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**The Impact of Preload Reduction with Head-up Tilt Testing on Longitudinal and Transverse Left Ventricular Mechanics: A Study Utilising Deformation**

**Volume Analysis**

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**KEY WORDS** Left ventricle, 2D- echocardiography, preload, strain, volume

## ABSTRACT

Background: Left ventricular (LV) function is dependent on load, intrinsic contractility and relaxation with a variable impact on specific mechanics. Strain ( $\epsilon$ ) imaging allows the assessment of cardiac function however the direct relationship between volume and strain is currently unknown. The aim of this study was to establish the impact of preload reduction through head-up tilt (HUT) testing on **simultaneous** left ventricular (LV) longitudinal and transverse function and their respective contribution to volume change.

Methods: A focused transthoracic echocardiogram was performed on 10 healthy male participants ( $23 \pm 3$  years,) in the supine position and following 1 min and 5 min of HUT testing. Raw temporal longitudinal  $\epsilon$  (Ls) and transverse  $\epsilon$  (Ts) values were exported and divided into 5% increments across the cardiac cycle and corresponding LV volumes were traced at each 5% increment. This provided simultaneous LV longitudinal and transverse  $\epsilon$  and volume-loops (deformation-volume analysis - DVA).

Results: There was a leftward- shift of the  $\epsilon$  -volume loop from supine to 1 min and 5 min of HUT,  $p < 0.001$ ). Moreover, longitudinal shortening was reduced ( $p < 0.001$ ) with a concomitant increase in transverse thickening from supine to 1min, which was further augmented at 5min ( $p = 0.018$ ).

Conclusions: Preload reduction occurs within 1 minute of HUT but does not further reduce at 5 minutes. This decline is associated with a decrease in longitudinal  $\epsilon$  and concomitant increase in transverse  $\epsilon$ . Consequently, augmented transverse relaxation appears to be an important factor in the maintenance of LV filling in the setting of reduced preload. DVA provides information on the relative contribution of

mechanics to a change in LV volume and may have a role in the assessment of clinical populations.

## **ABBREVIATIONS**

CO = cardiac output

DVA = deformation-volume analysis

$\epsilon$  = Strain

EDV = end diastolic volume

ESV = end systolic volume

EF = ejection fraction

HR = heart rate

HUT = head up tilt

IVRT = isovolumic relaxation time

LBNP = lower body negative pressure

LV = left ventricle

Ls = longitudinal strain

MST = myocardial speckle tracking

SV = stroke volume

TDI = Tissue Doppler imaging

Ts = Transverse strain

## INTRODUCTION

Left ventricular (LV) function is complex and dependent on inherent intrinsic contractility/ relaxation as well as preload and afterload (1). The assessment of LV function using echocardiography is often required in the clinical setting to guide fluid management especially where cardiac blood volume is reduced secondary to, traumatic hypovolemia, post-operatively and sepsis. Neurocardiogenic syncope (NCS) is a complex condition whereby individuals may collapse due to a sudden inappropriate drop in blood pressure caused either by an inappropriate vasodilatory response and/or drop in heart rate (cardioinhibitory response) or increase in heart rate (postural orthostatic tachycardia syndrome –POTS). One of the investigations used to unmask this condition is head up tilt (HUT) testing to 60 degrees, which may cause a drop in BP and/or increase or decrease in heart rate depending on the type of NCS. Typically, tilting a human from a supine to an upright position results in a redistribution of blood (approximately 500 mL) into the abdominal cavity and limbs (2) resulting in a “true” physiological reduction of preload. HUT testing may therefore provide additional insight into the contractile compensation during challenges to preload.

Echocardiography plays a crucial role in the assessment of LV function and the clinical examination may also require the use of techniques such as Tissue Doppler Imaging (TDI) and Myocardial Speckle Tracking (MST) to provide information on longitudinal velocities and strain ( $\epsilon$ ) (3). It is therefore important to understand the normal mechanical response to load alterations to accurately interpret longitudinal function. Some studies have provided information on cardiac mechanics in the presence of reduced preload and demonstrated the load dependency of peak data from these techniques (4,5). These peak data however provide only a snapshot of

function. Recent publications have demonstrated the feasibility and application of a novel 2D and MST technique that provides *simultaneous* temporal assessment of LV longitudinal and transverse  $\epsilon$  alongside volume (deformation-volume analysis - DVA) (6,7). This new technique may provide further insight into the physiological response to preload reduction on cardiac mechanics.

In view of this, the aims of this study were to assess temporal data over a full cardiac cycle and to characterize *simultaneous* LV longitudinal and transverse function and their contribution to volume change during HUT using MST and DVA.

We hypothesized that longitudinal velocities and strain would be reduced in response to a change in cardiac volume and that simultaneously, transverse contribution would increase in order to maintain LV stroke volume.

