Correlation of Angiographic Estimates of Myocardial Infarct Size and Accumulated Release of Creatine Kinase MB Isoenzyme in Man

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SUMMARY Accumulated creatine kinase MB isoenzyme release (Σ CK-MB) during acute myocardial infarction was correlated with biplane left ventricular (LV) angiographic estimates of percent abnormally contracting segment (%ACS) and ejection fraction (EF) in 35 patients who underwent diagnostic angiography at a mean of 33 ± 4 days post myocardial infarction (MI). Of the 35 patients, 18 had no evidence of prior MI and their Σ CK-MB showed good correlation with %ACS (r = 0.84) and with EF (r = −0.78). An additional two patients with first (inferior) infarct secondary to stenosis of the right coronary artery proximal to the origin of the right ventricular arterial blood supply had disproportionately large Σ CK-MB, suggesting a combination of LV and RV necrosis.

In the 15 patients with prior infarct, there was no significant correlation between Σ CK-MB and %ACS or EF. However, in the subgroup of patients with anterior MI, %ACS correlated with Σ CK-MB, both in patients with no prior MI (r = 0.88, N = 12) and in patients with prior MI (r = 0.69, N = 9).

These independent angiographic and enzymatic data suggest that enzymatic infarct size estimates utilizing accumulated CK-MB release may be a valid and reliable clinical measure for assessing the extent of LV necrosis in the setting of acute anterior myocardial infarction. However, limitations may exist in certain cases of inferior MI, possibly because of concomitant right and left ventricular necrosis.

RECENT INTEREST in methods to reduce the extent of myocardial necrosis during acute myocardial infarction has underscored the importance of accurate techniques to assess the magnitude of completed myocardial infarct size. Sobel et al.1-4 have proposed a mathematical model whereby estimates of myocardial infarct size might be obtainable from analysis of serial enzymatic assays of serum creatine kinase (CK) enzyme or CK-MB isoenzyme5-8 during the early infarct period. Although these workers have shown good correlation between accumulated serum CK enzymatic release and postinfarction myocardial CK depletion,1-8 they have furnished no direct histological and morphological validation of their enzymatic model for sizing infarction. The validity of CK infarct sizing, especially when the model is extrapolated to patients with acute myocardial infarction, has been challenged.8

Other independent descriptors of myocardial infarct size are needed clinically to corroborate the enzymatic estimates. One such independent clinical descriptor of infarct size might be the angiographic quantitation of left ventricular asynnergy during the early postinfarct convalescence period. The present report will describe the angiographic assessment of left ventricular infarct size and left ventricular function in patients following acute myocardial infarction and their correlation with the accumulated release of CK-MB isoenzyme during the evolving acute infarction period.

Methods

Patient Population

The study population was composed of all patients admitted to the coronary care unit at University of Alabama Medical Center from June, 1975, through August, 1976, satisfying all of the following criteria: 1) acute myocardial infarction, diagnosed by typical rise and fall of CK-MB isoenzyme; 2) admission within 16 hours of first symptom of infarction; 3) no evidence of significant valvular heart disease; and 4) availability of data from quantitative biplane left ventriculography and coronary angiography performed during the postinfarct convalescence period.

Enzymatic Estimate of Infarct Size

All study patients underwent placement of a 7F Swan-Ganz pulmonary artery catheter by an antecubital cutdown on admission to the coronary care unit. Blood samples drawn from this catheter at three hour intervals for 96 hours were collected in tubes containing sodium EDTA and immediately centrifuged to separate off the plasma, which was stored at 4°C for up to three weeks. Pilot studies showed that CK-MB isoenzyme activity remained stable for up to two months under these conditions.

CK-MB isoenzyme was separated from plasma by DEAE-Sephadex column chromatography1 employing mini-columns (0.7 cm internal diameter [I.D.] by 10 cm length beneath a 2 cm I.D. by 3 cm reservoir — "Econo-column," Biorad Laboratories, Richmond, California.) Enzyme activity of the column eluate was determined according to Rosalki.8 Recoveryability of CK-MB from the mini-columns was found to be 70% when CK-MB purified from autopsy myocardial tissue was assayed both before and after elution from the mini-columns. Coefficient of variation of replicate assays for CK-MB was 4.2%.

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Supported in part by the Specialized Center of Research for Ischemic Heart Disease, Contract Number 1P17HL17667-03, the Cardiovascular Research and Training Center, Program Project Grant Number HL 11,310 (Division of Heart and Vascular Disease, National Heart and Lung Institute), NIH Grant Number T01LM00154, the Clinical Research Unit Grant Number M01-RR0003213 (General Clinical Research Centers Program, Division of Research Resources), National Institutes of Health and VA Project Number 5566-01.

