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An Electrocardiographic Algorithm for the Prediction of the Culprit Lesion Site in Acute Anterior Myocardial Infarction

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Summary

Background: Although the 12-lead electrocardiogram (ECG) has been found useful in identifying the left anterior descending (LAD) coronary artery as the infarct-related artery in acute myocardial infarction (MI), it has traditionally been felt to be incapable of localizing the culprit lesion within the LAD itself. Such a capability would be important, because anterior MI due to proximal LAD lesions carry a much worse prognosis than those due to more distal or branch vessel lesions.

Hypothesis: This study investigated whether certain ECG variables—especially an ST-segment injury pattern in leads aVL and/or V_1—would correlate with culprit lesion site, and an ECG algorithm was developed to predict culprit lesion site.

Methods: The initial ECGs of 55 patients who had undergone cardiac catheterization after an anterior or lateral MI were reviewed to identify the leads with an ST-segment injury pattern; the corresponding catheterization films were then reviewed to identify the location of the culprit lesion; and these separate findings were then compared.

Results: The sensitivity and specificity of an ST-injury pattern in aVL in predicting a culprit lesion before the first diagonal branch were 91 and 90%, respectively; the same values in predicting a lesion prior to the first septal branch were 85 and 78%. ST-segment elevation in V_1, on the other hand, was a much less sensitive and specific predictor of a preseptal lesion. Overall, our algorithm correctly identified the culprit lesion location in 82% of our patients.

Conclusion: Based on our findings, we conclude that an ST-segment injury pattern in aVL during an anterior myocardial infarction predominantly reflects a proximal LAD lesion and therefore constitutes a high-risk finding.

Key words: myocardial infarction, electrocardiogram, left anterior descending artery

Introduction

The 12-lead electrocardiogram (ECG) is an effective tool for the rapid diagnosis of acute anterior myocardial infarction (MI).[1] Since it is well established that almost all anterior (and anterolateral) infarctions are due to occlusions somewhere within the left anterior descending (LAD) coronary artery[2–4] or within one of its branches,[5–7] the ECG thus correctly identifies the infarct artery in most cases; however, no well-established ECG criteria exist for more precise prediction of the occlusion site. Such a prediction, if it could be made, would be highly useful for several reasons. The first is that anterior infarctions due to occlusions within the proximal LAD carry a much worse prognosis than those due to more distal or branch vessel lesions,[5,8,9] a fact which would be quite significant for decision-making in our present era of thrombolysis and invasive intervention for acute MI. The second reason is that identification of the culprit lesion site, especially in relation to the origins of the first septal and first diagonal branches, would have implications regarding regional left ventricular function during an acute anterior wall infarction, since the first septal branch supplies the basal septum and the first diagonal branch supplies much of the anterolateral wall. Finally, information obtained from ECGs regarding the LAD occlusion site might also shed light on the accuracy of the commonly used subclassifications of anterior MIs, in particular the so-called "anteroseptal" and "apical" infarctions.

Based on the present literature on this subject and our own postulations, we developed several hypotheses which we decided to test in our study: first, that an acute injury pattern both in lead aVL and in at least two contiguous precordial leads (including either V_2 or V_3) during an acute anterior MI predicts a

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culprit lesion site in the LAD coronary artery prior to the origin of the first diagonal branch;[10] since the origins of the first diagonal and first septal branches are usually close to each other, we postulated that involvement of lead aVL would usually also predict a preseptal lesion; second, that an injury pattern in lead aVL in the absence of lead elevations in at least two of the right precordial leads predicts a first diagonal, ramus, or first obtuse marginal branch lesion;[5,11] third, that ST-elevation in leads V_1–V_2 predicts a culprit lesion in the LAD prior to the first septal branch.

We found one prior study[10] which correlated ECG findings during an anterior MI with the presence or absence of a prediagonal culprit lesion on coronary angiography. In this study, Birnbaum *et al.* found the presence of 0.1 mV of ST elevation in leads I and aVL to have a good predictive value for a prediagonal lesion; however, the sensitivity of their criteria was very poor (27, 46, and 27% for leads I, aVL, and I and aVL, respectively). In an attempt to improve this low sensitivity, we decided to evaluate only ST abnormalities in the lead apparently most sensitive for prediagonal lesions, that is, aVL, and we also chose to include lesser degrees of ST elevation and even isoelectric ST segments in aVL (the latter only if an abnormal Q wave was also present in this lead). To avoid compromising the specificity of this criterion, subtle degrees of ST elevation were required to be associated with symmetrical T-wave inversions to be considered significant.