## **METHODS**

### **Study Population**

Ten recreationally active men (mean  $\pm$  SD: age  $23 \pm 3$  years, height  $177 \pm 8$  cm, body mass  $70 \pm 9$  kg) provided verbal and written consent to take part in the study. All participants were healthy and free from cardiovascular disease and avoided alcohol and caffeine 24 h prior to data collection. They further refrained from training for at least 6 h prior to the examination. The Human Research Ethics committee of Liverpool John Moores University granted ethical approval for this study.

## **Experimental Procedures**

Participants attended the cardiovascular laboratory for a single visit. Upon arrival at the laboratory, body mass (Seca 217, Hannover, Germany) and height (Seca Supra 719, Hannover, Germany) were recorded. All participants completed a health questionnaire to exclude cardiovascular symptoms, family history of sudden cardiac death and any other cardiovascular history and/or abnormalities.

## **Head-Up Tilt**

Passive head-up tilt (HUT) was used to achieve a “true” physiological reduction in preload without the use of pharmaceuticals. Initially, participants rested in a horizontal position with the use of a footboard for weight bearing to acquire supine images. Straps were put around waist and knees to maintain position. Each individual was then tilted to a 60 degree upright position with the removal of the footboard to reduce antigravity muscle activity, and participants remained in this position for five minutes. To avoid fainting, participants were asked to report any signs of discomfort (i.e. dizziness, light-headedness). Participants unable to tolerate HUT were excluded from the study. Blood pressure and echocardiographic images were recorded in the supine position and at 1 and 5 minutes of HUT.

## **Standard Echocardiography**

The echocardiographic examination was undertaken by a single experienced sonographer using a commercially available ultrasound system (Vivid Q, GE Healthcare, Horten, Norway) fitted with a 1.5-4 MHz phased array transducer. Images were stored in a raw DICOM format and exported to an offline workstation

(EchoPac version 110.0.2, GE Healthcare, Horten, Norway) for subsequent offline analysis.

A focused LV using an apical-four-chamber orientation was acquired maximizing frame-rates between 70-90 frames<sup>-1</sup> and optimizing gain, compression and focusing to clearly delineate the endocardial border whilst maximizing speckle production. Standard measurements were made in accordance with American Society of Echocardiography (ASE) guidelines (8). LV end systolic volume (LVESV), end diastolic volume (EDV), SV, and ejection fraction (EF) were measured according to the Simpson's monoplane method utilising an apical four chamber orientation only to allow for the simultaneous assessment of  $\epsilon$  and volume and application of the DVA technique.

A pulsed wave Doppler spectral display of transmitral filling was acquired in the apical four-chamber view, with the sample volume at the tip of the mitral valve to provide early (E) and late (A) diastolic peak velocities. TDI was performed in the apical four-chamber view at the septal and lateral annulus and analyzed for myocardial velocities during systole (S') and early (E') and late (A') diastole. Isovolumic relaxation time was measured using the septal TDI spectral display and was indexed for heart rate using the Bazett's formula (9).

The 2D apical four-chamber image was subsequently used for offline analysis to determine simultaneous myocardial longitudinal and transverse  $\epsilon$  and volume. A region of interest was placed around the LV endocardial border from basal septum through to the basal lateral wall ensuring the whole of the myocardium was



encompassed within. This provided six myocardial segments and the average of these was used to calculate global index of LV longitudinal and transverse  $\epsilon$ . The software provided feedback on the validity of tracking across the six segments of the myocardium and accurate tracking was confirmed visually by the observer. Segments without acceptable tracking were excluded from the analysis.

### **Longitudinal / transverse strain and DVA**

DVA assessment of  $\epsilon$  -volume relationships were calculated for each participant. The raw  $\epsilon$  data was exported to a spreadsheet (Excel, Microsoft Corp, Washington, United States) and the global temporal values underwent cubic spline interpolation to provide 300 points in systole and 300 points in diastole to correct for variable heart rates (6). The 600  $\epsilon$  values were subsequently split into 5% increments of the cardiac cycle ensuring the raw peak value was included. Mean global temporal longitudinal and transverse strain for the three conditions was then plotted and analysed for differences across one heartbeat (GraphPad Prism 5, San Diego, CA). The absolute time points for each of the  $\epsilon$  values were noted and the same image and cardiac cycle were used to trace LV monoplane volume respectively providing simultaneous measurements of volume and  $\epsilon$  (longitudinal and transverse). A  $\epsilon$ -volume loop was created and mean for the cohort was plotted.

