Induced Hypertension in the Treatment of Severe Ischemia of the Foot

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SUMMARY
The present paper reports the results of angiotensin infusion in 11 patients with severe atherosclerosis of the lower limbs adding a brief discussion of indications with inherent dangers and contraindications.

The study confirms the results of Dahn et al.4, 5 that pharmacologically induced hypertension may increase distal perfusion pressure and flow and relieve resting pains. It is our opinion, however, that only a very limited number of patients presenting with severe foot ischemia and resting pains can profit from this treatment because of frequent contraindications such as coexistent hypertension and coronary heart disease.

Additional Indexing Words:
Conservative treatment of ischemic pain
Angiotensin infusion

Foot gangrene

In 1967 Dahn et al.4 reported good results in the treatment of resting pains and gangrene by increasing the blood pressure with angiotensin or norepinephrine infusions. In their series the blood pressure increase was followed in all patients by an almost immediate relief of pain and a concomitant considerable increase in flow in the anterior tibial muscle. Except for this original communication of Dahn and co-workers and two later reports from the same authors5, 15 very little has been reported about this treatment.

Because it may be an alternative treatment in patient who cannot be helped otherwise, and eventually may prevent amputation, we have found it justified to reevaluate the effect of pharmacologically induced hypertension on the resting blood flow in ischemic feet with threatening or manifest gangrene.

Material and Methods
The effect of angiotensin infusion on resting blood flow was studied in 11 patients, eight men and three women, aged 42–87 years. The systemic blood pressure was 150/90 or below in all patients. All had symptoms of severe arterial insufficiency in one or both legs with impending or manifest gangrene in the foot. Ten of the 11 patients complained of resting pains in the foot. The symptoms had lasted for 6 months to 15 years, but in the majority of the patients there had been an aggravation of the symptoms during the last 2 months. All patients experienced intermittent claudication. Seven had a walking distance of less than 50 m, and none could walk more than 100 m.

Most patients had a history of atherosclerotic disease in other parts of the arterial system. Six had sustained a myocardial infarction more than 2 years prior to the examination or presented with a mild-effort angina, but none had symptoms of cardiac insufficiency. Three patients had a previous history of cerebral stroke, three were chronic alcoholics, and three had a mild diabetes. Six of them were heavy cigarette smokers, one used chewing tobacco, two were nonsmokers, and smoking habits in two were unknown.

Arteriography was performed in 10 patients. Five revealed severe stenosis or complete occlusion of the iliac artery. All had occlusions or serious stenosis of the femoral artery and the popliteocrural arteries.

Resting blood flow in the forefoot was measured by the Dohn plethysmograph6 as described by Graf11 and Mune,19 and the systolic ankle blood pressure with a plethysmographic method described by Winsor.27

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Systemic blood pressure was measured on the upper arm using the indirect auscultatory method with a calibrated mercury manometer. The "collateral pressure gradient" was defined as the difference between the systolic arm and ankle blood pressure. Although it is not possible to calculate the true collateral resistance from the data obtained in this study, the collateral pressure gradient may give some indication of this resistance.

"Local peripheral resistance" (R') in the foot has been calculated from the equation R' = P/F, where P is the systolic ankle blood pressure and F the forefoot blood flow.3 19 The value thus calculated is not the true peripheral resistance in the foot, because flow and pressure are not measured in the same region. The value may, however, give a fairly good picture of the resistance that does exist, and how this resistance is influenced by various therapeutic means.

The examinations were performed in a room where the temperature could be kept constant within ±0.5°C. None of the patients used vasodilating or antihypertensive agents at the time of the study, and they were asked not to smoke or drink coffee, tea, or alcohol on the day of the examination. The patients were examined in the supine position on a couch with the foot a few cm below heart level. They all rested for 30 min before the registrations started.

Resting blood flow in the foot was registered in three periods of 10 min before and in three during angiotensin infusion. In five patients flow was also registered in a 10-min period starting 10 min after cessation of angiotensin infusion. Each flow value given in the tables represents the mean of 20 registrations. Flow was calculated in ml/100 ml/min, with the forefoot volume determined by the water displacement method.