Our aim was to develop and test an algorithm based on our postulations that would prove useful in the localization of the culprit lesion in acute anterior MIs.

Methods

We reviewed the final cardiac catheterization reports of all patients who had undergone cardiac catheterization at our institution between October 1993 and January 1996 (n = 2501); from these, we selected all patients with a listed diagnosis of an acute septal, anteroseptal, anterior or extensive anterior, anterolateral, or lateral MI (n = 93). Cardiac catheterization films on 82 of these patients were available for review. The admission ECG (or the first ECG during the admission available for review) was then obtained. Exclusion criteria were the following: the presence of complete bundle-branch block (n = 4), the absence of any ST elevation on the first available ECG (n = 4), and a duration > 30 days between the initial ECG and the subsequent cardiac catheterization (n = 8). The initial ECGs on eight additional patients, who had been transferred from other institutions for catheterization, could not be located.

The remaining 58 ECG tracings were then reviewed by two investigators who were blinded to clinical and cardiac catheterization data of the respective patients. The investigators were asked to evaluate the presence of ST elevation ≥ 0.1 mV in each of the precordial leads and limb lead aVL, and the presence of ST depression ≥ 0.1mV in any of the inferior leads; they were also asked to quantify the degree of ST elevation, if any, in leads V_1 and aVL to the nearest 0.05 mV, and also to note whether ST elevation was > 0 mV and < 0.05 mV in aVL. An injury pattern was considered present in aVL if any of the following criteria were met: first, ST elevation ≥ 0.05 mV; second, any lesser degree of ST elevation if associated with symmetrical T-wave inversion; third, any isoelectric ST segment associated with both symmetrical T-wave inversion and an abnormal Q wave (defined as ≥ 30 ms in duration). All measurements of ST-segment deviation were measured 60 ms after the J point. For the purpose of this study, ST-segment elevation was defined as being in reference to the preceding TP segment. Any disagreement between the two investigators was resolved by consensus.

Using our hypotheses, we developed an algorithm for the prediction of the culprit lesion site and delineated groups (Groups 1–5) accordingly (Fig. 1). It should be noted that the ECG criteria for the different subclasses of anterior MI are our own rather than more commonly used criteria. Electrocardiographic examples of the different groups in our algorithm are seen in Figure 2.

The cardiac catheterization films of the same patients were then reviewed by two investigators, who were blinded to clinical and ECG data of the respective patients. The investigators were asked to identify the location of the culprit lesion causing the acute MI. If the lesion was present in the LAD, they were asked to identify the location in relation to the origins of the first diagonal and the first septal branch and also to note whether the lesion was in the proximal, early-mid (the first half of the mid-LAD by visual estimate), late-mid, or distal LAD. If the culprit lesion was exactly at the origin of the first septal or diagonal, it was classified to be in the preseptal or prediagonal group. The site of the culprit lesion was determined by the presence of total or subtotal occlusion; if this was not present, then by the presence of residual thrombus or an ulcerated lesion; if these also were not present, then by the severity of stenosis alone. Any disagreement between the two investigators was resolved by consensus. Three patients were excluded from the study on the basis of their angiographic findings, two because of the absence of any lesion, the third because of the presence of uniformly severe diffuse disease precluding localization of the culprit lesion; this left 55 patients in our study.

The data compiled upon the completion of the above review were then analyzed. The patients were divided into those with first diagonal, obtuse marginal, or ramus intermedius culprit lesions and those with LAD culprit lesions; the latter were subdivided into those with prediagonal versus postdiagonal culprit lesions, and those with preseptal versus postseptal culprit lesions.

These groups were then compared using the ECG variables indicated in our hypotheses. All categoric data were analyzed for statistical significance using the chi-square test. A probability value ≤ 0.05 was considered to be significant.

