Acute Myocardial Infarct Extension into a Previously Preserved Subendocardial Region at Risk in Dogs and Patients

ROBERT FORMAN, M.D., SANGHO CHO, M.D., STEPHEN M. FACTOR, M.D., AND EDWARD S. KIRK, PH.D.

SUMMARY  In this study we quantitated the region of preserved myocardium between a subendocardial myocardial infarct (SEMI) and the endocardium in dogs and determined whether this preserved zone was within the region at risk and whether infarct extension could occur in this region. We also evaluated whether a similar subendocardial region exists in patients with SEMI. A 40-minute temporary occlusion of the left anterior descending coronary artery (LAD) in eight dogs resulted in a 35 ± 5% transmural infarct with 8 ± 1% subendocardial preservation as assessed by point-counting of the histologic specimens. In vivo perfusion of coronary vessels with Microfil showed that this preserved subendocardial zone was within the region at risk. The preserved subendocardial zone had significantly fewer cell layers in the dogs ventilated with room air than in dogs ventilated with 100% oxygen (8 ± 4 vs 19 ± 4, p < 0.001), which suggests that diffusion from the ventricular cavity was the mechanism of cell preservation. In contrast, the inspired oxygen concentration did not influence the size of the SEMI. Reocclusion of the LAD for 24 hours in an additional eight dogs, 1 week after a SEMI had been created by a 40-minute temporary occlusion, resulted in both subendocardial and subepicardial extension involving 5 ± 1% and 29 ± 9%, respectively, of the transmural myocardium at the infarct center. Subendocardial infarct extension of a similar dimension to that in dogs ventilated on 100% oxygen was observed in postmortem material from eight patients with infarct extension. The preserved layers of subendocardium presumably receive sufficient nutrients from the ventricular cavity to maintain the viability of this region during temporary, but not permanent, reduction of blood supply from the coronary arteries.

THE SUBENDOCARDIUM is the region of the ventricular wall that is most vulnerable to ischemia and subsequent necrosis,1 which may result from its greater reduction in systolic coronary flow compared with the subepicardium.2 After 40 minutes of temporary ischemia in dogs, Reimer et al.3,4 found a subendocardial myocardial infarct (SEMI) involving 28–38% of the transmural myocardium. After progressively longer periods of ischemia, a greater proportion of the region at risk became infarcted, until after 6 hours, 78–85% of the region was necrotic. Thus, a “wave front” occurs, extending from the subendocardium toward the subepicardium, which is dependent on the duration of ischemia.3,4

After myocardial infarction, observations of the subendocardial zone generally have revealed a small layer of preserved myocytes (one to three cells thick) immediately beneath the endocardium.5 However, in creating a model of acute myocardial infarction and extension in the dog, we observed an unexpectedly large region of subendocardial preservation after the initial infarct, which subsequently underwent necrosis during extension of the infarct.

In this study we investigated the dimensions and blood supply of this subendocardial layer of preserved myocardium after SEMI in the dog, and evaluated the magnitude and direction of infarct extension when a new infarct was superimposed on a healing SEMI. Finally, we examined postmortem specimens from patients who died with healed SEMI and acute infarct extension to determine whether a similar vulnerable region of subendocardial preservation exists in humans.

Methods

Studies in Dogs

A SEMI was produced in 12 dogs, eight ventilated with 100% oxygen and four with room air; the dogs were killed after 24 hours. In an additional eight dogs ventilated with 100% oxygen, a similar SEMI was created, infarct extension induced on the seventh day and the dogs were killed on the eighth day. These times were chosen in the infarct extension experiment so that the two infarcts could be readily distinguished histologically in the same specimen. Ventricular fibrillation and death occurred shortly after release of the temporary coronary occlusion in seven additional dogs ventilated with 100% oxygen and three additional dogs ventilated with room air. These dogs were not included in the subsequent analysis.

