The Effect of Cold Air Inhalation on Angina Pectoris and Myocardial Oxygen Supply

By Mark Hattenhauer, M.D., and William A. Neill, M.D.

SUMMARY
Inhalation of cold air (−20°C) for four minutes provoked angina pectoris in four of 17 coronary disease patients at rest and in four of seven of the patients while they were paced at a heart rate level which was subanginal at room temperature. The cold air did not increase myocardial O₂ consumption significantly, and the accompanying changes in systemic hemodynamic factors known to influence myocardial O₂ consumption were minor. Coronary blood flow determined by the xenon clearance method did not change significantly. In 18 patients, cold air inhalation for 1½ minutes caused no detectable constriction of coronary arteries visualized arteriographically. We conclude that angina pectoris induced by breathing cold air cannot be explained satisfactorily by a concurrent increase in myocardial work and O₂ consumption. Although neither large coronary artery constriction nor generalized coronary arteriole constriction seem to be involved, some other specific effect of cold air inhalation on coronary vasomotion, perhaps affecting collaterals or coronary blood flow distribution, is suspected.

Additional Indexing Words:
Coronary constriction  Coronary ischemia  Myocardial hypoxia
Coronary blood flow  Coronary disease

In certain susceptible patients with coronary disease, cold exposure can provoke attacks of angina pectoris or lower their threshold for exertional angina.1 In a previous investigation of the mechanism of this phenomenon, we found that cutaneous cold stimulation increased myocardial O₂ consumption and coronary blood flow,2 which could be attributed to the concomitant reflex systemic arterial hypertension.2–5 The chest pain which occurred in some of the patients appeared to be related to the increase in heart work in the setting of diminished coronary reserve. There was no evidence to corroborate the contention that cold exposure induces angina pectoris by constricting coronary arteries.1, 6, 7

When patients are in a cold environment under natural conditions, however, inhalation of cold air may produce cardiovascular effects differing from those caused by purely cutaneous cold stimulation.6 In the present investigation, patients with angina pectoris inhaled cold air. We studied the effect of this stimulus on 1) coronary blood flow at rest, 2) the coronary reactive hyperemia during subanginal atrial pacing and 3) the coronary arteries visualized by selective coronary arteriography.

Methods
Thirty-three men with exertional angina pectoris due to ischemic coronary heart disease were studied. Their ages ranged from 42 to 66 years (mean 52 years). Coronary arteriography demonstrated single vessel disease in eight patients, double vessel disease in eight patients and triple vessel disease in 15 patients. Two patients who experienced angina only during cold exposure were not considered candidates for coronary arteriography. Fourteen of the 27 patients with technically satisfactory left ventriculography had ejection fractions < .50 or decreased regional wall motion. NYHA functional classes were: I, two patients; II, six patients; III, 22 patients; IV, three patients. Thirteen patients had ECG evidence of prior myocardial infarction. No patient had clinical evidence of heart failure and none had significant hypertension. Eleven patients who stated that a cold environment definitely aggravated their angina pectoris were classified as cold intolerant by history. The other 22 patients experienced either no or only equivocal effect from cold exposure.

Experimental observations were made during cardiac catheterization performed to investigate the patients' reserve coronary response to atrial pacing and/or during diagnostic coronary arteriography. Written informed consent was obtained prior to the procedure. The patients fasted and received no premedication, and no atropine or nitroglycerin was administered within one hour of the experimental observations. Room temperature was approximately 20°C. Compressed air was refrigerated by liquid N₂ in a special apparatus and delivered to the patients at a rate of approximately 50 L/min via an insulated tube which attached to a loosely fitting soft rubber face mask.

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The air temperature at the face mask was monitored by a thermistor and kept at -20°C (-4°F). The cold air also chilled the nose, lips, mouth, and a small area of the cheeks and chin. Excess cold air escaped over the chin and did not seem bothersome. We encouraged the patients to inhale through the nose at a normal rate and depth. Control observations were made while the patients breathed room air through the same face mask.

In seventeen patients hemodynamic and metabolic studies were carried out during cardiac catheterization. Catheters were positioned in the brachial artery, left ventricle and coronary sinus midway between the ostium and left border of the coronary silhouette. Observations were made with the patients at rest breathing room air or cold air, in random sequence. The influence of cold air inhalation on the increase in coronary blood flow which normally occurs during tachycardia was also determined in seven of the same patients. Initially, each patient's angina threshold was evaluated by atrial pacing, which began at a heart rate of 100 beats/min and was increased every 3 min by 10 beats/min until angina occurred. After waiting at least 20 min, observations were made during atrial pacing at 10 beats/min below the previously established angina threshold while the patients breathed room air or cold air, in random sequence.

