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Effects of A_1 adenosine receptor blockade by bamiphylline on ischaemic preconditioning during coronary angioplasty

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Objective The role of A_1 adenosine receptors in preconditioning in humans is unknown. To establish whether bamiphylline, a selective antagonist of A_1 adenosine receptors, abolishes ischaemic preconditioning in man, 36 consecutive patients undergoing single-vessel coronary angioplasty were randomized to receive intravenous infusion of bamiphylline (5 mg . kg^{-1}) or placebo (0·9% NaCl) immediately prior to the procedure.

Design The mean values (± 1 SD) of ST segment shifts on the surface and intracoronary electrocardiograms were measured at the end of the first and second balloon inflations, both 2 min long. The severity of cardiac pain was obtained at the same time using a visual analogue scale.

Results In bamiphylline-treated patients, the mean ST segment shift and the severity of cardiac pain during the second inflation were similar to those during the first inflation (14 ± 15 vs 16 ± 16 mm, ns and 31 ± 28 vs 31 ± 29, ns, respectively). Conversely, in placebo-treated patients both the mean ST segment shift and the severity of cardiac pain during the second inflation were significantly less than those during the first inflation (10 ± 6 vs 17 ± 7 mm, $P<0·001$ and 25 ± 21 vs 39 ± 31 mm, $P<0·01$, respectively). Thus, bamiphylline abolishes ischaemic preconditioning observed in man during repeated coronary balloon inflations.

Conclusion These results suggest that, in this setting, ischaemic preconditioning is mediated, at least in part, by A_1 adenosine receptors.
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Key Words: A_1 adenosine receptors, bamiphylline, coronary angioplasty, ischaemic preconditioning.

Introduction

The ability of brief periods of ischaemia to limit cell death following a subsequent sustained episode of ischaemia has been called preconditioning[1]. The phenomenon of ischaemic preconditioning has now been demonstrated in several animal species, including dogs[1–3], pigs[4], rabbits[5], and rats[6]. Deutsch *et al.*[7], Cribier *et al.*[8], and we[9] have shown that, during coronary angioplasty, the severity of myocardial ischaemia during the second balloon inflation is less than that during the first inflation, thus suggesting that ischaemic preconditioning may also occur in humans. Moreover, Yellon *et al.*[10] have recently confirmed ischaemic preconditioning in the human heart in the setting of coronary artery bypass surgery.

We have recently demonstrated that, in man, the ischaemic preconditioning observed during coronary angioplasty following repeated balloon inflations is abolished by pretreatment with glibenclamide, thus suggesting that the activation of ATP-sensitive K^+ channels plays an important role[11]. Several studies have shown, however, that preconditioning results from a complex series of events, involving not only ATP-sensitive K^+ channels[3,12–14] but also adenosine receptors[5,15–23], G-proteins[24] and α_1-adrenergic receptors[25]. In particular, numerous recent experimental studies have shown that activation of A_1 adenosine receptors mimics and their blockade abolishes ischaemic preconditioning[5,15–20].

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Thus, A_1 adenosine receptors might also play an important role in preconditioning in humans, as recently shown in isolated human muscle[26].

To establish in man the role played by A_1 adenosine receptors in preconditioning, we assessed the effect of bamiphylline, the most selective antagonist of A_1 receptors available for clinical use in Europe[27], in patients undergoing repeated coronary occlusions in the setting of elective angioplasty of an isolated coronary stenosis.

Methods

Study patients

We studied 36 consecutive patients undergoing uncomplicated elective coronary angioplasty with: (1) history of chronic stable angina pectoris lasting ≥ 3 months; (2) isolated obstructive lesion (internal diameter reduction >70% by visual assessment) in the proximal two-thirds of a major epicardial coronary artery; (3) no history of previous myocardial infarction; (4) no angiographic evidence of coronary collateral vessels (grade 0, according to Rentrop's classification)[28]. No patient had evidence of left ventricular hypertrophy on the echocardiogram or conduction defects on the electrocardiogram (ECG) that could have interfered with the interpretation of ST segment changes. All patients had normal hepatic and renal function, and fasting blood glucose levels. All patients gave written informed consent for participation in the study, which was approved by the Institutional Ethics Committee in April, 1993.

