

# New Echocardiographic Techniques in Rare Cardiological Disorders

Doctoral Thesis

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# 1 Introduction

The new echocardiographic techniques characterize the mechanics of myocardial contraction and relaxation precisely and have been applied in numerous cardiac disorders.

There is no substantial amount of information available in cardiac tissue Doppler analysis and deformation imaging, as in strain and strain rate imaging by speckle tracking imaging in rare cardiologic disorders, such as constrictive pericarditis (CP), restrictive cardiomyopathy (RCM) and isolated noncompact cardiomyopathy (iLVNC).

Our studies were focusing on better understanding of the functional and pathophysiological changes in the heart within the above referenced disorders by new echocardiographic techniques. In addition, we have examined the additional benefit of echocardiography guided endomyocardial biopsy (EMB) in lieu of fluoroscopic guidance alone during the procedure relative to the recognition of hitherto unreported sequels.

**1.1** Tissue Doppler imaging (TDI) has further facilitated detection of CP. There are no substantive data on mitral annulus systolic velocity and tricuspid annulus velocity in CP. The effect of pericardiectomy on mitral and tricuspid annular velocities, which may provide further insight into the mechanism of

annulus motion in CP is unknown. The aim of this study was to assess these annular velocity changes in patients with CP who underwent pericardiectomy.

**1.2** Two-dimensional (2D) speckle tracking echocardiography (STE) is a new technique, based on frame-by-frame tracking of tiny echo-dense speckles within the myocardium and subsequent measurement of left ventricular deformation.

Mitral septal annular velocity is usually increased in patients with CP and higher than the lateral annular velocity. We hypothesized that the longitudinal strain of the lateral wall that is in contact with diseased pericardium is lower than that of the medial segments in CP. Our aim was to investigate the usefulness of the ratio of medial/lateral strain measurement by STE in the differential diagnosis of CP from restrictive myocardial diseases.

**1.3** At Mayo Clinic, Rochester, MN an interventional imaging service has been developed recently, which comprises a dedicated core group of sonographers and echocardiographers who provide echocardiographic imaging support in the interventional laboratory. On our patient pool we have noted a hitherto unreported complication of right ventricular endomyocardial biopsy: acute intracardiac thrombus formation.

**1.4** We hypothesized that SMI modalities in patients with iLVNC may be useful for an early functional diagnosis complimentary to the morphological criteria currently used, as well as provide partial proof of concept that indeed, iLVNC may be an independent cardiomyopathic entity with abnormal LV function early-on despite normal standard echocardiographic measurements such as EF.

## **2 Objectives**

- to assess the characterization of the mitral and tricuspid annular velocity changes by tissue Doppler imaging in patients with CP who underwent pericardiectomy in order to get further insight into the mechanism of annulus motion in CP,
- to investigate the usefulness of the ratio of medial/lateral strain measurement by speckle tracking echocardiography in the differential diagnosis of CP from restrictive myocardial diseases,
- to perform an analysis of echocardiography-guided EMB procedures in search of new complications previously undetected by fluoroscopy alone and to describe the characteristics, procedural details, clinical significance and

treatment of patients who developed an acute right sided thrombus during the procedure and

- to determine the potential role of speckle myocardial imaging (SMI) for identifying left ventricular dysfunction in patients with isolated left ventricular non-compaction (iLVNC) who have no evidence of cardiac impairment on 2-dimensional or standard Doppler echocardiography and to establish which of the SMI modalities is the most accurate for detection of early left ventricular dysfunction in patients with iLVNC.

### **3 Methods**

The study population consisted of a total of 366 patients in the four presented studies, 288 (99 patients with CP, 189 patients who underwent endomyocardial biopsies), retrospectively enrolled patients between January 2006 and April 2009 and 80 (15 patients with CP, 15 with cardiac amyloidosis (CA), 20 with iLVNC and 40 control subjects) prospectively enrolled patients between July 2006 through 2009 at the Cardiovascular Division of Mayo Clinic, Rochester, Minnesota. The protocols of the studies were approved by Institutional Review Board of Mayo Clinic. Informed consent was given to patients enrolled in the studies. All patients underwent comprehensive

echocardiographic examination. The following statistical methods were utilized with JMP software: Shapiro-Wilk test, student t-test, Wilcoxon-test, Spearman correlation analysis, Fisher test and ANOVA.

### **3.1 Methods and study population in tissue Doppler imaging study in constrictive pericarditis**

The study population consisted of 99 patients (72 men; mean age, 58±15 years) with surgically proven CP who had comprehensive echocardiographic examination before and after pericardiectomy. Since concomitant myocardial disease can affect annulus velocities, we divided patients into two groups based on the underlying etiology of CP, i.e. primary CP (idiopathic, postpericarditis, viral etiology; n=52) and secondary CP (due to surgery or radiation; n=47). The clinical profile and echocardiographic findings for both groups were compared before and after pericardiectomy.

