clinical

MEDICAL UNIVERSITY OF VIENNA

THESIS PROPOSAL

for the Doctoral Program at the
Medical University of Vienna

Working title (without abbreviations)

Two-Dimensional Strain for the Assessment of Left Ventricular Function in Low Flow - Low Gradient Aortic Stenosis: Relationship to Hemodynamics and Outcome

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Date: 07.2013
month, year

Signature of the applicant

Summary and aim

Decision-making in patients with low flow - low gradient aortic stenosis (LFAS) mainly depends on the actual stenosis severity and left ventricular function. Both are of prognostic importance.

The multicenter TOPAS Study (true or pseudo severe aortic stenosis study) aims to develop and validate new parameters to improve the assessment of stenosis severity, myocardial impairment, risk stratification and decision making in patients with LFAS. Currently risk stratification and decision making is based on left ventricular function (contractile reserve and ejection fraction during dobutamine stress echocardiography) and the severity of the aortic stenosis (increase in transvalvular gradients and valve area during dobutamine stress echocardiography) as well as brain natriuretic peptide. Especially current methods for quantification of left ventricular function have major drawbacks. Evolving new techniques to measure left ventricular function (strain and strainrate) have not been validated in the cohort with LFAS yet but may be promising tools for risk stratification.

The aim of this TOPAS substudy is to obtain and analyze the parameters of stenosis severity and left ventricular functional impairment measured by stress echo. In addition to standard parameters left ventricular function will be quantified using speckle tracking, a software algorithm to measure myocardial deformation during the heart cycle.
Parameters obtained by this method will be strain (percentage change in lenght) and its temporal derivate strainrate. Both will be measured at rest and during peak dobutamine stress. Its relationship to hemodynamic and outcome will be assessed. Fortyseven (47) patients will be included. The relationship of speckle tracking derived parameters with hemodynamics will be assessed at rest and peak stress. Furthermore the (additional) value of these parameters for risk stratification will be assessed.

List of abbreviations:
LFAS: low flow - low gradient aortic stenosis
TOPAS: true or pseudo severe aortic stenosis study
EF: Ejection fraction
NT-pro BNP: N-terminal pro brain natriuretic peptide
LV: left ventricular
2D: two dimensional
EuroSCORE: European System for Cardiac Operative Risk Evaluation
STS-Score: Society of Thoracic surgeons score
CT: Computed tomography
PET: Positron emission tomography

Background

The determination of the stenosis severity and the degree of myocardial impairment is essential in patients with LFAS due to differences in therapeutic management. In patients with true severe aortic stenosis the culprit is seen to be the diseased aortic valve leading to or cofounding myocardial impairment. Those patients may benefit from valvular intervention. However in patients where the left ventricular impairment is the primary problem and the aortic valve is only mild or moderate diseased may not benefit from valvular intervention. Therefore the discrimination of these groups is of major importance. Echocardiography at rest is not able to distinguish between the two states. However stress echocardiography has the potential to discriminate between true severe and pseudo severe AS.
The propagation of left ventricular function is of major prognostic importance. Monin and coworkers were the first to systematically assess propagation of left ventricular function in classical LFAS patients. They used the term "contractile reserve" which is defined by an increase in stroke volume ≥ 20% measured by doppler echocardiography. They were able to demonstrate that patients with contractile reserve had a low operative risk and a good long term outcome after valve surgery (1, 2). However the absence of contractile reserve was a predictor of excess operative mortality and poor outcome in this and the following studies. Further work by the same group provided evidence that patients with LFAS and no contractile reserve on DSE may nevertheless benefit from valve surgery 66. Therefore current guidelines advocate aortic valve replacement in patients with LFAS and true severe AS with contractile reserve (Class IIa level of evidence C) (3) and patients with LFAS and true severe AS but no contractile reserve (Class IIb level of evidence C) (3). In the TOPAS cohort a peak stress LVEF≤35% was superior to contractile reserve for the prediction of mortality64. The reason for the difference between those studies may be found in the discrepant cohorts regarding comorbidities and in the differences in the dobutamine protocol(4).
Stroke volume measure by doppler as well as the volumetric Simpson method for determination of stroke volume and ejection fraction have several limitations like doppler beam angle dependency, operator dependency, and inter- as well as intraobserver variability. Measurement of myocardial strain and strainrate may overcome this limitations. There is growing evidence that strain and strainrate echocardiography provides an accurate diagnostic tool for quantification of myocardial impairment. Furthermore it might have major advantages compared to traditional echocardiographic quantification of left ventricular function. Strain and strainrate have been validated in a variety of cardiac disease however there is still a lack of evidence of its prognostic power in patients with LFAS.
In the present study 2-dimensional strain parameters measured by speckle tracking at rest and during dobutamine stress echocardiography will be used to document the extent of myocardial impairment, its relationship with hemodynamic variables, and its prognostic value.

