Evaluating venous compliance in heart failure

Alfred HREC Number: **HREC/81404/Alfred-2021**

Alfred Project Number: 1/22

Principal Investigator: Prof David Kaye

Associate Investigators: Assoc Prof Justin Mariani, Dr Shane Nanayakkara, Dr Hitesh Patel, Dr Jason Bloom, Ms Donna Vizi, Ms Liz Dewar, Ms Jia Tang, Mr Nik Hemsley, Mr Justin Lineham

Version Number: v.1

October 2021

1 EXECUTIVE SUMMARY

Executive Summary: This is a single centre, investigator-led study of venous compliance in patients with heart failure (heart failure with reduced ejection fraction: HFrEF and heart failure with preserved ejection fraction: HFpEF) and the relationship with central haemodynamics.

Objectives: To assess the relationship between measures of venous compliance and central haemodynamics as assessed during clinically indicated right heart catheterisation.

To cross-correlate venous compliance with

- echocardiographic measurements
- renal function (eGFR)
- medications

Sample size: We aim to recruit 25 HFrEF, 25 HFpEF patients and 20 healthy controls.

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Heart failure is a complex clinical disorder with characteristic signs and symptoms, in which abnormalities of cardiovascular structure and function are the underpinning pathophysiologic mechanism. Whilst the range of methods available to assess the function of the heart has expanded markedly, the majority provide information that has a limited correlation with the true mechanical properties of the heart and blood vessels. For example, whilst echocardiography can provide key information regarding the size of the cardiac chambers and their capacity to eject (e.g. the left ventricular ejection fraction, LVEF), it is well known that the LVEF has a limited relationship with the actual contractile properties of the myocardium. The latter discrepancy is explained by the sensitivity of the myocardium to both preload and afterload. As such, the most informative and accurate way to represent the function of the ventricular (or atrial chambers) is by simultaneously measuring the pressure and volume of the chamber to construct a temporal profile of systolic and diastolic performance, the so-called pressure volume loop (Figure 1 below).

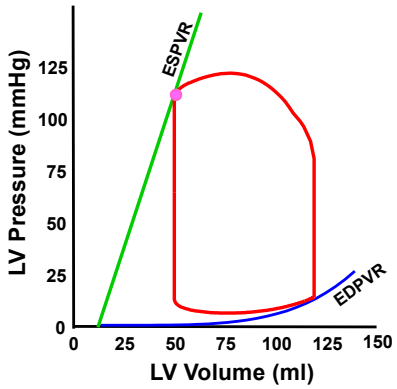

Fig 1. LV pressure volume loop

Accurate construction of the LV pressure volume loop requires sophisticated cardiac catheter techniques utilising a specialised conductance catheter that senses both pressure and volume. By obtaining this data it is then possible to define a contractile state (represented by the end systolic pressure volume line -ESPVR) and a diastolic stiffness state (end diastolic pressure volume relationship - EDPVR). Finally, to obtain the most accurate assessment of each of these true mechanical measures it is also preferable to vary the venous return (i.e. preload) typically by partial balloon occlusion of the inferior vena cava.

Whilst the above approach can be performed in patients (and has been conducted previously in other studies in the Department of Cardiology cardiac catheterisation laboratories) it is both time consuming and challenging to perform. As such, the development of sophisticated mathematical models of the circulation provides an alternative and quite accurate way of understanding the mechanical properties of the entire circulation. These models are based on electrical circuits (e.g. Figure 2 below)

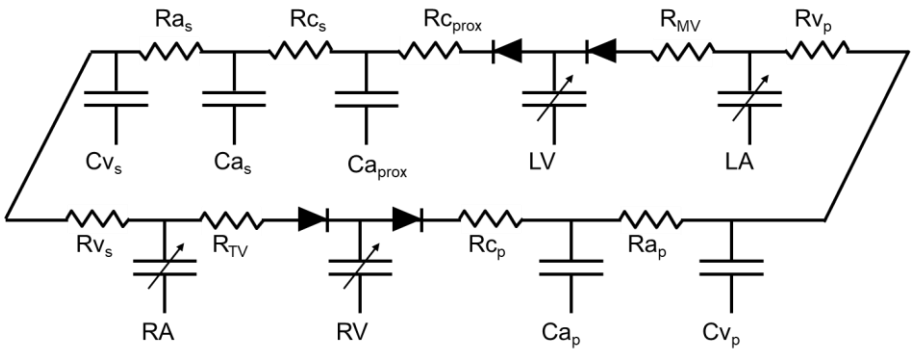

Fig 2: Circulatory model comprising characteristic proximal aorta, arterial and pulmonary resistance (Rc_{prox}, Rc_s and Rc_p), arterial and pulmonary vascular resistance (Ra_s and Ra_p), resistance to venous return (Rv_s and Rv_p), systemic and pulmonary arterial and venous compliance (Ca_s and Ca_p, Cv_s and Cv_p) and LA, LV, RA and RV chambers

With the inclusion of clinically obtained data, application of models such as these can be used at the level of an individual patient to develop a model of the entire circulation. Preferably clinical data to be included in such models includes the systemic blood pressure, left ventricular ejection fraction, cardiac output, right atrial pressure, pulmonary artery pressure and pulmonary capillary wedge pressure. All of these parameters can be provided during routine clinical echocardiography and right heart catheter studies.

