Vasoconstrictor peptides and cold intolerance in patients with stable angina pectoris

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Abstract

Background—The exact mechanism that explains the phenomenon of cold intolerance in patients with angina remains controversial. Although the response to the effects of a cold environment has been examined in these patients, their response to cold air inhalation has produced conflicting results. In addition, the possible role of vasoactive peptides in the pathophysiology has not been explored.

Objectives—The aims of this study were to examine the response of patients with stable angina to the effects of cold air inhalation during exercise testing, and to investigate the possible role played by the vasoconstrictor peptides endothelin-1 (ET-1) and angiotensin-II (AT-II) in the pathophysiology.

Methods—In a randomised order, 12 men with stable angina, whose medication had been stopped, underwent two separate symptom limited treadmill exercise tests. At one visit the patients exercised while breathing room air and at the other visit they exercised while breathing cold air from a specially adapted freezer. Serial peripheral venous blood samples were taken for ET-1 and AT-II estimations during each visit.

Results—Cold air inhalation resulted in a significant reduction in the mean time to angina (232·7 (20·4) s v 274·1 (26·9) s, P = 0·04) and the mean total exercise time (299·5 (27·0) s v 350·3 (23·9) s, P = 0·008), but no significant change in the time to 1 mm ST depression (223·3 (29·0) s v 241·3 (29·2) s, P = 0·25). There was no significant difference between the rate-pressure products at the onset of angina (P = 0·13) and the time to 1 mm ST depression (P = 0·85), but at peak exercise the rate-pressure product was significantly lower in patients breathing cold air as opposed to room air (P = 0·049). There was an equivalent significant decrease in ET-1 concentrations at peak exercise compared with that at rest at both visits (room air 5·0 (0·7) pmol/l v 4·3 (0·7) pmol/l, P = 0·03; cold air 4·4 (0·6) pmol/l v 3·8 (0·5) pmol/l, P = 0·02). There was a significant increase in AT-II concentrations 10 min after peak exercise in patients breathing room air (39·2 (6·1) pmol/l v 32·1 (4·8) pmol/l, P = 0·01) which was not repeated during cold air inhalation (36·6 (3·4) pmol/l v 28·3 (3·4) pmol/l, P = 0·07).

Conclusions—Cold air inhalation in patients with stable angina results in an earlier onset of angina and a reduction in exercise capacity. Both peripheral and central reflex mechanisms appear to contribute to the phenomenon of cold intolerance. Peripheral ET-1 and AT-II do not appear to play a significant role in the pathophysiology.

Many patients with coronary artery disease complain of a deterioration in their angina in cold weather.[1] The exact explanation for this cold intolerance remains controversial, as it is unclear whether cold air inhalation or the effects of a cold environment exhibit the major influence on the pathophysiology. Two physiological reflex responses have been proposed to account for the phenomenon, namely (*a*) an increase in peripheral vascular resistance resulting in an increase in cardiac work at any given level of exercise,[2 3] and (*b*) (coronary vasoconstriction (or the lack of normal coronary vasodilatation) during exercise.[4 5]

Most previous reports on the response of patients with angina to cold temperatures have examined the effects of a cold environment,[6 7] and very few studies have investigated the response to cold air inhalation. Furthermore, such studies have either produced conflicting results[8 9] or demonstrated cold intolerance only during the inhalation of very cold air.[10]

It is possible that naturally occurring vasoconstrictor peptides could play a role in the pathophysiology of cold intolerance in patients with angina pectoris. Endothelin-1 (ET-1) belongs to a family of potent vasoconstrictor peptides, and has been shown to induce vasoconstriction in both human resistance vasculature[11] and human coronary arteries.[12] Raised plasma levels of ET-1 have been found in healthy subjects following the cold pressor test,[13] and ET-1 has been implicated in the pathophysiology of Raynaud's phenomenon.[14]

Similarly the principal active component of the renin-angiotensin system, angiotensin II (AT-II), is known to produce vasoconstriction. The renin-angiotensin system has been implicated in the elevation of blood pressure in rats during exposure to cold,[15] and raised

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AT-II levels have been detected in response to pacing induced ischaemia in patients with stable angina.[16] It is possible therefore that either ET-1 or AT-II may have a role in the mechanism of cold induced angina.