Study protocol

In this double-blind study, patients were randomly allocated to two groups. One group consisted of 18 patients (16 men, 2 women; mean [± SD] age 55 ± 10 years, range 34–71) who received an intravenous infusion of bamiphylline (5 mg . kg^{-1} in 20 min) (bamifyllini hydrochloridum 300 mg/5 ml dissolved in 20 ml of 0·9% NaCl; Christiaens SA, Brussels, Belgium) after introduction of the femoral sheath, immediately prior to coronary angioplasty. The other group consisted of 18 patients (16 men, 2 women; mean [± SD] age 52 ± 9 years, range 38–69) who received an intravenous infusion of placebo (20 ml of 0·9% NaCl in 20 min) after introduction of the femoral sheath, immediately prior to coronary angioplasty. As the half-life of intravenous bamiphylline is of approximately 2 h[29], effective plasma levels of the drug were obtained during both balloon inflations. All patients were on oral aspirin (100 mg o.d.), diltiazem (60 mg t.i.d.) and isosorbide dinitrate (40 mg b.i.d.) for ≥ 48 h before coronary angioplasty. All patients received the morning dose of treatment prior to coronary angioplasty, which was performed within the following 4 h. No patient received sublingual or intravenous nitrates in the last 24 h prior to the study or throughout the study. Patients were not premedicated with diazepam or other sedatives.

Coronary angioplasty of the stenosed artery was performed as previously described[11]. Briefly, after placement of the guiding catheter and performance of baseline angiography, the guide wire was placed across the lesion in the distal segment of the stenosed artery. The balloon catheter was then placed within the stenosis and the balloon was inflated for 2 min. After balloon deflation and withdrawal proximal to the lesion, with the guide wire still across the lesion, a recovery period of ≥ 5 min was allowed to re-establish baseline haemodynamic and ECG conditions. A second balloon inflation for 2 min was then performed. In each individual patient balloon pressure during the first and second inflation was identical. After the first two inflations, coronary angioplasty was completed on the basis of the specific needs of individual patients.

Assessment of myocardial ischaemia

Standard surface 12-lead and intracoronary ECGs derived from the coronary guide wire were continuously monitored and simultaneously recorded (Mingograph 7, Siemens) at a paper speed 25 mm . s^{-1} throughout the study. To avoid electrode interference with fluoroscopic imaging during the angioplasty procedure, radiotranslucent precordial electrodes were used. The ECGs were analysed by a cardiologist who had no knowledge of the study protocol. At baseline (with just the guide wire across the lesion) and at the end of the first two inflations, ST segment shift was measured 80 ms after the J point. The severity of myocardial ischaemia was expressed as: (1) the summation of the absolute values of the ST segment elevation and ST segment depression from baseline, on surface ECG, from all 12 leads; (2) the absolute values of ST segment elevation or ST segment depression from baseline on intracoronary ECG; (3) the summation of the absolute values of ST segment elevation and ST segment depression on both the surface and the intracoronary ECGs. ST segment shifts were expressed in millimetres (1 mm=0·1 mV).

Assessment of cardiac pain

At the beginning of each coronary angioplasty procedure, patients were informed that they might develop chest pain. At the end of the first two balloon inflations, the intensity of cardiac pain was assessed by using a visual analogue scale[30]. Patients were asked to put a mark on a 100-mm scale marked from no symptoms to severe symptoms. The scale was measured from 0 to the subject's mark in millimetres.

Statistical analysis

Two-factor analysis of variance (ANOVA) with repeated measures on one factor was used to compare

Table 1 Clinical, anatomical and haemodynamic features

	Bamiphylline (n=18)	Placebo (n=18)
Age (years)	55 ± 10	52 ± 9
Male/female	16/2	16/2
Vessel disease (%)		
LAD	50	44
LCx	22	28
RCA	28	28
Heart rate, beats per minute		
Baseline	79 ± 15	79 ± 15
End of infusion	80 ± 11	79 ± 15
Inflation 1	79 ± 11	77 ± 14
Inflation 2	78 ± 11	76 ± 14
Mean aortic pressure (mmHg)		
Baseline	95 ± 12	96 ± 11
End of infusion	94 ± 10	96 ± 10
Inflation 1	96 ± 11	97 ± 12
Inflation 2	96 ± 12	96 ± 11

LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; RCA=right coronary artery.

haemodynamic and ECG data during balloon inflations in the two groups of patients. When significant differences were detected, pairwise comparisons were made using the Scheffé F-test. Comparisons of the remaining continuous or discrete variables between the two groups were performed using an unpaired Student's t-test or a χ^2 test, respectively. Visual-analogue scales were analysed using the Wilcoxon signed rank test or the Mann–Whitney U test as appropriate. Data are expressed as mean ± 1 SD; P values <0·05 were considered significant.

