β_2 Adrenergic receptors mediate important electrophysiological effects in human ventricular myocardium

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Abstract

Objective—To define the effects of β_2 adrenergic receptor stimulation on ventricular repolarisation in vivo.

Design—Prospective study.

Setting—Tertiary referral centre.

Patients—85 patients with coronary artery disease and 22 normal controls.

Interventions—Intravenous and intracoronary salbutamol (a β_2 adrenergic receptor selective agonist; 10–30 $\mu\text{g}/\text{min}$ and 1–10 $\mu\text{g}/\text{min}$), and intravenous isoprenaline (a mixed β_1/β_2 adrenergic receptor agonist; 1–5 $\mu\text{g}/\text{min}$), infused during fixed atrial pacing.

Main outcome measures—QT intervals, QT dispersion, monophasic action potential duration.

Results—In patients with coronary artery disease, salbutamol decreased QT_{onset} and QT_{peak} but increased QT_{end} duration; $\text{QT}_{\text{onset}}-\text{QT}_{\text{peak}}$ and $\text{QT}_{\text{peak}}-\text{QT}_{\text{end}}$ intervals increased, resulting in T wave prolongation (mean (SEM): 201 (2) ms to 233 (2) ms; $p < 0.01$). There was a large increase in dispersion of QT_{onset} , QT_{peak} , and QT_{end} which was more pronounced in patients with coronary artery disease—for example, QT_{end} dispersion: 50 (2) ms baseline *v* 98 (4) ms salbutamol (controls), and 70 (1) ms baseline *v* 108 (3) ms salbutamol (coronary artery disease); $p < 0.001$. Similar responses were obtained with isoprenaline. Monophasic action potential duration at 90% repolarisation shortened during intracoronary infusion of salbutamol, from 278 (4.1) ms to 257 (3.8) ms ($p < 0.05$).

Conclusions— β_2 adrenergic receptors mediate important electrophysiological effects in human ventricular myocardium. The increase in dispersion of repolarisation provides a mechanism whereby catecholamines acting through this receptor subtype may trigger ventricular arrhythmias.

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Keywords: β_2 adrenergic receptors; ventricular repolarisation; QT dispersion; salbutamol; isoprenaline

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Catecholamines acting predominantly through β adrenergic receptors have a widespread influence on cardiac function,¹ modulating both contraction and relaxation, and promoting arrhythmogenesis.² Historically, cardiac β adrenergic receptor responses were thought to be mediated exclusively through β_1 receptors, which promoted the development of selective β_1 receptor antagonists to reduce the extracardiac side effects of β_2 receptor blockade. More recently, however, this perspective has changed with the demonstration from binding studies that β_2 adrenergic receptors constitute 20–40% of the total number of β receptors in human heart,³ and that in the atrium β_2 receptors mediate increases in atrial contractility⁴ and sinoatrial activity.⁵ Ventricular responses are less well defined, but stimulation of β_2 receptors in vitro has been shown to be increase cardiac contractility,^{6–8} and β_2 receptor agonists mediate positive inotropic effects in vivo.^{9–10}

Characterisation of the electrophysiological responses to ventricular β_2 adrenergic receptor stimulation is required to define the role of cardiac β_2 receptors more fully under physiological and pathological conditions, and to refine the use of β_2 receptor antagonists in clinical practice. In vitro studies have shown model dependent changes with, for example, action

potential lengthening in single cells,¹¹ in contrast to the shortening seen in whole heart preparations.¹² In human isolated atrial tissue, β_2 as well as β_1 adrenergic receptors mediate arrhythmic contractions,¹³ but β_2 receptor responses in ventricle have not been characterised in view of the practical difficulties in obtaining ventricular tissue for study.

Our aim in this study was to define the electrophysiological responses to β_2 adrenergic receptor stimulation in the human ventricle. Surface electrocardiographic indices of cardiac depolarisation and repolarisation have been analysed, and the effects of β_2 adrenergic receptor stimulation on the patterns of dispersion of repolarisation assessed, using previously described ECG parameters.¹⁴ β_2 Adrenergic receptor responses were determined following administration of the selective β_2 receptor agonist salbutamol,^{15–16} and compared with responses with isoprenaline (isoproterenol), an agonist widely used clinically and active at both β_1 and β_2 receptors.⁷ The repolarisation responses to β_2 receptor stimulation were confirmed directly by endocardial monophasic action potential recordings. In order to account for the systemic haemodynamic effects of β receptor agonists, the responses to the predominantly arteriolar vasodilator hydralazine

Table 1 Characteristics of the patients enrolled

	Controls (n=22, 16 men)	CAD patients (n=85, 57 men)
Age (years) (mean (SEM))	54.8 (3.0)	59.7 (1.1)
CCS score		
0, 1	15	23
2, 3	7	62
Coronary disease		
1 vessel	0	35
2 vessel	0	24
3 vessel	0	26
Drug treatment		
β_1 AR antagonist	8	18
Calcium antagonist	10	43
Nitrates	5	35
Hypolipidaemics	4	23
Aspirin	18	75
Others	7	18

Values are numbers of patients unless stated otherwise.

