DR. THOMAS H MARWICK (Orcid ID : 0000-0001-9065-0899)

Article type : Original Investigation

Independence of Coronary Artery Disease to Subclinical Left Ventricular Dysfunction

Prasanna Venkataraman, MB BS^{a,b}; Leah Wright PhD^a; Quan Huynh PhD^a; Thomas H Marwick
MBBS, PhD, MPH^{a,b}.

Baker Heart and Diabetes Research Institute^a and Monash University, Melbourne^b; Australia

Running head: Coronary Artery Calcium and Subclinical LV dysfunction

Corresponding author: Prof Thomas Marwick

Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Vic 3004, Australia

Email: Tom.Marwick@bakeridi.edu.au; Phone: +61 3 8532 1550; Fax: +61 3 8532 1160

Abstract words 240, text ~2500 words

This study is supported by an NHMRC project grant 1080582

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ECHO.14657](https://doi.org/10.1111/ECHO.14657)

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Abstract

Objective: Epicardial atherosclerosis and heart failure while distinct clinical entities share common pathophysiological features including endothelial dysfunction and inflammation. Presence of subclinical disease could lead to early diagnosis and intervention in the other. The aim of our study was to assess the association between coronary calcium score (CCS), conventional cardiovascular risk factors and echocardiographic markers of subclinical left ventricular dysfunction (SLVD).

Methods: 159 participants aged 40-70 years and intermediate risk of coronary artery disease (5-year risk of 2-15%) were identified. Computed tomography (CT) CCS and 2-D transthoracic echocardiography were performed. Main outcomes included presence of subclinical left ventricular dysfunction defined by reduced average global longitudinal strain, left atrial volume enlargement and elevated E/e' .

Results: 15 participants had evidence of subclinical LV dysfunction (8 with systolic dysfunction and 7 with diastolic dysfunction) and 85 participants had $CCS > 0$. $CCS > 0$ was present in 10 participants with SLVD compared to 75 participants without SLVD (67% vs 53%, $p = 0.47$). There was no significant difference between in mean GLS (19.2 vs 19.5, $p = 0.14$), E/e' (7.2 vs. 7.5 $p = 0.33$) in those without or with coronary artery calcium. Elevated CCS was also not associated with a higher tertiles of indexed LV mass (OR 1.15, $p = 0.49$) or index left atrial volume (OR 1.15, $p = 0.49$).

Conclusions: In an asymptomatic, low-intermediate risk group, mechanistic processes that lead to atherosclerosis are not directly associated with subclinical LV dysfunction.

Keywords: Coronary artery calcification, diastology, global longitudinal strain, familial coronary artery disease,

Introduction

Some asymptomatic patients with heart failure (HF) risk factors have subclinical cardiac damage, evidenced by disturbances of cardiac geometry, and systolic or diastolic function. The identification of these changes by echocardiography reclassifies these patients into a subgroup with Stage B HF (SBHF), who are likely to progress to symptomatic HF (1-3). The progression of subclinical LV dysfunction to incident HF may be expressed as either preserved or reduced ejection fraction phenotypes (4). Both abnormal systolic strain (5) and diastolic function (6) may be the endpoint of a

variety of non-ischaemic pathologies, including hypertension, diabetes, renal impairment, obesity and cardiotoxins, and progress to symptomatic HF.

Coronary artery calcification (CAC) provides direct evidence of coronary artery disease (CAD) in the asymptomatic stage. Although there is a strong association between CAC and incident HF, only partly mitigated after adjustment for cardiovascular risk factors (7, 8), it seems likely that this reflects the contribution of overt CAD to HF. Previous studies suggesting a link between CAC and LV dysfunction were in patients with very high burdens of CAC (≥ 400) (9), greater severity of LV dysfunction measured by ejection fraction (10, 11), or high baseline risk, such as those with suspected CAD or known diabetes (12, 13). The role of CAD in the development of SBHF is unclear in the setting of early disease. Thus, we sought to investigate the relationship between CAC and echocardiographic markers of subclinical LV dysfunction in asymptomatic individuals.

