Weekend Educational Course – Cardiac Function, Perfusion, and Tissue Characterization

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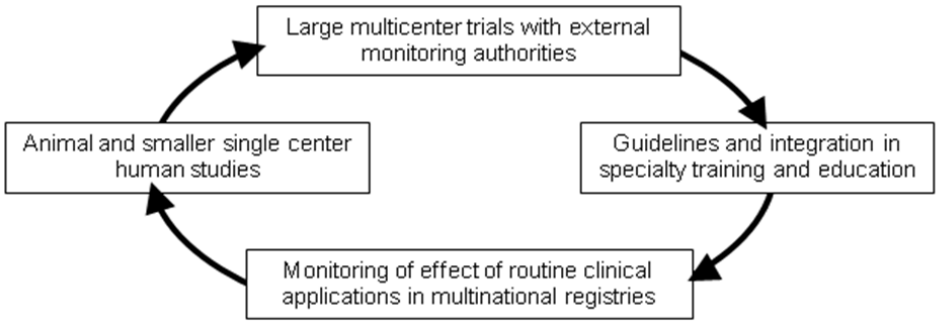
Evaluation of Cardiac Perfusion - Research Promises

Introduction

We can describe progress in medicine as a series of steps that are organized in loops. Within this concept perfusion-CMR has evolved rapidly during the past 10 years or so. Typically, an evolution in medicine starts with a clinical need, e.g. with the need to detect coronary artery disease (CAD) ideally with a non-invasive non-harmful technique which is not costly and detects CAD with high sensitivity and specificity. Such a technique is generally developed and tested in animal studies and then it is transferred into humans. If several single center studies are successful, large multicenter trials follow with external authority control (e.g. by FDA or EMEA). If successful, the technique can enter international guidelines of larger societies. This step together with the evidence of multicenter trials stimulates then the integration of the technique into training and educational courses of specialists. With this step the technique is becoming an integrated part of the state-of-the-art clinical practice. As a final step in this loop, the impact of the new technique in clinics requires a sound evaluation which is achieved by registry data. The results of registries then demonstrate whether research promises are met or not - and if met, to what extent the routine application of the new technique is able to improve medicine, i.e. patient outcome. At this stage, also cost-effectiveness considerations are relevant. And finally, from such registry results, unmet needs are identified in the current clinical practice, which simulates new ideas and concepts that are tested first in animal experiments, with which the first step of a new loop is launched.

The loop



Research promises of Perfusion-CMR

In the field of CAD, perfusion-CMR was developed to improve the detection of CAD, and it should identify the patients that are at risk for complications of CAD such as cardiac death, non-fatal myocardial infarction, development of heart failure and others, so that the patients that benefit from treatment (drug treatment and/or revascularization procedures, anti-arrhythmic treatment) can be discriminated from those that would need risk factor management only.

In the field of CAD, perfusion-CMR successfully accomplished step 1, i.e. several animal[1] and important single center studies[2-5] could demonstrate the potential of perfusion-CMR to detect CAD with high performance. Also, step 2 is accomplished with several positive multicenter trials that were performed under monitoring of external authorities,[6-8] which led also to the acceptance of contrast media for the use in cardiac MR examinations. Step 3 is was also successfully accomplished during the last 2 years or so with the listing of perfusion-CMR as a class 1 indication for heart failure work-up in patients with inadequate echocardiographic quality or when echocardiography is not able to define the etiology of heart failure[9] and in 2013 with its listing for the work-up of patients with suspected or known stable CAD.[10] At this stage, perfusion-CMR was also introduced into the syllabi of cardiology training programs[11] and it is now an integrated part of CAD work-up[12] in many hospitals in Europe[13] and the US. Also, the cost-effectiveness was shown of perfusion-CMR in the European CMR registry.[14]

Step 4 is probably the most relevant step in the loop and here, perfusion-CMR is on track. In the large European CMR registry, which holds currently more than 33'000 patients collected in 59 European centers from 19 countries, preliminary results of the sub-study "Suspect-CAD" yield first positive signals indicating clearly, that perfusion-CMR (in combination with LV function and viability assessment) is an excellent predictor of outcome. The current interim data indicate a rate of major adverse events (all cause

death, aborted sudden cardiac death, or non-fatal myocardial infarct) of 1.0%/year for patients with normal stress CMR in the group of 1'706 patients that underwent 12-month follow-up in this specific protocol (vs 2.3% with pathological CMR studies, $p<0.009$).[13] It is expected to "close the loop" with relevant results of this registry in 2014.

New research promises of CMR in the field of CAD

The results of the large studies testing perfusion-CMR and the registry data also indicate that the discrimination between patients with and without complications of CAD is not perfect. Thus, these imperfections observed can stimulate a second loop of perfusion-CMR developments. If modifications of perfusion-CMR pulse sequences show a potential for better performance in animal and single center studies, such sequences should go into multicenter trials and could finally find the way into guidelines and educational programs.

One major reason for the current imperfection might be the fact that a certain portion of patients yields inadequate study quality. Thus, future research promises in the field of perfusion-CMR will include modifications of pulse sequences to improve its robustness, i.e. to increase the portion of patients in which perfusion-CMR is able to produce high quality data. Currently, it is assumed to obtain suboptimal quality in 10-20% of studies, mainly due to breathing-induced artifacts or inadequate ECG triggering signals. Faster acquisitions could maybe reduce the level of artifacts due to motion[15] and 3D acquisitions[16] could allow for better breathing-motion correction/registration. Also, a quantitative analysis could probably decrease the inter-observer variability of the test.[17] Whether such quantitative analyses would benefit from "absolute" quantification yielding results in "milliliter per minute per gram tissue" would also need further investigation. Thus, first steps in a second loop are already under way.

It is generally known that a reduced myocardial perfusion goes along with a bad outcome. Thus, an imbalance of oxygen demand and oxygen supply is an indicator of an unfavorable evolution of a cardiac disease. Therefore, the evaluation of this supply/demand imbalance or of cardiac metabolism might be a strong extension of perfusion imaging. With novel MR techniques that are based on hyperpolarization of ^{13}C-carbon nuclei, signals up to 10'000 times higher than with conventional ^{1}H-proton MR can now be produced.[18] With signals several orders of magnitude higher than with conventional MR (at conventional magnetic field strengths) the metabolism of cardiac myocytes can now be studied in near real-time and non-invasively, without applying ionizing radiation. Cardiac metabolism could be characterized in different cardiac diseases such as hypertrophy,[19] fasting state,[20] or during ischemia/reperfusion[21, 22] in animals. This ^{13}C-hyperpolarisation CMR technique holds probably the most innovative research promises in the field of CAD diagnostics.

Literature:

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