CARDIOLOGY Rounds®

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The Role of Continuous ECG Monitoring in the Management of Acute Coronary Syndromes

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Accurate diagnosis and risk stratification are critical in the management of acute coronary syndromes (ACS) by enabling clinicians to appropriately triage patients and target pharmacological and interventional therapies. The standard 12-lead electrocardiogram (ECG) is a well-established tool in both the diagnosis and prognostication of ACS.[1,2] For example, the presence of persistent ST elevation is an indication for prompt reperfusion therapy, while in non-ST elevation ACS, ST depression on the admission ECG is a powerful independent predictor of adverse outcome[3,4] and identifies high-risk patients who may benefit from potent antithrombotic therapies and early invasive risk stratification.[5]

Although the admission ECG is crucial, it provides only a "snapshot" of valuable information. In addition to facilitating early detection of potentially fatal arrhythmias, continuous ECG (Holter) monitoring can identify dynamic ST segment shifts that are indicative of ongoing or recurrent ischemia (Figure 1), thereby improving the early diagnosis and prognostication of ACS. This issue of *Cardiology Rounds* provides an overview of the utility of continuous ECG monitoring in the management of ACS, cardiac pain mechanisms, the concepts of silent myocardial ischemia, and ischemic cascade. Since a discussion of the role of detecting silent ischemia in the management of asymptomatic and stable angina patients is beyond the scope of this article, the interested reader is referred to several excellent recent reviews.[6,7]

Silent myocardial ischemia and cardiac pain mechanisms

The term "angina pectoris" was first used by William Heberden in the 1770s, but the pathophysiology remained unclear for many decades.[8] In the early 20th century, a case series of patients with painless myocardial infarction (MI) was published; yet, this syndrome did not receive much attention until the 1970s.[8]

Silent myocardial ischemia is defined as objective evidence of transient ischemia (on ECG or other tests eg, perfusion imaging) in the absence of angina or its equivalents.[7] While the mechanism of cardiac pain remains incompletely understood, its anatomic pathway has now been better delineated. The atria and ventricles are innervated by numerous sympathetic sensory fibers that are connected to the upper 5 thoracic (T1-T5) dorsal roots of the spinal cord. The "convergence-projection theory," which states that sympathetic sensory input converges with the somatic sensory afferent pathway onto the same ascending spinal neurons, provides an explanation for cardiac pain that is often referred to the chest wall and arm.[7] In addition, vagal afferent innervation likely accounts for the referred pain in the jaw and neck, and the prominent vagal symptoms that sometimes accompany inferior myocardial ischemia. However, in general, due to the variable convergence of somatic and autonomic pathways, localization of pain does not reliably

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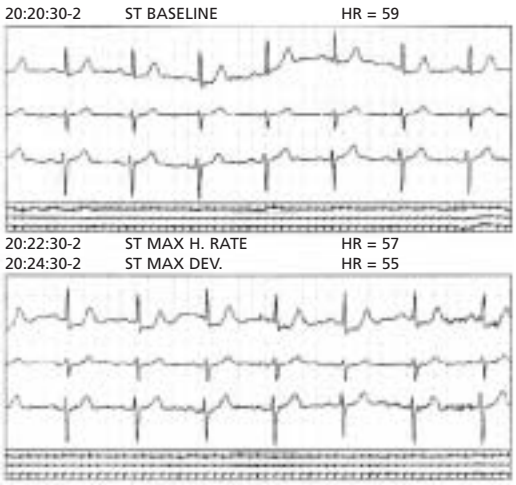
Figure 1: Holter monitor recording of a patient admitted with an acute coronary syndrome. The top panel depicts the baseline ECG tracing. A few minutes later (bottom panel), the patient developed 3 mm horizontal ST depression that was not associated with any symptoms. Note there was no significant change in the patient's heart rate.