### **3.2 Methods and study population in speckle tracking imaging study in constrictive pericarditis and restrictive cardiomyopathy**

A total of 45 patients (15 patients with CP, 15 patients with CA and 15 control subjects), who agreed to join the present study and gave informed consent were prospectively enrolled. The longitudinal strain was assessed by 2D speckle tracking analysis

from apical four chamber views using wall motion tracking software (Toshiba).

### **3.3 Methods and patients in the echocardiography guided endomyocardial biopsy study**

We identified all patients who underwent endomyocardial biopsy at Mayo Clinic, Rochester, MN from June 2008 to April 2009 and retrospectively reviewed all the charts of patients undergoing echocardiographic guided endomyocardial biopsies. At Mayo Clinic, echocardiography is used as a supplemental imaging modality to guide EMB in patients undergoing EMB to diagnose myocardial diseases in patients with ventricular dysfunction or who are undergoing surveillance biopsies who are less than 3 months post transplant. Patients who undergo biopsies beyond 3 months post transplant usually have the procedure performed under fluoroscopic guidance alone since cardiac perforation is considered unlikely. We recorded the indication for EMB, route of biopsy, number of biopsy specimens taken and whether the procedure was complicated by thrombus formation.

### **3.4 Methods and patients in speckle tracking imaging study of isolated noncompact cardiomyopathy**

Twenty consecutive patients with a confirmed diagnosis of iLVNC were enrolled and compared to 20 sex- and age-matched

control subjects. Longitudinal systolic peak values were determined for myocardial velocity (sMV), displacement (sD) strain rate (sSR) and strain (sS). Longitudinal early diastolic peak values were determined for myocardial velocity (dMV-E) and strain rate (dSR-E) by SMI. Radial and circumferential systolic and early diastolic peak values were measured for sSR, dSR-E, and sS.

## **4 Results**

### **4.1 Results in tissue Doppler imaging study in constrictive pericarditis**

Of the 99 patients, CP was secondary to previous cardiac surgery in 34 (34.4%), previous radiation therapy in 13 (13.1%), other causes (postpericarditis, autoimmune, etc.) in 19 (19.2%), and idiopathic in 33 (33.3%). Follow-up echocardiograms were obtained  $51 \pm 131$  days after pericardiectomy. Between primary and secondary CP groups there were significant differences in  $e'$  velocities except at the tricuspid annulus.

In both primary and secondary CP groups, early annular diastolic velocities decreased significantly after pericardiectomy, whether it was medial  $e'$  ( $p < 0.0001$  and  $p = 0.0004$ , respectively), mitral lateral  $e'$  ( $p = 0.022$  and  $p = 0.013$ , respectively) or tricuspid lateral  $e'$  ( $p = 0.0005$  and  $p = 0.028$ ,



respectively). Overall, the reduction in medial e' was somewhat more significant than mitral lateral e' velocity ( $p < 0.0001$  and  $p = 0.0004$ , respectively).

There were significant differences in all s' velocities between the subgroups before pericardiectomy. After pericardiectomy, only lateral s' was lower in the secondary group. Moderate to strong correlations were observed between s' and e' as well as between s' and a' velocities before pericardiectomy. These correlations were in general weaker after pericardiectomy.

Postoperative echocardiography showed persistent features of CP in 7 patients when defined by the presence of at least two of the followings: mitral E respiratory variation, hepatic vein diastolic flow reversals with expiration or inferior vena cava plethora. At the medial annulus where postoperative data was available in all cases, s', e' and a' were not significantly different between these patients and the 92 without persistent constrictive hemodynamics (all  $p > 0.35$ ).

#### **4.2 Results in speckle tracking imaging study in constrictive pericarditis and restrictive cardiomyopathy**

Longitudinal strain was significantly higher for CP in comparison with CA in both the septal and lateral basal segments and in the mid lateral segment, whereas for mid septal segment there was no such relationship. There were also

significant differences in the longitudinal strain basal septal/basal lateral (BS/BL) and mid septal and mid lateral (MS/ML) ratios for the two diseases, respectively.

### **4.3 Results in the echocardiography guided endomyocardial biopsy study**

In 8/189 (4%) of the echocardiographically guided procedures acute thrombus was identified at the time of the biopsy, usually towards the end of the procedure, in seven patients (1 patient experienced acute thrombus formation on two separate occasions). This rare complication occurred in 5.2% within the transplanted patient pool, whereas in 7.1% amongst suspected cardiac amyloid patients. Although the majority of procedures were performed from a right internal jugular approach acute thrombus formation occurred in only 3/143 (2%) of these procedures. Thrombus occurred most frequently when a right femoral vein access site was used; 5/35 procedures (12.5%). There was no clear association between number of biopsy specimens obtained and risk of thrombus.

### **4.4 Results in speckle tracking imaging study of isolated noncompact cardiomyopathy**

Twenty patients comprised the control group (group I), 10 patients had iLVNC with EF >50% (group II) and 10 patients had iLVNC with EF ≤ 50% (group III).

