The Genesis of the Initial Blood Pressure Peak Following iv Administration of Certain Catecholamines[1,2] (37533)

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The blood pressure changes in response to intravenous injection of certain sympathomimetic amines such as epinephrine have been described many times (1, 3, 7, 10, 11), yet never fully explained. The sequence of events following intravenous epinephrine injections of about 1 μg/kg: a rapid initial rise in arterial blood pressure, a slight fall or "dip," and a secondary rise and fall. With smaller doses of epinephrine, the secondary rise may disappear.

Of particular interest to us was the possibility that this initial blood pressure peak seen immediately after intravenous injection of epinephrine, and indeed other catecholamines, may be caused by stimulation of beta adrenergic receptors in the heart. The determination of blood pressure changes that are due to changes in peripheral resistance is dependent on defining this time course.

Nickerson and Nomaguchi (8) stated that this initial spike was probably largely or entirely due to cardiac stimulation with an increase in cardiac output. They made this statement based on the previous work of Huggins *et al.* (6) who determined rather long-lasting increases in cardiac output after epinephrine (about 3 min) by analyzing the carotid pressure pulse waves. Koh (7) has also declared this first rise was due to the acceleration of heart action but did not perform studies to prove this assertion.

The objective of the present study was to observe the time course of this initial peak in blood pressure to certain catecholamines and its relation to changes in ascending aorta blood flow, cardiac force and heart rate. Alpha and beta adrenergic blocking agents were also utilized to determine the nature of this initial rise. These experiments indicated that the initial pressor response to intravenous doses of epinephrine, norepinephrine, and isoproterenol are due to stimulation of the heart via beta adrenergic receptors.

Materials and Methods. Eight adult beagles of either sex were anesthetized with 30 mg/kg sodium pentobarbital intravenously, and maintained under positive pressure artificial respiration with room air. The heart was exposed by a midline sternal incision, the pericardium was opened and a calibrated strain-gauge arch was sutured to the right ventricle (2, 4). An electromagnetic flow meter probe was placed around a dissected portion of the ascending aorta to measure ascending aortic blood flow. Polyethylene catheters were introduced into the abdominal aorta and upper inferior vena cava via the femoral artery and vein to measure arterial and venous pressure, respectively. An additional polyethylene catheter was also placed in the abdominal vena cava through the contralateral femoral vein for the introduction of all drugs.

[1] This work was reported in part at the Fall Meeting of the American Society for Pharmacology and Experimental Therapeutics [Pharmacologist **13**, 319 (1971)].

[2] In conducting the reasearch described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

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Dose response relationships to epinephrine (0.25–2 μg/kg), norepinephrine (0.25–2 μg/kg), isoproterenol (0.0625–0.5 μg/kg) and angiotensin (0.05–0.4 μg/kg) were observed before and after the introduction of the adrenergic blocking drugs phenoxybenzamine and propranolol. A dose near the middle of the dose response curve was selected for illustration. In one group of four dogs, vascular responses to the agonists were observed before, 60 min after iv infusion of phenoxybenzamine, (1.0 mg/kg) and 60 min after iv infusion of propranolol (1.0 mg/kg). The sequence of the antagonists was reversed for four other dogs. Two dogs of each group had intact vagi while the two others had been bilaterally vagotomized and pretreated with iv atropine, 1 mg/kg.

Fast-speed records were taken during the blood pressure responses to the agonists previously listed and to phenylephrine, an alpha adrenergic agonist, before and after the administration of both phenoxybenzamine and propranolol to assess the effect of these antagonists on the period of time between injection and the appearance of a pressor response (latency). Total peripheral vascular resistance (TPVR) was also calculated from measurements made during this period as

$$\frac{\text{(Mean arterial pressure} - \text{Mean large vein pressure)}}{\text{Cardiac output}}.$$

Drugs used in this study were L-epinephrine HCl, L-norepinephrine bitartrate, L-isoproterenol HCl, L-phenylephrine HCl, angiotensin II amide, phenoxybenzamine HCl, atropine sulfate and L-propranolol. Drug doses are expressed as the base.

Results. All of the following illustrated recordings are indicative of the responses observed in 4 dogs. The responses in all figures are also from vagally intact dogs. The blood pressure increases were actually accentuated in the vagotomized, atropinized dogs.

