteriovenous anastomoses. The rate of capillary blood flow is important because it influences concentration and temperature gradients, rates of movement of heat and materials, and possibly metabolic rate of the parenchymal cell. A change in the latter parameter would influence the rates of production of heat and materials. If flow completely stops in some capillaries, diffusion distances and capillary surface area are also affected. The distribution of flow between the capillaries and the arteriovenous anastomoses depends on the relationship between the resistances to flow existing in these two pathways. A chemical may alter this relationship. For example, during intra-arterial infusion of a vasodilator, the resistance to flow through vessels leading to capillaries might fall more than the resistance to flow through the arteriovenous anastomoses. This would increase capillary flow proportionately more than anastomotic flow.

Capillary hydrostatic pressure is important because it influences the effective capillary filtration pressure which in turn affects the distribution of water and materials between intravascular and interstitial spaces. Capillary hydrostatic pressure, therefore, affects the absolute blood volume, the store of water in tissues, and the rate of movement of materials across the capillary wall. The absolute blood volume influences venous return to the heart which in turn affects filling pressure and, hence, cardiac output. Figure 3 indicates the determinants of capillary hydrostatic pressure. It is evi-

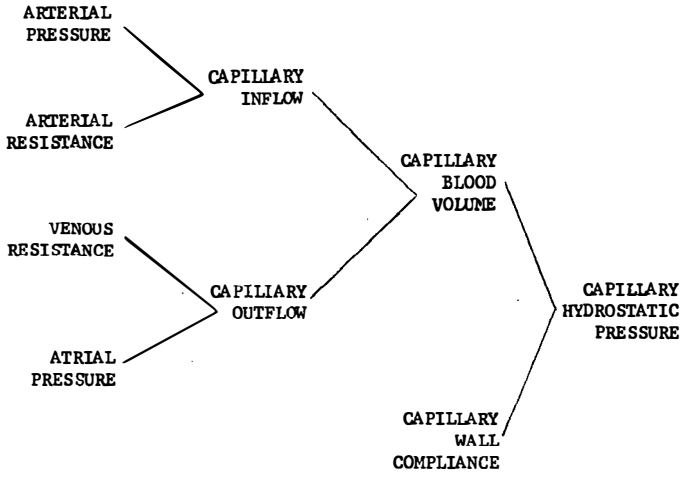

FIG. 3. Factors which determine capillary hydrostatic pressure.

dent that the four remote determinants (left-hand side of figure) also affect capillary flow rate. A chemical may influence capillary pressure and capillary blood flow by altering the driving pressure (aortic pressure), resistance to blood flow through vessels leading to the capillaries (arterial resistance, precapillary resistance), resistance to blood flow through vessels leading away from the capillaries (venous resistance, postcapillary resistance), or outflow pressure (central venous pressure, atrial pressure). For example, a fall in the driving pressure or a rise in the resistance to flow through vessels leading to capillaries would lower capillary inflow, volume and pressure, and decrease capillary flow rate. On the other hand, a rise in outflow pressure or an increase in the resistance to flow through vessels leading away from the capillaries would decrease capillary outflow, increase capillary volume, increase capillary pressure, and decrease capillary flow rate.

The amount of blood stored in the peripheral vascular bed is important because this influences the effective circulating blood volume and, hence, venous return, filling pressure, and cardiac output (Fig. 1). A chemical may change the quantity of sequestered blood by producing a localized or generalized change in the contractile state of vascular smooth muscle. For example, either localized hepatic venous constriction or generalized active dilation of the splanchnic bed will increase splanchnic blood volume and thereby reduce venous return to the heart.

Direct and Indirect Actions

The effect of a chemical on many of the above parameters is the net result of competing direct and indirect actions. For example, the steady-state rise in resistance following intra-arterial infusion of a vasoconstrictor agent is the net result of a direct vasoconstrictor action and an indirect vasodilator action. The latter action may result from rise in concentration of vasodilating metabolites subsequent to (*a*) decrease in flow, (*b*) increase in metabolic rate, or (c) a combination of (*a*) and (*b*). When the chemical is administered intravenously, the indirect vasodilating action might be augmented subsequent to (*a*) a rise in arterial transmural pressure and (*b*) reflex suppression of the sympathico-adrenal system. Similarly, the fall in strength following intravenous infusion of a chemical which depresses ventricular muscle is the net result of direct and indirect actions. The agent might depress strength by a direct action but increase strength through an indirect action. The latter action could result from a baroreceptor-induced sympathico-adrenal discharge subsequent to fall in arterial pressure.

Plan

The effects of some naturally occurring chemicals on the heart and peripheral vascular bed are described according to the above schemes.

Steady-state effects on the heart during intravenous infusion are described first. This is immediately followed by a consideration of whether the effects described result from direct or indirect actions of the chemical. Steady-state effects on the periphery during intravenous infusion are described next. Then follows a description of the direct actions of the chemical on the periphery. In order to make the description as complete as possible, it was necessary to consult the older literature. These papers are not cited. Citations include only selected review articles and relevant papers printed in 1964 and during the first five months of 1965. Thus, some observations are not followed by citations and a citation following an observation does not necessarily mean that the author cited was the first investigator to make the observation. Citations following section titles refer to review articles.

Angiotensin (3–6)

Effects on heart in the intact animal during intravenous infusion.—Angiotensin produces, in the steady-state, no change or a fall in cardiac output (7–10). There is no change (9, 11) or a fall in cardiac frequency (9, 10) and no change (9), slight rise (9), or a fall in stroke volume (8, 10). The change in frequency and stroke volume appears to be dose related since the dog may respond to a low infusion rate with no change in frequency and stroke volume, and to a higher infusion rate with decrease in frequency and increase in stroke volume (9). Angiotensin raises systemic arterial pressure (7–12). An unchanged or increased stroke volume in the face of a rise in arterial pressure implies an increase in contractile force due to increase in (*a*) diastolic ventricular volume, (*b*) strength, or (*c*) both diastolic ventricular volume and strength. Contractile force, diastolic ventricular volume, and strength have not been adequately studied in the intact animal. However, available studies suggest increases in both diastolic ventricular volume and strength (9). The mechanism of the increase in diastolic ventricular volume, when present, could be (*a*) increase in residual volume (9) caused by a rise in arterial pressure, (*b*) increase in filling time when frequency decreases, and (*c*) the increase in left atrial pressure. Ventricular compliance during diastole has apparently not been studied in the intact animal.