The aim of the present study was the evaluation of left ventricular contractile function in patients with LFAS at rest and peak dobutamine stress by two dimensional strain parameters measured by speckle tracking. In particular the aims are

- To document the extent of left ventricular contractile dysfunction in patients with LFAS at rest and peak dobutamine stress.

- To investigate the relationship of two dimensional strain parameters with hemodynamic variables and currently used parameters of left ventricular function in patients with LFAS at rest and peak dobutamine stress.

- To evaluate the prognostic value of two dimensional strain parameters at rest and peak dobutamine stress.

- To investigate the incremental value of two dimensional strain parameters to currently used parameters for risk stratification (clinical risk, peak stress left ventricular ejection fraction and NT-proBNP).

Operational objectives:

1st year

Aims:

Establishing new imaging-analysis techniques at the cardiac ultrasound laboratory. In particular deformation analysis (strain and strainrate echocardiography) from either tissue doppler and speckle tracking.
Feasability check of strain and strainrate imaging by the two techniques. Continuing enrollment of patients in the TOPAS study. Establish a new way to quantify aortic stenosis severity by dobutamine stress echocardiography: the projected effective orifice area (effective orifice area at a normalized flow rate of 250mL/s).

Description:

Strain and strainrate can be calculated by two different techniques: tissue doppler echocardiography uses the shift in frequence of the reflected ultrasound beam to calculate deformation. Speckle tracking is a software algorhythm which uses the so called speckles of the 2D grayscale ultrasound loop as natural acoustic markers and calculates strain and strainrate. There are feasibility issues with both techniques. Due to the positive chronotropic effect of dobutamine, patients usually have high heart rates at peak stress dobutamine infusion which may lead to further limitations due to the Nyquist sampling criterion.
The projected effective orifice area is a new way to quantify stenosis severity in patients with low flow-low gradient Aortic stenosis. There is growing evidence that it might be superior to conventional indices of stenosis severity and may be able to overcome the important limitation of stenosis severity grading in patients with no or minimal contractile reserve.

Operational objectives:

2nd year

Aims:
Build a databank for characterization of the study cohort and for statistical analysis. In particular:
1) Medical history: risk factors (clinical risk: EuroSCORE and STSscore), concomitant disease, medication.
2) Blood pressure and heart rate (at rest and peak dobuatmine stress), age, weight, gender, NYHA functional class.
3) Blood Biomarkers: NT-pro BNP
4) Dobutamine stress echocardiography: LV volumes end-systolic and end-diastolic (at rest and peak stress), LV ejection fraction (at rest and peak stress), stroke volume by either volumetry and doppler (at rest and peak stress), mean transvalvular flow (at rest and peak stress), Aortic valve hemodynamics e.g. peak jet velocity, mean pressure gradient and effective orifice area (at rest and peak stress).
5) Experimental measures of myocardial impairment and stenosis severity: peak systolic longitudinal strain and strainrate (at rest and peak stress), the projected orifice area.

Description:
All analyses will be performed offline by a blinded observer using GE EchoPac version 7.0.0, General Electric-Vingmed. Blood sampling was/will be done according to the TOPAS protocol: after 30 min of rest just before DSE. Lithium-heparine Vacuette® (Greiner Bio-one, Austria) tubes will be used for blood collection. NT-proBNP is quantified immediately after blood collection using commercially available immunoassays (Cobas® proBNP II, Roche diagnostics GmbH, Germany). Myocardial strain and strainrate will be assessed by the speckle tracking technique. This technique has major advantages: feasable at lower frame rates than tissue doppler derived strain, insonation angle independent, good reproducibility and already validated in other patient cohorts. Speckle tracking analysis in the longitiudinal fiber direction is possible in most of the patients undergoing dobutamine stress tests.

