MEA Summary Research Review:

Abnormal cardiac changes in ME/CFS *not* due to deconditioning

By: Charlotte Stephens 26th November 2018

Introduction

Linda van Campen and Frans Visser from the Netherlands have just published a study that examined stroke volume and cardiac output in ME/CFS. It confirmed earlier findings from a smaller study that changes occurred in these two key cardiac measures despite *normal* tilt-table results (Timmers *et al.,* 2002).

Both studies found *reduced* cardiac output and stroke volumes during a tilt table test in ME/CFS patients compared to healthy controls. However, these patients had *normal* tilt table results, meaning their heart rate and blood pressure *did not change* significantly enough to be diagnosed with orthostatic intolerance.

The authors of the earlier study suggested that these findings were due to deconditioning, but in this new, larger study, Van Campen and Visser showed they were *not* as they found *no difference* in results between different disease severities.

If it were a case of deconditioning, the cardiac measurements would be *worse* in the more severely affected compared to the mild, as they have poorer physical functioning.

What made this study better than the previous one?

1. Much larger patient cohort. The previous study tested 26 ME/CFS patients, whereas this current study involved 150 ME/CFS patients.
2. Improved method of measuring cardiac parameters. The reliability of the previous study's method (pulse contour analysis) is questionable, whereas the current study used a validated technique (suprasternal aortic Doppler echography) (van Geldorp *et al.,* 2011).
3. The latest study compared results across illness severities. This revealed that the cardiac abnormalities could not be due to deconditioning.

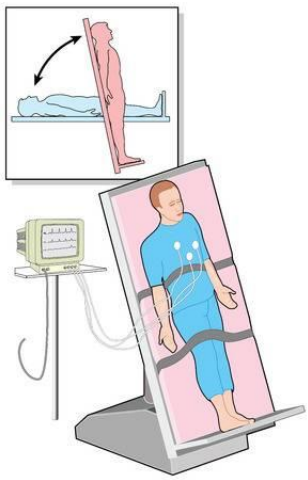
What were the two key measures found to be different?

Cardiac output = The volume of blood pumped by the heart per minute.

Stroke Volume = The volume of blood pumped by the left ventricle of the heart per heartbeat.

Both of these measures usually decrease upon standing. However, they were found to decrease *more* in the patients with ME/CFS, compared to the healthy controls.

What did the tilt table test involve?



- The patient starts by lying down flat on a table for 15 minutes, where baseline measurements are taken.
- They are then tilted upright at a 70-degree angle (almost standing), which is known as the 'head up' position.
- They are then held in this position for 25-30 minutes, or until the patient asks to stop as they feel unwell. During this time, the patient is asked to keep very still as movement of the legs can affect blood flow.
- Heart rate and blood pressure were measured continuously throughout the test and cardiac output and stroke volume were measured at the start, half way through and at the end of the test.

Recruitment

150 patients were selected, out of 636 who visited the clinic "…on suspicion of ME", after patient history was taken to ensure they met the international consensus criteria (ICC) (Caruthers *et al.,* 2011).

Of the 150 patients, 107 fulfilled the criteria for M.E. and 43 were classed as having 'atypical ME' (meaning they met criteria for post-exertional neuroimmune exhaustion but had two or less of the remaining criterial symptoms).

They included only patients with 'normal' tilt table test results. This meant the patients completed a tilt table test without an early tilt back and had a normal heart rate and blood pressure response during the tilt.

Those included did *not* present with orthostatic intolerance or conditions such as PoTS (Postural Orthostatic Tachycardia Syndrome), which are commonly co-diagnosed with ME/CFS.

Patients were also categorised into 3 illness severities – mild, moderate and severe – using results from a physical functioning questionnaire (RAM SF-36), together with patient history.

The control group was small (only 37 healthy volunteers) and they were not specified as sedentary, which may have had an effect on the results as physical fitness is also known to relate to cardiac output (Murrell *et al*., 2011).

Results

The heart rates of the ME/CFS patients were all significantly *higher* than that of healthy controls, both before and during the tilt test. And yet the percentage *change* in heart rate between resting and during the tilt was *not* different between patients and healthy controls.

This meant that the tilt table test *did not* have a greater effect on heart rate in ME/CFS patients than in controls. During the tilt, blood pressure was also significantly *higher* in patients compared to healthy controls.

Stroke Volume Index at all time points was significantly *lower* in ME/CFS patients compared to healthy controls. Cardiac Index (measure of cardiac output) was significantly *lower* at the end of the test in patients compared to controls.

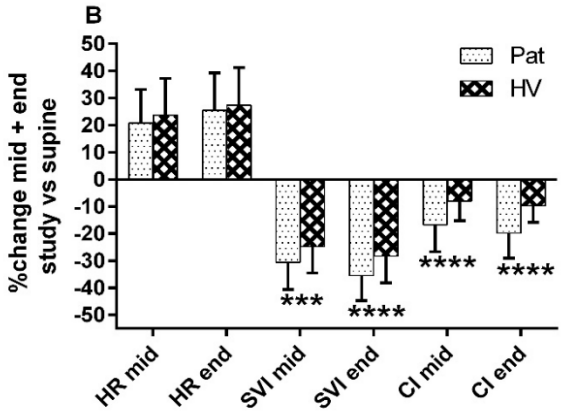


Fig 1. *Shows the % change in heart rate (HR), stroke volume index (SVI) and cardiac index (CI) in ME/CFS patients and healthy volunteers (HV) halfway through the tilt period (mid) and at the end of the tilt period (end). The *'s represent statistical significance; more meaning more significant difference.*

The decreases (% change) in stroke volume index and cardiac index between the supine period and during the test were all *significantly larger* in patients than in the healthy controls (see fig 1).