Direct effects on heart.—Decrease in frequency in the intact animal, when it occurs, apparently results largely or exclusively from reflex effects via the sino-aortic pressoreceptors. Angiotensin has little direct effect on frequency (13) and increases frequency after sino-aortic denervation. The latter effect is probably mediated by central (14) and ganglionic (15) stimulation of cardiac efferent nerves and by release of catecholamines from the adrenal medulla (16, 17, 18). Angiotensin has a direct stimulating effect on strength (13, 19, 20), though the effect is less than with levarternol. This might be augmented in the intact circulation by stimulation of the central nervous system (14), sympathetic ganglia (15), and adrenal medulla (16,

17, 18). It might be antagonized via the baroreceptor mechanism (8, 21) and through a coronary flow which is inadequate for the myocardial metabolic rate (19, 22). Angiotensin apparently had no direct effect on ventricular compliance (13).

Effects on peripheral circulation in the intact animal during intravenous infusion.—The most pronounced response in the intact circulation during intravenous infusion of angiotensin is a rise in total peripheral resistance (7–11) and hence arterial pressure. Since there probably is little effect on blood viscosity (at least the hematocrit does not consistently increase), the rise in total peripheral resistance results from net reduction in blood vessel radius due to activation of vascular smooth muscle. Apparently the changes in radius are not uniform. Flow decreases in the superior mesenteric (7), renal (7, 23, 24), and hepatic arteries (25), does not change in the carotid artery (7), decreases slightly (7) or increases in the femoral artery, and increases in the vertebral and pancreaticoduodenal (25) arteries. Portal venous flow falls transiently but then returns to the control value during the infusion (25). However, total hepatic flow falls because of the reduction in hepatic artery flow. Superficial and deep venous outflow decrease in the forelimb (26). Coronary flow has not been adequately studied during intravenous infusion with the circulation intact. However, coronary flow has been reported to increase during infusion at a rapid rate. The rise in total peripheral resistance results mainly from an increase in net arterial resistance (4, 27). Net venous resistance has not been studied during intravenous infusion of angiotensin into the intact circulation but, in man, there is no change (27) or only a slight decrease in venous compliance. There is also a slight increase of pressure in the intact isolated segment of a superficial forearm vein, an effect which can be abolished by local nerve blockade. The absolute blood volume and, by inference, average capillary hydrostatic pressure are little affected (27). Capillary hydrostatic pressure remains unchanged, apparently because the effect of rise in arterial pressure [and possibly rise in venous resistance and right atrial pressure (8)] is completely antagonized by the increase in arterial resistance. There appear to be no studies on the rate of capillary flow during intravenous infusion.

Direct effects on peripheral circulation.—The rise in total peripheral resistance results from a direct constrictor action on blood vessels. Intra-arterial administration increases resistance in all beds studied (3, 4, 5, 8, 19, 23, 24, 26, 28–32). Even coronary resistance rises during intracoronary administration (19). The consequent fall in coronary flow is often associated with a fall in myocardial strength (19). How the direct effect on total peripheral resistance is modulated in the intact system by the baroreceptors (33), adrenal medulla (16, 17, 18), central nervous system (14), and sympathetic ganglia (15, 23, 24) is not clear. In the forelimb of the dog (5) and the hindlimb of the cat, an intra-arterial infusion raises arterial resistance but apparently has little effect on venous resistance. This may pro-

duce a small fall in capillary hydrostatic pressure. The effect on venous resistance, however, might be more pronounced in the monkey (34) and man (31, 35).

Effects on pulmonary circulation and on metabolic rate.—Intravenous infusion apparently shifts blood into the pulmonary vascular bed. Associated with this is a small rise in pulmonary artery pressure and a small fall in pulmonary vascular resistance. Whether the rise in pulmonary blood volume in the intact animal results from an increase in venous return to the right heart, from diminished ejection by the left heart, or both is not clear. The available evidence tends to support diminished ejection by the left heart (4). The direct effect of angiotensin is to raise pulmonary vascular resistance (36). Intravenous infusion has no effect on total body oxygen consumption.

Epinephrine (6, 37, 38)

Effects on heart in the intact animal during intravenous infusion.—Epinephrine produces, in the steady-state, a rise in cardiac output (7, 39–43). This rise results from an increase in stroke volume (41) and, at low infusion rates, also from an increase in frequency (41, 43). At high infusion rates, frequency does not change, or it decreases. Systemic arterial pressure is unaffected by low rates of infusion (41) and rises with high rates of infusion (39), implying that the rise in stroke volume results from an increase in contractile force. While an increase in contractile force is regularly observed (39), its mechanism is not entirely clear since strength and diastolic ventricular volume have not been studied in the intact animal at either low or high rates of infusion. However, very low rates of infusion do not change right atrial pressure, filling time (42), or systemic arterial pressure, suggesting a constant diastolic ventricular volume. Indeed, diastolic ventricular volume is not regularly affected following intravenous injection of a small quantity of epinephrine (44). Thus it appears that the increase in contractile force during intravenous infusion at a very low rate results from an increase in strength. On the other hand, higher rates of infusion produce increases in left atrial pressure, systemic arterial pressure and filling time (by inference from the decrease in frequency), suggesting an increase in diastolic ventricular volume. In fact, the older literature indicates that the diastolic ventricular volume does rise following intravenous injection of a large quantity of epinephrine. Thus, the increase in contractile force seen during infusion at a high rate probably results both from an increase in diastolic ventricular volume and strength. There appear to be no studies on diastolic ventricular compliance in the intact animal.

Direct effects on heart.—Epinephrine increases cardiac frequency by a direct effect (45, 46, 47). This effect is reflexly antagonized via the baroreceptor mechanism during infusion into the intact animal at rates which raise systemic arterial pressure. Epinephrine increases strength by a direct effect (37, 45), an action which also might be antagonized by the barore-

ceptor mechanism when there is a rise in arterial pressure. Studies on the direct effect of epinephrine on diastolic ventricular compliance are not in complete agreement. However, most of the findings suggest an increase in compliance.

Effects on peripheral circulation in the intact animal during intravenous infusion.—Except at very high rates of infusion (11, 39), total peripheral resistance falls (7, 41, 42, 43) despite a rise in hematocrit and, by inference, blood viscosity. Hence, the fall in total peripheral resistance results from net increase in the radius of blood vessels. The changes in radius are apparently not uniform. Infusion at a rate which raises systemic arterial pressure by 5 per cent produces the following percentage changes in flow: ascending aorta +27, carotid artery −11, superior mesenteric artery +36, renal artery −3, femoral artery +37 (7). The corresponding changes during infusion at a rate which raises systemic arterial pressure by 35 per cent are +92, +17, +76, −22, and +136 (7). Outflow from a skin vein in the forelimb decreases at both low and high rates of infusion (26). In the human being, there is an increase in forearm and calf flow. Coronary flow apparently increases both during infusion (42) and following injection (48). Epinephrine appears to have no effect on the fraction of the cardiac output delivered to the submaxillary gland (48). Gastric flow has been reported to rise (40, 49), not change, or fall. Pancreatic flow apparently falls (50). Arterial and venous resistances have not been critically examined during intravenous infusion with the sympathetic nervous system intact. However, in those beds that dilate, the magnitude of the effect suggests that resistance falls mainly because of a decrease in arterial resistance. Similarly, in those beds that constrict, the magnitude of the response suggests that resistance rises mainly because of an increase in arterial resistance. Venous smooth muscle is also activated. This is indicated by a decrease in forearm venous compliance and, at times, by a decrease in forearm volume in the presence of an elevated flow. With prolonged infusion, there is a decrease in absolute blood volume (27) and, by inference, an increase in average capillary hydrostatic pressure. The latter apparently results from a rise in systemic arterial pressure, right atrial pressure, possibly net venous resistance, and from a fall in net arterial resistance. The rise in right atrial pressure, seen with moderate to rapid rates of infusion, probably results at least in part from generalized reduction of venous radius, compliance, or both. The clearance rate of NaI^{131} from skeletal muscle increases, suggesting an elevated capillary flow.

