Ventricular Function

V. The Circulatory Effects of Aramine; Mechanism of Action of “Vasopressor” Drugs in Cardiogenic Shock

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The cardiovascular effects of a new, long-acting, sympathomimetic amine, Aramine, are described. Cardiac output, aortic pressure, coronary flow, and ventricular stroke work rise while atrial pressures fall. A sustained increase in myocardial contractility is produced and the myocardium does not require more coronary flow per unit of ventricular work after its administration. The circulatory effects of ventricular failure produced by restricting coronary flow are reversed by the drug. The authors seriously question the premise that the ideal agent for the management of cardiogenic shock should act solely on the peripheral vascular bed.

THERE increased use of so-called vasopressor agents in the treatment of cardiogenic shock indicated the desirability of achieving a more complete understanding of the circulatory effects of this type of drug. One such agent, Aramine [levo-1-(m-hydroxyphenyl)-2-amino-1-propanol], is the subject of the experiments to be described below. The focusing of attention on this drug by Beyer resulted from that worker’s investigation on the relation of chemical structure to pharmacologic function in a series of aromatic amine compounds.1

Aramine has a relatively long-lasting effect after a single dose, is effective by oral, intramuscular or intravenous administration, and appears to be innocuous as regards cardiac arrhythmias. Previously it has been thought to exert its pressor effect solely by influencing the peripheral vascular bed. However, earlier observations in this laboratory suggested that it has a significant myocardial effect as well.2 3 In late hemorrhagic shock, Aramine produced a marked increase in coronary flow and a fall of the elevated left atrial pressure.4 Further studies suggested that the drug increased the survival rate of dogs subjected to oligemic hypotension.4

The objectives of this communication will be to demonstrate: (1) the effect of Aramine on atrial and arterial pressures, cardiac output, coronary flow and peripheral vascular resistance; (2) the effect of the drug on ventricular function (myocardial contractility) as well as its effect on the systemic vascular bed; (3) the effect of Aramine on coronary flow requirements per unit of ventricular work; (4) the drug’s effect on the hypotension and low cardiac output induced by coronary insufficiency. An attempt will also be made to indicate why a “vasopressor” agent is more likely to be therapeutically effective in cardiogenic shock if it also increases myocardial contractility.

For the purpose of clarity it is best to define the term myocardial contractility as used herein. It is quantitatively described by the relationship between ventricular filling pressure and the stroke work of that ventricle throughout the range of its function.5

METHOD

1. General. The methods used were similar to those described in previous publications.6, 6 The experiments were done in anesthetized (morphine-chloralose-urethane) open-chest dogs with a complete circulation. Briefly, they involved the continuous electrical recording of (a) pressures in the left and right atria and the pulmonary artery and aorta.7 (b) the total systemic blood flow with the Potter Electro-
such an arrangement the immediate effects of the intravenous injection of a rapidly acting agent can be differentiated in time and analyzed as regards its systemic and cardiac effects. For, after the drug arrives at the left ventricle and is ejected from it, it rapidly reaches the periphery and exerts its effect thereon (systemic effect). It also enters the right coronary artery immediately. In order to reach the left coronary artery, the drug in the meanwhile must traverse the coronary tubing-rotameter-cannula circuit, and only then does it affect the myocardium (cardiac effect). The time interval between the arrival of the drug at the periphery and at the myocardium is determined by the volume of the coronary circuit and the rate of flow through it. Further, the duration of the interval between the onset of the systemic and cardiac effects can be adjusted by varying the volume of the tubing between the rotameter and coronary cannula.

