Intracoronary Injections of Salbutamol Demonstrate the Presence of Functional \( \beta_2 \)-Adrenoceptors in the Human Heart

J.A. Hall, M.C. Petch, and M.J. Brown

To demonstrate the presence of functional cardiac \( \beta_2 \)-adrenoceptors in man, we studied the responses to intracoronary injections of salbutamol in three groups of six patients. We injected salbutamol, a selective \( \beta_2 \)-adrenoceptor agonist, into the right coronary artery to avoid peripheral vasodilator action and to stimulate the sinoatrial node directly. Salbutamol injections caused a sinus tachycardia. The same doses of salbutamol injected into the aortic root caused no change in heart rate, ruling out a systemic effect. The mean dose required to cause an increase in heart rate of 30 beats/min (IHR\(_{30}\)) was 2.6\( \mu \)g in the first group of six patients. In 12 other patients salbutamol was given after \( \beta \)-blockade to confirm the \( \beta_2 \)-selectivity of the responses. Doses of practolol (\( \beta_1 \)-selective blockade) and of propranolol (\( \beta_1 \)- and \( \beta_2 \)-blockade) that had equal \( \beta_1 \)-blocking activity were used. In six patients who were given practolol, the mean IHR\(_{30}\) dose was 2.1\( \mu \)g. In six patients who were given propranolol, the mean IHR\(_{30}\) dose was significantly greater at 64\( \mu \)g (\( p < 0.001 \), practolol vs. propranolol). This study demonstrates that direct cardiac \( \beta_2 \)-adrenoceptor stimulation in man has a positive chronotropic effect. (Circulation Research 1989;65:546–553)

In 1967, Lands et al\( ^1 \) presented evidence of the existence of two subtypes of the \( \beta \)-adrenoceptor: \( \beta_1 \) and \( \beta_2 \). They concluded from their experiments on rabbit ventricle that the heart contains only the \( \beta_1 \) subtype.

However, various radioligand binding studies in membrane preparations of human heart have shown that the \( \beta_2 \) subtype constitutes between 20% and 60% of the total number of \( \beta \)-adrenoceptors.\(^2\)-\(^4\) Autoradiography has shown that these \( \beta_2 \)-adrenoceptors are on myocardial cells.\(^5\) The \( \beta_2 \)-adrenoceptors are linked to adenylate cyclase\(^6\) and cAMP-dependent protein kinase.\(^7\) In vitro studies of paced human atrial and ventricular muscle strips have shown that stimulation of \( \beta_2 \)-adrenoceptors produces positive inotropic effects.\(^8\)-\(^12\)

The demonstration of functional cardiac \( \beta_2 \)-adrenoceptors in vivo is confounded by the peripheral vasodilation caused by \( \beta_2 \)-adrenoceptor stimulation. Positive chronotropic responses to intravenous isoproterenol are blocked more by nonselective \( \beta \)-receptor antagonists than by \( \beta_1 \)-selective antagonists, indicating a \( \beta_2 \)-receptor component to the tachycardia.\(^13\),\(^14\) However, this could be due either to direct cardiac \( \beta_2 \)-adrenoceptor stimulation or indirectly to \( \beta_2 \)-adrenoceptor-mediated vasodilation, causing baroreceptor-mediated reflex vagal withdrawal and increased sympathetic activity. The contribution of altered vagal activity to isoproterenol-induced tachycardia has been tested using atropine, but with varying results.\(^15\)-\(^20\) To exclude all baroreceptor-mediated reflexes, one study attempted to reverse the fall in diastolic blood pressure caused by isoproterenol with an infusion of angiotensin.\(^21\) This did not decrease the tachycardia, suggesting indirectly that baroreflex activation plays little part in isoproterenol tachycardia.

