The importance of good analysis of the ECG to take decisions in the catheterization laboratory

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Electrocardiography (ECG) was introduced more than a century ago by Waller and Einthoven. During the first half of the 20´th century there were numerous reports relating ECG changes to specific cardiac disorders. In the 1960´s much data was available about the diagnostic significance of the ECG in congenital and valvular diseases, but data regarding the ECG manifestations of ischemic heart disease was scarce. In the 1970´s Maroko and Braunwald introduced the concept of limitation of infarct size (1). At the same time the field of ECG in ischemic heart disease began to flourish with the expanded availability of coronary angiography and, later on, echocardiography. Reperfusion therapy for acute ST-elevation myocardial infarction (STEMI) became the standard of care in the late 1980´s. Defining the culprit artery from the ECG had clinical impact in the short era of intracoronary thrombolysis. With the introduction of intravenous fibrinolytic therapy (FT), treatment decisions have been based simply on the presence of ST elevations in the ECG. Not much attention has been paid to the morphologic information in the ECG about coronary anatomy and physiology.

THE CHAGING ROLE OF THE INTERVENTIONIST

In STEMI, primary percutaneous coronary intervention (PCI) is generally recognized as superior to FT due to its higher TIMI 3 (Thrombolysis in Myocardial Infarction) flow rates and lower rates of reinfarction, intracerebral hemorrhage and mortality (2,3). This has led to a rapid expansion of primary PCI around the world. However, primary PCI requires a hospital with a catheterization laboratory, a skilled interventional team and well-planned transport logistics. Primary PCI should be performed in a timely fashion (balloon inflation within 60-90 minutes of presentation). Superiority of primary PCI over prehospital thrombolysis has not been shown. Also, in STEMI patients who present very early after symptom onset and face potentially long delays to primary PCI, FT may be preferred. Guideline-based implementation of primary PCI, necessitating availability of invasive teams 24/7, as the number one reperfusion strategy world-wide, poses great challenges to the health care systems. Also, doubts about cost effectiveness could be raised.
In STEMI, therapeutic decisions have to be made within minutes from ECG recording (4). Risk stratification has become increasingly important in selecting the optimal type of reperfusion therapy. The intent is to identify those patients who might benefit the most from primary PCI and, on the other hand, those who may be safely treated with FT.

CHALLENGES IN DIAGNOSIS OF ACUTE CORONARY SYNDROMES

Especially during off hours, inexperienced young physicians on duty have to be in the front line of decision making in acute coronary syndrome (ACS). One potential concern might be a wrong diagnosis of MI, for example in patients with benign early repolarization, pericarditis, “sport heart” or in those with persistent repolarization changes induced by ventricular hypertrophy. False positive diagnosis exposes the patient to the complications of reperfusion therapy, like intracerebral haemorrhage from FT. Utilization of modern telemedicine systems to get an expert opinion in minutes by transmitting ECGs directly to a consulting cardiologist's wireless hand-held device (mobile phone or pocket computer) with web browsing capabilities might save both time and money, and has the potential to improve patient care (5).

BENEFITS FROM GOOD ECG INTERPRETATION IN THE CATHETERIZATION LABORATORY

This presentation shows the rationale behind an alternative to the recently adopted "trauma centre" treatment algorithm for urgent transport of practically all patients with STEMI to tertiary centres. We present an ECG-based algorithm aiming at optimal choice of reperfusion strategy and timing of invasive evaluation, considering patient risk and available resources (6). On the one extreme would be a high-risk patient with an extensive ischemic area-at-risk and severe ischemia without signs of reperfusion in the ECG. Patients belonging to this category should be provided all available resources to open the artery as soon as possible. On the other extreme, a low-risk patient with ECG signs of a side-branch- or distal coronary artery occlusion with low-grade ischemia may benefit from alternative treatment options. A prerequisite for this algorithm is skilled ECG interpretation complemented by critical data from patient history and clinical data (7). It is crucially important to develop regional logistic treatment strategies for ACS patients. Although most patients with STEMI should have an invasive evaluation as part of their risk stratification during hospital stay, it does not necessarily need to be done immediately.

