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EFFECT OF VASOACTIVE DRUGS ON THE BONE MARROW BLOOD FLOW

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Bone marrow vessels are peculiar in some respects. Thus the arteries are more thin-walled than in most other organs and partly consist of only a single layer of flattened cells (Yoffey 1965). The venous system consists of a spacious central vessel draining the capillaries and sinusoids via radiating venules. There is no muscle layer in the venous walls (Yoffey 1965). These morphological peculiarities of the bone marrow vessels suggest the possibility of peculiarities, also in their reactions to vasoactive drugs.

Contradictory results have been obtained in investigations of the effect of vasoactive drugs on the vascular bed of the bone marrow. Thus Brånemark (1961), who used vital microscopy, found that intravenous injection of histamine slowed down the linear flow in the bone marrow vessels of the rabbit fibula, and McPherson et al. (1961) and Shaw (1963), who used heat clearance as an indicator of changes in the blood flow, reported an increased blood flow through the bone marrow of the cat femur after intravenous injection of the same substance. McPherson, unlike Shaw, also noted an increased flow after intravenous or intraarterial adrenaline. Intraarterial injection of acetylcholine has been found to decrease the bone marrow pressure and blood flow in cats (Shaw 1963). Intraarterial infusion of this substance, however, has also been found to increase the intramedullary venous pressure, an equivalent to the bone marrow pressure (Michelsen 1967).

The aim of the present investigation was to elucidate the vasoactive control of the bone marrow vessels by studying the effect of vasoactive drugs on the elimination rate of a radioactive tracer deposited in the medullary cavity.

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MATERIAL AND METHODS

Six adult mongrels were used. They were anaesthetized with sodium pentobarbital (Nembutal®) intravenously in a dose of about 30 mg/kg bodyweight. Twenty-five milligrams of heparin was injected via the same route.

The radioactive gas ^{133}Xe was used as clearance substance, and the effect of vasoactive drugs on the marrow vessels was judged from changes in the slope of the elimination curves for ^{133}Xe deposited in the bone marrow. Although ^{133}Xe has been found to be inappropriate as clearance substance for calculating the blood flow through the bone marrow (Semb 1970), it was found in a pilot study that the elimination rate of this radioactive tracer from the bone marrow was changed by vasoactive substances administered intraarterially or intravenously. A small volume (0.3–0.5 cc) of a solution of ^{133}Xe (0.15 mCi) was slowly injected proximally in the bone marrow of each tibia via cannulas inserted through the cortex. This was immediately followed by injection of a small volume of isotonic saline sufficient for rinsing the cannula via a three-way stop-cock.

In four animals in which ^{133}Xe had been previously deposited bilaterally in the tibial bone marrow, various vasoactive drugs were injected intraarterially via a thin polyethylene catheter into one femoral artery and through a polyethylene catheter into a subcutaneous vein of one foreleg. The drugs tested were adrenaline, noradrenaline, histamine, acetylcholine, and bradykinin. The doses used were so small as to have only a negligible effect on the arterial blood pressure when given i.a. They correspond to those used in earlier investigations on the effect of vasoactive drugs on the bone marrow circulation (McPherson et al. 1961, Shaw 1963).

The effect of histamine, injected into the bone marrow, on the bone marrow circulation was studied in two dogs. In this separate study ^{133}Xe was supplemented by $^{131}I^-$, a tracer which in a pilot study was cleared about four times more rapidly than the lipophilic Xenon. $^{131}I^-$ was included as a clearance substance because it should be more sensitive to transient changes in the bone marrow blood flow.

The radioactivity was measured by two collimated scintillation detectors located over the regions where the tracer was deposited. The counts were recorded on a ratemeter connected to a two-channel recorder. When a mixture of ^{133}Xe and $^{131}I^-$ was injected in the same region, pulse height analysis was used and correction was made for the $^{131}I^-$ impulses recorded by the ^{133}Xe-channel.

