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Case report

Peri-vascular adipose tissue attenuation on chest computed tomography in patients with Marfan Syndrome: a case series

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Abstract. *Background and aim of the work*: Marfan Syndrome is a genetic disorder that determines histopathological alterations of the aortic vascular wall leading to increased inflammatory component. The peri-vascular adipose tissue attenuation is a method able to capture localized vascular inflammation by mapping spatial changes of perivascular tissue attenuation on computed tomography. *Methods*: We measured peri-vascular adipose tissue attenuation around the ascending aorta in three consecutive subjects with confirmed genetic diagnosis of Marfan Syndrome. All subjects received the genetic diagnosis of fibrillin-1 gene mutation as part of the family screening of patients with known Marfan Syndrome. Chest computed tomography was performed in such asymptomatic subjects after genetic confirmation of Marfan Syndrome. None of these subjects showed aortic aneurysms or suffered from chronic inflammatory/infectious disease. *Results.* In the three subjects identified with Marfan Syndrome the value of aortic peri-vascular adipose tissue attenuation measured at chest computed tomography was higher than normal and the volume of aortic peri-vascular adipose tissue was lower. *Conclusion*: These preliminary observations suggest that peri-vascular adipose tissue attenuation is unexpectedly high in patients with Marfan Syndrome, notwithstanding the normal aortic diameter at the time of computed tomography. Whether this observation may find a clinical use in suspected Marfan Syndrome or in predicting aortic complications in Marfan Syndrome is worth to be assessed in prospective studies. (www.actabiomedica.it)

Key words: Marfan syndrome, Peri-vascular adipose tissue attenuation, Computed tomography, Aorta, Fibrillin-1 gene mutation.

Introduction

Marfan syndrome (MFS) is a common autosomal dominant hereditary disease, and the occurrence rate in the general population is approximately 2–3/10,000 (1). The MFS is a systemic disorder of the connective tissue caused by heterozygous mutation in the fibrillin-1 (FBN1) gene on chromosome 15q21 encoding for the extra-cellular matrix protein fibrillin-1. Impaired FBN1 protein synthesis, secretion or incorporation in the extracellular matrix typically leads to pathological findings in multiple organ systems (1-6). The prognosis in MFS patients is dominated by cardiovascular life-threatening complications of the aorta due to progressive aortic dilation, potentially leading to aneurysm, dissection, and rupture (7). Chest computed tomography (CT) with intravenous contrast is the gold standard in the diagnostic process of thoracic aorta diseases; CT allows a complete evaluation of the thoracic aorta in terms of morphology and presence of potential aortic aneurysm, being able to assess also the presence of endovascular thrombus, the relationship with adjacent structures and signs of rupture (8,9). Peri-vascular adipose tissue (PVAT) attenuation by CT imaging is a non-morphological analysis that has been applied in coronary arteries and in other vascular beds, it is a marker of vascular localized inflammation and

reflects the histopathological alterations of perivascular adipose tissue (10-12). We have recently applied PVAT attenuation to the ascending aorta (Figure. 1), we found a statistically significant higher mean PVAT attenuation in patients with ascending aorta aneurysms compared with patients showing normal aortic diameter (-69.1 vs -75.1 Hounsfield Units-HU) (13). In non-MFS patients affected by ascending aorta aneurysm PVAT attenuation was apparently associated progressive substitution of perivascular adipose cells by fibrotic tissues (14). FBN1 is a major component of the core of microfibrils that play a key role for the development of a correct scaffolding of the extra-cellular matrix. Due to pathogenic variants in FBN1, elastic fiber composition is suboptimal and compensated by excessive collagen and proteoglycan deposition, which leads to increased stiffness and progressive weakening of the extra-cellular matrix (15,16). We have hypothesized that tissue alterations in MFS patients may lead to changes in peri-vascular adipose tissue, which may be uncovered by the analysis of the PVAT attenuation, well before the development of true aneurysms.

Based on the abovementioned hypothesis, we have studied the PVAT attenuation in three phenotype-negative asymptomatic patients having a genetic diagnosis of MFS. The chest CT scan was performed for screening purposes. The three subjects did not report a history of aortic aneurysm or aortic dissection, they had not undergone previous vascular surgery and they were not affected by chronic inflammatory or infectious diseases.

