ORIGINAL ARTICLE

Myocardial Tissue Characterization Using Electron Density Imaging: Relationship with Sex and Cardiovascular Risk Factors

Caracterización del tejido miocárdico a través de imágenes de densidad electrónica: relación con el sexo y factores de riesgo cardiovascular

GASTÓN A. RODRÍGUEZ-GRANILLO[1, MTSAC], BIBIANA RUBILAR[1, MTSAC], LUCIA FONTANA[1], NAHIR LUNA[1], SARAH GARRON-ARIAS[1], PEDRO LYLYK[1], ROSANA POGGIO[2]

ABSTRACT

Background: Electron density (ED) imaging might be able to detect myocardial tissue differences indistinguishable for conventional non-contrast computed tomography (CT).
Objectives: To evaluate whether there are differences in myocardial ED associated with sex, and if present, their relationship with cardiovascular risk factors or coronary calcification.
Methods: Patients were participants of a prospective single center observational study comprising asymptomatic subjects between 50 and 75 years old, referred for a low-dose chest CT. All images were obtained using a dual-layer detector spectral CT, and evaluated using conventional CT (120 kVp) and ED images.
Results: A total of 171 patients were included. Myocardial attenuation was not related to sex or coronary risk factors (all $p>0.05$), whereas the percent electron density relative to water (%EDW) was significantly higher among males ($p<0.0001$), and patients with diabetes ($p=0.007$), hypertension ($p=0.004$), and obesity ($p=0.004$). The extent of coronary artery calcification was unrelated to neither the myocardial attenuation, nor the myocardial ED. At univariate analysis, male sex was the only variable associated with a high %EDW ($p=0.011$), whereas age, diabetes, obesity, smoking, hypertension, and CACSIS (coronary artery calcification segment involvement score), were not. Logistic regression analysis including sex, obesity, diabetes, and hypertension in the model, identified male sex as the only independent predictor of a high %EDW (OR 2.51, 95%CI 1.23-5.34, $p=0.016$).
Conclusions: In this study, ED imaging identified myocardial tissue differences that conventional CT was unable to discriminate, with a higher %EDW in men and in patients with cardiovascular risk factors. Male sex was the only independent predictor of a high %EDW

Key words: Computed tomography - Dual energy - Spectral - Gender - Coronary calcification

RESUMEN

Introducción: Las imágenes de densidad electrónica (DE) podrían detectar diferencias miocárdicas tisulares no distinguibles mediante la tomografía computarizada (TC) convencional sin contraste.
Objetivos: Evaluar si existen diferencias de DE miocárdica asociadas al sexo, y de estar presentes, su relación con factores de riesgo cardiovascular o calcificación coronaria.
Material y métodos: Los pacientes pertenecían a un estudio prospectivo observacional de centro único que incluyó sujetos asintomáticos entre 50 y 75 años, derivados para realizar una TC de tórax de baja dosis. Todas las imágenes se obtuvieron mediante un equipo de TC espectral dual, y fueron evaluadas utilizando imágenes de TC convencional (120 kVp) y de DE,
Resultados: Se incluyó un total de 171 pacientes. La atenuación miocárdica no estuvo relacionada con el sexo o factores de riesgo coronarios (todos con $p >0,05$), mientras que el porcentaje de densidad electrónica respecto del agua (%EDW, por su sigla en inglés) fue significativamente mayor en la población masculina ($p<0,0001$), y en los pacientes con diabetes ($p=0,007$), hipertensión ($p=0,004$) y obesidad ($p=0,004$). La extensión de la calcificación coronaria no estuvo relacionada ni con la atenuación ni con la DE miocárdicas. En el análisis univariado, el sexo masculino fue la única variable asociada a un %EDW elevado ($p=0,011$), mientras que la edad, la diabetes, la obesidad, el tabaquismo, la hipertensión y el score CACSIS (score de calcificación de las arterias coronarias), no. Un modelo de regresión logística que incluyó sexo, obesidad, diabetes e hipertensión, identificó al sexo masculino como el único