Methods

Study Design. The Coronary Artery calcium score: Use to Guide Management of Hereditary CAD (CAUGHT-CAD) trial (ACTRN 12614001294640, <https://www.anzctr.org.au/>) is a randomised controlled trial to assess the utility of coronary calcium score (CCS) to guide risk evaluation and statin therapy in asymptomatic, intermediate risk patients (5 year risk 2-15%) of age 40-70 years with a family history of CAD, and who were free of clinical CVD at baseline (2). In this substudy, echocardiograms were performed at a single site on 156 participants. All participants had comprehensive baseline clinical assessment and standard baseline pathology (including lipid profiles). The research was approved by the relevant human research ethics committee and all participants provided informed consent.

Coronary calcium score. CCS was performed using dual-source 128-slice CT machines and derived from low-dose ($\sim 1\text{mSv}$), ECG-gated, non-contrast scans. The CCS, reported in Agatston units, was calculated by software from the area and density of manually identified coronary calcium lesions.

Echocardiography. Standard 2-dimensional resting echocardiograms were performed by an experienced cardiac sonographer on commercially available ultrasound system (Vivid E95, GE Medical, Milwaukee, Wisconsin). Echocardiographic images were digitally recorded and downloaded as DICOM files for offline analysis. Conventional echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography. LV mass was calculated according to the American Society of Echocardiography formula (15), and normalised to body surface area. Relative wall thickness (RWT) was computed as $2 \times \text{posterior wall thickness} / \text{LV end-diastolic diameter}$. LV volumes and LVEF were calculated by the biplane method of disks using 2-dimensional images and LV volumes were indexed to body surface area. Left atrial volume was calculated by the biplane modified Simpson's method using 2-dimensional images and indexed to body surface area. The transmitral early diastolic velocity (E) and its deceleration time were acquired in the apical 4-chamber view using pulsed-wave Doppler at the level of the mitral valve tips during

diastole. The early diastolic mitral annular tissue velocity (e') was calculated as the average of septal and lateral mitral annular velocities, and E/e' was calculated. Systolic pulmonary artery pressure was estimated from the tricuspid regurgitation pressure gradient and the maximum inferior vena cava diameter and its collapsibility. Abnormal echocardiography parameters were defined as annular velocities <7 cm/s, LA volume index >34 ml/m² and LV mass index >96 g/m² in women and 115 g/m² in men.

Myocardial strain. Speckle tracking analysis was performed offline using commercially available software (Echopac version 2018; GE Medical. Milwaukee, WI)(14). The software automated tracing of the endocardial border to define the region of interest (ROI) at the end of systole. The investigator visually assessed the detected ROI and, if necessary, manually modified the ROI to ensure correct tracking of the speckles. Any segments that failed to track were excluded. The dedicated software automatically tracked the myocardium throughout the cardiac cycle in the apical 4-, 3-, and 2-chamber views. Global longitudinal strain (GLS) was obtained by averaging peak values of segmental strain in the apical views (15); normal GLS was designated as $<-18\%$.

A random selection of 24 studies was used to assess for inter-observer variability in 2D strain measurements. A single independent observer performed speckle tracking analysis on the same cine loops as the investigator. Both the investigator and observer were blinded to other results and clinical details.

Subclinical LV disease. Subclinical LV systolic dysfunction was defined as average GLS $<-16\%$ or average GLS $16\%-18\%$ and LA volume index >34 ml/m². Subclinical diastolic dysfunction was defined as E/e' ratio ≥ 15 or E/e' ratio $10-15$ and LA volume index >34 ml/m².