Results

Clinical, anatomical and haemodynamic features in the two groups of patients are summarized in Table 1. During intravenous infusion of bamiphylline prior to coronary angioplasty, no patient experienced symptoms. In both bamiphylline- and placebo-treated patients, the values of heart rate and mean aortic pressure were similar at baseline, at the end of bamiphylline or placebo infusion and at the end of the first and the second inflations (Table 1).

Coronary angioplasty

Coronary angioplasty was successfully performed in all 36 patients (residual stenosis <50%). The mean balloon pressure was similar in bamiphylline- and placebo-treated patients (4·4 ± 1·2 vs 5·1 ± 1·3 atm, ns, respectively). The recovery period between the two balloon inflations was similar in bamiphylline- and placebo-treated patients (8·1 ± 1 vs 8 ± 2 min, ns, respectively).

Myocardial ischaemia

The ST segment shift values at baseline and at the end of the first two inflations, as changes from baseline, are reported in Table 2. In bamiphylline-treated patients, the mean ST segment shift during the second balloon inflation was similar to that during the first inflation on the surface ECG (7 ± 9 vs 8 ± 10 mm, ns), the intracoronary ECG (7 ± 8 vs 8 ± 8 mm, ns) and the surface plus intracoronary ECGs (14 ± 15 vs 16 ± 16 mm, ns). Conversely, in placebo-treated patients, the mean ST segment shift during the second balloon inflation was significantly less than that during the first inflation on the surface ECG (5 ± 4 vs 8 ± 5 mm, P<0·001), the intracoronary ECG (4 ± 3 vs 9 ± 5 mm, P<0·001) and the surface plus intracoronary ECGs (10 ± 6 vs 17 ± 7 mm, P<0·001) (Fig. 1). It is noteworthy that there was no significant difference between the two groups of patients in the degree of ST segment shift at baseline and at the end of the first inflation on either surface or intracoronary ECG (Table 2).

Cardiac pain

In bamiphylline-treated patients, the severity of cardiac pain during the second inflation was similar to that during the first inflation (31 ± 28 vs 31 ± 29 mm, ns). Conversely, in placebo-treated patients, the severity of cardiac pain during the second inflation was less than that during the first inflation (25 ± 21 vs 39 ± 31 mm, P<0·01) (Fig. 2). Of note, in bamiphylline-treated patients cardiac pain severity at the end of the first inflation was less than that in placebo-treated patients, although the difference did not achieve statistical significance (31 ± 29 vs 39 ± 31 mm, P=0·35) (Table 2).

Discussion

This study shows that the adaptation to ischaemia during coronary angioplasty may be prevented by pretreatment with bamiphylline, the most selective antagonist of A_1 adenosine receptors available for clinical use in Europe[27]. In fact, we found that, in bamiphylline-treated patients, the mean ST segment shift and the severity of cardiac pain at the end of the second balloon inflation were similar to those at the end of the first inflation, while in placebo-treated patients they were significantly less. Our findings, therefore, indicate that, in humans, A_1 adenosine receptors play an important role in ischaemic preconditioning, in agreement with the results of previous studies in animal models[5,15–20] and in isolated human muscle[26].

Pharmacology of bamiphylline

Bamiphylline, a 7,8-bisubstituted of aminophylline, has been used successfully to treat bronchial asthma and

Table 2 ST-segment shift values and cardiac pain severity

	Bamiphylline (n=18)			Placebo (n=18)	
	Baseline	Δ		Baseline	Δ
ST segment shift on S-ECG (mm)					
Inflation 1	2 ± 2	8 ± 10	*	2 ± 2	8 ± 5
Inflation 2	2 ± 1	7 ± 9		2 ± 1	5 ± 4‡
ST segment shift on IC-ECG (mm)					
Inflation 1	2 ± 2	8 ± 8	*	2 ± 2	9 ± 5
Inflation 2	2 ± 2	7 ± 8		2 ± 2	4 ± 3‡
ST segment shift on S- plus IC-ECG (mm)					
Inflation 1	4 ± 3	16 ± 16	†	4 ± 3	17 ± 7
Inflation 2	4 ± 2	14 ± 15		4 ± 3	10 ± 6‡
Pain severity (mm)					
Inflation 1	—	31 ± 29	*	—	39 ± 31
Inflation 2	—	31 ± 28		—	25 ± 21§

