Research protocol; Research project in cardiovascular medicine

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Prediction of heart failure and mortality by echocardiographic parameters and artificial intelligence in individuals with left bundle branch block - "Echo LBBB"

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List of abbreviations:

LBBB = left bundle branch block	CAD = coronary artery disease
ECG = electrocardiogram	LV = left ventricle/left ventricular
PVP = predominant ventricular pacing	CRT = cardiac resynchronization therapy
PM = pacemaker	BP = blood pressure
AI = artificial intelligence	HBP = his bundle pacing
NPR = Norwegian Patient Registry	EF = ejection fraction
RBBB = right bundle branch block	MACCE = major adverse cardiovascular and cerebral

1 Background

This study is a cardiovascular study, especially relevant for the elderly population, aiming to identify individuals with left bundle branch block (LBBB) who are at high risk for developing heart failure and increased risk for cardiovascular morbidity and mortality. In patients with LBBB, cardiac resynchronization therapy (CRT) has the ability to reverse heart failure and reduce morbidity and mortality with high effectivity (1,2). However, CRT is an invasive procedure with inherent short- and long-term complications and a substantial rate of non-responders. Improved patient selection will be needed for better outcome of an already well-established therapy. Low-risk patients with stable conditions need to be identified to be assigned to an individually adjusted follow-up. Thus, careful selection of potential CRT responders at the appropriate time-point is crucial for optimal patient treatment. For the time being, the identification of high and low-risk patients is the most important step before new randomized controlled trials for CRT treatment should be conducted.

LBBB is relatively common in the cardiovascular patient population and is known to be associated with increased risk for the development of congestive heart failure and risk for mortality (3). However, asymptomatic individuals with structurally normal hearts can also have LBBB. Prognosis of LBBB in population-based studies is highly dependent on age and comorbidity (4-8). Both, population based, and clinical studies demonstrate that electrocardiogram (ECG) criteria and clinical findings alone are not specific enough to develop risk assessment algorithms for cardiovascular morbidity and mortality in the LBBB population, thus the number of publications of the natural history of LBBB has rapidly decreased since 2005. However, recent experimental and clinical studies using modern echocardiographic tools as well as computer models for regional deformation imaging of the heart have given new insights into the pathophysiology of LBBB and the interplay between delayed electrical activation of parts of the left

ventricle (LV), and the presence of myocardial scars. Only recently the equal effect of loading and QRS on dyssynchrony has been better understood. Artificial intelligence (AI) can use information from strain-curve analysis together with other echocardiographic and clinical information to identify patients at risk and treatment responders (9). Based on these new insights, this study aims to investigate the potential of new echocardiographic and AI methods, in combination with clinical information and afterload assessment (ventricular dimensions and geometry combined with blood pressure (BP)). These easily obtainable parameters might hopefully become a new cornerstone for development of risk-assessment algorithms as a basis for individual treatment recommendation.

The recent development of ultrasound-based quantification of dyssynchrony seems to be a promising tool for individual risk-stratification(10-12). Patient at risk might undergo timely CRT treatment before heart failure is fully established or the mortality risk increases. To the best of our knowledge this will be the first longitudinal study on echocardiographic functional markers for dyssynchrony in the general LBBB population. Additionally, AI algorithms will hopefully improve identification of patients at risk for heart failure development. The aim is to identify the time-point when a stable state with LBBB turns into deteriorating heart failure, which is probably the best time-point when specific treatment needs to be applied and heart failure can be reversed.

This study will include prospectively clinical patients from the cardiological outpatients' clinics, and the cardiology wards in University Hospital of North Norway Tromsø and Harstad, Akershus University Hospital, Lørenskog, Oslo University Hospital, Rikshospitalet, Haukeland University Hospital, Bergen and Nordlands Hospital, Bodø. Furthermore, we intend to use retrospectively collected data of population-based study from the Katholieke Universiteit (KU) Leuven, Belgium and invite participants with LBBB or predominant ventricular pacing (PVP) from the Tromsø 7 study for the prospective study. The study is furthermore open to include retrospectively datasets where subjects with LBBB or PVP can be identified and echocardiographies are taken (e.g. St. Olav Hospital, Trondheim). Prospectively included patients will be followed by a repeated echocardiography study after one year and access to patient registries through 5 years (eventually up to 15 years). All studies abroad will follow their own study protocol and follow-up.