Longitudinal sMVI measures were abnormally reduced in group III patients compared to the other groups. Longitudinal sD measures, as well as sSR and sS values, including most of the clusters of segments and the global mean of 18 LV segments were significantly reduced in group II compared to group I. The dMVI-E measures were also significantly reduced in group II compared to group I considering the mean of the 6 middle segments, mean of the 6 apical segments, and the anterior and anteroseptal walls. Radial and circumferential sSR, dSR-E and sS were all reduced in group III compared to the other groups, whereas only radial sS was significantly reduced in group II compared to group I.

## **5 Summary**

We present the first comprehensive analysis of systolic, early and late diastolic velocities of the mitral and tricuspid annuli in a larger number of patients with constrictive pericarditis including analysis of etiological groups and post-pericardiectomy changes. We demonstrated that medial annulus  $e'$  velocity in patients with CP is usually higher than both mitral and tricuspid lateral  $e'$  velocity, which is a reversal of the observed relationship in normal individuals and patients with restrictive cardiomyopathy. It was also found that all mitral and tricuspid

annular velocities are higher in patients with primary CP compared to patients with secondary CP. This reduction may be attributed to the effects of radiation on myocardium, coronary artery disease or cardiac surgery itself. Furthermore, all mitral and tricuspid annular velocities ( $e'$ ,  $a'$  and  $s'$ ) were shown to be decreased after pericardiectomy.

We described a previously not reported differential method for CP and RCM. We found that the differential longitudinal strain assessment by speckle tracking echocardiography can be valuable in differentiating CP from restrictive diseases.

Using adjunctive echocardiography to guide EMB we have identified acute intracardiac thrombus formation related to the procedure - a hitherto unreported complication. This may have important clinical implications in patients undergoing routine repeated surveillance EMB post heart transplantation, particularly those with a prior history of thrombosis or clotting diathesis. We recommend that these patients should undergo routine ancillary echocardiography guided EMB rather than fluoroscopic guidance alone. Procedural echocardiography permits early recognition and treatment of this complication. Further studies are required to fully analyze the clinical consequences and the application of adjunctive

echocardiography in relation to a comprehensive interventional imaging service.

To the best of our knowledge, this is the first investigation to obtain SMI measurements of all 18 LV segments in patients with confirmed iLVNC with normal and abnormal ejection fractions, and to compare these measurements to SMI measurements from healthy subjects. We observed that abnormalities of different SMI modalities, in particular longitudinal sD, sS and sSR, as well as LV rotation/torsion measures, are present in patients with iLVNC, even in those asymptomatic patients with preserved EF and normal conventional TDI measurements. These findings provide evidence of an ongoing, subclinical myopathic process related to the morphologic presence of iLVNC. Longitudinal sS and LV rotation/torsion were the most accurate SMI modalities to differentiate between these patients and controls, and thus, may serve as a physiologic diagnostic complement to the current morphology-based diagnosis.

## **6 Conclusion**

Rare cardiac disorders are often underdiagnosed or undiagnosed due to their diagnostic challenges. This can have serious clinical

consequences, when patients do not receive appropriate treatment in a timely manner, which worsens their state of health and their prognosis such as delayed pericardiectomy in case of CP patients.

Delay in RCM diagnosis may result in patients being unsuitable for the most intensive forms of treatment, since they are not fit enough to survive such treatment programs.

Acute thrombus formation during endomyocardial biopsy is a recently detected phenomena with potential serious complications in lack of appropriate diagnosis and timely therapeutic management. Patients, especially with a history of prior thrombosis or clotting diathesis, should undergo routine ancillary echocardiography guided EMB rather than fluoroscopic guidance alone.

Diagnosis of NCCM is sometimes overlooked or delayed due to its rarity and low awareness. Because of the significant potential for cardiovascular complications such as arrhythmias and sudden cardiac death, early recognition is essential.

Development of echocardiography has made a significant contribution to the accurate and increasing diagnosis of rare cardiological disorders. New techniques help the early diagnosis and differential diagnosis of rare cardiologic diseases such as tissue Doppler imaging and speckle tracking imaging. Those

also provide prognostic information and assist in patient management. Our results proved the usefulness and clinical significance of new echocardiographic techniques.

## **7 Publications**

### **7.1 Publications related to the thesis**

**Veress G**, Bruce CJ, Kutzke K, Click RL, Scott CG, Oh JK, Rihal CS. Acute thrombus formation as a complication of right ventricular biopsy. *J Am Soc Echocardiogr* 2010;23(10):1039-1044.

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**Veress G**, Apor A, Merkely B. Constrictive pericarditis nowadays. *Cardiol Hung* 2011;41;263-268.

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**Veress G**, Kim KH, Masaki M, Espinosa RE, Oh JK. Differential diagnosis of constrictive pericarditis from restrictive



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**Veress G**, Apor A, Ling LH, Kim KH, Schaff H, Espinosa RE, Tajik JA, Sundth TM, Merkely B, Oh JK. Mitral and tricuspid annular velocities before and after pericardiectomy in patients with constrictive pericarditis. *Cardiol Hung* 2011;41:F8.

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Tihanyi L, **Veress G Jr.**, Simon A, Veress G. Early and late complications of the pericardium after heart surgery by 9 years retrospective study. *Cardiovascular Rehabilitation and Prevention* 2011;3: 24-26.