Direct effects on peripheral circulation.—The steady-state effect of epinephrine on the periphery (intra-arterial infusion) varies with the vascular bed and the infusion rate (37). Resistance in the kidney, whole forelimb (51), and skin of the forelimb (28) increases at all infusion rates. A rise in resistance is also the most frequent response in intestine (5, 29, 52) but occasionally, with very low infusion rates, intestinal resistance falls perhaps

because of passive dilation due to relaxation of the intestinal smooth muscle (52, 53). In man, resistance in skeletal muscle decreases with low rates of infusion (54). With higher rates of infusion, the decrease in resistance is quickly replaced by an increase in resistance (54). Coronary vascular resistance usually decreases at all rates of infusion. However, in some instances, very low rates of infusion produce a small increase in coronary resistance, and intracoronary injection frequently produces a transient increase followed by a prolonged decrease in resistance (55). These findings have been interpreted to mean that a direct constrictor effect is masked by a metabolically induced vasodilation. Cerebral vascular resistance is little affected (37). Intra-arterial injection raises splenic resistance (30). It is probable that these direct effects on the periphery are modulated by the baroreceptor mechanism during intravenous infusion at a rate which raises arterial pressure. Intravenous injection of epinephrine reduces the activity in sympathetic nerves leading to the hindlimb and kidney.

Rapid intra-arterial infusion of epinephrine into the denervated cat hindquarters produces an increase in both arterial and venous resistance. The increase in arterial resistance is proportionately greater than the increase in venous resistance, thereby causing a fall in capillary hydrostatic pressure and transcapillary inflow of extravascular fluid. It would be of interest to determine whether more prolonged infusion at a rapid rate would cause a gradual disappearance of the elevated arterial resistance in the presence of the elevated venous resistance. This would reverse the direction of transcapillary fluid flow. Such a response is often seen during sympathetic nerve stimulation and during prolonged rapid intra-arterial infusion of levarterenol. It would also be of interest to determine whether very slow intra-arterial infusion causes a fall in arterial resistance without an effect on venous resistance, a rise in capillary hydrostatic pressure, and a transcapillary efflux of intravascular fluid. This response is seen during intravenous infusion at a slow rate. On the other hand, intra-arterial infusion of epinephrine into the constantly perfused dog forelimb (51), where the ratio of skin to muscle is greater, causes a rise in arterial resistance at all rates of infusion. At least with the higher rates of infusion, resistance to flow through the larger veins also rises.

There are apparently no satisfactory studies on the rate of blood flow through capillaries.

Effects on pulmonary circulation and on metabolic rate.—Intravenous injection or rapid intravenous infusion causes an increase in pulmonary blood volume (56), undoubtedly from pulmonary inflow in excess of pulmonary outflow (57). This causes an increase in pulmonary capillary hydrostatic pressure and transcapillary outflow of intravascular fluid. The regularity of this response in the rabbit is advantageous for those interested in studying pulmonary edema (57). The direct effect of epinephrine on the pulmonary vascular bed is to increase pulmonary vascular resistance (58).

Intravenous infusion of epinephrine causes an increase in total body oxygen consumption as well as in the blood concentrations of glucose, lactate, pyruvate, and free fatty acids (38, 41). It also enriches the phosphorylase content of muscle. Many of these effects disappear following administration of propanolol, an agent which permits the emergence of a levarterenol-like activity on the cardiovascular system (41). An interesting area for future research is a comparison of the relationship of metabolism to resistance in various organs during administration of epinephrine. Large increases in metabolism in those organs in which there is dilation (for example, heart) and small increases in metabolism in those organs in which there is constriction (for example, kidney) would suggest that the direct constrictor action of epinephrine on blood vessels is partially or completely antagonized or converted to a dilation by metabolites depending upon the degree to which epinephrine affects the function of the parenchymal cells. Support for this interpretation would be provided if agents which block epinephrine's ability to dilate and stimulate myocardial strength also block its effect on metabolism.

Levarterenol (6, 37, 38)

Effects on heart in the intact animal during intravenous infusion.—In the steady-state, levarterenol has little regular effect on cardiac output (7, 39, 40, 59, 60, 61). A fall in frequency (59, 60, 62) is often balanced by a rise in stroke volume (59, 60). Since there is a rise in systemic arterial pressure (39, 59, 60, 62), the increase in stroke volume must be attributed to an increase in contractile force (39). The increase in force probably results from an increase in strength rather than from an increase in diastolic ventricular volume when the rate of infusion is slow, but these parameters have not been adequately studied in the intact animal. That diastolic ventricular volume might participate in the production of the increased force during infusion at a fast rate is suggested by a rise in left atrial pressure and filling time (59). Indeed, diastolic ventricular volume sometimes increases following intravenous injection (44). There appear to be no adequate studies on ventricular compliance and residual volume.

Direct effects on heart.—The direct effect of levarterenol is to increase frequency (13, 45) and strength (13, 20, 45, 63). The fall in frequency in the intact animal results reflexly via the baroreceptor mechanism (39) and possibly via some effect on the central nervous system (14). Whether the direct effect on strength is suppressed by the baroreceptor mechanism in the intact animal needs critical study. As in the case of epinephrine, the studies on diastolic ventricular compliance are not in agreement. However, any observed change is in the direction of an increased compliance.