AR, adrenergic receptor; CCS, Canadian Cardiovascular Society.

and the predominantly venous dilator isosorbide dinitrate were also assessed in independent interventions. The possible confounding effect of a β_2 receptor mediated fall in serum potassium was also addressed.

Methods

STUDY GROUP

Eighty five patients with coronary artery disease and 22 controls with normal coronary arteries were selected following routine coronary angiography (table 1). Significant coronary artery disease was defined as at least one coronary stenosis of $\geq 70\%$, assessed angiographically. All patients had normal (ejection fraction $> 50\%$) or mildly impaired left ventricular function (ejection fraction 40–50%), as assessed by planimetry, and were in New York Heart Association functional class I/II. Patients gave written informed consent before participating in the study, and approval was obtained from the local research ethics committee (Huntingdon Health Authority).

INFUSION PROTOCOLS

In each patient a 6 French bipolar pacing electrode (Bard UCSI, Billerica, Massachusetts, USA) was positioned in the right atrial

appendage under fluoroscopic guidance. Salbutamol (Allen and Hanbury's, Uxbridge, UK), 10–30 $\mu\text{g}/\text{min}$, and isoprenaline (Pharmax, Bexley, UK), 1–5 $\mu\text{g}/\text{min}$, were infused separately in each patient through the side arm of an introducer sheath into the right femoral vein. A dose-response curve for salbutamol and isoprenaline was obtained initially in each patient to establish individual heart rate responses to each agent (fig 1). To limit possible confounding effects from ischaemia, the heart rate was then maintained with atrial pacing (basic cycle length 500–600 ms) just above the intrinsic rate developed during the initial β adrenergic receptor agonist infusion, and simultaneous 12 lead ECG recordings at a paper speed of 50 mm/s and calibration 2 cm/mV were obtained during steady state at each incremental dose of either drug. A period of 10 minutes was allowed for stabilisation at each dose of salbutamol and isoprenaline, and 30 minutes between each infusion of β receptor agonist; salbutamol and isoprenaline were infused in random order in each patient. Haemodynamic monitoring was undertaken throughout each infusion, and serum electrolytes were sampled at each infusion rate. In 11 patients high dose salbutamol was infused from the outset (30 $\mu\text{g}/\text{min}$) with serial ECG recordings and serum potassium measurements performed at five minute intervals.

The effects of intravenous infusion with hydralazine (Ciba, Horsham, UK), 100–300 $\mu\text{g}/\text{min}$, and isosorbide dinitrate (Schwartz Pharma, Chesham, UK), 200–600 $\mu\text{g}/\text{min}$, on haemodynamic and ECG variables were each assessed in a further 10 patients during identical atrial pacing protocols.

HAEMODYNAMIC MONITORING

Intra-arterial pressure was monitored continuously in all patients. In addition, pulmonary capillary wedge pressure, pulmonary artery pressure, and right atrial pressure responses to salbutamol were obtained in a representative sample of 11 patients.

ECG MEASUREMENTS

Three QT parameters were measured: QT_{onset} , the time from the start of the QRS complex to the beginning of the T wave; QT_{peak} , the time from the start of the QRS complex to the peak of the T wave; and QT_{end} , the time from the start of the QRS complex to the end of the T wave. The end of the T wave was defined as the point of return to the TP baseline. If the T wave was interrupted by a U wave before the return to baseline, the interval was measured as the nadir between T and U waves. The QRS interval was measured to determine the JT interval for each cycle. Each ECG parameter was measured manually on three consecutive complexes and the average value determined for each lead. Mean overall QT intervals were calculated using all leads suitable ($n \geq 10$) for T wave measurements. The dispersion of repolarisation parameters (maximum minus minimum duration) was calculated using a standard method.¹⁷

Figure 1 Experimental protocols for infusion schedules, ECG, and monophasic action potential (mAP) data collection. See text for details. HR, heart rate; ISDN, isosorbide dinitrate.

Figure 2 Blood pressure responses following (A) intravenous salbutamol (0–30 µg/min) and (B) intravenous isoprenaline (0–5 µg/min). Systolic, diastolic, and mean blood pressure responses are shown.