The systemic arterial blood pressure was measured in one carotid artery. A polyethylene catheter filled with saline was inserted into the artery and was connected to a pressure transducer (Elema-Schönander, Stockholm, Sweden). The pressure was recorded on a mingograph recorder. Calibration was performed against atmospheric air and saline corresponding to a pressure of 50 mm Hg.

RESULTS

Each of the drugs tested (adrenaline, noradrenaline, histamine, acetylcholine, and bradykinin) produced an obvious and prompt effect of two to three minutes' duration on the disappearance curves of ^{133}Xe.

Adrenaline. Intraarterial injection of adrenaline (0.05 μg/kg) reduced the elimination rate of ^{133}Xe in the ipsilateral leg. The effect on the arterial blood pressure was negligible (Figure 1). Adrenaline (0.5 μg/kg) i.v. resulted in impaired clearance in both legs. There was a transient decrease of the arterial blood pressure followed by a small increase for about one minute.

Noradrenaline. Noradrenaline i.a. (0.3 μg/kg), like adrenaline, resulted in reduction of the disappearance rate of Xenon in the same leg. No change in the arterial blood pressure was observed (Figure 1). Noradrenaline i.v. (2.0 μg/kg) impaired ^{133}Xe-clearance in both legs. The arterial pressure rose 20 to 40 mm Hg for about two minutes (Figure 2).

Histamine. The disappearance rate of ^{133}Xe decreased after injection of histamine (1.0 μg/kg) into the femoral artery of the same leg.

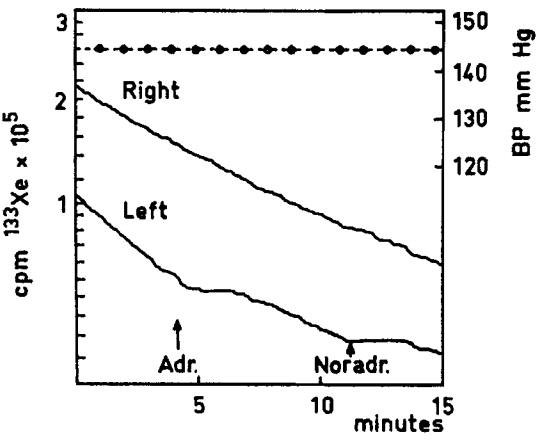

Figure 1. Effect of intraarterial adrenaline and noradrenaline on the disappearance rate of intramedullary deposited ^{133}Xe and on the systemic arterial blood pressure. Note the unaffected blood pressure and the insignificant effect on the disappearance rate of ^{133}Xe in the contralateral leg.

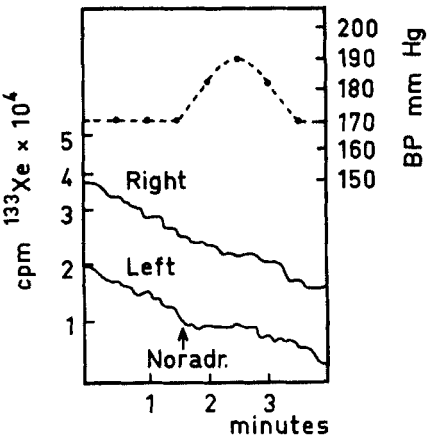

Figure 2. Effect of intravenous noradrenaline on the disappearance rate of ^{133}Xe administered in the bone marrow, and on the systemic arterial blood pressure. Note the pronounced effect on the blood pressure and the symmetric impairment of the disappearance rate of ^{133}Xe bilaterally.

A negligible, transient fall in pressure was seen (Figure 3). Histamine i.v. (2.0 μg/kg), however, resulted in a more pronounced decrease of the arterial pressure and impaired ^{133}Xe-clearance in both legs.

Acetylcholine. After intraarterial deposition of acetylcholine (0.5 μg/kg) the disappearance rate of Xenon was decreased in the ipsilateral leg. There was a pressure fall of maximum 30 mm Hg for a few seconds (Figure 4). Acetylcholine i.v. (5.0 μg/kg) impaired the ^{133}Xe-clearance bilaterally and resulted in a pressure drop to about 50 mm Hg for half a minute.