Statistical analysis. Baseline characteristics are presented separately for participants with CCS=0 and those with CCS >0 , as either mean $\pm$ SD or median [interquartile range] for continuous variables and as percentage for categorical variables. Between group differences were assessed using chi-square test for categorical variables and independent t-test for continuous variables. Logistic regression was performed to assess the predictive value of different risk factors for subclinical atherosclerosis and left ventricular dysfunction. For correlation analysis, the Pearson correlation coefficient was used. Ordinal logistic regression was used to assess the association between risk factors as the independent variable and echocardiographic parameters as the dependent variable categorised by tertiles. CCS was analysed after categorisation by the following levels: 0, 0-100 and ≥ 100 . The IRSAD score is a marker of neighbourhood socioeconomic advantage (higher scores are accorded to more advantaged suburbs) and was categorised by tertiles. Interobserver variation for calculating average GLS was assessed by intraclass correlation coefficient (two-way random-effects absolute agreement). All statistical analyses were conducted using the 'dplyr', 'statsr' and 'glm' package in R 3.5.1 (R Foundation for Statistical Computing) and STATA 15.1 (Statacorp, College Station, Texas, USA).

Results

Study participants. The study population consisted of 156 asymptomatic individuals from urban and rural areas of Victoria, Australia (Table I). Overall, approximately 45% of the population was male and the average age was 58 years. The median [IQR] 10-yr predicted risk using the Pooled Cohort Equation for the entire cohort was 4.8% [3.0% to 8.4%]. In total, 85 participants (55%) had evidence of coronary calcification with a median [IQR] coronary calcium score (CCS) of 51 [13-128] and 26 participants had CCS >100. Those with subclinical coronary calcification were more likely to be older, male and have higher predicted risk for symptomatic cardiovascular events (Table I).

LV function. The mean GLS for the cohort was 19.4 ± 2.0 and 29 participants had abnormal GLS (<-18%). The mean E/e' was 7.3 ± 1.9 and 12 participants had $E/e' \geq 10$. No single echocardiographic marker of systolic, diastolic function or left ventricular geometry was associated with positive coronary calcium. Subclinical LV dysfunction was present in 15 participants (9.6%), 7 due to subclinical diastolic dysfunction, 8 due to subclinical systolic dysfunction; no participant met criteria for both diagnoses. Of those with subclinical LV dysfunction, 10 participants had coronary calcification compared to 75 in the 145 participants without subclinical dysfunction (67% vs 53%, $p=0.47$). One or more abnormal echocardiography parameters (annular velocities <7 cm/s, LA volume index >34ml/m², LV hypertrophy, average GLS <-18%, or $E/e' > 14$) were present in 104 participants. Of these, 60 participants had CCS >0 compared to 25 of 51 participants without abnormal parameters (57% vs 49%, $p=0.40$). Similarly, 17.6% of abnormal echocardiograms had CCS >100, compared to 16.3% of those without abnormal parameters ($p=1.0$). There was no significant correlation between the log of CCS and average GLS ($r = 0.06$, $p=0.47$). We also evaluated CCS categorised into categories (0, 1-100, ≥ 100) and tertiles but no association with left ventricular dysfunction or echocardiographic abnormalities was evident.

Logistic regression identified age, sex, predicted cardiovascular risk and heart rate - but not LV dysfunction - to be associated with positive coronary calcium score (Table II).

Table III shows the association of risk factors with the tertiles of GLS (>-18% vs. -18 to -20.1% vs. <-20.1%), indexed LV mass (≤ 67 g/m² vs. 67 g/m² to 82 g/m² vs. >82 g/m²), average MV annular velocities (<8 cm/s vs. 8 - 9 cm/s vs. >9 cm/s) and indexed LA end-systolic volume (≤ 28 cm³ vs. 28 cm³ - 34 cm³ vs. ≥ 34 cm³). Male sex was associated with lower GLS and higher indexed LV mass, and older age was associated with lower annular velocities. Diabetes was associated with lower LV mass indexed to body surface area, but this likely represents a sampling error given overall low absolute numbers of participants with diabetes in our cohort and this association was not present for non-indexed LV mass. However, other risk factors for coronary events and heart failure including coronary calcium score were not associated with echocardiographic parameters relevant to detection of SBHF. Appendix Table AII seeks to examine the associations of risk factors with subclinical systolic and diastolic dysfunction, but shows similar trends to the individual components.

