

## Possible Survival Benefit from Concomitant Beta-but Not Calcium-Antagonist Therapy During Reperfusion for Acute Myocardial Infarction

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**To test the hypothesis that long-term  $\beta$ - or calcium-antagonist therapy begun before the time of myocardial infarction and coronary reperfusion might improve patient in-hospital survival compared with reperfusion alone, 424 consecutive patients successfully reperfused with coronary angioplasty within 12 hours of infarct symptom onset were carefully and retrospectively characterized. Forty-seven patients (11%) were taking  $\beta$  antagonists and 74 patients (17%) were taking calcium antagonists at the time of infarction. Patients receiving  $\beta$  antagonists had a more frequent history of hypertension ( $p \leq 0.001$ ) and prior infarction ( $p \leq 0.01$ ) than those not so treated and patients receiving calcium antagonists had a more frequent history of prior infarction, prior angina, hypertension and diabetes (all  $p \leq 0.001$ ) than their nontreated counterparts. Stepwise logistic regression analysis found significant independent correlations between in-hospital death and the following variables: recurrent ischemia ( $p \leq 0.001$ ); proximal left anterior descending coronary infarct ( $p \leq 0.001$ ); 3-vessel disease ( $p = 0.002$ ); patient age ( $p = 0.004$ ); and initial total occlusion of the infarct artery ( $p = 0.022$ ). After adjustment for these factors,  $\beta$  antagonist use (mortality = 0 vs 8% without treatment) was still significantly correlated with improved survival ( $p = 0.048$ ), whereas calcium-antagonist therapy made no difference in survival. Heart rate and left ventricular end-diastolic pressure upon presentation were significantly lower in patients treated with  $\beta$  antagonists. Thus,  $\beta$ -antagonist therapy, but probably not calcium-antagonist therapy, taken before reperfusion for acute myo-**

**cardial infarction, may improve early survival compared to reperfusion alone. Larger studies will be required to confirm or refute these observations.**

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In experimental models of acute myocardial ischemia and early reperfusion, concomitant administration of  $\beta$  and calcium antagonists have been shown to decrease infarct size and improve left ventricular function beyond that achieved with reperfusion alone.<sup>1-5</sup> However, it has been suggested that the administration of  $\beta$  antagonists after reperfusion may have deleterious effects and precipitate congestive heart failure.<sup>6</sup> Randomized trials of  $\beta$ - or calcium-antagonist therapy in conjunction with reperfusion for acute myocardial infarction are limited. In the Thrombolysis in Myocardial Infarction (TIMI) phase II trial,  $\beta$  antagonists administered to selected patients within 2 hours of chest pain onset were shown to decrease the combined incidence of death or recurrent myocardial infarction significantly.<sup>7</sup> This effect was not seen in patients treated >2 hours after symptom onset. A single study was unable to show a beneficial effect from nifedipine compared to placebo given during thrombolysis on left ventricular functional recovery or clinical outcome.<sup>8</sup> We retrospectively analyzed all patients with myocardial infarction and successful reperfusion by coronary angioplasty within 12 hours of symptom onset at the University of Michigan Medical Center to test the hypothesis that chronic  $\beta$ - or calcium-antagonist therapy begun before the time of myocardial infarction might improve survival with early reperfusion therapy.

### METHODS

**Study patients:** All patients undergoing coronary angioplasty for acute myocardial infarction at the University of Michigan since December 22, 1983, have been extensively characterized and followed in the University of Michigan Angioplasty in Acute Myocardial Infarction data bank.<sup>9</sup> The study group comprised 424 consecutive patients who, through August 1989, have had successful coronary angioplasty (final TIMI flow

