Background

Coronary artery disease (CAD) is a pathological condition of the coronary arteries caused by arteriosclerosis, where deposits or plaques build-up on vessel walls. These cause the lumens of the vessels to narrow and the vessels to become stiff. As a consequence, the blood circulation is impaired and the supply of oxygen to the myocardium restricted – a state termed myocardial ischemia (MI).

Arteriosclerotic processes take place insidiously and may progressively lead to a worsening of CAD – a chronic clinical picture that usually takes decades to manifest. In its progressive stage, the disease detracts from patients' quality of life and increases their probability of concomitant of illnesses like cardiac arrhythmias, heart failure and life-threatening complications such as heart attack or sudden heart death.

MI-related fatalities, especially in their acute manifestation as heart attack or myocardial infarction, rank among the most frequent causes of death in industrialized nations. In Germany, chronic ischemic heart disease was the most common (9.5%) and acute myocardial infarction the second most common natural cause of death (7.3%) in 2006.

CAD is defined according to angiographic criteria as an at least 50% obstruction of a coronary vessel lumen, regardless of the clinical symptoms. The course reflects a multifactorial clinical entity with asymptomatic forms ranging from silent myocardial ischemia and symptomatic (but stable) CAD across the entire spectrum of acute coronary syndromes through to sudden heart death.

The diagnostic problem associated with coronary artery diseases is that they can run an asymptomatic course, i.e. typical symptoms like angina pectoris (chest pain) may be absent, even during an acute myocardial infarction.

Basic diagnostics of CAD and MI primarily focus on medical history taking, analysis of symptoms, physical examination, laboratory tests, blood pressure measurements along with a 12-channel resting ECG (and a chest x-ray as appropriate). Resting ECG can reveal signs of previous infarctions as well as be of diagnostic relevance in acute coronary syndromes (ACS). However, in the non-acute (chronic) stage, diagnosis of CAD by ECG is thus inadequate or not even possible. Laboratory work-ups and blood chemistry also make just a minor contribution to the diagnosis of chronic CAD, while lipid and glucose levels only serve in establishing a patient's risk status.

The accuracy of exercise ECG, primarily used for diagnosing non-acute CAD, can be described as moderate at best, given that it only has a sensitivity of 67% and a specificity of 72% in patients without previous MI. Because the examination requires exercise on the part of the patient and takes around 20 minutes to perform, it is ordinarily only indicated as a secondary diagnostic procedure when there are reasonable grounds to suspect CAD, and is mostly limited to specialist settings. One major disadvantage of exercise ECG is that many patients have contraindications or physical limitations prohibiting the use of ECG or are unable to reach their target heart rate, thus rendering ECG diagnostically or technically unfeasible in a broad number of patients.
Imaging methods for visualizing the morphology of the coronary vessels (coronary angiography) or perfusion of the myocardium, such as myocardial scintigraphy or its special form, SPECT, magnet resonance imaging (MRI), positron-emission tomography (PET), are only performed as secondary or tertiary diagnostic procedures and also limited to specialist settings. Consequently, these examinations are only indicated when there is a concrete suspicion of CAD, i.e. hardly ever in asymptomatic patients.

Until now, no screening test had been established for broad clinical application that could identify patients with CAD, especially those without symptoms, by non-invasive, exercise-free means and was easy to apply and featured automated interpretation – and moreover constituted a screening method that was feasible for implementation in primary care settings.

The most serious clinical picture associated with MI or CAD is the acute coronary syndrome (ACS), characterized by angina pectoris lasting longer than 20 minutes. Hallmarks of this syndrome include both unstable angina pectoris (UAP, high-grade coronary stenosis with alternating occlusion, but without myocardial destruction) as well as acute myocardial infarction (complete occlusion of a coronary artery with infarction and/or myocardial destruction). Myocardial infarctions are differentiated into those with ST-segment elevations on the ECG (STEMIs) and those without (non-STEMIs). The infarction is unequivocally confirmed when the ST-segment elevation on the resting ECG is ≥0.1 mV in at least two consecutive extremity leads or ≥ 0.2 mV in at least two consecutive chest leads (STEMI). Unstable angina pectoris and non-STEMIs are subsumed under the acute coronary syndrome without ST-segment elevation (NSTE-ACS).

That said, the accuracy of resting ECG for diagnosing unstable angina pectoris or non-ST-segment elevations infarctions is extremely low. One study on this subject reported a sensitivity for detection of NSTE-ACS of a mere 20%. In such cases, the troponin test can bring ultimate certainty; yet, the enzymes relevant to this test are not excreted until 4-6h after the infarction and are thus not detectable by the troponin test until after this delay. Therefore, in patients presumed to have ACS without ST-segment elevation, there is a 4-6-hour window of uncertainty as to whether they are actually suffering from acute ischemic coronary syndrome, just UAP or whether a non-STEMI has already taken place. Particularly in the case of incipient infarction, the earliest possible detection and therapy of acute ischemic states is of paramount prognostic importance.

Cardiogoniometry (CGM) – an extended vectorcardiographic screening method utilizing only 5 electrodes that takes only 12 seconds to obtain a stress-free recording and fully automated analysis – has the potential to close the diagnostic gap in both stable CAD and acute-ischemic events associated with NSTE-ACS.
STUDY DATA (from 2007, major studies outlined bold)

The initial, more recent retrospective studies on CGM conducted between 2007-2008 variously employed statistical methods to separate patients with CAD from controls. To test logistic regression analysis, CGM data from 345 patients (236 males, 109 females) were analyzed; 212 (165 males, 47 females) of whom were suffering from CAD (stenoses ≥50% by coronary angiography). By extracting parameters from the vector loop and subsequently applying regression analysis, optimal parameter sets were established for the male (sensitivity 66.7%, specificity 83.1%) and female (sensitivity 63.8%, specificity 71.0%) patient groups, respectively. (1) Another publication investigated the suitability of methods using linear discriminant analysis and support vector machines on a cohort of females; since the diagnostic accuracy in females had previously proved to be lower than in men, a need for improvement was seen. The study cohort comprised 109 women (48 of whom had CAD). Linear discriminant analysis correctly classified CAD patients with a rate of 83.5% (sensitivity 78.7%, specificity 87.1%), while the support vector machine method had a 86% rate of correct classifications (sensitivity 80.5%, specificity 89.8%) (2).