### **Statistical analysis**

All standard 2D, Doppler, TDI and peak  $\epsilon$  data were presented as mean  $\pm$  SD. A one-way sample ANOVA was performed to establish differences between supine, 1-minute HUT and 5-minute HUT. If significant main effects were observed, a

Bonferroni post- hoc analysis was performed to correct for the familywise error rate. Temporal  $\epsilon$  over the cardiac cycle was assessed at each 5% increment (longitudinal and transverse  $\epsilon$ ) and the corresponding 95% confidence intervals (CI) were determined. Where CI did not overlap between the three conditions (supine to 1min HUT and supine to 5min HUT) was defined as significantly different to the supine condition. Previous work by our group presents good inter and intra observer variability for the measurements of  $\epsilon$ -volume loops (6,7).

## **RESULTS**

### **Conventional parameters during head-up tilt**

All subjects completed the study without any pre-syncopal signs or symptoms. HR increased significantly from supine values to the first min of HUT ( $p=0.001$ ) and remained elevated after 5 min ( $p=0.001$ , see Table 1). Systolic blood pressure did not change across the trial ( $p>0,05$ ), however, diastolic blood pressure increased by 9 mmHg after 5 min of HUT( $p=0.012$ ).

LVEDV and LVESV decreased from baseline to 1 min of HUT ( $p= 0.002$  and  $p=0.007$ ) respectively with no further change at 5 min ( $p>0.05$ ) and CO and EF were unchanged throughout the trial ( $p>0.05$ ). Peak septal S' was unchanged across the trial but lateral wall S' decreased significantly from supine to 1 min HUT ( $p=0.017$ , see Table 1). Peak trans-mitral E flow velocity decreased from baseline to 1 min of HUT with a further significant reduction at 5 min ( $p=0.025$ ). Peak trans-mitral A flow velocity did not change across the trial ( $p>0.05$ ). IVRT index significantly increased in the first min of HUT ( $p=0.001$ ), and remained elevated after 5 min ( $p=0.001$ ). Peak

septal E' and A' diastolic tissue velocities significantly decreased from supine to 1 min HUT ( $p=0.003$  and  $p=0.005$  respectively) with no further change at 5 min ( $p>0.05$ ). This pattern was mirrored in lateral wall diastolic tissue velocities.

Peak longitudinal  $\epsilon$  decreased significantly from supine to 1 min HUT ( $p<0.001$ ) with no further change at 5 min ( $p>0.05$ ). Peak transverse  $\epsilon$  increased after 5 min HUT when compared to supine ( $p=0.018$ ) and 1 min ( $p=0.030$ ).

INSERT TABLE 1

### **Temporal LV Mechanics**

Figure 1 and 2 demonstrate LV longitudinal and transverse  $\epsilon$  across 5% increments of the cardiac cycle at supine, 1 min and 5 min of HUT. For longitudinal  $\epsilon$ , separation of 95% CI occurred at several time points during late systole and early diastole between supine and 1 min HUT as well as supine and 5 min HUT (see Figure 1). For transverse  $\epsilon$ , 95% CI overlapped across the cardiac cycle between supine and 1 min HUT with some separation between 70% to 95% of systole between supine and 5 min (see Figure 2).

INSERT FIGURE 1 and 2

### **Longitudinal and Transverse DVA**

There was a leftward- shift of the  $\epsilon$ -volume loops from supine to both 1 min and 5 min of HUT associated with the decreased LVEDV ( $102 \pm 23$  mL vs.  $73 \pm 16$  mL vs.  $79 \pm 15$  mL respectively). At any given LVEDV, longitudinal  $\epsilon$  was reduced with a

concomitant increase in transverse  $\epsilon$  from supine to 1 min that was further augmented at 5 min (see arrows in Figure 3a and 3b). A linear or “coupled” relationship between systole and diastole was evident across all time points in the longitudinal plane, indicating equal changes in  $\epsilon$  for any given volume change throughout the cardiac cycle. In the transverse plane, there was evidence of systolic to diastolic “uncoupling” after 5 min of HUT.

INSERT FIGURE 3a and 3b

## **DISCUSSION**

The aim of this study was to provide a simultaneous assessment of LV longitudinal and transverse  $\epsilon$  with the additional calculation of volume following a reduction in preload associated with HUT. This novel DVA analysis revealed that in response to HUT 1) there was a reduction in longitudinal  $\epsilon$  with a concomitant increase in transverse contribution across the cardiac cycle and 2) systolic to diastolic uncoupling was noted for the  $\epsilon$ -volume loops at 5 min HUT in the transverse plane but not in the longitudinal plane.

### **Cardiac Mechanics in Response to HUT**

Based on standard 2D, Doppler and TDI echocardiography, a reduction in LV preload occurs within 1 min of HUT with no further reduction at 5 min. This is demonstrated by an initial reduction in LVEDV, reduced transmitral filling velocities and prolongation of indexed IVRT. These findings were accompanied by a significant increase in HR from supine values but without substantial changes in BP. This is in accordance with studies employing lower body negative pressure (LBNP) and is

commonly reported because of hypovolemia / dehydration (4,10,11). Despite these changes, CO and EF were maintained and no pre-syncopal signs or symptoms were noted.