Rev Argent Cardiol 2024;92:117-123. http://dx.doi.org/10.7775/rac.v92.i2.20752

Received: 02/02/2024 – *Accepted:* 03/14/2024

Correspondence: Gastón A. Rodríguez-Granillo: Instituto Medico ENERI, Clinica La Sagrada Familia. Av. Libertador 6647 (C1428ARJ), Buenos Aires, Argentina. Telephone: +541140147000. Email: grodriguezgranillo@gmail.com

[1] Instituto Medico ENERI, Clinica La Sagrada Familia, Buenos Aires
[2] MultiplAI Health LTD, UK

predictor independiente de %EDW elevado (OR 2,51, IC 95% 1,23-5,34, p=0,016).
Conclusiones: En este estudio, las imágenes de DE identificaron diferencias en el tejido miocárdico que la TC convencional fue incapaz de discriminar, con un mayor %EDW en hombres y en pacientes con factores de riesgo cardiovascular. El sexo masculino fue el único predictor independiente de %EDW elevado

Palabras clave: Tomografía computarizada - Energía dual - Espectral - Género - Calcificación coronaria

INTRODUCTION

After decades of female underrepresentation in most clinical studies, there is an increasing interest in the evaluation of the distinctive cardiovascular phenotypes of men and women. (1)

Aside from a different risk factor profile, clinical presentation, and higher susceptibility to myocardial injury associated with psychological stress, women have less coronary calcification, higher rates of microvascular disease, and a more hypercoagulable profile, underscoring the role of nonobstructive disease among them. (2-4) Furthermore, independent of smaller (adjusted for body surface) epicardial coronary arteries, women have higher resting myocardial perfusion and myocardial blood volume compared with men. (5) Indeed, gender differences endure even among the elderly, with males displaying consistently higher coronary calcification and total coronary plaque burden despite showing, interestingly, a similar extent of extra-coronary calcification. (6,7)

To date, characterization of myocardial tissue using computed tomography (CT) requires iodinated contrast. Nonetheless, the electron density (ED) of the atoms comprising the tissues, normalized to pure water, can be directly estimated using dual-layer spectral computed tomography (CT), without modifications of acquisition protocols. (8) Previous studies have suggested an incremented value of (non-contrast) ED imaging over iodinated contrast assessment for tissue characterization, although to the best of our knowledge, data regarding myocardial ED has not been explored. (9-11)

Therefore, we hypothesized that ED imaging might be able to detect differences indistinguishable for conventional non-contrast CT. To confirm this, we evaluated sex-related differences in myocardial ED and whether, if present, these are related to cardiovascular risk factors or coronary calcification.

METHODS

Study Population

Patients were participants of a prospective single center observational study that explored the ability of whole-blood transcriptome screening test assisted by deep learning to detect coronary calcium, whose main analysis (transcriptome) will be reported independently. The study population comprised 200 asymptomatic volunteers (men between 40 and 75 years old and women between 50 and 75 years old), or patients referred for a low-dose chest CT scan for smoking. Main exclusion criteria comprised a history of heart, renal, or liver failure, previous myocardial infarction, previous coronary revascularization or peripheral vascular disease, active pulmonary disease, immunosuppressant treatment or malignancy under current treatment, and COVID-19 infection in the past three months. To avoid age differences, males younger than 50 were further excluded for the present investigation.

Image acquisition and analysis

All images were obtained with a dual-layer detector CT scanner (IQon Spectral CT, Philips Healthcare, Best, The Netherlands) using the following parameters: collimation 64 x 0.625 mm; tube voltage 120 kV; current 70-140 mA based on patient size; rotation time 270 ms; slice thickness 2.0 mm. Dose modulation (3D Modulation) and hybrid iterative reconstruction (iDose 5) were used in all cases. This scanner enables extraction of spectral data using dual-layered scintillation detectors, being the inner layer an yttrium-based garnet low density scintillator for detection of lower energies, and the outer layer a gadolinium oxysulphide high density scintillator for detection of higher energies. ED estimation using this scanner is based on a two-base model comprising the combination of Compton scatter-like (SC) and photoelectric-like effects, with a dominating SC component. Images were assessed using multiparametric side-by-side view of conventional CT (120 kVp) and ED images and were analyzed offline by a cardiac imaging expert who was blinded to all demographic and clinical data. All images were assessed using average multiplanar reconstructions of short axis views (assisted by adjacent landmarks including the anterior and posterior interventricular groove, and coronary veins and arteries), adjusting window´s width and level at the best discretion of the observer. Using the American Heart Association 16-segment model, regions of interest (ROIs) were placed at the sixteen myocardial segments (Figure 1) starting with those involving the lateral, anterior, and inferior walls, and finally the septal wall. Care was taken to avoid areas with uniform band-like artifacts. Subsequently, the mean Hounsfield units (HU) and mean percent ED relative to water (%EDW) were calculated. It is noteworthy that ROIs were automatically co-localized and identical in size and location in both displays (conventional and ED, Figure 1).

