Adrenergic Drugs and Blockade on Coronary Arterioles and Myocardial Contraction

By Adam B. Denison, Jr., M.D., Suthip Bardhanabadya, M.D. and Harold D. Green, M.D.

The 3 adrenergic substances, epinephrine, levarterenol and isopropylarterenol, were injected into a coronary artery of anesthetized dogs while recording the coronary artery flow (electromagnetic meter) and pressure. The effects of these substances on the peripheral coronary pressure (PCP) were recorded by occluding the flow proximal to the pressure gage. All 3 substances caused a qualitatively similar increase in myocardial contraction and dilation of the coronary arterioles.

It has been postulated that arterenol does not have as much stimulant effect upon the myocardium as does epinephrine; therefore, the former has been favored in the treatment of hypotensive states and coronary occlusion where it is desirable to improve the arterial blood pressure by peripheral vasoconstriction without increasing excessively the myocardial metabolism.

This study was designed to explore this hypothesis by evaluating the effects of epinephrine and arterenol on the coronary arterioles and on the contractility of the myocardium and to evaluate the effect of a typical adrenergic blocking drug, azapetine (Hidar), on these responses. Isopropylarterenol was included in the group of adrenergic drugs because it appears to have a vasomotor action in skeletal muscle vascular beds similar to the dilator phase of epinephrine.

METHODS

The studies were done upon open-chested, mongrel dogs, premedicated with morphine sulfate 2.0 mg./Kg. subcutaneously and anesthetized with 0.25 ml./Kg. of a solution containing sodium pentobarbital, Dial, and Urethane. Positive pressure artificial respiration was administered with air. Oxygen was added continuously by tracheal catheter at the into of 0.5 L./min. The heart was exposed by removal of the anterior halves of the left fourth and fifth ribs and was suspended in a pericardial cradle.

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small doses were repeated at the end of a series, to check on the possibility of blockade becoming less effective during the course of the 9 injections. Coronary arteriolar dilation was considered to have occurred when the peripheral resistance (coronary perfusion pressure + coronary artery flow), measured at the end of diastole, decreased. This point in the heart cycle was chosen for estimating arteriolar dilation since at this moment extravascular compression is at a minimum and is undergoing a minimum change with time and since the inflow is minimally influenced by changes in the volume of blood contained in the arteries distal to the meter. Mean flows are of no value in estimating coronary arteriolar constriction or dilation, since in addition to this parameter mean flow is influenced also by the varying extravascular compression during systole and early diastole and by the varying duration of diastole with relation to that of the cycle.

Increased myocardial contraction is defined, for the purposes of this paper, as a more rapid and greater degree of shortening of the myocardial fibers. Augmentation of the systolic rise of intramyocardial tension occurring without significant rise of aortic systolic pressure would be indicative of such increased contraction. Qualitative evidence of increased systolic intramyocardial tension would be: (a) The occurrence in the flow curves of a greater degree of reduction of inflow or the appearance of backflow during isometric contraction and an increase in the computed resistance to inflow at the end of systole, (b) the observation in the pressure curves of a shortening of the ejection phase of systole, and (c) the registration in the PCP curves of an increase in the slope of the rise and fall and an elevation of the peak systolic pressure.7

Effects of Adrenergic Drugs on Resistance to Flow at End of Diastole. In all cases, within 5 to 10 sec. after the injection of the adrenergic drugs, the flow at the end of diastole began to increase and the resistance at this same moment in the heart cycle (table 1, A) began to decrease; the maximum effect was reached in 15 to 20 sec. and an additional period of 30 to 100 sec. was required for restoration to control values. The decrease in resistance was slightly more marked with isopropylarterenol and slightly less prominent with arterenol than with epinephrine. In many of the records isopropylarterenol and, to a lesser extent, epinephrine increased the flow at the end of diastole before producing effects attributable to change of contraction, whereas with arterenol the reverse was true. The larger doses caused a more prolonged decrease in resistance and elevation of systemic pressure but did not shorten the time for the maximum effect to be reached or cause an appreciably greater amplitude of response. The elevation of systemic arterial pressure always occurred 10 to 15 sec. after the maximum effect on coronary diastolic resistance had been reached, and so did not interfere with interpretation of the cardiac effects of the drugs.