We report a significant reduction in longitudinal  $\epsilon$  with a concomitant increase in transverse  $\epsilon$ , at any given LVEDV, from supine to 1 min that was further augmented at 5 min (see Figure 3a and 3b). This is supported by a change in temporal LV mechanics in the longitudinal plane with the separation of CI across various time points in both conditions. We further demonstrated a linear or “coupled” relationship between systole and diastole  $\epsilon$  across all time points at 1 min and 5 min HUT in the longitudinal plane, indicating equal changes in  $\epsilon$  for any given volume change throughout the cardiac cycle.

In the transverse plane, CI overlapped at 1 min HUT and separation occurred in systole from 70 to 95% at 5 min HUT. With the inclusion of the  $\epsilon$ -volume loops, we were able to characterize simultaneous LV longitudinal and transverse function and uniquely report a systolic to diastolic “uncoupling”, indicating that the maintenance of filling at 5 min appears to be driven by subtle changes in cardiac mechanics and their relative contribution to volume change.

LV filling is dependent on the rapid relaxation of the myocardium in both longitudinal and circumferential planes resulting in transverse ‘thinning’. This contributes to the LV pressure decline and thereby generates the left atrium LV pressure gradient leading to aortic valve opening. The maintenance of this process throughout diastole is achieved by a combination of compliance and active relaxation (i.e. the elastic recoil) of the deformed myocardium, resulting in the development of vortices which

ensure the “suction” of blood into the LV (6,12). A recent study utilising the DVA technique in a healthy athletic population demonstrated the importance of longitudinal  $\epsilon$  to overall global LV filling (6). Our current data, in the supine position, supports this finding with ‘normal’ longitudinal peak  $\epsilon$  and similar  $\epsilon$  values in systole and diastole for any given volume i.e. no systolic-diastolic difference. Conversely, there is a relatively low transverse  $\epsilon$ . In this ‘normal’ preload state it must be assumed that longitudinal shortening and lengthening predominates over circumferential shortening. During an initial reduction in LV preload, there is a marked reduction in longitudinal peak  $\epsilon$  with no shift in the systolic-diastolic relationship i.e. values are reduced throughout the cardiac cycle (see Figure 3a). This may be a manifestation of the Frank-Starling mechanism (13). To maintain output transverse thickening is enhanced due to the incompressibility of myocardial tissue, as a change in one dimension is usually accompanied by a reciprocal change in another dimension (13,14). This compensatory mechanism and a concomitant increase in HR allows the maintenance of CO. In addition, at 5 min HUT the increase in transverse  $\epsilon$  continues but with enhanced recoil (supported by an increased systolic-diastolic difference) which likely maintains the LA-LV pressure gradient and thus helps to facilitate LV filling (see Figure 3b).

### **Clinical Impact**

These data raise some important issues related to clinical application and interpretation of cardiac functional data in the setting of reduced blood volume/dehydration. The assessment of LV function in these patients in acute medicine is important to exclude intrinsic cardiac dysfunction. Likewise, when considering

longitudinal LV function in a clinical setting (e.g. traumatic hypovolemia, post-operatively and sepsis) it is important to consider blood volume status and to interpret  $\epsilon$  in conjunction with conventional indices in these settings.

HUT is often used as an investigation for patients with recurrent syncope or pre-syncope to unmask the different types of neurocardiogenic syncope (NCS), eg. sudden inappropriate drop in blood pressure caused either by an inappropriate vasodilatory response and/or drop in heart rate (cardioinhibitory response) or tachycardia (postural orthostatic tachycardiac syndrome - POTS). Our data demonstrated the normal response to reduced preload of increased transverse thickening and greater effective recoil in this mechanical plane. We therefore speculate that the drop in BP in patients with NCS may be due to impairment of this normal response and therefore further investigation into these patient populations is warranted. In addition, it is appropriate to question the impact of increased transverse thickening in a small LV that reduces in size further with preload reduction and the potential impact on a Bezold-Jarish reflex. In view of this, it would be useful to utilise the DVA technique in these clinical populations to provide some insight into possible mechanisms.

## Limitations

The aim of the study was to provide *simultaneous* longitudinal and transverse  $\epsilon$  with LV structure which restricted the method to a single 2D image. This dictates that transverse  $\epsilon$  is used as an indicator for radial  $\epsilon$  which is generally obtained from a short-axis view. The inherent reduction in lateral resolution from an apical 4-chamber view may affect the accuracy of this approach.

This technique may be applied to circumferential, radial and twist mechanics, but unlike transverse strain, cannot be obtained in the same cardiac cycle and was therefore not assessed in this study. A solution to this problem would be the use of 3D echocardiography. However, low frame rates during “real-time 3D acquisition” could “under-sample” important parts of the cardiac cycle. The development of high frame rate 3D imaging is in process and will be applied in the future and as such can be transferred to a “real-world” clinical setting.

