Failure of Methylprednisolone to Protect Acutely Ischemic Myocardium*  
A Contrast with Subsequent Beta-Adrenergic Blockade in Man  

Juhani Heikila, M.D., and Markku S. Nieminen, M.D.

Two grams of methylprednisolone was administered to ten patients with acute myocardial infarction at an average of 13 hours from the onset of symptoms; pain in the chest was not relieved in six of the ten patients. In one hour, no significant improvement was noted in the function of the ischemic segments (examined using a multiaxis echocardiographic method) or in the S-T segments of the 12-lead electrocardiogram. Left ventricular filling pressure soon increased by an average of 4 mm Hg (P < 0.005), without ventricular dilatation or a Frank-Starling response, suggesting a decrease (ischemic?) in myocardial compliance. Cardiac output by Swan-Ganz thermodilution later increased by 21 percent (P < 0.01) when a decrease in peripheral vasconstriction was evident. In contrast, small-dose β-adrenergic blockade using 0.2 mg of pindolol intravenously after administration of methylprednisolone immediately relieved pain in the chest in all six patients. Elevation of the S-T segments was reduced by 34 percent (P < 0.05) within 15 minutes, and the contractile function of the ischemic segments improved markedly, by 3 mm or to 34 percent of normal, from the 4 percent of normal before administration of pindolol (P < 0.005). Hemodynamic function did not deteriorate in the eight patients with uncomplicated infarction or moderate left ventricular failure. Therapy with pindolol thus reduced clinical, electrocardiographic, and myocardial mechanical signs of acute ischemia safely, while administration of methylprednisolone had no short-term protective effect.

The use of pharmacologic doses of glucocorticoids has recently been promoted for the protection of the ischemic myocardium in acute infarction; however, in man, the effects on acute myocardial ischemia in the few clinical series have been disturbingly controversial. More promising is evidence favoring the intravenous use of β-adrenergic blocking drugs to reduce the signs of myocardial ischemia in man. We therefore wanted to study the short-term effects of both of these types of drugs sequentially in the same patients with fresh myocardial infarctions. Signs of ischemia were directionally visualized without any delay, using an ultrasonic study of the myocardial segmental function, supplemented by mapping of the S-T segment, hemodynamic monitoring, and the clinical behavior of anginal pain in the chest.

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Materials and Methods

Patients

Ten patients (eight men and two women), ranging in age from 52 to 75 years, were studied during the acute phase of their first unequivocal myocardial infarction. Seven patients had anterior and three had posteroinferior infarctions. All patients were studied within 24 hours of the onset of pain, and four of them were examined within five hours; the average time was 13 hours. Four patients had uncomplicated infarction (Killip class 1), four had clinically moderate heart failure (Killip class 2), and two exhibited signs of an incipient state of low cardiac output (Killip class 3), but none was in cardiogenic shock or had frank pulmonary edema. Only analgesic drugs or lidocaine were given before the study. Two patients had previously received therapy with digitalis and diuretic drugs for hypertensive heart disease. Slight tolerable pain reappearing after the routine use of analgesic drugs was not treated if the patient did not request treatment, in order to observe the effect on the pain of the drugs studied. Informed consent for the procedure was obtained from the patients. All patients recovered from their infarction.

Swan-Ganz Thermodilution

A Swan-Ganz thermodilution catheter (No. 7) was advanced into the pulmonary arterial branch and was checked fluoroscopically. Cardiac output was measured with a ther-
S-T Segments

S-T segments were recorded from the standard 12 leads, so that inferoposterior infarctions could be included in the study. The standard 12-lead electrocardiogram has been shown to give a good reflection of the shifts in the S-T segment recorded by extensive mappings.6,8

Echoventriculographic Method

The echoventriculographic technique used to study the segmental motions of the left ventricular wall has been described earlier in detail.10-12 Regional function was assessed from the amplitude of wall motion separately at the remote uninvolved region, at the infarct's center, and at the ischemic border zone. "Total" regional function of the left ventricle (index of echocardiographic contraction) was assessed using normalized and summed systolic amplitudes of eight standard basic regions from multiaxis recordings.12 The precordial sites of the probe were marked each time to guarantee identical orientation in the repeat studies to the segments at the center of the infarction and at the bordering ischemic zone.