Results

Of the 55 patients included in our study, 2 were found to have a first obtuse marginal branch and 1 to have a first diagonal branch culprit lesion; the remaining 52 patients were found

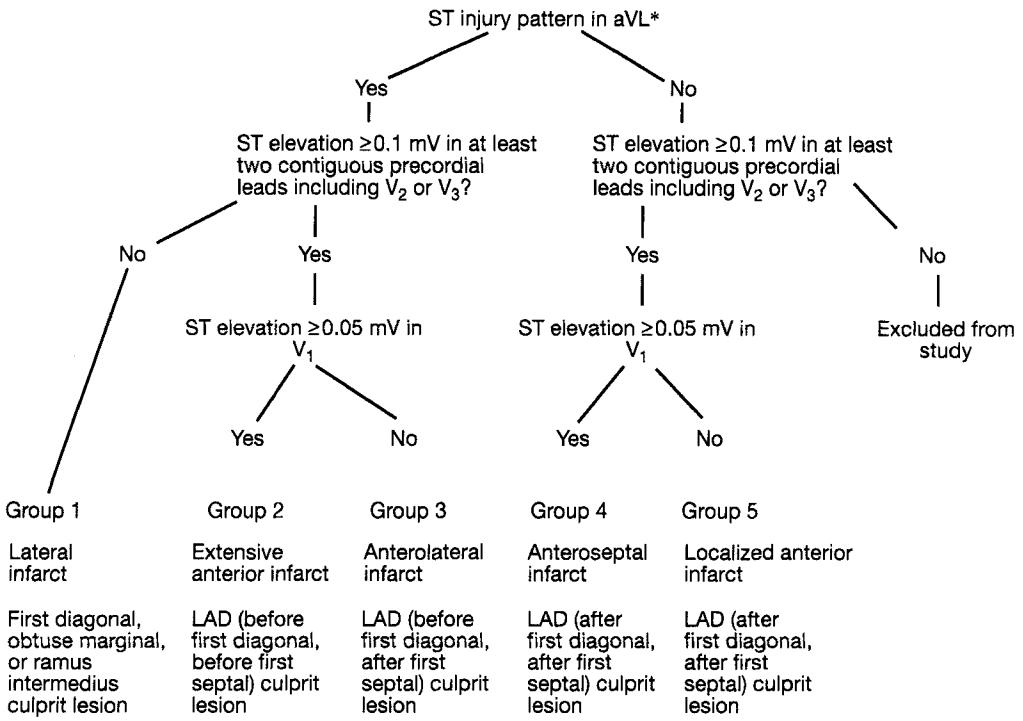

FIG. 1 Electrocardiographic algorithm for culprit lesion site prediction. *Defined as ST-segment elevation ≥0.05 mV; or *any* ST-segment elevation associated with symmetrical T-wave inversion; or an isoelectric ST segment associated with both an abnormal Q wave (≥0.03 s) and symmetrical T-wave inversion. LAD = left anterior descending artery.

to have a culprit lesion within the LAD. In these 52 patients, 23 culprit lesions were prediagonal and 29 were postdiagonal; 20 culprit lesions were preseptal and 32 were postseptal (see Tables I and II).

When we utilized the criteria of 0.1mV of ST elevation in lead aVL to differentiate pre- versus postdiagonal culprit lesions, our sensitivity and positive predictive values were similar to those attained by Birnbaum *et al.*: 48 and 92%, respectively (compared with Birnbaum's 47 and 81%). However, as indicated in Table I, 91% of those patients with LAD culprit lesions had an ST injury pattern (as defined above) in lead aVL, representing a dramatically improved sensitivity using our criteria. Despite this improved sensitivity, both the specificity and positive predictive value remained high: 90 and 88%, respectively; the negative predictive value was 93%. The criteria of ST depression in any inferior lead ≥0.1 mV had the same specificity of 90%, but the positive predictive value (84%), sensitivity (70%), and negative predictive value (79%) worsened (see Table III).

In identifying an LAD culprit lesion before the first septal branch, the presence of an injury pattern in aVL had only a fair positive predictive value (71%). However, its sensitivity and specificity were 85 and 78%, respectively, and the negative predictive value was 89%. In fact, these values are superior to those found when using the presence of ≥0.1 mV of ST elevation in lead V_1 to identify preseptal culprit lesions (sensitivity 65%, specificity 63%, positive predictive value 52%, negative predictive value 74%); when 0.05 mV was used as the cut-off

TABLE I Electrocardiographic variables in relation to pre- or postdiagonal culprit lesions