The aims of this study were to examine the effects of cold air inhalation during exercise testing at room temperature in patients with chronic stable angina and to investigate the possible part played by ET-1 and AT-II in the pathophysiology of cold intolerance.

Patients and methods

STUDY POPULATION

The study group consisted of 12 men (age range 52–69 years, mean age 61·0 years) with chronic stable exertional angina. Eight of the patients gave a positive history of cold intolerance. Each patient had angiographically confirmed coronary artery disease, with two patients having single vessel disease, seven double vessel disease and three triple vessel disease. Four patients had had a previous myocardial infarction. None of the study group gave a history of hypertension, renal disease, congestive cardiac failure or chronic respiratory disease (for example, asthma or chronic obstructive airway disease). Patients taking diuretic agents or angiotensin converting enzyme inhibitors were excluded from the study. Informed consent was obtained from each patient and the study was approved by the hospital ethical committee.

EXERCISE TESTING

The study involved each patient undergoing two symptom limited treadmill exercise tests using the Bruce protocol 1 week apart. At one visit the patient underwent exercise testing whilst breathing room air and at another visit the patient performed the exercise test whilst breathing cold air obtained from a specially adapted freezer. This freezer contained a heat exchanger immersed in a glycol solution capable of cooling air to a minimum temperature of −15°C. The heat exchanger was connected to a small fan unit capable of providing cold air at a maximum rate of 150 l/min. The fan unit was fitted with a short piece of insulated 38·1 mm diameter bore hose, and the patients breathed the cold air obtained from the freezer through a mask attached to this hose. An accompanying head strap was used to ensure that the mask fitted snugly to the patient's face. Exercise testing was performed in the early afternoon with each patient having fasted for at least 4 h. All antianginal medication was stopped for at least 2 days before exercise testing. Each patient wore a shirt and trousers and the order of their visits was randomised.

At each visit patients were asked to rest for 15 min after which peripheral venous blood samples were taken for measurement of ET-1 and AT-II concentrations. In addition, resting heart rate and blood pressure were measured. For the visit during which room air was breathed, each patient performed a treadmill exercise test during which the time to angina, the time to 1 mm ST depression, and the total

exercise time were recorded. Heart rate and blood pressure were measured at these time points at peak exercise and after 10 min recovery. Further peripheral venous blood samples were taken for determination of ET-1 and AT-II concentrations. For the visit during which cold air was breathed, each patient was asked to breathe cold air obtained from the modified freezer after the resting heart rate, blood pressure, and blood samples had been taken. Repeat ET-1 and AT-II samples were taken after 10 min of cold air inhalation at rest. The patient was then asked to perform an exercise test whilst continuing to breathe cold air and the time to angina, time to 1 mm ST depression, and the total exercise time were recorded. Heart rate and blood pressure were measured at these time points. Further ET-1 and AT-II samples were taken at peak exercise and after 10 min recovery whilst the patient continued to breathe cold air. Room temperature at each visit and the temperature of the inspired cold air entering the mask were measured.