In addition, we evaluated the relationship between myocardial ED and the extent of coronary artery calcifications. For this purpose, we evaluated the presence of any calcification and scored each patient according to the number of vessels involved, and to the numbers of segments involved (CACSIS).(12)

Ethical considerations

The protocol of the study, in accordance with the declaration of Helsinki and later amendments, was approved by the ethics review board (CEI FLENI registration code 4230), and all patients provided their written informed consent.

Statistical analysis

Discrete variables are reported as counts (%) and continuous variables are presented as mean ± standard deviation or median (interquartile range, IQR) for non-uniform

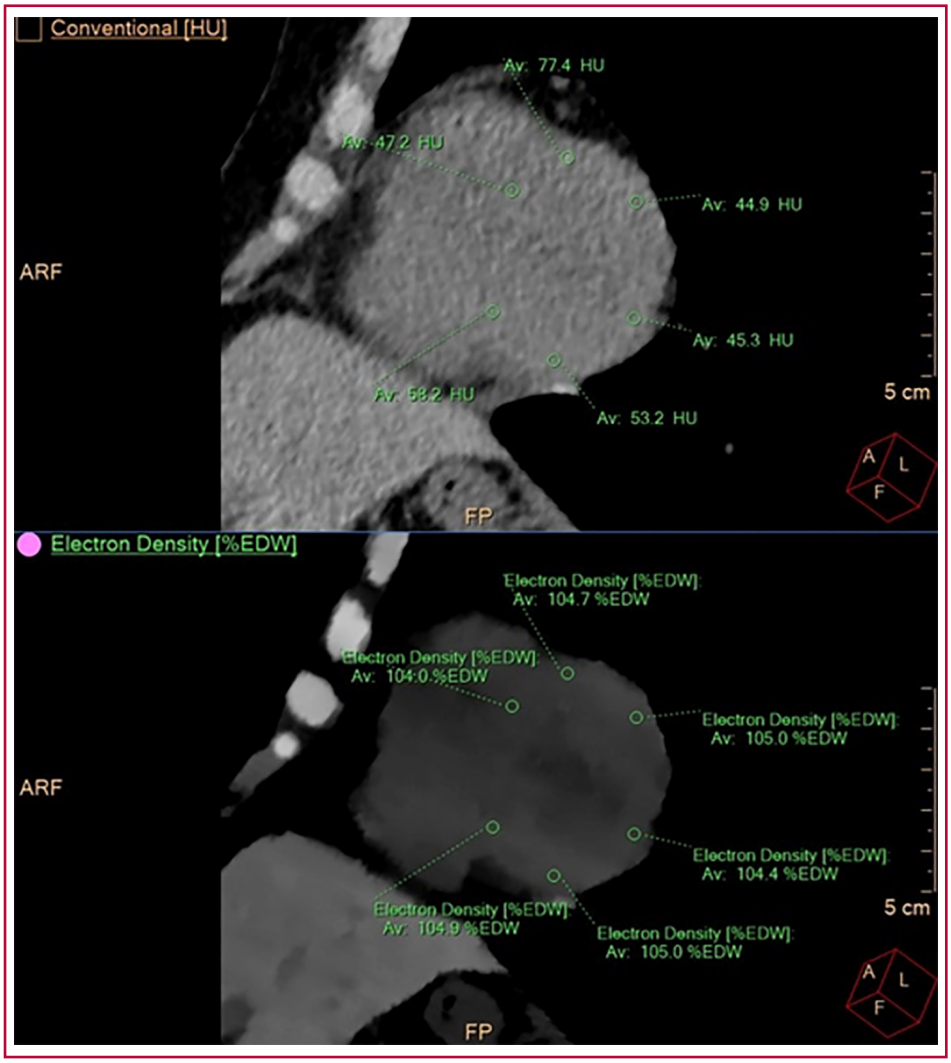

Fig. 1. Side-by-side short axis view of conventional CT (upper panel) and electron density (ED) imaging (lower panel). Mean Hounsfield units (HU) and percent ED relative to water (%EDW) calculated using regions of interest (ROI) placed at the sixteen ventricular segments. Note the exact co-localization and size of each ROI.

