Comparative Study of Effects of Levarterenol and Methoxamine in Shock Associated with Acute Myocardial Ischemia in Dogs

By James W. West, Ph.D., Arthur T. Faulk, M.D., and Santiago V. Guzman, M.D.

Shortly after levarterenol (norepinephrine) came into general clinical use, its application in the management of acute myocardial infarction associated with cardiac shock was tested, and many favorable reports appeared.1-5 Such use was originally based on the supposition that the drug raises blood pressure entirely by increasing the peripheral vascular resistance, and it was expected to be superior to drugs like epinephrine in cases of coronary occlusion because it does not stimulate the myocardium directly. This concept is still widely held, in spite of the fact that many investigators have confirmed the conclusion of Crismou and Tainter6 that levarterenol is at least as strong a stimulant to the heart as epinephrine. There appears to be a widespread belief that man represents a species difference in this respect, a belief that was further strengthened by studies which indicated that cardiac output of man is reduced by levarterenol, but increased by epinephrine.7-9 Shortly thereafter, when another drug, methoxamine (Vasoxyl), was shown to have properties which norepinephrine was originally supposed to possess,10-11 this drug was tried in the clinical management of myocardial infarction, and favorable results were reported in a few cases.3,13 This is not surprising because clinical myocardial infarction severe enough to produce generalized circulatory depression (shock) necessarily varies considerably both in degree of myocardial involvement and in capacity for compensatory adjustments adequate in rapidity and extent to permit survival regardless of treatment. Others, however, continue to prefer norepinephrine.2,4 The American Medical Association Council on Drugs, after a review of the pharmacological effects of methoxamine, recommended that the agent be used only in cases of mild shock. In general, the available reports dealing with cases of myocardial infarction in shock treated with various sympathomimetic amines show that the survival rate is as follows: (a) greater with levarterenol than with methoxamine or phenylephrine, another drug with primarily peripheral vasoconstrictor properties; (b) almost equally as good with Aramine and Wyamine (which are known to elicit a positive inotropic response) as with levarterenol; and (c) better with isoproterenol (a peripheral vasodilator with a potent inotropic response) than with phenylephrine or methoxamine. Therefore, a point of fundamental importance is involved here, viz., whether direct myocardial stimulation is desirable or undesirable in the presence of severe, but not immediately fatal, coronary occlusion.

The procedure of intracoronary injections of lycopodium spores gave us a means of producing a myocardial ischemia of graded and measurable severity, because a small occluding substance has the advantages of producing a more progressive and less immediately drastic effect on hemodynamics, and of permitting the comparison of coronary arterial injections of drugs in the same site before and after embolization. Our methods...
EFFECTS ON DRUGS IN MYOCARDIAL SHOCK

for direct injections into coronary arteries and for measuring myocardial contractility also were suitable for a definitive study of this problem. For reasons given above, we have paid chief attention to comparisons of levarterenol and methoxamine as agents for combating systemic hypotension produced by coronary occlusion of appropriate severity.

Methods

The experiments were performed on 38 adult mongrel dogs weighing 17.0 to 30.0 Kg. under light anesthesia from intravenous injections of pentobarbital sodium (30 mg./Kg.) after a previous administration of morphine (2 mg./Kg.). The trachea and the femoral artery and vein were cannulated, and systemic arterial pressure was recorded from a femoral artery by means of a capacitance or strain-gauge electromanometer and a direct-writing Sanborn polyviso recorder. Electrocardiograms were continuously monitored in the same recorder, using standard limb and precordial leads. Under fluoroscopic guidance, single lumen catheters were introduced through an external jugular vein into the main pulmonary artery and the right atrium, and into the descending aorta via a carotid artery. A double lumen catheter was also inserted via a femoral artery into the left ventricle and left atrium. The catheters in the various chambers of the heart were connected to strain-gauge transducers and monitored by one of the two polyviso recorders.