ET-1 AND AT-II ASSAYS

All peripheral venous blood samples taken for determination of ET-1 and AT-II concentrations were collected into prechilled tubes on ice containing EDTA as anticoagulant. The samples were centrifuged within 1 h of collection at 3000 rpm for 10 min at 4°C, and the plasma was stored at −20°C until assayed. Endothelin concentrations were measured using a radioimmunoassay technique (Nichols Institute Diagnostics Endothelin [125]I Assay (Saffron Walden, Essex)). Antiserum cross-reactivity was ET-1 100%, endothelin-2 52%, endothelin-3 96%, and big-endothelin 7%. The inter-assay and intra-assay coefficients of variation based on pooled samples of plasma were 9·2% (n = 5) and 4% (n = 12) respectively. The recovery of ET-1 from plasma samples was 83% (range 77-89) (n = 4). The lowest measurable concentration of the assay was 0·8 pmol/l. AT-II concentrations were also measured using a radioimmunoassay technique (Nichols Institute Diagnostics Angiotensin-II [125]I Assay). Antiserum cross-reactivity was Asp^1-$Ileu^5$-angiotensin-II 100%, Val^5-angiotensin-II 100%, Asp^1-$Ileu^5$-angiotensin-I 0·1%, Asn^1-Val^5-angiotensin-II 30%, and Sar^1-$Ileu^8$-angiotensin-II 0·02%. The inter-assay and intra-assay coefficients of variation were 5·7% (n = 9) and 3·5% (n = 12) respectively. The recovery of AT-II from plasma samples was 68% (range 62-74) (n = 4). The lowest measurable concentration of the assay was 3·6 pmol/l.

STATISTICAL ANALYSIS

Results are expressed as means (SEM). The data were normally distributed, and differences between variables were analysed using the Student's paired t test. Statistical significance was taken as $P < 0.05$.

Results

There was no significant difference in room temperature when the patients were breathing
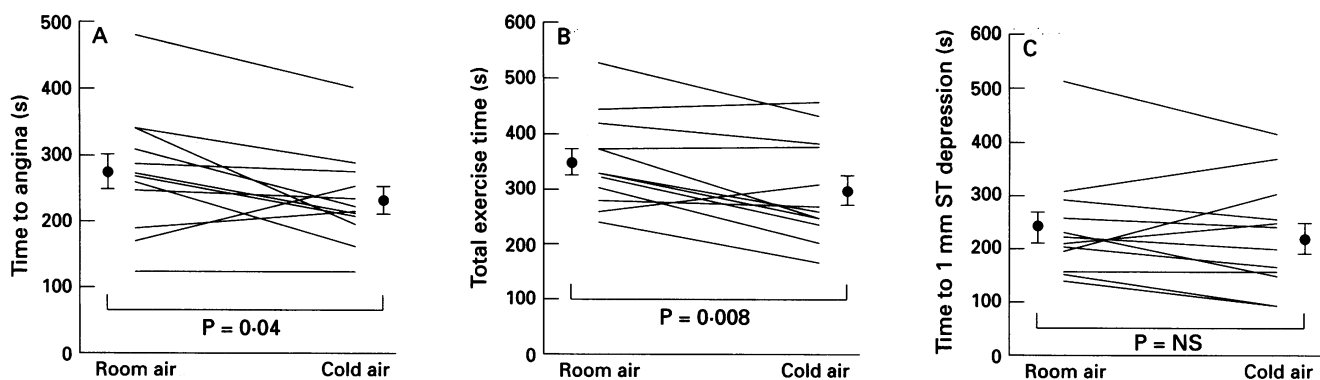
(A) Time to angina, (B) total exercise time, and (C) time to 1 mm ST depression in 12 patients undergoing exercise testing during inhalation of cold or room air. Bars represent means (SEM).

warm air (22·3 (0·1)°C) compared with that of cold air inhalation (22·5 (0·3)°C). The temperature of the inspired cold air was −8·8 (0·2)°C.

There was a significant decrease in the time to angina (fig (A)) and in the total exercise time (fig (B)) in patients breathing cold air as opposed to room air, but there was no change in the time to 1 mm ST depression (fig (C)).

There was no significant difference in the rate-pressure products at the onset of either angina or the 1 mm ST depression, but at peak exercise the rate-pressure product was

significantly lower when patients were breathing cold air as opposed to room air (table 1). There were no significant differences in heart rate, systolic blood pressure, or diastolic blood pressure at each of these time points (table 2).