MEASUREMENT OF MONOPHASIC ACTION POTENTIAL DURATION

Selected patients with a dominant right coronary artery with no significant stenoses (> 70%) along its course, underwent direct measurement of monophasic action potential duration (mAPD). A steerable 7 French mAPD catheter (EP technology, Mountain View, California, USA) was positioned against the endocardium of the right ventricular free wall, and a 6 French bipolar pacing electrode (Bard USCI) positioned in the right atrial appendage, under fluoroscopic guidance. mAPDs were amplified and filtered at a frequency of 0.05–500 Hz, and recorded on a chart recorder at a paper speed of 100 mm/s.

Figure 3 Typical ECG recordings obtained during fixed atrial pacing at baseline (left) and with intravenous salbutamol (30 µg/min) (right). QT_{end} interval for each ECG complex indicated by broken lines.

mAPDs were obtained in 12 patients during continuous haemodynamic monitoring. After a test dose of normal saline, salbutamol (1–10 µg) was infused into the right coronary artery, following a previously reported protocol,¹⁵ until the heart rate increased by (mean (SEM)) 30 (3) beats/min. The heart rate was fixed with atrial pacing with a basic cycle length 500–600 ms and mAPDs were recorded during repeat salbutamol infusion (fig 1). mAPD at 90% repolarisation (mAPD₉₀) was calculated using a standard method.¹⁸

STATISTICS

All measurements are given as mean (SEM) unless stated otherwise. QT and mAPD variables were compared between patients using analysis of variance, and a probability value of $p < 0.05$ was considered significant. The intra- and interobserver error on a selection of ECGs was calculated.

Results

HAEMODYNAMIC RESPONSE

Heart rate increased to a maximum of 25.7 (1.3) and 29.7 (1.7) beats/min during the preliminary dose-response determinations with salbutamol and isoprenaline, respectively. Both drugs increased systolic and lowered diastolic blood pressure (fig 2). Mean blood pressure fell slightly (–10.1 (2.1) mm Hg with salbutamol, –7.4 (1.9) mm Hg with isoprenaline). There were no significant changes in pulmonary capillary wedge pressure, mean pulmonary artery pressure, or mean right atrial pressure during salbutamol infusion.

Figure 4 Changes in mean QT_{end} , QT_{peak} and QT_{onset} during salbutamol infusion (0–30 µg/min) (left panel) and isoprenaline infusion (0–5 µg/min) (right panel). Responses have been separated for patients with coronary artery disease (CAD) and controls, and those taking (broken lines) and not taking (unbroken lines) atenolol. There is a dose dependent decrease in QT_{onset} and QT_{peak} but an increase in QT_{end} in coronary artery disease patients.

PRIMARY ECG VARIABLES

QT_{onset} and QT_{peak} decreased in the controls and the coronary artery disease patients during both salbutamol and isoprenaline infusion at fixed pacing rate (figs 3 and 4). QT_{end} increased in coronary artery disease patients but decreased in controls. The QT_{onset} – QT_{peak} and QT_{peak} – QT_{end} intervals increased; the greater increase in QT_{peak} – QT_{end} was largely responsible for the increased T wave duration seen. There was no significant change in QRS duration during infusion with either salbutamol or isoprenaline; hence the changes in JT_{onset} , JT_{peak} and JT_{end} were similar (data not shown). The intra- and interobserver error in the measurement of QT intervals on 10 randomly selected ECGs was 10 (2.6) ms and 12.5 (3.8) ms, respectively.

DERIVED ECG VARIABLES

Baseline QT dispersion was greater in coronary artery disease patients for each variable measured (coronary artery disease *v* controls: QT_{onset} , 85.2 ms *v* 68.5 ms; QT_{peak} , 80 ms *v* 48.5 ms; and QT_{end} , 70.3 ms *v* 49.4 ms; SEM < 5 ms for each variable; $p < 0.01$). All dispersion indices increased during infusion with

Figure 5 Changes in QT_{end} dispersion following (A) intravenous salbutamol and (B) intravenous isoprenaline. There are large increases in QT dispersion following both salbutamol and isoprenaline in coronary artery disease and control patients.

salbutamol and isoprenaline; in particular there was a large increase in QT_{end} dispersion in both controls and coronary artery disease patients (fig 5). The changes in QT intervals and dispersion parameters in the subset of patients who had initial high dose salbutamol infusion were similar to the above (for example, QT_{end} dispersion at baseline, 58.4 (4.3) ms; with salbutamol 30 µg/min, 104.3 (7.8) ms, $p < 0.001$) and occurred before any change in serum potassium (fig 6). In patients chronically treated with the β_1 adrenergic receptor selective antagonist atenolol, mean resting heart rate was lower, at 55 (2.4) beats/min. The haemodynamic and ECG responses to infused salbutamol were similar to those in patients not receiving atenolol (heart rate increase, 24.8

Figure 6 Changes in QT_{end} dispersion (QT_d) and serum potassium (K^+) during initial high dose intravenous infusion of salbutamol. There is a pronounced increase in QT_d before any significant decrease in serum potassium.

