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The influence of atherosclerosis on the mechanical responses of human isolated coronary arteries to substance P, isoprenaline and noradrenaline

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1 The responses to substance P, isoprenaline and noradrenaline were observed on human isolated coronary arteries removed from 30 human hearts, and were classified according to the age of the hearts, the presence or absence of cardiac failure and the degree of atherosclerosis.

2 The endothelium-dependent vasodilator, substance P (0.1 μM), relaxed rings precontracted with prostaglandin $F_{2\alpha}$, ($PGF_{2\alpha}$, 1 μM) when they were devoid of atherosclerosis. The presence of moderate or severe lesions of atherosclerosis abolished this response. There was no difference in the response, related to either the age of the hearts or to the presence or absence of cardiac failure.

3 The dose-response curves to isoprenaline (an endothelium-independent vasodilator) were also markedly altered by the presence of atherosclerotic lesions, while aging and the presence of cardiac failure did not alter the maximal relaxation. These last 2 factors induced only a rightward shift of the dose-response curves.

4 On severely atherosclerotic rings, β-adrenoceptor-mediated responses were so altered that the effect of noradrenaline was wholly vasoconstrictor (via α-adrenoceptors). This response was not modified after pretreatment with atenolol (10 μM).

5 It is concluded that atherosclerosis in human coronary arteries, induces alterations in the responses to substance P and to β-adrenoceptor agonists. The β-adrenoceptor-mediated relaxations seem more influenced by the presence of atherosclerosis than they are by aging or by the down-regulation induced by cardiac failure. Conversely, the α-adrenoceptor responses appear to be well preserved.

Introduction

α-Adrenergic coronary tone seems to play a role in chronic stable angina (Mudge *et al.*, 1976; Berkenboom *et al.*, 1986). However, this greater responsiveness of atherosclerotic arteries to α-adrenergic stimuli remains controversial. Indeed, *in vitro*, atherosclerotic human coronary arteries do not exhibit a supersensitivity to α-adrenoceptor agonists (Ginsburg *et al.*, 1984). Moreover, β-antagonists despite their unmasking effect on α-adrenergic coronary tone are very efficient drugs in the treatment of angina pectoris (Thadani *et al.*, 1979). Controversial results have also been reported for the effect of noradrenaline on human isolated coronary arteries: either the β-adrenoceptor effect or the α-effect prevailing (Godraind & Miller, 1983; Kalsner, 1985).

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We have recently characterized the coronary β-adrenoceptors of young human beings (Berkenboom *et al.*, 1987); they seem to be similar to those of dogs and mainly β_1. In the present investigation, we therefore studied the modifications of the β-adrenoceptor responses of human coronary arteries according to the age, the presence or absence of cardiac failure and the degree of atherosclerosis. In addition, the alterations of the response to noradrenaline according to these various factors were also determined.

The alterations in the endothelial function induced by these factors were also investigated. For this purpose substance P, an endothelium-dependent vasodilator was used.

Some of these results were presented at the Joint Meeting of the British Pharmacological Society in Amsterdam, July 1986.

Methods

Patient characteristics

Hearts were obtained from 6 children and 24 adults. The children aged 1 to 10 years (group A) were in irreversible neurological coma, their kidneys being used for transplantation but not their hearts which were too small for adult recipients. Group B consisted of 4 healthy hearts (aged 18, 19, 32 and 48 years) which were not used for transplantation because of medical complications in the awaiting recipients. Seven hearts (group C) were obtained from adults with non-ischaemic cardiomyopathy. Three of them (aged 25, 26 and 35 years) had an idiopathic cardiomyopathy and the 4 others (aged 51, 52, 54 and 58 years) had a valvular cardiomyopathy. All these patients of group C were in cardiac failure. Group D comprised 13 hearts obtained from patients (mean age 49 ± 5 years) with coronary artery disease. Ten of them were in cardiac failure while the remaining 3 had a good ventricular function (ejection fraction $>50\%$). All these hearts except 3 in group D were obtained in the operating room and immediately placed in ice-cold physiological solution. The 3 hearts in group D with good ventricular function were removed from cadavers 3 to 5 h after death.