Clinical series

Case 1

This case refers to a 49 year-old male subject, family member of a MFS patient, diagnosed with MFS

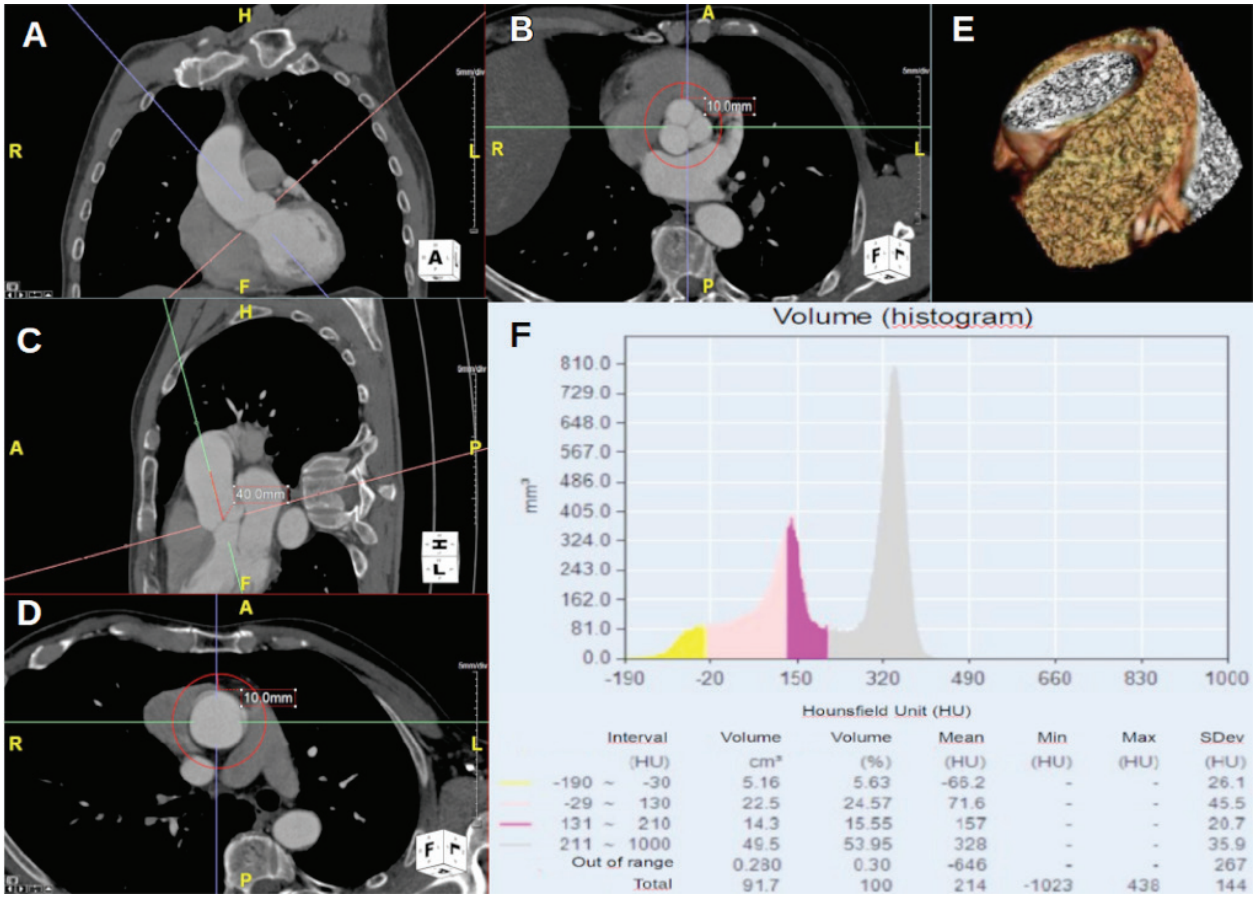

Figure 1. Left panels show the diameter of the ascending thoracic aorta, while right panels show the aortic peri-vascular adipose tissue attenuationon chest computed tomography scan, respectively for in case 1 (A and B), case 2 (C and D) and case 3 (E and F).

during family screening. The diameter of the ascending thoracic aorta is 34.1 mm (Figure. 2A). The mean PVAT attenuation was -66.2 HU, while fat volume was 5.16 cm^3 (Figure. 2B).