ECG BASED RISK STRATIFICATION IN ACUTE CORONARY SYNDROME

In everyday clinical practice, interventional cardiologists and experts in ECG interpretation do not usually collaborate to improve individual risk stratification and decision making in the catheterization laboratories; this is not the optimal scenario. The interventional cardiologist should work within the framework of telemedicine with immediate access to ECGs recorded on scene by paramedics or in emergency departments in the uptake area of the interventional centre. Also, access to previous ECG recordings is valuable. The interventionist should aim at improving personal skills in ECG interpretation, but also collaborate “online” with experts in the field. Studies have shown benefits from telemedicine in STEMI by increasing usage of reperfusion therapy and reducing time to reperfusion therapy (8).

Skills in ECG interpretation can be gained by learning from individual cases in the catheterization laboratory with ECG data from the acute and evolving phases, complemented by data from coronary angiography, echocardiography, scintigraphy or ventriculography (9). Follow-up ECGs give information about the dynamic ischemic process. In addition, cases should be shared with experts in ECG interpretation, "electrocardiologists". The different stages at which the ECG gives useful information to the interventional cardiologist are:

- The prehospital phase
- Immediately after the coronary angiography for planning of the PCI procedure
- Post-PCI in case of new signs of ischemia

It is important to appreciate that the ECG provides information about a totally different aspect of pathophysiology in acute MI than does the coronary angiogram. Coronary angiography identifies vessel *anatomy* whereas the ECG reflects the *physiology* of the myocardium during acute ischemia (10). For this reason, it is possible to observe severe coronary stenoses upon angiography without ECG evidence of acute ischemia. Moreover, it is possible to observe restored vessel patency upon angiography with ECG evidence of ongoing ischemia due to "no-reflow", reperfusion injury, or myocardial damage that has already developed before reperfusion occurs. Thus, while coronary angiography remains the "gold standard" for identifying the infarct related artery, the ECG remains the gold standard for identifying the presence and location of acute myocardial ischemia. Moreover, with current imaging techniques, including contrast ventriculography, echocardiography and radionuclide perfusion scanning, differentiation of ischemic but still viable from necrotic myocardium during the acute stage of MI is impossible.

Despite limitations, like baseline chronic ECG changes (ECG confounders) and individual variation in coronary anatomy, critically important anatomic and physiologic information is to be gained from the ECG in:

- Diagnosis of MI
- Estimation of the size of the ischemic myocardium at risk
- Identification of the site of the culprit lesion within the coronary tree
- Expected rate of progression of myocardial necrosis
- Stage of the infarction process
- Differentiation between necrotic and viable myocardium within the ischemic area

Principles for utilizing the ECG for decision making

DIAGNOSIS OF MI

In a patient with typical symptoms, presence of ST elevation measured at the J point, especially when accompanied with reciprocal changes, is highly predictive of acute MI. In everyday clinical cath lab practice it is unavoidable that some cases without acute STEMI will have an urgent coronary angiography. The angiogram may be normal in patients with Prinzmetal angina, pericarditis, left bundle branch block (LBBB) or normal ("early repolarization") variant J point elevation. Patients with aborted MI usually show some coronary pathology like atheroma or plaque rupture, although the vessel is open with normal flow. Features pointing to pericarditis are diffuseness of ST elevations in many leads, except in leads aVR and V1, without correlation to coronary artery related myocardial segments. In MI the ST elevations tend to be localized, often, but not always with reciprocal ST depressions. Also, the PR segment displacement, which has been attributed to subepicardial atrial injury, is often present, typically showing PR elevation in lead aVR and PR depression in the inferior extremity leads and lateral precordial leads (11). In borderline cases without severe symptoms or clinical findings, it may be advisable to start treatment with nitrates and aspirin, and wait for a control ECG within 20 – 30 minutes before deciding to perform an acute angiography. In the prehospital setting, patient transport to an emergency department in a centre with invasive facilities may be initiated, while final decision about need for urgent angiography may be deferred until hospital arrival. ECG changes induced by myocardial ischemia are more dynamic than those in pericarditis or early repolarization. The ECG from the acute phase should be compared with previous recordings, if available (12). Studies have shown that as many as one half of the missed acute MIs could have been diagnosed through improved ECG reading skills or by comparing the ECG to an old, baseline recording (13). Hence, the interventional centre should be part of regional logistic systems with immediate access to digitally stored ECGs, through internet based telemedicine (5).