Response to epinephrine. Figure 1 is indicative of the response seen with intravenous injection of 1 μg/kg of epinephrine. The first panel demonstrates that there is a rapid initial rise in arterial blood pressure which is associated with a simultaneous increase in as-

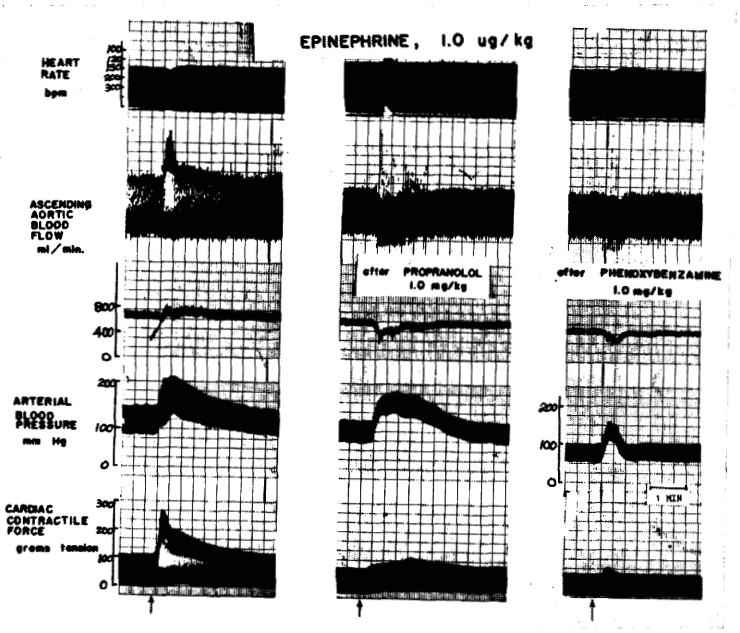

FIG. 1. The effects of iv injection of epinephrine on heart rate, ascending aortic blood flow (pusatile and mean signal in upper and lower position, respectively), arterial blood pressure and cardiac contractile force before; 60 min after propranolol, 1 mg/kg; and 60 min after phenoxybenzamine, 1 mg/kg. The arrows at the bottom indicate the point of epinephrine injection.

cending aortic blood flow, cardiac contractile force and heart rate. The second panel demonstrates the absence of the initial rise in arterial blood pressure and also the absence of the previous increase in aortic blood flow, contractile force and heart rate after the administration of propranolol. Indeed, there is actually a decrease in ascending aortic blood flow. Moreover, the time to onset is greater and the rate of increase of systolic blood pressure is less following epinephrine injection in this animal treated with propranolol. Phenoxybenzamine exerted its expected blocking effect on the vasopressor action of epinephrine.

In other experiments the adrenergic blocking agents were given in reverse sequence. The initial rapid rise in blood pressure to epinephrine was still quite evident after phenoxybenzamine although the secondary pressor phase was reversed. The increases in ascending aortic blood flow, cardiac contractile force and heart rate were concurrent with the initial rise in blood pressure. After propranolol, the initial blood pressure rise was absent and the development of hypertension was much less rapid.

Response to norepinephrine. Norepinephrine may also elicit multiphasic blood-pressure responses. The first panel of Fig. 2 shows the initial rapid rise in blood pressure with the simultaneous increases in aortic blood flow, cardiac contractile force and heart rate. The second panel demonstrates that propranolol effectively prevents this initial rise along with preventing the increases in aortic blood flow, cardiac contractile force and heart rate. The development of the pressor effect is also much less rapid. The third panel demonstrates a reduced vasopressor response to norepinephrine following phenoxybenzamine.

Response to isoproterenol. The blood pressure responses to intravenous isoproterenol are quite often biphasic and characterized by a brief initial rise followed by a depressor phase. The first panel of Fig. 3 demonstrates this initial rise and the contemporaneous increase of cardiac contractile force, heart rate