distributions. Comparisons between groups of continuous variables were performed using a t test for independent variables, one-way analysis of variance (ANOVA), or the Mann-Whitney U test; whereas comparisons of categorical variables were performed using Fisher exact test, and the chi square test (multiple groups). To identify independent predictors of an incremented %EDW, we built a multiple logistic regression model using the 75th percentile %EDW as dependent variable. Myocardial segments were re-evaluated by an independent cardiologist in a randomly selected subset of 20 cases (320 segments), and the agreement between observers was analyzed using intraclass correlation coefficients (ICC; two-way random effects model absolute agreement, and average measurement) with 95% confidence intervals. All statistical analyses were performed using SPSS software, version 22.0 (Chicago, Illinois, USA). A two-sided p value of less than 0.05 indicated statistical significance.

RESULTS

Two hundred patients were enrolled in the main study between June and October 2021, of which 29 men younger than 50 years old were excluded to attain a balanced age comparison, leading to a total of 171 patients (77 men and 94 women) in this analysis. Mean age was 60.2±6.8 years, without differences between groups (men 60.4±6.9 years, vs. women 60.0±6.8 years, p=0.714). We did not identify significant differences between groups regarding rates of diabetes (p=0.282), smoking (p=0.334), and hypercholesterolemia (p=0.076), whereas men showed a higher prevalence of hypertension (53% vs. 34%, p=0.012) and obesity (48% vs. 31%, p=0.034). Compared to women, men had larger extent of coronary calcification (coronary artery calcification segment involvement score, CACSIS: men 2.34±2.9, vs. women 1.38±2.3, p= 0.016).

Relationship between myocardial attenuation and %EDW, and risk factors

Myocardial attenuation levels (HU) were not related to sex or coronary risk factors (Table 1), whereas %EDW was significantly higher among males (104.5±0.2 %EDW, vs. 104.3±0.2 %EDW, p<0.0001). Despite the narrow differences, there was no overlap between the error bars based on 95% confidence intervals of the population mean (Figure 2).

Myocardial %EDW was also higher among pa-

	Myocardial HU	Myocardial %EDW
Sex		
Men (n=77)	46.2±2.2	104.5±0.2
Women (n=94)	45.7±2.6	104.3±0.2
p value	0.182	<0.0001
Diabetes		
Yes (n=25)	46.4±2.6	104.5±0.2
No (n=146)	45.9±2.4	104.4±0.2
p value	0.343	0.007
Hypercholesterolemia		
Yes (n=54)	45.6±2.4	104.4±0.2
No (n=116)	46.1±2.5	104.4±0.2
p value	0.220	0.722
Hypertension		
Yes (n=73)	45.9±2.3	104.5±0.2
No (n=98)	46.0±2.5	104.4±0.2
p value	0.653	0.001
Obesity		
Yes (n=66)	45.9±2.7	104.5±0.2
No (n=105)	46.0±2.3	104.4±0.2
p value	0.796	0.004
Smoking		
Yes (n=33)	45.6±2.1	104.4±0.2
No (n=138)	46.0±2.5	104.4±0.2
p value	0.323	0.503
Coronary calcification		
CACSIS 0 (n=82)	46.1±2.3	104.4±0.2
CACSIS 1-3 (n=51)	45.6±2.8	104.5±0.3
CACSIS ≥4 (n=38)	46.1±2.2	104.4±0.2
p value	0.556	0.382

CACSIS: coronary artery calcification segment involvement score
Continuous variables are presented as mean ± standard deviation

