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A tale of two formulas: Differentiation of subtle anterior MI from benign ST segment elevation

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Abstract

Background: It may sometimes be difficult to differentiate subtle ST-segment elevation (STE) due to anterior myocardial infarction (MI) from benign variant (BV) STE. Recently, two related formulas were proposed for this purpose. However, they have never been tested in an external population.

Materials and methods: Consecutive patients from May 2017 to January 2018, who were admitted with the diagnosis of acute anterior STEMI, were enrolled. Electrocardiograms were systematically reviewed and only subtle ones were included. First 200 consecutive patients with noncardiac chest pain were also enrolled as a control group. Relevant electrocardiographic parameters were measured.

Results: A total of 379 anterior MI and 200 BV-STE cases were enrolled during study period. A total of 241 patients in STEMI group were excluded for not matching subtleness criteria, four patients in control group were also excluded because of prior left-anterior descending artery intervention. The three-variable formula, with recommended cut-point of 23.5, had a sensitivity, specificity, and diagnostic accuracy of 73.9%, 86.7%, and 81.4%, respectively. The four-variable formula, with the published cut-point of 18.2, had a sensitivity, specificity, and diagnostic accuracy of 83.3%, 87.7%, and 85.9%, respectively.

Conclusion: Three- and four-variable formulas with recommended cutoffs have a reasonable sensitivity, specificity, and diagnostic accuracy in differentiating subtle STEMI with BV-STE. Although both perform well, the four-variable formula has a higher sensitivity, specificity, and diagnostic accuracy and should be preferred.

KEYWORDS

benign variant, early repolarization, electrocardiogram, myocardial infarction, ST segment elevation

1 | INTRODUCTION

Rapid identification of pathologic ST-segment elevation (STE) is the crucial first step for timely utilization of life-saving reperfusion therapies in patients with myocardial infarction (MI). However, it may sometimes be difficult to identify subtle STE due to anterior MI and/or to differentiate it from STE due to other common causes, mostly benign variant (BV) STE. Both entities may look very similar on electrocardiogram (ECG) and previous studies repeatedly showed that physicians have difficulty in distinguishing the two (Barge-Caballero

et al., 2010; Brady, 1998a; Brady, Perron, & Ullman, 2000; Brady et al., 2002; Jayroe et al., 2009; Kontos et al., 2010; Larson et al., 2007; Prasad, Richards, Sadick, Ong, & Kovoor, 2008; Turnipseed et al., 2006). While failure to identify subtle STEMI may have obvious dire consequences, false catheterization laboratory activations for BV-STE also puts the patient at risk of unnecessary procedures and their complications as well as excessive utilization of limited resources.

Despite its pivotal position in this time-sensitive diagnostic dilemma, there are very few studies concentrating on subtleties of ECG in differential diagnosis of STEMI and BV-STE. To our knowledge, the foremost attempt addressing this problem came from Smith et al. (2012), who derived a three-variable formula for distinguishing subtle STEMI from BV-STE. In this study, the authors reported that their formula, using ST segment elevation in V3, corrected QT interval and R-wave amplitude in V4, correctly distinguished BV-STE from STEMI with an overall sensitivity, specificity, and diagnostic accuracy of 86%, 91%, and 88%. Recently, the same group reevaluated their database for a new four-variable formula and showed an increased diagnostic accuracy (Driver et al., 2017). However, these formulas have never been tested in an external population and their diagnostic accuracy in patients outside of their derivation cohort is unknown. In this study, we sought to assess diagnostic accuracy of these three- and four-variable formulas in an independent patient population.

Highlights

- It may sometimes be difficult to differentiate subtle ST-segment elevation (STE) due to anterior myocardial infarction (MI) from benign variant (BV) STE.
- Recently, two related formulas based on three- and four-electrocardiographic variables were proposed for this purpose. However, they have never been tested in an external population.
- In this study, we tested these formulas in an independent population. Three- and four-variable formulas with recommended cutoffs have a reasonable sensitivity, specificity, and diagnostic accuracy in differentiating subtle STEMI with BV-STE.
- Although both perform well, the four-variable formula has a higher sensitivity, specificity and diagnostic accuracy and should be preferred.

2 | MATERIAL AND METHODS

The study was undertaken at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, a tertiary heart center in Istanbul, which has a large regional STEMI network with approximately 1,500 STEMI patients per year presenting for primary percutaneous coronary intervention. Local review board approval was acquired; the study was deemed to be exempt from formal evaluation because it involved only examination of existing records.

