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Ischemic-appearing electrocardiographic changes predict myocardial injury in patients with intracerebral hemorrhage^{☆,☆☆,★}

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Abstract

Objectives—Myocardial injury is common among patients with intracerebral hemorrhage (ICH). However, it is challenging for emergency physicians to recognize acute myocardial injury in this population, as electrocardiographic (ECG) abnormalities are common in this setting. Our objective is to examine whether ischemic-appearing ECG changes predict subsequent myocardial injury in the context of ICH.

Methods—Consecutive patients with primary ICH presenting to a single academic center were prospectively enrolled. Electrocardiograms were retrospectively reviewed by 3 independent readers. *Anatomical areas of ischemia* were defined as I and aVL; II, III, and aVF; V₁ to V₄; and V₅ and V₆. Medical record review identified myocardial injury, defined as troponin I or T elevation (cutoff 1.5 and 0.1 ng/mL, respectively), within 30 days.

Results—Between 1998 and 2004, 218 patients presented directly to our emergency department and did not have a do-not-resuscitate/do-not-intubate order; arrival ECGs and troponin levels were available for 206 patients. Ischemic-appearing changes were noted in 41% of patients, and myocardial injury was noted in 12% of patients. Ischemic-appearing changes were more common in patients with subsequent injury (64% vs 37%; $P = .02$). After multivariable analysis controlling for age and cardiac risk factors, ischemic-appearing ECG changes independently predicted myocardial injury (odds ratio, 3.2; 95% confidence interval, 1.3–8.2). In an exploratory analysis, ischemic-appearing ECG changes in leads I and aVL as well as V₅ and V₆ were more specific for myocardial injury ($P = .002$ and $P = .03$, respectively).

Conclusion—In conclusion, although a range of ECG abnormalities can occur after ICH, the finding of ischemic-appearing changes in an anatomical distribution can help predict which patients are having true myocardial injury.

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1. Introduction

1.1. Background

Intracerebral hemorrhage (ICH) accounts for 4% to 15% of cases of acute stroke and is the most fatal form of this disease [1-3]. Although no specific therapy has been demonstrated to improve outcome, clinical practice commonly includes treatments aimed at minimizing damage from the hematoma, minimizing the risk of ongoing bleeding, and preventing complications of the disease [4]. That admission to a stroke unit provides benefit [5] and that less aggressive care leads to worse outcome [6] suggest that, at least, some treatments in current use improve outcome.

Many clinical trials, both past and ongoing, exclude patients with concomitant myocardial ischemia [7-11]. Hemostatic therapy in particular is associated with an increased risk of cardiac events, although it is notable that many ICH patients suffer such events anyway [8]. It can be challenging to recognize acute myocardial “injury” in patients with ICH as electrocardiographic (ECG) abnormalities are common in this setting, possibly reflecting neurocardiogenic influences [12-19]. Indeed, the incidence of ischemic-appearing ECG changes in patients with ICH has been reported to be 14% to 35% [12,13,19,20]. For an example see Fig. 1.

1.2. Importance

The question, then, is whether an abnormal ECG finding on presentation in a patient with ICH should be considered as representing true myocardial injury. The answer has implications for blood pressure management, use of hemostatic therapy, medications used for anticoagulation reversal, and extent of a cardiac workup performed during hospitalization. The current literature that pertains to ischemic-appearing ECG changes in patients with ICH is limited, mostly describing the prevalence of ECG abnormalities without addressing their value in diagnosing acute cardiac events [12,13,19,20]. It has been suggested that neurocardiogenic influences characterized by increased sympathetic nervous system activity on the heart are responsible for the observed ECG changes after acute intracranial events including ICH [21,22]. Alternatively, ICH and coronary artery disease have common risk factors, and myocardial injury could occur in patients with ICH because of progression of concomitant coexisting coronary artery disease.

1.3. Goals of this investigation

We hypothesized that ECG abnormalities on presentation that meet criteria for myocardial ischemia and present in a coronary anatomical distribution predict myocardial injury in patients with ICH.

