Advanced cardiac imaging in heart failure : from subclinical myocardial dysfunction to therapy optimization

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SUMMARY AND CONCLUSIONS

The introduction of the thesis focused on the current status of literature on the role of advanced cardiac imaging in various stages of heart failure. The use of two major modalities, echocardiography and cardiac magnetic resonance, has been reviewed. Advanced echocardiographic techniques permit assessment of left ventricular dyssynchrony in overt heart failure patients and provide important prognostic data. These techniques may guide patients' selection for cardiac resynchronization therapy and device optimization. Global left ventricular longitudinal 2-dimensional strain may help detect early stages of myocardial dysfunction in diabetic patients with preserved left ventricular ejection fraction. Novel cardiac magnetic resonance imaging sequence analysis may allow tissue characterization, quantification of diffuse fibrosis and detection of early alterations in ventriculo-arterial coupling.

In **Part I**, the thesis focused on the prognostication of heart failure patients treated with cardiac resynchronization therapy. Three main determinants of outcome after cardiac resynchronization therapy have been identified: the degree of left ventricular dyssynchrony, the amount and location of scar tissue and the site of left ventricular lead implantation. The role of 3-dimensional cardiac imaging in assessing each of these determinants was reviewed in **Chapter 1**. Importantly, 3-dimensional imaging offers the possibility of assessing combined determinants of response to cardiac resynchronization therapy. Such an approach may provide further prognostic information on patients who are candidates for cardiac resynchronization therapy. Indeed, this hypothesis was further studied in **Chapter 2**. Response to cardiac resynchronization therapy was found in 86.3% of patients showing significant left ventricular dyssynchrony by 2-and 3-dimensional echocardiography modalities. In contrast, 97% of patients who did not show significant left ventricular dyssynchrony with any of the modalities were non-responders ($P<0.001$). Furthermore, the assessment of left ventricular dyssynchrony with both modalities showed incremental value for prediction of significant left ventricular reverse remodeling over its assessment with only one modality (chi-square 90.18; $P<0.001$). The use of advanced cardiac imaging also permits better understanding of the mechanisms of response and non-response to cardiac resynchronization therapy as shown in **Chapter 3**. In particular, the evaluation of the left ventricular sequence of mechanical activation by 2-dimensional radial systolic strain imaging has confirmed that resynchronization of the left ventricular sequence of activation with cardiac resynchronization therapy is an additional key determinant of patients' outcome after device implantation. Better assessment and consequent understanding of dyssynchrony pathophysiology in that uniquely challenging population may further guide therapy selection and tailoring. Left

ventricular dyssynchrony by tissue Doppler imaging assessed within 48 hours after cardiac resynchronization therapy implantation was also linked to long term outcome in **Chapter 4.** Importantly, it was shown that cardiac resynchronization therapy may induce left ventricular dyssynchrony in a subset of patients without significant left ventricular dyssynchrony at baseline. Such left ventricular dyssynchrony induction was independently linked to a worse survival (hazard ratio of 1.247 for each 20 ms increase, 95% confidence interval: 1.056-1.474, P=0.009) along with age, ischemic etiology of heart failure, baseline New York Heart Association functional class and baseline left ventricular ejection fraction. The induction of left ventricular dyssynchrony was also shown to have an important impact in a population of patients with sick sinus syndrome referred for pacemaker implantation. In **Chapter 5**, induction of left ventricular dyssynchrony measured by 2-dimensional radial strain imaging was independently associated with the combined outcome of all-cause death or hospitalization for heart failure with a hazard ratio of 3.369 (95% CI: 1.732-6.553, P<0.001) together with age. Therefore, advanced cardiac imaging techniques offer comprehensive assessment of pathophysiological aspects of heart failure and provide important prognostic data beyond conventional risk factors. Finally, **Chapter 6** focused on the role of cardiac imaging to optimize cardiac resynchronization therapy pacing delays to improve outcome at follow-up. Currently, cardiac resynchronization therapy optimization by built-in device algorithms or echocardiography does not provide further improvement in clinical or echocardiographic outcomes compared to standard device programming. Harmonization of optimization timing, techniques and selection of patients may help better define the role of cardiac resynchronization therapy optimization in clinical practice.

The second part of the thesis examined the mechanical properties and tissue characterization of diabetic patients. In **Chapter 7**, alterations in mechanical properties of the left ventricular were correlated to an increase in myocardial extracellular content assessed by post-gadolinium T1 mapping (R=-0.701 between 2-dimensional longitudinal strain and myocardial T1 time; P<0.001). Interestingly, the relationship between T1 time and left ventricular ejection fraction appeared relatively weak (R=0.14; P=0.32). Consequently, novel advanced cardiac imaging modalities such as 2D strain and T1 time appear more sensitive tools to evaluate changes in left ventricular mechanics and myocardial content than conventional tools (left ventricular ejection fraction, indices of diastolic function etc.). Interestingly, in **Chapter 8**, advanced indices of diastolic function such as left ventricular strain rate during isovolumetric relaxation and left atrial strain were strongly correlated to aortic pulse wave velocity assessed by velocimetry-encoded

magnetic resonance. These new modalities participate in defining an earlier stage of heart failure and may help to identify new targets for therapies to prevent clinical heart failure in this population.

In conclusion, advanced cardiac imaging provides invaluable information at every stage of the heart failure syndrome. It may help identify an earlier stage of the disease, help to select patients for cardiac resynchronization therapy, tailor therapies in selected individuals and offer important prognostic information. The use of these modalities is not yet part of a formal and guideline-recommended heart failure management. Furthermore, the role of advanced cardiac imaging in clinical decision making is not yet clearly defined. Future research will aim at prospectively establishing the advantages of advanced cardiac imaging driven clinical decision making and the cost effectiveness of such strategies.