*$P<0.05$; †$P<0.01$, bamiphylline vs placebo (changes from inflation 1 to inflation 2). ‡$P<0.001$ vs inflation 1 value; §$P<0.01$ vs inflation 1 value.
IC-ECG=intracoronary electrocardiogram; S-ECG=surface 12-lead electrocardiogram; Δ= changes from baseline values.

lung anaphylaxis in young children and infants[31] and chronic obstructive pulmonary disease in adults with an efficacy comparable to that of aminophylline but with substantially fewer side-effects[32,33]. The therapeutic threshold of bamiphylline is almost 50 times lower than that of aminophylline ($0.2\ \mu g \cdot ml^{-1}$ vs $10\ \mu g \cdot ml^{-1}$), whereas the tolerance range is almost 100 times wider[34,35]. In crude synaptic membranes prepared from rat brain, bamiphylline displaces radioligands from A_1 adenosine receptors with a potency similar to that of 8-phenil-theophylline, whereas it shows a much lower potency on A_2 adenosine receptors. This results in a high degree of A_1 receptor selectivity indicated by an A_2/A_1 ratio of 596[27]. A critical issue in our study was the choice of an appropriate dose of bamiphylline. At the dose used in the present study the mean plasma concentration of bamiphylline (about 0.5×10^{-5} M) displaces 80% of ^{3}H-Diethyl-8-phenyl-xanthine (an antagonist of A_1 adenosine receptors), 50% of ^{3}H-Cyclo-hexyl-adenosine (an agonist of A_1 adenosine receptors), but only 5% of ^{3}H-5'N-ethyl-carboxamino-adenosine (an agonist of A_2 adenosine receptors)[27]. Thus, at the dose used in this study, bamiphylline results in a rather selective blockade of A_1 adenosine receptors. Accordingly, we have recently shown that, at this dose, bamiphylline does not suppress adenosine-induced cutaneous vasodilation[36], or adenosine-induced coronary vasodilation[37], which are both mediated by vascular A_2 receptors[38]. Thus, it is very unlikely that, in our patients, bamiphylline prevented ischaemic preconditioning by limiting an A_2 receptor-mediated increase of coronary blood flow. Finally, we cannot exclude that ischaemic preconditioning was prevented through blockade of A_3 receptors, which appear to mediate preconditioning in rabbits[21,22]; however, the affinity of bamiphylline for A_3 receptors has not yet been investigated.

As A_1 adenosine receptor blockade by bamiphylline prevents the algogenic effects of adenosine[36,37], it is somewhat intriguing that, although in our patients treated with bamiphylline pain severity during the first inflation was less than that in patients treated with placebo, this difference did not achieve statistical significance in the presence of similar electrocardiographic changes in the two groups of patients. However, we have previously shown that during coronary angioplasty the anginal pain is also determined by the mechanical stretching of the arterial wall[9], thus probably accounting for the partial failure of bamiphylline to reduce the anginal pain in this study.

We have also previously shown that bamiphylline improves exercise-induced myocardial ischaemia[39], while in this study the severity of ischaemia during the first balloon inflation was similar following placebo or bamiphylline. This difference is probably related to the different pathophysiology of ischaemia caused by an increase of myocardial oxygen consumption as opposed to that caused by coronary occlusion.

Role of A_1 adenosine receptors in ischaemic preconditioning in man

A_1 adenosine receptors are present in perivascular sympathetic nerves and in cardiomyocytes[40,41]. The blockade by bamiphylline of A_1 adenosine receptors located in the perivascular nerves causes an increase in catecholamine release[42,43] and might influence the severity of myocardial ischaemia during balloon occlusion in two different ways. First, an increase of catecholamine release may increase myocardial oxygen consumption, thus worsening the severity of myocardial ischaemia during coronary occlusion. However, if this were the

