Diagnostic evaluation of chest pain

Valorisation

Relevance

In Europe, 85 million inhabitants have cardiovascular disease and over 3 million Europeans experience angina pectoris (i.e. chest pain related to myocardial ischemia) or an anginal equivalent for the first time every year.[1] Cardiovascular disease is the main cause of demise in developed countries.[1,2] The prevalence of cardiovascular disease and its impact on morbidity and mortality is even expected to increase in the following years due to ageing.

Chest pain is the most common cause for an emergency department visit.[3] The cause of chest pain ranges from a trivial ailment to more serious potentially life-threatening diseases. Non-invasive cardiovascular testing is often considered crucial in the diagnostic work-up of patients with chest pain. A substantial increase in the use of additional testing is observed over the last years.[4,5] Adequate selection of patients for the appropriate test is essential to prevent ineffective use of these costly diagnostics.

The central theme of this thesis is to investigate the role of non-invasive imaging in patients with acute or chronic chest pain. Ultimately, the results of the research presented in this thesis may contribute to a more (cost-)effective use of diagnostic tests and improve patient outcome.

Target groups

Patients investigated in this thesis represent the full spectrum of chest pain. The **first part** of this thesis provides a general introduction to this topic. The **second part** of this thesis discusses the use of non-invasive diagnostic testing in patients with acute chest pain. Among patients with acute chest pain at the emergency department, the patient history, electrocardiographic and laboratory findings provide important information for risk stratification. Based on this risk assessment, patients can be categorized as: 1) low risk for acute myocardial infarction (atypical symptoms, normal electrocardiogram and low-to-normal high-sensitivity cardiac troponin levels), 2) intermediate risk for acute myocardial infarction (near)normal or inconclusive electrocardiogram and minimally elevated high-sensitivity cardiac troponin levels), and 3) high risk or definite acute myocardial infarction (significant electrocardiographic changes and/or increased troponin levels). The third part of this thesis focusses on patients with chronic chest pain. Patients with chronic chest pain can be categorized as 1) patients with suspected coronary artery disease or 2) patients with stable or new onset angina pectoris in whom coronary artery disease is already known. In this thesis, all above mentioned subgroups are investigated.

The findings of the studies presented in this thesis are relevant for cardiologists, emergency department physicians, (nuclear) radiologists, clinical chemists, general practitioners, researchers and policy makers. A diagnostic decision tree for the evaluation of patients with acute chest pain is included in **chapter 10** of this thesis and may help physicians to decide whether additional diagnostic testing is indicated at all and to select the most appropriate modality for a specific clinical scenario.

Despite that this thesis is primarily targeted to physicians, its results could be informative for patients experiencing chest pain as well. Patients should be informed (preferably by a professional) about the diagnostic and/or prognostic value of additional cardiac testing based on their specific pre-test likelihood of having ischemic heart disease.

Activities/products and innovation

Evaluating patients with chest pain remains challenging and requires a high level of clinical experience of physicians. Categorizing patients into risk groups is a simplification of the underlying continuum in risk that ranges from 0-100% in an individual patient. It is expected that computer assisted patient care including decision support systems guided by machine learning/artificial

intelligence may assist the treating physician by providing more specific estimates of patients' risk along a continuous scale in the (near) future. However, clinical validation studies focused on patient outcome and cost-effectiveness are needed to confirm this hypothesis.

At present, identifying subgroups of patients with different risk profiles is not only practically useful, in that it structures the diagnostic strategy, it also allows performing and comparing research.

The diagnostic tests investigated in this thesis are often routinely available in academic and non-academic hospitals. The innovation lies in the selection of patients, timing of the diagnostic test, test quality and combined interpretation of clinical data and test results.

The results in this thesis suggest the following. First, additional diagnostic testing is not useful in patients with acute chest pain at low clinical risk. Second, CMR and CTA can be used as safe gatekeepers for invasive coronary angiography in patients with acute chest pain, an inconclusive electrocardiogram and elevated high-sensitivity cardiac troponin levels (suspected non-ST elevation myocardial infarction). Third, CMR plays a crucial role in the diagnostic process of patients with suspected myocardial infarction and normal coronary arteries on coronary angiography (invasive coronary angiography or CTA). Fourth, CMR provides insight into the infarct healing process and thereby allows estimating infarct age. Fifth, a negative non-invasive imaging test result yields an excellent prognosis for patients with suspected or known stable coronary artery disease.