All patients from May 2017 to January 2018, who were admitted with the diagnosis of acute anterior STEMI and underwent coronary angiography revealing acute occlusion of left anterior descending artery or its branches with TIMI 0/1 flow, were enrolled. To concentrate on the subtle ECGs, we systematically excluded those with obvious electrocardiographic clues which make the diagnosis of anterior STEMI clear-cut and obviate the need for distinguishing anterior STEMI from BV-STE. As described by Smith et al. (2012), ECGs with ST-segment elevation more than 5 mm, convex STE morphology in any of five leads from V2 to V6, reciprocal ST depression more than 1 mm in inferior leads, any concomitant anterior ST-segment depression, terminal QRS distortion, Q waves in any of V2 to V4, or T-wave inversion in any of V2 to V6 were disqualified. We also searched our ECG database for first 200 consecutive patients in the same period, who presented to the emergency department with chest pain, whose ECG results were coded by cardiologists as "BV-STE" and had a final diagnosis of nonischemic chest pain after confirmed negative high sensitivity cardiac troponin levels. For multiple ECGs on the same patient, only the first ECG was used.

All ECGs were measured manually by a senior cardiologist (E.A.). The measurements those relevant to the formula variables were recorded. R wave, T wave, and total QRS amplitudes were approximated to closest 0.5 mm. ST segment elevation was measured both at J point and at 60 ms after J point, but only the latter was used in the formulas. Bazett-corrected computerized QT was recorded when available (Bazett, 1920). If not, the longest of the 12 QT intervals on the 12-lead ECG was divided by the square root of the R-R interval, measured in seconds. The three-variable formula was calculated as (1.196 × STE60 in V3) + (0.059 × Bazett-corrected QT) − (0.326 × R-wave amplitude in V4; Smith et al., 2012). The four-variable formula was calculated as (0.052 × Bazett-corrected QT) − (0.151 × QRS amplitude in V2) − (0.268 × R-wave amplitude in V4) + (1.062 × STE60 in V3; Driver et al., 2017). Published cut points, specifically 23.5 for three-variable formula and 18.2 for four variable formula, were used for assessment of diagnostic performance of the formulas (Driver et al., 2017; Smith et al., 2012).

All measurements were presented as mean and standard deviation. These measurements were compared with independent samples *t* test and 95% confidence intervals for difference were calculated. Baseline characteristics were summarized using standard descriptive statistics. Multivariate logistic regression was used to check ECG measurements relevant to formulas which were anticipated to be independently predictive of STEMI versus BV-STE. All measurements given in Table 3 were evaluated in turn group by group to identify measurements independently differentiating STEMI from BV-STE. Next, independent variables from each group were assessed together. Goodness of fit was

assessed with the Hosmer–Lemeshow statistic. A receiver operating characteristics curve analysis was also performed to define best discriminative cut-points in our population. Statistical analyses were performed with SPSS (version 24.0; SPSS. Inc., Chicago, IL).

3 | RESULTS

A total of 379 anterior MI cases were enrolled during study period. Also, first 200 consecutive patients with a diagnosis of BV-STE were enrolled for control group. Of the 379 patients with documented occlusion of left anterior descending artery or its branches, 241 patients were excluded for one or more reasons (Table 1). Four patients in control group were also excluded because of prior coronary artery stenting history in left-anterior descending artery territory. Baseline characteristics for both groups were summarized in Table 2. ECG measurements were summarized in Table 3.

Both at the J point and at 60 ms after the J point, ST segment elevation in leads V1 ($p < 0.001$ for both) and V4 ($p < 0.001$ for both) was higher in STEMI cases compared with BV-STE cases. On the contrary, ST segment elevation in lead V2 was higher in BV-STE cases compared with STEMI cases for both time points (for the measurement at the J-point $p = 0.001$, and for the measurement at 60 ms $p = 0.005$). ST segment elevation in V3 was similar in both groups. R-wave amplitude in leads V2 to V4 was significantly lower ($p < 0.001$ for all), whereas only T-wave amplitude in leads V2 and V3 were significantly lower in patients with STEMI compared with BV-STE. The ratio of R-to-T-wave amplitudes was lower in leads V2 to V4 for STEMI versus BV-STE ($p < 0.001$ for all). Corrected-QT was also longer in STEMI ($p < 0.001$), but uncorrected QT was not different.

