CARDIOGONIOMETRY

New opportunities in the diagnosis of acute and stable coronary artery diseases

Symposium held at the occasion of the 77th Annual Meeting of the German Cardiac Society on Saturday, April 30, 2011 (Hall 5) from 11:30-12:30 CET. Organized by enverdis GmbH.

Chairpersons: H. Mudra (Munich), U. Zeymer (Ludwigshafen)

SYNOPSIS

T. Hübner | May 9, 2011

The dilemma of preclinical ischemia diagnostics: Optimization potentials with cardiogoniometry (CGM)

R. Wessely (Duisburg, Germany)

In introduction, Prof. Wessely presented data showing how mortality rates in North America have changed over the past 30 years as a function of the various underlying diseases. As ever, heart disease continues to be the most common cause of death; presently, however, this is being overtaken by cancer. By the year 2025, the number of patients with ischemic heart disease in Germany will rise by approx. 35%, the incidence of cardiomyopathy and heart failure will grow at a similar rate of progression (each expected to increase by approx. 20%). By contrast, the number of congenital heart defects will drop by approx. 10% (Bruckenberger Heart Report 2009). On a global scale, Germany ranks in the middle range of cardiac mortality, while at the same time, exhibiting considerable regional differences with regard to cardiac morbidity (which is markedly better in the federal state of Schleswig-Holstein than Mecklenburg-Vorpommern, for example). On two of his slides, Prof. Wessely illustrated the cost explosion in the cardiovascular sector; while the direct costs in North America will rise only moderately by approx. 50% over the next 20 years, the indirect costs will explode by around 200%.

When left undetected, coronary artery disease can have multifactorial sequelae; this fact is supported by the following evidence:

- 62-85% of patients with sudden cardiac death (SCD) have CAD (Zheng ZJ et al., Circulation 2001)
- In 15% of the cases, SCD is the initial manifestation of CAD (Kannel WB et al., Circulation 1975)
- Mortality in AMI in outpatient settings is approx. 20-25%
- Ischemic cardiomyopathy is the most common cause of heart failure (approx. 60%) (He J et al., Arch Int Med 2001)
- CAD plays a major role in the development of cardiac arrhythmias

It was concluded that effective early cardiac diagnostics might be suitable to prevent MACCE (major adverse cardiac and cerebrovascular events) in a timely manner. This stands in contrast with the large number of complicated coronary angiographies performed which do not verify CAD. As an example, one study investigated the coronary angiographies of nearly 400,000 patients (Patel MR et al., N Engl J Med 2010), reporting that CAD (stenosis >50%) was ruled out in 62.4% of all cases.

The following complex of topics focused on primary CAD diagnostics: In this context, symptomatology, medical history, scores and non-invasive methods all come into play. The central question is: how and when should the various tests be employed, giving consideration to the following:

- Pretest risk for CAD?
- How accurate are the other tests?
- Test costs and effects associated with health-related sequelae?
- Test selection for a specific patient?
Notwithstanding the above, the established non-invasive methods used for non-invasive early cardiac diagnostics must also be questioned with regard to their availability, cost efficiency, simplicity and suitability for all patients and how often and/or under which circumstances they are actually employed. In particular, questions should be asked as to whether and to what degree these methods contribute to cost efficiencies within the healthcare system and which prognostic relevance they have. In the general practitioner sector, EKG and/or ergometry predominate, whereas (stress) echocardiography and duplex IMT measurements are the prevailing methods in specialized settings.

Prof. Wessely introduced the topical complex of ergometry, describing it with the words: "a complex, harmless time-consuming and not very conclusive method of examination". The factors influencing this examination were cited:

- Patient characteristics (previous infarctions, abnormalities in the resting EKG, extent and grade of stenoses, age, sex and drugs)
- Intraobserver variability (EKG interpretation)
- Exercise protocol (definition of exertion limit, stop criteria, patient positioning, electrode system) as well as
- EKG criteria of positivity, e.g. interplay sensitivity/specificity in different ST-segment depressions: 0.5mm (80%/60%), 1.0mm (60%/90%), 2.0 mm (20%/98%)