Observations consisted of the following: ECG lead II or CM5 and brachial artery and left ventricular pressure were recorded on a photographic Electronics for Medicine recorder. Paired arterial and coronary venous blood samples were analyzed for PO2 and pH (Radiometer Co., Copenhagen), hemoglobin concentration (spectrophotometer) and lactate and pyruvate concentrations.2 Blood O2 concentrations were calculated assuming normal O2 dissociation curve, corrected for pH. In seven patients, O2 concentration of the same coronary venous blood sample was also determined manometrically. O2 concentration by manometric analysis was systematically slightly higher than that calculated from the PO2 data, but the mean differences during control (0.8 ml/100 ml) and cold (1.0 ml/100 ml) were comparable verifying that the cold air inhalation exerted no effect on blood O2 affinity other than that attributable to changes in pH, for which corrections were made.

An increase in coronary venous blood lactate/pyruvate concentration (L/P) greater than 12% (without accompanying increased arterial L/P) was interpreted as evidence of myocardial hypoxia.2 Coronary blood flow was determined by the exponential clearance rate of 133Xenon. The xenon was injected via the left ventricular catheter, and the clearance rate determined from sequential timed brachial arterial and coronary venous blood samples obtained simultaneously from the catheters via manifolds.2 Left ventricular myocardial O2 consumption was calculated as the product of coronary blood flow and coronary (A-V) O2 difference.

Eighteen patients were studied during coronary arteriography using the Judkins percutaneous technique with large, high resolution cut films following injection of 6–8 ml meglumine diatrizoate (66%) and sodium diatrizoate (10%) (Renografin-76, Squibb). (Two of these patients were among the 17 also studied during catheterization.) A selective injection of the right or left coronary artery in the lateral, LAO or RAO projection was chosen from the diagnostic films, based on the technical suitability of arterial segments for accurate measurement. Ten to 15 minutes later, the catheter was repositioned in the coronary ostium and filming repeated in the selected projection while the patient had been breathing the cold air through the face mask for 1–1 1/2 min. The diagnostic room air cut films were always preceded within 60 sec by a Renografin injection for cinearteriography. To avoid possible residual effects of Renografin on the coronary artery size, control cut films with the patient breathing room air were repeated in six patients after waiting 10–15 min from the last Renografin injection. The control and cold air films in these six patients were done in random sequence.

The films were identified only by a code, and coronary artery diameters were measured independently by two observers who did not know the code. Four to six films with the clearest definition were selected from each set. The values for the diameters of the vessels presented in table 2 represent the combined means of the two observers. Magnification factors for the coronary arteries were estimated from the mean diameter of two 25-cent pieces taped on opposite sides of the chest in six patients, realigning the quarters for the three projections. These 18 mean magnification factors ranged only from 1.27 to 1.38, with a mean of 1.31.

Results

Hemodynamic and Metabolic Study during Cold Air Inhalation at Rest

While breathing the cold air, the patients were conscious of the cold temperature but were not obviously apprehensive and experienced no facial or upper airway pain. Physiologic mean data are presented in table 1. The cold air caused slight increases in heart rate and systemic arterial blood pressure. The increases in blood pH and arterial blood PO2 and O2 concentration are consistent with mild hyperventilation. There was a slight but significant decrease in the PO2 but no change in O2 concentration in the coronary venous blood. There was no significant change in coronary blood flow or myocardial O2 consumption.

Four of the 17 patients experienced chest pain while inhaling the cold air at rest. They described the pain as mild but typical of their exertional angina pectoris. The chest pain was accompanied by other objective signs suggesting abnormal myocardial O2 supply: 1 mm ST-segment depression in two patients, significantly increased coronary venous blood L/P in two patients (16% and 38%), and greater than 1 mm Hg decrease in coronary venous blood PO2 in three patients (1.1, 2.5, and 3.0 mmHg). Similar objective changes occurred less often in the remaining 13 patients without pain (ST depression in one, significantly increased coronary venous L/P in one and greater than 1 mmHg decrease in coronary venous PO2 in three). Heart rate, systemic arterial blood pressure, and coronary blood flow data were no different for the patients with chest pain. All four patients who developed chest pain under these experimental conditions had given a history of cold intolerance. Among the 13 patients who did not experience pain, only two were cold intolerant by history.