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Characteristic	$\beta$ Antagonists	No $\beta$ Antagonists	Calcium Antagonists	No Calcium Antagonists
No. of patients	47	377	74	350
<b>Clinical</b>				
Age (yrs)	57 $\pm$ 9	55 $\pm$ 11	58 $\pm$ 11	55 $\pm$ 11
Male (%)	75	80	69	81
Systolic hypertension	83	50*	89	48*
Diabetes mellitus (%)	21	12	30	10*
Prior angina pectoris (%)	50	48	89	42*
Prior myocardial infarction (%)	30	15 <sup>†</sup>	42	11*
Prior long acting nitrates (%)	19	6 <sup>†</sup>	56	10*
Prior beta antagonists (%)	—	—	18	10*
Prior calcium antagonists	28	16 <sup>‡</sup>	—	—
Time to PTCA (hr)	5.0 $\pm$ 3.1	5.1 $\pm$ 3.0	5.3 $\pm$ 3.7	5.0 $\pm$ 2.9
Anterior infarction (%)	57	44	49	45
Cardiogenic shock (%)	6	9	8	9
<b>Angiographic/hemodynamic</b>				
<b>Infarct vessel</b>				
Left anterior descending (%)	57	44	47	45
Right coronary artery (%)	32	43	38	43
Left circumflex (%)	9	12	12	11
Bypass graft (%)	2	1	3	1
Total infarct artery occlusion (%)	57	51	50	52
<b>Multivessel disease</b>				
Left ventricular ejection fraction (%)	46 $\pm$ 10	48 $\pm$ 11	47 $\pm$ 11	48 $\pm$ 11
Heart rate (beats/min)	75 $\pm$ 18	91 $\pm$ 18 <sup>†</sup>	84 $\pm$ 12	86 $\pm$ 21
Systolic arterial pressure (mm Hg)	118 $\pm$ 21	114 $\pm$ 21	117 $\pm$ 23	114 $\pm$ 21
Diastolic arterial pressure (mm Hg)	81 $\pm$ 17	78 $\pm$ 15	74 $\pm$ 14	79 $\pm$ 16
Left ventricular end-diastolic pressure (mm Hg)	23 $\pm$ 7	26 $\pm$ 8 <sup>‡</sup>	24 $\pm$ 7	25 $\pm$ 8
<b>Outcome</b>				
Recurrent ischemia (%)	8	16	11	16
Change in left ventricular ejection fraction, 0 to 7 days (%)	4 $\pm$ 10	2 $\pm$ 9	5 $\pm$ 11	2 $\pm$ 9
In-hospital death (%)	0	8	8	7

\*  $p \leq 0.001$ ; <sup>†</sup>  $p \leq 0.01$ ; <sup>‡</sup>  $p \leq 0.05$ .  
PTCA = percutaneous transluminal coronary angioplasty.

grade  $\geq 2$ ) within 12 hours of symptom onset. Angioplasty was performed using standard techniques<sup>9</sup> and was based on the indications of persistent total occlusion, clinical evidence of ischemia or hemodynamic compromise, and in 16 patients randomly assigned to immediate angioplasty after successful thrombolysis in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) I Study.<sup>10</sup> Patients were not necessarily excluded because of advanced age or poor left ventricular function and, in fact, the concurrent presence of clinically evident left ventricular dysfunction and persistent chest pain often prompted referral for cardiac catheterization. Angioplasty was performed after the patient provided informed consent and under guidelines approved by the Committee to Review Clinical Research and Investigation at the University of Michigan Medical Center.

**Statistical analysis:** All data were entered into the University of Michigan Angioplasty in Acute Myocardial Infarction databank, a relational databank using SYSTAT software. Data are presented as mean values  $\pm 1$  standard deviation, except where noted. Unpaired Student's *t* tests or chi-square analyses, using the Yates' correction and Fisher's exact test when applicable, were used to compare continuous and categorical single variables with outcome. The independent correlates of in-

hospital survival and the determinants of systolic blood pressure and left ventricular end-diastolic pressure were determined using multiple stepwise linear regression analyses. The independent effects of  $\beta$ - and calcium-antagonist therapy were then determined by adjusting for the significant covariates by forcing them into the logistic regression equation and then entering the variables " $\beta$ -antagonist therapy" or "calcium-antagonist therapy" to assess their effect upon outcome.

## RESULTS

**Patient characteristics and outcome:** The clinical and angiographic characteristics, in-hospital survival and left ventricular functional recovery data for patients who were or were not receiving  $\beta$ - or calcium-antagonist therapy at the time of infarction are listed in Table I. In general, patients receiving  $\beta$  or calcium antagonists would be considered at higher risk for complications compared with their nontreated counterparts, as reflected by their higher incidence of prior myocardial infarction, diabetes and hypertension.

**Independent correlates of in-hospital death:** The independent correlates of death are listed in Table II. The following were the independent predictors: recurrent ischemia, proximal left anterior descending coronary artery infarct, 3-vessel coronary artery disease, age, and

total coronary occlusion of the infarct artery. After consideration of these predictors,  $\beta$ -antagonist therapy was still significantly correlated ( $p = 0.048$ ) with improved survival, whereas calcium-antagonist therapy was not (difference not significant).

**Effect of beta-antagonist therapy on hemodynamics in high-risk patient subgroups:** For the entire group, the independent predictors of systolic blood pressure were found to be patient age ( $p < 0.001$ ), diabetes ( $p = 0.001$ ) and prior myocardial infarction ( $p = 0.05$ ). The only independent predictor of left ventricular end-diastolic pressure was proximal left anterior descending coronary artery infarct ( $p = 0.03$ ). After adjusting for these factors in each of 4 prospectively defined high-risk groups (multivessel coronary disease [ $n = 226$ ], prior myocardial infarction [ $n = 70$ ], proximal left anterior descending coronary infarct [ $n = 87$ ] and proximal right coronary artery infarct [ $n = 93$ ]),  $\beta$ -antagonist therapy usage had no adverse effect in any subgroup on either blood pressure or end-diastolic pressure and, in fact, was associated with significantly lower end-diastolic pressure in patients with multivessel disease (coefficient =  $-4.8$  mm Hg,  $p = 0.04$ ) and in patients with prior myocardial infarction (coefficient =  $-6.4$  mm Hg,  $p = 0.005$ ).