1.1 Epidemiology and etiology

LBBB occurs frequently in various cardiac diseases of differing etiology. The presence of LBBB has been reported to adversely affect prognosis even in individuals who have no symptoms or known cardiovascular disorders and LBBB has been an incidental finding on ECG. Thus, individuals with LBBB are reported to have increased risk of death or heart failure (13,14).

LBBB almost never occurs before 35 years of age, suggesting it could be an acquired condition (15). In population-based studies the prevalence of LBBB ranges between 0.1 and 0.8% (3,7,16). The prevalence of LBBB strongly correlates with age with an average age at LBBB diagnosis being 70 ± 10 years in men and 68 ± 11 years in women (17). Proportion of those with LBBB increases progressively from <1% at age of 50 to 6% by 80 years (17,18). Factors found to be associated with its development included arterial hypertension, coronary artery disease (CAD), valvular heart disease, cardiomyopathies, myocarditis which all are states with known myocardial macro- or micro fibrosis (15,17). Recent human and animal studies suggest gene expression of connexin 40 and 43 to be involved in the development of LBBB and cardiomyopathy (19,20).

1.2 Prognosis

To date there is no consensus on LBBB-related prognosis as study results are clearly influenced by study design, population size, selection criteria and age (21). In 1979 the Framingham Study (4209 subjects, 55 with LBBB) (6) showed a clear association between LBBB and main cardiovascular diseases, such as hypertension, cardiac enlargement and CAD. Coincident with or subsequent to the detection of LBBB, 48% of these individuals developed congestive heart failure. Within 10 years from LBBB detection, cardiovascular mortality was 50% and at 18 years follow-up only 11% of subjects with LBBB remained free of detectable cardiovascular abnormalities. Several studies showed that once a LBBB is established, the prognosis worsens with age, established CAD or congestive heart failure (3,5,7,22,23). In patients with acute myocardial infarctions with LBBB, 30 days mortality, in-hospital death and 1 year's mortality were reported to be substantially increased (3,22,24,25).

1.3 Pathophysiology

In addition to patients with “spontaneous” LBBB, pacemaker (PM)- patients with PVP often develop conduction disturbances resembling an electro-mechanical activation pattern of a LBBB. LBBB or PVP result in regionally delayed electrical activation with comparable hemodynamic effect (26).

Individuals with LBBB or PVP develop delayed electrical activation of the lateral wall of the LV (27). During the septal contraction, the intraventricular pressure rise is low. The delayed lateral wall contraction leads to stretching of the septum during the ejection phase, which does not contribute to further pressure generation or stroke volume. Consequently, the regional work load of the septum is reduced, while the work load of the lateral wall increases due to initial pre-stretch. Perfusion imaging shows relative septal hypoperfusion (28,29). Animal-models have shown an unfavorable effect on LV remodeling including LV dilatation, asymmetric hypertrophy and decreased pump function (29), altered cellular Ca ++ transport and a pro-arrhythmic state (15). Deformation of the mitral valve apparatus with annular dilatation and dyssynchronous papillary muscle contraction lead to development and progression of functional mitral regurgitation (30,31) which aggravates heart failure development. However, the presence of LBBB alone seems not to cause ventricular dysfunction and heart failure. First, when the LV starts to become dyssynchronous and inefficient (32,33) a vicious cycle starts with progressive LV failure and progression of the conduction abnormality as well (34,35).

Recent computational, experimental and clinical studies showed the deleterious role of increased afterload, causing higher wall stress, when either the ventricle is dilated, or intraventricular pressure is high. These conditions seem to influence the degree of dyssynchrony and seem to contribute substantially to reduced cardiac performance when delayed electrical activation is present (36-38). These recent publications seem to be the missing link to be able to predict the prognosis on individual basis.

1.4 Specific therapy

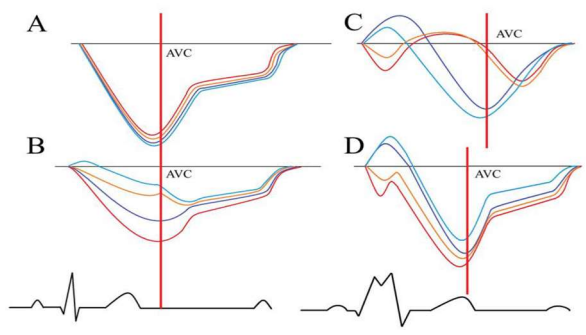
Development of heart failure might be disrupted by specific treatment such CRT where two ventricular PM leads are implanted at two opposite sites. This type of cardiac pacing provides resynchronized electrical activation of the LV. CRT has become one cornerstone of heart failure treatment of patients

with LBBB. According to current guidelines, only patients with established heart failure are being assigned to CRT (39).

