Integrated Cardiovascular Function

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Center for Cardiological Innovation:

The Center for Cardiological Innovation (CCI) was officially started November 2011. The center was one of seven new centers which received funding through the Norwegian Research Council's program "Centers for research-based innovation". Prof. Thor Edvardsen heads the CCI which is a collaboration with other groups including the Computational Cardiac Modeling group at Simula Research Laboratory and the main industrial partner GE Vingmed Ultrasound. The focus of CCI is improving diagnostic methods for patients with heart failure and patients at risk of sudden cardiac death. The center will constitute a major part of the research of our group the next 8 years.

General objectives:

The Integrated Cardiovascular Function group studies cardiac mechanics in experimental studies and studies in patients. The idea is to develop better diagnostic understanding and solutions into clinical practice.

Specific objectives:

1. To investigate mechanisms of left ventricular (LV) dyssynchrony and develop better methods for selecting patients for cardiac resynchronization therapy (CRT).
2. To investigate hemodynamic effects of CRT in patients with heart failure and narrow QRS.

Professor Otto A. Smiseth

3. To investigate LV mechanical-electrical interactions and improve risk stratification for ventricular arrhythmias.
4. To investigate mechanisms of LV diastolic dysfunction.
5. To develop better diagnostic methods to identify viable myocardium.
6. To develop better diagnostic tools to identify optimal timing of surgery in valvular heart disease.

1. Left ventricular dyssynchrony: Cardiac resynchronization therapy has been documented to be a powerful treatment in patients with severe congestive heart failure, causing reverse LV remodeling, improvement of symptoms and reduction of mortality (Cleland 2005). In left bundle branch block (LBBB) the LV wall contraction is dyssynchronous due to electrical conduction delay to the LV free wall, and CRT resynchronizes the contractions by bi-ventricular pacing and thereby improves the contractile function. Currently, patients are selected for CRT on basis of the presence of wide QRS in the ECG. However, in about 30% of these patients, there is no improvement in symptoms, and in some cases aggravation of symptoms by CRT (Jarcho, 2006). The high number of non-responders represents a major problem with CRT, and better criteria for selection of candidates for this treatment modality are therefore needed. Because ECG has limited ability to identify candidates who will benefit from CRT, several new methods based on the interpretation of myocardial motion as measured by echocardiography have been proposed as more sensitive and specific markers. However, so far echocardiography has no proven clinical value in selection of candidates for bi-ventricular pacing. We suggest that a better understanding of the underlying mechanism of dyssynchrony is important to interpret the echocardiographic findings, and thereby to improve patient-selection for CRT. In LBBB, the pathological motion of the inter-ventricular septum during early systole has been proposed as a good predictor of response to CRT. Previous studies had indicated that early systolic contraction of the

septum into the LV was due to a more rapid rise of right ventricular (RV) pressure than the rise of pressure in the late activated LV. In 2011 we published a new study which opposed the pressure theory and showed that the early-systolic abnormal septal motion is due to active contraction and not merely a passive consequence of pressure differences across the septum. This phase has not previously been considered active when assessing dyssynchrony, and this might explain the failure of most echocardiographic indices of dyssynchrony to predict CRT-response. Our ongoing LBBB research focuses on methods to noninvasively quantify regional myocardial work which is highly dependent on the electrical activation sequence. We have just validated the noninvasive work quantification method and are currently investigating if indexes based on regional work perform better than methods based on shortening/lengthening to identify candidates for CRT.

2. Narrow QRS: Cardiac CRT has been documented to be a powerful treatment in patients with severe congestive heart failure and LBBB. Interestingly, there has also been demonstrated clinical effect of CRT in patients with narrow QRS. As more than two thirds of heart failure patients do not have electrical conduction disturbances, extending the indications for CRT into this patient group is going to have considerate implications. The mechanisms of possible effects of this treatment in heart failure patients with narrow QRS have not been properly investigated. Two possible mechanisms have been suggested: CRT may correct electrical dyssynchrony not seen on ECG or CRT induces changes in the interventricular interaction. The change in ventricular interaction can be obtained by pacing in the left ventricular lateral wall. The LV is then activated earlier than the RV and a concomitant phase shift in the ventricular filling appears. A head start of LV filling relative to RV filling reduces the LV external constraint. External constraint is determined by the RV pressure and the pericardial pressure and constitutes the external resistance to LV filling. The hemodynamical result of reduced external constraint is improved LV filling and increased cardiac output. An experimental dog model is used to explore these electromechanical and hemodynamic consequences of CRT. The study is ongoing, but some preliminary results have already been presented at international congresses.

