Summary and Future Perspectives
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In this thesis an overall assessment of a variety of advanced diagnostic and treatment approaches (PET, VEGF gene and laser treatment, NOGA, ablation therapy and PCI after immediate graft failure) in subjects with complex cardiovascular disease is made during daily clinical practice. It is argued that such an evaluation is facilitated by creating a knowledge platform based on the three major interrelated entities in cardiovascular disease: ischemia, heart failure and arrhythmia. The main driving force to elaborate on this topic is to provide more insight into the added-value of the aforementioned cardiovascular modalities or clinical approaches for main stream patients.

For the readers - especially medical practitioners devoid of such modalities – this may contribute to understand practical thinking in daily practice of centres providing advanced clinical care. Subsequently, this may have a beneficial effect on referral flows, follow-up and quality of care. Clinical performance is assessed by dividing the investigations in a diagnostic, therapeutic and outcome section.

Part I: Diagnosis

In this section the clinical investigations targeted several diagnostic aspects in subjects with LV dysfunction. Underlying metabolic dysregulation, myocardial perfusion dynamics and electromechanical endocardial interaction are meticulously evaluated. These issues are addressed to acquire insight into the role of diagnostic tools (PET, NOGA versus contrast angiography) and intervention strategies, such as metabolic intervention, VEGF gene or laser therapy and percutaneous coronary revascularisation for example in chronic total occlusion.

In Chapter 1 the relation between myocardial glucose uptake and insulin resistance in idiopathic dilated cardiomyopathy (IDC) patients was investigated. Metabolic conditions may play a role in myocardial glucose metabolism in patients with IDC and may be related to the severity of heart failure. Seventeen patients underwent $^{18}$F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging with oral glucose load technique (glucose load) and 12 patients with hyperinsulinemic euglycaemic glucose clamp technique (clamp) to assess myocardial glucose uptake. Mean myocardial glucose uptake was not different between the groups. In glucose load patients a trend to positive correlation ($r=0.37, P=0.15$) was present between FDG uptake and left ventricular function, whereas in clamp patients a trend to negative correlation ($r=-0.38, P=0.22$) was demonstrated. Correlation coefficients were significantly different between the groups ($P=0.034$). In IDC clamp patients with left ventricular ejection fraction (LVEF) < 30% a trend for higher FDG uptake was observed. These data suggest that myocardial glucose uptake in IDC patients is influenced by metabolic conditions and seems to be related to the severity of heart failure.

The purpose of the study described in Chapter 2 was to appraise the value of PET in the assessment of the effect of supposedly proangiogenic new therapies such as gene therapy
with vascular endothelial growth factor (VEGF) gene and endomyocardial laser therapy. Thirty-five patients with end-stage coronary artery disease and class III (Canadian Cardiovascular Society) angina were included. Myocardial ischemia was evaluated with dipyridamole PET scanning and exercise tolerance with bicycle ergometry. Ten patients were treated with naked plasmid DNA encoding for human VEGF165 (VEGF) and 12 patients were treated with laser therapy (direct myocardial revascularization [DMR]) using an electromechanical mapping system. Thirteen patients were treated with standard medical therapy (control). The results showed that in both active treatment groups, angina was reduced in most subjects, except in 2 VEGF and 5 DMR patients. In the control group, no improvement in anginal classification was found, except in 3 subjects. On the PET scan, solely in the VEGF group, the stress perfusion was significantly improved (from 57 ± 33 to 81 ± 55 mL/min/100 g; P=0.031). Furthermore, in the VEGF group, the number of ischemic segments was reduced from 274 ± 41 to 234 ± 48 segments (P=0.004) but not in the DMR group (from 209 ± 43 to 215 ± 52 segments) or in the control group (from 218 ± 18 to 213 ± 28 segments). Bicycle exercise duration showed slight nonsignificant changes in the VEGF group (from 3.6 ± 2.0 to 4.6 ± 2.1 min), in the DMR group (from 5.1 ± 1.5 to 4.7 ± 1.3 min), and in the control group (from 3.3 ± 1.8 to 3.5 ± 2.3 min). We conclude that intramyocardial gene therapy with the human VEGF165 gene in contrast to laser DMR treatment effectively reduces myocardial ischemia.