Subdividing the patients dependent on whether they gave a history of cold intolerance revealed that, for the eight with such a history, there was a trend towards a reduction in the time to angina, time to 1 mm ST depression, and total exercise time during cold air inhalation compared with that of

Table 1 Rate-pressure product values during each exercise test

Patient no	Time to angina		Time to 1 mm ST depression		Peak exercise	
	Room air	Cold air	Room air	Cold air	Room air	Cold air
1	20 900	17 510	16 200	16 830	24 510	21 600
2	21 420	19 890	18 870	19 210	21 960	21 780
3	20 700	18 700	22 860	18 020	24 890	22 320
4	23 220	21 780	21 080	22 500	23 580	23 940
5	16 800	18 530	16 320	17 120	16 480	18 700
6	13 950	14 560	13 950	17 340	16 320	17 340
7	18 700	21 250	19 550	20 740	22 140	21 080
8	18 540	16 490	19 080	19 260	19 440	19 260
9	25 620	20 710	26 040	22 040	27 300	21 660
10	21 960	24 200	25 400	24 400	27 720	24 600
11	25 650	22 800	19 620	22 800	26 220	24 510
12	24 990	22 420	18 360	18 700	26 460	23 560
Mean (SEM)	21 037 (1043)	19 903 (819)	19 778 (1045)	19 913 (730)	23 085 (1138)	21 696 (672)*

*$P = 0.049$.

Table 2 Heart rate and blood pressure data during exercise tests

	Time to angina	Time to 1 mm ST depression	Total exercise time
Heart rate (beats/min)			
Warm air	115·2 (3·4)	112·3 (3·2)	122·9 (3·5)
Cold air	111·8 (3·1)	112·5 (2·5)	119·3 (2·7)
Systolic blood pressure (mm Hg)			
Warm air	181·7 (5·1)	175·8 (5·3)	186·7 (5·0)
Cold air	177·5 (3·5)	176·7 (3·3)	181·7 (2·7)
Diastolic blood pressure (mm Hg)			
Warm air	84·2 (1·5)	83·3 (1·4)	85·0 (1·5)
Cold air	86·7 (1·4)	86·7 (1·4)	87·5 (1·3)

Values are means (SEM).

Table 3 Exercise test data for patients intolerant and tolerant to cold

	Intolerant to cold			Tolerant to cold		
	Room air	Cold air	p Value	Room air	Cold air	p Value
Time to angina (s)	247·5 (28·9)	212·1 (18·6)	0·22	327·2 (51·4)	273·8 (45·9)	0·03
Time to 1 mm ST depression (s)	209·0 (20·6)	196·0 (32·8)	0·47	305·8 (72·7)	277·8 (52·5)	0·42
Total exercise time (s)	331·5 (26·6)	285·9 (34·0)	0·07	388·0 (47·7)	326·7 (47·4)	0·07

Values are means (SEM).

Table 4   Concentrations of ET-1 (pmol/l)

Patient no	Room air			Cold air			
	Rest	Peak exercise	10 min after exercise	Rest	Rest and 10 min of cold air	Peak exercise and cold air	10 min after exercise and cold air
1	8·0	8·2	8·2	5·6	4·9	3·1	4·4
2	2·3	1·7	1·8	1·7	1·6	1·6	1·6
3	1·5	1·4	1·5	1·2	1·7	1·3	1·5
4	2·3	2·1	2·2	2·5	1·9	1·9	2·1
5	5·3	3·6	3·7	3·1	3·2	3·6	3·1
6	3·6	3·4	3·5	4·2	3·3	2·8	3·7
7	4·5	4·9	5·7	5·9	6·5	5·3	4·4
8	6·2	5·1	4·4	4·3	4·5	4·4	4·7
9	4·6	4·0	4·3	5·0	6·1	5·2	5·5
10	6·0	2·8	3·9	4·3	4·6	3·5	3·8
11	7·3	7·3	7·4	7·0	6·0	6·2	5·6
12	8·9	7·1	7·5	8·6	8·6	6·9	7·2
Mean (SEM)	5·0 (0·7)	4·3 (0·7)*	4·5 (0·7)	4·6 (0·6)	4·4 (0·6)	3·8 (0·5)**	4·0 (0·5)***

*P = 0·03 v rest; **P = 0·02 v rest and 10 min of cold air; ***P = 0·04 v rest and 10 min of cold air.