In the multiple regression analysis, of the eight variables in the ST-segment elevation measurements group, ST-segment elevation in V1 at J point was the best at differentiating STEMI versus BV-STE (odds ratio [OR] 8.05; 95% CI 2.21 to 29.29). Of the eleven variables in the R-wave amplitude, T-wave amplitude and R-to-T-wave amplitude ratio group, R-wave amplitude V4 was the best (OR 0.74; 95% CI 0.64 to 0.84). Corrected-QT was evaluated alone, but showed limited discriminative value (OR 1.02; 95% CI 1.01 to 1.03).

TABLE 1 Primary reasons for exclusion of STEMI ECGs

Exclusion criteria	Number
ST-segment elevation more than 5 mm	84
Convex ST-segment elevation	7
Any inferior ST-segment depression of ≥1 mm	134
Anterior ST-segment depression	34
Terminal QRS distortion	25
T-wave inversion in any of V2–V6 and/or Q wave in any of V2–V4	63
Left bundle branch block	9
Total	241[a]

Note. [a]Some had more than one reason for exclusion.

The three-variable formula had an area-under curve (AUC) of 0.875 (95% CI, 0.837 to 0.914, $p < 0.001$) in our cohort. Youden index suggested 23.6 as the highest sensitivity and specificity point (73.2% and 89.3%, respectively). The original cut-point of 23.5 had a sensitivity, specificity, and diagnostic accuracy of 73.9%, 86.7%, and 81.4%, respectively. The four-variable formula had an AUC of 0.934 (95% CI, 0.907 to 0.960, $p < 0.001$). Youden index suggested 17.9 as the highest sensitivity and specificity point (87.0% and 86.2%, respectively). The published cut-point of 18.2 had a sensitivity, specificity, and diagnostic accuracy of 83.3%, 87.7%, and 85.9%, respectively. Finally, we performed the same analyses after excluding patients aged <35. This resulted in a BV-STE group of 48 patients (mean age, 38 ± 3), but the patient number in STEMI group did not change. Despite exclusion of younger patients, both the three-variable formula (73.9%, 85.4%, and 76.8%, respectively) and the four-variable formula showed similar sensitivity, specificity, and diagnostic accuracy (81.8%, 85.4%, and 82.7%, respectively).

4 | DISCUSSION

Since some ST-segment elevation is present in anterior chest leads in most individuals, third universal definition of MI included age and sex specific cut-offs for amount of ST-segment elevation required for STEMI diagnosis (Thygesen et al., 2012). However, these arbitrary cut-offs are far from being firmly supported with evidence (Macfarlane et al., 2004; Martin et al., 2007; Schmitt et al., 2001). Many patients with STEMI fall short of these criteria (including the majority of the patients in this study), whereas BV-STE can still exceed these "pathologic" ST-segment elevation thresholds. The patients in the former group suffer from inappropriate delays in treatment, sometimes even deprived of timely

TABLE 2 Baseline characteristics

	STEMI ($n = 138$)	BV-STE ($n = 196$)	p
Age, years	58 (14)	31 (5)	<0.001
Male, *n* (%)	101 (73)	191 (97)	<0.001
White, *n* (%)	138 (100)	196 (100)	1.0
Hypertension, *n* (%)	67 (48)	14 (7)	<0.001
Diabetes, *n* (%)	50 (36)	5 (3)	<0.001
Tobacco use, *n* (%)	65 (47)	32 (16)	<0.001
Prior MI, *n* (%)	20 (14)	1 (1)	<0.001
Prior PCI, *n* (%)	20 (14)	0 (0)	<0.001
Prior CABG, *n* (%)	3 (2)	0 (0)	0.038
Heart rate, bpm	82 (16)	76 (13)	<0.001
SBP, mmHg	145 (26)	129 (15)	<0.001

Note. BV-STE: benign variant ST-segment elevation; CABG: coronary artery by-pass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; STEMI: ST-segment elevation myocardial infarction.

TABLE 3 Electrocardiographic measurements[a]