Clinical decision making in intervention cardiology often depends on information on the presence of myocardial viability and the extend of ischemia. Especially in the case of an occluded collaterally filled coronary branch, on-line decision making in selected subjects may accelerate and improve patient care. The electro-mechanical NOGA-mapping system offers the opportunity for on-line viability assessment. In Chapter 3 we describe 3 cases in which this diagnostic tool was used during daily practice. In our opinion NOGA mapping can be helpful for ‘on-line’ viability evaluation in patients with an occluded collaterally filled coronary artery. In these patients noninvasive viability evaluation may cause unnecessary delay in the overall treatment approach.

There is a paucity of data on the diagnostic accuracy of global LV function assessment by electromechanical endocardial mapping (EEM). In Chapter 4 it was our aim to determine the relationship between global left ventricular (LV) function measured by EEM and biplane left ventricular contrast angiography (LVA) after ST-elevation myocardial infarction (STEMI). Thirty-seven patients underwent LVA and EEM during routine coronary angiography 4 months after primary percutaneous intervention for STEMI. Global LV function parameters were available from both techniques in all patients. LVA was regarded as reference standard. All procedures were carried out without adverse events. Average age was 55 ± 10 years and 84 % was male. EEM showed an overestimation of end-diastolic volume and end-systolic volume of 6.5 ml and 25.5 ml, respectively. Correlation (r) was 0.84 (P<0.001) for end-diastolic volume and 0.74 (P<0.001) for end-systolic volume. Average LVEF measured by EEM was 17.2 %-point (± 11.3 %-point) lower compared to LVA.
(r=0.69, P<0.001). It was concluded that although global functional parameters by EEM correlated well with LVA, the relatively large differences in terms of absolute values for ventricular volumes and LVEF render the two techniques non-interchangeable for global LV-function-data. These data are of clinical relevance, also for electrophysiologists when they use EEM for mapping of the atria or ventricles.

**Part II: Treatment**

In this section we describe two treatment options in patients who are difficult to treat for atrial fibrillation. Although large randomized controlled trials have shown that rate-control therapy is not inferior to rhythm-control therapy, rhythm control is indicated in specific patient populations. One of the main reasons for adopting rhythm control are symptoms caused by AF, and subsequently a low quality of life. However, pharmacological rhythm-control therapy is only effective in maintaining sinus rhythm in 40% of all patients. Adverse effects of antiarrhythmic drugs are another important disadvantage. Nowadays, left atrial catheter ablation is widely used to prevent recurrences of AF. In the past, such patients were candidates for the ‘ablate and pace’ strategy.

In Chapter 5 we describe long-term outcome of patients who are treated with an atrioventricular node ablation and permanent right ventricular pacing because of symptomatic refractory AF. After a mean follow-up of 4.3±3.3 years, no significant changes in New York Heart Association (NYHA) functional class for heart failure were observed (87% versus 77% in NYHA I/II at baseline versus end of follow-up) and LV end diastolic diameter (51±7 vs. 52±8 mm) were observed. Left ventricular end systolic diameter decreased (from 37±9 to 34±7 mm, P=0.03) and fractional shortening improved (from 28±10 to 34±9, P=0.02) in all patients and in patients with previous heart failure, but not in patients without previous heart failure. Hospitalizations for heart failure occurred in 24 patients (20%), predominantly those with previous heart failure. All-cause mortality occurred in 31 (26%) patients. At the end of follow-up, quality of life was comparable with the control group. Therefore, we concluded that long-term outcome of AV node ablation and permanent pacing is good. In my view, even this curative ablation area atrioventricular node ablation in combination with pacing remains a treatment option for AF.