RESULTS

1. Effect of Repeated Intravenous Doses of 0.01 mg. per Kilogram on the Arterial Pressure and Pulse Rate. In figure 2A, B and C, Aramine was injected in doses of 0.01 mg. per kilogram at two-minute intervals until a total of 0.1 mg. per kilogram had been given. With the dog already slightly hypertensive and the vagi intact (fig. 2A), the elevation of arterial pressure following this dosage schedule was slight (from a mean of 121 to 138 mm. Hg). The predominant effect was a bradycardia, which, presumably by reflex mechanisms, limited the elevation of arterial pressure. Figure 2B shows the effect of this same dosage schedule after the mean arterial pressure had been lowered to 62 mm. Hg by hemorrhage. Under these circumstances the pressure rose substantially (from 62 to 145 mm. Hg) and the pulse rate slowed appreciably only after the dog's pressure had returned towards the control level as a result of giving the drug. The effect of the same dosage schedule after vagotomy is shown in figure 2C. The reflex bradycardia having been eliminated by vagotomy, a substantial pressor effect (from a mean of 154 to 240 mm. Hg) was obtained. The data for figures 2A, B and C were obtained from the same dog over a seven-hour period, approximately three hours intervening between A and B, and B and C. The blood that was removed between A and B was returned between B and C.

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The administration of Aramine to the vagotomized dog in doses up to 0.05 mg. per kilogram was followed by an increase in cardiac output, left main coronary artery flow and aortic and pulmonary artery pressures. Right and left atrial pressures fell, the left more than the right. The administration of additional amounts of Aramine, which brought the total to 0.11 mg. per kilogram, elevated aortic pressure and coronary flow further but had only a slight further effect on atrial pressures and cardiac output.

The direction of the changes just described was consistent. The relative change of each value, however, varied considerably with the cardiovascular state being studied. When the control hemodynamic values were within the normal range, the decline of atrial pressure after Aramine was relatively small. When, however, failure was present (as evidenced by a high atrial pressure and a low cardiac output and aortic pressure) the decline of atrial pressure was a prominent part of the response. One such experiment is shown in figure 3. Changes similar to those shown in figure 3 were obtained in the same dog 19 minutes earlier as the result of giving one microgram per kilogram of norepinephrine (Levophed) intravenously. The only significant difference was the transient character of the norepinephrine response. The dog studied in figure 3 was anemic, the hematocrit being 23.7 per cent, thus accounting for the high coronary blood flows recorded. 12

The hemodynamic result of a large dose of
Aramine (more than 0.15 mg. per kilogram) in the vagotomized dog was a marked increase in aortic pressure, no significant increase in cardiac output and no change or a moderate rise in left atrial pressure. This was a consequence of the intense peripheral vasoconstriction which, by producing very high aortic pressures, masked the cardiac effect. See below.

3. Effect of Aramine on Right and Left Ventricular Function Curves; Differentiation of Myocardial and Systemic Effects by Graded Dosage. Full ventricular function curves were obtained in the control state and after the injection of doses of Aramine totaling 0.03, 0.06 and 0.11 mg. per kilogram. Figure 4A shows the effect of these doses on the right and left ventricular function curves. After 0.03 mg. per kilogram there was a marked increase in myocardial contractility. Additional doses of 0.03 and 0.05 mg. per kilogram did not greatly alter myocardial contractility.

The changes in peripheral vascular resistance and tone which occurred with these injections are shown in figure 4B. Peripheral resistance
was not increased with the first injection of 0.03 mg. per kilogram (except at high flows) but was substantially higher throughout the entire range after the subsequent injections.

4. Differentiation of Systemic and Cardiac Effects of Aramine by the Time-Dissociation Technic. Figure 5 shows the effects of 0.1 mg. per kilogram of Aramine on the systemic vessels and the myocardium. This dog was in myocardial failure as evidenced by the high left atrial pressure and low left ventricular work. Following the injection of Aramine through a right atrial catheter there was a period of about 75 seconds during which the effects shown were due solely to systemic vasoconstriction. During this period (systemic effect), aortic pressure rose while cardiac output fell slightly; simultaneously, peripheral resistance increased sharply, left atrial pressure rose to even higher levels, left ventricular work increased somewhat and coronary flow was also elevated. At the second dotted line a sharp break in the trend of values occurred (cardiac effect). Cardiac output rose substantially thereby producing a further increase in aortic pressure. Left ventricular work rose to almost 400 per cent of its original value while left atrial pressure declined markedly. Simultaneously, coronary flow also rose to appreciably higher levels. This increase in work with the decrease in filling pressure is strong presumptive evidence that the administration of

Fig. 6A. Experiment 83. Dog weight 29.8 Kg. Five left ventricular function curves. The two labeled C are control curves. The three curves labeled A were obtained 10, 30 and 60 minutes after the intravenous injection of 0.05 mg. per kilogram of Aramine.