Meaning, the tilt table test had more of an effect on the cardiac output of ME/CFS patients compared to the controls (the volume of blood pumped per minute reduced more).

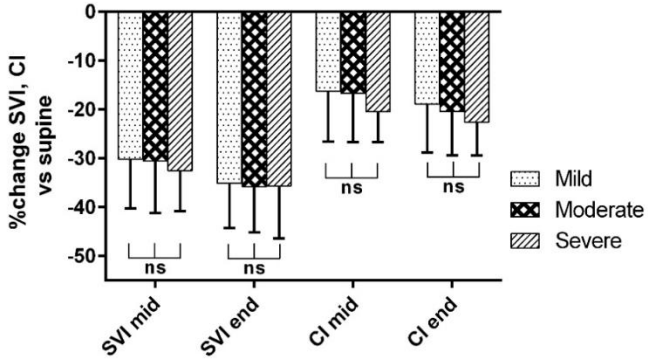


Fig 2*. Shows the % change of the stroke volume and cardiac index in ME/CFS patients with mild, moderate and severe disease. There are no significant differences between the three groups (ns).*

There were *no significant differences* in Stroke Volume Index and Cardiac Index changes during the tilt between patients with mild, moderate, and severe ME/CFS (see fig 2).

There were *no significant differences* in Stroke Volume Index or Cardiac Index between ME and atypical ME patients.

Discussion

Cardiac output and stroke volume decrease in everyone during a tilt test, they just appear to decrease to a greater extent in ME/CFS patients. However, these responses can be affected by other variables, such as age and gender (Murrell *et al.,* 2011).

Studies on healthy subjects report very large differences in responses during tilt testing. Therefore, as there appears to be variation even in healthy subjects, it would be hard to use this test as a diagnostic tool in ME/CFS.

Deconditioning does not explain cardiac abnormalities

Self-reported physical functioning scores are lower in severe ME/CFS patients compared to mild/moderate patients. This not only suggests that severe patients are more functionally impaired but that they might also be more deconditioned than milder patients.

Decreases in stroke volume and cardiac output are *not* significantly different between mild, moderate, and severe ME/CFS patients. Therefore, this suggests that deconditioning *does not* explain the larger decrease in stroke volumes and cardiac output in ME/CFS patients compared to healthy controls.

However, the authors did point out that the physical functioning scores of their severe patients were not as low as previous studies have found (Pendergrast *et al*., 2016).

This could be due to differences in techniques used to group severities; the current study used the RAND SF-36 subscale, whereas the DePaul symptom questionnaire has been shown to be more reliable (Murdock *et al.,* 2017). On the other hand, it could be due to differences in patient severity; the current study might have benefitted from a larger group of severely affected patients.

Only 11 out of the 150 patients (7%) were classed as severe. This means there may not have been enough patients in this group to allow for significant differences between groups to be recognised.

The study should be repeated with a larger number of patients in the severe group to accurately confirm the presence or absence of significant differences between disease severities. And it would benefit from a sedentary control group to better ensure the results are attributable to ME/CFS.

What might cause these abnormal results?

Suggested mechanisms for the reduction in stroke volume and cardiac output include reduced blood volume and an abnormal sympathetic and parasympathetic response. This would lead to excessive venous pooling (blood pooling in the legs instead of moving back to the heart) upon standing (Newton *et al*., 2007).

Previous studies have found reduced blood volume, including a recent paper by the same authors of this study (van Campen *et al.,* 2018). However, further research is needed to confirm this finding, as well as the reasons behind it.

The authors hypothesise that those with orthostatic intolerance (who would have an *abnormal* tilt tables response) have an even greater reduction in stroke volume and cardiac output and suggest that the body is unable to compensate, leading to feeling faint or fainting.

Conclusion

The results of this study confirm previous findings by Timmers *et al.* (2002) that ME/CFS patients who have a normal heart rate and blood pressure response to tilt testing have significantly lower stroke volume and cardiac output compared to healthy controls.

Furthermore, no differences in results were found between different disease severities, suggesting the findings are not due to deconditioning.

However, grouping to illness severities was not optimised, and there was a small control group which was not sedentary. So, while this study was large – which is welcomed – it could have been better.

It would be worth repeating the research with better recruitment, and an improved cohort (a greater number of severely affected patients and sedentary controls).

The authors said:

> "During a head-up tilt with a normal Heart Rate and Blood Pressure response, Stroke Volumes and Cardiac Output in ME/CFS patients decrease significantly more than in healthy volunteers."
>
> "The absence of a difference in the decreases of stroke volume and cardiac output between patients with mild, moderate, and severe disease suggests that the decrease of stroke volumes and cardiac output is not related to deconditioning."

This study may also add weight to suspected dysregulated autonomic nervous system involvement in ME/CFS pathology.

Further study is needed to address the extent to which the cardiac and blood volume alterations in ME/CFS have physiological and clinical significance.

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