Thus, although most of these studies are compatible with the conclusion that stimulation of cardiac \( \beta_2 \)-adrenoceptors contributes to isoproterenol-induced tachycardia, the precise mechanisms of isoproterenol-induced tachycardia has been tested using atropine, but with varying results.\(^15\)-\(^20\) To exclude all baroreceptor-mediated reflexes, one study attempted to reverse the fall in diastolic blood pressure caused by isoproterenol with an infusion of angiotensin.\(^21\) This did not decrease the tachycardia, suggesting indirectly that baroreflex activation plays little part in isoproterenol tachycardia.

The aim of this study was to determine if there are functional \( \beta_2 \)-adrenoceptors in the human heart. The resolution of whether there are functionally important cardiac \( \beta_2 \)-adrenoceptors in man is of potential therapeutic importance because this would open to question the assumption that \( \beta_1 \)-selective blockade and nonselective \( \beta \)-blockade have equal antiarrhythmic efficacy. 
The β₂-adrenoceptors were stimulated with the β₂ partial agonist salbutamol. Peripheral vasodilator action of the drug was avoided by use of intracoronary injections. For confirmation of the β₂-adrenoceptor selectivity of salbutamol's cardiac effects, the study was repeated after either practolol (selective β₁-blocker) or propranolol (nonselective β-blocker). The study used doses of these antagonists that were equipotent at β₂-receptors, that is, equally potent at blocking exercise-induced tachycardia.13

Subjects and Methods

Men less than 75 years of age and undergoing routine coronary angiography in the cardiac unit at Papworth Hospital were invited to participate in the study. All had chronic stable angina. Most were receiving long-term treatment with a β₁-selective antagonist, either atenolol or metoprolol. β₂-Blockers were stopped before catheterization, at least 28 hours for patients receiving atenolol and 18 hours for patients receiving metoprolol.

An initial study for demonstration of whether intracoronary salbutamol affected heart rate was performed in one group of six patients (group 1). A further group of 12 patients (group 2) was then randomized to receive intracoronary salbutamol after either practolol (β₁-blockade) or propranolol (nonselective β-blockade) in a single-blind manner.

The patients were fasting and received a standard premedication of 15–20 mg oral diazepam 1 hour before the procedure. Catheterization was by the femoral or brachial approach using local anaesthetic. Before the study coronary angiograms were performed in multiple projections using Urografin (Schering, Burgess Hill, UK).

A Swan-Ganz thermodilution catheter was inserted into the pulmonary artery for the measurement of right heart pressures, pulmonary capillary wedge pressure, and cardiac output. The coronary catheter was used for measurement of arterial pressure and for the injection of salbutamol. Group 2 patients were randomly assigned to receive either 8 mg practolol or 4 mg propranolol i.v. as bolus doses at the start of the study, 15 minutes before the baseline measurements were recorded. After the baseline measurements were recorded, bolus doses of salbutamol were injected into the right coronary artery. The salbutamol was given over 10 seconds. The starting dose was 0.4 μg; incremental doses were then given every 2 minutes and were doubled with each administration. Salbutamol solutions for injection were prepared by serial tenfold dilutions in normal saline. All injections had volumes of 1.2–8 ml. The first dose of 0.4 μg was in a volume of 8 ml; that is, the largest injection volume was given first to show that the responses were not merely due to the volume of diluent injected into the coronary artery. The intracoronary injections were continued until there was an increase in heart rate of 30 or more beats/min above baseline or a maximum dose of 400 μg was reached.

Cardiac output, right atrial pressure, and pulmonary capillary wedge pressure were recorded every 6 minutes and at the highest dose of salbutamol. Heart rate, systemic arterial pressure, and pulmonary artery pressure were recorded at the end of each 2-minute period. Cardiac output was determined by thermodilution using 10 ml of 5% dextrose at 4°C. Cardiac output measurements at baseline and at the highest dose were done in triplicate; during the dose response curve, measurements were in duplicate. Pressures were measured via the Swan-Ganz and coronary catheters. Phasic and mean pressure recordings were taken over 15 seconds and recorded on paper by use of a Siemens recorder (Siemens-Elema, Solna, Sweden). Heart rate was determined from mean R-R intervals over 15 seconds.

