Einthoven Dissertation Prize 2010

For the 21st time in a row, the Netherlands Society of Cardiology (NVVC), the Interuniversity Cardiology Institute of the Netherlands (ICIN), and the sponsor, Sanofi-Aventis, have supported the competition for the best three PhD theses on a cardiovascular subject published last year. The prize carries the name of one of the great Dutchmen in the history of cardiology: Willem Einthoven (1860-1927), the pioneer of the human ECG and winner of the Nobel Prize in 1924.

The jury received a total of 30 dissertations. The jury members were impressed and pleased by the scientific quality of the work of the young doctors.

Three nominees, Kevin Damman, Willem-Bob Meijboom and Daniël Pijnappels, presented their work at the spring meeting of the NVVC, which was held in Papendal on 9 April 2010. The ultimate winner of the first, second and third prize were chosen by the audience. Daniel Pijnappels won the first prize, Kevin Damman the second, and Willem-Bob Meijboom the third prize. Summaries of the three nominated PhD theses are given below. ■

Chairmen of the jury
W.H. van Gilst, E.E. van der Wall

Cardiorenal interaction in heart failure

Introduction

Renal impairment is not only frequently found in patients with chronic heart failure (CHF), but also associated with strongly decreased survival. Furthermore, evidence suggests that the incidence of combined heart and kidney failure has been increasing in the past decade, probably in part due to higher rates of diabetes and hypertension. This so-called cardiorenal syndrome is a challenge from a therapeutic point of view, since these patients are often older, have lower blood pressures, more signs and symptoms, are resistant to diuretics and their disease progression is very rapid. We aimed to elucidate some of the key pathophysiological elements of this cardiorenal interaction in heart failure.

Pathophysiology of reduced glomerular filtration rate in chronic heart failure

Two of the most important characteristics of heart failure are decreased organ perfusion and increased venous congestion. We investigated the relative contribution of decreased renal blood flow (RBF) and increased central venous pressure (CVP) on glomerular filtration rate (GFR) in patients with heart failure. We found that decreased RBF was the most important determinant of reduced GFR, accounting for over 70% of reduced GFR. Importantly, we found increased renal vascular resistance, in combination with decreased filtration fraction (GFR/RBF), which suggests afferent vasoconstriction in these patients, who were all treated with renin angiotensin system blockers. When reduced RBF was present, increased CVP was a strong and independent determinant of reduced GFR. Furthermore, in a substudy of the CIBIS-II trial, we found that

even signs and symptoms of venous congestion are associated with impaired GFR. Finally, in a large cohort of patients with a broader spectrum cardiovascular disease, we reproduced our findings, again acknowledging the independent relationship between increased CVP and GFR, even after adjustment for other confounders. In these last two studies, both signs and symptoms, as well as invasively determined CVP independently determined prognosis.

Worsening renal function in patients with heart failure

Not only baseline renal impairment is an important clinical risk factor in heart failure. In two studies we evaluated the effect of changes in renal function and outcome. In a meta-analysis of eight studies investigating the relationship between worsening renal function (WRF) and outcome, we found a 60% increase in the overall mortality rate in those patients experiencing WRF, as defined as an increase in serum creatinine $>26.5 \mu\text{mol/l}$. Furthermore, in a substudy of the COACH, we found that at any given point in time during or after hospitalisation for heart failure, a decrement in renal function was associated with impaired clinical outcome. Furthermore, we were the first to show that the normal decrement in estimated GFR in patients with heart failure ($5 \text{ ml/min/1.73m}^2/\text{year}$) is much higher compared with the normal population (0.5 to $1 \text{ ml/min/1.73m}^2/\text{year}$).

Emerging pathophysiological pathways in the cardio-renal connection

To understand how impaired renal function determines outcome, we evaluated different pathophysiological pathways. We found that a combination of renal perfusion, filtration efficacy, haemodilution and anaemia were the most

important factors. Finally, we investigated the prevalence and prognostic importance of tubular damage, a new renal entity in heart failure. We found that tubular damage is prevalent in patients with heart failure, and when present, associated with strongly increased mortality, even after adjustment for both GFR and albuminuria.