Operational objectives:

3rd year

Aims:
Finish data acquiration for statistical analysis, in particular outcome data. Evaluating of the data for normality using Shapiro-wilk's test. Comprehensive outline of data by graphical description. Analyse of the difference in hemodynamic variables, strain and strainrate at rest and peak stress using paired-students t-test. Correlate strain and strainrate with hemodynamic data by spearmans correlation coefficient. Censoring survival times. Univariate Cox regression of baseline variables. Arrangement od data by hierarchically nested multivariable Cox regression models for analysis of increments in prognostic value of different models. Bias correction of multivariable Cox regression in case of limited events [low flow low gradient is a rare disease affecting about 5-10% of patients with AS therefore we anticipate a relatively small sample size (5,6)]. Time-dependent receiver operating characteristic (ROC) analysis (using leave-one-out cross-validated linear predictors for sample size issues) to assess the predictive accuracy of the parameters to predict two-year survival. Publish data.

Description
Characterization of the cohort [risk factors, EuroSCORE, STSscore, concomitant disease, hemodynamic variables (at rest and peak dobuatmine stress), age, weight, gender, NYHA functional class, NT-pro BNP, Dobutamine stress echocardiographic variables hemodynamics, left ventricular function, projected effective orifice area)]. Table of baseline data grouped by patients with/without events. ROC curves to predict two year survival by single variables and models of combined variables. Construction of Kaplan-Meier survival curves. Data summary, hypothesis test summary. Manuscript drafting, submission to peer reviewed journal.

Working plan

1st year

Months 1-6

Literature research on speckle tracking echocardiography, strain and strain rate echocardiography, low flow low gradient aortic stenosis. Summary of current knowledge and study design.
Grant writing and application. Coordination of the substudy with the principal investigator, request for data from other centers collaborating in the TOPAS project (Canada: Laval University Quebec, University Ottawa Heart Institute; Germany: University Hospital Muenster)
Screening and recruitment of patients in the context of the echocardiography laboratory of the Vienna general hospital for the multicenter TOPAS study. Screening of the recruited patients for eligibility for the substudy.

Baseline visit coordination of new patients: Informed consent, prearrangement of dobutamine stress echocardiography, prearrangement of CT and PET scans, blood biomarker sampling, conduct 6 minutes walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index.
Analysis of dobutamine stress echocardiography and completion of online and hardcopy data forms. Analysis of 6 minutes walk tests and EuroSCORE.
Follow up visit coordination of already included patients: echocardiography appointment scheduling, prearrangement of dobutamine stress echocardiography. Analysis of follow up echocardiography (including 1-year follow up dobutamine stress echocardiography of patients in the medically treated group) follow up blood biomarker sampling. Discharge echocardiography and blood biomarker sampling. conduct 6 minutes walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index. Analysis of 6 minutes walk tests and EuroSCORE.

Working plan

1st year

Months 7-12

Literature research on speckle tracking echocardiography, strain and strain rate echocardiography, low flow low gradient aortic stenosis. Summary of current knowledge and study design.
Grant writing and application. Coordination of the substudy with the principal investigator, request for data from other centers collaborating in the TOPAS project (Canada: Laval University Quebec, University Ottawa Heart Institute; Germany: University Hospital Muenster)
Screening and recruitment of patients in the context of the echocardiography laboratory of the Vienna general hospital for the multicenter TOPAS study. Screening of the recruited patients for eligibility for the substudy.

Baseline visit coordination of new patients: Informed consent, prearrangement of dobutamine stress echocardiography, prearrangement of CT and PET scans, blood biomarker sampling, conduct 6 minutes walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index.
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Working plan

2nd year

Months 13-18

Analyze the patients already included in the substudy. Design and build-up of a data base for the patients included in Vienna. Speckle tracking analysis of strain and strainrate in an 18-segment model at rest, low dose dobutamine infusion and peak stress dobutamine infusion.

Calculation of standard echocardiographic parameters at rest, low dose dobutamine infusion and peak stress dobutamine infusion (LVEDV, LVESV, SV, Biplane Simopson EF, SV by doppler echocardiography, peak and mean pressure gradients, mean transvalvular flow rate, ejection time, time to peak aortic jet velocity, maximum velocity of the aortic blood flow) Calculation of the projected valve effective orifice area (valve area at a normalized flow rate of 250mL/s).

Statistical analysis of the collected data and preliminary results. Phrasing abstracts for international meetings.