	Total no. of patients	No. with ST elevation ≥ 0.1mV in aVL	No. with ST injury pattern[a] in aVL	No. with ST depression ≥0.05mV in inferior leads
Prediagonal culprit lesion	23	11 (48%)	21 (91%)	16 (70%)
Postdiagonal culprit lesion	29	1 (3%)	3 (10%)	3 (10%)
		$\chi 2 = 14.3$	$\chi 2 = 33.9$	$\chi 2 = 19.4$
		p Value < 0.001	p Value < 0.0001	p Value < 0.001

[a] Defined as ST-segment elevation ≥0. 05 mV; or *any* ST-segment elevation associated with symmetrical T wave inversion; or an isoelectric ST segment associated with both an abnormal Q wave (≥0.03 s) and symmetrical T-wave inversion.

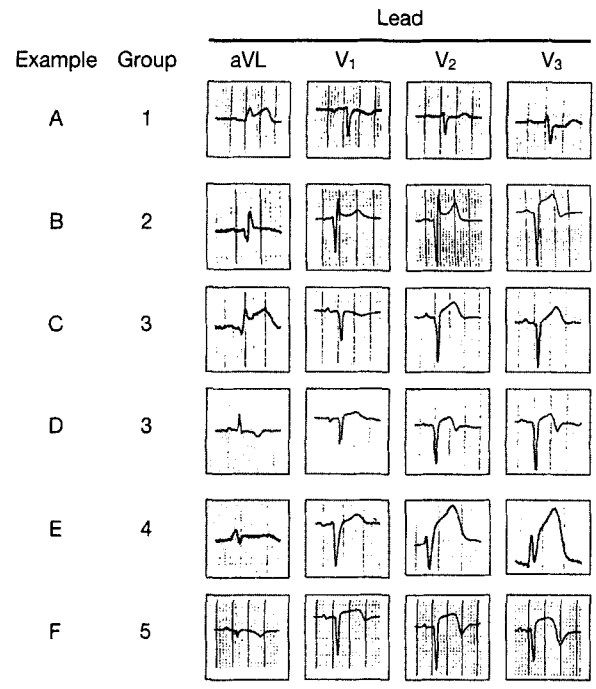

FIG. 2 Electrocardiographic examples of different algorithm groups: (A) Electrocardiogram (ECG) fulfilling the criteria for Group 1 in our algorithm: an injury pattern in aVL but not in precordial leads V_1–V_3. This patient's culprit lesion was in a large first diagonal coronary artery branch. (B) Group 2 ECG with an injury pattern in aVL, V_1 and in multiple contiguous right precordial leads. This patient had a proximal preseptal and prediagonal left anterior descending (LAD) coronary artery culprit lesion. (C) Group 3 ECG with an injury pattern in aVL, not in V_1, but in two other adjacent right precordial leads (i.e., V_2 and V_3). This patient had a prediagonal postseptal LAD culprit lesion. (D) Group 3 ECG with an injury pattern in aVL by our criteria (Q wave and symmetrical T-wave inversion) but without classical ST elevation, accompanied by ST elevation in V_2 and V_3 but not in V_1. Our algorithm correctly predicted a prediagonal culprit lesion in this patient that would have been missed by more formal standard criteria[10] (see text). (E) Group 4 ECG with an injury pattern in V_1 and the adjacent right precordial leads (V_2 and V_3) but not in aVL. This patient had a mid-LAD culprit lesion after the first diagonal and first septal branches. (F) Group 5 ECG with an injury pattern in the adjacent right precordial leads but not in V_1 or aVL. This patient (along with the patient in example E) also had postdiagonal, postseptal mid-LAD culprit lesion.

instead, the sensitivity (95%) and negative predictive value (92%) were excellent, but at the expense of a poor specificity (38%) and positive predictive value (49%) (see Table III).

Table IV summarizes the results obtained from our algorithm. Overall, the algorithm correctly identified the location of the culprit lesion in 82% of our 55 patients.

Discussion

Although the surface 12-lead ECG has been found in the past to be helpful for localizing the culprit lesion to the LAD artery in acute anterior wall MI, it has traditionally been felt to have a limited ability to localize the lesion *within* the LAD itself.[1] Looking at the relationship between the admission ECG and the site of LAD occlusion relative to the first diagonal branch alone, Birnbaum *et al.*[10] found the presence of ≥0.1 mV of elevation in the high lateral leads and ≥0.1 mV of depression in the inferior leads to have a high positive predictive value for a lesion proximal to the first diagonal branch, albeit with a low sensitivity. By modifying this criterion for acute high lateral wall injury, we were able to obtain excellent sensitivity, specificity, and positive and negative predictive values.