2. Methods

2.1. Study design

This was a retrospective review of data collected as part of a prospective cohort study of primary ICH outcome. Since 1994, consecutive patients with ICH presenting to Massachusetts General Hospital have been registered into a database and followed up prospectively [23-25]. Patients were identified by systematic review of emergency department (ED) logs; hospital discharge diagnoses; and lists of all admissions to the neurology, neurosurgery, and internal medicine services. Demographic data including age, medical history, and medications used were captured prospectively. Chart review (performed by physicians, M.F. and K.H.) was performed to capture ECGs, cardiac enzyme levels, echocardiogram findings, and stress test results. All aspects of the study were approved by the Institutional Review Board at Massachusetts General Hospital.

2.2. Study setting and selection of participants

All patients with ICH presenting from January 1998 to June 2004 were reviewed. Patients were excluded for age younger than 18 years or if ICH was secondary to head trauma, ischemic stroke with hemorrhagic transformation, brain tumor, vascular malformation, or vasculitis. Patients with do-not-resuscitate orders in the ED and those transferred from outside hospitals were also excluded. Renal failure or renal insufficiency was not an exclusion criterion, as cardiac enzyme elevations are equally valuable in predicting cardiac events and outcomes in this population [26].

2.3. Methods of measurement

The primary outcome of this study was myocardial injury within 30 days in patients with ICH. We operationally defined myocardial injury as any elevation of cardiac troponin level, as we found that we could not define “myocardial infarction” according to the 2007 European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation definition for 2 reasons: (1) this definition requires knowledge of patient symptoms and many patients with ICH are unable to report whether they are having chest pain and (2) ECG findings are part of this definition and as our study was explicitly designed to ask whether such changes are relevant in ICH, we needed an outcome that would be independent of ECG changes [27].

Our hospital ICH protocol recommends cardiac enzyme and ECG testing on all patients with ICH. *Myocardial injury* was defined as troponin I or T elevation. Troponin I levels were determined with first-generation assays (Siemens, Munich, Germany, and Biosite Diagnostics, San Diego, CA) before 2002 and between 2002 and 2004, respectively. Troponin T levels were determined with a third-generation enzyme-linked immunosorbent assay (Roche, Basel, Switzerland) between 2002 and 2004. The European Society of Cardiology and American College of Cardiology guidelines have suggested that levels above the 99th percentile be considered abnormal if they can be measured with 10% coefficient of variation [28]. When these criteria are not met, it is suggested that the lowest value with a 10% coefficient of variation be used. These values are 1.5 and 0.1 ng/mL for troponin I and T, respectively. The troponin data were censored at the time of hospital discharge, death, or 30 days after arrival, whichever occurred first.

The secondary outcome was mortality at 90 days, identified through review of medical records; follow-up telephone calls to family members; and a search of the Social Security Death Index, a database updated weekly containing vital information for individuals whose deaths were reported to the US Social Security Administration [24,29]. We used the Social Security Death Index to confirm vital status of all patients at 90 days.

2.4. Electrocardiographic readings

Electrocardiograms were analyzed retrospectively by 3 observers, K.H., M.F., and D.F.M.B., and categorized into 2 groups: ischemic-appearing ECGs and non-ischemic-appearing ECGs using the 2007 European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation definition [27]. The κ statistic was 0.85, which indicates high interobserver agreement. Differences were resolved by consensus. *The ischemic-appearing ECGs* were defined as any of the following: new or not known to be old ST-segment elevations (at the J point in 2 contiguous leads with 0.2 mV in men or 0.15-mV elevation in women in leads V_2 and V_3 and/or 0.1 mV in other leads), new or not known to be old ST-segment depressions (horizontal or downsloping ST depression 0.05-mV depression in 2 contiguous leads), new or not known to be old T wave inversions (at least 0.1 mV including inverted T waves in 2 contiguous leads), new or not known to be old Q waves in an anatomical distribution (0.02 seconds or QS complex in

leads V₂ and V₃, 0.03 seconds in width, and 0.1 mV in depth or QS complex in leads I, II, aVL, aVF, or V₄ to V₆ in any 2 leads of a contiguous lead grouping), and new bundle-branch blocks. *Anatomical distributions* were defined as inferior (II, III, and aVF), high lateral (I and aVL), anterior (V₁ to V₄), and lateral (V₅ to V₆).