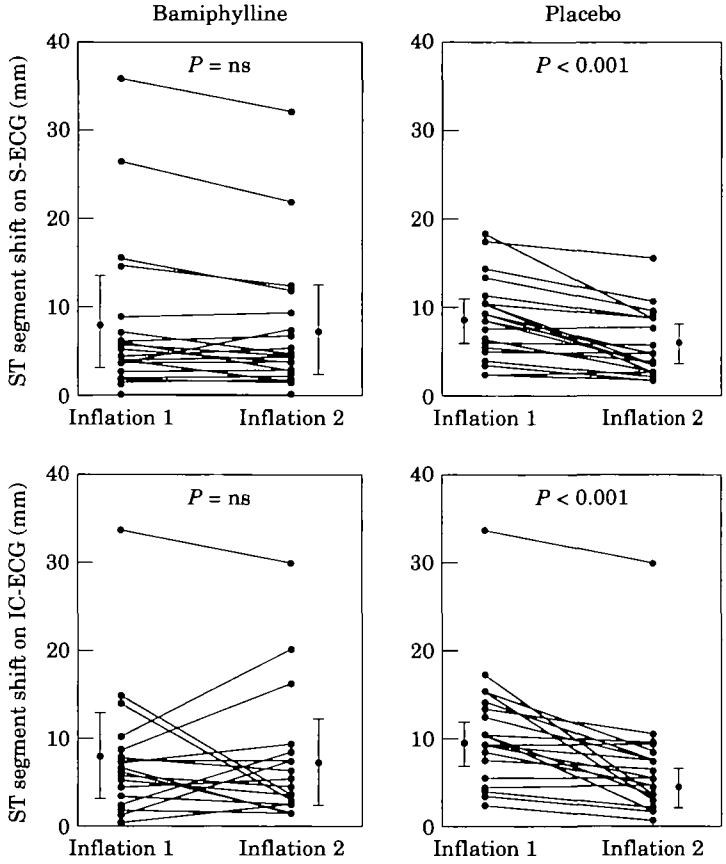

Figure 1 **Plots of individual values of ST segment shifts on the surface ECG (S-ECG) and the intracoronary ECG (IC-ECG) at the end of the first and second balloon inflations in the two groups of patients. In bamiphylline-treated patients, ST segment changes at the end of the second balloon inflation were similar to those at the end of the first inflation. Conversely, in placebo-treated patients, ST segment changes at the end of the second balloon inflation were significantly less than those at the end of the first inflation. Of note, two bamiphylline-treated patients had zero ST segment shift value on S-ECG during both inflations.**

case we should have obtained greater electrocardiographic changes and more severe pain in bamiphylline-treated patients also at the end of the first inflation. Instead, the magnitude of ischaemic electrocardiographic changes, the severity of pain and the systemic haemodynamic parameters at the end of the first inflation were similar in bamiphylline- and in placebo-treated patients. Second, an increase of catecholamine release may enhance preconditioning, as Banerjee *et al.*[25] demonstrated in isolated rat hearts that α_1-adrenergic receptors stimulation can mimic preconditioning. However, if this were the case, A_1 adenosine receptor blockade by bamiphylline should have resulted in cardioprotection rather than prevention of preconditioning. Thus, it would appear that the prevention of preconditioning by bamiphylline observed in our study, during repeated brief periods of coronary occlusion, is not mediated by the blockade of A_1 adenosine receptors located on perivascular sympathetic nerves, but, more likely, by A_1 or, perhaps, A_3 receptors[21,22] located on the surface of myocardial fibres. Indeed, experimental studies have shown that A_1 adenosine receptors appear to mediate ischaemic preconditioning by directly enhancing the opening of the ATP-sensitive K^+ channels[12,19]. In rat ventricular myocytes, Kirsch *et al.*[44] showed, indeed, that A_1 adenosine receptors are coupled to ATP-sensitive K^+ channels. Moreover, in dogs, glibenclamide, an ATP-sensitive K^+ channel blocker, not only prevents ischaemic preconditioning, but also A_1 adenosine receptor-mediated cardioprotection[12,45] and attenuates adenosine-induced bradycardia[46]. In agreement with the results of experimental observations[3,13,14], we have demonstrated in a previous study that glibenclamide completely abolishes the ischaemic preconditioning observed in humans during brief repeated coronary occlusions[11]. Thus, in man, both bamiphylline and glibenclamide appear to prevent ischaemic preconditioning. How A_1 adenosine receptors

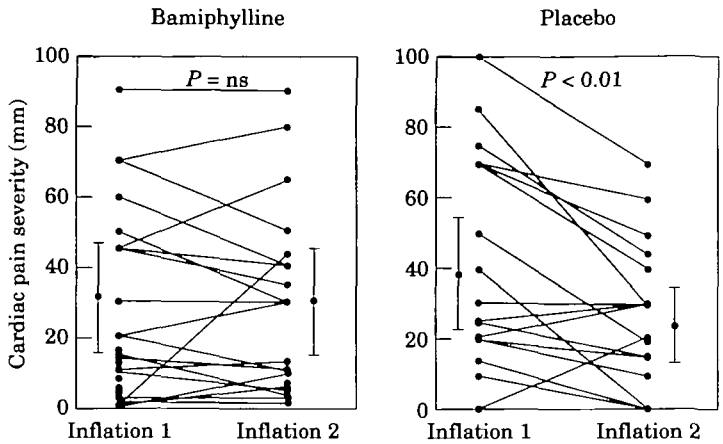

Figure 2 **Plots of individual values of cardiac pain severity at the end of the first and second balloon inflations in the two groups of patients. In bamiphylline-treated patients, cardiac pain severity during the second balloon inflation was similar to that during the first inflation. Conversely, in placebo-treated patients, cardiac pain severity during the second balloon inflation was significantly less than that during the first inflation. Of note, two bamiphylline-treated patients had no pain during either inflation.**