In an attempt to simulate the clinical picture of hypotension resulting from selective (right or left coronary artery) acute myocardial ischemia, injections of an occluding medium (1 per cent lycopodium spore suspension) in suitable dosages (0.1 to 1.0 ml.) were made into the right or left (anterior descending, circumflex) coronary branch. Following repeated injections of lycopodium spores (0.1 ml.) into the right or left coronary artery, a progressive picture of selective right- or left-sided heart failure could be produced. The injections were made through fine catheters introduced under fluoroscopic guidance into the coronary branches by way of the aorta without opening the chest. Thus we were able to control both the location and severity of the occlusion without exposing the heart or its blood vessels to external trauma. In all of these experiments, the chest was intact except those in which myocardial contractility was measured by means of a Walton strain gauge sutured directly to the exposed surface of the left or right ventricle. The myo-endiogram so obtained was also recorded on a multichannel Sanborn polyviso recorder.

Intra-coronary, intravenous, and intra-aortic (descending) administrations of levarterenol and methoxamine were made prior to and within a few minutes after acute coronary embolization.

Results

EFFECTS OF SELECTIVE MYOCARDIAL ISCHEMIA

Left coronary artery (anterior descending or circumflex) embolization by repeated small injections (0.1 to 0.2 ml.) of a 1 per cent lycopodium spore suspension produced gradual changes in various circulatory parameters. Immediately following the first injection, we regularly observed decreases in left ventricular and systemic arterial pressures and slight increases in left atrial and pulmonary arterial pressures. All of these effects, with the exception of the change in left ventricular pressure, are observed in figure 1. Repeated embolization produced an exaggeration of these effects and also caused a slow rise in pulmonary arterial and right atrial pressures.

The main electrocardiographic change during progressive embolization was progressive elevation of the ST-T complex after each embolization, with no alteration in rhythm except for a slight increase in heart rate. The first change occurred in the precordial lead within the first few seconds after the initial dose.

Myocardiographic records disclosed a decrease in myocardial contractility after each injection.

Right coronary artery embolization by repeated injections (0.1 to 1.0 ml.) of the same material produced similar circulatory changes. However, the sequence and direction of the changes in pressures differed somewhat from those during left coronary artery embolization. The first spore injection caused a fall in pulmonary and systemic arterial pressures along with a slight rise in right atrial pressure and essentially no change in left atrial pressure (fig. 2). Repeated embolization produced marked decreases in pulmonary and systemic arterial pressures accompanied by a rise in right atrial pressure and a fall in left atrial pressure (fig. 2). Alterations in the ST-T wave complex (elevation) of the electrocardiogram were also seen, as well as a decrease in contractility of the right ventricle.
Effects of Intracoronary, Intravenous, and Intraventricular (Descending) Injections of Levarterenol (Norepinephrine) and Methoxamine (Vasoxyl)

Intracoronary Injections

Prior to coronary embolization, injections into each of the three main arteries (right, left circumflex, left anterior descending) had similar effects. With levarterenol (0.1 to 0.22 µg./Kg.), these consisted of an immediate increase in strength of myocardial contraction, a rise in arterial blood pressure, a slight fall in left atrial pressure, and a marked lowering of S-T segment and peaking of the T wave of the precordial electrocardiogram over the area supplied by the coronary branch injected. In addition, injections into the right coronary and left circumflex branch were accompanied by changes in heart rate as a result of stimulation of the S-A and A-V nodes, respectively. Methoxamine (12 µg./Kg.) injected into the same sites produced a slight decrease in myocardial contractility and essentially no change, or a slight decrease in arterial pressure along with a slight rise or no change in left atrial pressure.

After coronary embolization, levarterenol injected into the same sites still increased myocardial contraction and systemic arterial blood pressure, and simultaneously lowered the markedly elevated left atrial pressure (fig. 3). Furthermore, it lowered the elevated S-T segment in those cases not too severely embolized. In addition, a further improvement was observed in the other pressure tracings, as evidenced by a decrease in the elevated pulmonary arterial and right atrial pressures (fig. 3). To demonstrate further that all of these beneficial effects resulted from the direct positive inotropic action of levarterenol on the myocardium, epinephrine, and isoproterenol, which are well-known cardiac stimulants, were compared with levarterenol and identical effects were observed. However, coronary arterial injections of methoxamine either did not change the already elevated left atrial pressure, or raised it further.

Intravenous Administration

Intravenous injection (1 µg./Kg.) or slow infusion (5 µg./Kg./min.) of levarterenol in dogs with normal hearts generally produced an increase in systemic and pulmonary arterial pressures accompanied by a decrease in left atrial pressure and a bradycardia. Larger intravenous injections, or a more rapid infusion of the drug, always increased systemic and usually raised pulmonary arterial pressure, but they decreased heart rate and produced variable changes in left atrial pressure. Arrhythmias developed in some instances, and these were always accompanied by an increase in left atrial pressure.