	STEMI (*n* = 138)	BV-STE (*n* = 196)	Difference (95% CI)
STEJ and STE60, mm			
STEJ V1	0.63 (0.5)	0.17 (0.3)	0.45 (0.34 to 0.56)
STEJ V2	1.35 (0.9)	1.68 (0.7)	−0.32 (−0.52 to −0.13)
STEJ V3	1.29 (1.0)	1.27 (0.6)	0.01 (−0.18 to 0.22)
STEJ V4	1.16 (1.0)	0.63 (0.5)	0.52 (0.32 to 0.73)
STE60 V1	0.72 (0.6)	0.20 (0.4)	0.52 (0.39 to 0.64)
STE60 V2	1.71 (1.0)	2.00 (0.7)	−0.29 (−0.50 to −0.08)
STE60 V3	1.70 (1.1)	1.72 (0.7)	−0.01 (−0.24 to 0.20)
STE60 V4	1.56 (1.1)	1.03 (0.7)	0.52 (0.30 to 0.73)
T-wave and R-wave amplitude, mm			
TA V2	5.2 (3.0)	6.6 (2.4)	−1.4 (−2.0 to −0.8)
TA V3	5.0 (3.0)	6.4 (2.3)	−1.3 (−1.9 to −0.7)
TA V4	5.3 (3.2)	5.6 (2.0)	−0.3 (−0.9 to 0.2)
QRSA V2	9.5 (5.4)	21.2 (7.6)	−11.7 (−13.1 to −10.3)
RA V2	2.4 (2.5)	6.2 (3.0)	−3.8 (−4.4 to −3.1)
RA V3	2.2 (2.3)	8.1 (4.4)	−5.8 (−6.6 to 5.1)
RA V4	4.8 (4.3)	15.2 (6.0)	−10.4 (−11.5 to −9.3)
R-to-T-wave amplitude ratio			
V2	0.5 (0.6)	1.0 (0.5)	0.4 (0.3 to 0.5)
V3	0.5 (0.5)	1.3 (0.9)	0.8 (0.7 to 1.0)
V4	1.0 (1.2)	3.0 (2.2)	2.0 (1.6 to 2.3)
Average V2-V4	0.7 (0.5)	1.8 (0.9)	1.1 (0.9 to 1.2)
QT measurements, ms			
QT	358 (34)	355 (25)	3 (−3 to 10)
QTc	421 (34)	400 (25)	21 (14 to 28)
Formulas			
3-variable	25.3 (3.1)	20.5 (3.1)	4.7 (4.0 to 5.4)
4-variable	21.0 (2.8)	15.2 (2.9)	5.7 (5.1 to 6.4)

Notes. The three-variable formula: (1.196 × STE60 in V3) + (0.059 × Bazett-corrected QT) − (0.326 × R-wave amplitude in V4). The four-variable formula: (0.052 × Bazett-corrected QT) − (0.151 × QRS amplitude in V2) − (0.268 × R-wave amplitude in V4) + (1.062 × STE60 in V3).

BV-STE: Benign variant ST-segment elevation; QRSA: QRS-complex amplitude; RA: R-wave amplitude; STE60: ST-segment elevation 60 ms after the J point; STEJ: ST-segment elevation at the J point; STEMI: ST-segment elevation myocardial infarction; TA, T-wave amplitude.

[a]Values shown are means (SD) unless otherwise indicated.

reperfusion therapy (Khan et al., 2017; Marti et al., 2014; Pride et al., 2010; Rokos et al., 2012). On the other hand, the patients in the latter group face with risk of unnecessary procedures and their complications. Also, inappropriate catheterization laboratory activations put a significant strain on on-call teams and other healthcare resources.

Disappointingly, it is repeatedly shown that physicians dealing with acute chest pain, including experienced cardiologists, have difficulty in discriminating acute coronary occlusion on the ECG, with an accuracy no better than 75% (Barge-Caballero et al., 2010; Brady, 1998a; Brady et al., 2000, 2002; Jayroe et al., 2009; Kontos et al., 2010; Larson et al., 2007; Prasad et al., 2008; Turnipseed et al., 2006). Nevertheless, the issue of systematic differentiation of BV-STE from anterior STEMI on the ECG is understudied despite this obvious clinical need. To the best of our knowledge, there have been only two attempts on this topic (Driver et al., 2017; Smith et al., 2012). In the first study, Smith et al. (2012) initially derived and then validated a three-variable formula, using ST segment elevation in V3, corrected QT interval and R-wave amplitude in V4, for distinguishing subtle STEMI from BV-STE. The same group recently modified their formula with a fourth variable, QRS amplitude in lead V2, and showed an increased diagnostic accuracy (Driver et al., 2017). However, these formulas have not been externally tested. Our primary aim was to test these formulas in an independent population. Although lower values were attained in our cohort, this study confirms that three- and four-variable formulas with recommended cutoffs have a reasonable sensitivity, specificity, and diagnostic accuracy in differentiating subtle STEMI from BV-STE. Four-variable formula showed a higher sensitivity, specificity, and diagnostic accuracy.