Protocol and Control Data

After the recording systems were applied, a period of 10 to 15 minutes was allowed for stabilization. The patients served as their own controls, due to the short duration of the study. Repeated control determinations were made on S-T segments and hemodynamic variables during the 20-minute interval before methylprednisolone was administered. The two determinations of the S-T segments remained within 5.6 percent (not significant) in nine patients; in one patient with fluctuating pain in the chest, S-T segments first increased markedly (70 percent) but remained stable thereafter during the last ten minutes. Spontaneous disappearance of elevations in the S-T segment characteristic of infarction are unlikely during a 60-minute period of observation.8,13 No significant variations in the hemodynamic variables occurred during this time.

In six other patients with acute myocardial infarction, the echocardiographic variables were additionally studied repeatedly within 1½ hours without any intervention; no significant variations were noted. Variability in repeated measurements of the echocardiographic amplitudes of wall motion remain within 1 mm.10

After the two control recordings, 2.0 gm of methylprednisolone sodium succinate (Solu-Medrol) diluted in 20 ml of physiologic saline solution was injected via the outlet of the right atrial catheter over a period of ten minutes. Collection of data was initially made at 15 minutes and then at 30 minutes after the injection was completed. Thereafter, a 0.2-mg dose of pindolol (Visken) was injected into eight patients over a period of two to three minutes, and the recordings were repeated 15 minutes later. Since the aim was to study the early effects of the medications on ischemic myocardium, with methods revealing the changes immediately, this sequential pharmacologic study was applied. In this way, even minor differences become better defined, despite the markedly varying nature of acute infarction in individual patients.

For long-term effects, this approach would not obviously be valid in a comparative sense. In two patients the ß-adrenergic blocking drug was not administered, due to the low state of cardiac output or due to a first-degree atrioventricular block (or both). The paired data at 60 minutes after injection of methylprednisolone were used as a reference for the short-term changes recorded after therapy with pindolol. Statistical analyses were made using the t-test for paired data.

RESULTS

Hemodynamic Functions

Methylprednisolone. The most conspicuous change after injection of 2.0 gm of methylprednisolone was a systemic increase in the left ventricular filling pressure. Pulmonary capillary wedge pressure increased without exception, by a mean of 4 mm Hg (39 percent; P < 0.005); the increase was al-

![Figure 1. Injection of methylprednisolone (MP) soon increased wedge pressure in patients with acute myocardial infarction. During control period, pressures remained stable (C1 and C2, control values at 20 minutes and one minute, respectively, before injection). Injection of pindolol (P) caused minor and variable changes only. Large solid circles indicate means.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21006/ on 06/25/2017)
Table 1—Hemodynamic Data and Left Ventricular Regional Contraction after Injection of Methylprednisolone and Subsequent β-Adrenergic Blockade*