Recent studies have focused on predicting response to CRT when heart failure is established (10,16,26,40). Dependent on criteria used for implantation of CRT devices, 30% and 50% are non-responders to CRT (41). This high number indicates either inappropriate patient-selection or irreversibly decreased ventricular function. Based on response defined by echocardiographic measures of volume or ejection fraction modern imaging modalities have been developed in order to predict outcome-prediction for CRT. Additionally, these modalities have shown to be of incremental value for outcome-prediction when a CRT is implanted (26,40).

1.5 "Novel echocardiographic indices"

Modern echocardiographic modalities like segmental strain imaging allows to visualize and quantify the typical early shortening of the septum followed by the delayed contraction of the lateral wall (10). This pattern has an important prognostic value in patients with established heart failure as its absence was shown to be associated with unfavorable outcome after CRT implantation with increased risk of death or transplantation (40). Computer models could show that the typical strain-patterns changed in dependence on global regional contractility of the septum and lateral wall.



Strain-patterns of different segments
A: normal synchonous contraction pattern.
B: regionally reduced myocardial function.
C: CPD (classic pattern dyssynchrony)
D: delayed electrical activation with synchronous late-systolic contraction.

Patients responded to CRT treatment when typical patterns for electro-mechanical dyssynchrony were present. These patterns can be quantitatively assessed by newly developed algorithms (42). In addition to qualitative and quantitative strain-curve analysis "LV workload quantification" and "analysis of energy loss and waste of myocardial work" have been recently introduced as new echocardiographic measures(43) also applicable in the presence of dyssynchrony (12). These are based on strain imaging combined with BP measurements, where strain loop areas can be derived. It has been demonstrated that

contraction of the septum in patients with LBBB and chronic heart failure perform a net negative work (systolic lengthening) while after CRT positive work (systolic shortening) increases dramatically (11). In small patient populations myocardial work showed to be a good indicator for CRT response(44).

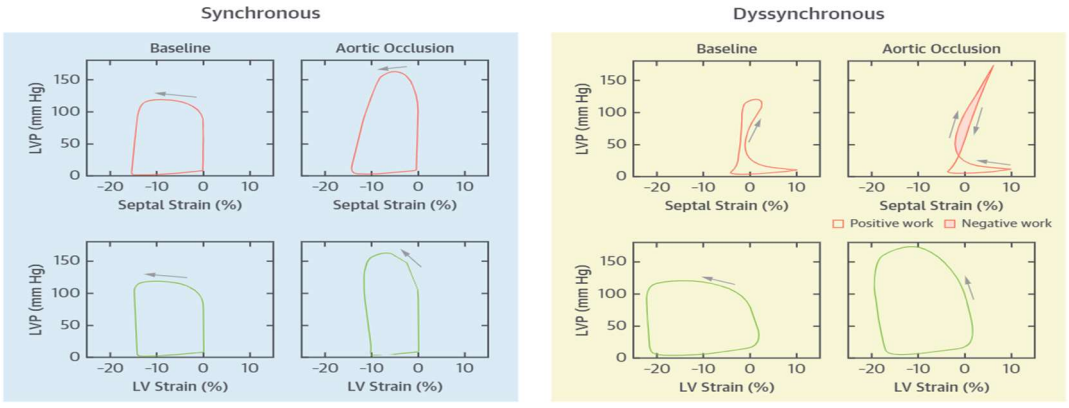


Figure 2: Pressure strain curves in simulations with narrow QRS complex and with LBBB, and changes with afterload. The area under the curve expresses segmental myocardial work in the septum (upper row) and lateral wall (lower row) (F.Prinzen, E.Willem, J. Lumens JACC-CVI 2019)

