Quality of life, fatigue and autonomic dysfunction in patients with heart failure: association with symptoms of low mood and depression – a protocol for an observational cross-sectional study.

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Protocol

1. Plain English summary

Many people in the North East and North Cumbria have heart failure, some of whom will also suffer with depression. Having both conditions is particularly difficult. It means you are more likely to have a worse quality of life, feel more tired (fatigued) and are more likely to need hospital treatment for your heart failure. It also increases the chances of poor outcomes, such as heart transplant or death. It is much harder to diagnose depression in people with heart failure, so you may be less likely to access specialist mental health support. Also, the usual treatments for depression (talking therapies and medication) do not appear to be helpful in patients with heart failure.

The autonomic nervous system controls the unconscious activity in our body. It has an important role in regulating heart rate. Normally there is variation to the heart rate: sometimes the heart beats a little faster and sometimes a little slower. We call this 'heart rate variability' and it is a sign of a healthy heart. Heart rate variability is often reduced in heart failure and in depression. Therefore, we wonder if dysregulation of the autonomic nervous system is an important link between heart disease and mood, leading to worse outcomes.

We want to learn more about depression in people with heart failure. We will interview people with heart failure and collect information about their mood, tiredness, quality of life and autonomic nervous system function. Many people with heart failure have implanted heart monitors. They allow us to measure their heart rates, and we will use these data to study heart rate variability – this will be an indicator of autonomic nervous system function. A single blood test will be taken to understand how well the heart is functioning, so that we can correlate heart disease severity with our findings.

2. Background

Heart failure (HF) and depression are leading causes of morbidity and mortality (Savarese and Lund, 2017; World Health Organization, 2017). It is estimated that about a quarter of patients with heart failure will also have depression (Rutledge et al., 2006). Depression leads to a particularly high symptom burden in patients with HF. Suffering with the comorbidity worsens quality of life (QoL) (van Jaarsveld et al., 2001), more than doubles the number of heart failure related clinic visits, increases heart failure related hospitalisations by 50% and more than doubles the risk of heart transplant or death (Sullivan et al., 2004; Rodriguez-Artalejo et al., 2005). Depression has been identified as the strongest predictor of decline in health status in HF patients, independently of HF aetiology, functional class, B-type natriuretic peptide (BNP) level or left ventricular ejection fraction (Rumsfeld et al., 2003). Altogether, comorbidity with depression increases overall health costs for HF patients by over a third (Smith et al., 2012).

Depression remission in HF patients is associated with improvements in physical and social function, QoL and performance in the 6-minute walk test (Xiong et al., 2012). However, depression in HF patients is often unresponsive

to antidepressant medication and psychological therapies (Zambrano et al., 2020). This is a significant problem, given the impact of depression on patients with HF, and how common the comorbidity is. Depression, even when not associated to cardiovascular disease, is often difficult to treat (McAllister-Williams et al., 2020). Factors that make depression difficult to treat include difficulties with psychosocial and cognitive function (Groves et al., 2018; Cha et al., 2017). Fatigue, a common and distressing HF symptom (Williams, 2017), is also a core symptom of depression. In HF, fatigue is associated with poor prognosis (Smith et al., 2010), reduced QoL and comorbid depression (Evangelista et al., 2008). Therefore, the overall picture is that of a cluster of correlated symptoms, shared by HF and depression. Direction of causality is not clear, but the overall effects negatively impact patients' quality and duration of life.