Bradykinin. Bradykinin i.a. (0.3 μg/kg) yielded a small reduction

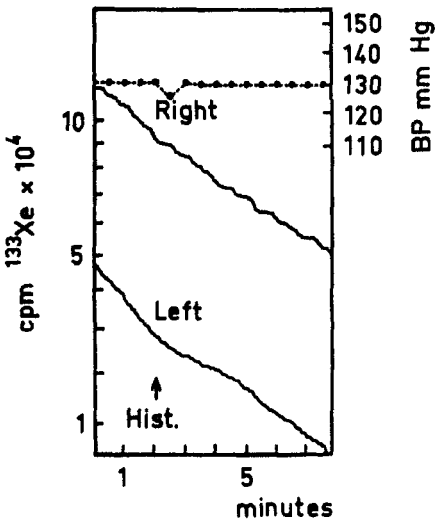

Figure 3. Effect of intraarterial histamine on the disappearance rate of intramedullarily deposited ^{133}Xe and on the systemic arterial blood pressure. Note the insignificant effects on the blood pressure and on the disappearance rate of ^{133}Xe in the contralateral leg.

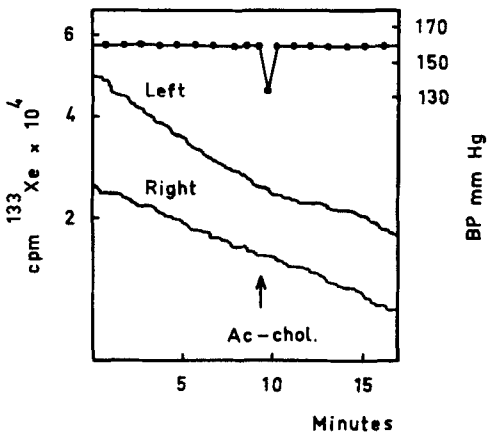

Figure 4. Effect on the ^{133}Xe-clearance from the bone marrow and the arterial blood pressure after intraarterial acetylcholine.

of the ^{133}Xe-clearance in the same leg. The arterial pressure was unaffected. Bradykinin i.v. (2.0 μg/kg) resulted in a slight bilateral decrease of the disappearance rate. The blood pressure dropped ten to 20 mm Hg for about one minute.

Deposition of histamine in the bone marrow of the tibia in the same region as the tracer substances (^{133}Xe and ^{131}I$^-$) had previously been administered and resulted in two minutes' enhanced clearance of both substances, especially of ^{131}I$^-$ (Figure 5).

The clearance of the test substance ceased completely in one leg after occlusion of the ipsilateral femoral vein.

DISCUSSION

^{133}Xe was used as a clearance substance in this study, first because a pilot study had shown that there was a prompt change of its disappearance rate after intraarterial administration of vasoactive substances and, second, because it is a tracer that is very easy to handle.

The local clearance of ^{133}Xe from the bone marrow of the tibia was affected in an unexpected way by administration in the ipsilateral femoral artery of histamine, acetylcholine, and bradykinin, vasoactive drugs known to dilate vessels in other regions.

Administration of vasoactive substances could impair the regional capillary blood flow by a centrol effect on the arterial blood pressure or by a peripheral vasomotor effect. It was found, however, that the systemic effect of the vaso-dilating drugs was negligible after intraarterial injection. This was reflected by a very slight change of the

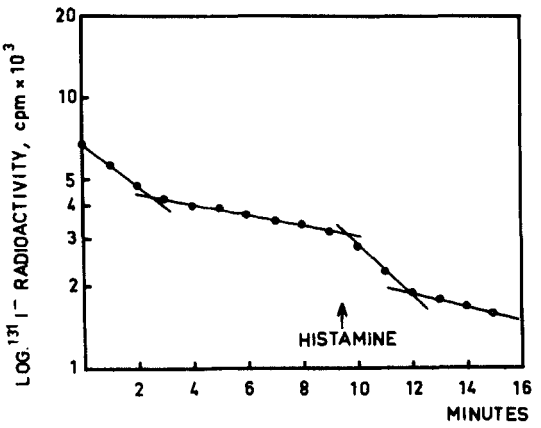

Figure 5. Effect of histamine, injected into the bone marrow, on the disappearance rate of ^{133}Xe, previously deposited in the same region.