Our additional findings have some similarities and dissimilarities with previous literature. Frequently reported corresponding findings in patients with BV-STE include a high R-wave amplitude, an early R-wave transition, higher R-to-T-wave amplitude ratio, a distinctive J wave, asymmetric T waves, upwardly concave ST-segments, and shorter corrected-QT interval (Brady, 1998b; Kambara & Phillips, 1976; Mehta & Jain, 1995; Zhou et al., 2000). Although it is not clearly diagnostic, the usefulness of tall R waves in differentiating BV-STE from subtle STEMI was also evident in our results. A low R-to-T-wave amplitude ratio in patients with STEMI was also present in our study, but it was predominantly due to high R-wave amplitude, as reported previously (Smith et al., 2012). We also found that T-wave amplitude in leads V2 and V3 significantly higher in patients with BV-STE compared with STEMI.

Our data confirm previous studies (Driver et al., 2017; Schmitt et al., 2001; Smith, 2006; Smith et al., 2012) and reemphasize that commonly used voltage criteria are not accurate for diagnosing anterior STEMI, whether measured at the J point or 60 ms after the J point. Even though guidelines still promote the use of millimeter criteria to diagnose STEMI and ECG algorithms focus on ST-segment elevation amplitude, our data show that the amount of ST-segment elevation cannot be used as a sole criterion for differentiating anterior STEMI from BV-STE. In our cohort, the amount of STE was higher in leads V1 and V4, lower in lead V2 and indifferent in V3. Our data also showed that the amount of STE in lead V1 had a stronger discriminative value than the amount of STE in lead V4. Interestingly, neither of the published studies measured STE in lead V1.

Lastly, although Bazett-corrected QT interval is a key variable in both formulas, it is reported that QT interval may be prolonged (Cinca et al., 1981; Doroghazi & Childers, 1978; Kenigsberg, Khanal, Kowalski, & Krishnan, 2007) or shortened (Maeda et al., 1992) during ischemia. In our population, Bazett-corrected QT was longer in STEMI compared with BV-STE, but the observed difference was lower than the previous studies.

In summary, we think that it is now feasible to recommend utilization of three- and especially four-variable formula both to recognize subtle left anterior descending artery occlusion and to avoid unnecessary emergency catheterization. Physicians may also prefer to choose a more sensitive or more specific cut-off according to circumstances and availability of their institutional resources.

4.1 | Limitations

Our study is a single-center, retrospective chart review study, which may cause some bias. The differences between STEMI and BV-STE cohorts in baseline characteristics, predominantly age, might also have resulted in a diagnosis bias. Although exclusion of patients aged <35 gave similar results; younger age in BV-STE group, which is known to be associated with higher R-wave and T-wave amplitudes, and shorter corrected-QT interval, may still have accounted for some of the difference (Lepeschkin, 1971; Surawich & Parikh, 2003). Because of retrospective nature of the study, standard lead placement could not be confirmed.

As our study was designed to externally validate the previously published formulas, it is a limitation to our study that we could not comment on the diagnostic performance of the variables used in these studies. However, our results hint that further refinement of the formulas could be possible. For example, the amount of ST-segment elevation at 60 ms after the J point was used in the formulas, but this can be viewed as a limitation as the recommended point for measurement in STEMI diagnosis is at the J point in current guidelines. However, our data show that the amount of ST-segment elevation at 60 ms after the J point and the amount of ST-segment elevation at J point is highly correlated. Replacing the latter with the former may not influence diagnostic accuracy of the formulas but may need new constants and new cut-off values. This should be investigated in further studies. Our data also showed that the amount of STE in lead V1 had a stronger discriminative value than the amount of STE in lead V4. Whether a new formula including ST-segment elevation in lead V1 would have a better performance requires further research.

5 | CONCLUSION

The differentiation of BV-STE from anterior STEMI on the ECG is an important clinical problem. Two decision formulas developed by recent systematic studies established the first attempt to solve this diagnostic dilemma (Driver et al., 2017; Smith et al., 2012), and our study now confirms that three- and four-variable formulas with recommended cutoffs have a reasonable sensitivity, specificity and diagnostic accuracy in differentiating subtle STEMI with BV-STE. Collectively, these studies constitute the largest database using angiographic outcomes to evaluate ST-segment elevation measurements in acute MI (Driver et al., 2017; Schmitt et al., 2001; Smith, 2006; Smith et al., 2012) and create a firm background which helps clinicians in making the critical decision of whether to proceed to acute reperfusion therapy. Although both perform well, the four-variable formula has a higher sensitivity, specificity, and diagnostic accuracy and should be preferred.

CONFLICT OF INTEREST

No authors have any conflicts of interest to report.

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