Case 2

This case refers to a 57 year-old male subject, family member of a MFS patient, diagnosed with MFS during family screening. The diameter of the

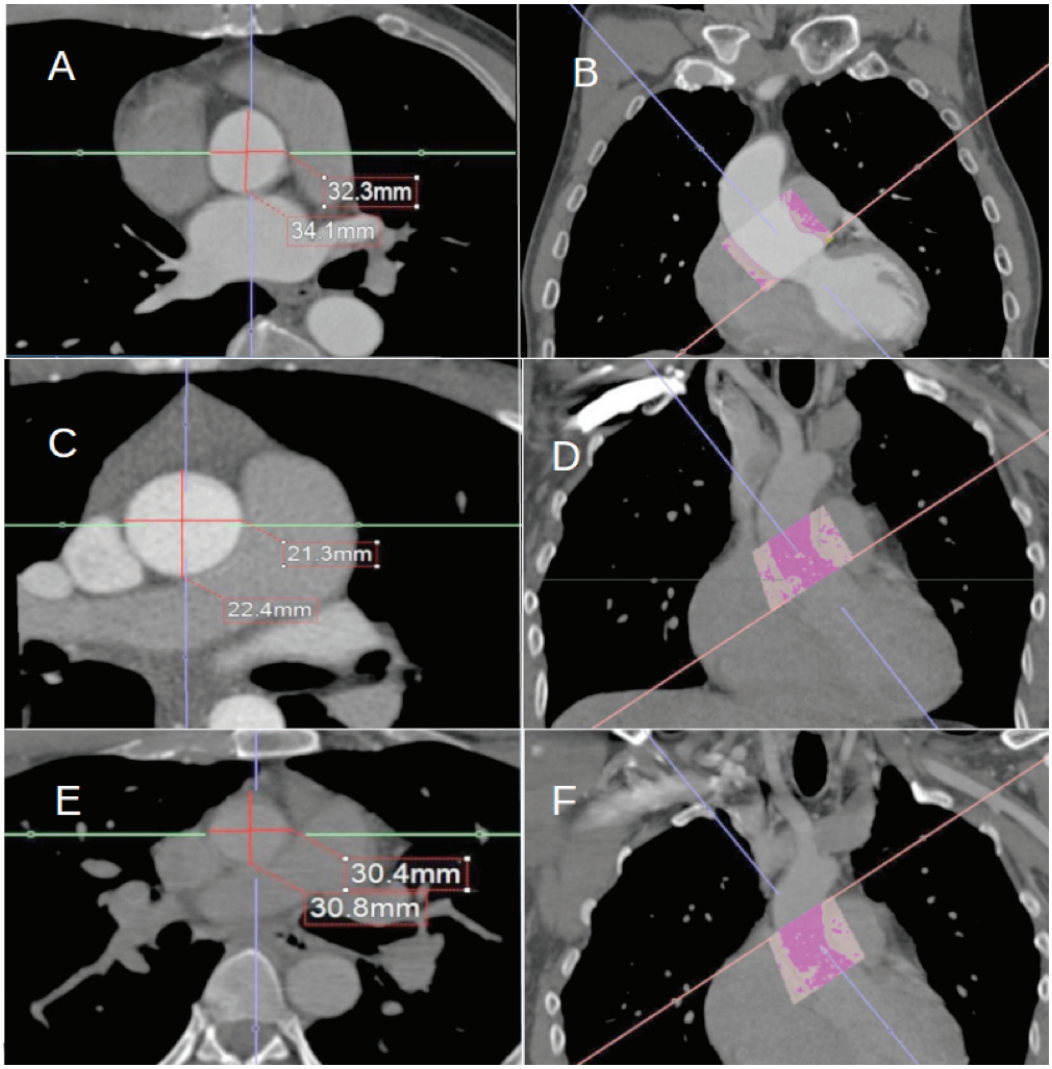

Figure 2. Step-by step process used to measure peri-vascular adipose tissue attenuation on computed tomography imaging. After spatial planes reorientation along the long and short axis of the ascending aorta (A) a 2D circle using an incremental +10mm radius beyond the aortic diameter at the cusps level is traced (B) and a second circle is then drawn 40mm distally (C), using an incremental +10mm radius beyond the diameter of the aorta at that level (D). The software (Aquarius Workstation version 4.4.13; TeraRecon Inc., Foster City, CA) automatically interpolates the volume between the two circles and builds the 3D volume sample (E), whose volume is known (91.7 cm3 in this case). The software also calculates the volume corresponding to a pre-determined Hounsfield Unit range; for fat sampling we used -190 to -30 Hounsfield units (HU) range (in this case a volume of 5.16 cm3 is automatically measured). Fat attenuation histogram shows that the mean attenuation of fat found in this custom sample volume is -66.2 HU (F). All measurements were performed on a 128-slice dual-source computed tomography system (Definition Flash, Siemens Healthcare, Forchheim, Germany TC) with tube voltage of 120 kV (high-iodine group).

ascending thoracic aorta is 22.4 mm (Figure. 2C) The mean PVAT attenuation was -63.1 HU while fat volume was 0.28 cm^3 (Figure. 2D).

Case 3

This index case refers to a 43 year-old male subject, family member of a MFS patient, diagnosed with MFS during family screening. The diameter of the ascending aorta is 30.8 mm (Fig. 2E). The mean PVAT attenuation was -54.8 HU, while fat volume was 1.02 cm^3 (Figure. 2F).

Results

Aortic PVAT attenuation on chest computer tomography is higher in subjects with Marfan syndrome although they have normal-diameter ascending aorta.

Prospective studies are needed to assess the specific potential role of this PVAT attenuation method in the potential diagnosis and/or risk-stratification of subjects with genetically-confirmed MFS.

Discussion

In this small case-series the aortic PVAT attenuation measurement was applied for the first time to subjects with MFS. Figure 1 shows the step-by-step post-processing method, as it was performed for the measurement of PVAT around the ascending aorta.