*Author's note: Exercise EKG, primarily intended to diagnose not-acute CAD, has an accuracy that can be termed moderate at best, with a sensitivity of 67% as well as a specificity of 72% (meta-analysis of approx. 11,000 patients without prior myocardial infarction, source: Gibbon RJ et al., Circulation 2002)*

Ergometry cannot be performed or not be adequately evaluated in patients with contraindications, classified as:

- absolute (e.g. acute infarction, IAP, uncontrolled arrhythmia, symptomatic aortic stenoses or heart defects, pulmonary emboli, myocarditis, pericarditis, active endocarditis, acute aortic dissection, acute non-cardiac diseases that limit exercise capability, lack of patient consent) as well
- relative (stenoses of the left main branch or equivalent, moderate stenosing atrial septal defect, abnormal electrolytes, severe hypertension > 200 mmHg systolic and/or 110 mmHg diastolic, tachyarrhythmia or bradycardia including atrial fibrillation with uncontrolled ventricular arrhythmia, hypertrophic cardiomyopathy and/or other obstructions of the outflow tract, limitations of mental or physical cooperation, high-grade AV blocks) (source: Gibbon RJ et al., Circulation 2002)

The probabilities for the presence of CAD is in many factors higher than with a positive exercise test (e.g. male sex 2.7, IDMM 2.14, dyslipidemia 1.62 and old age 1.29 compared to the positive exercise test 1.28) (source: Patel MR et al., N Engl J Med 2010). Other data presented in this connection included false EKG readings in the emergency room in patients with chest pain (T inversion: 50% false positive, 70% false negative as well as ST-segment depression: 20% false positive, 50% false negative).

In summation, Prof. Wessely concluded that EKG/exercise EKG is not the ideal method for guaranteeing a sufficiently high sensitivity and specificity in early cardiac diagnostics. As a result, there is an unmet need for a simple method for early detection of cardiac causes of chest pain which is particularly suitable for both preclinical and CPU use. As an example of how cardiogoniometry may hold the potential to fill this diagnostic gap, two studies were presented:

- In 2008, Schupbach et al. published the results of a larger CGM study (subdivided into a retrospective and a prospective section) on 793 patients who were given a CGM immediately prior to elective coronary angiography (cut-off: angiographically verified coronary stenosis ≥ 50%). A scoring algorithm was presented which achieved a sensitivity of 73% and a specificity of 87% in the retrospective population. In the prospective population, the diagnostic accuracy of CGM was 71%; in order words, highly significantly better than that of EKG (p <0.003).
- In 2011, Tolg et al. demonstrated on 216 patients with acute chest pain without ST-segment elevation that, compared to EKG and troponin, cardiogoniometry was the most sensitive and accurate method for
detecting a subsequently invasively verified NSTE-ACS (NSTEMI as well as instable angina pectoris). (See next lecture).

The merits of CAD screening for patients with markedly elevated risk (known CAD / status secondary to MI, chronic renal insufficiency, hereditary dyslipidemia, diabetes mellitus) were emphasized. Studies on cardiogoniometry in such risk populations are currently ongoing.

Prof. Wessely ascertained the status of cardiogoniometry as being an optimal non-invasive early detection method; stating that, even at present, cardiogoniometry already satisfies the following criteria:

- Not invasive
- Ease of use (assisting staff)
- Quick generation of findings, automated evaluation
- Can be performed in resting position
- User-independent and
- Cost effective

He cited further studies objectives and questions needing investigation:

- Prognostic effectiveness,
- High specificity and sensitivity in low, moderate and high pretest probability as well as
- Non-dependent on age, sex or medication.

In terms of perspectives for cardiologists, Prof. Wessely regards the use of CGM to be warranted by virtue of:

- Early referral potential (prevention of MACCE)
- Targeted use of invasive diagnosis
- Elevated compliance by patients
- Easy-to-use screening tool for referring staff
- Tool for risk stratification in clinical practice
- Ease of use (assisting staff), translating into higher implementation rates
- Follow-up monitoring after medical, interventional or surgical therapy

The lecture concluded with the words:

- We urgently need a more efficient, affordable and easy-to-use method for early cardiovascular diagnostics.
- CGM is a potential tool that can satisfy these conditions and generate a synergy effect between patient <> hospital <> practice
- Initial data on the use of CGM are now available, further will be coming soon!