2.5. Primary data analysis

As most variables were not normally distributed, continuous variables were analyzed with the Kruskal-Wallis test, and dichotomous variables, with Fisher exact test. For the multivariable analysis, variables initially included were those that previous studies have suggested to be risk factors for myocardial ischemia or that were significantly associated in univariate analysis: age, sex, history of diabetes, coronary artery disease, hypertension, serum glucose level on arrival, time to arrival, and initial hematoma volume. Variables were removed in a backward stepwise selection process for $P > .2$. The final model included only history of diabetes and ischemic-appearing ECG changes. All of the analyses were performed with Stata software (Stata Corp, College Station, TX).

3. Results

There were 218 patients with primary ICH who presented initially to our ED and did not have a do-not-resuscitate order during the study period. Twelve patients were excluded for unavailable initial ECGs or unavailable troponin I or T, leaving a study population of 206 patients (94%). Troponin I or T levels were determined in 177 patients (86%) on ED arrival, 181 patients (88%) by day 1, and 191 patients (93%) by day 2. One hundred fifty patients (73%) received serial troponin I or T testing. The median of frequency of testing was 2 (interquartile range, 1-4).

Patients ranged in age from 43 to 102 years (median age, 75 years), and 56% were male. Table 1 shows the demographics of this cohort. Overall, ECGs with new changes meeting the definition of ischemia were seen in 83 patients (41%).

Troponin elevations were noted in 24 patients (12%). Table 2 shows the demographics for this population. Predictors of elevated troponin included history of diabetes and ischemic-appearing ECG changes on presentation.

To determine whether any ECG findings were more specific for myocardial injury, we performed a stratified analysis by anatomical location. Table 3 shows an exploratory analysis of specific ECG findings and risk of myocardial injury. The anatomical distributions determined as described are not exclusive. Thus, patients can have ischemic-appearing ECG changes in multiple distributions. Overall, the risk of myocardial injury was 18% in those with T wave inversions, 19% in those with ST depressions, 23% in those with ST elevations, and 24% in those with Q waves.

It has been suggested that diffusely distributed ECG changes are more specific for neurogenic causes. We, therefore, examined whether ECG changes in more than 1 coronary anatomical distribution decrease the likelihood of myocardial injury. We found that myocardial injury was present in 17% (7/42) of those with changes in 1 distribution, 17% (5/30) of those with changes in 2 distributions, 44% (4/9) of those with changes in 3 distributions, and 0% (0/2) of those with changes in all 4 distributions. There was no significant association between ischemic-appearing ECG changes across multiple distributions and myocardial injury ($P = .58$).

Finally, multivariate logistic regression analysis was performed to determine independent predictors of myocardial injury. The only independent predictors were ischemic-appearing

ECG changes (odds ratio, 3.2; 95% confidence interval [CI], 1.3-8.2; $P = .01$) and history of diabetes (odds ratio, 3.4; 95% CI, 1.3-8.7; $P = .01$). Of note, after controlling for known predictors of poor outcome including age, initial GCS score, and hematoma volume, ischemic-appearing ECG changes did not independently predict 90-day mortality (not shown).

4. Discussion

Overall, we found that ischemic-appearing ECG changes on arrival were observed in 41% of patients with ICH and that such changes independently predict myocardial injury. Therefore, clinicians faced with such changes should not disregard these findings as nonspecific in the setting of ICH but, rather, consider such patients as having true myocardial injury.

The first account in the Western literature of an association between acute stroke and ECG changes appeared in 1947 [30]. Since then, many authors have observed ECG changes in patients with acute central nervous system events [12-20,30-47]. Abnormalities noted include prolonged QT interval, ischemic-appearing changes, U waves, tachycardia, and arrhythmias. Some of these studies have evaluated these measures in ICH specifically [14,20]. However, not all abnormalities are likely to be clinically relevant in the acute setting, and the emergency physician is faced with the question of which findings to take seriously.

