COMPARATIVE PERIPHERAL AND CORONARY HAEMODYNAMIC EFFECTS OF Rimiterol AND ISOPRENALINE

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- 1 Rimiterol and isoprenaline produced significant dose-related increases in cardiac output.
- 2 These changes in cardiac output were accompanied by increases in heart rate and myocardial oxygen consumption which were similar for each drug and dose-related.
- 3 Isoprenaline in contrast with rimiterol produced direct coronary vasodilation, i.e. coronary vasodilation in excess of that required to meet increases in myocardial oxygen demands.
- 4 It is suggested that the β -adrenergic receptors in the human coronary vasculature are mainly of the β_1 type.
- 5 Rimiterol, because it does not produce direct coronary vasodilation may be preferable to isoprenaline in the treatment of low-cardiac output syndrome where there is regional myocardial ischaemia, since it would be less likely to produce a 'coronary steal' effect.

Introduction

Low cardiac output states are frequently encountered following acute myocardial infarction or open-heart surgery. Until recently therapy has been directed towards inotropic stimulation of the heart with digitalis or sympathomimetic agents such as isoprenaline. It is now generally recognized that such an approach may be ineffective or even deleterious. Salbutamol, a β_2 -adrenergic receptor agonist has been shown to improve left ventricular function in patients with acute low cardiac output syndromes (Lal, Savidge, Davies Ali & Soni, 1972; Yacoub & Boyland, 1973; Wyse, Gibson & Branthwaite, 1974) and chronic congestive cardiac failure (Sharma, Goodwin & Steiner, 1977). This agent has a relatively prolonged duration of action after intravenous administration which is a disadvantage in the management of acutely ill patients with cardiac failure.

Rimiterol hydrobromide ('Pulmadil', Riker Laboratories) a new β_2 -adrenergic receptor agonist has been shown to be more rapidly acting after intravenous administration than salbutamol and to possess a shorter plasma half-life, comparable to that of isoprenaline (Griffin, Williams & Maughan, 1973; Marlin & Turner, 1975). Its cardiovascular effects were therefore compared with those of isoprenaline.

Methods

Rimiterol study

Ten patients undergoing cardiac catheterization for suspected coronary artery disease were studied. All medication was discontinued 48 h before the procedure, except for the administration of diazepam 10 mg for premedication. Informed consent was obtained in all cases. Coronary arteriography was performed using the transfemoral Judkins technique. Following the diagnostic procedure a number 7 Desilets-Hoffman cannula was placed in the femoral artery, for systemic arterial blood pressure measurements, arterial blood sampling and cardiac output measurement. A Cournand F7 catheter was advanced to the main pulmonary artery from the right femoral vein. A Ganz coronary sinus thermodilution catheter was advanced to the coronary sinus from a left antecubital vein. Lead II of the electrocardiogram was recorded. Systemic, pulmonary artery and coronary sinus pressures were measured using Bell and Howell transducers. Coronary sinus flow, which has been shown to represent left ventricular myocardial blood flow (Hood, 1968) was determined using the continuous thermodilution technique of Ganz, Tamura, Marcus, Donoso,

Yoshida & Swan (1971). These authors showed close agreement between this and other methods of measuring myocardial blood flow. Cardiac output was measured by the indocyanine green dye-dilution technique, the dye being injected into the pulmonary artery and sampled from the femoral artery.

Arterial and coronary sinus oxygen contents were measured by the fuel-cell technique (Lex O₂ Con) which has been found to give results in close agreement with those obtained using the manometric technique of Van Slyke (Adams & Cole, 1975).

After at least 40 min had elapsed since the injection of contrast medium (a period which has been shown to be adequate for recovery from the effects of contrast medium (Mullins, Leshin, Mierzwiak, Alsobrook & Mitchell, 1972) control recordings of heart rate, systemic arterial, pulmonary arterial and coronary sinus pressures, cardiac output and coronary sinus flow were made. Simultaneous arterial and coronary sinus blood samples were obtained for oxygen content estimation. This procedure was repeated after 10 min infusions of placebo (5% dextrose) and rimiterol 0.1 $\mu\text{g kg}^{-1} \text{min}^{-1}$ using a Harvard pump. In some patients rimiterol was infused at 0.2 $\mu\text{g kg}^{-1} \text{min}^{-1}$

instead of, or in addition to the lower dose. The total volume of placebo infused corresponded to the volumes of subsequent rimiterol infusions.