## DISCUSSION

Reperfusion with intravenous thrombolytic therapy has now been clearly established to decrease mortality in selected patients with acute myocardial infarction.<sup>11,12</sup> More controversial and less well studied is the possible benefit or deleterious effect of concomitant  $\beta$ - or calcium-antagonist therapy.

**Possible mechanisms resulting in a beneficial effect in the setting of acute myocardial infarction:** Experimental studies have shown  $\beta$  blockade to decrease heart rate and  $dp/dt$ , thus decreasing the determinants of oxygen consumption,<sup>1,13</sup> whereas regional myocardial blood flow has generally been found to be unchanged or slightly lower.<sup>1,14</sup> It has been suggested that the "window" during which reperfusion therapy is effective may be extended by slowing the rate of progression of the "wavefront" of necrosis<sup>15</sup> with  $\beta$  blockade begun before the onset of ischemia.<sup>1</sup> A decrease in experimental infarct size, more prominent when  $\beta$  antagonists were given with reperfusion, has been reported by multiple authors.<sup>1-3</sup> Data suggest there is a mild beneficial effect on infarct size in humans when reperfusion therapy is not given,<sup>16</sup> but studies with reperfusion therapy are lacking. A diminution of systolic bulging of the infarct zone has also been noted,<sup>1</sup> possibly decreasing the likelihood of infarct expansion and its adverse sequelae.<sup>17,18</sup> There is strong suggestive evidence that early  $\beta$  blockade without reperfusion decreases the incidence of cardiac rupture in humans.<sup>19</sup> Rupture may have accounted for the increased mortality within the first 6 hours for patients treated with streptokinase in GISSI-1,<sup>20</sup> and thus, early  $\beta$  blockade may be of particular importance in patients undergoing reperfusion therapy. The incidence of malignant ventricular arrhythmias may also be diminished.<sup>21,22</sup>

**TABLE II** Correlates of In-Hospital Death

Variables	Coefficient	Standard Error	T	p Value
Recurrent ischemia	0.11	0.03	3.21	$\leq 0.001$
Proximal left anterior descending infarct	0.09	0.03	3.25	$\leq 0.001$
Triple-vessel CAD	0.10	0.03	3.14	0.002
Patient age (yrs)	0.003	0.001	2.93	0.004
Initial total occlusion of infarct artery	0.054	0.024	2.30	0.022
$\beta$ -antagonist therapy	-0.07	0.04	-1.98	0.048
Constant	-0.18	0.06	-2.81	0.005

CAD = coronary artery disease.

In experimental preparations, calcium antagonists have been found to have mixed effects on the primary determinants of oxygen consumption, usually increasing heart rate and decreasing systolic arterial pressure.<sup>1</sup> Regional myocardial blood flow has usually been found to be augmented.<sup>23,24</sup> Infarct size has been shown to be decreased in some series.<sup>1</sup> Systolic bulging and the early myocardial dysfunction possibly due to calcium overload has been decreased.<sup>1,25,26</sup>

**Possible adverse consequences of therapy:** The primary concern with regard to both classes of agents in patients with acute myocardial infarction is that, due to their negative inotropic and chronotropic effects, congestive heart failure and/or bradyarrhythmias might be exacerbated.<sup>14,27,28</sup> A theoretical possibility that  $\beta$  blockade may decrease regional myocardial blood flow to the infarct zone because of unopposed alpha effect may also be of concern,<sup>6,14,29</sup> although several animal studies have not shown such an effect.<sup>1,30</sup>

**Results:** The results of this investigation support the findings of the TIMI Study Group of an overall favorable response to  $\beta$  antagonists, yet go beyond those results by suggesting that prior usage of  $\beta$  antagonists may improve survival in patients treated with reperfusion for acute myocardial infarction. However, in spite of the statistical significance of the beneficial effect of  $\beta$  antagonists shown in this investigation ( $p < 0.05$ ), conclusions regarding effects on mortality from relatively small numbers of patients should be interpreted with great caution.

The mechanism of the beneficial effect of  $\beta$ -antagonist therapy cannot be determined from this study, although it is interesting to note a decrease in left ventricular filling pressures in patients with multivessel disease suggesting a decrease in ischemia at a distance. The importance of multivessel disease and contralateral ischemia as a primary determinant of in-hospital outcome with myocardial infarction in patients treated with thrombolytic therapy has recently been emphasized by Grines<sup>31</sup> and Muller<sup>32</sup> and their co-workers from the TAMI Group.

Thus, these data suggest that prior  $\beta$  blockade, but quite possibly not calcium antagonists, may be beneficial for patients treated with reperfusion for myocardial infarction and that this hypothesis should be investigated in studies with larger numbers of patients. If these

data can be confirmed, the implications for the treatment of patients at risk for myocardial infarction would be profound.

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