In conclusion, cardiorenal interaction in heart failure is mainly dependent of decreased renal perfusion and increased venous congestion. Renal function should be monitored over a longer period of time, since worsening of renal function significantly impairs prognosis. Finally, next to reduced GFR and albuminuria, tubular damage is a new independent factor in cardiorenal interaction in heart failure, and may be a future target for therapy. ■

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Diagnostic performance of 64-slice CT coronary angiography

Conventional coronary angiography (CCA) is the standard of reference for the assessment of significant coronary artery disease (CAD). It is the key diagnostic procedure in the stratification of patients suspected of CAD towards medical therapy, percutaneous coronary intervention (PCI), or coronary artery bypass surgery (CABG). However, CCA is usually restricted to patients with a high probability of significant CAD due to its relatively high costs and invasive nature with a small, but not negligible, risk of procedure-related, potentially life-threatening complications. CT coronary angiography (CTCA) has emerged as a non-invasive diagnostic tool to detect and especially to rule out significant coronary stenoses. In a prospective multicentre, multivendor study we included 360 symptomatic patients who underwent CTCA which was compared with CCA. In a patient-based analysis, the sensitivity for detecting significant coronary stenosis was 99% and the specificity 64%. In conclusion, 64-slice CTCA was reliable to rule out significant CAD. However, CTCA overestimated the severity of atherosclerotic obstructions. A monocentre study of 402 patients comparing differences between men and women demonstrated a similar sensitivity and negative predictive value, whereas specificity and positive predictive value were slightly lower in women. Diagnostic performance of 64-slice CTCA in 104 patients with non-ST-elevation acute coronary syndrome showed similar good results. A newly introduced multi-slice CT scanner, dual-source computed tomography, which is able to obtain higher temporal resolution during image acquisition than single tube scanners, showed excellent diagnostic accuracy, even without the use of prescan β -blockers.

Clinical application of CT coronary angiography

The clinical utility of a test result requires knowledge of the sensitivity and specificity of the test as well as an assessment of the pretest probability. We divided patients in three groups with a low, intermediate and high pretest

probability for significant CAD. Results are shown in figure 1. We concluded that CTCA is useful in symptomatic patients with a low or intermediate pretest probability of significant CAD, and a negative CTCA reliably rules out CAD and obviates the need for further downstream diagnostic investigations. However, CTCA is of limited use in patients with a high pretest probability of CAD.

Other potential clinical indications are symptomatic patients with left bundle branch block, differentiation for new onset cardiomyopathy (ischaemic vs. non-ischaemic), evaluation of coronary anomalies, ostial lesions and cardiac masses.

Although CTCA provides excellent diagnostic sensitivity for identifying coronary stenoses, it does not provide information on its haemodynamic significance. The anatomical assessment of coronary stenoses determined either by visual CTCA, quantitative CTCA, CCA or QCA did not correlate well with the functional assessment of fractional flow reserve. Therefore, determining the haemodynamic significance of an angiographic intermediate stenosis remains relevant before referral for revascularisation treatment.

CTCA before and after cardiac surgery

Patients undergoing isolated cardiac valve surgery have a prevalence of concomitant CAD of 25 to 35%. Using a 64-slice CTCA, we were able to identify all patients with significant coronary stenosis. If this study had been set up as a protocol with CTCA as an initial screening test, 69% of patients would have avoided CCA, 26% would have undergone a CCA to confirm the findings from CTCA, and an 'unnecessary' CCA would have only been performed in 6%.

Imaging of CABGs is reliable, due to their larger diameter and lesser mobility. However, complete angiographic evaluation of post-CABG patients includes assessment of the grafts and the native coronary arteries, which often remains challenging due to the presence of extensive calcifications, stents and surgical clips. In patients who undergo

Figure 1. Influence of CTCA on probability of obstructive CAD as a function of pretest probability. The estimated post-test probabilities of CAD are shown after positive and negative findings on CTCA from various estimated pretest probabilities.

a redo CABG, CTCA can add incremental information in planning these complicated procedures.