One parameter that is of central importance is the venous pressure that drives the return of blood to the heart, i.e. preload. Venous pressure is determined by the amount of blood in the venous component of the circulation and the stiffness/tone of the venous vasculature. Our studies suggest that the increased venous pressure in HF patients could be the result of an increase in the blood volume, but the relative contribution of venous stiffness is not known. The aim of the study is to assess venous stiffness in a range of HF patients.

3 AIMS

To measure venous stiffness in HF patients and to correlate this with measures of HF severity.

4 STUDY DESIGN

VISIT SUMMARY TABLE:

(screening & study days are separate visits for healthy volunteers only)	**Screening Procedures**	**Study Procedures**	**Follow up (Phone call)**
Day of study	**Day -7 (±7)**	**Day 0**	**Day 7**
Informed Consent	**X**		
Inclusion/exclusion criteria check	**X**		
Physical examination	**X**		
Electrocardiogram (ECG)	**X**		
Medication Review	**X**		
Vital Signs	**X**		
Peripheral blood test	**X**		
Trans-thoracic echocardiogram (TTE) (if not one available within 3 months)	**X**		
Venous compliance test & blood collection		**X**	
Adverse Event report		**X**	**X**
Study review and close			**X**

Healthy (age matched**) Control Subjects: (n=20)** will be recruited by advertisement through newsletters, website and media. Subjects will undergo a detailed medical history check and clinical examination, together with the investigations outlined below. These subjects will not undergo right heart catheterisation.

Heart Failure Patients (up to n=50): Patients undergoing clinically indicated right heart catheterisation for the evaluation and management of heart failure.

Inclusion Criteria:

- Heart failure either HFpEF (n=25) or HFrEF (n=25)
- NYHA II-IV.
- Ischaemic or non-Ischaemic aetiology.
- Stable heart failure therapy for 1 month (a <50% adjustment to diuretics is permissible)
- Healthy volunteers aged 45-70 years old

Exclusion Criteria:

- Prior heart transplantation
- Complex congenital heart disease
- Unstable heart failure requiring high dose inotropes (milrinone >15ug/min, dobutamine >5 ug/kg/min or adrenaline > 2ug/min) or mechanical circulatory support.

Sample Size Estimate: We estimate that 25 HFrEF, 25 HFpEF and 20 controls will be required based on prior studies.

5 STUDY PROCEDURES

- **Medical history and concomitant illness:** will be obtained by interview to review eligibility.
- **Medication history:** will include medications currently taken and prescription medications taken up to 12 weeks before Consent/Screening. Assessment of eligibility will include a review of permitted and prohibited medications.
- **Vital signs**, **anthropometric measurements** and **physical examination:** will be conducted at the times detailed in the study schedule. NYHA class will be determined.
- **12 lead electrocardiogram (ECG):** will conducted by the study team. Any new clinically significant abnormalities will be reported to the patient's medical practitioner.
- **Trans-thoracic echocardiogram (clinically indicated):** data will be obtained from clinically indicated studies. Parameters will include chamber dimensions, LVEF, IVC diameter, RV strain, TAPSE and LV GLS.
- **Right heart (Swan-Ganz) catheterisation (clinically indicated – HF patients only):** A 7 Fr venous introducer sheath will be placed in an appropriate cubital vein in the right cubital fossa or the right internal jugular vein under local anaesthesia, using ultrasound guidance. Routine clinical data will be collected including right atrial, pulmonary artery and pulmonary capillary wedge pressure and cardiac output.
- **<u>Venous compliance</u>:** Venous compliance will be assessed after the right heart catheter is complete. A 20 Gauge Introcan intravenous cannula will be placed in the left cubital fossa vein (under ultrasound as required). A blood pressure cuff will be placed about the level of the cannula. The cuff will be slowly inflated to 30 mmHg in stepwise increments to progressively obstruct venous flow. Venous pressure will be measured from the intravenous cannula. The forearm volume will be measured by strain gauge plethysmography as has been done in our group for >20 years. Arterial (brachial) flow velocity will be measured by Doppler ultrasound. The diameter of a forearm vein will also be measured via ultrasound at each step. **Blood samples:** Blood will be drawn for NTproBNP levels, FBE and renal function. 20mL of blood will be drawn for analysis in Prof Kaye's lab at the Baker Institute. Inflammatory cytokine levels will be analysed by ELISA or Luminex (multiplex).
- **Statistical analysis:** Venous compliance curves will be constructed as a function of venous pressure and the forearm volume and the venous diameter (as separate curves). Between group comparisons will be performed by Student's t-test. Correlation with measures of haemodynamic severity will be performed. Statistical analysis will be performed using SPSS or R.

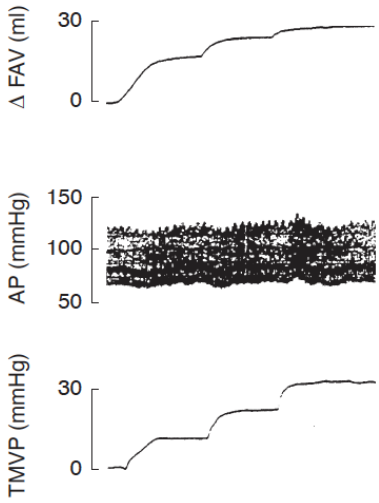

Fig 3. Forearm volume (FAV) during venous cuff inflation (TMVP). From Wilkinson BrJClinPharm 2001.