Effects on peripheral circulation in the intact animal during intravenous infusion.—Levarterenol raises total peripheral resistance (7, 39, 59). While hematocrit also increases (61), a large rise in peripheral resistance still oc-

curs in the splenectomized animal at a time when the change in hematocrit is negligible (11). Thus, the rise in peripheral resistance results predominately from reduction in net blood vessel radius due to activation of vascular smooth muscle. The changes in radius are more uniform than with epinephrine. Infusion at a rate which raises arterial pressure by 15 per cent produces the following percentage changes in blood flow: carotid artery +0.5, superior mesenteric artery +9.7, renal artery +3.6, femoral artery +11.1 (7). Intravenous infusion of levarterenol produces a fall in gastric flow (40) but apparently does not regularly affect pancreatic (50) or total hepatic flow. There is a decrease in superficial venous outflow in the dog forelimb (26), suggesting a fall in skin flow. While skin flow regularly falls in the forearm of man, the effects on total and muscle flow are variable. Coronary flow apparently increases in the intact man. Net arterial resistance and net venous resistance have not been critically examined during intravenous infusion in the intact animal. Judging from the magnitude of the increase in total peripheral resistance, however, there must be a substantial rise in net resistance to flow through arteries. That the venous smooth muscle is also activated is indicated by a decrease in venous compliance (62) and a fall in forearm volume without a significant change in flow. Blood volume falls (27, 61). This suggests that the elevation of arterial and right atrial pressures and possibly elevation of venous resistance act to raise capillary hydrostatic pressure despite the elevation of arterial resistance. The elevation of right atrial pressure probably results from generalized decrease in venous radius, compliance, or both. The rate of capillary blood flow has apparently not been studied during intravenous infusion.

Direct effects on peripheral circulation.—The direct effect of levarterenol in the steady-state is to increase total peripheral resistance, an effect which is apparently damped reflexly in the intact animal. Intra-arterial infusion raises the resistance to blood flow through almost all vascular beds (5, 28, 29, 30, 37, 51, 52, 62, 64, 65). Even the resistance to flow through the coronary vascular bed will sometimes rise when the rate of infusion is low, though this resistance always falls when the infusion rate is high. Levarterenol apparently has little effect on cerebral vascular resistance.

The rise in resistance to blood flow through an organ results predominately from an elevation in arterial resistance. Venous resistance also contributes to the rise in total resistance, at least at higher rates of infusion. In the skin-muscle region of the denervated hindquarters of the cat, short-term intravenous infusion increases arterial resistance out of proportion to venous resistance, thereby lowering capillary hydrostatic pressure and causing transcapillary inflow of fluid from the tissue spaces. Transcapillary inflow of fluid may also be seen during both short-term and long-term intra-arterial infusion in the skin-muscle region of the dog forelimb and in the vascular bed of the dog intestine (5). However, long-term intra-arterial

infusion sometimes produces transcapillary efflux of fluid. It is possible that this effect results from an increase in capillary hydrostatic pressure due to a gradual waning of the elevated arterial resistance (local regulation) without a proportional waning of the elevated venous resistance. A similar response has been observed in the cat intestine during stimulation of regional vasoconstrictor fibers (66). The effect on capillary flow has not been adequately studied.

Effects on pulmonary circulation and metabolic rate.—Intravenous infusion of levarterenol raises pulmonary blood volume (56) and, by inference, pulmonary capillary hydrostatic pressure. In this way, rapid administration can produce lung edema (57). While pulmonary vascular resistance may fall during intravenous infusion, the direct effect is to increase pulmonary vascular resistance (36). Total body oxygen consumption is increased but not to the degree seen with epinephrine (38, 67).

Vasopressin (68-72)

Effects on heart in the intact animal during intravenous infusion.—Vasopressin produces a fall in cardiac output due to decrease in frequency and stroke volume. Systemic arterial pressure rises but tends to return to the control value during the infusion. There seem to be no studies on strength and diastolic ventricular volume during infusion, but it has been established that an intravenous injection of a large amount produces an increase in heart size. Similarly, no studies seem to be available on filling time, filling pressure, diastolic ventricular compliance, and resistance to flow through the atrioventricular valve during intravenous infusion. However, filling time undoubtedly increases as frequency decreases and intravenous injection of a large amount produces a rise in left atrial pressure. These findings suggest but do not prove that vasopressin decreases strength in the intact animal.

Direct effects on heart.—Studies in the excised heart, Langendorf preparation, heart-lung preparation, and intact heart following intracoronary injection indicate that the direct effect of pituitrin and pitressin is to produce no change or a decrease in frequency and strength. The decrease in strength is often associated with a decrease in coronary flow. There appear to be no studies on the direct effect of vasopressin on diastolic ventricular compliance. While it seems likely that the decrease in frequency seen during intravenous infusion in the intact animal results at least in part via the baroreceptor mechanism, studies in this area are incomplete. If, in fact, strength does decrease in the intact animal, the explanation might be related to (*a*) a direct depressant effect on ventricular muscle, (*b*) a reduction in the ratio coronary flow to cardiac metabolic rate, and (*c*) the baroreceptor mechanism. Perhaps of relevance to these questions is the recent observation that vasopressin, unlike angiotensin, does not directly stimulate the adrenal medulla (16).

Effects on peripheral circulation in the intact animal during intravenous infusion.—Vasopressin causes a rise in total peripheral resistance. While there are no studies on blood viscosity, the rise in resistance undoubtedly results for the most part from net reduction in the radius of blood vessels due to activation of vascular smooth muscle. There are no complete studies on the distribution of the cardiac output but the available information suggests that the effect on the blood vessel radius is not entirely uniform. Intravenous infusion reduces flow in the coronary, superior mesenteric, epiploic, and femoral arteries, in the portal vein (portal venous pressure also falls), and in the hand. The effect on hepatic artery flow is not uniform. While the most frequent response is a decrease in flow, vasopressin sometimes causes an increase in flow. An initial fall in forearm flow is quickly followed by a rise above the control value. Intravenous injection reduces flow in the coronary, femoral, and carotid arteries, in the terminal abdominal aorta, and in the mesenteric, femoral, and jugular veins, but, at least in the cat and dog, may transiently reduce and then increase flow in the renal artery.

Net resistance to flow through arteries and veins, absolute blood volume, and net capillary hydrostatic pressure have not been studied during intravenous infusion. Neither has right atrial pressure been studied during infusion, but it has been established that it rises following injection. Judging from the large increase in total peripheral resistance, there must be a rise in net arterial resistance. Hepatic venous resistance is apparently unaffected. There are no studies on capillary flow during intravenous administration.

Direct effects on peripheral circulation.—Activation of vascular smooth muscle apparently results from a direct effect. Intra-arterial infusion of vasopressin produces a rise in the resistance to flow through most organs. These include heart, forelimb (5), hindlimb (73), and intestine (29). Renal resistance has been reported not to change or fall following intrarenal arterial injection in the cat, but this observation needs further investigation. Intravenous infusion at a rate which has no effect on arterial pressure in the normal subject produces a rise in arterial pressure after ganglionic blockade. This suggests but does not prove that the direct effect on peripheral resistance is partially buffered by the baroreceptor mechanism.

