February 2/24/2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO 8637-edited).

Title: Unreliability of Aortic Size Index to Predict Risk of Aortic Dissection in a Patient with Turner Syndrome..

Author: Jan Nijs, Sandro Gelsomino, Fabiana Luc à, Orlando Parise, Jos J Maessen, Mark La Meir.

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 8637

First of all, on behalf of all co-authors I would like to thank very much you, the Editorial staff and the reviewers for the positive comments. We revised the article following the reviewers' suggestions which certainly improved our paper and its message, and we do hope that we successfully provided all the required information and changes. The manuscript underwent English language revision by a professional native speaker, Dr Judith Wilson who was acknowledged at the end of the manuscript.
All changes are reported in red font in the revised version

Reviewer No 00396997

Comment of the Reviewer: This is an intriguing case report describing a case of aortic arch dissection observed in a patient with Turner's syndrome (TS) and its treatment. This report provides the idea and sound the alarm that the using only an aortic size index is not sufficient for the risk stratification for aortic dissection in patients with Turner's syndrome. The report is clearly described, the discussion is of good quality, and the conclusions well-justified. However, the manuscript could be improved through incorporation of the following suggestions.
1. Please provide brief general introduction about TS including its major phenotypes, frequency of cardiovascular abnormalities and frequency of aortic dilatation in TS.
2. Page 3 "A 23-year old woman with TS (45,X karyotype),Graves-Basedow disease and systemic arterial hypertension treated with β-blockers,presented to our hospital facility" Please provide this patient's blood pressure at the admission.
3. Page 3 "Since then the patient underwent close surveillance by yearly CT scan which did not show aortic dilatation". Please provide the latest Aortic size observed by CT scan before the admission.
4. Recently, there are several reports showing that cardiac MRI screening may be beneficial for the risk stratification for the cardiac risk in TS including aortic dissections. Since this patient seems like not to have been followed up using MRI, please provide the small discussion and summarize the current opinions related to the cardiac assessment in TS using CT vs MRI.
5. The authors should reorganize the abbreviations using in the whole manuscript. The abbreviation should be defined when it firstly appears in the manuscript and does not need to be defined again (or many times).
6. Figure legends and its title should include more detailed and appropriate descriptions for easy understanding for the readers. Please provide an appropriate title for each figure. For example, please provide an appropriate title for each figure such as "Axial plane CT image of the ascending aorta" for Figure 2.

First of all I would like, on behalf of all co-authors, to thank this reviewer for his/her positive comment.

1. As requested a brief general introduction was added giving the information requested

Page 3 Line 1:

"Turner syndrome (TS) is a relatively common chromosomal disorder, caused by complete or partial X monosomy in some or all cells1. This abnormality is denoted medically as the 45,X karyotype as opposed to the usual 46,XX female karyotype. Many TS patients are actually mosaic, meaning that they have cells with more than one karyotype and occasionally there is mosaicism for cells containing Y chromosome material (Table 1)2-4. Short stature and gonadal dysgenesis are two of the characteristic clinical features of the syndrome, although many

organ systems and tissues may also be affected to a lesser or greater extent. However, approximately 50% of karyotypically-proven, asymptomatic women with TS have evidence of abnormal cardiovascular development and most patients die from cardiovascular defects mainly involving the left ventricular outflow tract, left heart and/or aortic hypoplasia. Common congenital defects in surviving girls and adults with TS include bicuspid aortic valve (30%), aortic coarctation (12%) and partial anomalous pulmonary connection (18%) 5,6.

Nonetheless, the occurrence of aortic dilatation, dissection or rupture is one of major concerns in TS 1. The annual incidence of aortic dissection or rupture is 15 cases/100,000 for individuals <20 years of age, 73-78 cases/100,000 for women 20-40 yrs old and 50/100,000 for older women with TS."

Was added

We added also a table (Table 1) to summarize the phenotypes of TS and make this information more easily available to the reader.

6 new references were added along with the new introduction.