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**Early detection of acute coronary syndrome by cardiogoniometry**

**R. Tölg (Bad Segeberg)**

The lecture, showcasing the results of the CGM@ACS study, introduced this topic’s relevance with following quote:

“... Acute chest pain is one of the most common reasons for presentation to the emergency department (ED), accounting for approximately 7 million ED visits annually in the United States. This presentation suggests acute coronary syndrome (ACS), but after diagnostic evaluation, only 15% to 25% of patients with acute chest pain actually have ACS ...” (Marc S. Sabatine, Christopher P. Cannon; Chapter 53 in Braunwald’s Heart Disease)

Dr. Tölg illustrated the gain in time and resources associated with the use of CGM in patients with suspected acute coronary syndrome as follows (please note that this is not yet incorporated in the guidelines):
After a brief explanation, the CGM@ACS study was presented. This prospective and multicenter study, conducted in 2010/2011, investigated how well CGM identifies patients with acute coronary syndrome without ST-segment elevation (NSTE-ACS). Inclusion criteria included chest pain lasting > 20 minutes and a coronary angiography within 72 hours. A total of 216 patients were analyzed (162 patients with NSTE-ACS and 54 in the control group). The diagnosis of NSTE-ACS was ruled out or verified by coronary angiography.

CGM achieved a diagnostic accuracy that was highly significantly greater than EKG or the troponin test. The first CGM had a sensitivity that was two and a half times as high as the first EKG and over twice as high as the first troponin test. When decision-making was based on the rule that a patient counts as ischemic when either troponin levels or CGM are pathological, 83% of all NSTE-ACS patients in the study were identified as such. Additionally, a total of 3 out of 4 patients were evaluated correctly as ischemic or non-ischemic. Even in the NSTE-ACS patients whose EKG and troponin levels ultimately remained negative, CGM still detected two thirds of them properly.

The study had limitations, though. The CGM recordings were taken after the patients had been exhaustively treated with drugs and the acute ischemic status was potentially no longer present, i.e. the sensitivity was likely lower than if CGM had been recorded in patients without any pre-treatment. Dr. Tölg pointed out that this study was appropriate for determining the sensitivity of the methods, but only delivered limited conclusions about specificity and predictive values. The reason for this is that the population involved was a highly selective one and the patients in the control group also did not have healthy hearts, as evidenced by the fact that the cardiologists had already rendered the indication for coronary angiography. The control group was small (25%) and, to high and nearly overwhelming degree, had a prior history of heart problems (CAD and/or previous infarction and/or previous PCI). It is likely that, as a result, the specificity of CGM was slightly limited in this setting given that CGM primarily classifies these diseases as pathological. The diagnostic results are summarized in the charts and tables below. The results are currently in the process of being published.
Diagnostic yield of methods for NSTE-ACS

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>28% (45/162)</td>
<td>78% (42/54)</td>
<td>79% (45/57)</td>
<td>26% (40/159)</td>
<td>40% (87/216)</td>
</tr>
<tr>
<td>Trop.</td>
<td>50% (81/162)</td>
<td>96% (52/54)</td>
<td>98% (81/83)</td>
<td>39% (52/133)</td>
<td>62% (62/100)</td>
</tr>
<tr>
<td>CGM</td>
<td>69% (111/162)</td>
<td>53% (29/54)</td>
<td>82% (111/136)</td>
<td>36% (29/80)</td>
<td>65% (140/216)</td>
</tr>
</tbody>
</table>

Dr. Tölg summarized the results of the study thus:

- CGM is highly capable of detecting patients with NSTE-ACS at an early stage.
- In combination with EKG and troponin tests, CGM can promote an early-invasive and resource-saving therapeutic strategy.
- In the population presented, the specificity and predictive values of CGM were limited because the control group also contained a high proportion of patients with CAD or a prior history of heart problems and CGM detects ischemic and structural damage to the myocardium.
- CGM shows an added benefit in demonstrating acute ischemia in patients with normal EKG and normal troponin levels.