Conclusion

CTCA imaging is emerging as the most promising imaging modality for non-invasive coronary atherosclerotic disease detection. The possibility of identifying or excluding significant stenotic lesions and measurement of atherosclerotic plaque burden makes this imaging modality very enticing. The qualities of CCA with its high spatial resolution and its high temporal resolution providing information about coronary blood flow will probably not be met. Yet, CTCA may become an acceptable alternative to CCA. Long-term studies evaluating effectiveness, cost-effectiveness of various diagnostic workup algorithms using CTCA and functional tests prior to referral to CCA need to be performed to determine the clinical role of CTCA. ■

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Electrophysiological deterioration and resurrection in the scarred heart

The aim of this thesis was to explore, from a mechanistic and electrophysiological point of view, the integrative and functional aspects of cell modification and transplantation as therapeutic options to cure the damaged, ischaemic heart (*Chapter I, Ann N Y Acad Sci, 2010*).

Myocardial infarction results in the replacement of excitable and well-coupled myocardium by an unexcitable and poorly coupled mesh of myocardial scar fibroblasts. Genetic modification of these fibroblasts, by forced expression of transcription factors involved in cardiac development, may induce differentiation or expression of various cardiac proteins in these cells, and thereby improve their electrophysiological properties. Therefore in *Chapter II (FASEB J, 2007)*, it is tested whether transfer of the myocardin gene, a potent cardiac transcription factor, in cultured human ventricular scar fibroblasts, results in a phenotypic switch, favouring electrical conduction across these genetically modified cells.

Improved electrical conduction across genetically modified ventricular scar fibroblasts may restore rapid electrical activation of adjacent regions of cardiac tissue, thereby lowering the dyssynchronous nature of fibrotic myocardial tissue. This concept is explored in *Chapter III (Circulation, 2007)*, which studies the underlying mechanisms by which these scar fibroblasts contribute to dyssynchronous activation of cultured cardiac tissue. This chapter describes how genetic modification of scar fibroblasts can result in (1) resynchronisation of cardiac tissue by increased conduction velocity across these fibroblasts and (2) establishment of interconnecting tissue for electrical stimulation.

Although forced expression of myocardin in ventricular scar fibroblasts improved electrical impulse conduction across these cells, it did not generate functional, excitable cardiomyocytes. However, recently it was shown that forced expression of only four transcription factors in

adult fibroblasts reprogrammed these cells into induced pluripotent stem (iPS) cells, resembling many features of embryonic stem cells. However, to become a novel, clinically relevant cell type, the process of cardiomyogenic differentiation in these iPS cells should be at least as efficient as in embryonic stem cells. This is studied in *Chapter IV (Revision)*, which describes a detailed comparison of genetic, electrophysiological, and structural aspects between mouse iPS cells and mouse embryonic stem cells concerning their cardiomyogenic differentiation potential.

Transplantation of cells into damaged cardiac regions may improve the function of infarcted myocardium. In order to maximise therapeutic efficiency of cell therapy, and minimise the risk of adverse effects, these cells should functionally integrate with host cardiac tissue. However, the process of electrical integration of such transplanted cells with recipient myocardial tissue is incompletely understood. *Chapter V (Cardiovasc Res, 2006)* of this thesis evaluates the ongoing functional electrical integration of transplanted adult human bone-marrow derived mesenchymal stem cells in a syncytium of cultured cardiomyocytes, and the role of gap junctional coupling in this process.

The cardiac muscle has a typical anisotropic tissue structure, which influences both electrical and mechanical activation. Therefore, it seems that transplanted cells should also align properly with native cardiac cells in order to restore tissue structure and contribute to anisotropic conduction. However, it is unknown how and to what extent alignment of transplanted cells affects the process of functional integration. These aspects are studied in *Chapter VI (Circ Res, 2008)*, which explores the structural and functional effects of forced alignment of transplanted neonatal rat mesenchymal stem cells, undergoing cardiomyogenic differentiation, on functional integration with cultured cardiac tissue.

Epicardial cells are able to undergo epithelial-to-mesenchymal transformation, thereby contributing to cardiac development. Disturbances in this process of transformation are associated with seriously hampered cardiac function. However, there is a lack of knowledge regarding the electrophysiological properties of epicardial cells and whether such a transformation influences electrical conductivity of epicardial cells. These aspects are studied in *Chapter VII*

Chapter VIII (Ann N Y Acad Sci, 2010) provides the summary and conclusions of this thesis, as well as future perspectives related to the integrative and functional electrophysiological aspects of cell modification and transplantation for the treatment of damaged myocardium. ■

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