Table 5   Concentrations of A-II (pmol/l)

Patient no	Room air			Cold air			
	Rest	Peak exercise	10 min after exercise	Rest	Rest and cold air	Peak exercise and cold air	10 min after exercise and cold air
1	35·2	43·2	44·2	30·2	37·7	34·4	43·5
2	21·6	27·1	28·1	18·1	20·1	22·8	22·4
3	40·4	42·4	44·8	57·0	55·0	42·9	35·6
4	11·5	9·4	13·2	13·5	11·8	18·2	37·1
5	29·0	50·3	56·0	26·9	22·7	32·6	62·0
6	31·2	22·0	31·2	28·4	20·8	35·4	29·6
7	72·9	73·9	84·8	25·1	34·6	43·9	39·2
8	20·7	26·6	28·5	43·6	24·8	33·0	37·7
9	16·9	18·9	16·7	24·8	42·2	55·1	47·4
10	44·6	42·8	61·1	28·3	28·7	29·2	39·7
11	19·7	15·7	18·2	18·2	16·2	17·1	17·5
12	41·9	43·4	43·5	26·0	26·3	26·9	27·0
Mean (SEM)	32·1 (4·8)	34·6 (5·2)	39·2 (6·1)*	28·3 (3·4)	28·4 (3·5)	32·6 (3·2)	36·6 (3·4)

*P = 0·01 v rest and P = 0·02 v peak exercise.

room air inhalation, but these findings failed to reach statistical significance (table 3). For the four patients who stated that they were cold tolerant, however, there was a significant reduction in the time to angina when breathing cold air (table 3).

There was a significant decrease in ET-1 concentrations at peak exercise compared with that at rest at both visits (table 4), but the magnitude of this decrease at each visit was similar, and no significant difference could be established between the responses to room air (percent decrease 14·3 (4·9)) and cold air inhalation (percent decrease 11·6 (4·1)) (P = 0·70).

There was a significant increase in AT-II concentrations 10 min after peak exercise compared with that at both rest and peak

Table 6   Maximal ST depression achieved during exercise tests

Patient no	Maximal ST depression (mm)	
	Warm air	Cold air
1	3·0	3·3
2	1·4	1·7
3	1·1	1·2
4	2·0	2·0
5	2·3	3·0
6	1·9	1·6
7	2·4	1·7
8	2·2	1·0
9	1·6	1·1
10	1·4	1·0
11	2·8	2·3
12	2·2	1·9
Mean (SEM)	2·0 (0·2)	1·8 (0·2)

exercise during room air inhalation, but there were no significant changes in AT-II throughout the exercise test during cold air inhalation (table 5).

Discussion

In the investigation of cold intolerance in patients with angina, consideration has to be given to the potential differences between the effects of a cold environment and those of cold air inhalation. The results of this study indicate that in patients with chronic stable angina, cold air inhalation results in an earlier onset of angina and a fall in overall exercise capacity. It is the first study to demonstrate cold intolerance whilst breathing moderately cold air and indicates that cold air inhalation per se is an important factor in the phenomenon of cold intolerance. Peripheral ET-1 or AT-II do not appear to play a significant role in the mechanism of cold induced angina, but this is the first study to demonstrate a fall in ET-1 levels during exercise in patients with chronic stable angina.