The presence of ST depression in the inferior leads had a similar specificity (compared with our ST injury pattern criteria in aVL) in predicting a prediagonal lesion, but the sensitivity and negative predictive value worsened. In past studies, the presence of inferior ST depressions during an acute anterior MI was found to correlate with a much more complicated clinical course than if such depressions were absent.[12, 13] Some authors have felt that this correlation was due to the presence of coexisting inferior ischemia and thus multivessel coronary artery disease,[14] whereas other studies[10, 15] have refuted this correlation. Our own data indicate that inferior ST depressions were only present (in all but one of our patients with an anterior MI) when an ST-segment injury pattern was also present in aVL. This finding suggests that inferior ST depressions in acute anterior wall MIs are merely reciprocal changes (due to the fact that the ST-segment vector in aVL is relatively opposite to the ST-segment vector in III and aVF) and predict a complicated clinical course because they are an alternative marker (albeit less sensitive than the aVL criteria which we developed) for a proximal LAD culprit lesion.

TABLE II Electrocardiographic variables in Relation to pre- or postseptal culprit lesions

	Total no. of patients	No. with ST injury pattern[a] in aVL	No. with ST elevation >0.05mV in V_1	No. with ST elevation >0.1mV in V_1
Preseptal culprit lesion	20	17 (85%)	19 (95%)	13 (65%)
Postseptal culprit lesion	32	7 (22%)	20 (63%)	12 (38%)
		$\chi 2 = 19.8$	$\chi 2 = 7.0$	$\chi 2 = 3.8$
		p Value < 0.001	p Value < 0.05	p Value < 0.05

[a] Defined as ST-segment elevation ≥ 0.05 mV; or *any* ST segment elevation associated with symmetrical T-wave inversion; or an isoelectric ST segment associated with both an abnormal Q wave (≥ 0.03 s) and symmetrical T-wave inversion.

TABLE III Value of different electrocardiographic criteria in predicting the culprit lesion site in acute anterior myocardial infarction

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Pre- vs. post- first diagonal culprit lesions				
aVL injury pattern[a]	0.91	0.90	0.88	0.93
≥0.1mV ST depression in any inferior lead	0.70	0.90	0.84	0.79
Pre- vs. post- first septal culprit lesions				
aVL injury pattern[a]	0.85	0.78	0.71	0.89
≥0.1 mV ST elevation in V_1	0.65	0.63	0.52	0.74
≥0.05 mV ST elevation in V_1	0.95	0.38	0.49	0.92

[a] Defined as ST-segment elevation ≥ 0. 05 mV; or *any* ST-segment elevation associated with symmetrical T-wave inversion; or an isoelectric ST segment associated with both an abnormal Q wave (≥0.03 s) and symmetrical T-wave inversion.

The use of ECG criteria to predict a culprit lesion before or after the first septal branch of the LAD might initially seem more problematic since the myocardial region supplied by the first septal (i.e., the proximal septum) is expected to be electrically silent on the 12-lead ECG, similar to the posterior wall;[16] thus, injury in this region would be expected to be silent as well. However, we postulated that since the origins of the first septal and the first diagonal branches are usually close to each other, lead aVL could be used as a surrogate marker for the presence of proximal septal injury. In fact, our data indicate that the single lead which best reflected a pre- or postseptal culprit lesion was not V_1 (or V_2), the so-called septal leads, but rather lead aVL. These data are consistent with pathologic studies[17] which have found that extensive septal infarctions are associated also with extensive infarction in the anterolateral wall. Our data would thus indicate that the presence of an injury pattern in lead aVL constitutes a high-risk ECG finding in acute anterior MI, predicting most likely a proximal LAD lesion and extensive myocardial injury in the septal, anterior, and anterolateral walls. An interesting finding in a study of 72 patients[18] presenting with a first anterior Q-wave MI was that those patients who developed an infarction pattern in leads I or aVL were more likely to have higher end-diastolic volumes, more left ventricular contour distortion and, most important, had over a three and a half times greater chance of developing a left ventricular thrombus (57 vs. 16%) than those patients who did not have such an infarction pattern.