<table>
<thead>
<tr>
<th>Data</th>
<th>Control</th>
<th>Time after Injection of Methylprednisolone (2.0 gm)</th>
<th>15 min after Injection of Pindolol (0.2 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
<td>60 min</td>
<td></td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>142.3 ± 22.7</td>
<td>133.6 ± 25.2**</td>
<td>144.6 ± 26.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>141.5 ± 20.8</td>
<td></td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>93.0 ± 13.4</td>
<td>93.8 ± 12.4</td>
<td>97.1 ± 12.4</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>77.1 ± 24.4</td>
<td>79.9 ± 20.6</td>
<td>70.3 ± 15.7</td>
</tr>
<tr>
<td></td>
<td>69.9 ± 7.7**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge pressure, mm Hg</td>
<td>11.4 ± 3.4</td>
<td>15.5 ± 7.0†</td>
<td>15.8 ± 3.3†</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.8 ± 1.2</td>
<td>5.2 ± 1.6</td>
<td>5.8 ± 0.9**</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>69.4 ± 19.5</td>
<td>71.0 ± 22.2</td>
<td>76.3 ± 20.2†</td>
</tr>
<tr>
<td>Stroke work, gram-meters</td>
<td>89.6 ± 30.4</td>
<td>88.0 ± 39.8</td>
<td>103.6 ± 41.8</td>
</tr>
<tr>
<td>S-T segment, mv</td>
<td>14.5 ± 16.9</td>
<td>16.9 ± 15.3</td>
<td>13.2 ± 13.1</td>
</tr>
<tr>
<td>Left ventricular diastolic diameter, mm</td>
<td>50.4 ± 3.5</td>
<td>50.5 ± 3.2</td>
<td>49.8 ± 3.7</td>
</tr>
<tr>
<td>Ejection fraction, percent</td>
<td>39.2 ± 11.0</td>
<td>41.4 ± 17.4</td>
<td>40.2 ± 14.3</td>
</tr>
<tr>
<td>Amplitude of wall motion, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy zone</td>
<td>9.1 ± 2.7</td>
<td>9.8 ± 2.7</td>
<td>9.8 ± 2.7</td>
</tr>
<tr>
<td>Infarcted zone</td>
<td>-1.0 ± 1.1</td>
<td>-0.9 ± 1.6</td>
<td>-0.6 ± 1.3</td>
</tr>
<tr>
<td>Border zone</td>
<td>2.3 ± 2.2</td>
<td>1.8 ± 1.7</td>
<td>2.1 ± 2.1</td>
</tr>
<tr>
<td>Index of echoventriculographic contraction,</td>
<td>86.8 ± 22.2</td>
<td>64.7 ± 18.8</td>
<td>72.1 ± 17.2</td>
</tr>
<tr>
<td>percent</td>
<td></td>
<td>74.6 ± 23.2†</td>
<td></td>
</tr>
</tbody>
</table>

*Table values are means ± SD. †P < 0.005. ‡P < 0.01. **P < 0.05.

ready significant at 15 minutes (Fig 1 and Table 1). Cardiac output increased more gradually by 21 percent (P < 0.01). A transient fall was noted in the systolic pressure at 15 minutes after the injection. At this time, one patient developed hypotension (90 mm Hg) and the syndrome of low cardiac output, cardiac output, 2.9 L/min), which responded excellently to an infusion of fluid and a small dose of dopamine. This patients' data at 15 minutes only were included in the study. After an hour, peripheral vasoconstriction was noted clinically in seven of the ten patients. A clear-cut filling of the peripheral veins and a warming-up of hands and feet were conspicuous.

**Beta-Adrenergic Blockade.** The intravenous administration of a small dose of a β-adrenergic blocking drug (0.2 mg of pindolol) reduced the heart rate by 12 percent (P < 0.01; Table 1). No deterioration of cardiac pumping function took place, since all of the other circulatory changes remained insignificant. In fact, the stroke volume increased somewhat, and the wedge pressure was unchanged or decreased in five of eight patients (Fig 1 and Table 1). No clinical changes occurred in the peripheral circulation.

**Left Ventricular Regional Performance**

**Methylprednisolone.** After injection of the steroid, no significant alterations were observed in left ventricular mechanics (left ventricular end-diastolic diameter, ejection fraction, segmental function at the three zones [ie, the uninvolved myocardium, the infarcted region, and the ischemic zone between], or when these segmental motions were combined into the index of echoventriculographic contraction) (Table 1). The average change in the amplitude of motion of the infarcted zone and the border zone combined was only 0.2 to 0.3 mm (from 1.1 to 0.9 mm at 15 minutes and from 1.2 to 1.5 mm at 60 minutes).