For many patients with ischaemic heart disease, cold weather produces a deterioration in their symptoms and a reduction in exercise capacity. Furthermore, there is an overall increase in cardiac mortality during cold spells,[17] and a Canadian study has associated rapid drops in temperature with increasing deaths from coronary artery disease.[18] Of the two reflex responses that have been proposed to explain the phenomenon of cold

intolerance, published data in the setting of a cold environment have suggested that an increase in peripheral vascular resistance resulting in an increase in cardiac work for any given level of exercise is the more important mechanism.[6 7] This theory, however, has not met with universal support. Juneau *et al*[19] found that a subgroup of eight cold sensitive patients developed 1 mm ST depression 30% sooner during treadmill exercise testing in a cold chamber at $-8°C$ compared with that at 20°C. The rate-pressure product (heart rate × systolic blood pressure) at the onset of 1 mm ST depression was significantly lower in the cold, suggesting that ischaemia was occurring at a lower myocardial oxygen consumption. Juneau *et al* concluded that a reduction in coronary flow could explain the earlier onset of ischaemia in the cold.

The results of the present study suggest that a combination of both peripheral and central mechanisms could explain the phenomenon of cold induced angina during cold air inhalation. Cold air inhalation resulted in a significant reduction in the time to angina (fig 1(A)), with no significant difference in the rate-pressure product at this time point at each visit (table 1). Rate-pressure product has been shown to correlate well with myocardial oxygen consumption,[20] and therefore the earlier onset of angina during cold inhalation can be attributed to an increase in cardiac work. At each visit there was no significant difference in systolic blood pressure or heart rate at the onset of angina, suggesting that the increased myocardial oxygen consumption during cold air inhalation is likely to have been caused by a combination of the increase in both these variables. Cold exposure in patients with angina has been shown to produce peripheral vasoconstriction and a rise in blood pressure,[2] mediated via cold receptors in the skin which stimulate an increase in sympathetic outflow to the peripheral vessels. As cold receptors are also located in the upper airways, cold air inhalation is likely to stimulate these receptors and trigger a reflex increase in peripheral vascular resistance, a rise in blood pressure and an increase in cardiac work. Similarly, a sympathetically mediated reflex increase in heart rate during cold air inhalation would result in increased heart work.

In contrast, cold air inhalation resulted in a significant reduction in total exercise time, and this time point was reached at a significantly lower rate-pressure product compared with that of room air. This suggests that myocardial oxygen consumption was lower at peak exercise during cold air inhalation than at the same time point during room air inhalation. The implication of this result is that a central mechanism such as a reduction in coronary flow is the major determinant of maximal exercise capacity during cold air inhalation. Overall, the results of the study suggest that peripheral reflex responses account for the earlier onset of angina during cold air inhalation, but as exercise continues then central mechanisms play an increasing

role in the pathophysiology and determine a patient's overall exercise capacity.

Although there was a trend towards a decrease in the time to 1 mm ST depression in patients breathing cold air as opposed to room air, this failed to reach statistical significance. This could be explained by the size of the study group, and the change in this exercise test parameter may well have become significant if a larger number of patients had been studied. Furthermore, it is difficult to establish the effect of patient expectation during the cold air exercise test. Some patients may have assumed that they would experience angina sooner during the cold air exercise test, and this may have resulted in the early onset of chest pain and termination of exercise before the appearance of significant ST changes on the electrocardiogram.

Division of the study group into patients tolerant and intolerant to cold showed a significant reduction in the time to angina in patients tolerant to cold breathing cold air compared with that of breathing room air. Although there was a trend towards a reduction in the time to angina in patients intolerant to cold breathing cold air, this failed to reach statistical significance. One potential explanation for this finding is that patients intolerant to cold have developed an adaptive mechanism and are partially conditioned to the cold. This conditioning may modify their response to formal exercise testing during cold air inhalation, thus delaying the onset of symptoms and improving their overall exercise capacity. This adaptive response may not occur in patients tolerant to cold. In addition, it is uncertain as to the effect of patient expectation (that is—reluctance to go outdoors during cold weather, mode of dress) on the results. Patients who do not complain of cold intolerance may not have been exposed to, or may have taken steps to avoid, the phenomenon. Furthermore, clearly outdoor conditions are not exactly mimicked in the laboratory setting, and this could also contribute to these observed differences. In general, however, we would expect that the face is the only area significantly exposed to the cold, and that inhalation of cold air to be the major effect of cold weather.