Production of Subendocardial Infarct

SEMI was produced by the method of Jennings et al.6,7 After anesthesia with i.v. pentobarbital (30 mg/kg), endotracheal intubation and ventilation with 100% oxygen delivered by a pressure-cycled ventilator (Bird, Mark 7), a left thoracotomy was performed. Teflon cannulas were inserted into the left common carotid artery and left atrium and exteriorized at the back of the neck in dogs assigned to infarct extension experiments. The left anterior descending coronary artery (LAD) was isolated distal to the first major diag-
onal branch and temporarily occluded with silk thread for 40 minutes and then released. Aortic and left atrial pressures were monitored before and for the first hour after LAD occlusions. The systemic arterial blood 

the initial two microsphere injections until the time of sacrifice. Corrections could not be made for the two microsphere injections performed on the day before sacrifice, for the MBF in the infarcted region was not the same as MBF in the normal region before the second LAD occlusion.

**Definition of Blood Flows to Region at Risk**

The blood supplies of both the region at risk and normal zones were defined using two Microfil solutions, one red and one white (Canton Bio-medical Products). Microfil is a silicone rubber compound that has a low viscosity, fills the capillary microcirculation, and gels in situ. The dogs were reanesthetized before being killed and a second thoracotomy was performed. The left main coronary artery was dissected and cannulated through the left subclavian artery with a Gregg cannula, and perfused from the left carotid artery. The LAD was also cannulated at the site of the original occlusion and separately perfused. Reservoirs of white Microfil were connected to the LAD and red Microfil to the left main coronary artery, and simultaneously switched to perfuse each vasculature at identical pressures (100 mm Hg). The capillaries in the region at risk were filled with white Microfil and the remaining myocardium, not at risk, filled with red Microfil. These colors were apparent on both the gross sections and on the histologic sections using epi-illumination (i.e., light reflected from, rather than passing through, the section).

**Histology and Quantitation of Infarction and Preservation**

The excised hearts were fixed in 3.7% formalin and subsequently sectioned in layers perpendicular to the axis between the aortic valve and the left ventricular apex. The nonadjacent rings from the middle ventricular wall were sectioned for histologic evaluation. For the purpose of this study, a transmural section from each ring from the central portion of the histologically identified infarcts, excluding the anterior papillary muscle, was examined after staining with hematoxylin-eosin. The SEMI was readily distinguished by the presence of characteristic hyperesinophilia and hemorrhagic contraction-band necrosis associated with reperfusion infarcts. In addition, the 24-hour infarct showed hyaline degeneration and a polymorphonuclear infiltrate, whereas the 1-week-old infarct showed organizing granulation tissue and chronic inflammation.

The extent of transmural infarction preservation and, where relevant, infarct extension was calculated by point counting in the central infarct zone. Histologic sections were placed in a photographic enlarger, magnified eight times and photographed on print paper. Point counting was performed by overlaying the print with a transparent sheet having a line grid of 2.5-mm horizontal and vertical lines. The total number of points (grid crossings) falling on the SEMI, infarct extension and preserved myocardium were counted and the average from two nonadjacent rings was re-
corded. The depth of the preserved subendocardial zone was measured in cell widths by averaging this depth at 10 equidistant regions in the specimen.

Clinical Studies
Concurrent with these experiments we encountered a patient with a well-documented healing SEMI and subsequent acute extension who had histologic features similar to those in the dogs. We then retrospectively searched the cardiac pathology files of one of the authors for case material classified as old SEMI and acute infarct extension. The histologic sections from seven additional cases were retrieved and examined independently by two pathologists. This case file does not represent an inclusive indexing of consecutive cardiac cases, but is a compilation of interesting material observed personally. Therefore, the retrieval from this file of seven cases of SEMI with extension should not be taken as an indication of the prevalence of this condition.

The history of one patient is given in full because the clinical course and histology were similar to those in our dogs with myocardial infarct extension. The other patients with infarct extension were complicated by multivessel disease and a less precisely documented clinical course of infarct extension.