TABLE IV Analysis of groups as predicted by electrocardiographic algorithm

	Group 1 Lateral infarct	Group 2 Extensive anterior infarct	Group 3 Anterolateral infarct	Group 4 Anteroseptal infarct	Group 5 Localized anterior infarct
Leads with ST injury pattern/elevation	(+) aVL	(+) aVL, V_1, V_2	(+) aVL, two consecutive precordial leads including V_2 or V_3	(+) V_1, V_2	(+) Two consecutive precordial leads including V_2 or V_3
	(0) V_1–V_3		(0) V_1	(0) aVL	(0) V_1, aVL
Prediction	First diagonal, ramus, or obtuse marginal	LAD: Before first diagonal *and* first septal	LAD: Before first diagonal, after first septal	LAD: After first diagonal *and* first septal	LAD: After first diagonal *and* first septal
Prediction correct (no. of patients):	3*	14	4	16	8
Prediction incorrect (no. of patients):	0	6	0	3	1
Location of culprit lesion (no. of patients):	Proximal LAD	17	0	2	1
	Early-mid LAD	3	4	10	5
	Late-mid LAD	0	0	4	3
	Distal LAD	0	0	3	0

(+) = Injury pattern/elevation present; (0) = injury pattern/elevation absent.

[a] Two patients with culprit lesions in the first obtuse marginal; one with culprit lesion in the first diagonal.

Abbreviation: LAD = left anterior descending artery.

We also examined whether an association existed between the presence or absence of an injury pattern in leads V_1 and whether the culprit lesion was before or after the first septal branch. Contrary to the popular misconception that the right precordial leads, V_1 and V_2, face the proximal septum and that anteroseptal infarction denotes infarction of this region, ECG texts addressing this matter[16, 19] indicate that the "septal" in so-called "anteroseptal" infarction refers to the mid or even distal septum, a finding borne out by autopsy studies. Consistent with this were the findings in a recent study of 52 patients[20] who fit the traditional definition of an acute anteroseptal infarction, with ST elevations isolated to V_1–V_3 (and thus without ST elevations in the lateral limb leads). Of these patients, 92% had normal septal wall motion on echocardiography, and of the 44 patients who also underwent cardiac catheterization, 85% were found to have mid or distal LAD culprit lesions. Our findings also indicate that the acute anteroseptal infarct pattern, with ST elevation confined to lead V_1 and the adjacent precordial leads, predicts a mid or distal LAD culprit lesion, distal to both the first septal and first diagonal branches. In fact, when patients who were classified as having an anteroseptal infarct (Group 4 in our algorithm, Fig. 1) were compared with patients who were classified as having a localized anterior infarct (Group 5), there did not seem to be any significant difference in the culprit lesion location (see Table IV).

Another similar question that arises from review of our algorithm is whether patients in Group 2 differ significantly from patients in Group 3—that is, whether patients with an ST injury pattern in aVL and the right precordial leads who *did* have ST elevations in V_1 differed in any way from patients with an ST injury pattern in aVL and the right precordial leads who *did not* have ST elevations in V_1. It appears from our data that although patients in both groups were more likely to have pre- than postdiagonal culprit lesions, patients in Group 2 were much more likely to have a preseptal (and thus proximal LAD) culprit lesion in addition, than patients in Group 3. Again, however, the number of patients in Group 3 is much too small to make any firm conclusions regarding this question. It should also be pointed out that our algorithm would be incapable of predicting a culprit lesion within the LAD prior to the origin of the first septal and after the origin of the first diagonal.

Limitations

Although many of our findings appear to reach statistical significance, it cannot be overemphasized that this was a retrospective study done on a relatively small group of patients. Moreover, though it sought to deduce the location of occlusion during acute anterior MIs on the basis of ECG criteria, coronary angiography was performed on the patients in our study an average of 6.3 days after the initial ECG and thus some time after the initial infarction, during which time most of the patients in our study had reperfused, either spontaneously or with administered thrombolytics. Thus, especially since multiple significant lesions were occasionally seen, we cannot be certain that we correctly identified the culprit lesion in all cases. Moreover, because there could possibly have been proximal propagation of a thrombus during the acute infarction, the acute occlusion during the infarction may have been proximal to the septal or diagonal branch, whereas the culprit lesion on subsequent angiography may have been distal.