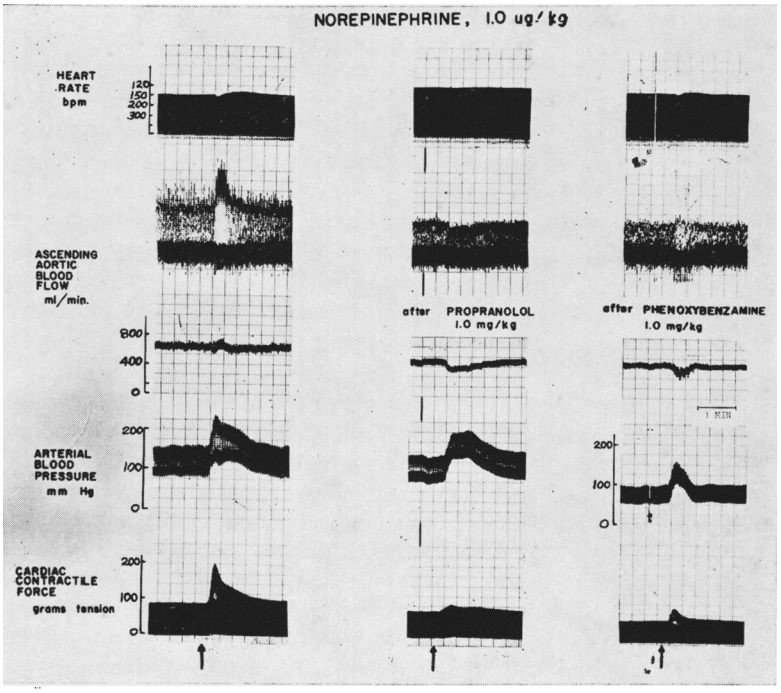

FIG. 2. The effects of iv injection of norepinephrine on heart rate, ascending aortic blood flow (pulsatile and mean signal in upper and lower positions, respectively), arterial blood pressure and cardiac contractile force before; 60 min after propranolol, 1 mg/kg; and 60 min after phenoxybenzamine, 1 mg/kg.

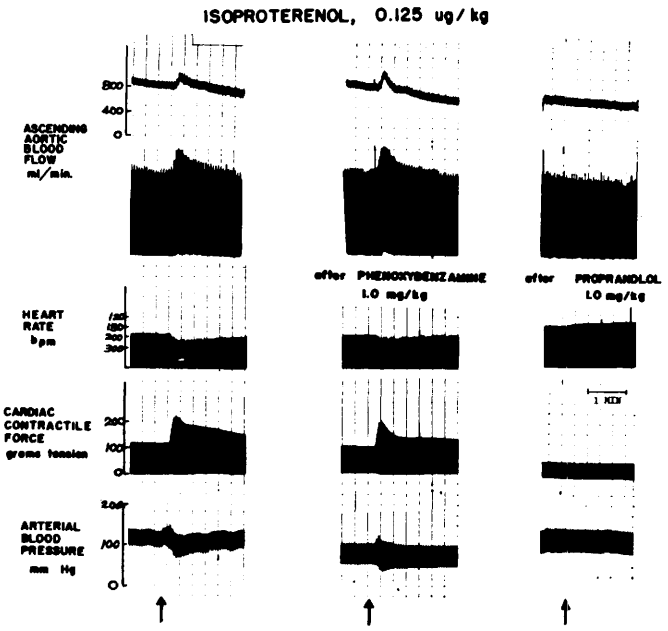

FIG. 3. The effects of iv injection of isoproterenol on ascending aortic blood flow (mean and pulsatile signal in upper and lower position, respectively), heart rate, cardiac contractile force and arterial blood pressure before; 60 min after phenoxybenzamine, 1 mg/kg; and 60 min after propranolol, 1 mg/kg.

and ascending aortic blood flow. After phenoxybenzamine, this initial peak is still present as are the previously observed changes in the other parameters. After propranolol, however, there is no initial rise in blood pressure nor is there a depressor phase following the injection of isoproterenol. There are also no changes in the other parameters measured.

Response to angiotensin. Observations of the responses to angiotensin, a nonadrenergic pressor agent, were also made. Figure 4 demonstrates that the character and degree of the pressor response to angiotensin are not affected by adrenergic blocking doses of phenoxybenzamine and propranolol. Moreover, aortic blood flow, cardiac contractile force and heart rate do not change appreciably in response to angiotensin administration. The pressor response is initiated less rapidly than those seen with the catecholamines.