Presented in part at the 49th Annual Scientific Session of the American Heart Association in Miami Beach, Florida, November 1976.

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Received January 14, 1977; revision accepted March 29, 1977.

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Accumulated CK-MB release (Σ CK-MB) was determined using the integrated appearance function of Sobel et al.1-4 (fig. 1) with individualization of the CK-MB disappearance constant K_D, in the manner described by Norris et al. for total CK.8 Data analysis was facilitated by an IBM 1800 computer. Σ CK-MB was expressed as I.U./L of CK-MB. Normalized Σ CK-MB was defined as the ratio of Σ CK-MB (I.U./L) to left ventricular (LV) mass (g), the latter determined angiographically.

Quantitative Angiography

Biplane cine (60 frames/sec) or large film (6 frames/sec) LV angiograms were obtained in all patients using techniques previously described.10 Quantitative angiographic volume measurements were made by the area-length method of Dodge et al.11 Excluded from analysis were films of poor angiographic quality and films exposed during premature ventricular contractions or during the following cycle. Left ventricular mass was determined angiographically by the method of Rackley et al.18 Percent abnormally contracting segment (%ACS) was calculated by the method of Feild et al.19 (fig. 2)

Statistics

Linear correlations were found by the method of least squares analysis. The nonpaired t-test and Chi-square test were used to assess differences between groups of nonpaired data. The test for equality of dependent correlation coefficients was performed according to Williams.14

Results

Clinical and Angiographic Data

Of 127 patients admitted with acute myocardial infarction during the study interval, 35 patients satisfied the study criteria (table 1). Of these, 20 had no history or ECG documentation of prior myocardial infarction (MI), and 15 patients had evidence of prior MI. Patients without prior MI were significantly younger, had greater incidence of single vessel coronary artery disease, smaller abnormally contracting segment size, larger ejection fraction, and smaller left ventricular (LV) mass. Accumulated CK-MB release was similar in the two groups.

In four of the 35 patients stenosis of ≥ 70% in the right
Table 1. Summary of Clinical and Angiographic Data

<table>
<thead>
<tr>
<th></th>
<th>No Prior MI</th>
<th>Prior MI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>53 ± 2</td>
<td>59 ± 2</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>M = 18, F = 2</td>
<td>M = 14, F = 1</td>
<td>NS</td>
</tr>
<tr>
<td>Location of MI</td>
<td>Ant = 12</td>
<td>Ant = 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inf = 8</td>
<td>Inf = 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Und = 3</td>
<td>Und = 3</td>
<td></td>
</tr>
<tr>
<td>Δt (hrs)</td>
<td>6 ± 1</td>
<td>7 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>PAEDP (mm Hg)</td>
<td>19 ± 1</td>
<td>22 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Σ CK-MB (IU/L)</td>
<td>111 ± 16</td>
<td>104 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Δt (days)</td>
<td>30 ± 3</td>
<td>36 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Extent of CAD</td>
<td>1V - 8</td>
<td>1V - 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2V - 5</td>
<td>2V - 6</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td></td>
<td>3V - 7</td>
<td>3V - 9</td>
<td></td>
</tr>
<tr>
<td>% ACS</td>
<td>15.5 ± 2.3</td>
<td>24.5 ± 2.9</td>
<td>0.02</td>
</tr>
<tr>
<td>EF</td>
<td>0.42 ± 0.02</td>
<td>0.33 ± 0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Mass (g)</td>
<td>212 ± 13</td>
<td>249 ± 15</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Normalized Σ CK-MB (IU/L/g)</td>
<td>0.49 ± 0.06</td>
<td>0.43 ± 0.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are means ± standard error of the mean.

Abbreviations: MI = myocardial infarction; M = male; F = female; Ant = anterior; Inf = inferior; Und = undetermined; Δt = time elapsed between onset of MI symptoms and insertion of right heart catheter; PAEDP = admission pulmonary artery end-diastolic pressure; Σ CK-MB = accumulated creatine kinase MB isoenzyme release; Δt = time interval from MI until diagnostic coronary and left ventriculography; CAD = coronary artery disease; LV = coronary vessel with ≥70% stenosis; ACS = abnormally contracting segment; NS = not significant.

corony artery proximal to the origin of the major right ventricular marginal branch was the major lesion. Since the right ventricle receives the majority of its blood supply from the branches arising from the proximal half of the right coronary artery, these four patients had potential for right ventricular necrosis as well as inferior wall left ventricular necrosis. Since the LV angiographic technique, by definition, assessed only LV morphology, these patients with proximal right coronary artery stenosis were analyzed separately in the correlations of enzymatic infarct size and angiographic data which follow (figs. 3 and 4). However, those inferior infarcts secondary to lesions in the distal half of the right coronary artery or circumflex coronary artery were analyzed together with the anterior infarcts because concurrent right ventricular necrosis was felt to be unlikely in these patients.