Clinical Summary Index Case
The patient was a 69-year-old man with no history of coronary artery disease who had 1 hour of severe central chest pain associated with diaphoresis. The ECG showed transient 1½-mm ST-segment elevation in the inferior leads and transient complete heart block with junctional rhythm. After 30 minutes, the ST segments became depressed in the inferolateral leads, but Q waves did not develop. Serum CK was 312 IU with 10% MB fraction, and SEMI was diagnosed. Before discharge he had a positive stress test and was treated with vasodilator therapy. Elective catheterization 1 month later showed 95% proximal lesion of the right coronary artery and a less than 50% lesion of the LAD. Immediately after catheterization, the patient developed severe chest pain associated with persistent inferolateral ST-segment elevation, transient complete heart block and recurrent episodes of ventricular tachycardia. Despite intraaortic balloon counterpulsation and administration of antiarrhythmic medication, the patient died after 24 hours.

Statistics
All results are expressed as the mean ± sd. Analysis of variance was used to compare heart rates and pressures in dogs ventilated with 100% oxygen or room air before and after LAD occlusion. A paired t test was used to compare the heart rates and pressures before and after the first and second LAD occlusions in dogs with infarct extension. The t test was used to compare the number of preserved layers of cells in the subendocardium of dogs ventilated with 100% oxygen and room air.

Results
Studies in Dogs
The results of hemodynamic measurements made before and after LAD occlusion in each group of dogs are presented in table 1. There was no significant difference between the measurements in the open-chest anesthetized dogs ventilated with 100% oxygen and those ventilated with room air. However, the heart rates and aortic pressures in the closed-chest and lightly sedated dogs before and after the LAD occlusion during infarct extension were significantly less than during the initial LAD occlusion under anesthesia (p < 0.002). LAD occlusion increased heart rate in both anesthetized and lightly sedated dogs (p < 0.02), but did not increase aortic pressure. The left atrial pressure increased in all dogs after LAD occlusion.

The MBFs in dogs with myocardial infarct extension are shown in table 2. They confirm the marked reduction in flow after the first and second LAD occlusion, which resulted in a greater reduction in subendocardial than in subepicardial flow, and partial restoration of MBF in the ischemic region after release of the temporary LAD occlusion. Reperfusion after production of the SEMI did not restore flows to control values, presumably because of early damage to the vasculature and diminished blood flow requirements in the infarcted myocardium. Uncorrected MBF, in the ischemic region measured with microspheres injected before the first occlusion averaged 0.718 ml/min/g; flow in the normal zone was 0.997 ml/min/g. If the flows in this preocclusion period were equal in both

<p>| Table 1. Hemodynamic Data After Left Anterior Descending Coronary Artery Occlusion |
|---------------------------------|---------|--------|--------|</p>
<table>
<thead>
<tr>
<th>Experimental design</th>
<th>FIO₂</th>
<th>Chest</th>
<th>Control</th>
<th>10 minutes after LAD occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>AOP (mm Hg)</td>
<td>LAP (mm Hg)</td>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>Single infarct</td>
<td>1.0</td>
<td>Open 8</td>
<td>149 ± 19</td>
<td>148/108 ± 22/15</td>
</tr>
<tr>
<td>Single infarct</td>
<td>0.2</td>
<td>Open 4</td>
<td>158 ± 18</td>
<td>142/110 ± 24/20</td>
</tr>
<tr>
<td>Infarct extension</td>
<td>Day 1</td>
<td>Open 8</td>
<td>146 ± 20</td>
<td>139/106 ± 13/13</td>
</tr>
<tr>
<td>Infarct extension</td>
<td>Day 7</td>
<td>Closed 8</td>
<td>95 ± 30</td>
<td>118/73 ± 10/9</td>
</tr>
</tbody>
</table>

Values for heart rate and aortic and left atrial pressures are mean ± sd.
Abbreviations: AOP = aortic pressure; FIO₂ = fraction inspired oxygen; HR = heart rate; LAD = left anterior descending coronary artery; LAP = left atrial pressure.
regions, it suggests that 28% of the microspheres were “lost” from the ischemic region. The correction of flow data in the same ischemic sample from microspheres injected 10 minutes after the first occlusion resulted in an increase in flow from 0.055 to 0.073 ml/min/g. The absolute increase is small, as observed by Murdock and Cobb,\(^\text{10}\) and does not change the conclusions drawn from these measurements. No correction can be made for blood flow measurements during the second occlusion because it could not be assumed that the flow before the second occlusion was the same as in the normal and ischemic regions.