and ATP-sensitive K^+ channels interact in humans in determining preconditioning cannot be deduced from the results of our studies.

Study limitations

We based the assessment of myocardial ischaemia on the electrocardiographic changes which do not represent direct evidence of ischaemia and on the anginal pain severity which is rather subjective. However, the surface 12-lead and the intracoronary ECGs represent well accepted methods for the evaluation of myocardial ischaemia during coronary angioplasty[7–9,47–49]. Moreover, we compared ST segment changes in the same patient where other variables being constant, the most important parameter determining the degree of ST segment shift appears to be the severity of myocardial ischaemia, as previously shown in experimental studies[50,51]. Regarding the assessment of the anginal pain, the visual analogue scale is a well accepted method for the evaluation of pain perception[30], which we utilized in several previous studies[9,36,37,52]. Finally, it is possible that the adaptation to ischaemia observed in this human model is mediated by progressive collateral recruitment[8], which we did not asses in our study. However, if this were the case, it would be difficult to explain the ability of bamiphylline to prevent the adaptation to ischaemia as, at the dose used in this study, bamiphylline does not appear to antagonise A_2 receptors, which mediate the vascular effects of adenosine[37]. Of note, the results of our study appear to confirm the observation that ischaemic preconditioning in isolated human muscle, a model where vascular effects can be ruled out, is mediated by A_1 adenosine receptors[26].

Conclusions and clinical implications

In patients with stable angina pectoris undergoing elective coronary angioplasty, ischaemic preconditioning occurring during brief repeated coronary occlusions is prevented by bamiphylline, a selective antagonist of A_1 adenosine receptors. These findings indicate that, in humans, A_1 adenosine receptors may play an important role in ischaemic preconditioning. Our study suggests that adenosine antagonists should be used with caution in those patients with ischaemic heart disease in whom ischaemic preconditioning is likely to play an important cardioprotective role, i.e. those with unstable angina or undergoing coronary artery bypass surgery.

References

[1] Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury is ischemic myocardium. Circulation 1986; 74: 1124–36.
[2] Li GC, Vasquez BS, Gallagher KP, Lucchesi BR. Myocardial protection with preconditioning. Circulation 1990; 82: 609–19.
[3] Gross GJ, Auchampach JA, Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. Circ Res 1992; 70: 223–33.
[4] Schott RJ, Rohmann S, Braun ER, Schaper W. Ischemic preconditioning reduces infarct size in swine myocardium. Circ Res 1990; 66: 1133–42.
[5] Liu GS, Thornton JD, van Winkle DM, Stanley AWH, Olsson RA, Downey JM. Protection against infarction afforded by preconditioning is mediated by A_1 adenosine receptors in the rabbit heart. Circulation 1991; 84: 350–6.
[6] Liu Y, Downey JM. Ischemic preconditioning protects against infarction in rat heart. Am J Physiol 1992; 263: H1107–12.
[7] Deutsch E, Berger M, Kussmaul WG, Hirshfeld JW, Herrmann HC, Laskey WK. Adaptation to ischemia during