## Conclusions

Preload reduction occurred within 1 min of HUT but does not reduce further at 5 min in this population and set-up. The reduction in preload was associated with a reduction in longitudinal  $\epsilon$  and concomitant increase in transverse  $\epsilon$ . Enhanced transverse recoil appears to be an important factor in the maintenance of LV filling in this setting. DVA provides information on the relative contribution of mechanics to a change in LV volume and may have a role in the assessment of clinical populations.



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## Figure and Table Legends

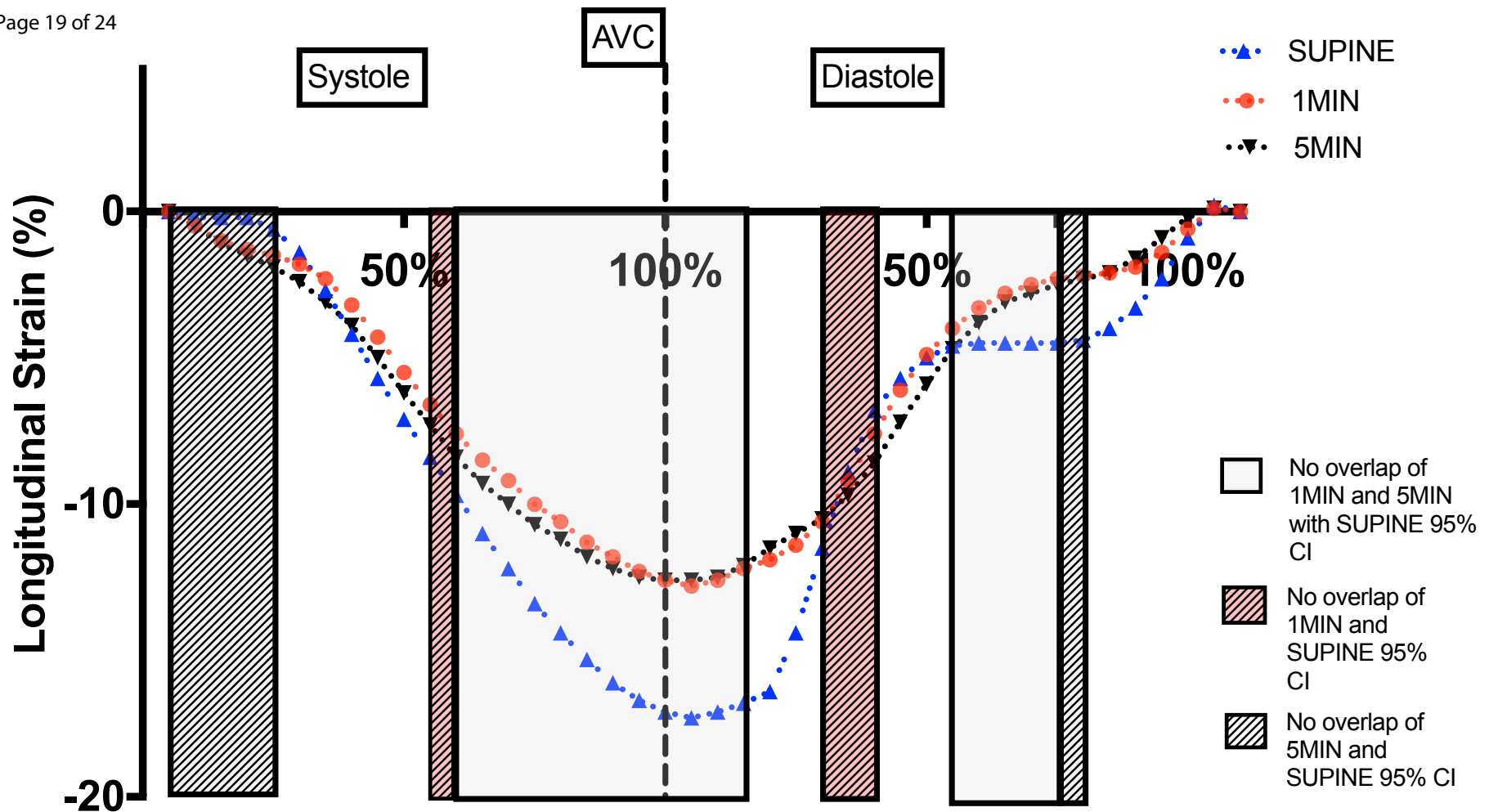
**Table 1** Conventional parameters in the supine position and at 1min and 5min HUT

**Figure 1** Longitudinal strain (%) across one cardiac cycle, presented in 5% increments in systole and diastole in the supine position and at 1 min and 5 min HUT

**Figure 2** Transverse strain (%) across one cardiac cycle, presented in 5% increments in systole and diastole in the supine position and at 1min and 5min HUT