The purpose of Chapter 6 was prospective to describe the success of pulmonary vein isolation for prevention of paroxysmal and persistent AF in a single operator referral center in the Netherlands and to determine predictors of success. A total of 99 consecutive patients were included with paroxysmal or persistent AF. All patients underwent pulmonary vein isolation by the same electrophysiologist. Successful pulmonary vein isolation was defined as absence of AF on Holter or electrocardiogram, and no complaints of AF. After 6 months of follow-up 60 (61%) patients did not have any AF episode, neither on 96-Holter monitoring nor on electrocardiograms, and had no complaints related to AF. 39 of these 60 patients (65%) were no longer treated with any class I or III AAD. Independent determinants of successful
pulmonary vein isolation were paroxysmal AF. Since at the moment long waiting lists exist for this therapy, we suggest focusing on patients with paroxysmal AF. Patients with persistent AF often need additional lines to cure them from AF.

**Part III: Outcome**

The final section focuses on clinical outcome after surgical revascularisation. The relation between outcome and the presence of exposed risk factors is evaluated. In addition, the impact of PCI after bypass surgery is assessed. The clinical conception that PCI early after bypass surgery especially in grafts and at anastomoses is hazardous is challenged.

The retrospective study described in Chapter 7 sought to assess differences in graft patency and clinical outcome between women and men after coronary artery bypass graft surgery (CABG). A less favorable clinical outcome has been reported in women as compared with men. Its relation to graft patency has not been studied. We analyzed one-year follow-up data of 912 patients (120 women) who entered a randomized clinical drug trial. All patients received vein grafts; in 494 patients (56 women) internal mammary artery (IMA) grafts were also used. Graft patency was assessed by coronary angiography at one year. Primary clinical end points were myocardial infarction, revascularization procedures and death; secondary clinical end points included recurrent angina, heart failure and arrhythmias. Occlusion rates of vein grafts were 16.7% in women and 12.4% in men (odds ratio [OR] 1.62, 95% confidence interval [CI] 0.88 to 3.00, P=0.12); occlusion rates of IMA grafts were 3.4% and 5.7% in women and men, respectively (OR 0.56, 95% CI 0.08 to 3.96, P=0.56). Primary clinical end points were observed in 16.7% of women and 9.2% of men (OR 1.97, 95% CI 1.10 to 3.34, P=0.022), and any clinical end point in 41.7% of women and 25.8% of men (OR 2.06, 95% CI 1.39 to 3.04, P=0.0004). Myocardial infarction (15% vs. 7.6%, OR 2.15, 95% CI 1.24 to 3.75, P=0.013) and recurrent angina (26.7% vs. 15.4%, OR 2.00, 95% CI 1.28 to 3.11, P=0.004) occurred most frequently. Multivariate regression analysis did not identify gender as an independent risk factor for graft occlusion or the clinical end points. Graft occlusion was an independent predictor of the composite primary clinical end point (OR 2.75, 95% CI 1.59 to 4.75, P=0.0003) and each of the secondary clinical end points. The observed differences were due to an imbalance of risk factors at baseline and to surgical and graft characteristics. One-year occlusion rates of vein and IMA grafts were comparable in women and men. Clinical outcome was related to graft patency and was less favorable in women owing to their uneven distribution of risk factors among both groups.

The aim of Chapter 8 was to identify patients with recurrent ischemia after coronary artery bypass surgery (CABG) treated by percutaneous coronary intervention (PCI). Graft failure after CABG may be managed conservatively or treated by surgery or PCI. We thought to investigate clinical, angiographic and procedural characteristics in relation to clinical outcome. This was a retrospective single-centre study. Patients who underwent revascularization
by PCI with a previous CABG were analyzed. Patients were divided in 3 groups, depending on interval between CABG and index-PCI; Group 1: Interval <72 hours. Group 2: Interval between 72 hours and 1 year. Group 3: Interval >1 year. 221 patients were studied. Clinical characteristics and survival curves were comparable in groups 2 and 3. Post-operative CK-MB and troponin values were significantly higher in group 1 (P=0.000). From group 1, significantly more patients (10.5%) required emergency-CABG after the index-PCI than compared to group 2 (2.1%) and group 3 (0%), (P=0.003). There were more off-pump CABG’s in group 1 than in the other two groups. Group 1 received less PCI’s in native ungrafted vessels compared to the other two groups. Mortality in group 1 (18.4 %) was higher than in the other 2 groups (7.4 and 4.5% respectively; P<0.05). Mortality in group 1 was higher in the acute phase of follow-up. PCI performed less than 72 hours after CABG is feasible but accompanied by a higher mortality and redo CABG. This outcome is probably related to the high-risk patient category.

