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Editorial

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Sarcopenia in Fontan patients: a sign of frailty-associated premature ageing?

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On November 10, 1942, after winning the battle of Alamein, Winston Churchill delivered these famous words: "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

Adults living with CHD are a growing population, as they are now surviving into adulthood and even reaching geriatric ages thanks to the emergence of surgical and medical innovations.[1] In all adults with CHD, the fastest-growing population is the one with complex congenital lesions.[1] Fontan patients are among the most resource-intensive populations from a health service perspective. They experience multiple extracardiac complications that are mainly related to sustained decreased cardiac output and increased systemic venous pressure.[2] This means that Fontan patients are living with a lifespan state of compensated or decompensated heart failure.[2] The functional consequences of their singular cardiovascular physiology have been expressed as both a reduced life expectancy when compared to other CHD population[3] and a decreased exercise capacity.[4] Moreover, skeletal muscle strength has been shown to be similar to that of patients with advanced heart failure,[5] since they have increased adiposity and, as shown by Cordina et al., Fontan-associated myopenia.[6] The advent of the Fontan operation has certainly improved outcomes for patients with univentricular heart, but given the ensuing complications, treating physicians feel this is "the end of the beginning," to use Churchill's words.

Psoas muscle area, an indicator of sarcopenia, has proven to be an important marker of worse cardiovascular outcomes and of increased risk of mortality in patients with long-standing heart failure and increased cardiovascular burden.[7-11] It has also been shown to be correlated with indicators of physical frailty such as low handgrip strength and short physical performance battery.[12] Frailty is a broad multidimensional syndrome that reflects a patient's vulnerability. It encompasses multiple clinical elements such as muscle mass, strength, malnutrition, and functional performance.[13] Sarcopenia is therefore a crucial element in the assessment of frailty. We hypothesised that Fontan patients, despite their young age, exhibit sarcopenia resembling that more often seen in elderly patients with cardiovascular comorbidities rather than in healthy age-matched controls.

At the McGill Adult Unit for Congenital Heart Disease (MAUDE clinic, Montreal, Canada), a total of 67 patients with Fontan are actively followed. Multiple imaging modalities are used as part of the routine screening for Fontan-associated liver disease, including abdominal ultrasound, CT, and magnetic resonance. In this setting, 17 out of 67 Fontan patients had a CT of the abdomen performed and thus were included in the study. The psoas muscle areas were measured on the CT scan using the validated web-based software Coreslicer.com.[14] Measurements were done in the axial plane, at the highest level of the L4 vertebrae. There is no gold standard number to define sarcopenia using psoas muscle area. Studies have not always used specific cut-offs but rather found an association between lower psoas muscle area and a higher incidence of major adverse events. As an indicator, a study by Derstine et al., looking at psoas muscle area in healthy patients aged 20 to 40 years, defined sarcopenia as less than 23.4 cm^2 in males and 14.3 cm^2 in females.[15]

The psoas muscle area measurements of the Fontan patients were compared to a group of 125 age-matched healthy controls and 425 patients with aortic stenosis who were candidates for transcatheter aortic valve replacement (the aortic stenosis group) using sex-stratified medians. The data for the healthy cohort and the aortic stenosis group were obtained from the McGill Frailty Registry. The comparisons in psoas muscle areas were done with Kruskal–Wallis to take into account the limited sample size of the Fontan group.

The Fontan cohort had 6 males and 11 females with a mean age of 24 and 32 years, respectively. Among the males, 33% had systemic left ventricle and 33% had heterotaxy syndrome. Among the females, the proportions were 82% and 18%, respectively. For Fontan females, the median psoas muscle area was 18.1 cm^2 and the interquartile range was 14.85–21.12 cm^2. For males, these were 23.41 cm^2 and 22.25–30.21 cm^2, respectively. The aortic stenosis group was composed of 241 males and 184 females aged 70 to 99 years. The median psoas muscle area for this group was 15.01 cm^2 (interquartile range 12.16–16.90 cm^2) for females and 21.56 cm^2

(interquartile range 18.69–24.27 cm^2) for males. The healthy cohort consisted of 59 males and 66 females aged 20 to 40 years, similar to our cohort of Fontan patients. They had a median psoas muscle area of 18.71 cm^2 (interquartile range 17.07–21.50 cm^2) for females and 32.01 cm^2 (interquartile range 27.54–36.08 cm^2) for males. No studies have reported psoas muscle areas in healthy elderly patients to which we could compare the aortic stenosis group, but it has been shown that muscle mass is expected to decrease with advancing age, even in healthy patients.[16,17]

The Fontan males were found to have significantly lower psoas muscle areas than the healthy controls ($p = 0.006$), but the difference between them and the aortic stenosis patients was non-significant ($p = 0.106$) (Figure 1, Panel A). The Fontan females had psoas muscle areas that were not statistically different from those of the healthy controls ($p = 0.308$), but higher than those of the aortic stenosis patients ($p = 0.009$) (Figure 1, Panel B).

To our knowledge, this is the first observation to directly compare Fontan patients to a group of elderly patients with an increased cardiovascular disease burden using sarcopenia measurements. Our results show that men with Fontan had reduced muscle mass, resembling that of candidates for transcatheter aortic valve replacement and lower than that of age-matched healthy controls. The comparison was not statistically significant in women with Fontan.

The differences in intrinsic cardiovascular anatomy between males and females in our cohort may account for the sex discrepancy seen in the results. Most of our Fontan females (82%) had a systemic left ventricle as opposed to only one-third of the males. It is well documented that Fontan patients with systemic left ventricle have better long-term survival rates compared to patients with systemic right ventricle or an indeterminate one.[18,19] Moreover, 33% of males from our cohort versus 18% of females had heterotaxy, a syndrome also associated with decreased survival.[18] The statistical difference between these proportions is not reported as the sample size is not sufficiently powered to constitute a robust measure of effect. These anatomical characteristics of good prognosis that were observed mainly in Fontan females in our cohort may confer better Fontan haemodynamics, which potentially protects them from the early development of sarcopenia.