The 35 patients had the following potential sources for extracardiac CK release: 1) antecubital cutdown — all patients; 2) intramuscular injections — 4 patients; 3) cardiac catheterization preceding MI — 1 patient; 4) cardiac arrest with closed chest massage and/or defibrillation — 10 patients. Because of potentially large contributions of total CK from skeletal muscle, enzymatic infarct size estimation using accumulated total CK was felt to be inappropriate, and therefore measurements of accumulated CK-MB release were obtained in each patient as the enzymatic estimate of infarct size.

Angiographic vs Enzymatic Estimates of Infarct Size

Patients having no prior MI showed good correlation between angiographic %ACS and normalized Σ CK-MB (r = 0.84, N = 18). No correlation between the two variables could be found in the 15 patients with prior MI (fig. 3). In many instances, the angiographic %ACS in patients with prior MI was disproportionately large compared to enzymatic infarct size, probably reflecting the contribution of the angiographic scar from the prior MI.

In the subgroup of patients with anterior MI, there was an excellent correlation (r = 0.88, N = 12) between %ACS and Σ CK-MB: %ACS = (41 ± 10) Σ CK-MB - (1 ± 5). Anterior infarcts with history of prior infarction showed a weaker, though still good, correlation (r = 0.69, N = 9): %ACS = (34 ± 10) Σ CK-MB + (10 ± 5). The preceding two regression equations differed in intercept (P = 0.02) but not in slope. With anterior MI a quantitative relation between %ACS and enzymatic infarct size can be postulated which, in patients with prior MI, is manifest as an upward (but parallel) shift in the regression line of the patients with first infarct, undoubtedly secondary to the pre-existent angiographic scar, in the patients with prior infarct. Similar analysis was not possible in the inferior MI subgroup because of smaller numbers of patients.

Separate analysis of the four patients with proximal right coronary artery stenosis showed that the two patients with no prior MI had Σ CK-MB markedly disproportionate to the angiographic infarct size when compared with the regression analysis of figure 3. This finding would be compatible with CK-MB release from other than left ventricular sources in these two patients.

Figure 3. Correlation of angiographic and enzymatic estimates of infarct size. Patients with no prior infarct showed good correlation between angiographic percent abnormally contracting segment and accumulated CK-MB release normalized for LV mass, but patients with prior infarct tended to have larger angiographic infarct size in relation to accumulated CK-MB release. The linear least squares regression line is shown with equation, y = 44 x -3.6. Open symbols refer to patients with proximal right coronary artery stenosis who were felt to have potential for concurrent right and left ventricular necrosis and were not included in the statistical analysis. Abbreviations: ANT = anterior, INF = inferior, UND = undetermined myocardial location by electrocardiogram.
Left Ventricular Ejection Fraction vs Enzymatic Estimate of Infarct Size

Patients without prior MI showed a good correlation between ejection fraction and normalized ∑ CK-MB (r = −0.78, N = 18; fig. 4). The intercept of the least squares regression line on the ordinate predicted an ejection fraction of 0.63 ± 0.05 for a noninfarcted ventricle (zero enzymatic infarct size), in close agreement with the reported normal value for the angiographic left ventricular ejection fraction (0.67 ± 0.08). Several patients maintained an ejection fraction of 0.5 or greater despite significant CK release, probably reflecting LV contractile reserve.

In patients with prior MI, there was no correlation between ejection fraction and enzymatic infarct size (fig. 4), since, in many cases, ejection fraction was disproportionately low compared to enzymatic infarct size, probably a consequence of myocardial dysfunction secondary to the previous infarct.

The two patients with no prior MI and proximal right coronary artery lesions showed poor agreement with the regression analysis of figure 4 because of the disproportionately large enzymatic infarct size, again compatible with non-left ventricular CK-MB release.