After the series of intracoronary injections, the effects of the intracoronary salbutamol were allowed to decay until the heart rate was within 10 beats/min of the baseline (5–15 minutes). The same doses as were given into the coronary artery were then given into the ascending aorta. Again, heart rate, systemic arterial pressure, and pulmonary artery pressure were recorded at the end of each 2-minute period. Cardiac output, right atrial pressure, and pulmonary capillary wedge pressure were recorded every 6 minutes and at the highest dose of salbutamol. After completion of the injections of salbutamol, a left ventricular angiogram was performed in the right anterior oblique projection.

The coronary angiograms were used for confirmation that the sinoatrial node artery arose from the right coronary artery. For quantification of the size of the artery into which the salbutamol was injected, the vessels were scored using American Heart Association (AHA) criteria22; scores were awarded for the territory served by the artery proximal to any stenoses. This score indicated the volume of tissue to which the salbutamol was distributed. Left ventricular ejection fraction was determined by planimetry of the left ventricular angiogram. Ejection fractions of >50% were considered normal; ejection fractions of 40–50% were considered representative of mild left ventricular dysfunction.

Ethical Considerations

This study was performed according to the ethical considerations laid down in the Declaration of Helsinki (Tokyo and Venice Amendments). The study was approved by the District Medical Ethics Committee of the Huntingdon Health Authority, which considers all studies in patients at Papworth Hospital. Patients gave their informed written consent before taking part in the study.

Statistics

Measurements of variables recorded at baseline and maximum dose of salbutamol were compared by paired Student's t test. Baseline heart rates between groups were compared by unpaired Student's t test. The log doses of salbutamol required
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Practolol</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>55.0±5.3</td>
<td>56.5±3.7</td>
</tr>
<tr>
<td>Body surface area (M²)*</td>
<td>1.88±0.04</td>
<td>1.87±0.07</td>
</tr>
<tr>
<td>Angina (n)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>NYHA grade III</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drug therapy (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ca-channel blocker</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Nitrates</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3VD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2VD</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1VD</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ejection fraction (%)*</td>
<td>59±3</td>
<td>63±3</td>
</tr>
<tr>
<td>RCA AHA score (mean)</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

n, number of subjects; NYHA, New York Heart Association; 1VD, 2VD, 3VD, one, two, or three major epicardial coronary arteries with stenoses >70%; RCA, right coronary artery; AHA, American Heart Association. Values given are mean±SEM.

Materials

Agents used in this study were salbutamol sulfate (500 µg/ml; Allen & Hanburys, Greenford, UK) diluted in normal saline, propranolol hydrochloride (1 mg/ml, ICI Pharmaceuticals, Macclesfield, UK), and practolol (2 mg/ml; ICI Pharmaceuticals).

Responses to Salbutamol

Group 1 responses to intracoronary salbutamol (Figure 1, Table 2). All subjects showed an increase in heart rate in response to intracoronary salbuta-
mol. The basal heart rate was 67.5±3.3 beats/min (mean±SEM). The mean dose required to increase heart rate by 30 beats/min (IHR<sub>30</sub>) was 2.6 μg (log dose, 0.41±0.1 μg, mean±SEM). There were no significant changes in right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), mean arterial pressure (MAP), or cardiac output (CO).

**Group 1 responses to intra-aortic salbutamol** (Figure 2, Table 2). None of the subjects showed any increase in heart rate in response to intra-aortic salbutamol. The small changes in other variables were not statistically significant.

**Group 2 responses to intracoronary salbutamol after practolol** (Figure 3, Table 2). The basal heart rate was 62.5±5.0 beats/min (mean±SEM). The mean IHR<sub>30</sub> dose of 2.1 μg (log dose 0.32±0.2 μg, mean±SEM) was not significantly different from group 1. There were no statistically significant changes in RAP, PCWP, SVR, MAP, or CO.