**Figure 3a** Left ventricular  $\epsilon$ /volume loops supine and at 1 min HUT

**Figure 3b** Left ventricular  $\epsilon$ /volume loops at 1min and at 5min HUT- *Long* longitudinal, *Trans* transverse



Systole

AVC

Diastole

- ▲● SUPINE
- 1MIN
- ▼ 5MIN

- No overlap of 1MIN and 5MIN with SUPINE 95% CI
- ▨ No overlap of 1MIN and SUPINE 95% CI
- ▩ No overlap of 5MIN and SUPINE 95% CI

50%

100%

50%

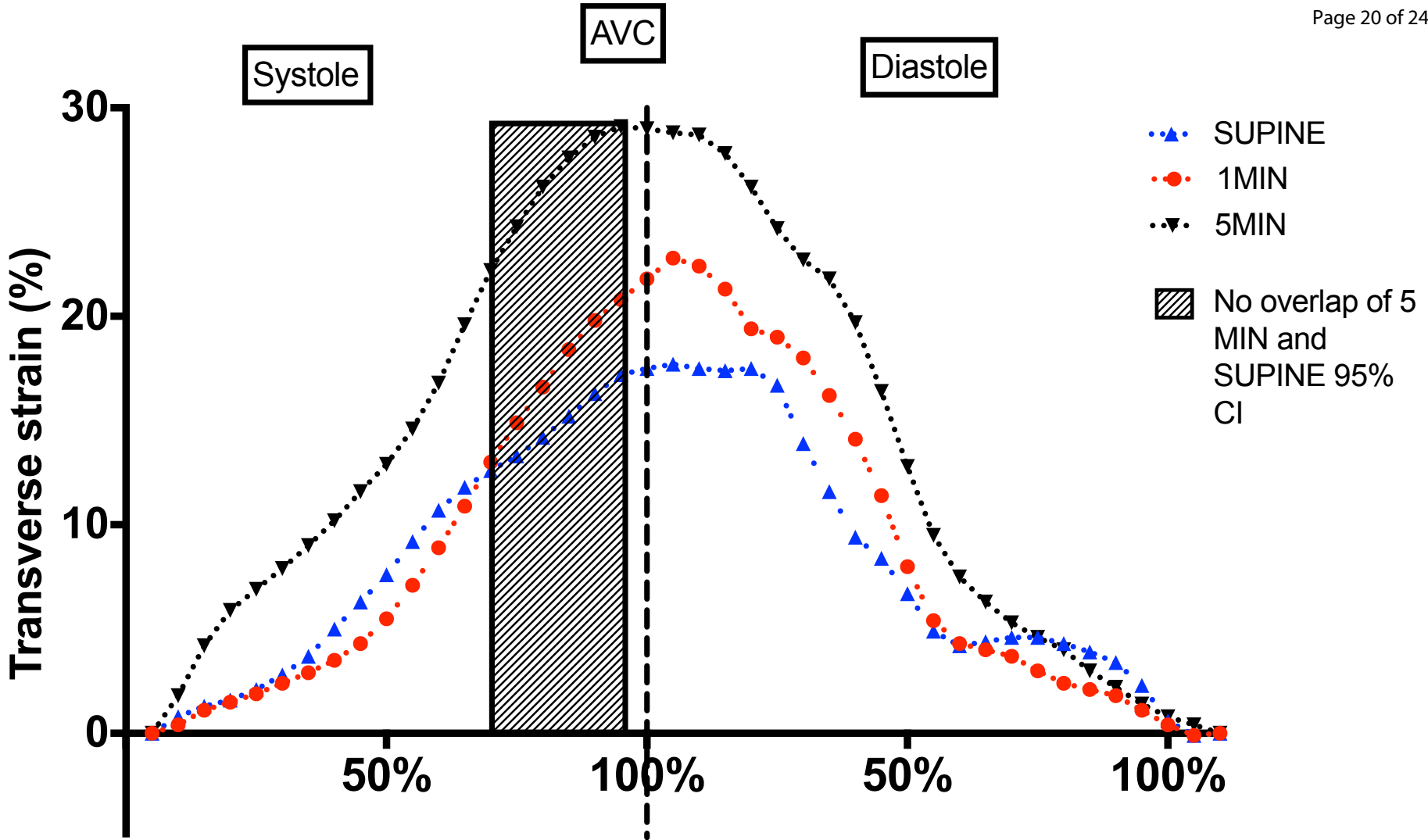
100%

Longitudinal Strain (%)