Cardiogoniometry vs. cardiac MRI – a clinical monitoring study and case examples
R. Birkemeyer (Villingen-Schwenningen)

Dr. Birkemeyer presented the results of a pilot study conducted in 2010/2011 that prospectively evaluated the accuracy of CGM compared to cardiac MRI (regarded as the non-invasive gold standard of ischemic diagnostics). First, terms were defined and methods illustrated:

- CGM = electrocardiographic method for detecting ischemia and myocardial scars
- Perfusion cardiac MRI (CMRI): standard and sensitive method for non-invasive ischemia diagnostics
- Late enhancement visualization in cardiac MRI: established standard for detecting myocardial scars

This study non-selectively enrolled 40 patients who underwent CGM as part of their routine diagnostics prior to cardiac MRI. The CGM results were compared with perfusion deficits and/or the presence of late enhancement; the reference group consisted of patients with normal perfusion and without late enhancement. CGM achieved a sensitivity of 70% and a specificity of 95%; the positive predictive value was 93%.

Its high specificity and high positive predictive value, in particular, are indicators of CGM’s suitability for screening examinations. These results deliver further corroboration of the theory that the only moderate specificity achieved in the CGM@ACS study was chiefly attributable to the frequency of prior cardiac pathologies in the reference group.

The following chart illustrates the accuracy of CGM compared with similarly evaluated EKG criteria:
This pilot study formed the basis for the currently ongoing CGM@MRI study.

Next, Dr. Birkemeyer reported on three selected cases where the CGM findings were thoroughly consistent with the clinical findings. The third case is of special interest: A 64-year-old, male patient presenting with acute ST-elevation myocardial infarction (STEML on July 29, 2010 underwent early primary PCI for thrombotic occlusion of the RCA, no history of CAD, no late enhancement in the CMR taken on Aug. 5, 2010 (abortive myocardial infarction).

- 6 days after primary PCI, pathological CGM finding showing spread of R- and T-vectors;
- CGM on the same patient 4 months later was normal, the vector spread had resolved

This observation caused Dr. Birkemeyer to question/theorize about the extent to which CGM has an early memory after acute ischemic episodes.

The lecture then came to a close with the following conclusions:

- In this pilot study, cardiogoniometry demonstrated solid sensitivity and specificity compared to the combination of adenosine-stress perfusion and late gadolinium enhancement
- The sensitivity was markedly better than that of resting EKG
- In view of the method’s simplicity and availability, further studies should be conducted as larger series.

In the ensuing discussion, Dr. Birkemeyer emphasized that CGM is well validated for patients with no abnormalities in their rhythm patterns; whereas its use in left and right branch blocks and atrial fibrillation still needs to be improved and validated. CGM detects these special rhythmological disorders while evaluating them with regard to suspected ischemia using different algorithms; given the small number of patients (which back the present algorithms), such diagnoses should currently be viewed with reservations.

When questions were posed concerning the additive benefits of CGM in the context of further and presently available tests for CAD and ischemia, Dr. Birkemeyer answered that he sees its particular merits in the preclinical and outpatient settings (patients with unclear or angina pectoris symptoms and with contraindications to exercise testing). Emphasis was again placed on the very solid specificity that warrants CGM’s use in this context and hardly results in referrals of false positive patients to hospitals.

When asked about the learning curve and possible sources of error when placing the electrodes, Dr. Birkemeyer stated that electrode placement is done with a special ruler and is really easy to master (no more complicated than EKG); he considers the error rate to be essentially comparable to that of EKG. The time spent on prepping the patient and performing the CGM is similar to EKG.

In answer to the repeated question about CGM’s optimal use, Dr. Birkemeyer responded that the device is also equipped with a 12-channel EKG for routine diagnostics; on top of this, he would use the CGM particularly in patients with unclear histories as a sort of pre-screening filter. The problematical situation associated with exercise EKG was once again stressed and that many patients cannot perform this test or cannot be stressed exhaustively. This is where CGM makes the most sense, particularly in the pre-hospital setting.
One question addressed the comparison to early vectorcardiography. Dr. Birkemeyer described how much easier CGM is to interpret because its planes basically correspond to the anatomical planes of the human heart (and not with the body planes as previously). Moreover, the CGM method analyzes many new parameters (such as beat-to-beat variability), a function that was not available with early vectorcardiography, and also generates a fully automated, but reproducible finding.

enverdis GmbH would like to extend its appreciation to the chairmen and the speakers for a well-attended and very successful symposium!