2. **Page 4, Line 10:**

The blood pressure ad admission was added: "Blood pressure was 110/82".

3. As requested the diameter of ascending aorta at latest control before adnmission was added. It was 26 mm.

4. **Page 6:**

"Although CT scan with contrast is the most widely used diagnostic procedure, recent studies12,13 have demonstrated that cardiac magnetic resonance imaging (CMRI) is an important tool for clinical care and will improve risk stratification of TS patients. Indeed, CMRI is outstanding to detect degrees of aortic dilatation and coarctation that are not visible on echocardiography14, but is limited by its high cost and poor tolerability due to claustrophobia and anxiety in some TS patients . Meanwhile, fast scan seeds, low radiation dose and increased anatomic coverage are improving the image quality of cardiac multidetector computed tomography (MDCT) and reducing patient risks in children. Cardiac MDCT is also considered to effectively bridge the gaps among echocardiography and cardiac MRI in children with congenital heart disease. In addition, cardiac MDCT has better cost benefit compared with cardiac CRMI."

Was added

As well as 3 new related references (Ref 12-14).

5. The abbreviations were reduced and explained at their first appearance in the manuscript.

6. A requested, an appropriate title for the two figure legends was provided

Reviewer No ***00978545***

Comment of the Reviewer: This is an interesting case study describing the presence and treatment of aortic arch dissection in a patient with Turner's syndrome. The case highlights the unreliability of the aortic size index in assessing risk of aortic dissection in patients with Turner's syndrome. While the single case study is of some significance, its presentation could be improved.
1. "Patients" should read "Patient" in the title.
2. "Aortic size index" should be defined in first line of the Abstract.
3. The abbreviations TS, MF, and ASI were defined in the Introduction and do not need to defined again in the Discussion.
4. The ascending aorta could be labeled in Figure 2 to improve readability.

Authors would like to thank this reviewer for his/her words of appreciation

1) It was corrected as suggested
2) Done
3) Done
4) The label was added as requested

Reviewer No ***00389505***

Comment of the Reviewer: This case report by Nijs et al describes a case of aortic dissection in a Turner patient with a low ASI. Even though it is only a case report it is interesting case and underlines the importance of not looking solely at the ASI when risk stratifying TS patients. Specific comments:
1. At any point, were the patient investigated with a MRI?
2. A recent study has found in TS patients that aortic coarctation, bicuspid aortic valves, age, diastolic blood pressure, body surface area and antihypertensive treatment all were associated with ASI. This could well be discussed in relations to risk stratification/follow up. (Prediction of aortic dilation in Turner syndrome - enhancing the use of serial cardiovascular magnetic resonance. Mortensen KH, Erlandsen M, Andersen NH, Gravholt CH. J Cardiovasc Magn Reson. 2013 Jun 6;15(1):47.)

On behalf of all co-authors I would like to thank this reviews for his/her comments.

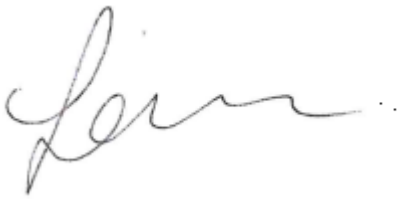
1. No, the patients had no MRI and this was explained and discussed as requested also by the reviewer No 00396997 (please see above)

2. **Page 6 Line 12:**
"A recent study11 employing mathematical models of aortic disease in TS, showed that growth of the thoracic aorta is dynamic over time and risk factors such as aortic coarctation, bicuspid aortic valves, age, diastolic blood pressure, body surface area and antihypertensive treatment preferentially accelerated growth of the ascending aorta. Unfortunately this model was not linked to aortic dissection and rupture".
Was added

the reference suggested by the reviewer was added as reference n 11.

References and typesetting were corrected

Sincerely yours



Sandro Gelsomino, MD, PhD
Cardiothoracic Department, Maastricht University Hospital
Maastricht, The Netherlands
Telephone: 0031 43 38881066
E-mail: sandro.gelsomino@libero.it