Methoxamine, when administered by intravenous injection (100 to 200 µg./Kg.) or slow infusion (8 to 25.0 µg./Kg./min.), generally increased all measured parameters (systemic and pulmonary arterial pressures, left and right atrial pressures) except heart rate, which decreased.

Following embolization, a large appropriate intravenous infusion of levarterenol elicited the same general circulatory improvements as did intracoronary injection and, in addition, produced a greater rise in systemic arterial pressure as the result of increased peripheral resistance (fig. 4). However, when the single intravenous dose was too large or the infusion rate too rapid, there was only an initial improvement (increased systemic arterial pressure, decreased left and right atrial and pulmonary arterial pressures) followed by rises in both atrial and pulmonary arterial pressures during the period of hypertension. In this latter instance, the heart’s work load probably exceeded its capacity, and no amelioration of this abnormal condition was observed until the height of the systemic blood pressure fell to a range within which the heart could successfully meet the increased demands. Improvement was accomplished by the disappearance of the effects of the single drug injection or, in the case of infusion, by decreasing the rate of the intravenous infusion. This condition resulting from “over-treatment” with levarterenol parallels the situation observed with all doses of methoxamine. When methoxamine was given in the experimentally ischemic preparations not too severely embolized, it elevated the systemic
EFFECTS ON DRUGS IN MYOCARDIAL SHOCK

FIGURE 1
Effects of repeated injections of lycopodium spores into the left anterior descending coronary branch of a dog. The records (from top to bottom) are continuous and show: right atrial pressure (R.A.P.), pulmonary arterial pressure (P.A.P.), left atrial pressure (L.A.P.), and femoral arterial pressure (F.A.P.). These mean pressures were recorded with capacitance and strain-gauge transducer electromanometers. Timer, seconds. Dog under pentobarbital anesthesia. A is the control; B, C, D, E, F, G and H show each successive injection of lycopodium spores. Note that the sequence of the progressive changes with each successive embolizing injection is a decrease in femoral arterial pressure accompanied by a rise in left atrial, pulmonary arterial, and right atrial pressures.

atrial pressure in most instances, but a general worsening of the animal’s condition was observed. This was characterized by further increase in the already elevated atrial and pulmonary arterial pressures, a greater elevation of the ST-T wave complex of the electrocardiogram, and further enlargement of the already widely dilated left ventricle, as evidenced by a shift in the baseline of the myogram (fig. 3). However, when an intra-
FIGURE 2

Effects of repeated injections of lycopodium spores in the right coronary artery. From top to bottom, the records are continuous. Electrocardiograms (V₁ and aV₁R): right atrial pressure (R.A.P.), pulmonary arterial pressure (P.A.P.), left atrial pressure (L.A.P.), and femoral arterial pressure (F.A.P.). All mean pressures were recorded with strain-gauge transducer electromanometers. A is control and during first two successive lycopodium injections; B, C, D, E, and F were taken during continued embolization. Note with repeated embolization, the pulmonary and systemic arterial pressures fall while right atrial pressure rises and left atrial pressure falls. Speed of pressure and electrocardiogram records are 1 mm./sec. and 25 mm./sec., respectively.
Effects of levarterenol and methoxamine on myocardial ischemia. The records were taken from two different experiments. Top record (from top to bottom) shows: femoral arterial pressure, left atrial pressure, and myogram (strain gauge attached to the anterior wall of the left ventricle). Note in this extremely hypodynamic condition (markedly low systemic arterial pressure, elevated left atrial pressure, and decreased myocardial contraction) produced by repeated coronary embolization (left anterior descending branch) that intracoronary injection of levarterenol into the same site produced a marked improvement in the animal's condition as characterized by an increased height of contraction, a decrease in the elevated left atrial pressure, and a rise in the hypotensive arterial pressure. Bottom record (from top to bottom) shows: right atrial pressure, pulmonary arterial pressure, left atrial pressure, and femoral arterial pressure. Note that when systemic arterial blood pressure is raised even slightly by an intravenous infusion of methoxamine in the presence of a markedly elevated left atrial pressure, high pulmonary arterial pressure and right atrial pressure, it is accompanied by an increase in all of these already elevated pressures (atrial and pulmonary). However, when an intracoronary injection of levarterenol was given, it produced an even greater rise in systemic arterial pressure, but was accompanied by a dramatic decrease instead of an increase in the elevated atrial and pulmonary arterial pressures. Timer, seconds.
Comparative effects of levarterenol and methoxamine in severe hypotension resulting from myocardial ischemia. The records taken from the same experiment show: femoral arterial pressure, left atrial pressure and myogram (strain gauge attached to the anterior wall of the left ventricle). In the top record, note in this severely embolized (coronary) condition, characterized by a markedly low systemic arterial blood pressure, elevated left atrial pressure, and decreased myocardial contraction, that an intravenous infusion of levarterenol greatly improved the circulatory picture. The improvement is evidenced by a marked increase in amplitude of contraction, a large decrease in left atrial pressure, and a marked increase in the arterial blood pressure. Bottom shows the effects of methoxamine in the same hypodynamic condition of coronary embolization. Following methoxamine, there is a slight increase in arterial blood pressure and myocardial contraction, but instead of a fall in the already markedly elevated left atrial pressure, there is a further rise. Timer, seconds.