The single 40-minute temporary occlusion of the LAD in eight dogs ventilated with 100% oxygen resulted in an infarct that involved 35 ± 5% (mean ± SD) of the myocardium at the center of the infarct. A preserved layer of 59 ± 7% of the myocardial thickness was observed between the infarct and the epicardium and 8 ± 1% between the infarct and the endocardium. The subendocardial preserved zone was 19 ± 4 cell layers deep.

Gross examination of the cross-sectional ring of myocardium (fig. 1) and histology showed that the entire region of the hemorrhagic SEMI, with its adjacent subepicardial and subendocardial preserved zones, was filled with white Microfil. Epi-illumination showed only white Microfil in the capillaries in those preserved zones and focally in the region of the SEMI (fig. 2).

Forty-minute temporary occlusion of the LAD in the additional eight dogs in which infarct extension was produced 1 week later by permanent occlusion of that vessel for 24 hours resulted in an infarct that involved 29 ± 15% of the myocardium at the center of the infarct. This was similar in size to the single-infarct experiment. Infarct extension occurred in both an endocardial (fig. 3) and an epicardial direction. The new necrosis, or infarct extension, involved an additional 21 ± 9% of the myocardium toward the epicardium, and 5 ± 1%, or 11 ± 2 cell layers, in an endocardial direction. The subendocardial preserved zone was now reduced to 3 ± 1%, or 7 ± 3 cell layers. Thus, the original preserved zone was 8% and the same size as that observed in the dogs with single 40-minute temporary occlusion.

Examination of the histologic specimens from dogs ventilated with room air showed that the zone of subendocardial preservation had significantly fewer cell layers (8 ± 4) than that in the dogs ventilated with 100% oxygen (\(p < 0.001\)). In dogs ventilated with room air, the sizes of this preserved zone (7 ± 1%) and the SEMI (36 ± 9%) were similar to those in dogs ventilated with 100% oxygen. Thus, each cell layer in this preserved zone was thicker than that in dogs ventilated with 100% oxygen. The absolute thickness of the preserved zone was not different in each group of dogs. The arterial PO\(_2\) was 383 ± 78 mm Hg in the dogs ventilated with 100% oxygen and 96 ± 7 mm Hg in those ventilated with room air.

![Figure 1](http://circ.ahajournals.org/issue/1/1/120/CIR.jpg)  
**Figure 1.** A gross cross-sectional ring of canine myocardium after subendocardial myocardial infarction (SEMI) and perfusion of the tissue at risk with white Microfil. Dark, hemorrhagic, well-demarcated SEMI extends laterally within the white Microfil-perfused zone. Note the large uninvolved epicardial zone and the very narrow uninvolved endocardial region immediately subjacent to the hemorrhagic infarct (arrow).
Patient Material

Autopsy of the index patient described in the Methods section revealed a 50% luminal occlusive lesion of the proximal right coronary artery and superimposed acute thrombus mixed with cholesterol and foamy histiocytes completely occluding the vessel. Fresh rupture of the coronary artery atherosclerotic plaque was shown on serial sections. There was an insignificant lesion, but no obstruction, of the LAD. Histologic examination of the myocardium revealed a healed SEMI with the appearance of organized reperfusion necrosis extending 22% across the inferior wall consistent with 1-month-old infarct. There was evidence of acute (approximately 24-hour-old) infarct extension into previously preserved myocardium in both epi- and endocardial directions (fig. 4). The infarct had extended 34% in an epicardial direction and 5%, or 10 cells in an endocardial direction, leaving a 4% subendocardial preserved layer six cells deep.