Approximately 5 cm of the proximal ends of the left anterior descending artery, circumflex artery and right coronary artery were cleared of connective tissue and cut into ring segments 3–4 mm long. The segments were either studied immediately or stored overnight at 4°C in Krebs-Henseleit solution aerated with 95% O_2: 5% CO_2.

None of the 30 patients, within 4 weeks of study, received α-adrenoceptor antagonists, β-antagonists or amiodarone which is claimed to have β-blocking properties (Nokin *et al.*, 1983).

Pharmacological studies

By means of steel hooks, the segments were suspended between a plastic holder and a force transducer (Grass FT03C) for continuous recording of isometric tension with a transducer amplifier (Janssen Scientific Instruments; Beerse, Belgium) and a pen recorder. The organ chambers were filled with Krebs-Henseleit solution of the following composition (mmol l^{-1}): NaCl 118.1, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25 and glucose 5, gassed with a 95% O_2: 5% CO_2 mixture and kept at 36 ± 1°C. Before the experiments, the segments were equilibrated for 60 min in the bathing medium under 3 to 5 g of tension for coronary arteries of children (group A) and 6 to 8 g for coronary arteries of adults (group B, C, D).

Thereafter, the viability of each ring was checked by assessing the contractile response to 30 mM KCl for 4 min. Contraction induced by this concentration of KCl was in a range between 85 and 90% of the maximal response. The rings were then repeatedly washed with fresh solution for 15 min. Endothelial function was determined by testing the relaxant response to substance P, on rings precontracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 1 μM). Contractions induced by $PGF_{2\alpha}$ 1 μM were in a range between 60 and 75% of contractions induced by KCl 30 mM. $PGF_{2\alpha}$ was added to the bath for only 4 min, to avoid the appearance of rhythmic activity. On a few rings of group A, the endothelium was removed by gently rubbing the intimal surface with a cotton pellet.

Modification, by removal of endothelium, of the response to isoprenaline was investigated in coronary arteries isolated from the same hearts.

Cumulative concentration-response curves were constructed for isoprenaline on rings precontracted with KCl 15 mM. The concentration of isoprenaline required to induce half-maximum relaxation (ED_{50}) was assessed graphically for each curve. The ED_{50} value for isoprenaline is, thus, defined as the concentration causing 50% of isoprenaline maximal relaxation. In another set of experiments, the effect of noradrenaline (10 μM) was assessed alone and after pretreatment with atenolol. The concentration of 10 μM was chosen from concentration-response curves and is a submaximal concentration (Berkenboom *et al.*, 1987). After 2 controls (without β-antagonist), the response to noradrenaline (10 μM) was assessed after 30 min preincubation with increasing concentrations of atenolol (1 μM and 10 μM). These concentrations were chosen from Schild plots for isoprenaline, assessed in our previous study (Berkenboom *et al.*, 1987). At the end of each experiment, the response to noradrenaline was assessed after pretreatment with a mixture of atenolol 10 μM and prazosin 1 μM.

Histological examination

After completion of the pharmacological studies, each ring was fixed in 10% formalin and stained with haematoxylin and eosin. The degree of atherosclerosis was scored blind by two observers who did not know the pharmacological results. The final score was the mean value from the two independent readings. Four morphological criteria were used (identical to those used by Ginsburg *et al.*, 1984): (1) degree of luminal occlusion; (2) degree of fragmentation of internal elastic lamina; (3) degree and distribution of calcium; (4) degree of intimal proliferation.

Each criterion was scored on a scale from 1 to 3; 1 being normal and 3 being severely diseased. On the basis of these four criteria, the rings were categorized in 3 classes: Class I (score 4, 5, 6) without atherosclerosis, class II (score 7, 8, 9) with moderate atheros-

clerosis, and class III (score 10, 11, 12) with severe atherosclerosis.

Statistical analysis

The results shown in the text and figures are expressed as mean values ± s.e.mean. Statistical analysis was made using Student's *t* test or Wilcoxon rank sum test for unpaired observations, where appropriate.