Baseline visit coordination of new patients: Informed consent, prearrangement of dobutamine stress echocardiography, prearrangement of CT and PET scans, blood biomarker sampling, conduct 6 minutes walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index.
Analysis of dobutamine stress echocardiography and completion of online and hardcopy data forms. Analysis of 6 minutes walk tests and EuroSCORE.
Follow up visit coordination of already included patients: echocardiography appointment scheduling, prearrangement of dobutamine stress echocardiography. Analysis of follow up echocardiography (including 1-year follow up dobutamine stress echocardiography of patients in the medically treated group) follow up blood biomarker sampling. Discharge echocardiography and blood biomarker sampling. conduct 6 minutes walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index. Analysis of 6 minutes walk tests and EuroSCORE.

Working plan

2nd year

Months 19-24

Analyze the patients already included in the substudy. Design and build-up of a data base for the patients included in Vienna. Speckle tracking analysis of strain and strainrate in an 18-segment model at rest, low dose dobutamine infusion and peak stress dobutamine infusion.

Calculation of standard echocardiographic parameters at rest, low dose dobutamine infusion and peak stress dobutamine infusion (LVEDV, LVESV, SV, Biplane Simopson EF, SV by doppler echocardiography, peak and mean pressure gradients, mean transvalvular flow rate, ejection time, time to peak aortic jet velocity, maximum velocity of the aortic blood flow) Calculation of the projected valve effective orifice area (valve area at a normalized flow rate of 250mL/s).

Statistical analysis of the collected data and preliminary results. Phrasing abstracts for international meetings.

Baseline visit coordination of new patients: Informed consent, prearrangement of dobutamine stress echocardiography, prearrangement of CT and PET scans, blood biomarker sampling, conduct 6 minutes walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index.
Analysis of dobutamine stress echocardiography and completion of online and hardcopy data forms. Analysis of 6 minutes walk tests and EuroSCORE.
Follow up visit coordination of already included patients: echocardiography appointment scheduling, prearrangement of dobutamine stress echocardiography. Analysis of follow up echocardiography (including 1-year follow up dobutamine stress echocardiography of patients in the medically treated group) follow up blood biomarker sampling. Discharge echocardiography and blood biomarker sampling. conduct 6 minutes walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index. Analysis of 6 minutes walk tests and EuroSCORE.

Working plan

3rd year

Months 25-30

Baseline visit coordination of new patients: Informed consent, prearrangement and enforcement of dobutamine stress echocardiography, prearrangement of CT and PET scans, blood biomarker sampling, conduction of 6 minute walk tests, medical history and physical evaluation, NYHA functional class evaluation, execution of the Duke activity status index.
Analysis of dobutamine stress echocardiography and completion of online and hardcopy data forms. Analysis of 6 minutes walk tests and EuroSCORE.
Follow up visit coordination of already included patients: echocardiography appointment scheduling enforcement of echocardiographic exams, prearrangement of dobutamine stress echocardiography and enforcement of dobutamine stress echocardiography exams. Analysis of follow up echocardiography (including 1-year follow up dobutamine stress echocardiography of patients in the medically treated group) follow up blood biomarker sampling. Discharge echocardiography and blood biomarker sampling. conduct 6 minute walk tests, medical history and physical evaluation, NYHA functional class, the Duke activity status index. Analysis of 6 minute walk tests and EuroSCORE.

Working plan

3rd year

Baseline visit coordination of new patients: Informed consent, prearrangement and enforcement of dobutamine stress echocardiography, prearrangement of CT and PET scans, blood biomarker sampling, conduction of 6 minute walk tests, medical history and physical evaluation, NYHA functional class evaluation, execution of the Duke activity status index.
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Timelines

	1st year		2nd year		3rd year	
	Months 1-6	Months 7-12	Months 13-18	Months 19-24	Months 25-30	Months 31-36
Literature research on speckle tracking echocardiography, strain and strain rate echocardiography, low flow low gradient aortic stenosis. Summary of current knowlege and study design. Screening and recruitement of patients						
Grant writing and application. Coordination of the substudy with the principal investigator, request for data from other centers collaborating in the TOPAS project. Establishing new techniques (strain, strainrate, projected effective orifice area) Sample size calculation. Screening and recruitement of patients						
Analyzation of the patients already included in the substudy. Design and build-up of a data base for the patients included in Vienna. Screening and recruitement of patients						
Build a databank for characterization of the scohort and for statistical analysis. Screening and recruitement of patients						
Outline data by graphics, preliminary results. Drafting first abstracts. Finishing data acquiration for statistical analysis, in particular outcome data. Statistical analysis: Correlation of hemodynamic variables with strain and strainrate. Cox regression, ROC curves to predict two- year survival						
Statistical analysis: Multivariable Cox regression for models and increments in prognostic power. Manuscript drafting and submission						