Time coure of pressor response. Table I gives the period of time (latency) between the injection of selected doses of several vasoactive agents and the initiation of a pressor response. In the control state, the latency period for epinephrine, norepinephrine and isoproterenol (agents possessing beta adrenergic agonist properties) is less than for phenylephrine and angiotensin, which do not react through beta adrenergic receptors. Administration of phenoxybenzamine, an antagonist of alpha adrenergic vasconstriction, did not change the latency period with these agents indicating that alpha adrenergic receptor activation is not involved in the initial blood pressure response. Conversely, administration of propranolol did increase the latency period for epinephrine and norepinephrine to the same value as that observed for phenylephrine and angiotensin and completely abolished the pressor response to isoproterenol. Table II indicates the total peripheral vascular resistance values during the initial blood pressure peak produced by epinephrine, norepinephrine and isoproterenol were not different from preinjection values. Values obtained during the initial, and only, blood pressure peak to phenylephrine and angiotensin were higher than preinjection ones. TPVR values calculated during the secondary

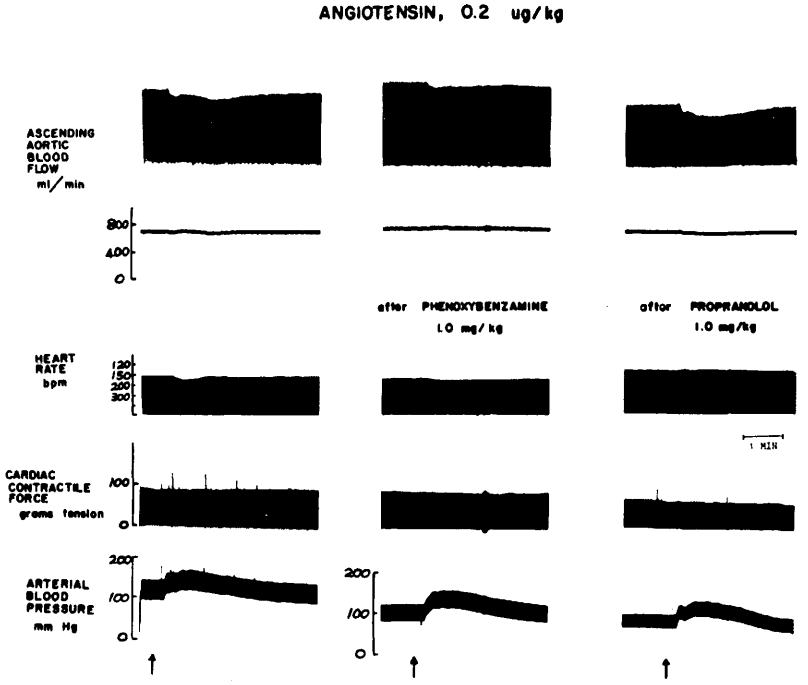

FIG. 4. The effects of iv injection of angiotensin on ascending aortic blood flow (pulsatile and mean signal in upper and lower position, respectively), heart rate, cardiac contractile force and arterial blood pressure before; 60 min after phenoxybenzamine, 1 mg/kg; and 60 min after propranolol, 1 mg/kg.

pressor phase to epinephrine and norepinephrine were also greater than preinjection ones.

Discussion. Results from these experiments demonstrate that the initial blood pressure peak observed in response to iv injection of certain doses of epinephrine, norepinephrine and isoproterenol is due directly to cardiac stimulation via the beta adrenergic receptors and to an increase in aortic blood flow. As was expected, dogs which had been bilaterally vagotomized and atropinized demonstrated a greater degree of cardiac stimulation than the vagally intact animals because of the elimination of this reflex pathway. Previous statements as to the cause of this initial blood pressure spike have been made with only suggestive experimental evidence. Nickerson and Nomaguchi's suggestion (9) that this spike was of cardiac origin as an increase in cardiac output, was based on a previous work (6) and a method (5) which did not measure instantaneous changes in cardiac performance and output. The present study does utilize techniques and instrumentation which allow for rapid instantaneous recording of the decisive parameters.

More recently, Koh (7), after studying the phasic responses in blood pressure to epinephrine administration, indicated that the initial pressor action of this substance might be mediated through acceleration of the heart. He did not, however, attempt to prove this assertion. Work with other sympathomimetic amines has also produced important data. Dopamine, the biochemical precursor of norepinephrine, has been demonstrated to produce an initial blood pressure peak with a simultaneous increase in cardiac contractile force (8). These authors' experiments demonstrated that both of these responses were eliminated by prior treatment of the dog with dichloroisoproterenol, but, unfortunately, these results were not discussed. Any sympathomimetic amine with strong beta adrenergic stimulating properties should elicit an analogous effect.