Figure 7 QT_{end} dispersion following (A) intravenous hydralazine (0–300 μg/min) and (B) intravenous isosorbide dinitrate (ISDN) (0–600 μg/min). There were no significant changes seen during infusion with either agent.

(3.2) beats/min; mean blood pressure reduction, 9.8 (2.8) mm Hg; QT_{end} dispersion peak, 105 (4.7) ms; all $p < 0.01$). In contrast, in atenolol treated patients isoprenaline responses were reduced (heart rate increase, 21.2 (4.3) beats/min; mean blood pressure reduction, 7.4 (2.7) mm Hg; QT_{end} dispersion peak, 98.3 (4.5) ms). Hydralazine and isosorbide dinitrate each increased heart rate (by 7.1 (2.2) and 5.4 (2.1) beats/min, respectively) and lowered mean blood pressure (by 7.8 (2.1) and 5.2 (1.4) mm Hg) during the preliminary dose-response study. At fixed heart rate with atrial pacing there was no significant change in QT interval and dispersion parameters during infusion with either drug (fig 7).

MONOPHASIC ACTION POTENTIAL DURATION

Monophasic action potential duration at 90% repolarisation during intracoronary infusion of salbutamol (mean dose 9.1 (1.2) μg) was significantly reduced ($mAPD_{90}$, 278 (4.1) ms to 257 (3.8) ms; $n = 12$; $p < 0.05$).

Discussion

Both salbutamol and isoprenaline caused significant, dose dependent changes in QT interval parameters, with increases in QT_{onset} , QT_{peak} , and QT_{end} dispersion. The results obtained with salbutamol support a direct effect on ventricular β_2 adrenergic receptors. Salbutamol, a selective β_2 agonist,^{4,5} would not be expected to stimulate β_1 adrenergic receptors under the conditions applied. An effect on presynaptic β_2 adrenergic receptors with potentiation of noradrenaline release and indirect stimulation of β_1 adrenergic receptors is also unlikely, as there was no blunting of the effects of salbutamol in patients taking the β_1 selective adrenergic receptor antagonist atenolol. Reflex changes in preload and afterload secondary to β_2 adrenergic receptor mediated vasodilatation are not likely to be contributory factors, as hydralazine and isosorbide dinitrate—agents that have their principal haemodynamic effects on arterial and venous vessels, respectively—had no significant effect on the dispersion indices assessed. Although a contribution from ischaemia to the effects seen with salbutamol and isoprenaline cannot be completely excluded, the pronounced increase in QT_{end} dispersion was seen both in controls and in coronary artery disease patients. The increase in QT dispersion seen with initial high dose salbutamol occurred before the onset of hypokalaemia, excluding this as a cause for the changes seen.

The decrease in $mAPD$ with intracoronary salbutamol was also consistent with the direct stimulation of ventricular β_2 adrenergic receptors. There were no significant changes in $mAPD$ with intracoronary saline, indicating the absence of an important volume effect, and no patient developed chest pain or ischaemic ECG changes during salbutamol infusion, consistent with at worst a small contribution from ischaemia to $mAPD_{90}$ shortening. Furthermore, the mean intracoronary dose of salbutamol used (9.1 μg) has previously been shown to produce no change in mean arterial

pressure, pulmonary capillary wedge pressure, cardiac output, or systemic vascular resistance when infused into the right coronary artery,³ thus excluding indirect effects mediated by vascular β_2 adrenergic receptors.

Systemic isoprenaline, a mixed β_1/β_2 agonist, produced similar changes to salbutamol in the ECG variables measured. The reduction in responses seen in atenolol treated patients is consistent with a β_1 adrenergic receptor component of the effect of isoprenaline. Previous studies with isoprenaline have shown either biphasic responses, with an initial lengthening and subsequent shortening of the QT_{end} interval (corrected for heart rate (QT_c))¹⁹ or a shortening in absolute QT_{end} interval and an increase in QT_c .²⁰ In addition, isoprenaline infusion has been shown to modulate T wave amplitude and polarity.^{19–20}