Isoprenaline study

Five patients with suspected coronary artery disease were studied. The study was designed in such a way that isoprenaline was infused in doses which produced changes in cardiac output similar to those found with rimiterol, making it possible to compare equivalent effects on coronary haemodynamics. The procedure was similar to that of the rimiterol study except that cardiac output was measured by the thermodilution technique (Ganz & Swan, 1972). Each patient received a lower and a higher dose of isoprenaline. The doses given ranged from 0.005 $\mu\text{g kg}^{-1} \text{min}^{-1}$ to 0.05 $\mu\text{g kg}^{-1} \text{min}^{-1}$ (Table 4).

Calculations

Mean systemic arterial pressure ($\overline{\text{BP}}$) and mean coronary sinus pressure ($\overline{\text{CSP}}$) were obtained by

Table 1 Angiographic data—Rimiterol group

Patient	Age (years)/Sex	Coronary arteriogram	Patient	Age (years)/Sex	Coronary arteriogram
R.F.	52 M	Totally occluded LAD and RCA	A.H.	57 M	Normal coronaries
H.W.	63 M	90% Stenosis CX	P.C.	62 M	Totally occluded LAD
J.H.	63 M	Normal coronaries	C.S.	58 M	Reduced EF
		Reduced EF			Dilated left ventricular cavity
		LAD—90% Stenosis			
		CX } Totally occluded			
		RCA }			
L.D.	50 M	Normal coronaries	J.P.	54 F	Normal coronaries
J.B.	50 M	LAD	A.S.	48 M	Normal coronaries
		CX } 90% Stenosis			
		RCA }			

LAD=Left anterior descending branch; CX=Circumflex branch; EF=Left ventricular ejection fraction; RCA=Right coronary artery.

Table 2 Angiographic data—Isoprenaline group

Patient	Age (years)/Sex	Coronary arteriogram
S.G.	43 M	50% Stenosis LAD
		>75% Stenosis CX
W.Z.	58 M	>50% Stenosis LAD
M.S.	41 M	Normal coronaries
J.R.	37 M	Normal coronaries
R.T.	50 M	Totally occluded LAD
		>75% Stenosis CX
		>75% Stenosis RCA

LAD=Left anterior descending branch
CX=Circumflex branch
RCA=Right coronary artery

} Left coronary artery

electronic integration of the phasic pressures. For convenience, changes in left ventricular filling pressure were taken to be represented by changes in pulmonary arterial end diastolic pressure (Bouchard, Gault & Ross, 1971; Mantle, Russell, Moraski & Rackley, 1976; Bussman, Löhner & Kaltenbach, 1977).

Cardiac index (CI) ($\text{l min}^{-1} \text{m}^{-2}$) = cardiac output (CO)/body surface area. Stroke volume index (ml m^{-2}) = stroke volume/body surface area. Systemic vascular resistance (dyn s cm^{-5}) = $(\bar{\text{BP}} - \text{CSP})/\text{CO} \times 80$. Coronary vascular resistance (dyn s cm^{-5}) = $\bar{\text{BP}} - \text{CSP}/\text{CSF} \times 80,000$, where CSF = coronary sinus flow in ml min^{-1} .

Myocardial oxygen consumption (ml min^{-1}) = $\text{CSF} \times \text{A-V O}_2$ difference where A-V O_2 difference, $\text{ml}/100 \text{ ml}$ = coronary arteriovenous oxygen content difference.

Myocardial oxygen extraction (%) = A-V O_2 difference/arterial O_2 content $\times 100$.

Statistical analysis was by Student's *t*-test.

Results

No patient complained of symptoms related to either drug. In particular no patient experienced angina. Neither drug produced ventricular premature beats.