Intra-arterial infusion of vasopressin in the forelimb apparently increases arterial resistance out of proportion to venous resistance, thereby producing a slight fall in capillary hydrostatic pressure and in the tissue store of water (5). Further, vasopressin has little effect on the resistance to flow through large veins in the forelimb (5) and mesentery (29). On the other hand, injection directly into a small digital vein causes a rise in digital venous pressure suggesting that these veins will respond to vasopressin in high concentration (73). There are no adequate studies on capillary flow.

Effects on pulmonary circulation and metabolic rate.—The pulmonary vascular bed has not been adequately studied during intravenous infusion. Intravenous injection of a large amount of vasopressin produces a rise in pulmonary artery pressure in the intact animal. Intravenous infusion of vasopressin produces a fall in total body oxygen consumption.

ACETYLCHOLINE

Effects on heart in the intact animal during intravenous infusion.—Acetylcholine must be infused very rapidly to affect the cardiovascular system. In normal man, infusion of 0.5 mg/min into the pulmonary artery is without effect on cardiac output, frequency, or systemic arterial pressure. Infusion of 30 to 140 mg/min into a peripheral vein apparently produces no change in cardiac output, no change or a slight rise in frequency, and no change or a slight fall in systemic arterial pressure. In the intact dog, infusion of up to 25 μg/min into the right ventricle or pulmonary artery does not produce marked changes in cardiac output (58), but infusion of 40 to 50 μg/kg per min into a peripheral vein increases cardiac output and frequency and decreases systemic arterial pressure. Left atrial pressure is unaffected. There appear to be no studies on stroke volume, myocardial strength, diastolic ventricular volume, resistance to flow through the atrioventricular valve, or diastolic ventricular compliance in the intact animal.

Direct effects on heart.—The direct effect of acetylcholine is to reduce frequency (74) and strength (74). There is no effect on diastolic ventricular compliance. The increase in frequency which occurs in the intact animal during intravenous infusion probably results reflexly via the baroreceptor mechanism and possibly via a local stimulatory effect on the adrenal medulla (75).

Effects on peripheral circulation in the intact animal during intravenous infusion.—In the dog, infusion of 40 to 50 μg/kg per min produces a fall in total peripheral resistance. While the effect on blood viscosity has not been studied, this fall in resistance undoubtedly results from a net increase in blood vessel radius due to a relaxation of the vascular smooth muscle. This interpretation is supported by measurements of systemic arterial pressure, cardiac output (pulse contour method), and hematocrit in the splenectomized dog during intravenous infusion of 5 to 10 μg/kg per min (11). Under these circumstances, total systemic resistance falls despite a decrease in arterial transmural pressure and no change in arterial hematocrit. The relative effects on resistances in the various parallel circuits during intravenous infusion in the intact animal are unknown because the distribution of the cardiac output has not been studied by modern techniques. Skeletal muscle flow apparently increases during infusion of 20 μg/kg per min into the dog. There is a rise in skin temperature during intravenous infusion of 30 to 140 mg/min in man. Gastric vascular resistance is unaffected in the dog (76).

Net resistance to blood flow through arteries and veins has not been

studied during intravenous infusion in the intact animal but, judging from the magnitude of the reduction of total systemic resistance in the dog, there must be a fall in arterial resistance. Neither have net capillary hydrostatic pressure and absolute blood volume been studied. The absence of an effect on hematocrit in the splenectomized dog (11) suggests that changes in average capillary hydrostatic pressure and, hence, absolute blood volume are small. Perhaps the effects on capillary pressure of changes in arterial pressure, arterial resistance, venous resistance, and right atrial pressure counterbalance one another. It has been suggested from indirect measurements that intravenous infusion of 20 μg/kg per min in the dog causes an increase in flow through arteriovenous anastomoses and a decresase in flow through capillaries in skeletal muscle. It is evident that the area of capillary flow needs further study.

Direct effects on peripheral circulation.—The reduction in total systemic resistance apparently results from a direct effect on peripheral blood vessels (77). Intra-arterial administration reduces the resistance to flow through the gastric, superior mesenteric (29), skeletal muscle (78, 79, 80), hindlimb, forelimb (5), renal (81, 82, 83) and coronary vascular beds (55). The resistance to flow through an ileal segment of gut first decreases and then increases above the control value as a function of the infusion rate, the latter response apparently resulting from vascular compression subsequent to activation of the intestinal smooth muscle (52). Injection into the splenic artery decreases splenic resistance (30). During intravenous infusion, these direct effects are incompletely buffered by the sympathico-adrenal system.

During intra-arterial infusion in the forelimb (84), the fall in resistance results from decrease in both arterial and venous resistance. This also appears to be the case in skeletal muscle (80). Studies with methacholine (5) suggest that the fall in venous resistance is in proportion to the fall in arterial resistance. Prolonged intra-arterial infusion of metacholine into the dog forelimb has little effect on the tissue store of water. Capillary flow has not been carefully examined during natural perfusion. It has been studied during perfusion at a constant rate but the results seem to be in conflict (78, 80).

Effects on pulmonary circulation and metabolic rate.—In normal man, infusion of 0.5 mg/min into the pulmonary artery causes a slight fall in pulmonary arterial pressure due to a fall in pulmonary vascular resistance. This infusion is without effect on total body oxygen consumption, but infusion of 30 to 140 mg/min into a peripheral vein apparently produces an increase in total body oxygen consumption.

Histamine (85–88)

Effects on heart in the intact animal during systemic administration.—Slow intravenous infusion appears to produce a small rise in cardiac output (40) as a result of a rise in cardiac frequency. The stroke volume remains

constant or decreases slightly despite a fall in systemic arterial pressure. This indicates decrease in strength, decrease in diastolic ventricular volume, or decrease in both strength and diastolic ventricular volume, but these variables have not been studied in the intact animal. There is a fall in left atrial pressure and left ventricular filling time (inferred from increase in frequency) changes which tend to decrease diastolic ventricular volume. However, diastolic ventricular compliance and resistance to flow through the atrioventricular valve have not been studied.

There appear to be no studies of cardiac output in the intact animal during intravenous infusion at rates more rapid than 5 μg/kg per minute. However, subcutaneous injection of a very large amount of histamine produces a fall in cardiac output despite a rise in cardiac frequency. Stroke volume obviously falls, as does systemic arterial pressure. As in the case of slow infusion, the data necessary to evaluate the mechanism of the fall in stroke volume are not available. However, some of the peripheral actions (see below) suggest that the mechanism is at least in part related to a reduction in ventricular filling.

Direct effects on heart.—Modern techniques should be applied in this area. The older literature (86) suggests that cardiac frequency and strength are little affected by low concentrations, increased by moderate concentrations, and decreased by high concentrations (the decrease in frequency apparently resulting from effects on the conduction system). The direct effect of histamine on ventricular compliance has apparently not been studied. The rise in frequency observed during intravenous infusion in the intact animal could result from (*a*) a baroreceptor induced sympathico-adrenal discharge subsequent to a fall in systemic arterial pressure, (*b*) a direct stimulatory effect of histamine on central and peripheral sympathetic nerve cells, (*c*) a direct stimulatory effect of histamine on the adrenal medulla (18), and (*d*) possibly a direct stimulatory effect on the heart.