Inter-observer variation. Of 24 randomly selected participants, the mean difference between average GLS was -0.74 with 95% limits of agreement between -2.25 to 0.77. Intraclass correlation coefficient was 0.82 (95% CI of 0.67 to 0.92) showing good inter-observer reliability.

Discussion

Our study supports the hypothesis that in an asymptomatic, low-intermediate cardiovascular risk population, subclinical LV dysfunction and epicardial coronary atherosclerosis are a result of separate pathophysiological mechanisms. In addition, no participant met criteria for both subclinical diastolic and systolic dysfunction, consistent with distinct phenotypes previously noted in diabetic cohorts (16). While the prevalence of subclinical dysfunction was low it was not uncommon but no clear association with typical heart failure risk factors was identifiable. This highlights the potential role of early screening and gaps in our understanding of causal mechanisms to improve prevention of symptomatic heart failure.

Subclinical LVD. Symptomatic HF is a major cause of morbidity in the elderly and its prevalence continues to increase (17). While ischaemic heart disease still remains the leading cause of health loss globally, the ageing population and increasing burden of hypertension, diabetes and obesity will likely augment the number of patients with HF with preserved ejection (HFpEF), the most frequently diagnosed form of heart failure (18). SBHF is a recognisable precursor to the development of overt HF (19). At present, echocardiography appears to be the most feasible diagnostic test to identify both SBHF phenotypes, but accessibility, labour and resource constraints mean that implementing a population-based screening program is challenging. Similarly, while early intervention with multidisciplinary care has been shown to prevent progression from SBHF, similar resource concerns mean that optimal patient selection is essential (20). While additional biomarkers like ECG and natriuretic peptides can improve patient selection, the heterogeneity of causes of myocardial dysfunction add to their uncertain utility in risk assessment (20, 21). On the other hand, as CCS is increasingly incorporated into primary prevention guidelines for CAD its use and accessibility will increase (22). If CCS were able to improve risk stratification for SBHF and progression to overt HF, existing HF guidelines and the cost-effectiveness of CCS would need to be revisited. Unfortunately, however, our study shows that CCS is not a marker of subclinical myocardial disease in a low-intermediate risk, non-diabetic population.

Commonalities of CAD and LV dysfunction. The possible intermediaries of CAC and subclinical LV dysfunction include microvascular disease and endothelial dysfunction. Coronary microvascular disease impairs augmentation of blood flow and oxygen delivery to meet the metabolic demands of the myocardium. Previous autopsy studies have found HFpEF patients compared to controls have a propensity for diffuse CAD and sequelae of microvascular endothelial dysfunction including microvascular rarefaction and myocardial fibrosis (23). Microvascular dysfunction is also an important predictor of both reduced strain reserve post-exercise in asymptomatic patients as well as in

HFpEF (24, 25). Inflammation is now recognised as a key component of atheroma progression and vascular calcification (26), and up-regulation of inflammatory pathways and development of endothelial oxidative stress are similarly implicated in the development of HFpEF (27, 28). Nonetheless, the results of this study suggest that subclinical atherosclerosis does not seem to be an important unifying feature in the development of subclinical LVD, so that when the two do co-exist, the latter is less likely mediated through overall atherosclerotic burden than through shared risk factors like diabetes, renal impairment and obesity. However, subclinical atherosclerosis may identify a cohort of those with SBHF likely to progress to Stage C heart failure (8).

The proposed mechanisms behind the development of SBHF include myocardial dysfunction, fibrosis, hypertrophy and microangiopathy. Hyperinsulinaemia and disturbed myocardial substrate metabolism are important causes of these metabolic derangements (3), and may also contribute to the development of CAD. The results of our study show that the development of myocardial dysfunction seems to occur at a lower level of exposure than is required for the development of coronary calcification.