TABLE I. Latency (Seconds) Following iv Administration of Certain Vasoactive Agents and the Initiation of a Blood Pressure Increase.[a]

Agent (doses)	Control	After phenoxybenzamine[b]	After propranolol[c]
Epinephrine (1 μg/kg)	6.8 ± 0.4	6.6 ± 0.4 (10)	12.9 ± 0.3[d]
Norepinephrine (1 μg/kg)	6.8 ± 0.5	6.8 ± 0.3 (9)	12.7 ± 0.4[d]
Isoproterenol (0.25 μg/kg)	6.9 ± 0.3	7.1 ± 0.4 (10)	Pressor effect abolished
Phenylephrine (5 μg/kg)	11.4 ± 0.5	Pressor effect abolished (6)	12.6 ± 0.5
Angiotensin (0.2 μg/kg)	11.2 ± 0.4	11.9 ± 0.3 (10)	12.7 ± 0.4

[a] Value given is mean latency in seconds ± SEM. The number in parentheses indicates the number of observations.

[b] 1.0 mg/kg, iv.

[c] 1.0 mg/kg, iv. Given after responses obtained following phenoxybenzamine administration.

[d] $p < 0.05$ indicates that the probability of the value being the same as the control is less than 0.05.

The time course for the development of an elevation in arterial blood pressure was significantly longer after the introduction of a beta adrenergic blocking agent. This, we contend, is due to the ablation of that pressor phase resulting from cardiac stimulation and increased cardiac output. The possibility that the beta adrenergic blocking agent, by reducing cardiac output and increasing circulation time, delayed the presentation of the injected agonist to the vasconstrictive receptors was considered. It was dismissed because the observed degree of cardiac output reduction is not nearly as marked as the delay in the elevation of blood pressure. The absence of any increase in total peripheral vascular resistance during the initial blood pressure peak following injection of the beta adrenergic agonists further indicates that this is not a peripheral vascular response.

Moreover, beta adrenergic blockade completely abolished the initial peak in pressure as well as the increase in cardiac contractile force, heart rate and aortic blood flow. These data plus the additional facts that an alpha adrenergic antagonist did not decrease this spike response and the non-beta adrenergic agents, angiotensin and phenylephrine, did not produce this spike response at all, clearly substantiate our initial discussion statement, that the initial blood pressure rise after epinephrine, norepinephrine and isoproterenol is due to stimulation of the beta adrenergic

TABLE II. Total Peripheral Vascular Resistance (TPVR) Before and After iv Injection of Certain Vasoactive Agents.[a]

Agent (dose)	5 Sec prior to drug injection	At peak of initial blood pressure increase
Epinephrine (1 μg/kg)	0.157 ± 0.004 (10)[b]	0.159 ± 0.005
Norepinephrine (1 μg/kg)	0.156 ± 0.004 (9)	0.158 ± 0.003
Isoproterenol (0.25 μg/kg)	0.159 ± 0.003 (10)	0.158 ± 0.004
Phenylephrine (5 μg/kg)	0.160 ± 0.005 (6)	0.184 ± 0.008[c]
Angiotensin (0.2 μg/kg)	0.156 ± 0.003 (10)	0.188 ± 0.009[c]

[a] Units for TPVR are mm Hg/(ml/min) ± SEM.

[b] Number in parentheses indicates the number of paired observations.

[c] $p < 0.05$ indicates that the probability of the value being the same as the control is less than 0.05.

receptors.

Summary. The blood pressure changes in response to injection of certain sympathomimetic amines, epinephrine, norepinephrine and isoproterenol have been described many times, yet the genesis of the initial blood pressure peak has not been adequately explained. Measurements of cardiac contractile force, ascending aortic blood flow and heart rate in open chest dogs made during the iv injection of graded doses of epinephrine, norepinephrine and isoproterenol demonstrated that these parameters increased simultaneously with the initial blood pressure peaks. Total peripheral vascular resistance was not increased during the initial blood pressure peak produced by the beta adrenergic agonists. Administration of propranolol (1 mg/kg) blocked this initial blood pressure peak response while phenoxybenzamine (1 mg/kg) did not. The latency period between injection of the beta adrenergic agonists and the appearance of the first rise in blood pressure was lengthened to about the same values observed for phenylephrine and angiotensin. Results from these experiments indicate that the initial blood pressure peak in response to iv injection of certain doses of epinephrine, norepinephrine and isoproterenol is due directly to beta adrenergic cardiac stimulation and an increase in aortic blood flow.

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