Individualization of KD

Computer-calculated individualized CK-MB KD ranged from −0.00061 to −0.00215 min⁻¹ with a mean of −0.00121 ± 0.00006 min⁻¹ (table 2), the latter in close agreement with data of Yasmineh et al. Normalized ∑ CK-MB was recomputed for each patient with no prior MI using mean KD, rather than individualized KD and correlated with the independent angiographic estimate of infarct size. Table 2 shows that the correlation with %ACS obtained when infarct size was calculated using individualized KD was stronger than when mean KD was used. However, the difference in correlation coefficients did not reach statistical significance, due possibly to the limited number of patients in this series.

Rationale for Normalization of Enzymatic Infarct Size by LV Mass

As previously noted, enzymatic infarct size in this study was expressed as I.U./L CK-MB released normalized by LV mass (CK-MBr/LV mass). However, infarct size has been expressed by others as measurable CK released (CKr), as CKr body weight · K (e.g., CK gram equivalents), and as CK gram equivalents per m² of body surface area. Table 2

<table>
<thead>
<tr>
<th>Definition of CK-MB IS</th>
<th>CK-MB IS vs %ACS</th>
<th>P (r1 vs r2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using mean KD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB IS = CK-MBr/LV mass (I.U./L/g LV)</td>
<td>r1 = 0.79</td>
<td>NS</td>
</tr>
<tr>
<td>Using individualized KD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB IS = CK-MBr/LV mass (I.U./L/g LV)</td>
<td>r2 = 0.84</td>
<td>—</td>
</tr>
<tr>
<td>CK-MB IS = CK-MBr (I.U./L)</td>
<td>r3 = 0.75</td>
<td>NS</td>
</tr>
<tr>
<td>CK-MB IS = CK-MBr/BSA (I.U./L/m²)</td>
<td>r4 = 0.78</td>
<td>NS</td>
</tr>
<tr>
<td>CK-MB IS = CK-MBr · BW · K (CK g equiv)</td>
<td>r5 = 0.68</td>
<td>P &lt;0.10</td>
</tr>
<tr>
<td>CK-MB IS = CK-MBr · BW · K/BSA (CK g equiv/m²)</td>
<td>r6 = 0.73</td>
<td>NS</td>
</tr>
<tr>
<td>CK-MB IS = CK-MBr · BW · K/LV mass (CK g equiv/g LV)</td>
<td>r7 = 0.80</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: CK-MB IS = creatine kinase MB isoenzymatic infarct size, KD = constant defining rate of CK-MB disappearance from plasma; CK-MBr = CK-MB released (the integrated appearance function); BSA = body surface area; BW = body weight; K = a constant relating units of CK-MB to grams of myocardium; %ACS = percent abnormally contracting segment; EF = ejection fraction, g equiv = gram equivalent; NS = not significant.
2 compares the correlation coefficients obtained between the angiographic and enzymatic estimates of infarct size in the patients without prior MI (exclusive of patients with proximal right coronary artery stenoses) when enzymatic infarct size was calculated in these various ways. CK-MB/LV mass correlated most favorably with the independent angiographic descriptor of infarct size. The improved correlation with %ACS using (CK-MB/LV mass) rather than (CK, body weight K) yielded a P < 0.10.

Discussion

This study provides unique independent angiographic documentation of the usefulness and limitations of an enzymatic technique in estimating the extent of acute necrosis in patients with acute myocardial infarction. Although enzymatic techniques have been used to quantitate infarct size in many studies during the past several years, independent documentation of the accuracy of the enzymatic technique in humans has been limited, and controversy about the validity of the method has arisen.

Enzymatic Infarct Size and Myocardial Morphology

Previous experimental animal studies documented that myocardial tissue CK content following an experimental infarction was inversely related to the morphological extent of infarction. Subsequently it was shown that post-infarction myocardial CK depletion in the animal model could be accurately estimated by mathematical analysis of the plasma CK time-activity curve. Until recently, however, direct evidence was lacking that cumulative CK release actually correlated with histological or anatomical extent of infarction. Such direct evidence was provided in a recent report by Bleifeld et al. which showed that, in humans who died shortly after acute myocardial infarction, CK infarct size correlated closely (r = 0.93), with morphological infarct size determined at postmortem exam. Since it might be argued that patients succumbing to acute myocardial infarction represent a peculiar and select population, we have attempted in the present study to assess the validity of enzymatic infarct size estimates in patients surviving acute myocardial infarction.

Although there is, as yet, no "gold standard" for quantitating infarct size in living patients, left ventricular angiography has proved a valuable tool for estimating extent of segmental ventricular wall dysfunction in patients following acute infarction. The procedure can be performed at low risk, and when coupled with coronary angiography, may be of considerable diagnostic benefit to the patient convalescing from acute myocardial infarction.