**Group 2 responses to intracoronary salbutamol after propranolol** (Figure 4, Table 2). The basal heart rate of 59.5±2.0 beats/min (mean±SEM) was not significantly different from the practolol group. The mean IHR<sub>30</sub> dose was 64 μg (log dose 1.81±0.15 μg, mean±SEM); this dose was significantly different from the response after practolol (p<0.001) (Figure 5). There were no significant changes in RAP, PCWP, SVR, MAP, or CO.

Responses to intra-aortic salbutamol after practolol and propranolol were similar to those responses seen in the control group, that is, there were no significant changes in heart rate or in any other variable measured.

**Discussion**

We have shown that injections of salbutamol into the right coronary artery cause a tachycardia. The failure of identical doses injected into the aortic root to do likewise shows that this is a direct cardiac effect. This is likely to be due to a direct effect on the sinoatrial node.

Previous attempts to show that cardiac β<sub>1</sub>-adrenoceptor stimulation causes a tachycardia have been indirect and dependent on the interpretation of the results of treatments intended to eliminate baroreceptor reflexes. Pretreatment with atropine has been found to decrease, increase, or not affect isoproterenol-induced tachycardia. Atropine has also been found to produce varying effects on the modification of isoproterenol tachycardia by β-blockers. Atropine enhances the effect of selective β<sub>1</sub>-blockade, attenuates the effects of the highly selective β<sub>1</sub>-blocker ICI118551, has no effect on

---

**Table 2. Hemodynamic Changes in Response to Salbutamol**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Intracoronary</th>
<th>Group 1 Intraaortic</th>
<th>Group 2 Practolol (intracoronary)</th>
<th>Group 2 Propranolol (intracoronary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>2.2±4.6</td>
<td>2.3±2.0</td>
<td>1.5±3.7</td>
<td>-0.8±2.3</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>-1.5±0.9</td>
<td>0.0±0.9</td>
<td>-1.3±0.4*</td>
<td>0.0±0.6</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>-2.3±0.9</td>
<td>0.8±0.4</td>
<td>-0.7±1.1</td>
<td>-0.7±1.0</td>
</tr>
<tr>
<td>CO %</td>
<td>9.3±4.6</td>
<td>15.8±10.2</td>
<td>13.8±3.8†</td>
<td>9.2±11.0</td>
</tr>
<tr>
<td>SVR %</td>
<td>-4.8±5.6</td>
<td>3.0±10.0</td>
<td>-10.0±4.9</td>
<td>-6.2±6.0</td>
</tr>
</tbody>
</table>

Values reflect changes between highest dose of salbutamol and baseline. Values are mean±SEM. No changes reached significance at the 1% level. MAP, mean arterial pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; SVR, systemic vascular resistance [(MAP–RAP)/CO].

*p<0.025.

†p=0.016.
nonselective β-blockade, and has no effect on the difference between β₁-selective and nonselective β-receptor blockade. Some, but not all, of the discrepancies can be explained by methodological differences (e.g., isoproterenol given by infusion or by bolus injections). The studies are all complicated by the inevitable alteration of baseline hemodynamic status caused by pretreatment with large doses of atropine. A study that used an infusion of angiotensin to reverse peripheral vasodilatation attempted to prevent both the vagal and sympathetic consequences of baroreceptor activation. Unfortunately, however, because of the difficulty of measuring diastolic blood pressure by use of a sphygmomanometer during an isoproterenol infusion, this study would probably have required direct intra-arterial pressure recording to be accurate. Therefore, we felt it was important to test the effects of direct and selective cardiac β₂-adrenoceptor stimulation. Can we be certain that direct stimulation of sinoatrial β₂-adrenoceptors is the correct interpretation of our results? Could the tachycardia have been due to alterations in coronary blood flow? Replacement of the coronary blood with non-oxygen-carrying saline could produce ischemia. Because we gave the largest volume of injectant as the first dose (which produced no changes in any subject), we showed that the tachycardia is not due to this mechanism. Also, despite the fact that all our subjects had coronary artery disease, only one subject developed symptoms of ischemia (i.e., chest pain). Overall, there was evidence that no significant ischemia developed before or during the tachycardia since mean PCWP did not rise and the trend was for it to fall (left ventricular dysfunction producing a rise in PCWP is a sensitive index of myocardial ischemia). Increased coronary blood flow may have occurred since coronary vasodilatation would be expected to follow β-adrenoceptor stimulation by salbutamol. This is unlikely to be the mechanism whereby salbutamol induces a tachycardia since intracoronary nicardipine causes direct coronary vasodilation but no tachycardia.