**Beta-Adrenergic Blockade.** In contrast to therapy with methylprednisolone, injection of pindolol thereafter improved the contractile function of the single ischemic segments (Table 1). The increase in their amplitudes was now even more clear when analyzed as combined (from 0.4 ± 2.8 to 3.5 ± 4.1 mm [ie, from 4 percent of normal before to 34 percent of normal regional wall motion] after injection of the drug; P < 0.005). The systolic motion of the healthy myocardium decreased slightly (by 10 percent; P < 0.05), but the overall segmental contractile function by the index of echoventriculographic contraction increased 11 percent (P < 0.05). The recovery of systolic wall motion at the ischemic segments was often quite marked after β-adrenergic blockade (Fig 2 and 3). The improvement was evident within a few minutes after injection but increased for 10 to 15 minutes. The dias-
tolic size of the left ventricular cavity did not change.

S-T Segments and Pain in the Chest

Methylprednisolone. Therapy with the steroid had no significant effect on the electrical injury current. After 15 minutes the S-T segments were 16 percent higher (not significant) and after 60 minutes were 8 percent smaller (not significant) (Table 1). Some angina pain was present in six of the ten patients at the time of injection. Administration of methylprednisolone did not relieve the pain; in three patients the pain in the chest became more marked. An alarming increase in signs of ischemia after the injection was particularly obvious in one patient (Fig 3). In another patient the mean wedge pressure soon increased from 15 to 32 mm Hg, and the stroke volume decreased, along with somewhat worse pain in the chest.

Beta-Adrenergic Blockade. Therapy with pindolol reduced the elevations in the S-T segments by 34 percent, from 15.0 ± 16.4 mv to 10.0 ± 9.8 mv (P < 0.05) within a few minutes of the injection (Table 1 and Fig 2 and 3). Pain in the chest also disappeared within two to three minutes in all six patients, even if this was severe (Fig 3).

Adverse Effects

Methylprednisolone. Three patients experienced an increase in pain in the chest soon after the injection, and one patient developed hypotension and a more marked state of low cardiac output (as noted previously). Many patients mentioned a metallic taste.

Beta-Adrenergic Blockade. No adverse effects were noted in the eight patients with uncomplicated infarction or moderate heart failure.

Discussion

The selection of the method plays a role when the myocardial effects of therapy with methylprednisolone are studied; for instance, the widely used method utilizing creatine phosphokinase may provide only a deceptive appearance of protection with administration of corticosteroids. Since steroids have potent membrane-stabilizing effects, the plasma enzyme levels may remain low because even the dead cells retain their contents for long periods of time.14,15

Ischemia of the myocardium is immediately related to deterioration of the pattern of segmental wall motion.16 The systolic wall motions of the left ventricle thus provide an instantaneous and sensitive direct indicator of increasing or decreasing myocardial ischemia.18 Abnormalities in the segmental wall motions can be visualized directly and noninvasively by echocardiographic methods.11,16,17 The multidirectional echocardiographic method used here has been documented to be highly accurate in detecting regional asynchrony in patients with myocardial infarction.11,12 Reflection of ischemia in the electrocardiographic shifts in the S-T segment is also rapid.19 In man the motions of ischemic myocardial segments were parallel with the changes in the S-T segment when induced pharmacologically.19

Methylprednisolone

Only two reports have described the effects of administering massive doses of methylprednisolone on the size of the infarct in man; the results were contradictory.5,4 The recent histologic study in the
dog remained completely negative.29 In the present study, therapy with methylprednisolone in a dose of 2.0 gm failed to limit on a short-term basis the human "size of the infarct," as assessed by the function of the ischemic myocardial segments and by the shifts in the S-T segment for one hour. Pain in the chest was not relieved either, or it even increased.