Of the nine patients in whom coronary arteriography was performed, four had significant coronary arterial stenoses while five had normal coronary arteries. Left ventricular cineangiography showed a reduction in ejection fraction in two patients. The ejection fraction was normal in the remaining eight patients.

Three patients had coronary artery stenoses while two had normal coronary arteries. Left ventricular ejection fraction was normal in all patients (Tables 1 and 2).

Rimiterol study (Table 3)

There was a dose-related increase in mean cardiac index (25% and 43%). This was associated with corresponding falls in systemic vascular resistance with no change in mean arterial pressure. Mean stroke volume index increased significantly for the lower dose (15%) but this increase was not further augmented by the higher dose. The increase in cardiac index observed with the higher dose was largely therefore a result of an increased heart rate which was small for the lower dose (mean increase of 5 beats/min) but substantial for the higher dose (mean increase of 20 beats/min).

There was a dose-related increase in mean coronary sinus flow (26% and 38%) with corresponding falls in coronary vascular resistance. There was no significant change in mean myocardial oxygen extraction. There was a dose-related increase in myocardial oxygen consumption (mean 17% and 38%). Left ventricular

Figure 1 Relation between changes in cardiac index (ΔCI) and heart rate (ΔHR) for rimiterol (●) and isoprenaline (○).

filling pressure was unchanged by the lower dose but was increased by the higher dose.

Isoprenaline study (Table 4)

Changes in cardiac index were similar to those observed for rimiterol (mean 15% and 44% for the lower and higher doses respectively). Changes in heart rate and myocardial oxygen consumption accompanying increases in cardiac index were not significantly different from those found with rimiterol (Figures 1 and 2). There was no significant change in mean arterial pressure. Systemic vascular resistance fell in association with increased cardiac output. There was a dose-related increase in stroke volume index. Unlike rimiterol, the greater response in stroke volume

Figure 2 Relation between changes in cardiac index (ΔCI) and myocardial oxygen consumption (ΔMVO_2) for rimiterol (●) and isoprenaline (○).

Table 3 Haemodynamic effects of rimiterol

Patient	HR			$\overline{BP}$			PADP			CI			CSF					
	C	P	R ₁	R ₂	C	P	R ₁	R ₂	C	P	R ₁	R ₂	C	P	R ₁	R ₂		
R.F.	90	88	100	—	103	101	101	—	28	24	30	—	3.8	3.5	5.4	171	—	
H.W.	58	61	65	—	92	93	89	—	9	10	12	—	2.9	2.6	3.7	81	—	
J.H.	86	82	86	94	70	76	76	76	30	28	30	35	2.4	2.2	2.3	222	225	
L.D.	78	75	81	90	97	100	97	90	12	13	12	16	2.7	2.8	3.9	170	215	
A.S.	70	75	—	110	92	93	—	97	10	10	—	9	3.0	4.4	—	71	80	
J.B.	52	52	57	70	76	85	89	84	12	12	12	20	3.1	3.1	3.4	92	113	
A.H.	90	90	—	113	118	120	—	125	10	10	—	11	2.2	2.5	—	—	—	
P.C.	92	86	94	—	104	99	103	—	10	10	8	—	2.6	2.5	3.0	106	—	
C.S.	62	65	65	—	77	77	77	—	18	16	15	—	—	—	—	183	—	
J.P.	70	72	90	—	117	100	98	—	8	8	8	—	2.7	2.2	3.0	75	101	
Mean	75	75	80	95	94	94	91	94	15	14	16	18	2.8	2.8	3.5	110	146	
±s.e. mean	4.4	3.8	5.6	7.6	5.4	4.1	3.5	8.5	2.5	2.2	3.2	4.5	0.1	0.2	0.3	15	20	
P	NS			<0.0125			<0.01			NS			<0.0125			NS		
Patient	MVO ₂			O ₂ Ext			SVI			SVR			CVR (×10 ⁻³)					
	C	P	R ₁	R ₂	C	P	R ₁	R ₂	C	P	R ₁	R ₂	C	P	R ₁	R ₂		
R.F.	16.9	16.3	19.8	—	64	64	64	—	40	42	54	—	1120	1193	710	54	44	
H.W.	6.9	6.7	8.1	—	63	63	63	—	50	43	57	—	1480	1618	1062	99	80	
J.H.	17.0	19.0	22.0	23.0	69	69	68	69	30	27	27	27	1175	1458	1346	29	31	
L.D.	20.3	19.4	24.1	27.6	62	63	61	69	35	37	48	49	1517	1504	1031	20	24	
A.S.	9.2	8.4	—	8.9	65	63	—	59	42	58	—	54	1055	782	615	45	33	
J.B.	8.5	8.8	10.6	12.4	69	66	66	64	60	60	60	60	975	970	1088	615	93	
A.H.	—	—	—	—	—	—	—	—	24	27	—	29	989	885	—	894	71	
P.C.	15.0	12.5	13.2	—	66	64	62	—	28	29	32	—	1859	1835	1569	712	—	
C.S.	16.2	11.9	18.7	—	63	61	55	—	—	—	—	—	—	—	—	72	75	
J.P.	7.5	7.9	9.4	—	70	71	63	—	39	31	33	—	2260	2354	1694	40	32	
Mean	13.0	12.9	15.7	18.0	66	65	63	65	39	39	44	43	1381	1400	1214	124	74	
±s.e. mean	1.7	1.7	2.1	4.5	1.0	1.1	1.4	2.4	3.7	4.3	4.9	6.2	147	168	129	70	54	
P	NS			<0.01			<0.05			NS			<0.05			NS		
P	NS			<0.01			<0.05			NS			<0.05			<0.05		