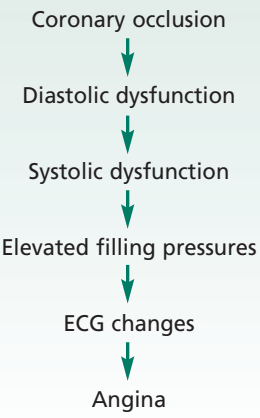


predict the site of myocardial ischemia. Consistent with this theory is the observation that patients who have undergone cardiac transplantation or plexectomy do not experience angina.

Early work suggests that adenosine may be the actual chemical trigger of cardiac sensory fibers. Crea et al performed a series of experiments on patients with chronic stable angina who had positive exercise stress tests and documented coronary artery disease. An intracoronary infusion of adenosine provoked chest pain that was very similar to exertional angina, but without ECG evidence of ischemia.[9] The severity of chest pain was significantly reduced after administration of aminophylline, an adenosine P1-receptor antagonist. In a single-blind, placebo-controlled, randomized study, aminophylline also decreased the intensity of exercise-induced angina, despite similar peak exercise levels and degrees of ST depression. Finally, another single-blind randomized study compared patients with predominantly painful ischemia to patients with silent ischemia who tolerated a longer duration of adenosine infusion and developed less severe chest pain. Together, these findings suggest that adenosine plays an important causative role in angina.

Anecdotal observations indicate that stretching the coronary artery wall can produce angina. Tomai and colleagues randomly assigned 48 consecutive patients undergoing coronary angioplasty to 2 balloon inflations of either

Figure 2: The ischemic cascade



equal atmospheric pressures, or a higher pressure during the second inflation.[10] In keeping with the phenomenon of ischemic preconditioning, the mean ST-segment shift during the second balloon inflation was significantly less than during the first inflation in both groups. However, the latter group experienced more intense cardiac pain during the second inflation that produced greater angiographic coronary stretching. Therefore, mechanical factors such as physical stretch may also mediate cardiac pain.

Several theories have been proposed to explain the lack of pain during myocardial ischemia. Patients with silent myocardial ischemia appear to have a higher somatic pain threshold.[11] Using positron emission tomography to measure cerebral blood flow, Rosen et al postulated that abnormal central processing of afferent pain signals was an important factor.[12] Other mechanisms include a hyposensibility to pain due to the destruction of nociceptive pathways by infarction or neuropathy and may account for the higher prevalence of silent myocardial ischemia among diabetic patients.[13,14] Studies implicating endorphins (endogenous opioid-like substances) as negative modulators of sensitivity to cardiac pain have been inconclusive.[7]

Ischemic cascade

The sequence of events that occur during myocardial ischemia is sometimes referred to as the "ischemic cascade." During transient balloon occlusion of coronary arteries in humans, relaxation parameters are the earliest changes reflecting myocardial ischemia (Figure 2).[7] A similar sequence of events is also observed when ischemia is induced by increased demand such as during exercise. Pain is the final event in the ischemic cascade and follows

ECG changes; therefore, pain is not a sensitive and reliable indicator of myocardial ischemia.

Because hemodynamic and electrical abnormalities are present despite the absence of angina, the term "total ischemic burden" has been introduced to encompass both symptomatic and painless episodes of ischemia. Although not universally adopted, treatment strategies to improve clinical outcomes by reducing the total ischemic burden rather than alleviating symptoms alone have gained increasing support.[15,16]

Non-ST elevation acute coronary syndromes

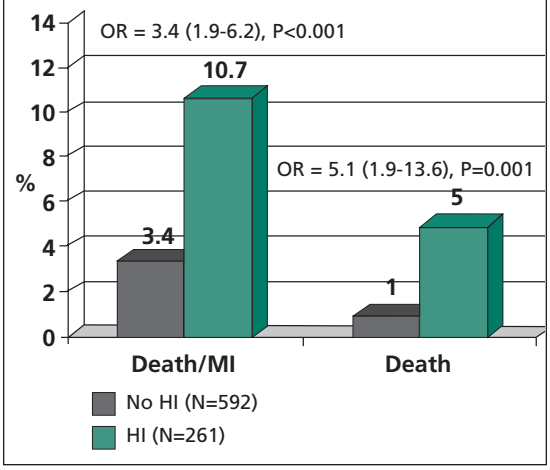
Continuous ECG monitoring has been used to detect silent myocardial ischemia in ACS for almost 2 decades and numerous studies have examined its prognostic value. Most investigators define Holter-detected ischemia (HI) as an episode of transient ST elevation or depression (≥0.1 mV at 0.08 seconds after the J point that lasts for at least 1 minute). To qualify as discrete episodes, they have to be separated by the return of the ST segment to baseline for at least 1 to 10 minutes.