Drugs

The following drugs were used: (−)-noradrenaline bitartrate (Winthrop); (±)-isoprenaline hydrochloride (Winthrop); prazosin hydrochloride (Pfizer); yohimbine hydrochloride (Sigma); prostaglandin $F_{2\alpha}$ (Upjohn); atenolol hydrochloride (ICI), substance P (Peninsula). Stock solutions of the drugs were dissolved in distilled water except noradrenaline and isoprenaline which were dissolved in distilled water containing ascorbic acid (1 mM).

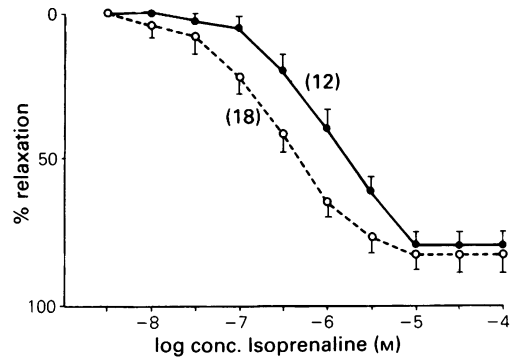

Figure 1 Concentration-response curves for isoprenaline on coronary arteries removed from hearts of children (<10 years; group A, $n = 6$) (○) and from hearts of adults without cardiac disease (>18 years; group B, $n = 4$) (●). The rings were precontracted with KCl 15 mM. Data are shown as means (with s.e.mean shown by vertical lines) and are expressed as percentage of depression of the responses to KCl. Numbers in parentheses indicate the number of preparations used.

Results

Effect of age on β-adrenoceptor-mediated responses

In groups A and B, all the rings could be classed as having no atherosclerosis. Since in groups A and B, there was no evidence of heart failure, we were able to assess accurately the effect of age on the concentration-response curves to isoprenaline (Figure 1). The curve for the adults was shifted to the right and the ED_{50} was significantly higher ($P < 0.05$): 1.1 ± 0.5 μM ($n = 12$, group B) versus 0.37 ± 0.05 μM ($n = 18$, group A).

Atenolol (1 μM), shifted the curves to the right by 11 ± 3 fold ($n = 10$, group A) and 15 ± 4 fold ($n = 10$, group B).

On these rings of group A and B, substance P (0.1 μM) relaxed the preparations precontracted with $PGF_{2\alpha}$ 1 μM (47 ± 8% of $PGF_{2\alpha}$-induced contraction).

Role of the endothelium on β-adrenoceptor-mediated responses

On a few rings of group A, the endothelium was gently removed. The substance P (0.1 μM)-induced relaxation was completely abolished on these rings ($n = 6$) and in some instances substance P caused a small further increase of the contraction induced by $PGF_{2\alpha}$ 1 μM (5 ± 4% of $PGF_{2\alpha}$-induced contraction).

The concentration-response curves to isoprenaline were very similar on rings with and without endothelium (Figure 2). The maximal relaxation was not altered 76 ± 4% (on rings with endothelium, $n = 6$) versus 81 ± 4% (on rings without endothelium, $n = 6$). The ED_{50} was also similar: 0.29 ± 0.04 μM versus 0.20 ± 0.08 μM (NS).

Role of the presence of cardiac failure on β-adrenoceptor-mediated responses

In group C, the coronary arteries of the 3 youngest hearts (aged 25, 26 and 35 years) were all in class I of

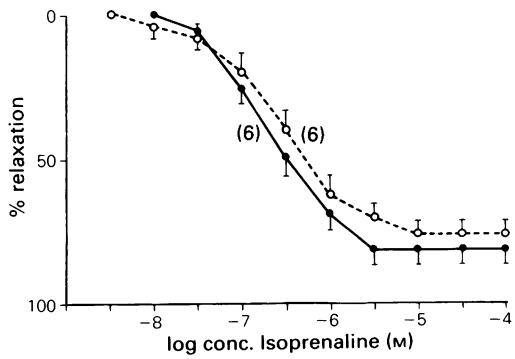

Figure 2 Concentration-response curves for isoprenaline in presence (○) and absence (●) of endothelium. All the rings were removed from hearts of children (group A). The rings were precontracted with KCl 15 mM. Data are shown as means (with s.e.mean shown by vertical line) and are expressed as percentage of depression of the response to KCl. Numbers in parentheses indicate the number of preparations used.