HR = heart rate (beats min⁻¹); BP = mean arterial pressure (mmHg); PADP = pulmonary artery end-diastolic pressure (mmHg); CI = cardiac index (l min⁻¹ m⁻²); CSF = coronary sinus flow (ml min⁻¹); MVO₂ = myocardial oxygen consumption (ml min⁻¹); O₂Ext = myocardial oxygen extraction (%); SVI = stroke volume index (ml m⁻²); SVR = systemic vascular resistance (dyn-s cm⁻⁵); CVR = coronary vascular resistance (dyn-s cm⁻⁵); R₁ = rimiterol 0.1 µg kg⁻¹ min⁻¹; R₂ = rimiterol 0.2 µg kg⁻¹ min⁻¹.

Table 4 Haemodynamic effects of isoprenaline

Patient	HR			BP			PADP			CI			CSF			Isoprenaline doses ($\mu\text{g kg}^{-1} \text{ min}^{-1}$)
	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	
S.G.	90	95	115	100	90	80	16	16	16	3.8	4.1	5.4	173	235	262	<i>I</i> ₁ = 0.006 <i>I</i> ₂ = 0.008
W.Z.	55	60	65	90	90	96	10	10	8	2.3	2.7	3.5	126	158	198	<i>I</i> ₁ = 0.007 <i>I</i> ₂ = 0.014
M.S.	73	81	102	80	80	80	12	12	12	4.3	5.8	7.4	166	278	380	<i>I</i> ₁ = 0.025 <i>I</i> ₂ = 0.05
J.R.	70	78	86	100	100	100	13	13	10	4.1	4.5	5.5	204	228	322	<i>I</i> ₁ = 0.005 <i>I</i> ₂ = 0.01
R.T.	70	77	94	95	98	100	7	7	8	2.3	2.5	2.9	156	200	222	<i>I</i> ₁ = 0.007 <i>I</i> ₂ = 0.014
Mean	72	78	92	93	92	91	12	12	11	3.4	3.9	4.9	165	219	277	
±s.e. mean	5.6	5.6	8.3	3.7	3.5	4.6	1.5	1.5	1.5	0.4	0.6	0.8	12.6	19.8	33.2	
<i>P</i>	<0.0005 <0.0025			NS NS			NS NS			<0.05 <0.01			<0.01 <0.005			
Patient	MVO ₂			O ₂ Ext			SVI			SVR			CVR ($\times 10^{-3}$)			Isoprenaline doses ($\mu\text{g kg}^{-1} \text{ min}^{-1}$)
	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	<i>C</i>	<i>I</i> ₁	<i>I</i> ₂	
S.G.	20.2	24.0	25.2	62	55	51	42	44	47	966	791	546	43	28	23	<i>I</i> ₁ = 0.006 <i>I</i> ₂ = 0.008
W.Z.	15.9	19.1	20.8	74	68	60	42	45	54	1678	1467	1130	55	45	36	<i>I</i> ₁ = 0.007 <i>I</i> ₂ = 0.014
M.S.	25.1	33.4	38.4	72	53	49	59	72	72	633	465	368	35	22	35	<i>I</i> ₁ = 0.025 <i>I</i> ₂ = 0.05
J.R.	20.6	22.3	34.4	51	49	51	60	58	64	855	808	661	46	42	29	<i>I</i> ₁ = 0.005 <i>I</i> ₂ = 0.01
R.T.	17.2	22.0	25.5	70	70	68	33	32	31	1771	1634	1452	48	38	35	<i>I</i> ₁ = 0.007 <i>I</i> ₂ = 0.014
Mean	19.8	24.2	28.9	66	59	56	47	50	54	1181	1033	831	45	35	28	