There is limited evidence, but it is possible that the negative interactions between HF and depression are mediated by the autonomic nervous system (Angermann and Ertl, 2018). Imbalances in the autonomic nervous system contribute to worsening HF and increase mortality (Nolan et al., 1998). They have also been independently associated with depression (Sgoifo et al., 2015), fatigue (Slomko et al., 2020), cognitive impairment (Thayer et al., 2009) and poor quality of life (Renno-Busch et al., 2021). The vagus nerve is central to the autonomic nervous system, controlling much of the unconscious activity in our body, including regulation of heart rate. Heart rate variability (HRV) can be used as a proxy for autonomic function in both HF and depression (Sgoifo et al., 2015; Bilchick et al., 2002), being associated with depression status in HF (Walter et al., 2019). Vagus nerve stimulation (VNS) is useful in difficult to treat depression (Aaronson et al., 2017), improving QoL (Conway et al., 2018). VNS has also been researched in HF (Anand et al., 2020; Zannad, 2019), where improvements to QoL were also noted. The mechanisms behind this are not clear. We do know that VNS causes changes to HRV in both HF (Nearing et al., 2020) and depression (Sperling et al., 2010). Therefore, HRV could be a useful proxy to study autonomic function in patients with comorbid HF and depression, helping to understand its relation with symptom burden.

HF is a complex disease to manage, with many different demands being placed on patients, their families and care teams. Given this and the overlap in symptoms, comorbid depression can be challenging to diagnose. Similar difficulties can be experienced in identifying fatigue, poor QoL or cognitive problems. Tools such as questionnaires can be very helpful at identifying people who need extra help and referring them to the appropriate teams. If these tools are shown to match up well with a full medical assessment, they can be deployed earlier and wider, potentially helping more people.

Currently there is a lack of research in this group of patients, as the comorbidity is often an exclusion factor for trials. Addressing the imbalance between regional prevalence and research activity in both heart failure and in mental health has been identified as a priority locally. We need to better understand the underlying mechanisms, but it is clear that interactions between heart failure and depression lead to worse clinical outcomes. If the mechanisms are shared and related to autonomic dysfunction, we could develop treatments that address this directly, having a specific impact in improving patient's quality of life and reducing symptom burden.

3. Aims and objectives

This pilot study has the following aims:

Primary goal: Determine the relationship between depression scores and fatigue, QoL, cardiac, cognitive and autonomic nervous system function in patients with HF.

Longer terms goals:
1) Determine the level of agreement between a full structured interview and the application of self-rated questionnaires for the assessment of mood, fatigue, quality of life and autonomic nervous system function in patients with HF.
2) Determine prevalence of depression in HF in the North East.

The ultimate goal is to generate pilot data for future studies. We hypothesize that depression in HF is associated with autonomic nervous system (ANS) dysfunction, and that this correlates with fatigue and quality of life, opening a pathway for possible future targeted treatments.

4. Methods

4.1. Data Sources

a) Structured interview informed by the Mini-International Neuropsychiatric Interview (MINI).
b) Clinical information from participants' Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) clinical records.
c) THINC-it cognitive screening tool.
d) Beck Depression Inventory II (BDI-II) for depression severity.

e) The Quick Inventory of Depressive Symptomatology (QIDS), clinician (QIDS-C_{16}) and self-rated (QIDS-SR_{16}).
f) 5-level EuroQol 5D version (EQ-5D-5L) scale for quality of life.
g) 21-item Minnesota Living with Heart Failure (MLHF) questionnaire for quality of life.
h) Multi-dimension fatigue inventory (MFI).
i) Composite Autonomic Symptom Scale-31 (COMPASS-31) self-rating questionnaire for autonomic function.
j) HRV data downloaded from the participants' cardiac implantable electronic device (CIED).
k) N-terminal pro-brain natriuretic peptide (NT-proBNP) level obtained from blood test.

4.2. Study design

4.2.1. Setting

This will be an observational cross-sectional study run at NuTH, with involvement of staff from the Cumbria, Northumberland, Tyne and Wear (CNTW) NHS Foundation Trust and Newcastle University. NuTH are sponsoring the research.

4.2.2. Inclusion criteria

- ≥ 18 years of age.
- Open to the Heart Failure clinics at the Freeman Hospital or Royal Victoria Infirmary (RVI), NuTH.
- Diagnosis of heart failure with reduced ejection fraction (HFrEF) - severe left ventricle systolic dysfunction (LVSD) with ejection fraction (EF) < 35%.
- Cardiac implantable electronic device (CIED) implanted, such as cardioverter-defibrillator (ICD) or cardiac resynchronisation defibrillators (CRT-D).
- Able to provide written informed consent.