ESTIMATION OF THE SIZE OF THE ISCHEMIC MYOCARDIUM AT RISK AND IDENTIFICATION OF THE CULPRIT LESION WITHIN THE CORONARY TREE

The immediate prognosis in patients with acute MI is inversely related to the amount of myocardial reserves, the latter being dependent on myocardial mass less the myocardium involved in the ongoing ischemic process and areas with non-functioning tissue due to previous MIs or fibrosis (10). Among patients without prior MI and without major pre-existing stenotic lesions in the coronary arteries, prognosis is related to the size of the ischemic myocardium supplied by the culprit coronary artery distal to the occlusion. Therefore, in addition to accurate diagnosis, there is a need for early estimation of the size of the ischemic myocardium at risk and myocardial reserves.

Several studies have tried to estimate the ischemic area at risk or final infarct size with the admission ECG. In these studies, either the number of leads with ST deviation (elevation and/or depression) or

the absolute amplitude of ST deviation was used. However, the results were conflicting (14-16). All of these studies were based on the hypothesis that each lead represents the same amount of myocardium and that a similar size of ischemic area in different locations of the left ventricle will result in similar magnitude of ST deviation in the same number of leads. However, the 12-lead ECG does not equally represent all myocardial regions and, moreover, ischemia in opposed regions may attenuate or augment ST deviation. For different scores to be clinically useful, their reproducibility should be verified in large cohorts of patients, and they should be an integral component of commercial automated ECG analysis programs. Also, factors like width of the chest wall, the distance of the electrode from the ischemic zone, the myocardial mass, and presence of "ischemic preconditioning" and collateral circulation have a major influence on the absolute magnitude of ST deviation (10). Alternatively, the size of the area at risk may be estimated by morphologic ECG analysis, aiming at determining the site of the culprit lesion within the coronary tree (Table 1).

Steps in the decision-making process, where there is a potential role for the ECG as a useful tool for the interventionist:

- When to transport a patient from a long distance acutely for primary PCI
- Need for a doctor in the ambulance
- When to collect an invasive team during night hours
- Case priority in catheterization laboratories with heavy workloads
- To define the culprit lesion with the angiography available in multi-vessel disease when the culprit artery is open
- Re-ischemia early post-PCI – re-occlusion or other etiology?

Anterior ST elevation

In patients with maximal ST elevation (the core of ischemia) in leads V2-V4 (*anterior STEMI*), the culprit artery is usually the left anterior descending coronary artery (LAD) (17). Studies indicate that acute anterior MI caused by proximal occlusion of the LAD, is associated with unfavourable outcome and should be recognized by simple non-invasive methods like the 12-lead ECG (18). It has been shown that the ECG is useful in defining the level of obstruction in the LAD (19-22). ST elevation in the extremity leads I and aVL, reciprocal ST depression in the inferior leads II, III and aVF and ST elevation in lead aVR have been associated with a culprit lesion in the proximal part of the artery. Surprisingly, in a recent study in patients randomized to either primary PCI or FT, ECG or angiographic signs of lesion proximality were not associated with worse outcome at 30 day or 2.7 year follow-up (Eskola M et al, in press). Hence, the prognostic significance of the level of occlusion in the LAD in the modern era of acute ST elevation MI treatment should be reassessed. Still, cases with ECG signs of proximal LAD occlusion should have high priority for immediate reperfusion therapy.

A minority of patients with LAD occlusion show simultaneous ST elevation in the precordial and the inferior leads II, III and aVF (23). Autopsy reports have shown that in the majority of patients the LAD wraps around the LV apex and extends up the posterior interventricular sulcus to a variable extent (24). Studies have shown that the proportion of patients with a large LAD wrapping around the apex is significantly higher in anterior MI patients with simultaneous inferior ST elevation, and conversely significantly lower in those with ST depression (25). Occlusion in a big wrap-around the apex artery may result in ischemia of two electrically opposite areas, the anterior and the inferior. This in turn may attenuate the ST elevations in the electrically opposite leads aVL and III resulting in an isoelectric or even depressed ST-segment in lead aVL despite a proximal LAD occlusion (7). Not only the culprit artery, but also the size of the artery should be appreciated as an important prognostic marker.