±s.e. mean	1.6	2.4	3.2	4.2	4.2	3.6	5.3	6.8	7.1	229	221	200	3.3	4.3	3.8	
<i>P</i>	<0.01 <0.005			<0.05 <0.05			NS <0.05			<0.0025 <0.0025			<0.0025 <0.0025			<0.0005

Abbreviations are the same as those used in Table 3.

Figure 3 Relation between changes in cardiac index (ΔCI) and coronary sinus flow (ΔCSF) for rimiterol (●) and isoprenaline (○).

index occurred at the higher dose levels. Left ventricular filling pressure did not change significantly. Compared with rimiterol, isoprenaline produced greater increases in coronary sinus flow ($P < 0.05$, Figure 3) associated with a significant fall in mean myocardial oxygen extraction (Figure 4).

Discussion

Isoprenaline is a potent β_1 and β_2 adrenergic receptor agonist which has been used extensively in the treatment of post myocardial infarction and post cardiac surgery, low cardiac output syndromes. Its ability to produce haemodynamic improvement in these situations has however been questioned (Gunnar, Loeb, Pietras & Tobin, 1967).

Furthermore, considerable evidence has accumulated concerning its deleterious effects which include myocardial necrosis (Magnusson & Hansson, 1973) and extension of myocardial ischaemic injury (Maroko & Braunwald, 1973; Puri, 1974) following coronary occlusion. A 'coronary steal' syndrome has been postulated by which dilatation by isoprenaline of normal vessels in parallel with diseased vessels, causes a re-distribution of blood flow from ischaemic to normal myocardium thereby increasing the size of the infarcted zone (Sharma, Kumar, Molokhien & Messer, 1971).

Figure 4 Comparative changes in myocardial oxygen extraction (O_2 extr.%) for rimiterol (▨) and isoprenaline (■).

There is some evidence that β_2 -adrenergic receptor agonists may not possess these properties with respect to the ischaemic myocardium. It has been shown that salbutamol is significantly less likely to produce myocardial necrosis in rats than is isoprenaline (Magnusson & Hansson, 1973). Further, when compared with isoprenaline, salbutamol produces only a minor degree of coronary vasodilation in the dog (Ross, 1974) suggesting that its potential for producing 'coronary steal' is minimal.

