output. The changes in blood pressure and tissue blood flow caused by histamine are shown in Table 1. Blood flows to the heart and stomach were increased despite the falls in blood pressure. Blood flows to the brain, kidney, skin and liver (arterial flow only) were maintained at the lower histamine infusion rates but declined at the highest infusion rate. In the other organs blood flow was maintained despite the falls in blood pressure.

These experiments suggest that histamine does not dilate resistance vessels equally in all tissues indicating unequal distribution of histamine or histamine receptors. Although the changes in tissue blood flow during histamine infusions were due to the local vascular effects of histamine they may have been complicated by reflex vascular changes caused by the accompanying hypotension. It is hoped that these and further experiments using histamine antagonists will reveal the distribution of H_1- and H_2-receptors in resistance vessels.

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A procedure to demonstrate the release of a vasoactive metabolite by catecholamines from perfused guinea-pig hearts

K.J. BROADLEY

Department of Pharmacology, University of Wales Institute of Science and Technology, King Edward VII Avenue, Cardiff CF1 3NU

The action of catecholamines on the coronary circulation is complex. They both constrict and dilate the coronary arterioles by directly stimulating α- and β-adrenoceptors (Parratt, 1968). The accompanying positive inotropic and chronotropic responses also indirectly constrict through extravascular compression and cause a coronary vasodilatation which is attributed to the release by the increased myocardial activity, of a vasoactive metabolite (Berne, 1964). This component is the predominant and most controversial effect. Proposed transmitters of this response have included potassium ions, lactate, kinins, adenosine (Berne, 1964) and prostaglandins (Talesnik & Sunahara, 1973), with a local anoxia possibly serving as an intermediate stimulant. However, most of the evidence is circumstantial, based upon the modification of the response by other drugs. This study was undertaken to develop a procedure and apparatus that could clearly demonstrate the presence of a metabolite during the coronary vascular response to catecholamines.

Guinea-pig (350-600 g) isolated hearts were set up as described previously (Broadley, 1970) perfused at a constant rate (5 ml/min) with Krebs-bicarbonate solution (37°C) gassed with carbogen. Records of coronary perfusion pressure and isometric force and rate of contraction were obtained on a Devices M19 polygraph. The pulmonary vein and venae cavae were tied off and after trimming the lungs free, the cut pulmonary artery was cannulated enabling the perfusate to pass to a second guinea-pig perfused heart (II) (Figure 1). This was perfused at a constant rate exactly matching that of heart I and identical parameters recorded. An open reservoir serving as an air trap was included between hearts I and II, where perfusate was regassed and fresh Ringer could be added. The volume of reservoir and tubing was minimal to keep small amounts of any metabolite concentrated.

With two hearts thus connected in series, adrenaline (0.25 μg) added to heart II increased the force and rate of contraction and produced a characteristic coronary vascular response consisting of a biphasic constriction followed by the predominant vasodilatation. Adrenaline (0.25 μg) added to heart I also produced these responses,

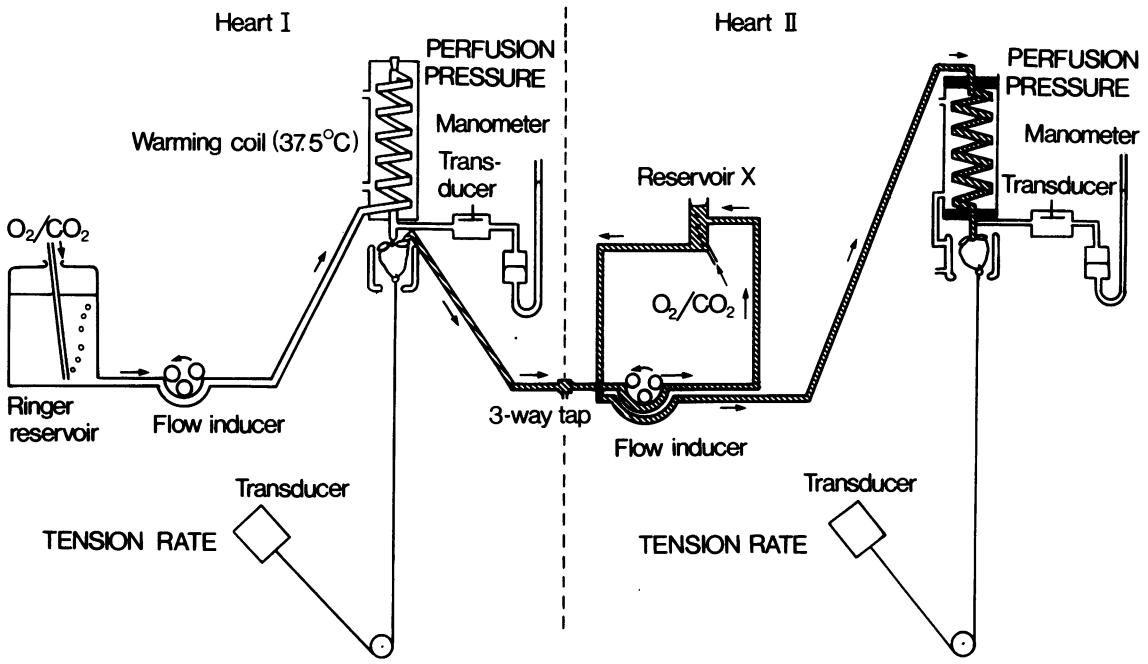

Figure 1 Diagram of apparatus for perfusing guinea-pig isolated hearts (I) and collecting the perfusate for supplying a second perfused heart (II).

but it was carried in the perfusate to heart II where it again produced similar responses, although the coronary response was sufficient to mask any effects due to a metabolite from heart I. These direct β-adrenergic effects on heart II were antagonized by propranolol (15 μg). Adrenaline repeated in heart I gave normal responses but a coronary vasodilatation followed in heart II unaccompanied by rate or force changes. This vasodilatation was abolished when the rate and force changes in heart I were also blocked by propranolol. It can therefore be attributed to a vasodilator substance released from heart I by the increased activity and not by the adrenaline itself.

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