Another question that arises is how to diagnose myocardial injury in the setting of ICH. Troponin elevations have been found to occur relatively commonly in this disease and are associated with poor outcome [48]. However, this association may well reflect that there has been true myocardial injury. Both troponins I and T are highly specific for myocardial necrosis and currently considered the criterion standard for detection of myocardial injury [49]. In addition, coronary angiography and cardiac stress testing may not be feasible in the acute setting for many patients with ICH.

Recent studies in patients with subarachnoid hemorrhage have shown cardiac troponin elevations in 17% to 28% of patients [50-52]. In patients with stroke of varied origin, troponin elevations occurred in roughly 17% and were associated with an adverse prognosis over time [53]. Overall, then, myocardial injury appears to be relatively common after cerebrovascular emergencies in general.

The source of myocardial injury in patients with central nervous system emergencies is not fully understood. Although one possibility is coronary artery occlusion, many have suggested that myocardial injury after stroke can be attributed to abnormally high levels of plasma catecholamines [54,55]. The assertion that cardiac alterations are mediated by catecholamines is supported by the fact that disrupting the sympathetic chain at the cervical level prevents arrhythmias, whereas a vagotomy does not [56,57]. These changes can be inhibited by catecholamine blocking agents [58,59]. Furthermore, myocardial catecholamine concentrations rise and fall rapidly after an intracranial catastrophe [60].

Catecholamine-mediated myocardial injury is believed to be multifactorial: tachycardia, coronary spasm and vasoconstriction, toxic effects on cardiac myocytes, and an increased intracellular concentration of calcium [61]. The histologically confirmed lesions in the myocardium are small foci of subendocardial hemorrhage and myocytolysis surrounding epicardial nerves. Myocytolysis represents acute cardiac muscle fiber stress, a phenomenon different from the coagulation necrosis seen in coronary ischemia [62]. These observations provide evidence that pathologic changes in the myocardium as well as ECG changes may result from cerebral injury and may be mediated by the autonomic nervous system.

In an exploratory, hypothesis-generating analysis stratifying ECG findings by anatomical distribution, it appeared that changes in I and aVL as well as V₅ and V₆ were more specific for myocardial injury. However, it is possible that this finding was an artifact of multiple hypothesis testing; future studies are necessary to confirm whether specific anatomical ECG changes can be used to predict troponin elevations in this population.

It has traditionally been thought that diffuse ECG changes are more consistent with cerebrovascular changes [63]. However, our study suggested no association between ischemic-appearing ECG changes among multiple anatomical distributions and myocardial injury. Thus, from an operational standpoint, we were unable to demonstrate that the clinician in the emergency setting can safely ascribe ischemic-appearing changes in multiple distributions to nonspecific neurocardiogenic influences.

5. Limitations

Our study has several limitations. The most important limitation to this study is its retrospective design. Care was not standardized across the cohort, and not all initial ECGs were available. In addition, serial cardiac enzymes were sent at the discretion of the clinical care team rather than in a controlled fashion. It is possible that some patients would have developed troponin elevations later in their course but that these went unmeasured, leading us to underestimate the frequency of myocardial injury as happened in the FAST clinical trial [8]. We attempted to minimize this by excluding patients with any order for limitations in care, such as do-not-resuscitate orders.

Second, as echocardiograms, stress testing, and cardiac catheterizations were performed infrequently in this cohort (12 patients), the type and degree of myocardial injury could not be elucidated. Therefore, it remains possible that secondary events such as pulmonary embolism, renal failure, and relatively benign cardiomyopathy secondary to ICH such as Tako-Tsubo cardiomyopathy rather than coronary thromboembolic events may play a role in an elevation of troponin [64–68]. Likewise, the limited data on cardiac evaluations in this cohort make it difficult to definitively assign an underlying etiology to each instance of ECG abnormality. In fact, 81% of patients with ischemic-appearing ECG changes showed no evidence of myocardial injury. It remains possible that the etiologies of these changes are heterogeneous including ventricular hypertrophy, cardiomyopathy, preexisting coronary artery flow-limiting disease, and unstable angina. Future prospective trials with standardized protocols will be necessary to control for such potential confounders.