Our study should thus be considered hypothesis-generating rather than definitive. A larger prospective study, comparing the ECG variables which we studied with coronary angiographic findings, preferably during the acute stages of MI (such as during primary angioplasty), would be necessary to resolve many of our uncertainties.

Conclusions

Our findings suggest that the presence of an injury pattern in lead aVL (as we have defined it above) in association with precordial ST-segment elevations in at least two contiguous leads (including V_2 or V_3) is an ECG marker with very high sensitivity, specificity, and negative and positive predictive values for a culprit lesion proximal to the first diagonal, and very high sensitivity and negative predictive value for a lesion prior to the first septal branch. The presence or absence of inferior ST depressions usually went in tandem with the presence or absence of an ST injury pattern in lead aVL and added little to our ability to predict a proximal or distal lesion based on studying aVL alone. Thus, the presence of an injury pattern in lead aVL should be considered a high-risk finding in acute anterior MI, indicative of a relatively proximal LAD lesion and extensive myocardial injury; in contrast, the presence of an injury pattern in lead V_1 is only a moderately sensitive and specific predictor of a lesion proximal to the first septal branch. The algorithm we developed based on our hypotheses should prove useful in localizing the site of coronary occlusion during an acute anterior myocardial infarction.

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Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

Retavase® (Reteplase) is indicated for use in the management of acute myocardial infarction (AMI) in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, Retavase® is contraindicated in the following situations:

- **Active internal bleeding**
- **History of cerebrovascular accident**
- **Recent intracranial or intraspinal surgery or trauma (see WARNINGS)**
- **Intracranial neoplasm, arteriovenous malformation, or aneurysm**
- **Known bleeding diathesis**
- **Severe uncontrolled hypertension**

WARNINGS

Bleeding

The most common complication encountered during Retavase® therapy is bleeding. The sites of bleeding include both internal bleeding sites (intracranial, retroperitoneal, gastrointestinal, genitourinary, or respiratory) and superficial bleeding sites (venous cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to bleeding. In clinical trials some of the hemorrhage episodes occurred one or more days after the effects of Retavase® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during Retavase® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites, and needle puncture sites). Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from noncompressible sites. Should an arterial puncture be necessary during the administration of Retavase®, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with Retavase®. Venipunctures should be performed carefully and only as required.

Should serious bleeding (not controllable by local pressure) occur, concomitant anticoagulant therapy should be terminated immediately. In addition, the second bolus of Retavase® should not be given if serious bleeding occurs before it is administered.

Each patient being considered for therapy with Retavase® should be carefully evaluated and anticipated benefits weighed against the potential risks associated with therapy. In the following conditions, the risks of Retavase® therapy may be increased and should be weighed against the anticipated benefits:

- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy
- *Previous puncture of noncompressible vessels*
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- Hypertension: systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Severe hepatic or renal dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded AV cannula at a seriously infected site
- Advanced age
- Patients currently receiving oral anticoagulants, e.g., warfarin sodium
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Cholesterol Embolization

Cholesterol embolism has been reported rarely in patients treated with thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, "purple toe" syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and should be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when Retavase® is administered.

PRECAUTIONS

General

Standard management of myocardial infarction should be implemented concomitantly with Retavase® treatment. Arterial and venous punctures should be minimized (see **WARNINGS**). In addition, the second bolus of Retavase® should not be given if the serious bleeding occurs before it is administered. In the event of serious bleeding, any concomitant heparin should be terminated immediately. Heparin effects can be reversed by protamine.

Readministration

There is no experience with patients receiving repeat courses of therapy of Retavase®. Retavase® did not induce the formation of Retavase® specific antibodies in any of the approximately 2,400 patients who were tested for antibody formation in clinical trials. If an anaphylactoid reaction occurs, the second bolus of Retavase® should not be given, and appropriate therapy should be initiated.

Drug Interactions

The interaction of Retavase® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin, dipyridamole, and abciximab) may increase the risk of bleeding if administered prior to or after Retavase® therapy.

Drug/Laboratory Test Interactions

Administration of Retavase® may cause decreases in plasminogen and fibrinogen. During Retavase® therapy, if coagulation tests and/or measurements of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. Retavase® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of PPACK (chloromethylketone) at 2 μM concentrations was used in clinical trials to prevent *in vitro* fibrinolytic artifacts.[1]

Use of Antithrombotics

Heparin and aspirin have been administered concomitantly with and following the administration of Retavase® in the management of acute myocardial infarction. Because heparin, aspirin, or Retavase® may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Retavase®. Studies to determine mutagenicity, chromosomal aberrations, gene mutations, and micronuclei induction were negative at all concentrations tested. Reproductive toxicity studies in rats revealed no effects on fertility at doses up to 15 times the human dose (4.31 u/kg).