1.6 Integration of multifaceted data by artificial intelligence

All these new echocardiography-based measures have significantly improved our understanding of the nature of LBBB, its cardio-mechanic effect and the hemodynamic consequences of abnormal electrical activation. Thus, these new measures alone have high potential to improve the selection of adequate treatment strategy. Furthermore, it had been shown that the presence of LBBB morphology on ECG is not always associated with typical mechanical patterns. 30% of patients with LBBB on ECG selected for CRT did not have typical contraction patterns as indicated by speckle tracking strain echocardiography (40). The mismatch between ECG and myocardial mechanics was independently associated with increased risk of adverse outcome. Conversely typical dyssynchrony patterns were observed in 20-26% of patients without typical LBBB morphology at ECG, where the majority responded to CRT (26). All these findings clearly demonstrate that echocardiography may have high potential for accurately selecting patients needing CRT independently of ECG morphology.

As a result of computer-models (38), experimental and clinical studies (36), the interplay of delayed electrical activation, afterload, global and regional myocardial function and the influence on ventricular dyssynchrony or inefficient myocardial work is much better understood. In addition to ECG criteria and

assessment of ejection fraction (EF), echocardiography renders useful information about ventricular loading and function. However, to date CRT management is only based on EF, QRS length, LBBB morphology and NYHA class with a failure rate of still >30% (41). Several echocardiographic studies on CRT response have shown that the failure rate would be expected to be dramatically reduced if imaging would be involved (40,41,45,46).

The development of heart failure and its reversibility is dependent on multiple factors. Unsupervised AI algorithms are recently developed tools being able to integrate individual phenotypic subgroups and identifying isolated characteristics based on strain-curves, echocardiographic phenotypes, flow characteristics, genetics and co-morbidities. A recent important publication has re-analyzed the randomized MADIT CRT study population using AI and were able to identify subgroups with substantially better CRT-outcome in a AI selected patient group with a HR of 0,31 on mortality and adverse cardiovascular events compared to ICD treated patients (9), while the original outcome of the study did not show significant risk reduction by CRT treatment overall.

According to these recent publications, the present study intends to use AI algorithms including evolved echocardiography-based imaging modalities like strain imaging and regional work assessment. We aim to show that these are promising tools to improve assessment of patients with LBBB to identify patients at risk for development of heart failure that might respond to early medical treatment preventing the development of heart failure or identifying patients early who will respond to CRT treatment.

1.7 Clinical significance:

LBBB is highly prevalent among patients with chronic heart failure (25%). Morbidity and mortality are high among patients with LBBB, but ECG detected LBBB has not been shown to be a sufficiently accurate predictor of outcome. Early medical treatment or CRT for carefully selected individuals might help to lower morbidity and mortality among individuals with LBBB or PVP. However, criteria for an optimal time-point and patient characteristics for CRT responders are still missing.

In conclusion, the study aims to identify new predictors for the appropriate time point for initiating specific treatment, as well as specific patient characteristics for treatment response based on AI and novel echocardiographic measures. Risk- algorithms for heart failure and increased mortality are

urgently needed in this large group of cardiological patients (25% of heart failure patients). Studies on patients with CRT have demonstrated high specificity of echocardiographic parameters when heart failure is established. Other newer parameters like “septal and lateral work” and as well as integration of all accessible features by AI have been recently introduced and shown to provide a powerful tool for differentiating degrees of dyssynchrony in patients with LBBB. This study aims to contribute to a more specific patient selection for specific heart failure treatment, when LBBB or PVP is present. Patients with His bundle pacing (HBP) might provide synchronous pacing and are also included as a special control-group for patients with permanent ventricular pacing.

2 Hypotheses, aims and objectives:

2.1 Primary hypotheses

1. Typical strain-pattern and myocardial work assessment improve substantially prediction of heart failure development, hospital admission, death and adverse cardiovascular events and can help to establish more effective patient selection criteria for CRT or medical heart failure treatment.
2. AI, incorporating strain imaging and myocardial work assessment as well as conventional clinical patient characteristics is able to improve additionally risk assessment and treatment response in the LBBB population

2.2 Secondary hypotheses

1. Patients with high afterload have typical dyssynchrony patterns with earlier deterioration of cardiac function over time.
2. Repetition of echocardiographic assessment and clinical parameters increases accuracies of outcome-prediction.
3. Predictors for major adverse cardiovascular and cerebrovascular events (MACCE) indicate also CRT- or medical treatment- response. These factors might be useful indicators for risk reduction through treatment of carefully selected patient-groups
4. Patients showing ability to increase or sustain myocardial work during a stress test with no classic pattern of dyssynchrony have a good long-term prognosis.
5. HBP can prevent development of heart failure compared to usual ventricular pacing.