In conclusion, although a range of ECG abnormalities can occur after ICH, the finding of ischemic-appearing changes in an anatomical distribution can help predict which patients are having true myocardial injury.

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Fig. 1.

A, Head computed tomographic scan of patient OF on admission. An illustrative patient, OF is a 70-year-old woman with no history of coronary artery disease who presented with confusion. Her head computed tomographic scan showed right temporoparietal ICH. Her ECG showed T wave inversions in leads I, aVL, and V₁ to V₆. Her peak troponin was 1.8 ng/mL. The patient subsequently underwent a stress test performed with technetium Tc 99m sestamibi that disclosed a modest degree of reversible inferoapical defect. B, Electrocardiogram of patient OF on admission.

Table 1

Demographics of study population, by ischemic-appearing vs non-ischemic-appearing initial ECG

Variable	Nonischemic, n = 123	Ischemic, n = 83
Age (y)	75 (64-82)	73 (66-82)
Male sex	56%	55%
Hypertension	81%	90%
Diabetes	20%	23%
CAD	21%	30%
Atrial fibrillation	22%	15%
Warfarin	21%	20%
Glucose	133 (114-179)	136 (113-180)
Initial SBP	190 (170-208)	184 (156-204)
GCS score	14 (9-15)	14 (9-15)
ICH volume (mL)	19 (6-46)	13 (3-49)
IVH	47%	43%
Lobar location	33%	34%
Time to arrival (h)	3 (2-24)	5 (1-24)
Myocardial injury	7%	19%
90-day mortality	28%	31%

Continuous variables are presented as median (interquartile range). CAD indicates coronary artery disease; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage.

Table 2

Predictors of myocardial injury

Variable	Troponin negative n = 181	Troponin positive n = 25	P
Age (y)	75 (66-82)	73 (63-82)	.9
Male sex	57%	44%	.3
Hypertension	83%	92%	.4
Diabetes	18%	43%	.01
CAD	23%	34%	.3
Atrial fibrillation	21%	8%	.4
Warfarin	20%	24%	.8
Glucose	133 (113-176)	161 (134-192)	.05
Initial SBP	188 (160-208)	184 (160-188)	.3
GCS score	14 (9-15)	14 (8-15)	.6
ICH volume (mL)	19 (5-48)	12 (2-46)	.2
Lobar location	35%	24%	.4
IVH	45%	48%	.8
Time to arrival (h)	3 (1-24)	12 (3-24)	.1
Ischemic-appearing ECG	37%	64%	.02
90-day mortality	28%	44%	.1

Continuous variables are presented as median (interquartile range).

Table 3

Specific ECG changes and risk of ischemia

Distribution	Frequency	Myocardial injury (95% CI)
All patients	206 patients	12% (8%-17%)
I, aVL	18 patients	39% (16%-62%)
TWI	14	43% (16%-70%)
STD	3	33% (-32%-99%)
STE	0	–
QW	1	0% (NA)
II, III, aVF	38 patients	13% (2%-24%)
TWI	15	0% (NA)
STD	11	18% (-6%-42%)
STE	1	100% (NA)
QW	14	14% (-5%-33%)
V ₁ -V ₄	37 patients	19% (6%-32%)
TWI	9	11% (-11%-33%)
STD	5	20% (-19%-59%)
STE	24	21% (4%-38%)
QW	4	25% (-24%-74%)
V ₅ -V ₆	44 patients	23% (10%-35%)
TWI	23	13% (-1%-27%)
STD	24	21% (4%-38%)
STE	1	0% (NA)
QW	5	60% (12%-100%)
New BBB	5	20% (-20%-60%)
Early repolarization	15	13% (-5%-31%)

TWI indicates T wave inversions; STD, ST-segment depressions; STE, ST-segment elevations; QW, Q waves present; NA, not applicable; BBB, bundle-branch block.