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Table 1

Hemodynamic and Metabolic Effects of Cold Air Inhalation (1% to 4 minutes)

<table>
<thead>
<tr>
<th></th>
<th>Rest (17 patients)</th>
<th>Sublingual pacing (7 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>Cold air</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>69 ± 2.5†</td>
<td>72 ± 2.5*</td>
</tr>
<tr>
<td>SAP systolic (mm Hg)</td>
<td>143 ± 4.8</td>
<td>155 ± 4.3†</td>
</tr>
<tr>
<td>diastolic (mm Hg)</td>
<td>73 ± 2.3</td>
<td>80 ± 1.7†</td>
</tr>
<tr>
<td>mean (mm Hg)</td>
<td>100 ± 3.0</td>
<td>100 ± 2.5†</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>11 ± 1.3</td>
<td>13 ± 1.5</td>
</tr>
<tr>
<td>O₂ conc. a (ml/100 ml)</td>
<td>18.5 ± .24</td>
<td>18.7 ± .23*</td>
</tr>
<tr>
<td>a-cv (ml/100 ml)</td>
<td>12.3 ± .33</td>
<td>12.4 ± .33</td>
</tr>
<tr>
<td>PO₂ a (mm Hg)</td>
<td>74 ± 3.0</td>
<td>79 ± 4.0*</td>
</tr>
<tr>
<td>cv (mm Hg)</td>
<td>20.8 ± .58</td>
<td>20.1 ± .53†</td>
</tr>
<tr>
<td>pH a (units)</td>
<td>7.40 ± .005</td>
<td>7.43 ± .014†</td>
</tr>
<tr>
<td>cv (units)</td>
<td>7.35 ± .004</td>
<td>7.39 ± .013†</td>
</tr>
<tr>
<td>CBF (ml/100 g·min)</td>
<td>97 ± 4.8</td>
<td>101 ± 5.0</td>
</tr>
<tr>
<td>MVO₂ (ml/100 g·min)</td>
<td>11.9 ± .73</td>
<td>12.6 ± .73</td>
</tr>
<tr>
<td>Lactate a (mM)</td>
<td>.50 ± .02</td>
<td>.51 ± .03</td>
</tr>
<tr>
<td>a-cv/a (mM)</td>
<td>.23 ± .03</td>
<td>.20 ± .04</td>
</tr>
<tr>
<td>Lactate/Pyruvate a</td>
<td>5.0 ± .24</td>
<td>5.0 ± .20</td>
</tr>
<tr>
<td>cv</td>
<td>5.0 ± .14</td>
<td>5.2 ± .14</td>
</tr>
</tbody>
</table>

*P < 0.05 cold vs room air.  
†P < 0.01.  
‡P < 0.001.  
¶Mean ± SEM.  
Abbreviations: HR = heart rate; SAP = systemic arterial pressure; LVEDP = left ventricular end diastolic pressure; conc = concentration; a = arterial; cv = coronary venous; CBF = coronary blood flow; MVO₂ = myocardial O₂ consumption.

In order to evaluate further the hypothesis that cold exposure provokes angina pectoris by increasing myocardial O₂ consumption needs, the product of heart rate and systolic systemic arterial blood pressure (HR × SAP) during angina induced by cold air inhalation and by atrial pacing are compared in figure 1. The HR × SAP during angina induced by cold air inhalation in the four patients is near their resting level and far below the level at which angina was provoked during pacing.

Hemodynamic and Metabolic Study during Cold Air Inhalation and Simultaneous Atrial Pacing

Mean values for the seven patients are presented in table 1. Systemic arterial blood pressure and arterial blood PO₂ and pH were slightly higher during cold air inhalation. The mean paced heart rate was 112 beats/min. Coronary blood flow, which was increased above the control value by the tachycardia, was not further influenced significantly by simultaneous inhalation of cold air at the same heart rate. The cold air precipitated angina pectoris at the sublingual pacing level in three patients and in another intensified mild angina present at the same heart rate even while the patient was breathing air at normal room temperature. Two of these four patients were among those who developed chest pain while breathing cold air at rest. Two of the four patients with chest pain had 1 mm ST-segment depression, two had significantly increased coronary venous blood L/P (each 23%) and one had significantly decreased coronary venous blood PO₂ (2.5 mmHg). These signs of myocardial hypoxia occurred in none of the three patients who did not develop chest pain. Two of the seven patients were cold intolerant by history; both developed chest pain and ST-segment depression. Heart rate, systemic arterial blood pressure, and coronary blood flow data were not different between patients with or without chest pain.

