PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Protocol of the CARDIOBESE study: A cross sectional and prospective follow-up study to detect early signs of cardiac dysfunction in obesity</th>
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<td>AUTHORS</td>
<td>Snelder, Sanne; de Groot - de Laat, Lotte; Biter, L; Castro Cabezas, Manuel; van de Geijn, G; Birnie, Erwin; Boxma - de Klerk, Bianca; Klaassen, R; Zijlstra, Felix; van Dalen, Bas</td>
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VERSION 1 – REVIEW

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<tr>
<th>REVIEWER</th>
<th>Kirstie De Jong</th>
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<td>University Medical Center Hamburg-Eppendorf, Germany.</td>
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<td>REVIEW RETURNED</td>
<td>31-Jul-2018</td>
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<th>GENERAL COMMENTS</th>
<th>Recommendation: minor revision</th>
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6. Page 8, Line 18: The authors state “the fact that the vast majority of the parameters that we will use to identify subclinical cardiac dysfunction have not been assessed in obesity before”. Please specifically state which parameters are novel and provide some justification for assessing them.

7. Will the authors be assessing plasma insulin?

REVIEWER
Carl Lavie
Ochsner, USA

REVIEW RETURNED
21-Aug-2018

GENERAL COMMENTS
This should be a nice study. My only comment is instead of my old ref 1, the authors could use a more recent and up to date on this topic (Lavie CJ et al. Prog Cardiovasc Dis 2016;58:393-400) and could also use one from the UCLA group (Horwich TB et al. PCVD 2018; published on-line ahead of print). Also, instead of reference 13 which is over a decade old, more recent major EPI one from this same first author could be used (Piche M-E et al. Prog Cardiovasc Dis 2018; published on-line ahead of print.) Additionally, a very up to date state of the art on the impact of obesity on cardiac structure and function from the Missouri group could be included (Alpert MA et al. PCVD 2018; published on-line ahead of print).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Recommendation: minor revision

Review: Firstly, the authors should be commended on undertaking a study with high clinical significance and importance. The study has clear aims that have been communicated nicely by the authors. I look forward to the completion of the study and study results.

We would like to thank dr. de Jong for these kind words.

1. Introduction – Please include a more balanced review of the past literature in the discussion. There have been many studies in the past suggesting obesity as defined by BMI, does not relate to an increased CVD risk and that a higher BMI may associate with better patient outcomes (obesity paradox).

We fully agree with dr. de Jong that BMI may not be the optimal parameter to reflect increased cardiovascular risk in obesity. Therefore we added a sentence concerning this issue and added a reference to a previous study published in BMJ open in order to indeed provide a more balanced review of past literature.

Also, BMI may not be the optimal parameter to reflect increased cardiovascular risk in obesity.
2. In the introduction briefly discuss current risk assessment guidelines for obese patients (for example, monitoring blood pressure, fasting glucose). And then provide evidence from the previous literature as to why you hypothesise these current guidelines are inadequate.

We believe that current risk assessment is mostly adequate, but that the enormous increasing prevalence of obesity warrants identification of obesity patients with the highest risks. One may hypothesize that risk assessment, follow-up and treatment of obesity patients should be more intense when there are already signs of cardiac dysfunction. We added the following sentences to highlight this issue:

Present-day guidelines recommend screening of obesity patients on presence of cardiac risk factors and inclusion of obesity patients in cardiovascular rehabilitation programs directed to reduce body weight and increase physical activity, thereby improving cardiac risk factors. The enormous and still growing prevalence of obesity warrants efficient screening of obesity patients with the highest need for such further risk assessment, follow-up and treatment. Current knowledge on the role of obesity in causing cardiac dysfunction is insufficient to optimally develop such strategies for obesity patients.

3. Please explain why speckle tracking echocardiography will be used. Particularly make reference to the practicality of producing data from a technology that is not widely available clinically. What are the benefits of being able to identify alterations in LV function using speckle tracking echocardiography, if these methods cannot be applied to most clinics?

Indeed, probably a large part of clinics do currently not have speckle tracking available. However, echo-machines from all "big" vendors are currently routinely equipped with speckle tracking software. Also, the technique has been significantly improved the past decennium and inter-vendor differences have been minimized (Voigt et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2015 Jan;16(1):1-11.). We therefore strongly believe that, like tissue Doppler imaging, use of speckle tracking will increase and finally become a standard tool in most echolabs. Two sentences were added to discuss this.

Although availability of speckle tracking echocardiography may still be limited, echo-machines from all well-known vendors are currently routinely equipped with speckle tracking software. Also, the technique has been significantly improved the past decennium and inter-vendor differences have been minimized, optimizing clinical applicability.

Furthermore, speckle tracking allows analysis of myocardial deformation in the radial, longitudinal and circumferential direction and LV rotation/twist. For the second objective of our study, to gain insight in the pathophysiology of obesity causing cardiac dysfunction, we will use this to investigate whether there are specific changes in the deformation patterns in obesity, for example leading to diastolic dysfunction (e.g. decreased LV untwisting? decreased diastolic strain rate?).

4. Please provide a more detailed inclusion list. Will obese patients with elevated HbA1c still be included in the study, or hyperlipidaemia? Furthermore, will hypertensive patients be included? Or those with a history of hypertension? A detailed list of metabolic abnormalities that you will accept within your obese patients is required. And if type 2 diabetic and hypertensive patients are included within the study perhaps the authors should reconsider the focus of their study. As this would no longer be a study assessing these alterations specifically in obesity. This study would instead be relying on statistical analysis to tease out the effects of obesity, independent from associated co-morbidities.