Our findings may suggest sex differences in skeletal muscle composition in Fontan patients, similar to what was observed in a larger cohort of 40 Fontan patients by Possner et al. These authors found a statistically significant reduction in the skeletal muscle index measured by magnetic resonance in male patients with Fontan when compared to healthy controls, a difference that was not established in the female cohort.[20] Shiina et al. also found that Fontan patients have reduced muscle mass when compared to controls, but their analyses were not sex-stratified.[21] This renders it difficult to interpret their results and correlate them with our findings, since it is known that the muscular composition of men and women is very different.

Sarcopenia is a known marker of worse outcomes and mortality in patients with cardiovascular disease.[7-12] Our observation that sarcopenia mainly affect male Fontan patients could explain an unrevealed cause, elucidating the higher rate of complications and reduced long-term survival noticed in male patients with Fontan.[22,23] Furthermore, oestrogen has been postulated as cardioprotective, which could suggest better single-ventricle haemodynamics and possibly explain the sex disparity seen in muscle mass.[23,24] On the other hand, we may wonder whether testosterone, or lack thereof, can negatively impact males. Finally, males also have a higher lean muscle mass at baseline.[15,25] The degree of loss could therefore be more pronounced when exposed to sustained low cardiac output.

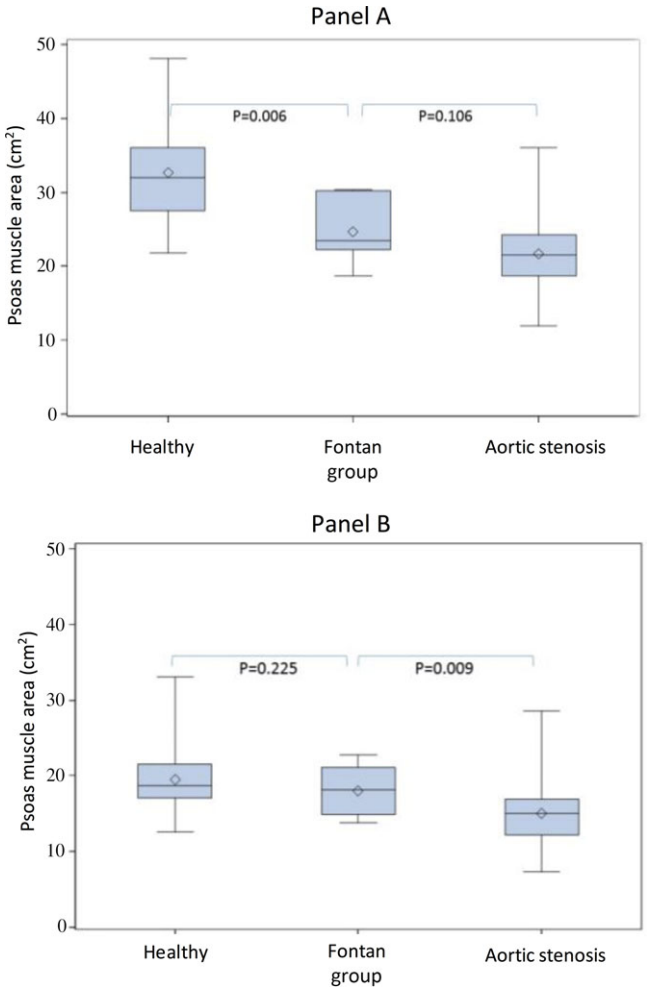

Figure 1. Boxplots illustrating the distribution of psoas muscle area for Fontan, healthy and aortic stenosis patients among males (Panel A) and females (Panel B).

Limitations of our observation include the small sample of patients. There is also a potential risk of selection bias, given only 17 of our 67 patients had a recent CT of the abdomen done and were included in this observation. Screening for Fontan-associated liver disease is done by abdominal ultrasound, by abdominal CT, or by liver MRI, as no modality of choice has been defined in the guidelines.[26] The choice of imaging technique is made on a case-by-case basis and does not necessarily reflect the disease severity of Fontan patients, but may reflect a finding on ultrasound or in biochemistry leading to consideration of a CT. This could potentially introduce an ascertainment bias if Fontan patients included in the study were the ones with the greatest risk of liver disease. Even so, our findings point to an observation that can be clinically important if confirmed by prospective cohorts with systematically collected imaging data. Finally, many confounders would need to be addressed to help us understand better this potential sex-specific adverse effect and its mechanism in relation to the Fontan physiology.

In conclusion, our observation shows that male Fontan patients have reduced muscle mass resembling that seen in elderly patients with aortic stenosis more than that of age-matched controls. This observation was not seen in females. Further studies are needed to

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elucidate the impact of sarcopenia on long-term cardiovascular outcomes in Fontan patients and the sex differences relative to sarcopenia in patients with single-ventricle physiology. These findings may reflect the fragile state of homoeostasis arising from the Fontan physiology and may be a marker of premature ageing. Our findings should guide tailored interventions to understand and prevent this adverse effect. Future directions are to evaluate this in a larger setting of Fontan patients with an approach that encompasses imaging and clinical markers.

"Before Alamein we never had a victory. After Alamein we never had a defeat."—Churchill

Although Fontan patients endure an array of systemic complications due to their unique physiology, the Fontan procedure has been a major turning point for patients with a univentricular heart who have now been offered another chance at life. The complications that arise from this procedure cannot be counted as a defeat, but as challenges for our scientific minds to provide solutions.

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Conflicts of interest. None.

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