2.3 Primary objectives:

1. To identify patients with LBBB eligible for timely CRT treatment by evaluating myocardial work by echocardiography as predictors in for a) deterioration of myocardial function, b) risk for mortality, c) heart failure development and hospital admissions d) risk for MACCE
2. To investigate the ability of AI to improve risk assessment and treatment response in the LBBB population

2.4 Secondary objectives:

1. To investigate the dependency of strain-patterns on afterload and ventricular geometry
2. To investigate the predictive value of repeated echocardiographic measures after one year
3. To compare indicators for increased morbidity and mortality risk with indicators for CRT or medical treatment response
4. To assess development of strain-patterns for dyssynchrony, ventricular volume and clinical and echocardiographic parameters for systolic function over time in dependency on myocardial work during stress testing
5. To compare outcomes between usual ventricular pacing and HBP.

3 Project arrangements, method selection and analyses

3.1 Patients

This is a longitudinal prospective cohort-study intending to include at least 1000 patients with LBBB from University Hospital of North Norway Tromsø and Harstad, Akershus University Hospital, Lørenskog, Oslo University Hospital, Rikshospitalet, Haukeland University Hospital, Bergen and Nordlands Hospital, Bodø, over a 2-year inclusion period.

Information about present and previous diseases, medication, surgical- or invasive treatment, PM, ICD or CRT implantation, clinical examination and present and previous echocardiographic imaging and blood samples (Hb, Thrombocytes, CRP, Kreatinine, eGFR, Urate, HbA1C, Cholesterol, ProBNP, Troponins, ALAT and Ferritin) will be accessed by the patient`s journal.

All prospective study participants will answer one customized and two standardized (EQ5D and HeartQoL) questionnaires. They will undergo general clinical investigation comprising height and weight measurements, baseline ECG, blood samples when not found in the patient`s journal, standardized BP measurements and echocardiography with a 3 minutes- hand-grip test at baseline and in a 18 month follow-up study.

Clinical outcome data including death and hospital admissions due to heart failure and CRT implantation will be assessed after 3 and 5 years (eventually after 10 and 15 years) by linkage to data from the patient`s clinical records through access to Norwegian Patient Registry (Norsk pasientregister (NPR)), Norwegian Causes of Death Registry (Dødsårsaksregisteret) and Norwegian Cardiovascular Disease Registry (Hjerte- og karregistereret).

St Olavs Hospital, Trondheim, might provide retrospective patient data with echocardiography loops, where outcome-data will be extracted from the same registries.

3.2 Population-based studies:

In addition to the prospective study, we intend to include retrospective data from a population-based study with echocardiography from Katholieke Universiteit Leuven, Belgium. This study has already been approved for baseline echocardiography and follow-up assessment. Participants with LBBB or PVP of the Tromsø 7 study will be invited to be prospectively included into the study-population from University Hospital of North Norway, Tromsø .

3.3 Planned inclusion of participants of Tromsø 7

The main focus of this study is to identify individuals with LBBB or ventricular pacing who have characteristics for stable disease or those who are soon developing clinical heart failure.

Asymptomatic Individuals with LBBB are usually not referred to the cardiologist. In order to create a suitable control-algorithm for these stable diseases and to identify individuals who present with subclinical heart failure who are in need of either medical treatment or even CRT it will be important to include the broad spectra of patients and “healthy” participants of epidemiological studies. ECG of the participants of Tromsø 7 have been analyzed and we wish to include all participants with increased QRS width >130ms and LBBB configuration or predominant ventricular pacing, excluding those with

RBBB configuration. Echocardiography in individuals with LBBB and predominant ventricular pacing is clinically indicated.

3.4 Primary outcome

Deterioration, stability or improvement of markers for myocardial function over time. Outcome-variables will be measured by deterioration or non-deterioration of LV function by defining deterioration of ventricular function by using either echocardiographic parameters that are classically used for the definition of CRT responders: EF decrease by >5% with EF initially <55% or >10% with EF initially ≥ 55%, LV diastolic or systolic volume enlargement by 10%, NYHA class deterioration or proBNP increase by >10%.