Coronary injection of levarterenol was given during this stage of the action of methoxamine, a general improvement in the circulation was evident in a decrease in both atrial and pulmonary arterial pressures and an increase in systemic arterial pressure (fig. 3).
Injections into the Descending Aorta

These injections obviated the initial direct cardiac and pulmonary actions of the drugs. The immediate responses produced by both levarterenol and methoxamine were identical. Initially, there occurred a rise in systemic arterial and left atrial pressures accompanied by a bradycardia and a slight increase in pulmonary arterial and right atrial pressures. However, in the ischemic animals, a greater increase in both atrial and pulmonary arterial pressures was produced by both drugs during the rise in systemic pressure. In the normal animals, myocardial contractility tended to increase slightly as the blood pressure increased during the period of elevated peripheral resistance, while in the embolized animals, there was no change or a decrease in myocardial contraction. Upon circulation of levarterenol to the heart in the dogs with myocardial ischemia, there occurred a marked fall in the elevated left atrial pressure as well as an initial decrease in the pulmonary and right atrial pressures, in spite of the fact that systemic pressure continued to increase. However, during the circulation of methoxamine, there occurred a continuous rise in systemic and pulmonary arterial and both atrial pressures.

Discussion

The more important conclusion to be derived from these experiments is that when it is deemed desirable to raise the blood pressure after it has been lowered by myocardial ischemia, levarterenol is to be preferred to methoxamine. The superiority of the former is shown by its ability to lower the elevated atrial and pulmonary pressures, which are only raised further by methoxamine. The difference between the two drugs appears to be chiefly due to a direct positive inotropic action of levarterenol on the myocardium, a property which is completely lacking in methoxamine.

In addition to the positive inotropic effect that levarterenol and similar pressor amines produce, they also differ in another important way from pressor amines, like methoxamine, in being able to increase coronary blood flow by a local action, and thereby increase the oxygen delivery to the tissues. We have observed this in normal dogs, while Sayen and associates have demonstrated similar effects as indicated by striking rises in polarographic estimations of intramyocardial oxygen availability in localized areas of myocardial ischemia in dogs with coronary obstruction, following small intravenous injections of norepinephrine.

Although the increases in coronary blood flow and oxygen tension in the heart muscle produced by these drugs are important, they are not directly responsible for the improvement in the elevated atrial and pulmonary pressures seen in our experiments after intracoronary and intravenous administration of levarterenol. Intravenous administration of either levarterenol or methoxamine will increase coronary blood flow and oxygen delivery to heart muscle by increasing mean arterial blood pressure and decreasing heart rate, but the elevated atrial and pulmonary pressures fall only during the action of levarterenol. This latter finding is in agreement with the studies made with metaraminol by Sarnoff and associates, who also showed that an increased coronary flow alone did not improve the elevated left atrial pressure.