Table 1. Myocardial attenuation levels (Hounsfield units, HU) and percent electron density relative to water (%EDW) according to sex, risk factors, and coronary artery calcification

tients with diabetes (104.5±0.2 %EDW vs. 104.4±0.2 %EDW, p=0.007), hypertension (104.5±0.2 %EDW, vs. 104.4±0.2 %EDW, p=0.001), and obesity (104.5±0.2 %EDW, vs. 104.4±0.2 %EDW, p=0.004). Hypercholesterolemia (p=0.722), smoking history (p=0.503), and treatment with statins (p=0.184) were not related to the myocardial ED. After discrimination according to body mass index (BMI) categories (BMI <25 kg/m^2; 25-29.9 kg/m m^2 2; and ≥30 kg/m^2), myocardial attenuation levels were not related to sex among patients with normal weight (p=0.242), overweight (p=0.913), or obesity (p=0.445); whereas myocardial ED was significantly higher among males irrespective of the BMI (normal weight: 104.5±0.2 %EDW vs. 104.3±0.2 %EDW, p=0.046; overweight: 104.5±0.2 %EDW vs. 104.4±0.2 %EDW, p=0.002; and obesity: 104.6±0.3 %EDW vs. 104.4±0.2 %EDW, p=0.006). The extent of coronary artery calcification was unrelated to neither the myocardial attenuation (p=0.554), nor the myocardial ED (p=0.382). When discriminated in tertiles (Table 2), we identified a significant relationship between the myocardial %EDW and sex (p<0.0001), diabetes (p=0.038), and hypertension (p=0.049).

Regarding reproducibility, the interobserver reliability was modest when assessing the myocardial attenuation levels (ICC 0.58, 95%IC -0.07 - 0.83) and good by means of %EDW (ICC 0.86, 95%CI 0.64-0.94).

Predictors of high myocardial electron density

At univariate analysis, sex was the only variable associated with a high %EDW (p=0.011), whereas age (p=0.702), diabetes (p=0.154), obesity (p=0.073), smoking (p=0.454), hypertension (p=0.421), and CACSIS (p=0.842), were not. At multiple logistic regression analysis including sex, obesity, diabetes, and hypertension in the model, male sex was identified as the only independent predictor of a high %EDW (OR 2.51, 95%CI 1.23-5.34, p=0.016), whereas obesity (OR 1.97, 95%CI 0.91-4.14, p=0.0823), diabetes (OR 1.89, 95%CI 0.76-5.02, p=0.206), and hypertension (OR 1.53, 95%CI 0.74-3.46, p=0.284) remained outside the model.

DISCUSSION

The main finding of our study was the identification of significant sex-related differences in myocardial ED,

with male sex being identified as the only independent predictor of a high %EDW. Furthermore, myocardial ED was significantly higher in patients with cardiovascular risk factors, perhaps indicating a common pathophysiological process. Interestingly, attenuation levels estimated using conventional CT were unable to detect such associations.

Women's heart is not just a smaller kind of men's. As aforementioned, several studies have identified substantial phenotypical differences between men and women that exceed the most common structural and functional aspects, including the microstructural architecture even at a cellular, metabolic, and electrical level. (13-16)

Our findings are in line with the results of a large cohort of healthy biobank participants among whom the cardiovascular magnetic resonance radiomic profile was evaluated. In that study, both male sex and

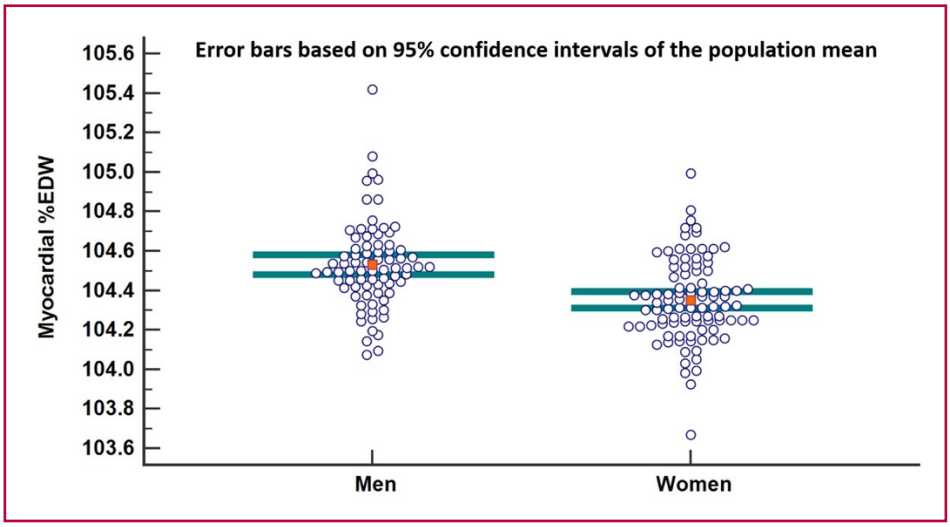

Fig. 2. Myocardial percent electron density relative to water (%EDW) discriminated by sex