Effects of Saline on Resistance at End of Diastole. Saline injections caused minimal decreases of apparent resistance at the end of diastole which reached a maximum in 5 to 10 sec. and returned to control within a total of 10 to 15 sec. after the beginning of injection. Thus, artifacts caused by the injections could readily be differentiated from responses to the drugs.

Effects of Adrenergic Drugs on Resistance at End of Systole. In most cases, the apparent resistance at the end of systole increased. The results were erratic, however, due probably in part to difficulties in reading a satisfactory point on a line of rapid slope and in part to artifacts caused by inertia effects in the tubing system and the coronary artery.

Effects of Adrenergic Drugs During Isometric Contraction. Normally, coincident with the onset of isometric contraction, the rate of inflow rapidly declined toward 0 (fig. 1) and occasionally a small amount of backflow was noted
**TABLE 1.—Effects of Adrenergic Substances on A. Coronary Arterioles as Indicated by End-Diastolic Resistance and B. Flow Parameters Indicating Changes in Contraction During the Control Periods**

<table>
<thead>
<tr>
<th>Dose in mg.</th>
<th>Per cent of control PRU end diastole (D)</th>
<th>Per cent of control PRU end systole (S)</th>
<th>Flow in isometric contraction (f)</th>
<th>Per cent of control peripheral coronary pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>(51-100)</em></td>
<td><em>(36-248)</em></td>
<td><em>(7-19)</em></td>
<td><em>(105-123)</em></td>
</tr>
<tr>
<td>1</td>
<td>71</td>
<td>402</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>126</td>
<td><em>(9)</em></td>
<td><em>(98)</em></td>
</tr>
<tr>
<td>10</td>
<td><em>(79)</em></td>
<td><em>(119-125)</em></td>
<td><em>(12)</em></td>
<td><em>(136)</em></td>
</tr>
<tr>
<td></td>
<td><em>(150-1000)</em></td>
<td><em>(36-248)</em></td>
<td><em>(5-19)</em></td>
<td><em>(78-125)</em></td>
</tr>
<tr>
<td>Epinephrine</td>
<td><em>(54-96)</em></td>
<td><em>(119-125)</em></td>
<td><em>(7-19)</em></td>
<td><em>(69-144)</em></td>
</tr>
<tr>
<td></td>
<td><em>(48-159)</em></td>
<td><em>(62-1000)</em></td>
<td><em>(5)</em></td>
<td><em>(122-141)</em></td>
</tr>
<tr>
<td></td>
<td><em>(48-159)</em></td>
<td><em>(62-1000)</em></td>
<td><em>(5)</em></td>
<td><em>(122-141)</em></td>
</tr>
<tr>
<td>Levaterenol</td>
<td><em>(87)</em></td>
<td><em>(353)</em></td>
<td><em>(8)</em></td>
<td><em>(109)</em></td>
</tr>
<tr>
<td></td>
<td><em>(69-101)</em></td>
<td><em>(71-625)</em></td>
<td><em>(2)</em></td>
<td><em>(93-125)</em></td>
</tr>
<tr>
<td>10</td>
<td><em>(102)</em></td>
<td><em>(48)</em></td>
<td><em>(9)</em></td>
<td><em>(86-106)</em></td>
</tr>
<tr>
<td>Isopropylarterenol</td>
<td><em>(77-134)</em></td>
<td><em>(48)</em></td>
<td><em>(9)</em></td>
<td><em>(94-179)</em></td>
</tr>
<tr>
<td></td>
<td><em>(56-142)</em></td>
<td><em>(0-19)</em></td>
<td><em>(2)</em></td>
<td><em>(96-157)</em></td>
</tr>
<tr>
<td>3</td>
<td><em>(62)</em></td>
<td><em>(224)</em></td>
<td><em>(8)</em></td>
<td><em>(80)</em></td>
</tr>
<tr>
<td>10</td>
<td><em>(59)</em></td>
<td><em>(122)</em></td>
<td><em>(7)</em></td>
<td><em>(85)</em></td>
</tr>
<tr>
<td></td>
<td><em>(30-89)</em></td>
<td><em>(111-136)</em></td>
<td><em>(12)</em></td>
<td><em>(116)</em></td>
</tr>
</tbody>
</table>
| * Data are, in most cases, the averages and range (in parentheses) of five successful experiments. 
† Coronary inflow at moment of maximum reduction of inflow, or maximum backflow (minus sign) just before onset of ventricular ejection. 
‡ Observation in the experimental period divided by the observation in the control period times 100. 
§ Measured at end of diastole, just before onset of isometric contraction. 
|| Measured at end of systole, just before onset of protodiastole. 
¶ Measured at the peak of the Peripheral Coronary Pressure curve in mid-systole. 