Although increased endothelin and renin-angiotensin levels have been demonstrated in patients following acute myocardial infarction,[21 22] whether these vasoactive peptides are activated during episodes of acute myocardial ischaemia is less well defined. Raised AT-II levels have been detected in response to pacing induced ischaemia in patients with stable angina,[16] but no data are available on the possible part played by either ET-1 or AT-II in the pathophysiology of cold induced angina.

In the present study, there was a similar significant decrease in ET-1 concentrations at peak exercise compared with that at rest irrespective of whether the patients were breathing room or cold air. Concentrations of ET-1 returned to resting levels 10 min after peak exercise during the warm air exercise

test, but remained significantly reduced compared with resting levels 10 min after peak exercise during the cold air exercise test. The effect of exercise on ET-1 has not been studied in man, although a decrease in the mean plasma concentration of ET-1 after exercise performed until semi-exhaustion or exhaustion has been demonstrated in rats.[23] The decrease in ET-1 concentrations seen in our study group at peak exercise could be the result of its rapid removal by different tissues, especially the lungs, during exercise. Overall, the findings of our study suggest that peripheral ET-1 does not play a significant role in the phenomenon of cold intolerance in patients with stable angina.

There was a significant increase in AT-II concentrations 10 min after peak exercise compared with that at both rest and peak exercise in patients breathing room air. During cold air inhalation, however, there were no significant changes in AT-II concentrations. A rise in AT-II levels in response to exercise has been demonstrated in normal men,[24] with exercise stimulating the secretion of renin via sympathetic stimulation of the juxtaglomerular apparatus and by other mechanisms such as a loss of sodium and a reduction in the extracellular volume through sweating. Consequently, plasma renin activity and the plasma concentration of AT-II rise during exercise. In addition, exercise induced myocardial ischaemia in patients with ischaemic heart disease may produce left ventricular dysfunction, and subsequent renal hypoperfusion could also result in renin release from the kidney.

When the study group were breathing room air, their exercise capacity and maximal workload would have been less than that of normal subjects undergoing maximal exercise testing. Consequently, although activation of the mechanisms stimulating a rise in the level of AT-II would have started during exercise testing, they would not have produced a significant increase in AT-II by the time that the exercise was completed. It seems likely that these mechanisms will remain active at least during the early stages of recovery and result in a significant rise in AT-II 10 min after peak exercise. There was a significant reduction in total exercise time in patients breathing cold air as opposed to room air, and therefore it is likely that there was little stimulation of the renin-angiotensin response to exercise before peak exercise was reached. This may explain the fact that there were no significant changes in AT-II concentrations with exercise during cold air inhalation. This possibility seems more likely than any effect of ischaemia induced left ventricular dysfunction on AT-II, as there was no significant difference in maximal ST depression during exercise with either room air or cold air inhalation (table 6). Similar to the ET-1 findings, it appears unlikely that peripheral AT-II plays a significant role in the pathophysiology of cold intolerance in patients with stable angina.