Histologic evaluation was performed on seven additional patients with SEMI and acute extension identified retrospectively after the index case was recognized. The cases had features similar to those in the dogs and the index case. Healed SEMI was present in all cases. In six cases, the old infarct was typified by densely collagenized scar, which did not permit estimation of age. In one case, scar tissue was still organizing and had the appearance of myocytolytic necrosis consistent with a relatively recent reperfusion injury. In all seven patients, there was a subendocardial layer of myocardium averaging 19 cells thick that had survived the SEMI. Within this zone, however, there was recent (less than 24-hour-old) acute necrosis that was 13 ± 2 cells thick, extending toward the endocardial surface. Preserved subendocardial tissue, which histologically survived the acute extension, was 6 ± 1 cells deep.

Discussion

In this study we found a subendocardial layer of preserved myocardium 19 cells thick beneath a SEMI in dogs ventilated with 100% oxygen. When infarct extension was induced, it occurred in both an epi- and endocardial direction, leaving a layer of only seven subendocardial cells that survived and an epicardial layer of varying thickness. The injection of different-colored Microfil solutions into the vessels of the region

FIGURE 2. Subendocardial myocardial infarction (SEMI) in a dog 24 hours after a 40-minute temporary occlusion of the left anterior descending coronary artery (LAD). A well-demarcated SEMI is seen above, and a zone of 10-15 layers of preserved myocardial cells is seen below the arrows, extending to the endocardial surface. The entire preserved region is perfused by capillaries, filled with white Microfil, demonstrating that it is supplied by the LAD. The SEMI at this level has no Microfil perfusion, presumably because capillaries have been destroyed or obstructed by the infarct process. Epi-illuminated; hematoxylin-eosin stain; magnification × 150.

FIGURE 3. Subendocardial myocardial infarction (SEMI) in a dog produced by a temporary occlusion of the left anterior descending coronary artery 1 week before can be seen undergoing healing. After permanent occlusion of the same vessel at the same location, there is extension of acute myocardial infarction toward the endocardial surface into the previously preserved subendocardial zone. Acute necrosis is also present in the previously preserved subepicardial region (not shown). The hyper-eosinophilic, acutely necrotic cells (slightly darker cells between the arrows) extend to within three cells of the endocardium. Thus, the zone of preservation in the subendocardium, now corresponds to what is usually seen with transmural infarctions. Hematoxylin-eosin stain; magnification × 150.
at risk and normally perfused myocardium showed that the subendocardial preserved cells, which survived the temporary coronary artery occlusion and into which extension occurred, were in the region at risk.

A thin zone of noninfarcted muscle between the endocardium and the myocardial infarct has been observed histologically in patients who died after acute myocardial infarction associated with partially occluded coronary arteries. These patients often had subendocardial rather than transmural myocardial infarcts. Frenoligio et al. observed a similar layer of preserved cells, after 1 hour of coronary occlusion in the dog. After longer periods of ischemia, this layer of viable myocytes decreased in thickness and by 14 hours only Purkinje fibers remained structurally intact. This same group also showed that the blood flow, as measured by microspheres, was as markedly reduced in the subendocardial preserved zone during ischemia as flow to the adjacent SEMI.

After transmural myocardial infarction in the dog, spontaneous diastolic depolarization and marked prolongation of the action potential are found in the surviving Purkinje fibers and are thought to be responsible for the ventricular arrhythmias occurring at 24 hours. However, before 14 hours of ischemia or after 2 hours of ischemia with reperfusion, markedly abnormal electrical activity has been found in a 10–20-cell layer of subendocardial myocardium, while the Purkinje fibers showed significantly less abnormality. Under these latter circumstances, the surviving subendocardial myocardium is considered responsible for the ventricular arrhythmias.