4.2.3. Exclusion criteria

- Previous diagnosis of bipolar affective disorder, psychotic disorder or personality disorder.
- Previous diagnosis of dementia.
- Previous diagnosis of primary neurological injury (eg, anoxic injury, stroke or traumatic brain injury) or disorder (eg, Parkinson's disease).
- Myocardial infarction (MI) within the previous 3 months.
- Not fluent in English.

4.3. Recruitment procedure

Figure 1 summarizes the flow of patient recruitment and data collection during the study.
Appendix 1 is a schedule of procedures for this study.

4.3.1. Patient identification

The CIED registry from NuTH will be searched for trial eligibility by members of the usual direct care team. The CIED registry will not be accessed by members of the research team not involved in direct clinical care. No other clinical records will be screened for patient identification. Once potentially eligible patients are identified, the respective responsible consultant cardiologist will be contacted to confirm suitability, before any study invitation is done. Study patient information sheets will also be handed over to eligible patients during clinic visits at NuTH.

4.3.2. Initial contact

After suitability is confirmed by the usual care team, an invitation letter will be sent on behalf of the responsible consultant cardiologist, part of the direct clinical care team. The invitation letter will ask permission to share contact details with the research team. Together with the invitation letter, we will send a patient information sheet and contact details for the opportunity to discuss the study further with a member of the study team. Eligibility and study invitation will be documented in the clinical notes by members of the study team, as per NuTH standard operating procedures.

4.3.3. Informed consent

Patients interested in participating will be invited to meet a member of the study team. The potential participants will have a minimum of 24 hours after receiving the information sheet to reflect and get in touch with the study team to discuss any concerns relating to the study, before they are invited to meet. This meeting will be an opportunity to discuss the study further, answer any questions and obtain written informed consent for participation. This meeting will preferably be done virtually, via a secure videoconference channel or via phone. Alternatively, this meeting can be embedded into a planned clinical visit for management of the CIED, to reduce burden. It will be made clear participation in the study has no impact on clinical care.

Written informed consent can be obtained in several ways, as per the participants preference:
a) Online via secure form on REDCap (e-Consent).
b) By returning to the study team a signed paper consent form via post.
c) By signing a paper consent form during the consent visit.

The consent visit and respective outcomes will be documented in the clinical notes by a member of the study team, as per NuTH standard operating procedures.

4.4.4. Participant registration

After informed consent is obtained, each participant will be given a study specific individual identifier number. This will allow for pseudonymization of all study data, with the individual identifier number being used to label each research record. An electronic password protected record containing the full name, date of birth, Trust ID number / NHS number will be used to link the individual identifier number to the patient identity. This will allow us to identify patients on study and their visit dates. This linked record will be kept on NuTH Trust computers and will be only accessible by the research team, being kept separate from the pseudonymized study database. No data allowing for individual identification (real-world identifiers) will be stored within study databases, apart from the linked record.

4.4. Study procedures

4.4.1. Self-reported questionnaires

After informed consent is obtained, participants will be asked to complete self-reported questionnaires in their own time. Preferably these will be completed online, via REDCap. If participants prefer, paper copies can be used instead and the information transcribed entered by study staff. Participants might also prefer face-to-face support to complete the questionnaires. This will be checked by a member of the study team. We estimate that the self-reported questionnaires will take 60 minutes to complete. The questionnaire sequence will be consistent to avoid confounding.