3.5 Secondary outcomes

Hospital admissions, adverse cardiovascular events, mortality, CRT implantation and initiation of medical treatment for heart failure.

3.6 Inclusion criteria

Patients with typical LBBB, thus QRS complex >130 ms and R-wave duration in V6 >70 ms or atypical LBBB or patients with predominantly ventricular pacing will be included. Atypical LBBB is present, when the Minnesota code criteria for typical LBBB are not met, at a QRS of >130ms and the absence of right bundle branch block (RBBB). Several subgroups will be defined as follows: 1. PM dependent patients with ventricular pacing over 50% including new implanted PM with AV block grade 3 or in need of heavy rate reduction (His bundle ablation), 2. Bundle branch block following acute myocardial infarction. 3. Baseline investigation of patients with CRT indication will be performed shortly before CRT implantation. In case of already implanted CRT, in addition to the inclusion to the prospective study, previous echocardiograms will be retrospectively analyzed for strain-patterns, ventricular geometric properties and clinical assessment from the patient`s records. Patients with HBP will be included as a control-group.

3.7 Exclusion criteria

Typical RBBB. No ability to give informed consent, non-cardiovascular co-morbidities with reduced life-expectancy < 1 year or patients with complex congenital heart disease.

In-hospital patients will be included during the in-hospital period and the baseline echocardiogram and BP monitoring will be performed as part of the routine clinical investigations. From the “Out-patients’ clinics the patients will be recruited after assessing ECGs from patient`s records.

In a Pilot-study feasibility of patient recruitment will be tested. The incidence of heart failure and deterioration of ventricular function in the first 100 included patients will be assessed in order to define the power of the final study-population size.

3.8 Echocardiography

Participants will be examined with transthoracic echocardiography using a commercially available system (Vingmed Vivid E9 or E95 with M4S-RS Sector Probe, General Electric Healthcare, Horten, Norway). The general echocardiography protocol, optimizing imaging loops for two-dimensional speckle tracking analyses and myocardial work analysis and the generation of wall stress-strain loops.

3.9 Artificial intelligence

An unsupervised AI algorithm (Multiple Kernel Learning and K-means clustering) will be used to categorize subjects by similarities in clinical parameters, LV volume, wall stress and deformation traces at rest and after hand-grip test. All available input data will be converted into a compact representation space where subjects are positioned according to their similarity. Afterwards subjects will be clustered with K-means algorithm to identify phenotypically-distinct categories patients with adverse outcomes.

3.10 Statistical power

It is unknown how high the percentage in this study population will be who suffer from deterioration of LV function. Therefore, a pilot-study on the first 100 study-subject of the different subgroups will be performed in order to calculate the power of the final population size. Pilot participants will be included into the final study population. Assuming different proportions of 5%, 10%, 20% and 30% of patients with deteriorating ventricular function, a difference in septal or global strain between at 5% at a SD of ±6% the sample size needed for hypothesis 1 in each subgroup will be 220, 129, 73 or 57, respectively for a two-sided test and a Type I error of 0.05.

For calculation of hazard-ratios between patients with against without deterioration of LV function for the primary outcome variable: hospital admission due to CVD, assumed that 5% of all patients either

deteriorate function and the presence of decreased segmental work indicates at least a relative risk of 1.8, at an alpha of 0.05 with 500 patients included, the statistical power will be 82%.

3.11 Statistics

Patients with deteriorating myocardial function will be identified by increasing proBNP by more than 10%, increasing NYHA class, increasing diastolic volume by more than 10% and/or decreasing EF by more than 5%. ANOVA will be used to compare parameters between patients with deteriorating myocardial function and those with unchanged clinical condition after one year. ROC curve analysis will serve to find the ideal cut-off values for continuous variables and assessing sensitivity and specificity of the tests. Univariate and multivariate logistic regression tests will be performed in order to identify the most powerful parameters predicting development of heart-failure with hospital admissions as primary outcome and predicting death (or transplantation) as secondary outcome.