However, when used to estimate infarct size, ventriculography has several potential theoretical limitations. First, regions of left ventricular asynergy (or abnormally contracting segments) could conceivably result from myocardial ischemia in viable, noninfarcted tissue, and conversely, regions of normally contracting myocardium or hypokinetik myocardium might contain significant proportions of infarcted tissue. On the other hand, a recent report documented histopathologically that normal or hypokinetik ventriculographic segments contained no evidence of myocardial necrosis, and that asynergic zones almost uniformly showed significant muscle loss, though of variable degree. The method of quantitating asynergy used in the present study was of particular advantage, therefore, since it ignored hypokinesis and focused attention on akinetic and dyskinetic segments.

A second theoretical limitation of ventriculography might be that single plane ventriculography may fail to assess regions of asynergy lying outside the plane of the ventriculogram. Biplane ventriculography, as used in the present study, is recommended to remedy this limitation. Thirdly, regions of recently infarcted myocardium cannot be differentiated angiographically from old scar. This is an important limitation and necessitates division of the patient population into those with no prior infarct and those with prior infarct, as determined by historical and electrocardiographic criteria.

Finally, LV angiography obviously assesses only morphological features of the left ventricle; non-LV necrosis (e.g., right ventricular necrosis) is not quantitated. Thus it is necessary to subdivide the population further into those patients with and without potential for non-LV infarction. In the present study this subdivision was done retrospectively based on coronary anatomy and reported anatomical distribution of blood flow to the right ventricle. However patients with right ventricular necrosis can also be identified prospectively using electrocardiographic, hemodynamic, and scintigraphic criteria.

Despite these potential limitations of ventriculography and the recognized limitations of enzymatic estimates of infarct size, our data showed a surprisingly good correlation between ventriculographic percent abnormally contracting segment and accumulated CK-MB release (Σ CK-MB) (fig. 3) in patients without prior infarct (r = 0.84, N = 18). Two patients with inferior myocardial infarction secondary to severe stenosis of the right coronary artery proximal to the origin of the right ventricular marginal branches had disparately large Σ CK-MB as compared with the angiographic data and we hypothesized that infarction in other regions of the heart (e.g., right ventricular infarction) had caused excess release of enzyme. Clinical data to substantiate right ventricular infarction in these patients were lacking however.

Enzymatic Infarct Size and Myocardial Function

Left ventriculography has the potential for assessment of left ventricular performance through quantitation of systolic ejection phase indices such as left ventricular ejection fraction. Our data show that Σ CK-MB correlated inversely with left ventricular ejection fraction in patients with no prior infarct (r = -0.78, N = 18, fig. 4). This finding is in agreement with the study by Kostuk et al. showing good correlation (r = -0.71) between enzymatic infarct size and ejection fraction determined scintigraphically in a series of patients with acute myocardial infarction, although in the latter study no attempt was made to exclude patients with prior infarction. Our study shows that patients with prior infarction tended to have disproportionately lower ejection fractions compared to Σ CK-MB, probably explained by the cumulative insult to ventricular function.
Technique for Assessing Enzymatic Infarct Size

Correlations between the enzymatic and independent angiographic data in the patients with no prior infarct allow certain conclusions to be drawn about the technique for calculating enzymatic infarct size. First, individualization of the disappearance constant, $K_D$ as recommended initially by Norris et al.,* yields stronger correlation with %ACS (table 2) than when mean $K_D$ is used to calculate infarct size; however, the difference in correlation between the two methods did not reach statistical significance in the present series.

Secondly, as shown in table 2, correlations between %ACS and the isoenzymatic estimate of infarct size were improved when accumulated isoenzyme release was "normalized" by left ventricular mass determined angiographically. A greater than three-fold range of left ventricular mass (115-396 g) was noted in our study. A 100 gram infarct in a 396 gram ventricle might produce only mild or moderate left ventricular dysfunction, but in a 115 gram ventricle, a 100 gram infarct would be hemodynamically devastating. The "normalization" process converts the enzymatic infarct size estimate from an "absolute value" to an index of the proportion of the ventricle infarcted which, understandably, improves the correlation of the infarct size estimate with the angiographic estimates of percent abnormally contracting segment and global left ventricular function.