(table 1, B2). This was accompanied by a rise in the coronary perfusion pressure, which was probably a "water hammer" effect. Consistently, the smallest doses of all 3 adrenergic drugs intensified this effect so that in most cases a rather large component of backflow was recorded, accompanied by an accentuated "water hammer" effect on coronary perfusion pressure. These effects were slightly more marked with arterenol and epinephrine than with isopropylarterenol.

**Effects of Adrenergic Drugs on the Peripheral Coronary Pressure and on the Ejection Phase.** In the PCP curves the maximal pressure during systole was significantly increased and the diastolic pressure was usually lowered (table 1) and the pressures rose and fell more abruptly with the heart cycle (fig. 1). In the aortic pressure curves the duration of isometric contraction was not significantly altered, but the ejection phase was significantly shortened and the pressure rose more abruptly.

Other Effects of the Adrenergic Drugs. The electrocardiographic tracings showed that arterenol in the 3 and 10 μg. doses frequently caused ventricular premature beats. Either no change of heart rate or a slight cardiac slowing was noted.
Effects of Adrenergic Blockade

Ilidar produced no reversal of the adrenergic effects such as is seen in skeletal muscle; there was a lessening of the responses to all 3 adrenergic drugs with increasing doses of Ilidar. With 100 mg. of Ilidar the responses to 1, 3 and 10 μg. of the adrenergic drugs could be blocked completely (table 2). As the doses were progressively increased, the Ilidar caused cardiac slowing and occasional ventricular premature beats. Of 9 experiments, ventricular fibrillation or standstill occurred after the following doses of Ilidar: 3 mg., 2 dogs; 10 mg., 2 dogs; and 30 mg., 4 dogs. One dog survived 300 mg. Counter shock and massage were unable to revert the fibrillation. The various doses of Ilidar caused in general small decreases in
Table 2.—Doses of Ilidar in mg. Required to Abolish Indicated Effects of 1 µg. Doses of the Three Adrenergic Substances

<table>
<thead>
<tr>
<th>Effect</th>
<th>Epinephrine</th>
<th>Levarterenol</th>
<th>Isopropylarterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmented isometric backflow (I)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Decreased diastolic resistance (D)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Increased systolic resistance (S)</td>
<td>1</td>
<td>1</td>
<td>*</td>
</tr>
<tr>
<td>Decreased diastolic PCP</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Increased systolic PCP</td>
<td>100±</td>
<td>60±</td>
<td>1-10</td>
</tr>
<tr>
<td>Accelerated rise and fall of PCP</td>
<td>30±</td>
<td>30±</td>
<td>30±</td>
</tr>
</tbody>
</table>

* Almost no effect prior to Ilidar, see table 1.

Discussion

In the latter part of diastole extravascular compression is changing minimally, and there are minimal inertia effects due to sudden fluctuations of aortic pressure. Furthermore, in our experiments, the aortic diastolic pressures in the experimental period were, in each case, essentially the same as those in the control period. In view of these considerations, we believe we can interpret changes of resistance, measured at the end of diastole, as a reasonably reliable estimate of the extent of contraction or relaxation of the coronary arterioles. On the basis of our data we believe that all 3 adrenergic substances caused a small degree of coronary arteriolar dilation. Since isopropylarterenol and, to a lesser extent, epinephrine caused a slightly greater degree of dilation and at times induced dilation before other changes referable to contractility were noted, it is probable that the dilation was, at least in part, a direct effect of these substances on the arterioles.

All 3 substances caused a markedly greater increase of intramyocardial tension during systole as estimated from the effects on flow during isometric contraction, resistance at the end of systole, abruptness of relaxation and contraction and amplitude of the peripheral coronary systolic pressure. While changes in any one of these might have minimal significance, the coincident change in all four and the consistency with which they were noted with all 3 adrenergic drugs makes it reasonably certain that all 3 substances caused increased myocardial contraction as defined earlier in this paper. The increased contraction was least prominent with isopropylarterenol; with arterenol the effect was at least equal to and perhaps more prominent than that with epinephrine.