In 2008, Schüpbach et al. published the results of a larger CGM study (subdivided into retrospective and prospective sections) conducted on 793 patients undergoing a CGM examination immediate prior to elective coronary angiography (the cut-off was angiographically detected coronary stenoses ≥ 50%). The authors proposed a scoring algorithm that achieved a sensitivity of 73% and a specificity of 87% in the retrospective cohort (461 subjects; 154 females/264 CAD; 69 females). In the prospective cohort (332 subjects; 116 females/207 with CAD; 49 females), the diagnostic accuracy of CGM was 71% and thereby highly significantly better than that of ECG (p <0.003) (3).

In 2009, Schüpbach and Sanz published the diagnostic results of scoring algorithms applied to their study database comprising 1,027 patients (CGM vs. coronary angiography). The authors used 5 different parameter sets to assess the patients (subdivided into men and women) according to T-wave rhythm and amplitude. In 696 patients (459 males), CGM proved to have a sensitivity of 84% and a specificity of 90% when assessed using a standardized score. Separate diagnostic scores for detecting CAD in the presence of a low-voltage (LowT), left bundle branch block (LBBB), right bundle branch block (RBBB) or atrial fibrillation (AFIB) were determined retrospectively and presented (4).

In 2010, the prospective multicenter CGM@ACS study investigated the effectiveness of CGM in discriminating patients with acute coronary syndromes without ST-segment elevation (NSTE-ACS) (Toelg et al.) (5, 6). Inclusion criteria included chest pain >20 minutes and coronary angiography within 72 h. A total of 210 patients were analyzed (157 with NSTE-ACS plus 53 controls). The diagnosis of NSTE-ACS was confirmed or ruled out by coronary angiography. Compared to ECG or the troponin test, CGM achieved a highly significantly better diagnostic accuracy. For example, the first CGM examination was two and a half times more sensitive than the first ECG examination and twice as sensitive as the first troponin test. When the decision-making rule that a patient is presumed to be ischemic when either troponin or CGM produces pathological results was applied, this study found that 85% of all NSTE-ACS patients were detected as such and that an aggregate of 3 of 4 patients were interpreted correctly (as being ischemic or non ischemic). Even in NSTE-ACS-patients, in whom both ECG and troponin testing ultimately remained negative, CGM still achieved a two-thirds detection rate. The study had its limitations, however. CGM was recorded after the patients had been exhaustively treated with drugs and their acute-ischemic state was potentially no longer present (likely making the sensitivity lower than if CGM had been performed in patients without pretreatment). The control group was small (approx. 25%) and showed a high proportion of patients with previous cardiac diseases (e.g. 19% in the control group had CAD, 19% a previous PCI and 11% an earlier infarction). It is likely that the specificity of CGM was slightly limited in this setting. The diagnostic results are summarized in the chart below. (6) These results are currently in publication.
Birkemeyer et al. prospectively evaluated the accuracy of CGM versus Cardio-MRI (to be considered as the non-invasive gold standard of ischemia diagnosis) in 2010. They included 40 patients unselectively and performed CGM before Cardio-MRI within routine diagnostic pathway. CGM findings were compared against pathological perfusion and/or presence of late enhancement (20 patients in total) during Cardio-MRI. CGM reached a sensitivity of 70% and a specificity of 95%, the positive predictive value was 93%. Especially the high specificity and the high PPV confirm CGM’s suitability for screening. These findings also corroborate the thesis, that a moderate specificity within the CGM@ACS trial was mainly caused by the high prevalence of cardiac history in the reference cohort. This pivotal study was the basis for the larger CGM@MRI trial (ongoing).

In 2010, Huebner et al. applied a methodological approach to 658 patients (405 with coronary stenosis ≥50%) to demonstrate that there is at least one CGM parameter that is (highly) significant and suitable for detection of each individual CAD category. The study used angiographically defined CAD categories: 3 categories with single-vessel stenoses (RCA, LAD, LCX), 3 categories with two-vessel stenoses (RCA+LAD, RCA+LCX, LAD+LCX – including main stem stenosis), one category with three-vessel disease and one global CAD category. One significant parameter found to be electrophysiologically plausible was allocated to one CAD category. The parameter set was used to derive the overall ROC curve; the area under the curve was 0.8 (8).

The same patient cohort described above (8) was subjected to a smaller approach using a methodology published by Huebner et al. in 2010 (9): This time, the investigation focused on how a single CGM parameter – the spatial position of the T-loop – was able to distinguish healthy patients
from those with CAD. The authors showed that this singular CGM parameter was able to retrospectively achieve the same accuracy (sensitivity 67%, specificity 72%) as that prospectively reported by meta-analyses for exercise ECG.

In a review published in 2010, Huebner et al. described the state of the art and perspectives for electrocardiologic and related methods in the non-invasive detection and risk stratification of myocardial ischemia (10). Based on the meta-analyses reviewed, CGM was accurate in detecting ≥50% stenoses at rest (sensitivity 73%, specificity 84%).
References