3. LV mechanical-electrical interactions: Evaluating patients with susceptibility for cardiac arrhythmias and sudden cardiac death is a major challenge in daily cardiology practice. Electrophysiological studies have demonstrated that damaged myocardium (e.g. infarcted or genetically altered) provides the substrate for malignant arrhythmias. Echocardiographic techniques can accurately quantify regional myocardial function. Over the last few years we have studied the correspondence between myocardial mechanical function and risk for ventricular arrhythmias and demonstrated how mechanical dispersion can predict ventricular arrhythmias in patients with long QT syndrome and in myocardial infarction. In a new study we showed that right ventricular mechanical dispersion by strain was related to ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy. The study was published in European Heart journal and won Oslo University Hospital excellent publication award fall 2011.

4. Diastolic dysfunction: About half the patients with heart failure seem to have problems related to filling of the heart as the ejection fraction is normal. Main challenges are therefore to understand what causes diastolic dysfunction and how it can be diagnosed. Measurement of the lengthening velocity of the LV during early filling is a standard measurement in the clinic for assessment of diastolic function. We recently studied what factors determined this velocity in an experimental model. The study was published in Circulation 2009 and a mathematical model study that explained the physics of this velocity and generation of early diastolic suction was published in American Journal of Physiology 2011. The Circulation article was announced as one of the most read articles in Circulation in 2011 and it was recognized as among the most important articles in myocardial disease by the editors. The lengthening velocity is one of the Doppler echocardiographic indexes that are used in hemodynamic assessment including prediction of the LV filling pressure. This noninvasive method is highly desired as the invasive gold standard is not without risks. In a prospective multicenter study together with Methodist DeBakey Heart and Vascular Center in Houston we showed that these noninvasive measurements could be used for reliable hemodynamic assessment and determination of filling pressure in patients with acute decompensated heart failure. New echocardiographic technology has recently made assessment of LV twisting and untwisting easily accessible and created an interest in untwisting rate as a potential marker of diastolic function. Similarly to our previous investigation of the determinants of the lengthening velocity we are currently stuying the determinants of untwisting rate.

5. Coronary artery occlusion: Although acute myocardial infarction is treated preferably by early percutaneous coronary intervention (PCI), there is limited access to this treatment, and a large fraction of patients receive intravenous thrombolytics as primary treatment. These patients are referred for "rescue PCI" only when there is no reperfusion after thrombolytic treatment. The main problems with the latter strategy are that all myocardium at risk may have un-

dergone necrosis and therefore PCI is unnecessary. Furthermore, we lack reliable methods to determine if reperfusion has been achieved by the thrombolytic. One of our main objectives is to develop better functional imaging in order to differentiate between viable and necrotic myocardium and to determine when reperfusion has been achieved.

6. Optimal timing of cardiac surgery for chronic valvular regurgitations has been a challenge for years. Development of systolic dysfunction precedes the onset of symptoms in more than one fourth of the patients with this condition. Traditional echocardiographic methods like preoperative left ventricular ejection fraction (LVEF) and cavity dimensions are the most important determinants of survival and LV function after valve replacement for regurgitations. However, volume derived measures of LV function have important limitations in assessing myocardial contractile function where a series of compensatory mechanisms, including an increase in end-diastolic volume and hypertrophy, can mask underlying changes in myocardial force development. Therefore, the purpose of these studies is to investigate whether global systolic strain measured by 2-dimensional speckle tracking echocardiography could detect early onset of myocardial dysfunction in patients with chronic regurgitations and preserved LVEF.

Anders Opdahl

Sebastian Sarvari

Anders Opdahl was the first author of the Circulation paper outlining the determinants of the myocardial lengthening velocity during early diastole. This paper was one of the most read imaging articles in Circulation and was considered by the editors among the most significant research in the area of myocardial disease. Sebastian Sarvari was the first author of the European Heart Journal paper on a new method to detect patients at risk for malignant arrhythmogenic right ventricular cardiomyopathy. This publication received an outstanding research paper price from Oslo University Hospital.

Collaborators

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