- In an early study, Gottlieb and co-workers reported a high prevalence of silent ischemia (52.9%) on blinded continuous ECG monitoring in 70 patients with unstable angina.[17] Importantly, over 90% of the ischemic episodes were silent and patients with HI were more likely to suffer an MI and require revascularization for refractory angina over the following month.
- Langer et al evaluated the prognostic significance of HI in 135 unstable angina patients.[18] Like Gottlieb's study, 89 patients (66%) had HI and the majority (68%) of episodes were silent. Left main or multivessel coronary artery disease and the composite endpoint of death and non-fatal MI were more common in the group with HI. Importantly, Holter ECG monitoring was a more sensitive marker of unfavourable outcomes than the admission ECG. While these and other early studies reported a high prevalence of HI, it should be noted that most patients did not receive the standard antiplatelet and antithrombotic therapies (eg, aspirin, heparin) that are currently routinely administered. It remains unclear whether such treatment would reduce the prevalence of HI or even negate its prognostic value.
- More recently, Patel and colleagues enrolled 285 patients with unstable angina to undergo 48 hours of continuous ECG monitoring.[19] All patients were treated with aspirin and half were randomized to receive unfractionated heparin. HI occurred in 32 patients (15.1%), of which 80% was silent. Over a median follow-up of 2.6 years, the presence of HI was the second strongest predictor (after hypertension) of death or MI (hazard ratio= 2.81; 95% CI, 1.23-6.39; P=0.01). Furthermore, more prolonged HI correlated with worse outcomes. The authors concluded that continuous ECG monitoring should be considered in the routine assessment of patients with unstable angina.
- Jernberg et al examined the utility of continuous ECG monitoring (≥9 hours) among 630 consecutive patients admitted to a coronary care unit with chest pain and non-diagnostic ECG.[20] In multivariable analysis, only elevated troponin (P<0.001) and the presence of HI (P=0.004) were independent predictors of cardiac death or MI after a median follow-up of 6 months. Moreover, HI was a better predictor than ST depression on the admission ECG. This study was the first to show that HI alone was a significant predictor of cardiac death.
- In the largest study to date, Akkerhuis pooled data from 995 patients enrolled in 3 clinical trials (CAPTURE, PURSUIT, and FROST).[21] HI was detected in 27% of these patients. At 30 days, the risk of death/MI and death alone increased by 25% and 40%, respectively, for each additional episode of HI (normalized to 24 hours). This relationship persisted after controlling for other clinical characteristics, but because cardiac biomarkers were not included in the multivariable model, the incremental prognostic value of HI could not be determined. However, in another smaller study, troponin and HI were found to carry independent prognostic information.[22] A protocol that incorporated continuous ECG monitoring for the triage of patients with suspected ACS was also proposed.

Insights from the ESSENCE Holter substudy and the INTERACT study

The ESSENCE Holter substudy and the INTERACT trial provide a valuable opportunity to evaluate the role of continuous ECG monitoring in the contemporary era of antiplatelet and antithrombotic therapies. Details of these trials have been published.[23,24] Briefly, ESSENCE enrolled ACS patients who had rest angina lasting ≥10 minutes with either ECG changes or documented coronary artery disease. INTERACT included patients with rest angina ≥10 minutes with either ST deviation or positive cardiac biomarkers. All patients received aspirin and heparin (unfractionated or enoxaparin); INTERACT patients were also given the glycoprotein IIb/IIIa inhibitor, eptifibatide. As part of the original study protocol, patients underwent 96-hour Holter monitoring. These two study populations were pooled (N=853) after excluding patients with incomplete data, left bundle branch block, or repolarization