atherosclerosis (subgroup Ic). In a 58-year-old heart, 4 rings were in class I (subgroup Ic) while 2 others were in class II (subgroup IIc). In the 3 remaining hearts of group C (aged 51, 52 and 54 years) all the segments ($n = 11$) studied exhibited a moderate degree of atheromatosis (subgroup IIc). No segments were judged to be in class III of atherosclerosis. On the rings of subgroup Ic, precontracted with $PGF_{2\alpha}$ (1 μM), the relaxation induced by substance P (0.1 μM) was 55 ± 7% of the $PGF_{2\alpha}$ (1 μM)-induced contraction (no difference versus group A and B).

In this subgroup Ic, the concentration-response curves to isoprenaline are shown in Figure 3. On comparing with group B, the maximal relaxation to isoprenaline was similar: 77 ± 6 ($n = 14$) versus 80 ± 4% ($n = 12$, group B).

There was a slight shift to right of the concentration-response curve but the changes in the ED_{50} did not reach statistical significance: 2.0 ± 0.6 μM ($n = 14$) versus 1.1 ± 0.5 μM ($n = 12$, group B).

In subgroup IIc ($n = 13$), the concentration-response curves to isoprenaline were altered: the maximal relaxation was 33 ± 9%, which was significantly ($P < 0.05$) decreased in comparison with subgroup Ic (77 ± 6%, $n = 14$) and also with group B (80 ± 4%, $n = 12$). On these 13 rings of subgroup IIc, precontracted with $PGF_{2\alpha}$ (1 μM), no relaxation was observed with substance P (0.1 μM).

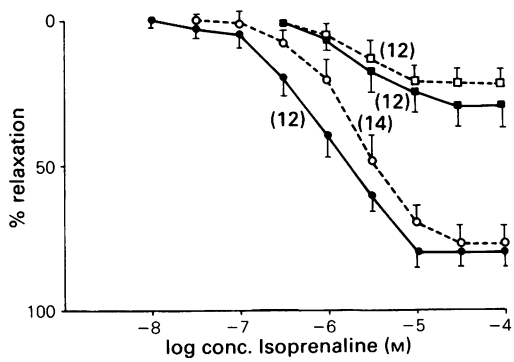

Figure 3 Concentration-response curves for isoprenaline on coronary arteries removed from hearts of adults without cardiac disease (group B, class I) (●), of adults with cardiac failure (group C, class I) (○), of adults with cardiac failure and moderate atheroma (group D, class II) (■), and of adults with cardiac failure and severe atheroma (group D, class III) (□). The rings were precontracted with KCl 15 mM. The maximal relaxation for IID and IIID was significantly reduced ($P < 0.01$) in comparison with IB and IC (n = number of preparations used; vertical lines represent s.e.mean).

Role of atherosclerosis on β-adrenoceptor-mediated responses

In group D, 40 rings were studied. Only 4 rings (from 2 failing hearts) were in class I (subgroup ID), 19 were in class II (subgroup IID) and 17 in class III (subgroup IIID). Substance P (0.1 μM) relaxed the 4 rings of class I (41 ± 7% of $PGF_{2\alpha}$ (1 μM)-induced contraction). In subgroup IID, substance P (0.1 μM) relaxed only 3 of the 19 segments. These 3 rings were removed from failing hearts. In subgroup IIID, relaxation induced by substance P (0.1 μM) was either not observed ($n = 9$) or was modified into a small contraction 5 ± 3% ($n = 8$), (% of $PGF_{2\alpha}$ (1 μM)-induced contraction).

There was no difference in the responses to substance P when rings obtained from failing hearts were compared to rings obtained from non-failing hearts.