Table 2. Frequency distribution of sex, risk factor, and coronary artery calcification according to myocardial electron density (%EDW) tertiles

	Lower tertile %EDW	Mid tertile %EDW	Upper tertile %EDW	p value
Sex				<0.0001
Men (n=77)	11 (14%)	31 (40%)	35 (46%)	
Women (n=94)	46 (49%)	28 (30%)	20 (21%)	
Diabetes				0.038
Yes (n=25)	3 (12%)	10 (40%)	12 (48%)	
No (n=146)	54 (37%)	49 (34%)	43 (30%)	
Hypercholesterolemia				0.674
Yes (n=54)	18 (33%)	21 (39%)	15 (28%)	
No (n=116)	39 (40%)	38 (33%)	39 (34%)	
Hypertension				0.049
Yes (n=73)	18 (25%)	25 (34%)	30 (41%)	
No (n=98)	39 (40%)	34 (35%)	25 (26%)	
Obesity				0.072
Yes (n=66)	18 (27%)	20 (30%)	28 (42%)	
No (n=105)	39 (37%)	39 (37%)	27 (26%)	
Smoking				0.464
Yes (n=33)	11 (33%)	14 (42%)	8 (24%)	
No (n=138)	46 (33%	45 (33%)	47 (34%)	
Coronary calcification				0.485
CACSIS 0 (n=82)	32 (39%)	26 (32%)	24 (29%)	
CACSIS 1-3 (n=51)	14 (28%)	17 (33%)	20 (39%)	
CACSIS ≥4 (n=38)	11 (29%)	16 (42%)	11 (29%)	

CACSIS: coronary artery calcification segment involvement score

cardiovascular risk factors were associated with a dimmer and less texturally complex myocardium. Notably, in keeping with our findings, Raisi-Estabragh et al. identified diabetes and hypertension as the risk factors with the closest associations with left ventricular features, but not smoking. (17) Of note, we did not find a relationship between the extent of coronary artery calcification and myocardial ED, although our findings did not address the effect of flow-limiting lesions in myocardial ED.

The dual-layer configuration of single-source dual energy CT scanners such as the one used in the present study allows simultaneously obtaining spectral data, and a significant reduction of image noise (reflected in this study by the exceedingly low standard deviation), without affecting the routine workflow of the CT scanner, and makes it compatible for retrospective reconstruction. (18,19) For decades, the main purpose of ED imaging was radiation therapy planning, although single-energy CT requires scanner-specific calibration curves for dose calculation performed by skilled medical physicists. (20) In turn, dual-energy CT allows direct calculation of the ED on a voxel basis. In a phantom study using the same dual-layer spectral CT scanner as in our study, Hua et al. demonstrated a high accuracy of ED measurements compared with the expected values, with a median deviation from all tissue inserts ranging from 0.1% to 1.1%. In keeping with our findings, such negligible error might explain to some extent the incremental value of ED over conventional CT to detect subtle differences between tissues that cannot be conveyed without using contrast-enhanced images. Notably, in the study of Hua el at. all soft tissue materials near water ED (adipose, brain, breast, and liver) were well separated, and results were not sensitive to acquisition or reconstruction parameters. (21)

The seemingly synchronic effect of male sex and cardiovascular risk factors might potentially be related to a shared pathophysiological process such as fibrosis, or water or fat content, although interpretation of our results in this regard should be cautious since they don't offer explanations about the underlying pathophysiological mechanisms related to observed differences. (8) In this regard, despite the significant differences between genders and the relationship with risk factors, it should be acknowledged that the clinical relevance of our results is uncertain. Nonetheless, if confirmed, our findings suggest that ED might become in the future a valuable unsophisticated tool for non-contrast CT myocardial tissue characterization.