Our data and the flow measurements of the above authors suggest that the layer of 19 preserved cells in the subendocardium beneath a SEMI is within the region at risk and not independently supplied by coronary collateral vessels. The number of layers of preserved myocardial cells beneath the SEMI in dogs ventilated with room air was significantly less than that in dogs ventilated with 100% oxygen, but the thickness of this zone was similar. This smaller number of preserved cell layers may reflect a greater degree of ischemic damage accompanied by more marked cellular swelling and interstitial edema. Tissue swelling has been reported to occur in the early stages after reperfusion of temporary ischemic myocardium. Preservation of these cells is probably due to direct supply of nutrients from the ventricular cavity either by diffusion from the ventricular cavity or perfusion via subendocardial channels. The significant reduction in the number of cell layers of this region and the associated similar size SEMI when the arterial Po2 was decreased fourfold favors diffusion as the operative mechanism. The distance between perfused and anoxic tissue in the contracting heart is one or two cells, but the distance can be increased 10-fold in the asystolic heart. If diffusion maintained the viability of a layer as thick as 19 cells in our specimens, presumably the metabolism of these cells must have diminished as a result of their ceasing to contract. However, the preservation was only temporary and did not prevent either extension of infarction or more prolonged occlusion from infarcting this zone.

We found no difference in the transmural dimension of the SEMI produced in dogs ventilated with room air and those ventilated with 100% oxygen. However, Maroko et al. using different methods of infarct production and assessment of infarct size, found smaller infarcts in dogs ventilated with 40% oxygen than in dogs ventilated with room air.

Our histologic findings of infarct extension in the eight patients with subepicardial infarct extension revealed a similar phenomenon of subendocardial extension. The dimensions of the subendocardial infarct extension in patients were the same as those in the dog. The one case described in detail appears similar in its pathophysiology to our dog model of infarct extension. This patient had a SEMI associated with healed reperfusion necrosis, suggesting a temporary coronary artery occlusion, possibly due to spasm or thrombus. The fixed atherosclerotic lesion in the coronary artery supplying the infarct zone involved no more than 50% of the luminal diameter. Subsequent total occlusion
occurred acutely at the site of the initial obstruction, with a thrombus superimposed on the atheromatous plaque. Thus, this sequence of events mimics our experimental production of a transient coronary occlusion followed by permanent occlusion at the same site.

Recurrence of infarction is frequent in patients with SEMI and has been recently reported to occur at the same site as the initial infarct in 86% of cases by Marmor et al. and 70% of cases by Hutter et al., often within 14 days of the original infarct. Marmor et al. suggested that the same site of coronary arterial obstruction was involved in both infarctions, that transitory improvement in flow had left viable myocardium at risk for infarct extension and that recurrent infarction may depend upon spasm associated with incomplete obstruction. Our model of SEMI with extension approximates the sequence of events postulated above.

It has been suggested that acute reperfusion of ischemic myocardium may increase the infarct size and result in hemorrhagic necrosis. However, numerous reports have shown that reperfusion decreases the size of infarction. Because vascular tissue is more resistant to ischemic injury than myocardium, the hemorrhagic necrosis is considered to occur in regions that are predestined, at the time of reperfusion, to show signs of infarction at subsequent histologic examination. Significant hemorrhage was only observed in myocardium in which the blood flow had been reduced to less than 15% of control.

Recognition of infarct extension from specimens stained with hematoxylin-eosin may underestimate the incidence of infarct extension. For infarct extension to be recognized from human postmortem material, not only must the infarct and its extension be separated by several days, but death must also occur within days of the infarct extension.

From our experiments in dogs and human postmortem material described above and that reported previously, we expect to find a band of preserved subendocardial myocardium still at risk in patients or dogs with SEMI. Consequently, the presence of subendocardial extension of acute myocardial infarction appears to be an excellent marker of the more extensive epicardial extension that it accompanies in both dogs and patients. A new infarct on the lateral or epicardial aspect of an older SEMI may be interpreted as either extension of the original infarct or as a new infarct not within the region at risk. However, the new necrosis seen on the subendocardial aspect of an old SEMI is within the region at risk and therefore implies extension of the older infarct.