On the 4 rings of subgroup ID, the concentration-response curves to isoprenaline were similar to those of group B and of group IC: the maximal relaxation was 85 ± 6% and the ED_{50} was 3.9 ± 0.9 μM. In subgroup IID, 12 rings were removed from failing hearts. For these rings, the concentration-response curves to isoprenaline are shown in Figure 3: the maximal relaxation was 30 ± 7% ($n = 12$) (Figure 3) ($P < 0.01$ versus 80 ± 4%, group B). The remaining 7 rings of subgroup IID were obtained from hearts with good ventricular function; the maximal relaxation was 35 ± 7% (NS versus 30 ± 7%) ($P < 0.01$ versus 80 ± 4%, group B). In subgroup IIID, 12 and 5 rings were removed from failing hearts and non-failing hearts, respectively. The maximal relaxations were 22 ± 5% ($n = 12$) (Figure 3) ($P < 0.01$ versus 80 ± 4%, group B) and 27 ± 6% ($n = 5$) (NS versus 22 ± 5%) respectively.

Effects of noradrenaline according to the age, the presence or absence of cardiac failure and the degree of atherosclerosis

The results are summarized in Table 1. The effects of noradrenaline are expressed as a percentage of KCl (30 mM)-induced contraction.

The response to K^+ 30 mM was significantly ($P < 0.05$) decreased on rings of subgroup IIID 3.0 ± 0.5 g ($n = 12$) versus 4.7 ± 0.8 g in subgroup IID ($n = 12$) and 5.0 ± 0.4 g in subgroup IB ($n = 12$). In children (IA), the response to K^+ 30 mM was 3.6 ± 0.4 g ($n = 18$), also significantly ($P < 0.05$) less than in IB. Noradrenaline (10 μM) induced a relaxation of 12 ± 4% (% of KCl) ($n = 10$) in group IA. After pretreatment with atenolol (1 μM), the response to noradrenaline was converted into a contraction: 39 ± 8% of KCl ($n = 10$). After pretreatment with a higher concentration of atenolol (10 μM), the noradrenaline (10 μM)-induced contraction was significantly larger (76 ± 6% of KCl, $n = 10$) ($P < 0.05$).

On rings of group IB, there was either no response to noradrenaline (10 μM) or a small contraction. However, after pretreatment with atenolol (1 μM and 10 μM), the noradrenaline (10 μM)-induced contraction was 50 ± 9% and 71 ± 9% of KCl ($n = 10$) respectively. On rings of group IC, the response to noradrenaline (10 μM) was purely a contraction of 57 ± 11% ($n = 9$) which was significantly ($P < 0.05$) increased to 71 ± 7% ($n = 9$) after pretreatment with atenolol (10 μM).

In groups ID, IIC and IID, the results were similar (shown in Table 1) to those of group IC: noradrenaline (10 μM) induced a contraction (59 to 65% of KCl) which was significantly increased only after pretreatment with atenolol (10 μM) ($P < 0.05$).

In group IIID, noradrenaline (10 μM) induced a large contraction (98 ± 10% of KCl) ($n = 12$) which was not significantly modified after pretreatment with atenolol (even at 10 μM).

In groups IID and IIID, there was no difference in the results when rings obtained from failing hearts (shown in Table 1) were compared to rings obtained from non-failing hearts.

Pretreatment with a mixture of prazosin (1 μM) and atenolol (10 μM) reduced the noradrenaline-induced contraction (40 to 56%) in all cases (Table 1). A mixture of prazosin (1 μM) and yohimbine (1 μM) (in the presence of 10 μM atenolol) completely abolished the noradrenaline-induced contraction in all cases.

Discussion

The role of the endothelium in the responses to adrenoceptor agonists and to substance P has been previously studied in human coronary arteries. It has been demonstrated that the effects of noradrenaline (Toda, 1986) and isoprenaline (Försterman *et al.*, 1986) are endothelium-independent while those of substance P (Toda, 1986) are endothelium-dependent. In the present study, the influence of other factors such as aging, atherosclerosis and cardiac failure has been examined.