Conclusive remarks
What may one conclude from aforementioned findings? It may me prudent to bear in mind that widespread use of many of these techniques/approaches such as PET, NOGA, ablation of all types of atrial fibrillation or PCI immediately after CABG in mainstream patients should not be propagated considering the potential hazards and cost benefit ratios. These modalities should be implemented within standardized and expert care systems or adapted to individual cases.

For analyzing LV dysfunction, PET measurement of glucose uptake in the myocardium using FDG in patients with euglycaemic glucose insulin clamping and PET measurement of myocardial perfusion/metabolism using FDG and 13-N ammonia appears to be a time consuming technique. It requires several highly skilled and dedicated workers in an environment with necessary hardware such as a PET camera and PET dedicated isotope tracer lab.

A prerequisite for evaluation of laser therapy and VEGF gene administration on LV dysfunction is a catheterization lab equipped with a NOGA mapping system and experienced operators.

To treat refractory AF for reasonable and comparable success rates in a time efficient way, a smooth running organizational planning, secretarial facility, and electrophysiology lab working in close harmony with skilled operators is essential.

Finally, outcome of post CABG patients in the first hours after the operation, can be influenced by catheterization with or without subsequent PCI and requires close cooperation between the departments of intensive care, cardiac surgery, anesthesia and the catheterization laboratory.

In addition, outcomes of the investigations as reported in this thesis have contributed to understand pathophysiological mechanisms in complex cardiovascular disease. This may aid medical practitioners in the design and creation of clinical strategies in daily clinical practice.
Future Perspectives

The role of myocardial glucose metabolism in heart failure and a potential role of metabolic intervention is still unsolved and new data are awaited to settle this clinical mystery.

The interesting question whether laser therapy of the heart resolves myocardial ischemia has been answered. PET data in this study, amongst others, have showed that laser does not improve myocardial ischemia in measurable figures. VEGF therapy, however, is yet a promising modality for the future.

Electromechanical mapping to assess myocardial ischemia and necrosis has been shown to be a viable diagnostic tool. Newly developing techniques such as remote control catheter navigation systems (Hanson or Stereotaxis), allowing to reach all parts of the heart easier, may considerably reduce procedure time. This will facilitate the more frequent use of NOGA in routine cases.

Atrial fibrillation is a disease affecting an ever growing numbers of patients. Therapy may be divided into rate and rhythm control. Rate control will leave the patient in atrial fibrillation and centers around the control of the ventricular heart rate. Rhythm control aims for sinus rhythm. AV node ablation and pacemaker implantation is an example of rate control, pulmonary vein isolation of rhythm control. To date, there has been no proven superiority of rhythm over rate control. Pharmacological treatment is the first line therapy. Drug therapy failure or adverse effects may introduce AV node ablation and pacemaker implantation or pulmonary vein ablation as a second line therapy. The challenge of the future will be to select the right patient for the right therapy, making optimal use of limited resources. Drug therapy will probably remain the first line therapy because of more advantageous cost benefit ratios. Selected patients with serious complaints, paroxysmal atrial fibrillation of shorter duration, without a significant left atrial enlargement may be suitable for pulmonary vein isolation. Patients with longstanding atrial fibrillation, heart failure and other determinants for low success of pulmonary vein ablation may benefit more from AV node ablation and pacemaker implantation.

PCI in the first hours after CABG may be a valuable alternative for routine reoperation, when signs of acute graft failure are present. It is less cumbersome to perform and may be less hazardous in highly compromised heart failure patients. PCI after a longer time period following CABG has already been incorporated in daily practice. Our results highlight a reciprocal interaction between cardiac surgery and PCI, predominantly directed towards percutaneous strategies. Therefore, it may be argued that surgical backup is not the right term to qualify the current mutual collaboration between intervention cardiologists and cardiac surgeons.

In the management of female CABG patients, care should be taken to the uneven distribution of risk factors, whereby a better prognosis for women with heart disease may be attained.

In a more distant future, in general, one may see an expanding workload for the catheter supported technology in cardiology, backed up by several new imaging modalities.