continuously recorded blood pressure and by an unaffected disappearance rate of the tracer from the bone marrow of the contralateral tibia. Thus there was a local effect of the intraarterially injected substances. It seems strange, however, that normally vasodilators such as histamine and bradykinin could decrease the elimination rate of the tracer ^{133}Xe. On the other hand, the apparently paradoxical reaction of the bone marrow vessels might be explained by vasodilatation with lowered resistance and enhanced blood flow in surrounding muscles. This might cause an increase of the blood flow through the muscles at the expense of that through the bone marrow of the limb. Deposition of one vasodilator substance, histamine, directly into the bone marrow, in the same dose as administered intraarterially, raised the capillary blood flow in the same region, which implies a regional vasodilation. This finding suggests that in spite of their peculiar anatomy the bone marrow vessels can respond to vasomotor stimuli. It seems probable, however, that the vasomotor response of the thin-walled bone marrow arteries is weaker than that of the muscle arteries. This supports the suggestion that the reduced bone marrow blood flow following deposition of vasodilator substances in the ipsilateral femoral artery may be an effect of redistribution of blood flow between bone marrow and surrounding muscles due to more active dilatation of the blood vessels of the muscles compared with that of the bone marrow vessels.

As expected, intravenous injection of acetylcholine and histamine resulted in a marked drop of the arterial blood pressure. This drop was probably the main cause of the impaired elimination of ^{133}Xe from the bone marrow. The possibility of a central haemodynamic effect

after intravenous injection is supported by the finding of a parallell decrease of the ^{133}Xe clearance in both legs. After intravenous administration of noradrenaline, however, the blood pressure increased, whereas the bone marrow clearance of ^{133}Xe decreased, implying a systemic as well as a regional vasoconstrictor effect of noradrenaline.

The effect of intraarterially and intravenously administered vasoactive drugs on the bone marrow blood flow in cats has been studied by Shaw (1963), who used heated thermocouples for qualitative measurement of the regional blood flow. He found that adrenaline, noradrenaline and acetylcholine decreased the marrow blood flow, observations which were confirmed in the present investigation. He also found that acetylcholine increased muscle blood flow. This supports the theory presented above, i.e. vasodilators cause a redistribution of the blood flow in a limb. However, he found that histamine i.v. increased the bone marrow flow, in contrast with the present findings and with those of Brånemark (1961), who found that such treatment dilated capillaries and sinusoids but decreased the blood flow through the fibular bone marrow in rabbits.

Occlusion of the femoral vein has been found to increase the blood flow through the femoral bone marrow in cats owing to a shunting of blood through the bone marrow cavity (Shaw 1963). However, in the present investigation, the immediate effect of the same procedure was complete inhibition of the disappearance of ^{133}Xe in the tibial bone marrow, obviously as an effect of increased venous pressure. It must be emphasized, however, that venous stasis of the tibial bone marrow, as an effect of venous occlusion in the thigh, does not preclude the possibility of blood shunting proximally via the femoral bone marrow.

SUMMARY

The effect of vasoactive drugs on the bone marrow blood vessels was studied in dogs. Changes in the disappearance rate of ^{133}Xe deposited locally in the tibial bone marrow were recorded after intraarterial and intravenous injection of the drugs. Adrenaline, noradrenaline, acetylcholine, histamine, and bradykinin decreased the disappearance rate. However, intramedullary deposition of one vasodilator substance, histamine, resulted in enhanced elimination of ^{133}Xe. It is concluded that the bone marrow vessels have the ability to respond to stimuli of vasomotor drugs in spite of their structural peculiarity. Intraarterial administration of vasodilator drugs probably causes a redistribution of the blood

flow through the limb, viz. an increase in flow through the muscles at the expense of that through the bone marrow.

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