Inferior ST elevation

In *inferior STEMI*, the core of ischemia is in leads II, III and aVF. The vast majority of patients with ST elevation in these leads have an occlusion of the right coronary artery. However, an occlusion of the left circumflex artery can produce a similar ECG pattern. In addition to ST elevation in the inferior leads, reciprocal ST depression in lead aVL is seen in almost all patients with acute inferior MI (26).

ECG confirmation of the infarct related artery during acute inferior MI may be particularly valuable when coronary angiography indicates lesions in both the right and left circumflex coronary arteries. Algorithms for differentiation of right coronary artery- from left circumflex artery related occlusion have been published (27-33). For the interventionist, the most important ECG signs are those of a dominant artery, of right coronary artery occlusion associated to 2- or 3-vessel disease and of lesion proximality.

For the interventionist, it is important to realize that in some patients, ST elevation in leads V1–V4 signifies proximal right coronary artery occlusion with concomitant right ventricular infarction. Right ventricular infarction that produces ST elevation in leads V1–V4 can be distinguished from anterior MI by observing ST elevation in lead V1 greater than in lead V2, ST elevation in the right precordial leads V3R and V4R, ST depression in lead V6, and often, concomitant ST elevation in the inferior leads II, III, and aVF (34-37). In inferior MI, lead V1 ST elevation is a sign of an occlusion proximal to a right ventricular branch. The area at risk is usually not extensive in these cases, as there are no ECG signs of inferolateral extension (no ST elevation in lateral precordial leads or reciprocal ST depression in right precordial leads V1-V3). FT may be considered as an alternative to primary PCI in these cases.

Lateral ST elevation

ST elevation in V4–V6 without ST elevation in V1–V3 is usually due to left circumflex artery or left obtuse marginal occlusion (*lateral STEMI)*. If not accompanied by ST elevation in the inferior extremity leads, the area at risk is usually rather small. Patients with the core of ischemia in leads I and aVL, usually have side branch occlusion in coronary angiography. Concomitant ST elevation in lead V2 has been described as mid-anterior MI caused by occlusion of the first diagonal branch (38). ST depression in lead V2, on the other hand has been associated to obtuse marginal branch occlusion. Variation in coronary anatomy will affect the patterns, and hence the message for the interventionist is high probability of side-branch occlusion representing low short-term risk.

ESTIMATION OF SEVERITY OF ISCHEMIA

A qualitative approach for predicting final infarct size by the admission ECG based on the grades of ischemia has been reported by Sclarovsky and Birnbaum *et al* (39,40). In patients without ECG signs of myocardial necrosis (Q waves) or reperfusion (inverted T waves), the following definition has been proposed:

- Grade I ischemia : Tall, symmetrical, and peaked T waves
- Grade II ischemia: ST elevation without distortion of the terminal portion of the QRS
- Grade III ischemia: Changes in the terminal portion of the QRS complex:
    - Emergence of the J point ≥50% of the R wave in leads with qR configuration, or disappearance of the S wave in leads with an Rs configuration

The grades of ischemia predict final infarct size, but not the size of the ischemic area at risk. Impact on choice of reperfusion therapy has to be studied in prospective, randomized studies. Studies have shown that patients with grade III ischemia compared to the less severe grades I and II have:

- More severe ischemia and worse short-and long-term prognosis
- Less myocardial protection and faster progression of necrosis
- Less benefit from fibrinolytic therapy or primary angioplasty