It should be stressed that it is unclear whether the improved discrimination compared with conventional imaging was related to the intrinsic value of ED imaging, or to the almost lack of image noise and minimal error associated with such approach. (8) In this regard, a previous study has shown that compared with other spectral parameters such as the effective Z number, ED imaging has the lowest deviation (within 1%) from phantom inserts. (21) It should also be recognized that our results might be influenced by the challenging multiplanar reformatting and ROI placement in non-contrast images. Finally, despite the effect of motion artifacts for non-coronary imaging is mild, future studies are warranted in order to confirm our findings using ECG-gated ED imaging. (22,23)

In conclusion, ED imaging was able to identify myocardial tissue differences that conventional CT was unable to discriminate, with a higher %EDW in men and in patients with cardiovascular risk factors.

Conflicts of interest

Dr. Gastón A. Rodriguez-Granillo declares consulting fees from MultiplAI Health, Caristo Diagnostics, Fundacion INICIAR, and RDCom. Dr. Rosana Poggio is employee of MultiplAI Health. None of the other authors have conflicts of interest to declare related to the content of the manuscript.

(See conflicts of interest forms on the website).

Funding

MultiplAI Heath.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020 Mar 3;141:e139-e596. https://doi.org/10.1161/CIR.0000000000000757.

2. Reynolds HR, Picard MH, Spertus JA, Peteiro J, Lopez Sendon JL, Senior R, et al. Natural History of Patients With Ischemia and No Obstructive Coronary Artery Disease: The CIAO-ISCHEMIA Study. Circulation. 2021;144:1008-23. https://doi.org/10.1161/CIRCULATIONAHA.120.046791.

3. Kott KA, Morel-Kopp MC, Vernon ST, Takagi Y, Di Bartolo BA, Peter K, Y et al. Association of Global Coagulation Profiles With Cardiovascular Risk Factors and Atherosclerosis: A Sex Disaggregated Analysis From the BioHEART-CT Study. J Am Heart Assoc. 2021;10:e020604. https://doi.org/10.1161/JAHA.120.020604.

4. Vaccarino V, Wilmot K, Al Mheid I, Ramadan R, Pimple P, Shah AJ, et al. Sex Differences in Mental Stress-Induced Myocardial Ischemia in Patients With Coronary Heart Disease. J Am Heart Assoc. 2016;5:e003630. https://doi.org/10.1161/JAHA.116.003630.

5. Nickander J, Themudo R, Sigfridsson A, Xue H, Kellman P, Ugander M. Females have higher myocardial perfusion, blood volume and extracellular volume compared to males - an adenosine stress cardiovascular magnetic resonance study. Sci Rep. 2020;10:10380. https://doi.org/10.1038/s41598-020-67196-y.

6. Lee SE, Sung JM, Andreini D, Al-Mallah MH, Budoff MJ, Cademartiri F, et al. Sex Differences in Compositional Plaque Volume Progression in Patients With Coronary Artery Disease. JACC Cardiovasc Imaging. 2020;13:2386-96. https://doi.org/10.1016/j.jcmg.2020.06.034.

7. Rodriguez-Granillo GA, Campisi R, Reynoso E, Capunay C, Carrascosa P. Atherosclerotic plaque burden evaluated from neck to groin: effect of gender and cardiovascular risk factors. Int J Cardiovasc Imaging. 2019;35:907-15. https://doi.org/10.1007/s10554-018-1512-0.

8. Mei K, Ehn S, Oechsner M, Kopp FK, Pfeiffer D, Fingerle AA, et al. Dual-layer spectral computed tomography: measuring relative electron density. Eur Radiol Exp. 2018;2:20. https://doi.org/10.1186/s41747-018-0051-8.

9. Nagano H, Takumi K, Nakajo M, Fukukura Y, Kumagae Y, Jinguji M, et al. Dual-Energy CT-Derived Electron Density for Diag-

nosing Metastatic Mediastinal Lymph Nodes in Non-Small Cell Lung Cancer: Comparison With Conventional CT and FDG PET/CT Findings. AJR Am J Roentgenol. 2022;218:66-74. https://doi.org/10.2214/AJR.21.26208.