Our results show that the substance P-induced relaxations were abolished after removal of the endothelium in coronary segments isolated from young human beings (group A). They were also abolished in most of the adult preparations with moderate stages of atherosclerosis (class II scores 7, 8, 9) and in all preparations with severe atherosclerotic lesions (class III scores 10, 11, 12).

This modification does not seem to be related to cardiac failure or aging since on rings removed from failing hearts, older than 50 years, substance P induced a relaxation provided these segments were devoid of atherosclerosis (class I). As suggested by Ross & Glomsett (1976), the endothelial dysfunction could be the initial stage of the atherosclerotic lesion. This assumption might explain why early stages of atherosclerosis detected by histological examination were

Table 1 Effects of KCl (30 mM) and noradrenaline (10 μM) on developed tension of coronary artery rings

		KCl	*Noradrenaline*			
Class	*Group*		*Control*	*Atenolol* (1 μM)	*Atenolol* (10 μM)	*Prazosin* (1 μM) plus *Atenolol* (10 μM)
	A	3.6 ± 0.4 g	− 12 ± 4	39 ± 8	76 ± 6°*	40 ± 6
		(18)	(10)	(10)	(10)	(10)
I	B	5.0 ± 0.4 g	1 ± 5	50 ± 9	71 ± 9°*	45 ± 9
		(12)	(10)	(10)	(10)	(10)
	C	5.3 ± 0.6 g	57 ± 11	59 ± 13	71 ± 7°	43 ± 10
		(9)	(9)	(9)	(9)	(9)
	D	4.9 ± 0.7 g	59 ± 11	59 ± 14	75 ± 10°	44 ± 11
		(4)	(4)	(4)	(4)	(4)
II	C	5.4 ± 0.6 g	61 ± 10	66 ± 10	84 ± 91°	48 ± 9
		(9)	(9)	(9)	(9)	(9)
	D	4.7 ± 0.8 g	65 ± 10	70 ± 10	83 ± 9°	44 ± 7
		(12)	(12)	(12)	(12)	(12)
III	D	3.0 ± 0.5 g†	98 ± 10	112 ± 15	114 ± 14	56 ± 13
		(12)	(12)	(12)	(12)	(12)

Noradrenaline effects are expressed as % of contraction produced by 30 mM K^+. All values are means ± s.e. of n observations (in parentheses).

°$P < 0.05$ Atenolol (10 μM) versus noradrenaline (10 μM) (control); *$P < 0.05$ Atenolol (10 μM) versus atenolol (1 μM); †$P < 0.05$ versus IB, IC, ID.

associated with marked alteration of the response to substance P. Another explanation for the absence of relaxation to substance P on atherosclerotic rings could be that the 'endothelium derived releasing factor' (EDRF) is still present but that its diffusion to the smooth muscle cells is impaired, due to thickening of the intimal layer (Verbeuren *et al.*, 1986).

On the other hand, if isoprenaline-induced relaxations were not modified in the absence of endothelium, in isolated coronary segments from young human beings as previously described (Furchgott, 1984; Förstermann *et al.*, 1986), they were markedly influenced by the degree of atherosclerosis. We have been able to observe that the maximal responses induced by isoprenaline in rings isolated from the same hearts were diminished according to the stage of atherosclerosis detected by histological examination (class II or III). This does not seem to be related to cardiac failure as, in other experiments we could demonstrate that in coronary arteries isolated from failing hearts and devoid of atherosclerosis (group C, class I) there was only a slight rightward shift in the ED_{50} to isoprenaline and no modification in the maximal responses when compared to dose-response curves assessed in rings from adult healthy hearts (group B, class I).

These results are in agreement with those of Venter (1979) who did not observe any modification of the maximal responses induced by isoprenaline in cardiac tissues isolated from failing hearts. This assumption of 'spare' β-adrenoceptors in failing hearts (Venter, 1979) has not been challenged, however, by other authors (Colucci *et al.*, 1981; Bristow *et al.*, 1982).

Therefore our results suggest that on human coronary arteries, the β-adrenoceptor-mediated responses are affected more by atherosclerosis than they are by the down-regulation induced by cardiac failure. The reason why the maximal relaxation to isoprenaline was so altered in the presence of atherosclerotic lesions deserves further investigation.