percutaneous transluminal coronary angioplasty. Clinical, hemodynamic, and metabolic features. Circulation 1990; 82: 2044–51.
[8] Cribier A, Korsatz L, Koning R *et al.* Improved myocardial ischemic response and enhanced collateral circulation with long repetitive coronary occlusion during angioplasty: a prospective study. J Am Coll Cardiol 1992; 20: 578–86.
[9] Tomai F, Crea F, Gaspardone A *et al.* Mechanisms of cadiac pain during coronary angioplasty. J Am Coll Cardiol 1993; 22: 1892–6.
[10] Yellon DM, Alkhulaifi AM, Pugsley WB. Preconditioning the human myocardium. Lancet 1993; 342: 276–7.
[11] Tomai F, Crea F, Gaspardone A *et al.* Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K^+ channel blocker. Circulation 1994; 90: 700–5.
[12] Grover GJ, Sleph PG, Dzwonczyk S. Role of myocardial ATP-sensitive potassium channels in mediating preconditioning in the dog heart and their possible interaction with adenosine A_1-receptors Circulation 1992; 86: 1310–6.
[13] Toombs CF, Moore TL, Shebuski RJ Limitation of infarct size in the rabbit by ischemic preconditioning is reversible with glibenclamide. Cardiovasc Res 1993; 27: 617–22.
[14] Tan HL, Mazòn P, Verberne HJ *et al.* Ischemic preconditioning delays ischaemia induced cellular electrical uncoupling in rabbit myocardium by activation of ATP sensitive potassium channels. Cardiovasc Res 1993; 27: 644–51.
[15] Thornton JD, Liu GS, Olsson RA, Downey JM. Intravenous pretreatment with A1-selective adenosine analogues protects the heart against infarction Circulation 1992; 85: 659–65.
[16] Tsuchida A, Miura T, Miki T, Shimamoto K, Iimura O Role of adenosine receptor activation in myocardial infarct size limitation by ischemic preconditioning. Cardiovasc Res 1992; 26: 456–61.
[17] Thornton JD, Daly JF, Cohen MV, Yang X, Downey JM. Catecholamines can induce adenosine receptor-mediated protection of the myocardium but do participate in ischemic preconditioning in the rabbit. Circ Res 1993; 73: 649–55.
[18] Hale SL, Bellows SD, Hammerman H, Kloner RA. An adenosine A_1 receptor agonist, R[-]-N-[2-phenylisopropyl]-adenosine (PIA), but not adenosine itself, acts as a therapeutic preconditioning-mimetic agent in rabbits. Cardiovasc Res 1993; 27: 2140–5.
[19] Auchampach JA, Gross GJ. Adenosine A_1 receptors, K_{ATP} channels, and ischemic preconditioning in dogs. Am J Physiol 1993; 264: H1327–36.
[20] Downey JM, Liu GS, Thornton JD. Adenosine and the anti-infarct effects of preconditioning. Cardiovasc Res 1993; 27: 3–8.
[21] Armstrong S, Ganote CE. Adenosine receptor specificity in preconditioning of isolated rabbit cardiomyocytes: evidence of A_3 receptor involvement. Cardiovasc Res 1994; 28: 1049–56.
[22] Liu GS, Richards SC, Olsson RA, Mullane K, Walsh RS, Downey JM. Evidence that the adenosine A_3 receptor may mediate the protection afforded by preconditioning in the isolated rabbit heart. Cardiovasc Res 1994; 28: 1057–61.
[23] Claeys MJ, Vrints CJ, Bosmans JM, Conraads VM, Snoeck JP. Aminophylline abolishes ischemic preconditioning during angioplasty (abstr). Circulation 1994; 90: I–477.
[24] Thornton JD, Liu GS, Downey JM. Pretreatment with pertussis toxin blocks the protective effects of preconditioning: evidence for a G-protein mechanism. J Mol Cell Cardiol 1993; 25: 311–20.
[25] Banerjee A, Locke-Winter C, Rogers KB *et al.* Preconditioning against myocardial dysfunction after ischemia and reperfusion by an α_1-adrenergic mechanism. Circ Res 1993; 73: 656–70
[26] Walker DM, Walker JM, Pugsley WB, Pattison CW, Yellon DM. Preconditioning in isolated superfused human muscle. J Mol Cell Cardiol 1995; 27. 1349–57.
[27] Abbracchio MP, Cattabeni F. Selective activity of bamiphylline on adenosine A_1-receptors in rat brain. Pharmacol Res Commun 1987; 19: 537–45.
[28] Rentrop KP, Cohen M, Blanke H, Phillips R. Changes in collateral filling immediately following controlled coronary artery occlusion by an angioplasty balloon in man. J Am Coll Cardiol 1985; 5: 587–92.
[29] Dodion L, Aylward M. Metabolic and pharmacokinetic studies on bamiphylline: a review. Revue Inst Hygiene Mines 1978; 33: 204–10.