10. Kaichi Y, Tatsugami F, Nakamura Y, Baba Y, Iida M, Higaki T, et al. Improved differentiation between high- and low-grade gliomas by combining dual-energy CT analysis and perfusion CT. Medicine (Baltimore). 2018;97:e11670. https://doi.org/10.1097/MD.0000000000011670.

11. Onishi S, Fujioka C, Kaichi Y, Amatya VJ, Ishifuro M, Takeshima Y, et al. Utility of dual-energy CT for predicting the vascularity of meningiomas. Eur J Radiol. 2020;123:108790. https://doi.org/10.1016/j.ejrad.2019.108790.

12. Ferencik M, Pencina KM, Liu T, Ghemigian K, Baltrusaitis K, Massaro JM, et al. Coronary Artery Calcium Distribution Is an Independent Predictor of Incident Major Coronary Heart Disease Events: Results From the Framingham Heart Study. Circ Cardiovasc Imaging. 2017;10:e006592. https://doi.org/10.1161/CIRCIMAGING.117.006592.

13. Peirlinck M, Sahli Costabal F, Kuhl E. Sex Differences in Drug-Induced Arrhythmogenesis. Front Physiol 2021;12:708435. https://doi.org/10.3389/fphys.2021.708435

14. Wittnich C, Tan L, Wallen J, Belanger M. Sex differences in myocardial metabolism and cardiac function: an emerging concept. Eur J Physiol 2013;465:719-29. https://doi.org/10.1007/s00424-013-1232-1

15. Parks RJ, Howlett SE. Sex differences in mechanisms of cardiac excitation-contraction coupling. Pflugers Archiv. Eur J Physiol 2013;465:747-63. https://doi.org/10.1007/s00424-013-1233-0

16. Walker CJ, Schroeder ME, Aguado BA, Anseth KS, Leinwand LA. Matters of the heart: Cellular sex differences. J Mol Cell Cardiol. 2021;160:42-55. doi: https://doi.org/10.1016/j.yjmcc.2021.04.010. E

17. Raisi-Estabragh Z, Jaggi A, Gkontra P, McCracken C, Aung N, Munroe PB, et al. Cardiac Magnetic Resonance Radiomics Reveal Differential Impact of Sex, Age, and Vascular Risk Factors on Cardiac Structure and Myocardial Tissue. Front Cardiovasc Med 2021;8:763361. https://doi.org/10.3389/fcvm.2021.763361.

18. Abdullayev N, Große Hokamp N, Lennartz S, Holz JA, Romman Z, Pahn G, et al. Improvements of diagnostic accuracy and visualization of vertebral metastasis using multi-level virtual non-calcium reconstructions from dual-layer spectral detector computed tomography. Eur Radiol 2019;29:5941-9. https://doi.org/10.1007/s00330-019-06233-5

19. Ehn S, Sellerer T, Muenzel D, Fingerle AA, Kopp F, Duda M, et al. Assessment of quantification accuracy and image quality of a full-body dual-layer spectral CT system. J Appl Clin Med Phys. 2018;19:204-17. https://doi.org/10.1002/acm2.12243.

20. Guan H, Yin FF, Kim JH. Accuracy of inhomogeneity correction in photon radiotherapy from CT scans with different settings. Phys Med Biol 2002;47:N223-31. https://doi.org/10.1088/0031-9155/47/17/402

21. Hua CH, Shapira N, Merchant TE, Klahr P, Yagil Y. Accuracy of electron density, effective atomic number, and iodine concentration determination with a dual-layer dual-energy computed tomography system. Med Phys 2018;45:2486-97. https://doi.org/10.1002/mp.12903. https://doi.org/10.1148/ryct.2019190008

22. Nuffer Z, Baran TM, Krishnamoorthy V, Kaproth-Joslin K, Chaturvedi A. Accuracy of Non-Electrocardiographically Gated Thoracic CT Angiography for Right Atrial and Right Ventricular Enlargement. Radiol Cardiothorac Imaging 2019;1:e190008.

23. Rodriguez-Granillo GA, Colla J, Fontana L, Diluca P, Cirio J, Lylyk P. Non-Contrast Electron Density Detection of Pulmonary Thromboembolism and Myocardial Infarction. Rev Argent Cardiol 2024;92:79-81. http://dx.doi.org/10.7775/rac.v92.i1.20733