The PVAT attenuation values in our MFS cases (mean -61.7 HU), expressed in Hounsfield Units, were high in absolute terms (high means PVAT attenuation values closer to 0 HU, due to adipose tissue attenuation being negative in Hounsfield Units) and relatively if compared with the reference value for non-inflamed PVAT in healthy controls. In fact, mean PVAT in our MFS cases with normal-diameter aorta was significantly higher in comparison with values from the only existing prior study reporting on PVAT in normal-diameter ascending aorta in non-MFS subjects (mean -75.1 HU, lower-upper quartile -79.2 to -70.3, $p<0.0001$) (13). The PVAT volume in our MFS cases was also reduced compared with the abovementioned non-MFS control subjects without ascending aorta aneurysm ($p=0.031$) (13). The finding of a lower PVAT volume in our case series reinforces the speculation that the modifications of the Fibrillin1 protein in MFS leads to a reshaping of the PVAT with a reduction of adipose tissue and an increase of mean PVAT attenuation.

Antonopoulos et al have shown that the histopathological correlate of coronary PVAT attenuation is secondary to a localized inflammatory state (10). While the histopathology of coronary arteries and ascending aorta is different, it is known from histopathological studies that localized vascular inflammation is greater in patients with aortic aneurysms and MFS than in the ones not affected by MFS. Other findings in patients with aortic aneurism and MFS are: greater glycosaminoglycan accumulation, angiogenic remodeling, matrix metalloproteinase-2 expression, smooth muscle cell turnover and loss/fragmentation of elastic fibers (17). The role of the abovementioned structural changes in influencing the PVAT attenuation and volume is unknown. In particular, it is not known whether the higher PVAT attenuation values in MFS patients truly correspond to a localized inflammatory state of the ascending aorta or to other structural changes. Although the predisposition of MFS patients to aortic vascular disease is well known, not all patients do develop an aortic aneurysm during their lifetime and the onset of an aneurysm may occur at different age. It is likely that vascular and peri-vascular structural changes play a key role in the development of aortic aneurysm in MFS patients, and we speculate that aortic PVAT attenuation may have a diagnostic and/or prognostic role in MFS patients, as demonstrated for the coronary arteries (18).

Conclusion

Peri-aortic adipose tissue attenuation is unexpectedly high in patients with MFS, notwithstanding the normal aortic diameter. Whether this observation may find a clinical use in suspected MFS or in predicting aortic complications in MFS is worth to be assessed in prospective studies.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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