Pregnancy Category C

Reteplase has been shown to have an abortifacient effect in rabbits when given in doses 3 times the human dose (0.86 U/kg). Reproduction studies performed in rats at doses up to 15 times the human dose (4.31 U/kg) revealed no evidence of fetal anomalies; however, Reteplase administered to pregnant rabbits resulted in hemorrhaging in the genital tract, leading to abortions in mid-gestation. There are no adequate and well-controlled studies in pregnant women. The most common complication of thrombolytic therapy is bleeding and certain conditions, including pregnancy, can increase this risk. Reteplase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Retavase® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retavase® is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Retavase® in pediatric patients have not been established.

ADVERSE REACTIONS

Bleeding

The most frequent adverse reaction associated with Retavase® is bleeding (see **WARNINGS**). The types of bleeding events associated with thrombolytic therapy may be broadly categorized as either intracranial hemorrhage or other types of hemorrhage.

- Intracranial hemorrhage
  In the INJECT clinical trial the rate of in-hospital, intracranial hemorrhage among all patients treated with Retavase® was 0.8% (23 of 2,965 patients). As seen with Retavase® and other thrombolytic agents, the risk for intracranial hemorrhage is increased in patients with advanced age or with elevated blood pressure.
- Other types of hemorrhage
  The incidence of other types of bleeding events in clinical studies of Retavase® varied depending upon the use of arterial catheterization or other invasive procedures and whether the study was performed in Europe or the USA. The overall incidence of any bleeding event in patients treated with Retavase® in clinical studies (n = 3,805) was 21.1%. The rates for bleeding events, regardless of severity, for the 10 + 10 U Retavase® regimen from controlled clinical studies are summarized below.

Retavase® Hemorrhage Rates

Bleeding Site	INJECT	RAPID 1 and RAPID 2	
	Europe n = 2,965	USA n = 210	Europe n =113
Injection Site*	4.6%	48.6%	19.5%
Gastrointestinal	2.5%	9.0%	1.8%
Genitourinary	1.6%	9.5%	0.9%
Anemia, site unknown	2.6%	1.4%	0.9%

*includes the arterial catheterization site (all patients in the RAPID studies underwent arterial catheterization).

In these studies the severity and sites of bleeding events were comparable for Retavase® and the comparison thrombolytic agents.

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, any concomitant heparin should be terminated immediately. In addition, the second bolus of Retavase® should not be given if the serious bleeding occurs before it is administered. Death and permanent disability are not uncommonly reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during Retavase® therapy. Therefore, Retavase® therapy requires careful attention to potential bleeding sites (e.g., catheter insertion sites, arterial puncture sites).

Allergic Reactions

Among the 2,965 patients receiving Retavase® in the INJECT trial, serious allergic reactions were noted in 3 patients, with one patient experiencing dyspnea and hypotension. No anaphylactoid reactions were observed among the 3,856 patients treated with Retavase® in initial clinical trials. In an ongoing clinical trial two anaphylactoid reactions have been reported among approximately 2,500 patients receiving Retavase®.

Other Adverse Reactions

Patients administered Retavase® as treatment for myocardial infarction have experienced many events which are frequent sequelae of myocardial infarction and may or may not be attributable to Retavase® therapy. These events include cardiogenic shock, arrhythmias (e.g., sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation), AV block, pulmonary edema, heart failure, cardiac arrest, recurrent ischemia, reinfarction, myocardial rupture, mitral regurgitation, pericardial effusion, pericarditis, cardiac tamponade, venous thrombosis and embolism, and electromechanical dissociation. These events can be life-threatening and may lead to death. Other adverse events have been reported, including nausea and/or vomiting, hypotension, and fever.

Reference

1. Martin U, Gärtner D, Markl HJ, et al. D-PHE-PRO-ARGCHLOROMETHYLKETONE prevents *in vitro* fibrinogen reduction by the novel recombinant plasminogen activator BM 06.022. *Ann Hematol.* 1992;64(suppl) A47.

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