B. Same experiment as in 6A. Left ventricular work per minute in kilogram meters plotted against left main coronary artery flow in cubic centimeters per minute.
the drug had, by a direct action on the myocardium, placed the ventricle on a much more favorable Starling or ventricular function curve.5 (See fig. 4A and 6A.)

It might be felt that in this instance left ventricular function improved only because of the increased coronary flow that immediately preceded the cardiac effect. That this is not the case is indicated by the fact that two minutes prior to the injection of Aramine shown in this figure, mechanical coronary perfusion at a rate of 257 cc. per minute for one and one-half minutes had failed to produce a similar salutary effect.

5. Effect of Aramine on the Ventricular Function Curve of the Failing Ventricle. More complete information about the effect of Aramine on the failing heart was revealed by examining the full range of ventricular function before and after its administration. Further, it seemed desirable to know at least a minimal duration of time that this effect of the drug lasted. The left ventricular function curves obtained from a dog in a moderate degree of myocardial failure, that is, high left atrial pressures for the stroke work obtained is shown in figure 6A. Two control curves were obtained before and three curves, 10, 30 and 60 minutes after the intravenous injection of 0.05 mg. per kilogram of Aramine. Simultaneous left main coronary flows, aortic pressures and stroke volumes are also shown. Left ventricular function was strikingly improved by the drug and this lasted for at least one hour. Longer periods were not studied.

6. Coronary Flow Requirements per Unit of Left Ventricular Work Before and After Aramine. From the data in figure 6A a plot
was made of the coronary flow per minute against left ventricular work per minute. This data, shown in figure 6B, indicates that the heart did not require a greater coronary flow for any given work output after Aramine. Coronary arteriovenous oxygen differences were not obtained in this experiment, but in other experiments it was shown that the increased oxygen requirement of the heart is normally met by an increase in the coronary flow, not by increased oxygen extraction. This suggests that the oxygen requirement as well as the coronary flow requirement per unit of work was no greater after the Aramine than before it.

7. The Effect of Aramine on the Arterial Hypotension and Low Cardiac Output of Coronary Insufficiency. After the usual preparation was completed, a control period was obtained (fig. 7A). Following this a screwclamp on the tubing to the left main coronary artery was tightened until the aortic pressure, cardiac output and stroke work fell in the face of a rising left atrial pressure (fig. 7B to E). It may be presumed that at this stage the coronary vessels could not dilate further as a result of myocardial hypoxia; at least they did not dilate sufficiently to permit coronary blood flow to keep up with the requirements of the left ventricle. Then, with the coronary screw clamp still in place, 0.03 mg. per kilogram Aramine was injected intravenously (at the signal in the beginning of E). This was followed by a fall in left atrial pressure and a rise in coronary flow, arterial pressure, cardiac output and stroke work to or near their control levels. Note the time dissociation effect.

8. Summary of Data. A comparison of ventricular function curves before and after Aramine was done in eight dogs and in three of these left main coronary artery flow was also measured as shown in figure 4A. In one dog the Aramine had little cardiac effect even in high doses. It was of interest that this dog’s heart was also refractory to epinephrine, the potency of which was subsequently verified on another dog. In the other seven dogs the Aramine produced a significantly higher left ventricular function curve. Of the five dogs in which right ventricular function curves were obtained a higher curve was found after Aramine in three.

The type of time dissociation of myocardial and systemic effects shown in figures 3, 5 and 7 was observed 22 times in 10 dogs.

Discussion

The use of multiple ventricular function curves is probably the most precise means presently available for quantitating the effect of an intervention on the myocardium. The data presented above demonstrate that Aramine increases myocardial contractility in the normal dog heart (fig. 4A), in the heart with an anemic or a nonspecific type of failure (fig. 6A) and in the heart in which failure is due to coronary insufficiency (fig. 7). With a single intravenous dose of 0.05 mg. per kilogram the increase in myocardial contractility lasts for more than one hour (fig. 6A).