THE PREINFARCTION ISCHEMIC SYNDROME VERSUS EVOLVING MI

Sudden occlusion of a coronary artery or a major side-branch, results within seconds in positive and tall T waves followed by elevation of the ST segment (“injury vector”) in the ECG. In patients with acute chest pain this “pre-infarction syndrome” (PIS) represents the window of opportunity to treat before irreversible myocardial damage develops (7). Successful reperfusion results in normalization of the ST-segment usually accompanied by T-wave inversion, a marker of an open infarct related artery with restored myocardial blood flow (41,42). The preinfarction stage may evolve towards MI with or

without Q-waves (evolving MI; EMI). A recent study showed a higher overall event rate in the EMI group compared to the PIS group (43). The EMI pattern was independently predictive of adverse outcome in multivariable analysis. The PIS pattern was associated with lower event rate in patients treated with primary PCI compared with FT. No significant difference in outcome between treatment strategies was observed in the EMI group as a whole. However, in patients with anterior EMI without ECG signs of reperfusion (=Q waves and ST elevation with a positive T wave present), superiority of primary PCI was shown. It is evident that more detailed ECG analysis, involving also Q and T wave morphology, should be introduced into everyday clinical practice. This will enable rapid identification of high risk patients in whom every effort should be made to transfer for primary PCI, or vice versa, for identifying low risk patients in whom FT might be an alternative option.

NON-ST-ELEVATION ACUTE CORONARY SYNDROME

Patients presenting with NSTE-ACS - non-ST elevation MI and unstable angina - represent a wide spectrum of severity of coronary artery disease and, therefore, have major differences in outcome. Urgent reperfusion therapy with FT has been shown to be beneficial only in patients presenting with ST elevation, whereas in those without ST elevation (including those with ST depression) it may be harmful. Moreover, recent studies have shown a superiority of an invasive strategy over a conservative one in high-risk patients with NSTE-ACS (44,45). The increasing number of patients with NSTE-ACS is placing an enormous economic burden on health care systems. Guidelines have clarified the recommendations for how these patients should be treated (46). Compared to STEMI, the ability of the ECG to predict coronary anatomy in cases with ACS without ST elevation is more limited. However, sub-groups with varying risk profile can be identified by the presenting ECG pattern, especially when recorded during ischemic symptoms. Urgent cases with ECG signs of left main or severe three-vessel disease should have coronary angiography on an emergency basis. In those with signs of less severe ischemia, there is time for more effective pre-treatment with antithrombotic and anti-ischemic therapy before invasive evaluation.

Table 2 describes five different ECG patterns of non-ST elevation ACS representing different pathophysiology and clinical significance (47). Patients with the ECG pattern of circumferential subendocardial ischemia, represent a very high-risk subgroup with a high probability of left main or severe three-vessel disease and high in-hospital event rate (48,49). These patients should have coronary angiography on an emergency basis. There is a high probability for urgent bypass surgery. The ECG pattern of regional subendocardial ischemia is caused by a subtotal obstruction of the LAD or a total obstruction of a diagonal or intermediate side branch (48). These patients do not represent emergency cases for invasive evaluation. However, coronary angiography within 24-48 hours, after pre-treatment with anti-thrombotic and anti-ischemic medication is preferable. There is high likelihood of one-vessel disease treatable with PCI. Deep inverted T waves maximally in leads V2-4 in ACS represent a post-ischemic reperfusion pattern with high probability of LAD disease (50,51). The ECG pattern indicates good myocardial perfusion and an open infarct-related artery. In case of spontaneous or FT-induced reperfusion, there is risk for reocclusion of the artery. Coronary angiography within 48-72 h is preferable. "Pseudo-normalization" of the T waves with or without ST elevation is a sign of reocclusion. Finally, patients with ST-segment depression maximally in leads V1-V3 (irrespective of the direction of the T wave) typically have a distal occlusion of a small circumflex artery (52). Reperfusion therapy should be considered, especially if ST elevation is present in leads recorded from the posterior thorax (V7-V9).

Still, in the modern era of high technology, the ECG has a very central role in clinical decision-making in ACS. Unfortunately, anatomic and physiologic information from then ECG recorded during ischemic symptoms is under-utilized. Collaboration between experts in ECG and interventionists should be improved. The modern catheterization laboratory should be integrated into telecardiology networks with "online" access to the actual ECG from a patient outside hospital or in the emergency

department. Also, modern technology makes it possible to get an expert opinion even from long distances within minutes.

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