The mechanisms by which β_2 -adrenergic receptor agonists increase cardiac output are complex. It is probable that their primary effect is to reduce peripheral arterial tone and hence left ventricular afterload. This would increase left ventricular ejection fraction and stroke volume (Cohn, 1973). Further, arterial vasodilation without venodilation may increase venous return to the left ventricle. The consequent increase in left ventricular end-diastolic volume could cause an indirect augmentation of left ventricular contractility by the Frank-Starling mechanism. At higher doses reflex baroreceptor activity may induce an increase in heart rate which becomes an important mechanism in increasing cardiac output to maintain arterial pressure in the face of a falling peripheral vascular resistance. It is possible that there may be a degree of direct inotropism. Changes in heart rate (Sarnoff, Braunwald, Welch, Carse, Stainsby & Macruez, 1958), left ventricular wall tension and contractility (Graham, Covell, Sonnenblick, Ross & Braunwald, 1968) would act to increase myocardial oxygen consumption.

The results of this study are consistent with this hypothesis. Rimiterol increased cardiac output as a result of increased stroke volume for the lower dose. At the higher dose cardiac output was increased largely by a rise in heart rate. Left ventricular pressure increased for the higher dose suggesting an

increase in left ventricular end-diastolic volume. These haemodynamic changes occurred at the expense of a rise in myocardial oxygen consumption. Although the mechanisms involved are probably different, rimeterol and isoprenaline were similar in their effect upon myocardial oxygen consumption. Presumably the β_1 -adrenergic effects of isoprenaline (heart rate increase and inotropic effect) were the important determinants of myocardial oxygen consumption for this drug.

Although, in this study, both drugs were similar with respect to their net haemodynamic effects they differed in one important respect; that is in their effects on the coronary vasculature. The increases in coronary sinus flow observed with rimeterol were associated with only minor changes in myocardial oxygen extraction. This suggests that flow largely increased in response to increased myocardial oxygen demand (autoregulatory coronary vasodilation (Berne, 1964)) rather than as a result of a direct coronary vasodilator effect. In contrast isoprenaline produced greater increases in coronary sinus flow than rimeterol which were associated with a significant decrease in myocardial oxygen extraction. It appears therefore that isoprenaline has a significant direct coronary vasodilator action, increasing myocardial blood flow in excess of that required to meet increased myocardial oxygen demands. These findings lend support to the findings in animals with regard to the relative effects of β_2 -adrenergic receptor agonists and isoprenaline on the coronary vasculature discussed above.

The reason for the failure of rimeterol to produce direct coronary vasodilation is unclear, since such an effect would be expected if the coronary vasculature in man, as in the dog (Bussmann, Rauh & Krayenbuehl, 1970) possesses β -adrenergic receptors (β_2) distinct from those of the myocardium (β_1). Given that both drugs possess similar potency with regard to β_2 -adrenergic receptor stimulation, a possible explanation is that the coronary β receptors in man are of the β_1

type, and that β_2 -receptors, if present, play only a minor role in the regulation of coronary flow.

Clinical implications

In this study rimeterol was as effective as isoprenaline in increasing cardiac output. Since it does not possess significant direct coronary vasodilating properties it may provide a useful alternative to isoprenaline in the management of patients with left ventricular failure particularly in the presence of regional myocardial ischaemia where a 'coronary steal' effect may be harmful.

Since in the conditions of this study, it does not cause arterial hypotension its use in low-cardiac output states may be preferable to that of vasodilating agents such as sodium nitroprusside which cannot be used in the presence of severe hypotension for fear of further compromising coronary arterial perfusion pressure. Although rimeterol produces an increase in myocardial oxygen consumption, other currently used inotropic drugs such as dopamine and dobutamine also have this effect (Vatner, McRitchie, Maroko, 1974). Since afterload reduction is probably more important than inotropic stimulation in left ventricular failure, rimeterol may be the more effective agent in its treatment. These arguments require further clinical evaluation.

The apparent absence of β_2 -adrenergic receptors in the coronary vasculature raises the question of the relevance of cardioselective versus non-cardioselective β -adrenergic receptor blocking drugs in the treatment of angina pectoris, with regard to the coronary circulation. If, as has been proposed, β -adrenergic blocking drugs produce coronary vasoconstriction by exposing the coronary vasculature to unopposed α -adrenergic receptor stimulation, the use of either type of drug would be immaterial since both would have the same effects in this regard.

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