The following questionnaires will be applied:

a) Beck Depression Inventory II (BDI-II)

   The BDI-II is a self-report scale with 11 items, developed to assess severity of depression, based on recall for last 2 weeks. It has been validated in HF (Lahlou-Laforet et al., 2015) and in post-myocardial infarction patients (Smarr and Keefer, 2011). One of the concerns motivating the development of the second version of the BDI was to address the overlap between somatic symptoms from medical illness and depression (Delisle et al., 2012).

b) The Quick Inventory of Depressive Symptomatology - Self-rated (QIDS-SR_{16})

   The QIDS is a 16-item scale of depression severity, derived from the 30-item Inventory of Depressive Symptomatology (IDS), available in both self-report (QIDS-SR_{16}) and clinician-rated (QIDS-C_{16}) formats (Rush et al., 2003). It is based on recall for the last 7 days. It has been validated in patients with difficult to treat depression (Bernstein et al., 2007) and in patients with chronic medical disease (chronic kidney disease) (Jain et al., 2016).

c) 5-level EuroQol 5D version (EQ-5D-5L) scale

   The EQ-5D-5L is a self-rated instrument for describing and valuing health (Herdman et al., 2011). It includes five dimensions in its descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each with 5 levels, as well as a visual analogue scale for overall health. It has been validated in HF patients (Boczor et al., 2019).

d) 21-item Minnesota Living with Heart Failure (MLHF) questionnaire for quality of life in people with heart failure.

   The MLHF is a self-rated instrument to assess quality of life in HF patients (Middel et al., 2001). It has 2 domains, the physical (8 items) and the emotional (5 items), with each item being scored on a 6-point Likert-type scale. The MLHF has been mapped to the EQ-5D-5L in patients with heart failure (Kularatna et al., 2020).

e) Multi-dimension Fatigue Inventory (MFI) to assess fatigue.

The MFI is a self-rated instrument to assess fatigue (Smets et al., 1995). It has 5 dimensions (General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity), for a total of 20 items. It has been used in patients with HF and comorbid depression (Bunevicius et al., 2011). A simple fatigue visual analogue scale (0 - 100cm) will be added at the end of the MFI.

f) Composite Autonomic Symptom Scale-31 (COMPASS-31)

The COMPASS-31 was derived from the gold standard Autonomic Function Testing (AFT) and consists of 6 domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor), providing an autonomic symptom score that ranges from 0 to 100 (Sletten et al., 2012). The COMPASS-31 is self-rated and has excellent internal validity and test-retest reliability, with a medium to strong convergent validity (Sletten et al., 2012; Treister et al., 2015).

Patients will be contacted by a member of the study team 2-4 weeks after the questionnaires are sent out, to confirm these have been completed and to book the study visit.

4.4.2. Study visit

Apart from an initial meeting to obtain informed consent, there will be only one study visit. We estimate the whole visit will take 90 minutes. The following will be completed during the study visit:

a) Structured interview

The objective of the interview will be to establish a clinical diagnosis of depression informed by the Mini-International Neuropsychiatric Interview (MINI). The MINI is a short structured diagnostic interview developed for DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998). The major depression (current) module of the MINI will be used in this study. The interview will be conducted face-to-face by a member of the research team with specialist training in the assessment of mood disorders (Psychiatry higher trainee), at the Freeman Hospital or RVI (NuTH).

b) The Quick Inventory of Depressive Symptomatology - Clinician-rated (QIDS-C_{16})

This will be completed by the member of the study team delivering the interview. No direct input from the participant will be required. The components are identical to the self-rated version, already described.

c) The THINC-it cognitive screening tool

The THINC-it was designed to screen for cognitive dysfunction in patients with depression (McIntyre et al., 2017). It is comprised of the 5-item Perceived Deficits Questionnaire (PDQ-5), in addition to four traditional objective cognitive assessments, which have been reconfigured and gamified for computer-based administration. It will be completed using a tablet.

d) Obtain a blood sample to test for N- terminal pro-brain natriuretic peptide (NT-proBNP) level

Bloods will be collected by a member of the study team (either a medical doctor or a screen). A single sample will be required.

If a first diagnosis of depression is made during the study visit, and if the participant is agreeable, a letter will be sent to their GP recommending the usual referral pathways are followed. In the unlikely event that a participant presents in a mental health “crisis”, the member of the study team conducting the interview will directly contact the appropriate Crisis Resolution and Home Treatment Team and inform the participant’s GP.