Atherosclerosis could alter the intrinsic capacity of the rings to relax. This alteration has already been described for severely atherosclerotic segments of aortae isolated from hypercholesterolaemic rabbits (Verbeuren *et al.*, 1986), while in our study, even moderately atherosclerotic lesions (class II) induced modifications in the maximal response to isoprenaline. Changes in the biochemical effects produced by β-adrenoceptor activation in smooth muscle cells is a more likely explanation. Indeed, in vascular tissues from hypercholesterolaemic animals, disturbances in activity of several enzymes have been observed (Papahadjopoulos *et al.*, 1973; Weigensberg *et al.*, 1982).

The diminished relaxant response to isoprenaline in atherosclerotic segments of coronary arteries might for instance be attributed to a reduction in the production of adenosine 3', 5'-cyclic monophosphate (cyclic AMP) which has been shown to mediate β-adrenoceptor-mediated relaxation in these vessels (Seidel *et al.*, 1975).

The effect of aging on isoprenaline-induced responses is difficult to assess since atherosclerosis increases with aging. However, comparison could be made between coronary segments isolated from young human beings (group A) and from adults devoid of atherosclerosis (group B, class I): a significant rightward shift in the ED_{50} to isoprenaline could be observed between the two groups, which suggests that aging could decrease either the number or the sensitivity of β-adrenoceptors. The influence of aging has been previously described by Godfraind (1979) in aortic smooth muscles from senescent rats: a diminution of the maximal responses to isoprenaline was described. However, the degree of atherosclerosis was not examined in these preparations and since early stages of atherosclerosis have been described in this species (Roberts & Strauss, 1965) it might be that the effect described was also partially due to atherosclerosis.

We have also attempted to study the influence of aging, cardiac failure and atherosclerosis on the responses to noradrenaline. On coronary arteries of children (<10 years), the β-adrenoceptor effect of noradrenaline is dominant. This effect is counterbalanced by the α-effect on coronary arteries of adults without cardiac disease and therefore no response is observed with noradrenaline. This α-effect of noradrenaline becomes predominant in coronary arteries removed from failing hearts. However, atherosclerosis seems again to be the most important factor in the modification of the responses to noradrenaline; the α-effect of noradrenaline is completely unmasked on severely atherosclerotic segments (class III) so that atenolol does not further significantly modify the noradrenaline-induced contraction. Interestingly, the contractions induced by noradrenaline are not reduced in these severely atherosclerotic segments when compared to those induced by KCl. Nevertheless, the maximal tension developed to potassium depolarization was decreased on these severely diseased rings. These results are in agreement with those of Ginsburg *et al.* (1984) who have found a reduction of the maximal tension developed in response to all vasoconstrictor stimuli tested. Unlike the β-adrenoceptor responses, the α-adrenoceptor responses appear to be less altered by the age, the degree of cardiac failure and the degree of atherosclerosis. The partial resistance to prazosin that we have already observed (Berkenboom *et al.*, 1987) on coronary arteries of children occurs also in adult arteries and can be ascribed to the fact that human vascular α-adrenoceptors belong to α_1 and α_2 subtypes (Flavahan & McGrath, 1984).

Our results could explain why patients with chronic

stable angina pectoris exhibit an abnormal coronary vasoconstrictor response after adrenergic stimuli like the 'cold pressor' test (Mudge *et al.*, 1976) or isometric exercise (Brown *et al.*, 1984). Indeed the pronounced alteration in the β-adrenoceptor-mediated coronary vasodilatation induced by atherosclerosis would allow the α-effect of noradrenaline to predominate.

In conclusion, this study indicates that atherosclerosis in human coronary vessels, induces alterations in the responses to substance P and to the β-adrenoceptor agonist, isoprenaline.

The β-adrenoceptor-mediated relaxations seem more influenced by the degree of atherosclerosis than they are by aging or the down-regulation induced by cardiac failure. Conversely, α-adrenoceptor-mediated responses appear to be well preserved and do not seem to be markedly modified by these factors.

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