Summary

Epinephrine, levarterenol and isopropylarterenol cause markedly different vasomotor responses in many vascular beds, particularly that of skeletal muscle. However, in the coronary vascular bed they are qualitatively similar.

All 3 cause a relatively small dilation of the coronary arterioles, as manifested by decreases in resistance to flow in the coronary vascular bed, measured at the end of diastole; and all 3 increase to a marked degree myocardial contraction, as indicated by the vigor and abruptness of contraction and the rapidity and completeness of relaxation of the myocardium. Levarterenol shows a greater tendency than the others to cause premature ventricular beats, to increase myocardial contraction and a slightly lesser tendency to cause coronary arteriolar dilation.

The primary effect of adrenergic blockade (Ilidar) is to reduce progressively the above effects at extremely high doses. The intra-coronary artery injections of the large doses of Ilidar usually cause a moderate dilation of the coronary arterioles, cardiac irregularities and often ventricular fibrillation.

The greater effectiveness in hypotensive states of arterenol, as compared with epinephrine, would appear, therefore, to be due to differences in their systemic rather than their cardiac effects since the direct effect on the myocardium seems to be, if anything, more marked with arterenol than with epinephrine.

Summario in Interlingua

Epinephrina, levarterenol, e isopropylarterenol evoca mareatemente differente responses
ADRENERGIC EFFECTS ON CORONARY CIRCULATION

vasomotori in le vasculatura del muscosos skeletal e etiam in multe altere vasculaturas. Tamen, in le vasculatura coronari lor effectos es qualitatively simile.

Le 3 drogas causa un relativamente leve dilatation del arteriolas coronari, manifesto in reductiones del resistencia al fluxo in le vasculatura coronari mesurate al fin del diastole; e le 3 drogas causa un marcate augmento del contraction myocardial, manifesto in le abrupte vigor del contraction e in le rapidezza e le completessa del relaxation del myocardio. Levarterenol monstra un plus grande tendencia que epinephrina e isopropylarterenol a causar prematur pulsos ventricular e a augmentar le contraction myocardial e un levemente minus forte tendencia a causar dilatation del arteriolas coronari.

Le effecto primari de blocage adrenergic (Ilidar) es reducer progressivamente le supra-descritbe effectos, si le agente de blocage adrenergic es active in extrememente alte doses. Injectiones del plus grande doses de Ilidar in le arterias coronari causa usualmente un moderate grado de dilatation del arteriolas coronari, irregularitates cardiac, e frequence-mente fibrillation ventricular.

Le plus grande efficacia in statos hypotensive que distingue arterenol de epinephrina pare per consequente resultar de differentias del effectos systemic plus tosto que cardiac in le caso del duo agentes, proque le directe effect super le myocardio es apparentemente plus marcate in le caso de arterenol que in le caso de epinephrina.

ACKNOWLEDGMENTS

Epinephrine (methyl arterenol, adrenaline) was supplied in 1 ml. ampules of 1:1000 solution without preservative by Parke, Davis & Company, Detroit, Mich. Doses are expressed in terms of the hydrochloride.

Levarterenol (arterenol, norepinephrine, levophed bitartrate) was supplied in 4 ml. ampules containing 0.2 per cent (expressed as the salt). Isopropylar-terenol (isoproterenol, Isuprel) was supplied as the hydrochloride. Doses of both are expressed in terms of the base. Both were obtained from Winthrop Laboratories, Inc., Baltimore, Md.

Azapetine (Ilidar hydrochloride) was supplied in 5 ml. ampules containing 10 mg./ml. by Hoffmann-LaRoche, Inc., Nutley, New Jersey. Doses are expressed in terms of the hydrochloride.

The intravenous anesthetic was composed of equal parts of: (1) a solution containing 60 mg./ml. of sodium pentobarbital and (2) Dial with Urethane. The latter contains in each ml.: Diallylbarbiturie acid 0.1 Gm., Urethane 0.4 Gm., and monoethylurea 0.4 Gin., and was supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

REFERENCES

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