**Results**

Angiotensin (5 mg Hypertensine Ciba in 1000 ml 5% glucose) was given as a slow intravenous infusion, the rate of which was adjusted so as to give a rise in systolic blood pressure of about 50 mm Hg (table 1). Blood pressure during infusion showed a slight fluctuation, but was fairly constant throughout in most patients.

In 10 of 11 patients the blood pressure rise was followed by a concomitant and equivalent increase in forefoot blood flow, with a maximal flow increase of 103% 30 min after angiotensin infusion was started (table 1). In one patient the forefoot blood flow decreased considerably shortly after start of the infusion,
but thereafter increased slowly to the preinfusion level.

In five patients the systolic ankle blood pressure was also measured in connection with the flow measurements (table 2). Resting foot blood flow and systolic arm blood pressure increased with 91.2% and 40.9%, respectively, during infusion. The mean increase in systolic ankle blood pressure during infusion was 36.7 mm Hg or 15 mm less than the concomitant mean increase in systemic blood pressure.

The “collateral pressure gradient” increased slightly in all the patients indicating a moderate constriction of collateral vessels during infusion. The “local peripheral resistance” in the foot increased in one patient (the patient in whom the foot blood flow decreased during infusion), but changed little in the others indicating very small changes in the arteriolar tone of the ischemic foot during infusion.

In three patients foot blood flow, systolic arm and ankle blood pressure, “collateral pressure gradient” and “local peripheral resistance” were followed before, during, and after angiotensin infusion (fig. 1). Resting blood flow and systolic ankle blood pressure increased to almost the same degree during angiotensin infusion, while the “collateral pressure gradient” increased slightly and the “local peripheral resistance” in the foot remained almost unchanged. When the infusion was stopped, flow and pressure decreased almost instantly to near preinfusion values.

In four of the patients resting pains, which had lasted for up to several weeks, disappeared a few minutes after start of the infusion. In the others pain was relieved, but did not disappear completely. One patient got an attack of angina pectoris during infusion, but this was promptly relieved by nitroglycerin.

**Further Treatment**

Three patients had surgery with arterial reconstruction, two with considerable and permanent success. One of them was given a continuous angiotensin infusion for 2 days prior to the operation and was kept free of pain. Amputation was necessary in four patients, in three after a sympathectomy had been performed without effect. One was prior to the amputation treated with a mineralocorticoid and with sodium chloride resulting in a small increase in systemic blood pressure, but without obvious clinical improvement.

The remaining patients were not given any further treatment except for tobacco abstinence and elevation of the head end of the bed. In two there was a considerable spontaneous improvement, while the condition remained unchanged in the others.

**Discussion**

The intraarterial pressure distal to an occluded artery is always reduced. By means of autoregulation mechanism the resting flow of skeletal muscles is kept more or less constant and independent of small changes in
the perfusion pressure, while the resting flow in an ischemic foot is always reduced. In such a low-pressure region the reduced distal perfusion pressure is the determinant factor, and the local blood flow will fluctuate as a passive function of the perfusion pressure. It has been shown that it is not possible to increase the flow in ischemic tissues by means of pharmacologic or surgical therapy (Hansteen V, Lorentsen E: Unpublished data). The reason for this is that the vascular tone in the ischemic areas more or less has been abolished by high local concentration of vasodilating metabolites.

If the intraarterial pressure falls below the surrounding tissue pressure this may lead to an increase in peripheral resistance, or even to complete collapse of the arterioles with cessation of flow. This is presumed to be the mechanism of "paradoxical gangrene."
after sympathectomy, and the blanching of the foot during muscular hyperemia of the leg in patients with intermittent claudication.

On the other hand, it has been shown that a local increase in intraarterial pressure in the ischemic foot is followed by a flow increase, regardless of the means by which this pressure increase is obtained. This also confirms the common experience reported by many patients that resting pains are relieved when the ischemic foot is lowered.