3.12 Data management

Data from patient`s visit and patient`s journal will be stored as de-identified data in an a password secured internet-based database (Viedoc). Viedoc is approved by The Norwegian Data Protection Authority for use in scientific studies. Echocardiographic data will be stored as de-identified DICOM files including locally performed measurements, labeled by the patient`s study ID, all ECGs will be taken in digitalized format and be stored as de-identified image files as well as DICOM files. All de-identified files will be locally stored at a dedicated server. Key files coupling personal patient information to ID`s will be stored locally on a server with restricted access. All de-identified ECGs, echocardiography-studies and key-files will be centrally collected at University Hospital of North Norway, Tromsø, latest after end of the second patient`s visit. Echocardiographic data will be analyzed in the core-lab at University Hospital of North Norway, Tromsø. Readers of the strain-data will be blinded for the outcome-data. Other researchers assess outcome-data from NPR and The Norwegian Cause of Death Registry will be added to the database. The de-identified dataset and DICOM images from echocardiography and ECG will also be transferred to NTNU Trondheim for automated reading of the echocardiographic imaging and AI purposes.

3.13 Participants, organization and collaborations

The following Co-workers and institutes are involved:

The main-supervisor Assami Rösner, cardiologist, consultant, and associate professor is expert in strain imaging. Henrik Schirmer is the supervisor`s main co-worker at UiT The Arctic University of Norway and has been involved in project-planning and writing. Helge Skulstad is also specialist on strain-imaging and has been involved in development of myocardial work assessment. Espen Holte is strain-expert and also involved in AI processes performed in NTNU, Mai-Tone Lønnebakken, Harald Kjekshus, Knut Tore Lappegård and Siri Malm will be local project leaders. Lasse Løvstakken is professor in engineering, conducting the AI process in his institute, NTNU Trondheim. Tatiana Kouznetsova is specialist in strain-imaging in context with epidemiologic research and is one of the first who implemented myocardial work into her epidemiological studies. Tove Aminda Hanssen will lead research about quality of life assessment.

4 Plan for activities, visibility and dissemination

Data collection will start after final Regional Ethics Committee (REK) and Data Protection Officer (PVO) approval. A long-term follow-up of at least 5 years, possibly 10 to 15 years is planned after an inclusion period of at least 2 years plus one-year clinical control. A core-lab will be established in Tromsø for analyses of all echocardiographic measurements and post-processing. University Hospital of North Norway, Tromsø will coordinate and assess the quality of data acquisition and database from the different centers. All registry-data from NPR and The Norwegian Causes of Death Registry as follow-up data will be retrieved by a dedicated research administrator.

4.1 Communication/planned publications

At least three contributing centers will form a central steering-committee to coordinate planned publications. Upon study completion and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results. The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations. Personnel who have contributed significantly with the

planning and performance of the study may be included in the list of authors (Vancover convention 1988).

4.2 Plan for implementation

The strategy of the cardio-vascular research group of Institute of Clinical Medicine, UiT The Arctic University of Norway and the Heart-lung clinic, University Hospital of North Norway, Tromsø, supports the topic of cardiovascular imaging, including improvement and implementation of new cardiac imaging modalities, thus also strain-imaging. Morbidity and mortality in the heart failure population is high and often associated with the presence of LBBB (25%) in the heart failure population. This project has high potential to render results being implemented into clinical use with facilitating patient-selection for early and successful treatment, thus preventing further disease-development and hospital-admissions. Thus, the study is central in improving patient care, reducing progress of chronic cardiac disease and reduction of hospital-admissions. We hope that the results of the study help to establish a substantially improved patient selection for CRT treatment.

4.3 User involvement

Tor Bosch from Landsforening for hjerte lunge syke (LHL) is the patient-representative in the Heart-lung clinic, University Hospital of North Norway, Tromsø.

He has been an active part in planning of the study, he has initially worked out the patient information and consent and given shared considerations about patient recruitment. He or other patient-represents from LHL will be active in distributing the results to potential users.

5 Ethical considerations

Data collection for the current study is approved by the Ethics Committee “Regional committee for medical and health research ethics (REK2019/134)”. All data collection and storage have been done in accordance with the regulations for data protection including the appropriate use of written informed consent by study participants. Data made available for scientific analysis is de-identified and excludes personal identifiers. All patients have signed a written informed consent. The transfer of data between institutions is de-identified, while the key files of all Norwegian hospitals will be transferred to University Hospital of North Norway, Tromsø .

5.1 Intellectual property rights:

The project is not confounded with intellectual property rights issues that would cause restrictions regarding the dissemination and use of the results.

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