When graded doses were given it was seen that with small doses the effect was primarily on the myocardium and that further doses caused an increase in peripheral vascular resistance and tone. A differentiation of the effect of this drug on the myocardium and systemic vessels was also demonstrated by the time dissociation technic, using single intravenous doses, of 0.03 to 0.1 mg. per kilogram. There can be little doubt that both effects occur and are of significance. It is of additional interest that the myocardium did not require a greater blood flow per unit of work performed after the administration of this agent (fig. 6B), nor did it produce significant arrhythmias in the presence of severe myocardial hypoxia (fig. 7).

It was realized how approximate must be the attempt to simulate clinical coronary insufficiency experimentally. Nevertheless, in the experiment shown in figure 7, acute coronary insufficiency was induced as shown by the fall of arterial pressure, cardiac output and stroke work with a rising left atrial pressure when coronary flow was arbitrarily restricted. It is of considerable interest that, with the coronary screw clamp still in place, the administration of Aramine was followed by an elevation of cardiac output, aortic pressure and coronary flow to or near control levels; and, as important, the left atrial pressure fell
below control levels after the drug arrived at the myocardium.

Somehow the view has become widespread that a "vasopressor" agent which elevates arterial pressure solely by its effect on peripheral vascular resistance has a peculiar virtue. "The aim of the use of vasopressor drugs in the treatment of shock following acute myocardial infarction is to increase the mean aortic pressure and thus reestablish an adequate coronary blood flow." 9 The ideal pressor drug would elevate blood pressure, increase peripheral resistance, produce a proportionate increase of coronary flow, have minimal side effects, and would not decrease cardiac output or produce serious arrhythmias. 10 It is, of course, desirable to have an adequate coronary perfusion pressure and recent data from this laboratory attest to the importance of this factor in the myocardial failure of late hemorrhagic shock. 8 The data presented above, however, are not consonant with the view that this is the sole or most important single characteristic of an agent for the treatment of shock due to myocardial infarction. The lung edema that too frequently accompanies this syndrome must be influenced by the level of left atrial pressures when these are elevated. But more important, examination of the time-dissociation graph in figure 5 and the tracing in figure 7 shows that, when the sole effect is peripheral constriction, cardiac output is not augmented or even falls, and left atrial pressure rises further as it must for the ventricle to do the increased work. 5 A more desirable therapeutic goal, namely, an increased arterial pressure and cardiac output at lower atrial pressures is achieved only when the drug arrives at the myocardium and improves its function. The more favorable ventricular function curves obtained after Aramine make it apparent why this occurs.

The authors do not wish to indicate by the above that the cardiovascular effects of Aramine are unique to this particular sympathomimetic amine. Gazes, Goldberg and Darby, 16 using a strain gage attached to the right ventricle, showed that the latter contracted more forcefully after the administration of norepinephrine (Levophed). Simultaneous atrial pressures were not described so that it cannot be ascertained from their experiments whether or not the agent actually increased myocardial contractility or whether the ventricles were contracting more forcefully because of an increased filling pressure. Preliminary experiments in this laboratory, which included the simultaneous determination of filling pressures and ventricular work, indicate that norepinephrine does increase myocardial contractility. These data and the data on Aramine presented above support the views of Gazes, Goldberg and Darby who seriously question the premise that the therapeutic benefit resulting from the use of "vasopressor" agents derives solely from their peripheral vascular action.

Basically, coronary insufficiency depresses the ventricular function curve which leads to a descending spiral involving lowered output, lowered coronary perfusion pressure and higher atrial pressures. 4 The effect of certain of the aromatic amines is to reverse this spiral by producing a higher output, increased peripheral resistance, and higher coronary perfusion pressure at lower atrial pressures. It is clear that little can be achieved without enough residual functioning parenchyma to put to work. Ultimately, concern must be directed at those circumstances wherein temporary support may avert an acute disaster until the myocardium regains more adequate function.