As a final point of contrast between levarterenol and methoxamine, the latter drug decreases cardiac output, whereas it has recently been shown that levarterenol can increase it. The experiments of Wilhurt and Brust clearly demonstrate that levarterenol increases cardiac output markedly in humans when the powerful reflex vagal effect (bradycardia) initiated by the drug is eliminated by atropine or tetraethylammonium chloride (TEAC). This effect of levarterenol results from a direct stimulation of the heart by the drug, as demonstrated by others. In view of these results, it is clear that dif-

---

†Abstracted in Circulation 14: 947, 1956.
‡Abstracted in Circulation 16: 950, 1957.
ferences in species in reference to norepinephrine's lack of effect on the human heart may be dismissed.

In the case of methoxamine, there is no increase in cardiac output, but rather a decrease resulting from both reflex (vagal) bradycardia and, to a lesser degree, direct depression of the left ventricle. This was evidenced by a slowing of heart rate accompanied by an increase in left atrial and pulmonary arterial pressures. The latter two effects suggest insufficiency of the left ventricle, because the increased pulmonary arterial pressure apparently results from the elevated left atrial pressure and not from pulmonary constriction as in the case with levarterenol, since studies by Ewing and associates,* and by Aviado and Schmidt,18 have shown that methoxamine either has no direct effect on pulmonary arterial pressure, or causes a significant reduction in it. Furthermore, the elevation of left atrial pressure by methoxamine, as seen in our animals prior to as well as following embolization, is not dependent upon a change in heart rate (slowing), since it often occurred when heart rate was unchanged, as well as in experiments in which atropine (0.1 mg./Kg., I.V.) was given to prevent slowing of heart rate. The insufficiency of the left ventricle is the result of an increased resistance to left ventricular emptying, i.e., of an increase in peripheral vasoconstriction which is not attended by an increased force of ventricular contraction, and of a direct negative inotropic effect of the drug. This latter effect was shown by Melville and associates10 and by our own previous experiments which demonstrated that methoxamine decreases myocardial contraction by a direct action of the drug on the myocardium, rather than by an important coronary vasoconstrictor action. In addition, the former effect was shown by descending aorta injections of levarterenol and methoxamine which demonstrated that when the direct positive inotropic effect of levarterenol is initially obviated, both drugs behave alike by increasing systemic, atrial and pulmonary pressures, as a result of an unequal balance between cardiac stimulation (myocardial contraction) and peripheral vascular resistance. The increased peripheral resistance evidently compromises the capacity of the heart. This finding has also been reported by other investigators.17, 28

Summary
Coronary arterial injections of levarterenol in dogs in shock from acute experimental myocardial ischemia (by selective coronary embolization with lycopodium spores) directly increased myocardial contraction and resulted in a lowering of both atrial and pulmonary arterial pressures while at the same time raising systemic arterial pressure. Appropriate intravenous administration of the same drug had similar effects and produced a greater rise in systemic arterial pressure. Methoxamine, when administered intravenously, elevated the lowered systemic arterial pressure, but produced a further elevation in the already high atrial and pulmonary arterial pressures. These experiments demonstrate that during acute myocardial ischemia with arterial hypotension, and even in the presence of elevated atrial and pulmonary pressures, a more favorable effect, i.e., increased systemic pressure at lower atrial and pulmonary pressures, is achieved by employing a pressor amine with a direct cardiac stimulating action which increases myocardial contraction in addition to a peripheral vasoconstricting effect. By selective coronary arterial injections, levarterenol has been shown to have a direct cardiac stimulating effect, and therefore satisfies the above requirement, whereas methoxamine does not, since it fails to stimulate myocardial contraction, or actually depresses it, when given into the same site.

Acknowledgment
The authors are indebted to Dr. Carl F. Schmidt for his guidance, interest, and continued encouragement in these experiments. We are grateful to Dr. Samuel Bellet, Director, Division of Cardiology, Philadelphia General Hospital, for his interest and to Mr. Sherman M. Bannett for his technical assistance.


Circulation Research, Volume X, May 1962
EFFECTS ON DRUGS IN MYOCARDIAL SHOCK

References


Circulation Research, Volume 9, May 1952
Comparative Study of Effects of Levarterenol and Methoxamine in Shock Associated with Acute Myocardial Ischemia in Dogs
James W. West, Arthur T. Faulk and Santiago V. Guzman

doi: 10.1161/01.RES.10.5.712

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/10/5/712

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/