Effects on peripheral circulation in the intact animal during systemic administration.—Slow intravenous infusion into the intact circulation produces a fall in total systemic resistance despite a rise in the hematocrit and, possibly, cell aggregation (89). This indicates that the fall in resistance results from a net increase in blood vessel radius. While distribution of the cardiac output has not been systematically studied, the available data suggest that the increase in vessel radius is not generalized. Flow rises in the left gastric artery, arm, and leg, does not change (90) or rises (40, 49) in the stomach, does not change in the pancreas (50), and falls in the superior mesenteric artery. Coronary flow has apparently not been measured. There are no studies on total systemic resistance during rapid intravenous infusion of histamine into the completely intact animal. However, subcutaneous injection of a very large amount sometimes produces a rise rather than a fall in total systemic resistance. This rise in resistance seems to be partly related to a rise in blood viscosity since only a fall in resistance is seen when

the rise in hematocrit is prevented by splenectomy. Hence, a net increase in vessel radius apparently occurs even following massive amounts of histamine. Since arterial transmural pressure falls to a low level, the increase in net blood vessel radius must result from an active mechanism. Apparently, there are no studies on flow distribution during rapid intravenous infusion into the intact animal. However, subcutaneous injection of a large amount in the splenectomized dog produces a fall in the splanchnic blood flow.

Net arterial and venous resistances have not been critically examined during intravenous infusion at any rate. However, during slow infusion, the magnitude of the fall in total systemic resistance suggests an appreciable reduction in net arterial resistance, and microscopically there is a visible widening of the smaller arterioles in skin and skeletal muscle. On the other hand, the larger mesenteric and intestinal veins are visibly narrowed. Skin capillary hydrostatic pressure apparently rises slightly during slow infusion (probably because of fall in arterial resistance), but this effect cannot be generalized since there is no appreciable change in the absolute blood volume. Neither is there a significant change in the absolute blood volume following subcutaneous administration of a massive amount of histamine. It is possible that the forces which determine capillary hydrostatic pressure (Fig. 3) change in such a way that they counterbalance one another. For example, a fall in net arterial resistance and a rise in net venous resistance might be counterbalanced by decreases in systemic arterial and right atrial pressures. A fall in right atrial pressure is seen during rapid infusion, and this may result from a decrease in the effective blood volume subsequent to rise in intestinal venous resistance and, at least in the dog, hepatic venous resistance. There are apparently no critical studies on capillary flow during systemic administration.

Direct effects on peripheral circulation.—The direct effect of histamine is to lower total systemic resistance through relaxation of vascular smooth muscle. Intra-arterial infusion reduces the resistance to blood flow through the forelimb (5), skeletal muscle (80), stomach (91), and intestine (29). Intra-arterial injection reduces resistance to flow through the kidney (32). Resistance to blood flow through these organs apparently falls solely because of a decrease in the resistance to flow through arteries (80, 88). With rapid infusion in the forelimb, the fall in resistance to flow through arteries is accompanied by a rise in the resistance to flow through veins (88). This rise in venous resistance results at least in part from an adrenal medullary discharge (88), but may also result from a local action of histamine (88, 92). The fall in arterial resistance, especially when accompanied by a rise in venous resistance, apparently drives capillary hydrostatic pressure to high levels, thereby causing rapid efflux of fluid from the capillary (88, 92). The effect of the rise in capillary hydrostatic pressure on fluid efflux might be abetted by an increase in the permeability of the capillary membrane (80). There appear to be no critical studies on the effect of

intra-arterially administered histamine on capillary flow but those that are available suggest an increase in capillary flow.

The direct peripheral effects of histamine are modulated in the intact animal by (*a*) a sympathico-adrenal discharge which tends to antagonize the relaxed vascular smooth muscle and to raise blood viscosity (splenic contraction) and (*b*) a fall in transmural pressure which tends to passively constrict vessels. Indeed, following massive subcutaneous injection of histamine, these indirect actions may overbalance the direct action (see above).

Effects on pulmonary circulation and metabolic rate.—In the intact animal, intravenous infusion at a slow rate produces an increase in pulmonary blood volume and in total pulmonary vascular resistance. These findings, together with studies in the open-chest animal, suggest a rise in the resistance to flow through pulmonary veins.

Total body oxygen consumption rises during slow intravenous infusion and falls following subcutaneous injection of a large amount.

Bradykinin (71, 93–97)

Effects on heart in the intact animal during intravenous infusion.—The steady-state effect of bradykinin is to increase cardiac output (98–101) due to a rise in cardiac frequency (99, 101). Stroke volume is not regularly affected (98–101). Systemic arterial pressure is unchanged or decreased (98–101). There have been no studies on strength and diastolic ventricular volume during intravenous infusion. Left atrial pressure is unchanged (101) and diastolic filling time probably falls (inferred from increase in frequency). The resistance to flow across the atrioventricular valve and left ventricular diastolic compliance have not been measured.

Direct effects on heart.—Bradykinin has little effect on frequency and strength in the isolated heart. Ventricular diastolic compliance has not been studied. The rise in cardiac frequency in the intact animal apparently results from a sympathico-adrenal discharge subsequent to (*a*) a direct stimulating action of bradykinin on the adrenal medulla (16, 17, 18, 102), (*b*) a direct stimulating action of bradykinin on sympathetic ganglia (15), and (*c*) a fall in systemic arterial pressure which is sensed by the baroreceptors. There is also some evidence which suggests a stimulating action on parasympathetic centers (94). This would tend to minimize the increase in cardiac frequency.

Effects on peripheral circulation in the intact animal during intravenous infusion.—Bradykinin produces a large fall in total systemic resistance (98–101). This must result from a net increase in blood vessel radius due to relaxation of vascular smooth muscle since it is associated with a rise in hematocrit and a fall in arterial transmural pressure. There have been no systematic studies of the relative effects of intravenously infused bradykinin on resistances in the various parallel circuits, but the available data

suggest that the effects on the vessel radius are not uniform. Indirect measurements suggest a rise in hand flow (100), no change or a rise in forearm (100), coronary, and renal (100, 103) flow, and no change in hepatic (99) flow. Resistance falls in the hand (100), coronary and splanchnic (99) beds, remains unchanged or falls in the kidney (100, 103), and apparently is unaffected in the forearm (100).

There have been no studies on net arterial or net venous resistance during intravenous infusion. However, judging from the magnitude of the fall in total systemic resistance, arterial resistance undoubtedly falls. Venous compliance has been reported to increase in the hand (100). Average capillary hydrostatic pressure and absolute blood volume have not been studied. Right atrial pressure does not change or falls slightly. The effects on capillary flow are unknown.