The hemodynamic effects of therapy with methylprednisolone in patients with acute myocardial ischemia or infarction have been rather varied.5,4,4 An unexpected hemodynamic change in the face of vasodilatation and reduced afterload12 was the constant increase in the left ventricular filling pressure with injection of methylprednisolone. Gould et al4 also noted a tendency toward elevation of wedge pressure after therapy with methylprednisolone in acute myocardial infarction. Since the wedge pressure was quite stable (varying only by 0 to 2 mm Hg) during the preceding control period of 20 minutes, the change observed in our study is not explained by a spontaneous progression of early ischemia in the myocardium.

One is then forced to consider the possibility that therapy with methylprednisolone might have increased myocardial ischemia (at least, the therapy did not prevent a spontaneous increase in ischemia) or otherwise decreased ventricular compliance,21 since the left ventricular diameter did not change at all. Neither was the Frank-Starling response evident initially.

It is well known that during the initial stages of myocardial infarction, the sympathetic drive is high.2,8 The theory that corticosteroids potentiate inotropic cardiac effects of catecholamines has not been confirmed;20 however, both catecholamines and methylprednisolone enhance the hypoxic-induced influx of calcium ion into the cardiac muscular cell,24 with possible harmful consequences of necrotic damage (and decrease compliance?). In connection with coronary vasodilatation1,2 of a "steal" type,4 even the transient fall of blood pressure (Table 1) may have been detrimental to the ischemic myocardium. Admittedly, the shift in pressure was rather moderate and occurred during systole only, and this was not reported by others in a similar clinical context.6

Pindolol

Injection of the small dose of a potent β-adrenergic blocking drug, pindolol, significantly reduced both mechanical and electrical signs of acute regional myocardial ischemia. Pain in the chest also disappeared in all patients. After therapy with analgesic drugs, relief of pain is not usually accompanied by a reduction in the elevation of the S-T segment.7 These effects contrast with the inability of therapy with methylprednisolone to influence these signs for the preceding one hour in the same patients. Blocking of cardiotonulatory effects of

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**Figure 3.** Serial motions of left ventricular anterior wall (AW) determined by echocardiographic studies at center of zone of infarction and lead V4 ECGs in patient with acute myocardial infarction four hours after onset of symptoms. Injection of methylprednisolone did not prevent vague pain in chest from increasing during 15 minutes, nor further elevation of S-T segments and worsening of paradoxical pulsation, which increased from −2 to −3.5 mm Hg. Injection of pindolol relieved pain in chest and markedly reduced deviation of S-T segment. Paradoxical bulge was now replaced by akinesia (0.5 mm).
steroids obviously is not even a contributing factor. We previously have observed quantitatively similar hemodynamic, echocardiographic, and ST-segmental behavior with intravenous administration of the β-adrenergic blocking drugs, pindolol or practolol, alone, without the preceding administration of methylprednisolone, in 40 patients with acute myocardial infarction.

Improvement of the S-T segments with injection of 0.2 mg of pindolol was of the same order as that reported by Gold et al with administration of an average dose of 6.5 mg of propranolol within the first eight hours of the onset of pain. Hemodynamic measurements did not deteriorate after injection of 0.2 mg of pindolol in these patients with uncomplicated infarctions or moderate heart failure. The rapid mechanical recovery of myocardial segments from ischemia after therapy with β-adrenergic blockade (P < 0.005) was often quite dramatically documented by echocardiographic studies. Reduction of the heart rate and the myocardial inotropic state (Table 1) are possible mechanisms.

In conclusion, when immediate protection of the ischemic myocardium is sought in man, a small dose of a β-adrenergic blocking agent is safe and superior to a large dose of glucocorticoid; methylprednisolone failed to reduce the signs of ongoing ischemia, in contrast to the β-adrenergic blocking drug given subsequently or alone. Although our data do not exclude possible long-term protective effects (eg, on cellular integrity), we certainly emphasize caution in the use of therapy with methylprednisolone in the acute, evolving human myocardial infarction. Interference with healing of the infarction must also be considered in this connection.

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