Coronary Arteriography during Cold Air Inhalation

Cold air inhalation caused chest pain in one of the 18 patients, who was among the five patients of this group with a history of cold intolerance. No focal coronary artery constriction was seen in any of the 18 patients. Coronary artery diameters are given in table 2 for the six patients with control films taken 10-15 minutes after the last intracoronary Renografin injection. Under these conditions, there was no consistent difference in the coronary artery diameters whether the patient was breathing room air or cold air. On the other hand, coronary artery diameters of the initial

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diagnostic films, which were always immediately preceded by cinearteriography, were consistently larger ($P < 0.001$). There was no detectable effect of cold air on collateral vessels visible in two of the six patients with rigidly comparable control observations.

Chest Pain and Cold Intolerance History

Table 3 summarizes the relationship between a previous history of cold intolerance and the development of chest pain during cold air inhalation at rest in the laboratory, including observations made during metabolic and arteriographic studies. Chest pain was induced by cold air more frequently in patients who had initially stated that they were cold intolerant, a correlation which is similar to that found with cutaneous cold stimulation.²

Discussion

In investigating the mechanisms by which exposure to a cold environment aggravates patients’ angina pectoris, we elected to separate cold exposure as it naturally occurs into two components: cutaneous chilling and inhalation of cold air. In a previous study,² an intense cutaneous cold stimulus applied to the forehead of patients with coronary heart disease increased the systolic systemic arterial blood pressure by 27% and the myocardial O₂ consumption by 31%.

The evidence in those studies suggested that the chest pain and increased coronary venous L/P that were provoked in several patients were due to augmented myocardial O₂ consumption in excess of available coronary reserve.

In the present investigation of cold air inhalation, however, it is difficult to explain the chest pain that developed in four patients at rest by an increase in myocardial O₂ consumption needs beyond available coronary reserve since 1) myocardial O₂ consumption calculated from the product of coronary blood flow and (A-V) O₂ difference remained essentially constant and 2) changes in systemic hemodynamic factors

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**Table 2**

*Coronary Angiography*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Coronary artery</th>
<th>Room air diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Delay</td>
</tr>
<tr>
<td>DM</td>
<td>LAD prox</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>LAD dist</td>
<td>2.3</td>
</tr>
<tr>
<td>WW</td>
<td>RC prox</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>RC mid</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>RC dist</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>RC rv</td>
<td>2.3</td>
</tr>
<tr>
<td>FK</td>
<td>LAD prox</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>LAD dist</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>LC prox</td>
<td>2.5</td>
</tr>
<tr>
<td>AL</td>
<td>LAD prox</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>LC om</td>
<td>2.9</td>
</tr>
<tr>
<td>IW</td>
<td>RC prox</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>RC pd</td>
<td>2.2</td>
</tr>
<tr>
<td>MH</td>
<td>LAD prox</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>LAD dist</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Mean = SEM

$2.8 \pm 0.16^*$

$2.4 \pm 0.18$

$2.4 \pm 0.16$

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*$P < 0.001$ initial vs delay and initial vs cold air.

Numbers represent the diameters of arteries measured on the cut films, uncorrected for magnification. Initial = initial diagnostic series, preceded by intracoronary Renografin injection within 1 min. Delay = room air with a 10-15 min interval since the last Renografin injection; Cold air = cold air with a 10-15 min interval since the last Renografin injection.

Abbreviations: LAD = left anterior descending; LC = left circumflex; RC = right coronary; prox = proximal; dist = distal; rv = right ventricular branch; om = obtuse marginal branch; pd = posterior descending branch.

---

**Table 3**

*Correlation between Chest Pain Induced by Cold Air Inhalation and Previous History of Cold Intolerance*