Direct effects on peripheral circulation.—The fall in total systemic resistance results from a direct relaxing action on vascular smooth muscle. Such a direct action is supported by a wealth of evidence. Intra-arterial administration produces a fall in the resistances to flow through the coronary, renal (82), whole forelimb, whole hindlimb (98, 104), forearm, hand, skeletal muscle (80, 104), skin (104), superior mesenteric (105), stomach (76, 91), and cerebral and salivary gland vascular beds.

It appears that the fall in resistance results solely from a decrease in resistance to flow through arteries (80, 105). There is no evidence to suggest a decrease in the resistance to flow through veins. Intra-arterial infusion of bradykinin into the dog forelimb and into the superior mesenteric artery (105) has little effect on the resistance to flow through the large veins. Intra-arterial infusion into a skeletal muscle vascular bed (80) has no appreciable effect on venous volume. Indeed, there is evidence to suggest that bradykinin constricts the smaller veins (92). A fall in arterial resistance in the absence of a fall in venous resistance would increase capillary hydrostatic pressure. This could account, at least in part, for the striking capillary efflux of fluid and protein observed during local administration. The effect of a rise in capillary hydrostatic pressure on fluid and protein efflux might be enhanced by an increase in the permeability of the capillary membrane. Intra-arterial infusion of bradykinin apparently increases capillary blood flow in skeletal muscle.

In the intact animal, the direct relaxing action on vascular smooth muscle is minimized by an increase in sympathico-adrenal activity (see above).

Effects on pulmonary circulation and metabolic rate.—Bradykinin, infused intravenously, produces a fall in pulmonary vascular resistance in both man (101) and dog. Pulmonary arterial pressure does not change in man (101) but may fall in the dog. There appear to be no studies on pulmonary blood volume in the intact animal. Bradykinin apparently increases the resistance to blood flow through the isolated lung (106, 107).

Total body oxygen consumption does not change (100) or rises slightly during intravenous infusion.

Other similar agents.—For information on the cardiovascular actions of agents similar to bradykinin such as kallidin and eledoisin, see the following references: (71, 93–97, 102, 105–111).

Serotonin (112, 113)

Effects on heart in the intact animal during intravenous infusion.—Serotonin produces an increase in cardiac output due to a rise in cardiac frequency. The stroke volume is unaffected. In unanesthetized man and in the anesthetized dog, slow and moderate rates of infusion have little regular effect on systemic arterial pressure. However, in the anesthetized dog, rapid infusion most often produces a fall in pressure (26). Ventricular strength and diastolic volume have not been studied. Left atrial pressure is unaffected (58), but ventricular filling time probably decreases (inferred from increase in frequency). The resistance to flow through the atrioventricular valve and left ventricular compliance have not been studied.

Direct effects on heart.—Injection of serotonin directly into the coronary artery produces little effect on cardiac frequency (114, 115). Neither does it greatly affect the left ventricular contractile force (115), suggesting a negligible direct effect on cardiac strength. The direct effect on diastolic ventricular compliance has not been studied. The rise in cardiac frequency seen during intravenous infusion in the intact animal apparently results from some indirect action of serotonin. In this regard, there is some evidence to indicate that serotonin causes an adrenal medullary discharge by a local action (18).

Effects on peripheral circulation in the intact animal during intravenous infusion.—Serotonin causes a fall in total systemic resistance. This fall in resistance appears to result from a net increase in vessel radius due to relaxation of vascular smooth muscle because it is associated with a rise in hematocrit, an aggregation of blood elements (89), and, frequently, a fall in arterial transmural pressure. All of the latter changes tend to raise resistance. The effects on resistances in the various parallel circuits have not been systematically studied. Intravenous infusion in the anesthetized dog apparently increases coronary blood flow. There is no change (90) or a rise in gastric blood flow. Flow through the whole forelimb is little affected at low to moderate rates of infusion but frequently decreases at high rates of infusion, probably because of a reduction in skin flow (26). On the other hand, plethysmographic techniques suggest a rise in the forearm flow in man. The studies on renal blood flow in the dog are not in agreement. Flow has been reported to increase or decrease. In man, however, clearance techniques suggest no change or a fall in renal blood flow. There appear to be no studies on net arterial resistance, net venous resistance, average capillary hydrostatic pressure, or absolute blood volume. The right atrial pressure is unaffected.

There is evidence to suggest that the response of total systemic resistance is conditioned by the degree of activity in the sympathetic nervous system (112). Intravenous infusion of serotonin produces a fall in systemic arterial pressure in the neurogenically hypertensive dog and a rise in systemic arterial pressure in the neurogenically hypotensive dog. Cardiac output, however, has not been measured under these conditions.

Direct effects on peripheral circulation.—The effect of serotonin is not the same in all peripheral vascular beds. Intra-arterial infusion regularly raises resistance in the kidney but has small and irregular effects on vascular resistance in the intestine (5, 29, 52) despite increased activity of the surrounding intestinal smooth muscle (52). The effects on vascular resistance are also small and irregular in the whole forelimb (28). In this structure, high rates of infusion decrease outflow from the superficial vein and increase outflow from the deep vein, suggesting a rise in skin resistance and a fall in skeletal muscle resistance (28). Intracoronary injection reduces the resistance to flow through the coronary vascular bed (114, 115). Plethysmographic studies suggest a fall in forearm and hand flow in man, but there is reason to question the validity of this technique during intrabrachial infusion of serotonin.

The direct effects of serotonin on arterial and venous resistances are unusual. Intra-arterial infusion in the forelimb appears to shift resistance away from the arteriole into the large macroscopic arteries (leaving net arterial resistance essentially unchanged) and appears to raise venous resistance (113). The shift of resistance away from small vessels into large macroscopic arteries is also seen in the more homogeneous vascular bed supplied by the superior mesenteric artery (29). The large veins in the latter circuit, however, are reported to be insensitive to infusion of serotonin (29). Studies in the human being also suggest an increase in forelimb venous resistance. Intrabrachial infusion of serotonin produces a decrease in forearm and hand venous compliance. Thus it appears that, at least in the limb, the small vessel dilation is associated with constriction of both large arteries and large veins. This might shift the blood volume from large vessels into small vessels and account for the characteristic changes in skin coloration.

The response of total resistance in the forelimb, hindlimb, and kidney to intra-arterial infusion is conditioned by the activity in the sympathetic nervous system. When resistance is high because of increased sympathetic activity, serotonin lowers the resistance. When resistance is low because of decreased sympathetic activity, serotonin raises the resistance. Studies in the forelimb (113) and hindlimb suggest the following explanation. When arteriolar resistance is high, serotonin lowers arteriolar resistance more than it raises large artery resistance. The net effect is a decrease in resistance. When arteriolar resistance is low, serotonin raises large artery resistance proportionately more than it affects arteriolar resistance. The net effect is an increase in resistance. Administration of dichloroisoproterenol

abolishes the ability of serotonin to antagonize neurogenic vasoconstriction. The significance of this observation deserves further study.