The theoretic background for the use of pharmacologically induced hypertension in the treatment of severe foot ischemia is that the vascular tone in ischemic tissues is more or less abolished, and that the resistance vessels in such vascular beds are less responsive to vasopressor stimulation than are normal vessels, probably because of the high local concentration of vasodilating metabolites. As a consequence, the local resistance in the ischemic region is not increased in response to general and local blood pressure increase, the result being a flow increase in the region.

Resting blood flow in the forefoot increased in 10 of 11 patients in the present study during induced hypertension and returned to preinfusion level when the angiotensin infusion was stopped. In all except one of the patients so far studied, the ankle blood pressure increased while local peripheral resistance in the foot remained unchanged. This is in accordance with the theory stated above. In one patient resting blood flow in the forefoot decreased and local peripheral resistance increased. This indicates that the resistance vessels in the foot had retained their responsiveness to vasoconstrictor stimulation. In this situation the reason for the flow reduction in the foot may have been a shunting of blood to vascular beds where the resistance is less affected by the pressor effect of angiotensin, for instance, skeletal muscle.

This illustrates that the usual local blood flow increase induced by angiotensin infusion may be lacking. The increase of anterior tibial muscle blood flow during angiotensin infusion found by Dahn and co-workers cannot, therefore, be taken as a proof of a concomitant increase of flow in the skin of the foot.

The best indication for the use of induced hypertension seems to be patients in whom a later arterial reconstruction may be done, and in patients with acute arterial thromboembolic occlusions. The use of induced hypertension is much more open to criticism in patients with disseminated arterial occlusions with threatening gangrene, and where direct arterial surgery is not possible. Relief of otherwise intractable pain may be an indication for this treatment. The main rationale for the use of induced hypertension in such patients must, however, be the possibility of promoting collateral growth, thus leading to permanent increase of the distal perfusion pressure. The basis for this theory, which concurs with the theoretic background for systematic muscular exercise in patients with intermittent claudication, seems to be somewhat speculative, although there is some experimental evidence in favor of it.

Our study indicates that the systemic blood pressure increase during angiotensin infusion is partly lost across the collaterals. The reason for this may be an increase in collateral resistance because of increased collateral tone induced by angiotensin.

The hazards of induced hypertension as a treatment in aged patients with cerebrovascular or coronary heart disease are obvious. The danger of provoking cerebrovascular accidents, myocardial infarction, or acute cardiac insufficiency must, however, be weighed against the possibility of avoiding an amputation, which also represents a considerable risk in these patients.

The danger of induced hypertension increases with the duration of the infusion, although continuous angiotensin infusion has been given for a period of up to 5 days without serious side effects. Angiotensin infusion should be given with great care and guided by frequent blood pressure readings. When the infusion is extended to several days, the patient should preferably be treated in an intensive care unit with continuous ECG monitoring. If possible, an infusion pump...
should be used to preserve a constant infusion rate in order to avoid dangerous fluctuations in the systemic blood pressure, as may be seen when an ordinary drip infusion is used.

In some patients it would seem preferable to extend the treatment with pharmacologically induced hypertension to several weeks or months. Lassen et al. have shown that this can be achieved by the combined use of a mineralocorticoid and sodium chloride. The practical value of this treatment is difficult to evaluate from their study because the treated group is small without a proper control group, and because blood flow measurements were obtained from the anterior tibial muscle, not from the ischemic foot itself. Nevertheless, the results are promising and this treatment may be an alternative in selected patients who cannot be helped otherwise. On the other hand, it should not be forgotten that in addition to the risk of provoking complications from the cardiovascular system, induced hypertension may in itself accelerate further atherosclerosis. It should also be kept in mind that a considerable number of patients not suited for arterial reconstruction may improve on conservative treatment including correction of cardiac insufficiency, elevation of the head end of the bed, tobacco abstinence, and treatment of local infection. This conservative regimen should be given a due chance before an amputation is performed.

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