<table>
<thead>
<tr>
<th>Laboratory cold air inhalation</th>
<th>Cold intolerance history</th>
<th>No cold intolerance history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>No chest pain</td>
<td>6</td>
<td>22</td>
</tr>
</tbody>
</table>
known to influence myocardial metabolic requirements were relatively small. In an individual patient, angina ordinarily occurs at a reproducible HR × SAP level under various stress conditions, which is consistent with the observation that HR × SAP is a major determinant of myocardial \( O_2 \) consumption. After ingestion of a meal, for example, exertional angina occurs at a lower work level but at the same HR × SAP required to precipitate angina in the fasting state. The increase in HR × SAP which occurred in the four patients who developed chest pain during cold air inhalation, however, did not approach that needed to precipitate angina by atrial pacing in the same four patients (fig. 1). Leon also found that cold air inhalation increased HR × SAP only slightly but postulated that the cold stimulus might increase myocardial \( O_2 \) needs by means of augmented cardiac contractile state from sympathetic stimulation, which exerts a separate effect of myocardial \( O_2 \) consumption. Although left ventricular dp/dt was not determined in the present study, nevertheless, the constant calculated myocardial \( O_2 \) consumption does not support the postulation of augmented contractile state and provides strong independent evidence that the effect of cold air inhalation on myocardial \( O_2 \) consumption needs is not sufficient by itself to explain the chest pain.

One might question the significance of the subjective symptom of chest pain alone. Its correlation with accompanying ECG and coronary venous blood chemical signs indicative of myocardial hypoxia, however, corroborates our conclusion that the chest pain during cold air inhalation did, in fact, represent myocardial hypoxia.

The slight decrease in the mean value for coronary venous blood \( O_2 \) for all patients (table 1) can be attributed to increased blood \( O_2 \) affinity due to the rise in blood pH, which suggests that involuntary hyperventilation may contribute to myocardial hypoxia when patients are exposed to cold. When correction was made for pH changes, there was no other discrepancy between \( O_2 \) and \( O_2 \) concentration of blood samples (see Methods), demonstrating that cold air exposure exerted no specific effect on blood \( O_2 \) affinity. Leon found that inhalation of cold air produced no significant change in blood temperature which would influence \( O_2 \) affinity.

Coronary arteriole vasomotion is a major factor regulating myocardial \( O_2 \) supply. We interpret the lack of effect of cold air inhalation on coronary blood flow at rest or during atrial pacing as evidence that neither generalized coronary arteriole constriction nor inhibition of coronary reactive hyperemia is responsible for the influence of cold exposure on angina. In regard to the question of inhibition of reactive hyperemia, it is acknowledged that the stimulus for the coronary hyperemia was atrial pacing, not exercise, and the cold air breathing was instituted after the hyperemia was already established.

Cutaneous cold stimulation causes reflex peripheral vasoconstriction mediated by alpha adrenergic receptors. Although coronary vasomotion appears to be dominated by myocardial metabolic needs and is thought not to participate in reflex vasoconstriction, reversible focal constriction of large coronary arteries sometimes seen in the setting of mechanical manipulation during surgery or during ostial catheterization and apparently occurring without mechanical provocation in a patient with Prinzmetal angina support the possibility that reflex coronary vasoconstriction might be induced under physiologic conditions, such as cold exposure. Our arteriographic observations showed no evidence of coronary vasoconstriction during cold air inhalation even though the method was adequate to demonstrate easily the coronary vasodilation effect of Renografin (table 2, initial vs delay). Although one might reason that the failure of the arteries to increase in diameter in response to the higher arterial pressure during cold air inhalation is evidence for opposing vasoconstriction, this interpretation seems doubtful considering the small amount of pressure rise. Cold air provoked chest pain in only one of the 18 patients during arteriography. The arteriographic observations, therefore, pertain more to what might be considered the typical response to cold and do not eliminate completely the possibility that a unique coronary vasomotor response might lead to chest pain under exceptional circumstances which we were not able to bring about experimentally during the arteriographic procedure. On the other hand, the absence of widening of coronary \( (A-V) \) \( O_2 \) difference in the other patients who did develop chest pain during the cardiac catheterization studies is further evidence against constriction of a major coronary artery as the basis of the angina.

Coronary arteriography visualizes large and medium-sized arteries, whereas coronary blood flow determined by myocardial clearance rate of xenon is dominated by the regions of relatively normally perfused myocardium. Neither method is capable of detecting changes in blood flow distribution which might be brought about by vasomotion of very small arteries, and both are especially insensitive to changes in blood flow in the most ischemic regions. We believe that the chest pain and evidence of myocardial hypoxia provoked by cold air inhalation despite only minor increase in heart work, together with the absence of evidence of generalized coronary arteriole constriction or focal constriction of large conducting coronary arterioles, supports the theory that the effects of cold air inhalation on myocardial oxygen consumption and possibly on coronary vascular resistance are important factors in the production of chest pain during cold.
arteries, suggest that cold air constricts minute coronary collaterals or other blood vessels specifically affecting blood flow to potentially ischemic regions of the myocardium.

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