4.4.3. Other sources of data

a) CIED heart rate data

Heart rate data will be downloaded from participants’ CIEDs. This can be done remotely using the clinical tools already in place and doesn’t require any relevant time commitment: the patient only needs to press a button before going to bed. We will be looking at data already being routinely collected for clinical

purposes. Collection of data from the CIED does not require any change whatsoever to its normal clinical functioning and will be done by specialist NuTH staff, members of the usual care team. The main variable of interest will be the R-R intervals in milliseconds. This can then be computed into HRV measures of interest.

b) Information from patients' NuTH clinical records

Data will be collected by an appropriately trained delegated member of the study team. The following data will be collected:
• Demographic information including age, sex, gender identity, sexuality, ethnicity, marital status and occupation.
• Physical health diagnosis.
• Mental health diagnosis.
• Current medication, including doses.
• Medication taken over the previous year, including doses.
• New York Heart Association (NYHA) functional classification, when available.
• Left Ventricular Ejection Fraction (LVEF) and left ventricular dimensions, calculated from echocardiogram, when available.
• NuTH records are linked to the regional Health Information Exchange, which includes clinical information from other specialist care providers and the GP. This will be accessed to ensure completeness of the information listed above. No additional information will be extracted from the Health Information Exchange.

4.5. Data collection and storage

This will be an observational cross-sectional study and data collection will occur conceptually at only one point in time. Figure 1 summarizes the flow of patient recruitment and data collection during the study. Completed consent forms and other patient documents with identifiable personal information will be kept in the site file, which is kept in a locked officer within the Cardiology Research Department, accessed only by the NuTH Cardiology Research Team. All other study generated data will be stored on REDCap, a secure web application for building and managing online surveys and databases. Each member of the study team with access to the REDCap database will have an individual and password protected login. All study generated data will be stored directly on REDCap or inputted into REDCap by a member of the study team, namely:

a) Self-reported questionnaires will be delivered preferentially online via REDCap. Questionnaires completed on REDCap will be automatically entered into the study database. REDCap will allow participants to start the questionnaires, save progress and finish them later. Participants will be asked to complete the questionnaires over the shortest amount of time they can manage, so that all answers relate to approximately the same period of time. If the participant is unable to complete the questionnaires online, or if that is the preference, these can be completed on paper and later inputted into the study database on REDCap by a member of the study team. Questionnaires completed on paper will be stored in the site file.
b) The THINC-it cognitive screening tool will be delivered using a tablet device. The results are stored on the device memory using a date and time stamp, but no participant information. Results will be entered into the study database on REDCap by a member of study team. The source data will be exported to an Excel spreadsheet, kept on a secure online storage and a print-out stored in the site file. After export, the source data will be deleted from the tablet device.
c) Results of the NT-proBNP blood test will be reported on the clinical ICE online platform used by the NuTH blood sciences department. A member of the study team with access to ICE will input the date of sample collection and results into the study database on REDCap.
d) CIED heart rate data will be collected by a member of the usual care team in NHS computers. This data will be pseudonymized and given a unique study identifier. It will then be shared with a member of the study team (Psychiatry higher trainee) via secure NHS.net email addresses, to be analysed in Newcastle University computers. No patient identifiable data will be transferred to Newcastle University computers. Once statistical outputs are obtained, data will be inputed into REDCap by a an appropriate member of the study team.
e) Clinical data will be collected from the participants NuTH clinical records by an appropriate individual, either NuTH staff or a member of the research team. This data will be inputted into the study database on REDCap.

Patient identifiable data will only be stored in NuTH computers and never transferred elsewhere. An electronic password protected record containing full name, date of birth, Trust ID number / NHS number will be used for a patient ID Log, in order to identify patients on study and their visit dates. This record will be kept on NuTH Trust computers and will only be accessible by the research team

In line with NuTH Trust guidelines, personal data will be stored for up to 12 months. All data generated by the study

will be stored for up to 5 years after the last data is collected, to allow adequate time for review, reappraisal or further research, and to allow any queries or concerns about the data, conduct or conclusions of the study to be resolved. Any paper documentation, including the master file will be archived in line with local procedures in secure storage provided off site. Access will be restricted by appropriate staff by locking the storage room. During the consent procedure participants will be informed of this.