Figure 3: Presence of Holter-detected ischemia and 30-day outcome



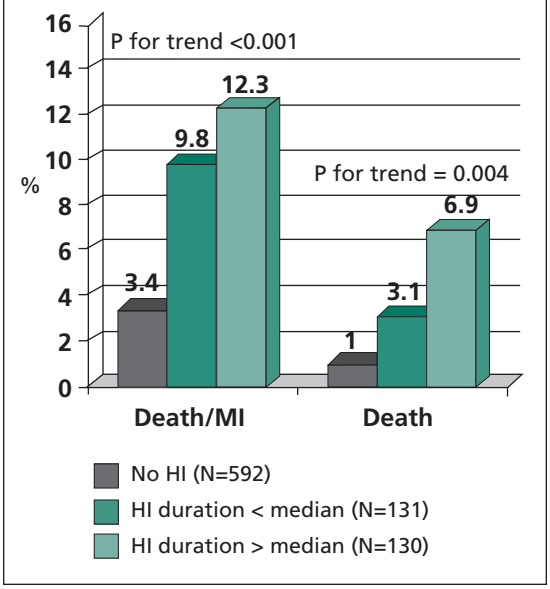
HI = Holter-detected ischemia; MI = myocardial infarction; OR = odds ratio (95% confidence interval)

changes secondary to left ventricular hypertrophy, or digoxin that precluded ST segment interpretation.[25] Holter analysis was initially performed by an automated algorithm, and subsequently reviewed by a cardiologist blinded to clinical data and outcome. The composite endpoint, death or MI at 30 days, was independently adjudicated. Overall, 261 patients (31.6%) experienced HI; these patients had a significantly higher risk of death/MI or death at 30 days (Figure 3). There was also a graded relationship of the duration and severity of HI with outcome (Figures 4 and 5). After adjusting for age, diabetes, and cardiac biomarker status, HI remained an independent predictor of death/MI (odds ratio = 3.43; 95% CI, 1.86-6.35; P<0.001). In contrast, ST depression on the admission ECG was not a significant predictor once HI was considered. Furthermore, HI was independently associated with higher all-cause mortality (odds ratio=4.30; 95% CI, 1.59-16.64; P=0.004) after controlling for advanced age. These results suggest that continuous ECG monitoring remains a useful prognostic tool in the current management of ACS.

ST-elevation myocardial infarction

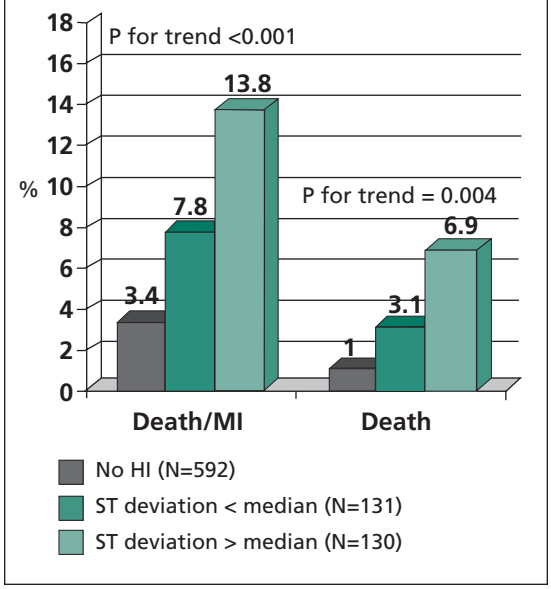
Several studies have demonstrated that early ST resolution after fibrinolytic therapy implies patency of the infarct-related artery and portends a favourable outcome.[26-28] However, dynamic ST-segment shifts may be present during the acute phase; ST elevation may reflect culprit artery re-occlusion, while ST depression may be related to culprit artery stenosis, thrombosis, or vasospasm. Theoretically, continuous ECG monitoring is a convenient and noninvasive surrogate marker of underlying pathophysiology and may identify high-risk patients who require interventional therapy more urgently. In the GUSTO-I ST-segment substudy, continuous ECG monitoring was performed in 734 patients with resolution of