The volume of muscle preserved in this subendocardial region is insufficient to be of hemodynamic consequence, but could be important in the origin or pathway of arrhythmias in the presence of SEMI or in the early hours of transmural infarction. It therefore was of interest to observe that a similar zone of subendocardial preservation could be found in human postmortem material.

Acknowledgment

The authors gratefully acknowledge the technical assistance of Walter Leon and Herbert Parker and the secretarial assistance of Marilyn Sasso.

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Increased Exercise Tolerance After Nitroglycerin Oral Spray: A New and Effective Therapeutic Modality in Angina Pectoris

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SUMMARY  The prophylactic antianginal efficacy of nitroglycerin (NTG) oral spray was assessed in 20 patients with angiographically documented coronary disease and stable angina pectoris. The evaluation was by a randomized crossover trial involving treadmill exercise testing. On study day 1, a control treadmill exercise test was performed, followed 30 minutes later by a second exercise test 2 minutes after administration of either placebo (group A, 10 patients) or NTG spray 0.8 mg (group B, 10 patients). One week later, on study day 2, the patients again underwent control treadmill exercise testing followed by a second exercise test after either NTG spray (group A) or placebo (group B). NTG spray delayed the onset of anginal pain during exercise by a mean of 100 ± 64 seconds (p < 0.001) in 13 patients and prevented pain entirely in seven. Placebo did not significantly delay the appearance of angina and prevented chest pain in only one patient. NTG spray increased treadmill exercise duration by 31% before the onset of angina (p < 0.001); placebo did not significantly alter the duration of exercise. NTG spray abolished in six patients and delayed in 14 patients the onset of exercise-induced ST-segment depression of 1 mm (p < 0.001). Patients achieved a higher rate at peak exercise with NTG spray, and yet the maximal exercise-induced ST-segment depression of 2.1 ± 1.0 mm during the control study declined to 1.3 ± 0.9 mm on NTG spray (p < 0.001). Placebo had no effect on exercise ST-segment depression. These data indicate that the oral NTG spray is an effective prophylactic for exercise-induced angina.

THE MAINSTAY of treatment for angina pectoris for the last hundred years has been nitroglycerin (NTG).1 NTG reliably relieves angina and augments exertional tolerance when used prophylactically.2 When administered sublingually in tablet, NTG reaches peak blood levels 2 minutes after its dissolution.7 However, the time required for the tablet to dissolve varies from person to person and further delays the onset of action for pain relief. NTG oral spray theoretically should eliminate the time required for tablet dissolution. When sprayed onto the tongue, it is directly absorbed and thus might afford more rapid and reliable action.

We assessed the therapeutic efficacy of NTG spray in patients with exercise-induced angina and obtained subjective and objective measurements during treadmill exercise testing. Our initial experience with NTG spray has been presented in preliminary form.8

Methods

Patients

Twenty patients (17 males and three females), mean age 61 years (range 50–74 years), with stable, exercise-induced angina pectoris participated in this trial. Their history of angina ranged from 6 months to 12 years (average 44 months). All patients had angiographically demonstrable coronary artery disease, and had at least 70% narrowing of luminal diameter in at least one major coronary artery. Ten patients had had a myocardial infarction at least 6 months before the study. Five patients had undergone coronary artery bypass graft surgery but continued to have stable angina. None of the patients were hypertensive or had clinical or radiologic evidence of heart failure. All patients had undergone treadmill exercise testing within 6 months before the study; treadmill exercise-induced angina and ischemic ST depression of 1.0 mm or more lasting at least 0.08 second occurred in each patient. All patients tolerated a 0.8-mg dose of sublin-
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Circulation. 1983;67:117-124
doi: 10.1161/01.CIR.67.1.117

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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