Planning & implementation

We have shown that routine use of non-invasive cardiac testing in patients with acute chest pain and normal high-sensitivity cardiac troponin T levels has a low diagnostic yield. Restricting additional non-invasive diagnostic testing to only patients with a higher risk, was suggested in our observational study described in **chapter 3**. Similar conclusions were drawn in a recent manuscript concerning a larger multicenter trial.[6] Both studies suggest that standardized clinical risk stratification (including troponin measurement) for the selection of additional diagnostic testing may improve the efficacy of care while maintaining patient safety. Although promising, more robust evidence provided by randomized controlled clinical trials, large matched cohort studies preferably employing registry-based recruitment (proposed study design: no test versus test with an adequate sample size to assess patient outcome) are needed to further convince cardiologists and emergency department physicians.

Chapters 5 & 6 describe a randomized controlled clinical trial in patients with suspected non-ST elevation myocardial infarction (i.e. acute chest pain, inconclusive electrocardiogram and elevated high-sensitivity cardiac troponin T levels). This trial shows that a CMR and CTA first strategy prevents (unnecessary) invasive coronary angiography. Despite that no difference in patient outcome was observed between groups (secondary endpoint), verification of patient safety in a larger multicenter trial is warranted. The observed trend of having less events and complications in both non-invasive imaging arms compared to a routine invasive strategy, suggests that early CMR or CTA are appropriate alternatives to a routine invasive strategy in suspected non-ST elevation myocardial infarction and should be considered in hospitals with sufficient expertise. Furthermore, it is expected that the results of the CARMENTA trial will initiate non-invasive imaging guided trials in patients with suspected non-ST elevation myocardial infarction. Likewise, a recent study showed the significance of non-invasive MR-imaging in stable coronary artery disease.[7] It needs to be awaited whether our trial will already be a true game-changer in the diagnostic approach of patients with suspected non-ST elevation myocardial infarction. Given these initial results, we expect that such an "imaging-first" strategy in suspected non-ST elevation myocardial infarction patients shall provide a safe, cost effective,

rapid and patient-friendly diagnostic and treatment approach. We anticipate this approach to fundamentally change the way the cardiovascular community will diagnose coronary artery disease and related conditions.

CMR allows us to visualize different aspects of the infarct healing process. Prior studies argued that T2-weighted CMR was able to differentiate acute and chronic myocardial infarction. We show in **chapter 7**, that T2-weighted hyperintensity may persist for several months after acute myocardial infarction and therefore likely does not represent myocardial edema. Moreover, we postulated a multicomponent CMR approach involving cine, T2-weighted, and delayed enhancement imaging to determine infarct age more accurately. Despite that many myocardial infarctions result in acute chest pain, triggering an emergency department visit and subsequent diagnosis of acute myocardial infarction, also silent myocardial infarction occurs frequently. In this case, the timing of the event is unknown. It is crucial for patient management to know whether a myocardial infarction is (sub)acute or chronic. For instance, dual antiplatelet therapy is only indicated in acute myocardial infarction. Another clinical implication of detecting acute myocardial infarction is related to the identification of the culprit lesion. Many patients with acute myocardial infarction have multivessel disease, in whom identification of the culprit coronary artery is often challenging. CMR may help identifying the culprit coronary artery by locating the infarcted segment and differentiate any prior injury from acute myocardial infarction.[8] In our study, we used standard CMR sequences. Therefore, we believe that this approach is robust, and can directly be incorporated into clinical practice without extra costs or requirement for additional training.

The meta-analysis on patients with suspected or known coronary artery disease presented in **chapter 9** concludes that prognosis is excellent when ischemia or obstructive coronary artery disease is absent, regardless of the cardiac imaging modality. Arguably, this challenges the need for additional, more advanced testing even when a more 'simple' test (for instance exercise testing) does not suggest stress-induced cardiac ischemia. However, information of patient management and any follow-up testing was not available in this study. In general, meta-analyses may only indirectly change clinical care, by informing physicians about the mean prognostic value of a modality in a specific patient population. Decision making for the individual patient, however, requires a more sophisticated approach.

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