These considerations suggest that salbutamol caused a tachycardia by direct stimulation of myocardial receptors. Salbutamol is a β₂-adrenoceptor agonist and was used by Carlsson et al (the first to suggest the presence of β₂-adrenoceptors in the heart) in isolated cat hearts. They found that the effects of salbutamol were strongly blocked by the β₂-selective H25/35 but weakly blocked by β₁-selective practolol. Quantitative estimates of the selectivity of salbutamol in isolated spontaneously beating guinea pig atria suggest a β₂-selectivity of eightfold for the ability of salbutamol to block the effects of full agonists. The β₂-selectivity of its agonist activity may be considerably greater since the positive inotropic effects of salbutamol on human atrial muscle strips in vitro are blocked by ICI118551 (a highly selective β₂-adrenoceptor antagonist) but not by CGP20712A (a highly selective β₁-adrenoceptor antagonist) (Hall, J.A., unpublished data). Similarly, in normal volunteers the cardiovascular effects of oral salbutamol are abolished by ICI118551. However, these demonstrations of selectivity are not sufficient to allow us to conclude that in our study intracoronary salbutamol is acting by β₂-adrenoceptor stimulation. Unfortunately, the best drug to test β₂-selectivity, ICI118551, is no longer available for human use, having been withdrawn by the manufacturer. We therefore compared the blockade of salbutamol tachycardia by the β₂-adrenoceptor antagonists propranolol (nonselective) and practolol (β₂-selective).

Intravenous injection of both drugs causes rapid onset of β-blockade with long half-lives (propranolol, 2.4 hours; practolol, 10 hours). The doses of practolol and propranolol were chosen so as to have equal β₁-blocking activity (defined as having equal effects on exercise-induced tachycardia) from Brick et al. Also, these doses would theoretically be predicted to produce equal β₂-blockade. After

---

**Figure 3.** Change in heart rate in response to intracoronary salbutamol in the six patients in group 2 who received practolol 8 mg i.v. before salbutamol administration. Each symbol represents responses of an individual patient. Mean dose to increase heart rate by 30 beats/min was 2.1 μg. H.R., heart rate; b.p.m., beats per minute.

**Figure 4.** Change in heart rate in response to intracoronary salbutamol in the six patients in group 2 who received propranolol 4 mg i.v. before salbutamol administration. Each symbol represents responses of an individual patient. Mean dose to increase heart rate by 30 beats/min was 64 μg. H.R., heart rate; b.p.m., beats per minute.
administration of practolol 8 mg i.v., estimated plasma levels of practolol would be 1.1 μM. Assuming 5% protein binding and an equilibrium dissociation constant ($K_B$) for $\beta_1$-receptors of 0.25 μM, a plasma level of 1.1 μM practolol would produce a log dose ratio of 0.71 for $\beta_1$-receptor-mediated effects. After administration of propranolol 4 mg i.v., estimated plasma levels of propranolol would be 0.12 μM. Assuming 90% protein binding and a $K_B$ for $\beta_1$-receptors of 2.5 nM, a plasma level of 0.12 μM propranolol would produce a log dose ratio of 0.78 for $\beta_1$-receptor-mediated effects.