[30] Huskisson EC. Measurement of pain. Lancet 1974; 2: 1127–31.
[31] Thomet G, Renault M. Essai d'une nouvelle medication 'theophylline like' dans les affections dyspneisantes de l'enfant. Quest Mèd 1969; 5. 402–5.
[32] Kofman J, Grosclaude M, Ouechni M, Parrin-Fayolle M. Action comparee de la bamifylline et de la theophylline sur le bronchospasme allergique induit par test inhalatoire de provocation Etude en double aveugle et croise. Poumon-coer 1982; 38: 194–202.
[33] Cottin S, Veran P. Etude clinique du Trentadil (AC 3810). Nouvel analeptique respiratoire et bronchodilatateur. Quest Mèd 1965; 18: 839–42.
[34] Foutillan JP, Lefebvre MA, Ingrand I, Patte F, Boita F, Ouchni MM. Pharmacokinetic study of bamiphylline (and metabolites) in healthy volunteers using chromatography and mass spectrometry. Therapie 1983; 38: 647–58.
[35] Dodion L, Dusart P, Temmerman P. Study on the metabolism of bamiphylline in man. Arzneimittel-Forsch Drug Res 1969; 19: 785–9.
[36] Pappagallo M, Gaspardone A, Tomai F *et al.* Analgesic effect of bamiphylline on pain induced by intradermal injection of adenosine. Pain 1993; 53: 199–204.
[37] Gaspardone A, Crea F, Tomai F *et al.* Muscular and cardiac adenosine-induced pain is mediated by A_1 receptors. J Am Coll Cardiol 1995; 25: 251–7.
[38] Belardinelli L, Linden J, Berne R. The cardiac effects of adenosine. Prog Cardiovasc Dis 1989; 32: 73–97.
[39] Gaspardone A, Crea F, Iamele M *et al.* Bamiphylline improves exercise-induced myocardial ischemia through a novel mechanism of action. Circulation 1993; 88: 502–8.
[40] Bohm M, Pieske B, Ungerer M, Erdmann E. Characterization of A_1 adenosine receptors in atrial and ventricular myocardium from diseased human hearts. Circ Res 1989; 65: 1201–11.
[41] Fredholm BB, Gustafsson LE, Hedqvist P, Sollevi A. Adenosine in the regulation of neurotransmitter release in the peripheral nervous system. In: Berne RM, Rall TW, Rubio R, eds. Regulatory function of adenosine. The Hague: Martinus Nijhoff; 1983: 479–95.
[42] Ragazzi E, Wu SN, Shryock J, Belardinelli L. Electrophysiological and receptor binding studies to assess activation of the cardiac adenosine receptor by adenine nucleotides. Circ Res 1991; 68: 1035–44.
[43] Burnstock G. Vascular control by purines with emphasis on the coronary system. Eur Heart J 1989; 10: 15–21.
[44] Kirsch GE, Codina J, Birnbaumer L, Brown AM. Coupling of ATP-sensitivie K^+ channels to A_1 receptors by G proteins in rat ventricular myocytes. Am J Physiol 1990; 259: H820–6.
[45] Yao Z, Gross GJ. A comparison of adenosine-induced cardioprotection and ischemic preconditioning in dogs. Efficacy, time course, and role of K_{ATP} channels. Circulation 1994; 89: 1229–36.
[46] Belloni FL, Hintze TH. Glibenclamide attenuates adenosine-induced bradycarida and coronary vasodilatation. Am J Physiol 1991; 261: H720–7.
[47] Wohlgelernter D, Cleman M, Highman HA *et al.* Regional myocardial dysfunction during coronary angioplasty: evaluation by two-dimensional echocardiography and 12 lead electrocardiography. J Am Coll Cardiol 1986; 7: 1245–54.
[48] Feldman T, Chua KG, Childers RW. R wave of the surface and intracoronary electrogram during acute coronary artery occlusion. Am J Cardiol 1986; 58: 885–90.
[49] Friedman PL, Shook TL, Kirschenbaum JM, Selwyn AP, Ganz P. Value of the intracoronary electrocardiogram to

monitor myocardial ischemia during percutaneous transluminal coronary angioplasty. Circulation 1986; 74: 330–9.

[50] Angell CS, Lakatta EG, Weisfeldt ML, Shock NW. Relationship of intramyocardial oxygen tension and epicardial ST segment changes following acute coronary artery ligation: effect of coronary perfusion pressure. Cardiovasc Res 1975; 9: 12–8.

[51] Khuri SF, Flaherty JT, O'Riordan JB *et al.* Changes in intramyocardial ST segment voltage and gas tension with regional myocardial ischemia in the dog. Circ Res 1975; 37: 455–63.

[52] Crea F, Pupita G, Galassi AR *et al* Role of adenosine in pathogenesis of anginal pain. Circulation 1990; 81: 164–72.