It should be noted that left ventricular mass can be obtained not only by left ventricular angiography but also non-invasively by both echocardiography37-30 and by specialized electrocardiographic techniques. Both angiographic and echocardiographic techniques for LV mass determination may be limited if there is gross variation in LV wall thickness (e.g., LV aneurysm), and in such cases, the specialized electrocardiographic techniques are recommended.38

Perhaps the most idealized representation of enzymatic infarct size would be an exact estimate of percent of left ventricle infarcted, determined as the ratio of enzymatic infarct size in CK-gram equivalents to left ventricular mass in grams. Unfortunately, calculation of infarct size in CK-gram equivalents requires knowledge of CK plasma distribution space as well as CK concentration in normal and in infarcted myocardium,44 all of which are difficult, if not impossible, to ascertain in individual patients.

Reliability of Enzymatic Infarct Sizing

This study consisted of a small, select population of coronary care unit patients, who survived their acute myocardial infarction and subsequently agreed to undergo diagnostic coronary and LV angiography. Nevertheless, the findings are of importance and suggest that enzymatic infarct size estimates employing accumulated CK-MB release may be reliable and useful clinically in estimating the magnitude of LV necrosis following anterior infarction. However, the enzymatic technique may be limited in assessing the extent of LV necrosis present in patients with inferior infarction, especially if concomitant right ventricular necrosis occurs in one-third of inferior infarcts, as previously reported.42 Likewise, the enzymatic technique might be limited in the occasional anteroseptal LV infarct in which there is extension of the necrotic process to contiguous right ventricular septum or free wall. Therefore, if CK-MB infarct size is to be used as an assessment of left ventricular compromise, acute right ventricular infarction and prior left ventricular infarct must be excluded or concurrently quantitated by independent techniques.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Mrs. Ani Haynes and Miss Debbie Glaister and the secretarial assistance of Mrs. Virginia Quick.

References

SUMMARY In a randomized, double-blind, crossover study, 19 patients with angina were exercised 2 min after 0.4 mg sublingual nitroglycerin and after sublingual placebo and before and 1, 3, and 5 hours after oral isosorbide dinitrate (ISDN) and oral placebo. After initial testing, patients took the dose of ISDN they had had during the study (mean dose 29 mg) for a mean period of 5.6 months before retesting using the same protocol.

Compared to placebo, exercise time after sublingual nitroglycerin increased 56% (P < 0.001) initially and 51% (P < 0.001) at retest. Compared to placebo, exercise time increased 58% (P < 0.05) initially and 58% (P < 0.005) at retest 1 hour after ISDN, 38% (P < 0.05) initially and 27% (P < 0.005) at retest 3 hours after ISDN, and 13% (NS) initially and 21% (P < 0.02) at retest five hours after ISDN. The mean exercise times initially and at retest were not significantly different.

Hemodynamic changes (decrease in systolic blood pressure and increase in heart rate) at 15 min persisted through 300 min after ISDN during both initial testing and during retesting. However, these changes were significantly less during retesting. We conclude that a partial tolerance to the hemodynamic effects of the drug develops after chronic use of high dose oral ISDN but that the antianginal efficacy of both sublingual nitroglycerin and oral ISDN is unimpaired.

ORALLY ADMINISTERED ISOSORBIDE DINITRATE (ISDN) has sustained hemodynamic effects when given acutely.1-4 Our own recent study also demonstrated that a majority of patients with angina pectoris will have a sustained anti-anginal effect after high dose oral ISDN.1 Unfortunately, such acute studies do not establish the long-term efficacy of ISDN. Side effects may prevent chronic use or tolerance may develop to the therapeutic effects.

Tolerance may develop with the chronic use of nitrates. Rapid tolerance to nitrate-induced headaches has commonly been observed.6-8 and tolerance to the hemodynamic effects of nitrates has been documented.4 * Concern has been raised not only for the development of tolerance to the therapeutic effect of long-acting drugs such as oral isosorbide dinitrate but also for crossover tolerance impairing the efficacy of sublingual nitroglycerin. Previous studies have not shown tolerance to the antianginal effects of nitrates when used chronically.10-12 However, the doses of nitrates used in many of these studies were small and probably inadequate to produce chronic vasodilatation. The high doses of ISDN which we employed in our recent study may be double-edged swords, and "carry within them the seeds of their own therapeutic failure via the development of tolerance."9

This study was designed to answer two questions regarding the chronic use of oral ISDN in patients with angina pectoris: Will adverse side effects prevent the chronic use of high doses of oral ISDN? Will tolerance to the therapeutic effects...
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Circulation. 1977;56:199-205
doi: 10.1161/01.CIR.56.2.199

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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