Prior administration of $\beta_1$-selective practolol produced no significant blockade of the effects of intracoronary salbutamol compared with group 1 controls, but the power of this comparison is limited by the fact that the controls were historical, that is, the patients were from the initial study. Whether there was a small $\beta_1$ component in the salbutamol-induced tachycardia was not important, however, provided we could show a difference between the practolol- and propranolol-treated patients. Compared with practolol, propranolol increased by 30 beats/min have been determined for each individual from linear interpolation of each curve. Curves for the six group 1 patients, the six group 2 patients after practolol (prac), and the six group 2 patients after propranolol (prop) are shown. Points are mean values for each group; bars represent SEM. The mean doses to increase heart rate by 30 beats/min for propranolol and practolol groups are significantly different (p<0.001). H.R., heart rate; b.p.m., beats per minute.

What effect might prior drug treatment have had on the responses to intracoronary salbutamol? The three groups were well matched in terms of prior therapy. All $\beta$-blockers were discontinued as soon as practicable before the study but not long enough to expect plasma levels to fall to zero. After 28 hours, plasma levels of atenolol fall to <280 nM, a level that produces a <10% fall in exercise tachycardia. After 18 hours, plasma levels of metoprolol fall to <18 nM, a level that produces a <5% fall in exercise tachycardia. Therefore, residual $\beta_1$-blockade was at a low level in all subjects and was well-balanced between the groups.

Prior chronic $\beta$-blockade may have produced sensitization of these patients to $\beta_2$-adrenoceptor stimulation. We have recently demonstrated that human atrial tissue from patients previously treated with atenolol is more responsive in vitro to $\beta_2$-adrenoceptor stimulation. In this context it is interesting to note that the one patient in the propranolol group who had not been pretreated with $\beta$-blockers was the least sensitive in that group to the effects of intracoronary salbutamol.

Could the underlying diseases in this group of patients have modified their responses to salbutamol? All had ischemic heart disease, but only two had mild left ventricular dysfunction (i.e., ejection fraction of 40–50%), and modification of $\beta$-adrenoceptor density or sensitivity has only been demonstrated in patients with more pronounced left ventricular failure.

Although we have demonstrated that $\beta_2$-adrenoceptor stimulation can produce a tachycardia, we have not shown such receptor stimulation to be physiologically relevant. The bolus doses of salbutamol produce unknown concentrations of sal-
butamol at the receptors on the sinoatrial node pacemaker cells. Studies of the highly β₂-selective antagonist IC118551 in normal volunteers suggest that β₂-adrenoceptor stimulation plays no part in exercise-induced tachycardia. However, the sensitivity of tissues to the effects of β-adrenoceptor stimulation may be modified in a variety of conditions. This makes it unwise to extrapolate uncritically to patients the results obtained in normal volunteers.

β₂-Adrenoceptor stimulation may not play a role in the mediation of exercise tachycardia in normal subjects but may play an important role in controlling heart rate in conditions where there are high circulating levels of adrenaline (the endogenous β₂-adrenoceptor agonist), such as myocardial infarction. Also, β₂-adrenoceptor stimulation may take on a relatively more important role either in patients treated with β-blockers or in patients with heart failure. Tissues from patients treated with β-blockers are more sensitive to adrenaline due to a selective sensitization of the tissues to β₂-adrenoceptor stimulation. Tissues from patients with heart failure show a pronounced desensitization to β₁-adrenoceptor stimulation, but β₂-adrenoceptor sensitivity is unaltered. It may be that control of heart rate and, thereby, myocardial oxygen consumption under these circumstances would be better achieved by use of nonselective β-blockade.

This study provides conclusive evidence that stimulation of cardiac β₂-adrenoceptors in man has positive chronotropic effects. The circumstances under which these receptors have a role in the control of heart rate and also whether β₂-adrenoceptor stimulation has other important effects on myocardial function have yet to be determined.

References


**KEY WORDS** • β<sub>2</sub>-adrenoceptors • human heart
Intracoronary injections of salbutamol demonstrate the presence of functional beta 2-adrenoceptors in the human heart.

J A Hall, M C Petch and M J Brown

Circ Res. 1989;65:546-553
doi: 10.1161/01.RES.65.3.546

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/65/3/546