0

-10

-20



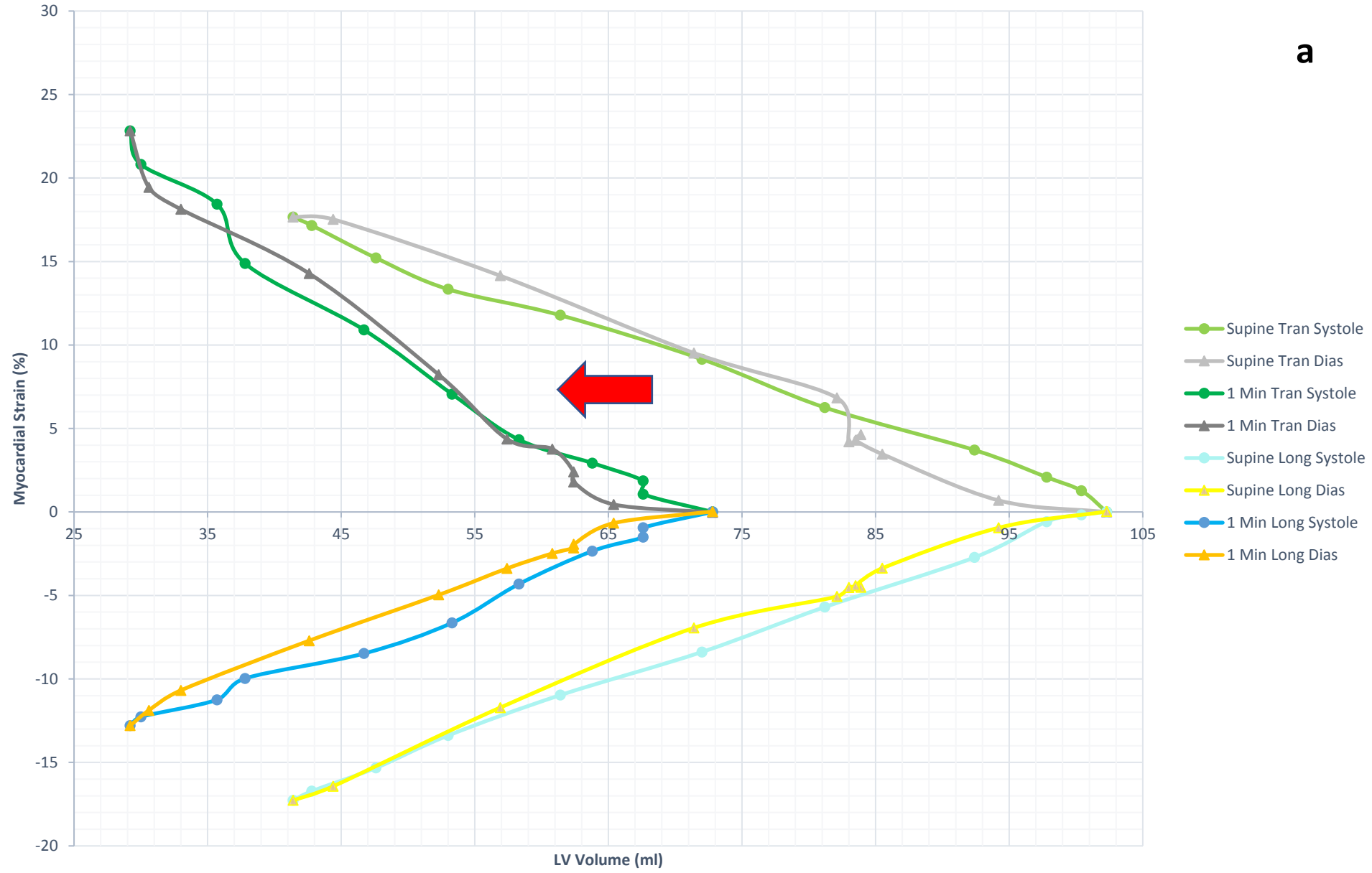
Systole

AVC

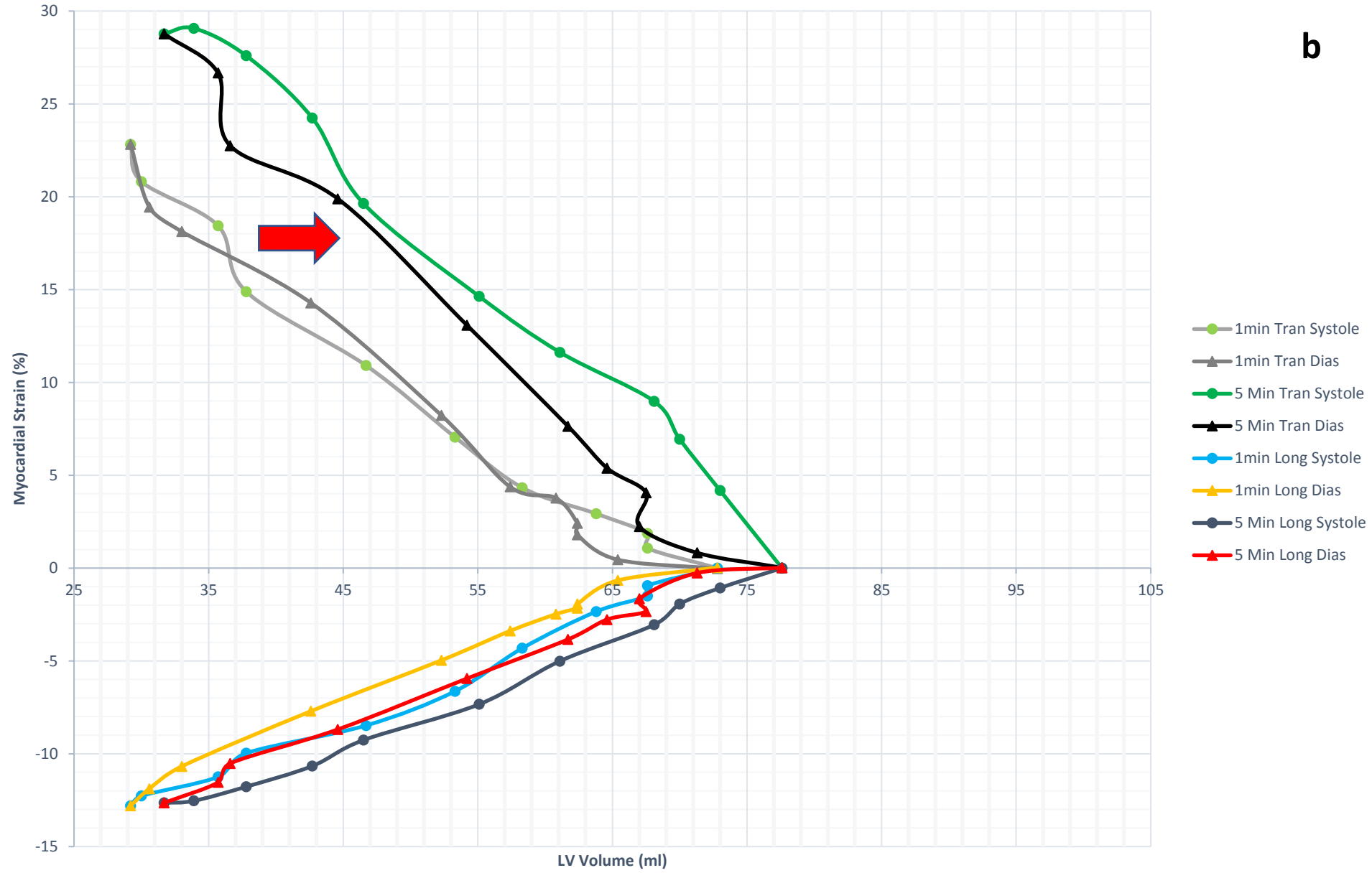
Diastole

- ▲• SUPINE
- 1MIN
- ▼• 5MIN
- ▨ No overlap of 5 MIN and SUPINE 95% CI

**a**



**b**



**Table 1** Conventional parameters in the supine position and at 1min and 5min HUT

<b>Conventional parameters</b>	Supine	1 min tilt	5 min tilt
Heart Rate (bpm)	67±13	80±13*	82±10*
Systolic Blood Pressure (mmHg)	127±8	123±10	125±6
Diastolic Blood Pressure (mmHg)	70±8	76 ±10	79 ± 8*
Cardiac Output (l/min)	4.1±1	3.6± 0.76	3.8±0.58
EDV (ml)	102±23	73 ±16*	79± 15*
ESV (ml)	40± 10	28 ±10*	31 ±10*
LV Ejection Fraction (%)	61±5	62±9.8	61±7
E Wave Velocity (m/s)	0.77± 0.16	0.71 ±0.13	0.67± 0.09*
A Wave Velocity (m/s)	0.48±0.13	0.48±0.15	0.53 ±0.23
E/A	1.7±0.6	1.6±0.5	1.4± 0.5
IVRT index (ms)	74±16	105±18*	102±16*
<b>Tissue Doppler Imaging</b>			
Sept E' (cm/s)	13±2	8±2*	9±2*
Sept A' (cm/s)	8±1	5 ±2*	5±2*
Sept S' (cm/s)	9±1	9±2	8±3
Lat E' (cm/s)	18±3	9±2*	9 ±1*
Lat A'(cm/s)	7±1	5 ±1*	5±1*



Lat S' (cm/s)	13±2.0	10±2*	11±3
<b>Strain</b>			
Peak Longitudinal Strain (%)	-17±2	-13±2*	-13 ±2*
Peak Transverse Strain (%)	21±9	25±9	34±9 <sup>a*</sup>

\*Significantly different to supine ( $P \leq 0.05$ ), <sup>a</sup> significantly different to 1 min HUT