Figure 4: Duration of Holter-detected ischemia and 30-day outcome



HI = Holter-detected ischemia; MI = myocardial infarction

Figure 5: Magnitude of ST deviation on Holter monitoring and 30-day outcome



HI = Holter-detected ischemia; MI = myocardial infarction

initial ST elevation.[29] Of these, 243 (32%) developed recurrent ST segment shifts 6- to 24-hours after fibrinolytic treatment that were independently associated with both higher 30-day and 1-year mortality rates. It is noteworthy that ST shifts provided additional prognostic information beyond that of the validated GUSTO-I mortality model. A direct relationship between the duration of ST shifts and 1-year mortality was observed. Interestingly, ST depression appears to be a stronger predictor of 1-year outcome than ST elevation, possibly because it is a better marker of the extent of underlying coronary artery disease. These results support the use of continuous ST monitoring in the early risk stratification of ST-elevation MI. Data from the ASSENT-2 substudy also suggest that online ST monitoring after ST-elevation MI is feasible and can be performed accurately in the clinical setting.[30]

Conclusions

Although the mechanism of cardiac ischemic pain remains to be fully elucidated, accumulating evidence suggests that adenosine is an important mediator, while mechanical factors may also play a causative role. Pain is not a sensitive indicator of cardiac ischemia; ischemia is often asymptomatic, but can be readily detected by continuous ECG monitoring in the setting of ACS. Despite treatment with potent antithrombotic and anti-ischemic regimens, HI remains relatively common among contemporary ACS patients and is a powerful independent predictor of adverse outcome. Continuous ECG monitoring is a simple, useful, and noninvasive tool that can be readily integrated into the current risk stratification for the broad spectrum of ACS. As such, it has the potential to further improve patient care.

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Abstract of Interest

Continuous ST-segment monitoring is useful for the selection of patients with non-ST-elevation acute coronary syndromes who most benefit from early myocardial revascularization

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BACKGROUND: In non-ST-elevation acute coronary syndromes (ACS), early risk stratification is essential for guiding cost-effective management. Continuous ST-segment monitoring adequately reflects the dynamic nature of myocardial ischemia and coronary thrombosis in these patients (pts). We investigated whether continuous ST-segment monitoring may be useful for early identification of those who most benefit from myocardial revascularization (MyoRev).

METHODS: We studied 304 pts admitted due to chest pain at rest (≥1 episode of chest pain at rest in the previous 24 hrs lasting ≥20 min) suggestive of an ACS without ST-elevation on the admission ECG. Pts whose ECG was not interpretable for ischemia were excluded. ST-segment monitoring was performed continuously for 24 hrs after admission. An ST episode was defined as a transient deviation of ≥0.1 mV lasting ≥1 min. In-hospital MyoRev was performed at the discretion of the attending physician. Endpoint was death or nonfatal (re) myocardial infarction, whichever occurred first by 30 days follow up.

RESULTS: 203 ST episodes (135 clinically silent) were detected in 76 pts (25.0%). MyoRev was performed in 200 pts (65.8%), through percutaneous intervention in 146. Median time from admission to MyoRev was 24 to 48 hrs. ST episodes were independently associated with worse 30-day outcome, even after adjustment for baseline clinical characteristics, ECG changes and cardiac troponin I levels (adjusted OR 4.9; 95% CI: 1.9 , 12.9; p=0.001). In pts with ST episodes, MyoRev had a benefitial prognostic impact (10.5% event rate vs 36.8% in pts not revascularized; OR 0.2; 95% CI: 0.1, 0.7; p=0.022). In pts without ST episodes, the effect of MyoRev was modest (2.8% event rate vs 5.9% in those not revascularized; OR 0.5; 95% CI: 0.1, 1.8; ns).

CONCLUSION: In non-ST-elevation ACS, continuous ST-segment monitoring provides early prognostic information, additional to that of clinical characteristics and biochemical markers of myocardial injury and is useful for selection of pts who most benefit from early MyoRev.

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