It appears that the rise in venous resistance drives capillary hydrostatic pressure to high levels (92, 113). Forelimb weight and forearm volume progressively increase during an intra-arterial infusion of serotonin because of movement of fluid out of the capillary. The capillary wall also becomes permeable to larger molecules. Subcutaneous injection of serotonin in the rat elicits local exudation of a vital dye previously injected into the circulation (92). Whether this exudation results only from rise in capillary hydrostatic pressure or also from a specific alteration of the membrane by the serotonin molecule remains to be determined. Of interest is the observation in the forelimb that epinephrine, levarterenol, angiotensin, or vasopressin potentiates the ability of serotonin to increase the resistance to flow through large veins (5). This might be relevant to the changes in blood volume that occur in stressful situations which influence the circulating concentrations of more than one vasoactive agent.

The effect on capillary flow has not been studied in detail. Observations in the perfused rabbit ear during intra-arterial infusion suggest a preferential constrictor action on the musculation of the arteriovenous anastomoses.

Effects on pulmonary circulation and metabolic rate.—Intravenous infusion of serotonin causes a rise in pulmonary arterial pressure due to increase in both cardiac output and pulmonary vascular resistance. The resistance response apparently results both from increase in arterial resistance and increase in venous resistance. These changes result, at least in part, from a local action (36, 58) which might include aggregation of blood cells (89). Intravenous infusion of serotonin has little effect on total body oxygen consumption.

Other Agents

Many other naturally occurring chemical agents influence the function of the heart and blood vessels. Notable among these agents are Pitocin (oxytocin), glucagon, oxygen, carbon dioxide, adenosine, AMP, ADP, ATP, cations (H^+, K^+, Mg^{++}, Ca^{++}), anions (pyruvate, acetate, citrate, fumarate, malate, α-ketoglutarate, oxaloacetate, succinate), and water (as demonstrated by the actions of hypotonic and hypertonic solutions of urea, glucose, and sodium chloride). Only studies selected from the 1964 and 1965 literature will be reviewed here. The older literature on the local actions of cations, anions, and water has recently been reviewed in detail (116).

Elevation of the serum magnesium concentration from 1.8 to 8.2 meq per liter by intravenous injection or infusion in the intact anesthetized dog produces no change in cardiac output, a rise in cardiac frequency, and no change or a fall in stroke volume (117). Arterial pressure falls slightly, apparently due to a reduction in total peripheral resistance. Total pulmonary resistance also falls slightly. There are no significant changes in either

coronary blood flow or coronary vascular resistance. Total body oxygen consumption is unchanged despite a rise in ventilation rate.

Intravenous infusion of calcium gluconate into the intact anesthetized dog at a rate which raises the serum concentration of calcium to 10.6 meq per liter produces no change in cardiac output, a fall in cardiac frequency, and a rise in stroke volume (118). Arterial pressure rises, apparently because of an increase in peripheral resistance. There is also an increase in coronary vascular resistance which prevents a change in coronary blood flow. The fall in cardiac frequency can be prevented by the administration of atropine. In the dog heart-lung preparation, elevation of the calcium concentration over the range 1.6 to 14.0 meq per liter produces a progressive rise in cardiac frequency and strength (119). This provides additional evidence that the fall in frequency seen in the intact animal is mediated by an indirect action.

Intra-arterial infusion of each of the Krebs' intermediate metabolites (pyruvate, acetate, citrate, fumarate, malate, α-ketoglutarate, oxaloacetate, succinate) produces a fall in the resistance to blood flow through the vascular beds of the forelimb and kidney (116, 120). Whether these vasodilating metabolites play a role in the local regulation of the blood flow remains to be determined.

Recent studies provide information relevant to the dramatic action of a hypertonic solution of sodium chloride or dextrose on the cardiovascular system. It appears that multiple effects must be considered when attempting an explanation of the changes in pressure and flow. Hypertonic solutions may alter (*a*) blood viscosity through red cell aggregation, red cell crenation, and red cell dilution with cellular and extracellular water (116, 121, 122), (*b*) vascular caliber through smooth muscle relaxation (116, 123) and dehydration of the vessel wall (116), and (*c*) myocardial strength through a depressant effect on cardiac muscle (116, 124).

The fall in resistance produced by intra-arterial infusion of ATP in skeletal muscle perfused at constant flow apparently results from both a decrease in arterial resistance and a decrease in venous resistance (80). Associated with these actions is a slow movement of intravascular fluid into the tissue spaces (80). The response of the renal vascular bed to some of the adenyl compounds is unusual (125). Intra-arterial injection of adenosine produces a rise in the resistance to flow. The response to AMP and ADP is variable. ATP produces a slight fall in renal resistance. ADP causes platelet aggregation (126–130) which appears to be of sufficient magnitude to raise renal vascular resistance (131, 132). Adenosine, on the other hand, appears to suppress spontaneous platelet aggregation (126). Thus, the changes in renal vascular resistance produced by ADP and adenosine may result from more than one mechanism.

A direct effect on the heart of nucleotides and bases containing an —OH group as a substitute on the number 6 pyrimidine ring-carbon (i.e., ino-

sine, uridine, guanosine, and hypoxanthine) is to increase strength, while a direct effect of those containing an $-NH_2$ group as a substitute at this position (i.e., adenosine, cytidine, cytosine, and adenine) is to decrease strength (133).

Glucagon, which increases myocardial strength and frequency in the dog heart-lung preparation, apparently has metabolic effects on the perfused rat heart which are identical to those of epinephrine (134).

Infusion of gastrin into the arterial supply causes a reduction in the resistance to blood flow through the stomach (91). Whether this response results from a direct effect on vascular smooth muscle or is secondary to an increase in metabolic activity remains to be determined.

Summary

The aims of this review have been threefold. Schemes have been presented in an attempt to systematize the description of the physiological actions of chemicals on the heart and blood vessels. Using these schemes, the steady-state actions of some important naturally occurring chemicals have been described, using data from both the old and the recent literature. Review articles and relevant papers appearing during 1964 and the first five months of 1965 have been cited. Finally, an attempt has been made to indicate areas which have been inadequately studied. It appears that more effort should be directed at determining the effects of these chemicals on ventricular strength, diastolic ventricular volume and compliance, distribution of the cardiac output, rate of capillary blood flow, relationship of arterial to venous resistance, capillary hydrostatic pressure, absolute and effective blood volumes, venous return, and blood viscosity, particularly during intravenous infusion with the circulation intact.

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