4.6. Data analysis

4.6.1. Planned sample size

No formal power calculations have been conducted, as this is a pilot study. The target sample size for analysis will be 30 patients. The study was costed for a total of 50 patients, which is the sample we want to obtain for more accurate estimates to inform future applications. This is in line with other exploratory studies in the field.

4.6.2. Quantitative analysis

Effect sizes for the variables of interest will be calculated, to perform power and sample size calculations for future studies.

The pseudonymised and coded quantitative data will be imported to SPSS for analysis. Variables of interest will be compared between those with and those without a diagnostic of depression, using univariate analysis. As the diagnosis of depression will be operationalized as a dichotomic variable, we will perform a logistic regression using depression as the dependent variable; selection of independent variables for the logistic regression will be informed by the univariate analysis.

5. End of study

The end of study will be date of the final visit from the last participant.

6. Patient and Public involvement and engagement

In the early stages of study design we met with the NECTAR (Newcastle Cardiovascular Trials and Research) patient group, the RDS (Research Design Service) NENC consumer panel and the VOICE Research Support Group. They have been helpful in:

- Considering the overall design, including number of visits and options for delivery of questionnaires online. We considered that some participants might prefer face-to-face support to complete this.
- Discussing that our study explores themes – such as suicidal ideation – potentially distressing for some participants. We explored how to best manage this.
- Improvements to the participant information sheet (PIS). This included clarification of the project summary and schedule of events.
- UK English localization work on the questionnaires.
- Consideration of safeguards around patient recruitment, blood sampling and confidentiality of heart rate data from ICDs.

7. Governance and ethical considerations

The Newcastle upon Tyne Hospital NHS Foundation Trust (NuTH) will be sponsoring the research. It has been reviewed by the Joint Research Executive Scientific Committee (JRESC), representing NuTH and Newcastle University.

Ethical approval to be sought via the Health Research Authority (HRA) process.

8. Funding

This study has been reviewed by the JRESC, representing NuTH and Newcastle University. Following that review process, it has been awarded a research grant of £11,547 by the NuTH charity.

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9. Study location and contacts

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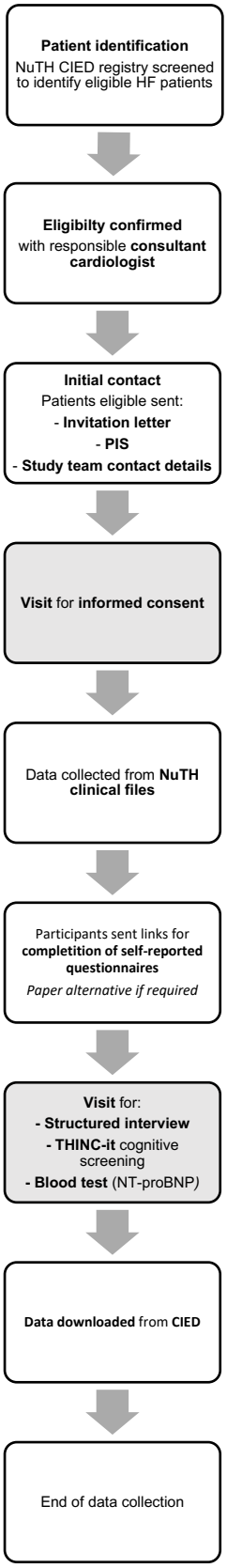
Figure 1. Flow of patient recruitment and data collection during the study



Appendix 1. Schedule of procedures

Study period	Enrollment	Baseline	Study visit
Timepoint	Week -2	Week 0	Week 2-4
Enrollment			
- Eligibility screen	X		
- Informed consent	X		
Procedures			
- Clinical records data collection		X	
- Self-reported questionnaires . BDI-II . QIDS-SR16 . EQ-5D-5L . MLHF . MFI . COMPASS-31		X	
- Interview			X
- THINC-It cognitive scale			X
- Blood sample collection			X
- ICD heart rate data collection		◄	►