The QT_{end} interval represents the total duration of ventricular depolarisation and repolarisation. Accordingly, as there was no significant effect on QRS interval duration seen during either salbutamol or isoprenaline infusions, the observed changes in QT duration result entirely from altered repolarisation. To refine the analysis of repolarisation, the individual variables QT_{onset} and QT_{peak} were studied along with the $QT_{onset}-QT_{peak}$ and the $QT_{peak}-QT_{end}$ intervals, representing, respectively, the early and late contributions from the T wave. These analyses show that under β adrenergic receptor stimulation the total T wave duration increases, and that this is mainly secondary to an increase in the late T wave phase. These changes in T wave morphology are likely to reflect selective coupling of β adrenergic receptors to individual ion channels. Recent reports of specific T wave appearances corresponding to individual ion channel mutations in the long QT syndrome¹⁴ are consistent with such an observation.

Dispersion of the QT_{end} interval duration between ECG leads has been shown to reflect regional variation in ventricular repolarisation and an overall increase in repolarisation heterogeneity.^{17–21} In studies this has been correlated with arrhythmia risk,^{17–22} sudden cardiac death,²³ and total mortality,²⁴ but this has not been a universal finding.²⁵ The pronounced effects of salbutamol and isoprenaline on QT_{end} dispersion suggest that heterogeneity of repolarisation is strongly influenced by adrenergic stimulation.

RELATION TO VENTRICULAR ARRHYTHMIAS

Adrenergic stimulation is known to be important in the genesis of ventricular arrhythmias^{2–26} through the mechanisms of increased automaticity, induction of early afterdepolarisations, and a reduction in fibrillation threshold. Adrenergic activation also leads to a shortening of ventricular refractoriness both in dogs²⁷ and humans.²⁸ It is known that stimulation of cardiac sympathetic nerves leads to an increase in the dispersion of repolarisation and refractoriness,^{27–29} thereby enhancing the conditions for cardiac reentry.^{30–31} The individual contributions of β_1 and β_2 adrenergic receptors to these effects are not known, but the results seen here

provide a mechanism whereby circulating adrenaline, acting through β_2 receptors, may increase dispersion of repolarisation and contribute to the triggering of arrhythmias in susceptible patients. This mechanism may be especially important when circulating plasma concentrations of adrenaline are high—for example, around the time of myocardial infarction³² and during heart failure.³³ Indeed salbutamol is known to increase the incidence of ventricular arrhythmias in patients with heart failure,³⁴ and experimentally β_2 receptor antagonists have been shown to protect against ventricular fibrillation.³⁵

β BLOCKERS DECREASE RISK

The finding that β_2 adrenergic receptors mediate significant electrophysiological effects has implications for the use of β_1 receptor blocking drugs. While these drugs may reduce the unwanted peripheral side effects associated with β blocking treatment, they will not block electrophysiological responses mediated through β_2 receptors. This may explain the significant body of data suggesting that non-selective β blockers have a greater antiarrhythmic effect than β_1 selective blockers after acute myocardial infarction.³⁶ In heart failure patients, although β_1 receptor selective antagonists have been found to reduce mortality,³⁷ a recent meta-analysis has shown that this is greater for non-selective β blockers than for β_1 receptor selective antagonists.³⁸

LIMITATIONS OF THE STUDY

Although we used a β_2 adrenergic receptor selective agent—salbutamol—and showed no reduction in responses in β_1 receptor blocked patients, we cannot completely exclude effects mediated through β_1 receptors. There are no selective β_2 receptor antagonists available for use in vivo, and hence the selectivity of the responses to salbutamol could not be confirmed with β_2 receptor blockade. In addition extracardiac effects of salbutamol and isoprenaline may have contributed to the effects seen. However, reflex responses through arteriolar and venular dilatation alone would not account for the ECG changes seen (as demonstrated by the lack of effect seen with hydralazine and isosorbide dinitrate), and the reduction in $mAPD_{90}$ with intracoronary salbutamol could not be mediated through an alteration of central adrenergic tone. The paced heart rates during salbutamol and isoprenaline infusion were chosen to be as low as possible in order to avoid inducing ischaemia, and the changes in QT indices and dispersion seen occurred in both coronary artery disease and control patients, showing that ischaemia was not solely responsible for the changes found. A contributory effect of ischaemia during high dose catecholamine infusion cannot, however, be excluded.

CONCLUSIONS

This study shows the important electrophysiological responses mediated through β_2 adrenergic receptors in human ventricular myocardium, with in particular the pronounced effects

on temporal dispersion of cardiac repolarisation. This provides further insights into the mechanisms whereby sympathetic activity increases arrhythmia risk, and should help to rationalise the use of β blockers in clinical practice.

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