For the CARDIOBESE study we decided to use rather liberal inclusion criteria, allowing inclusion of obesity patients with other cardiac risk factors such as diabetes, hyperlipidaemia or hypertension. The main reason for this is that we wanted to optimally reflect daily practice (with obesity patients often having other cardiac risk factors). Therefore, the current inclusion/exclusion criteria as described on page 7 cover the actually used criteria and we cannot provide a more detailed list.

However, we fully agree with dr. de Jong that this implies that we may not be able to differentiate whether early signs of cardiac dysfunction in our obesity patients are a result of the obesity itself or an associated co-morbidity. Nevertheless, this was actually one of the reasons for the second objective.
of our study and for wanting to also investigate the patients one year after bariatric surgery. For example, when it would turn-out (as we expect) that LV diastolic dysfunction as identified by conventional echocardiography may be an early sign of cardiac dysfunction in a significant portion of obesity patients, it may indeed be difficult to statistically tease out the effects of obesity, independent from associated co-morbidities. Nevertheless, from previous studies by other groups, we know that one year after bariatric surgery, diastolic function will improve. We will then study whether this improvement is most strongly related to for example weight loss, improvement of diabetes regulation, and so on, thereby providing insight into the influence of obesity per se and the role of co-morbidities.

For the moment we decided not to further discuss this in the manuscript, being afraid that it may confuse somebody who does not read the manuscript in detail. However, if dr. de Jong or the editor would prefer that we do discuss it, we are of course more than willing to do that.

5. I appreciate the difficulty in being able to, or attempting to gauge at which at age and/or stage of obesity that early cardiac dysfunction occurs. However, the authors need to address their ability to specifically focus on early cardiac dysfunction. How can the authors have confidence that they are recruiting those with either normal cardiac function or early cardiac dysfunction? They have chosen a relatively wide age range of 35-60 years, for which the stage of disease progression will vary. Furthermore, the authors need to specifically specify what they will characterise as early or subclinical cardiac dysfunction. And if participants show more severe alterations than this in speckle tracking echocardiography will they still be included in the study?

In the CARDIOBESE study, only subjects without a known cardiovascular history are included (please see exclusion criteria, page 7). It is therefore that we consider any sign of cardiac dysfunction that we do identify to be a sign of early cardiac dysfunction. Dr. de Jong is right concerning the fact that we will not be sure whether this identified dysfunction will truly be "early" in a sense that it has developed recently. However, as said, we will consider it to be "early" because it had not led to a clinical diagnosis of cardiac dysfunction in this patient yet.

On page 8 (Endpoints) we describe that "An early sign of cardiac dysfunction is considered to be present when a studied parameter is significantly different from a well-defined cut-off value. When such a cut-off value is not available, a studied parameter is considered to be an early sign of cardiac dysfunction when significantly different between obesity patients and non-obese controls."

At the time of inclusion, results from the echocardiogram, blood/urine tests, and holter monitoring are not known and will therefore not be used to decide on in-/exclusion. Consequently, identification of even rather severe alterations in the speckle tracking echocardiogram would not be considered to be an exclusion criterion.

6. Page 8, Line 18: The authors state “the fact that the vast majority of the parameters that we will use to identify subclinical cardiac dysfunction have not been assessed in obesity before”. Please specifically state which parameters are novel and provide some justification for assessing them.

We would like to thank dr. de Jong for this comment, because when trying to formulate a proper response, we concluded that the sentence she referred to is actually not fully right. When reviewing available literature it becomes clear that most parameters that we will study, have been investigated before (please see Appendix 1). Nevertheless, it is the combination of echocardiography, blood/urine biomarkers and holter monitoring that has never been used before. We have changed the text accordingly:

The fact that the combination of parameters that we will use to identify subclinical cardiac dysfunction has not been investigated in obesity before, complicates a well-defined and evidence-based sample size calculation.

7. Will the authors be assessing plasma insulin?

We would like to thank dr. de Jong for this suggestion and we will definitely consider assessing plasma insulin (from the stored blood samples).
Reviewer: 2

This should be a nice study.

We would like to thank professor Lavie for this kind complement.

My only comment is instead of my old ref 1, the authors could use a more recent and up to date on this topic (Lavie CJ et al. Prog Cardiovasc Dis 2016;58:393-400 PubMed) and could also use one from the UCLA group (Horwich TB et al. PCVD 2018; published on-line ahead of print). Also, instead of reference 13 which is over a decade old, more recent major EPI one from this same first author could be used (Piche M-E et al. Prog Cardiovasc Dis 2018; published on-line ahead of print.) Additionally, a very up to date state of the art on the impact of obesity on cardiac structure and function from the Missouri group could be included (Alpert MA et al. PCVD 2018; published on-line ahead of print.)

The references have been added/updated as suggested (reference 1, 3, 14 and 15).

VERSION 2 – REVIEW

| REVIEWER            | Kirstie De Jong
|                    | University Medical Center Hamburg-Eppendorf, Germany. |
| REVIEW RETURNED    | 23-Oct-2018 |

GENERAL COMMENTS

The author's addressed all questions and concerns. I look forward to see this manuscript published and the completion of the study.