The results of the present study differ from the previously reported effects of cold air inhalation in patients with angina. Hattenhauer and Neill[9] studied a population of 33 male patients with coronary artery disease, 11 of whom gave a positive history of cold intolerance. Seventeen of these patients underwent inhalation of cold air at $-20°C$ for 4 min, and this resulted in typical angina at rest in four patients. Cold air inhalation also produced angina in four of the seven patients who were paced at a heart rate which was subanginal at room temperature. Cold air inhalation did not significantly increase myocardial oxygen consumption, or alter coronary blood flow determined by the xenon clearance method. In a separate arm of the Hattenhauer and Neill study, cold air inhalation for 90 s in 18 patients produced no detectable constriction of coronary arteries visualized arteriographically. The authors concluded from these findings that cold induced angina could not be explained by an increase in cardiac work and myocardial oxygen consumption. In addition, as neither large coronary artery nor generalized coronary arteriole constriction seemed to occur during cold air inhalation, the authors proposed that cold induced angina could be the result of constriction of minute coronary collaterals or other vessels specifically affecting blood flow to potentially ischaemic regions of the myocardium. The differences between the results of Hattenhauer and Neill and the present study are likely to be a consequence of the use of different modalities of stress testing, particularly as atrial pacing is a relatively non-physiological form of exercise testing. Furthermore, a greater proportion of patients in the present study gave a positive history of cold intolerance (75% v 33%).

Lassvik and Areskog[10] studied 12 male patients with exertional angina and a positive history of cold intolerance using exercise bicycle tests with separation of inspiratory and room air. They demonstrated that inhalation of moderately cold ($-10°C$) or very cold ($-35°C$) air whilst resting in a room at 20°C produced no change in heart rate, systolic blood pressure or rate-pressure product compared with that of control conditions (inhalation of air at 20°C in a room at 20°C). Inhalation of cold air at $-35°C$ in a room at 20°C resulted in a significant decrease in work capacity expressed as workload at the onset of angina and maximal workload compared with that of control conditions. There was no significant difference between the rate-pressure products at maximal workload in control conditions and during cold air ($-35°C$) inhalation, and the authors concluded that the decrease in work capacity during very cold air inhalation was because of an increase in cardiac work and myocardial oxygen demand. Lassvik and Aveskog,[10] however, failed to demonstrate any decrease in workload at either the onset of angina or maximal workload during inhalation of moderately cold air ($-10°C$) in a room at 20°C.

One potential limitation in our study is that during the control exercise tests the patients were not wearing a mask or breathing through

the same equipment as they did during the cold air exercise tests. This raises the possibility that during the cold air tests patients performed additional work in breathing through the face mask and accompanying equipment, contributing to the earlier onset of angina and reduction in overall exercise capacity. The specially adapted freezer, however, contained a small fan unit capable of providing cold air at a maximum rate of 150 l/min, connected to the face mask by a short piece of 38·1 mm diameter hose. This equipment ensured that the cold air was actively supplied to the patient and that no extra work was required to breathe through the face mask and accompanying equipment.

Another potential limitation of our work is that laboratory conditions do not exactly replicate the outdoor conditions experienced by patients during cold weather. It is difficult to accurately reproduce outdoor conditions in an exercise room, but our study does show that breathing cold air is an important factor in the pathophysiology of cold induced angina. In response to strong winds, snow and freezing temperatures patients normally wear warm clothing such as coats, gloves and hats, but pay little attention to protecting themselves from the effects of direct cold air inhalation. Our work suggests that such practices as covering ones nose and mouth with a scarf or other such accessory may help to limit the effect of direct cold air inhalation and improve the patient's exercise capacity during cold spells.

Conclusion

When investigating the mechanisms involved in cold induced angina, potential differences exist between the response to cold air inhalation and the effects of a cold environment. Cold air inhalation in patients with chronic stable angina results in an earlier onset of symptoms and a significant reduction in exercise capacity. Haemodynamic data suggest that a combination of peripheral and central reflex mechanisms is the most likely explanation for these clinical findings.

There was a similar significant decrease in concentrations of ET-1 during exercise testing irrespective of the temperature of the inhaled air, and a significant increase in AT-II concentrations in response to exercise while breathing room air which was not repeated during cold air inhalation. Peripheral ET-1 and AT-II do not appear to play a part in the pathophysiology of cold intolerance in patients with stable angina.

Further work into cold intolerance in patients with angina should aim at clarifying potential central reflex mechanisms and explore a possible central action for vasoactive peptides.

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