Additional information on the hemodynamics of induced coronary insufficiency and the influence thereof on the ventricular function curves may be found in a previous publication. 6 The renal and cardiovascular effects of Aramine in normal man have recently been reviewed by Beyer. 1 A study of this agent in patients with hypotension resulting from myocardial infarction has been undertaken and will be published subsequently.

The above data have not been herein evaluated in terms of the effect of Aramine on coronary vascular tone. This stems from the authors' belief that coronary tone is controlled preponderantly by the work and oxygen requirements of the myocardium (fig. 6B). Figures 3 and 5 do show a decreased coronary
resistance following the administration of Aramine as do previous studies.\textsuperscript{2,3} Similarly, in figure 7, after Aramine, left coronary artery flow came back almost to its control level at similar aortic pressures, although the perfusion pressure in the vessel must have been substantially lower since the screw clamp was still in place. Myocardial work plays such a large role in controlling coronary tone that it is difficult to state whether or not Aramine is a direct coronary vasodilator. In any case its administration is followed by an increase in coronary flow both in the normal dog and one in which coronary stenosis, hypotension and a low cardiac output have been induced. Perhaps of greater importance is the fact that the drug increases the amount of work per unit of filling pressure without requiring more coronary flow per unit of ventricular work.

**SUMMARY AND CONCLUSIONS**

1. In the normal anesthetized dog Aramine produces a slight to moderate elevation of arterial pressure and a bradycardia. When the bradycardia is abolished either after vagotony or during hemorrhagic hypotension Aramine produces marked elevations of arterial pressure.

2. The effects of the drug on cardiac output, coronary flow, atrial and arterial pressures and peripheral vascular resistance have been presented.

3. In small doses Aramine produces a striking improvement in the ventricular function curves of both the right and left ventricles (more stroke work at any given filling pressure). Subsequent doses do not further improve myocardial contractility but do increase peripheral vascular resistance and tone.

4. This bivalent effect on heart and periphery was also demonstrated by a timedissociation technic.

5. The myocardium does not require a greater coronary flow per unit of work after the administration of Aramine.

6. Acute coronary insufficiency was induced by adjusting a clamp on the tube feeding the left main coronary artery. This produced a fall of arterial pressure, cardiac output and ventricular stroke work, and a rise of left atrial pressure. The subsequent intravenous injection of Aramine (with the screw clamp still in place) returned these values to or near their control levels.

7. The authors seriously question the premise that an agent for treating the hypotension of cardiogenic shock should achieve its effect solely or predominantly by producing peripheral vasoconstriction.

**SUMARIO ESPAÑOL**

1. En el perro normal anestesiado “Aramine” produce de una ligera a una moderada elevación en la presión arterial y una bradicardia. Cuando se abole la bradicardia o después de vagotomía o durante la hipotensión hemorrágica “Aramine” produce marcadas elevaciones de presión arterial.

2. Los efectos de la droga en la producción total cardíaca, circulación coronaria, presiones atrales y arteriales y resistencia periferal vascular han sido presentados.

3. En pequeñas dosis “Aramine” produce mejoria sorprendente en las curvas de función ventricular de ambos, ventrículo derecho e izquierdo (mayor trabajo por contracción a cualquier presión de henchimiento). Dosis subsiguientes no mejoran más la contracción del miocardio pero aumentan la resistencia perifero-vascular y el tono.

4. Este efecto bivalente en el corazón y periferia también se demostró por la técnica de disociación de tiempo.

5. El miocardio no requiere una circulación coronaria mayor por unidad de trabajo luego de la administración de “Aramine”.

6. Insuficiencia coronaria aguda fue inducida ajustando una grampa al tubo de alimentación de la arteria coronaria principal izquierda. Esto produjo un decremento en presión arterial, producción cardíaca y trabajo por contracción ventricular y un incremento en presión atrial izquierda. La subsiguiente inyección intravenosa de “Aramine” (con la grampa tornillo aún en sitio) reintegró los valores a, o cerca de los niveles controles.

7. Los autores seriamente dudan la premisa de que un agente para el tratamiento del choque cardiógeno pueda producir su efecto solamente o predominantemente por la vasoconstricción periférica.
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