Limitations. Our study has a number of limitations which may have contributed to our study findings. First, the low absolute numbers of those with subclinical LV dysfunction may mean our study is underpowered to identify a relationship with subclinical atherosclerosis. Nonetheless, several significant associations are consistent with previous literature and argue against a sampling problem. For example: males tend to have lower average GLS values than women, and higher LV mass, and age is associated with lower e' . Moreover, when GLS, indexed LV mass and E/e' were used as the dependent variables, no association was found with CCS (Appendix Table A1). Diabetes is a potent risk factor for both atherosclerosis and heart failure, and the low burden of in our population may explain to lack of association between CAC and heart failure in our study (29). However, our intention was to replicate the asymptomatic, low-intermediate cardiovascular risk population who are considered from screening. Similarly, the low rates of heavy coronary calcification (<20% of participants had CCS >100) may mean the overall atherosclerosis burden in our cohort was low and insufficient to significantly impact coronary microvasculature, coronary flow and myocardial function, at least at rest (30).

Second, we did not assess microvascular function or coronary flow reserve. Exercise testing may unmask microvascular disease and endothelial dysfunction. GLS reserve post-exercise may better correlate with overall burden of coronary calcification and Michelsen et al. found GLS reserve was a more sensitive marker of microvascular dysfunction than absolute resting GLS values (24). Coronary flow reserve by reflecting both epicardial and microvascular function could further illuminate the interaction between subclinical atherosclerosis and myocardial dysfunction.

Conclusion. These results, show that in an asymptomatic, low-intermediate risk group, suggest that mechanistic processes leading to atherosclerosis are not directly associated with subclinical LV

dysfunction. Subclinical systolic and diastolic dysfunction occurred independently highlighting the additional value of GLS to diagnose SBHF.

References

1. Mogelvang R, Biering-Sorensen T, Jensen JS. Tissue Doppler echocardiography predicts acute myocardial infarction, heart failure, and cardiovascular death in the general population. *Eur Heart J Cardiovasc Imaging*. 2015;16(12):1331-7.
2. Wang Y, Yang H, Huynh Q, Nolan M, Negishi K, Marwick TH. Diagnosis of Nonischemic Stage B Heart Failure in Type 2 Diabetes Mellitus: Optimal Parameters for Prediction of Heart Failure. *JACC Cardiovasc Imaging*. 2018;11(10):1390-400.
3. Holland DJ, Marwick TH, Haluska BA, Leano R, Hordern MD, Hare JL, et al. Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart*. 2015;101(13):1061-6.
4. Naylor M, Enserro DM, Vasan RS, Xanthakis V. Cardiovascular Health Status and Incidence of Heart Failure in the Framingham Offspring Study. *Circ Heart Fail*. 2016;9(1):e002416.
5. Voigt JU, Cvijic M. 2- and 3-Dimensional Myocardial Strain in Cardiac Health and Disease. *JACC Cardiovasc Imaging*. 2019;12(9):1849-63.
6. Kosmala W, Marwick TH. Asymptomatic Left Ventricular Diastolic Dysfunction: Predicting Progression to Symptomatic Heart Failure. *JACC Cardiovasc Imaging*. 2019.
7. Kalsch H, Lehmann N, Mohlenkamp S, Neumann T, Slomiany U, Schmermund A, et al. Association of coronary artery calcium and congestive heart failure in the general population: Results of the Heinz Nixdorf Recall study. *Clin Res Cardiol*. 2010;99(3):175-82.
8. Bakhshi H, Ambale-Venkatesh B, Yang X, Ostovaneh MR, Wu CO, Budoff M, et al. Progression of Coronary Artery Calcium and Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2017;6(4).
9. Osawa K, Miyoshi T, Oe H, Sato S, Nakamura K, Kohno K, et al. Association between coronary artery calcification and left ventricular diastolic dysfunction in elderly people. *Heart Vessels*. 2016;31(4):499-507.
10. Enomoto M, Ishizu T, Seo Y, Kameda Y, Suzuki H, Shimano H, et al. Myocardial dysfunction identified by three-dimensional speckle tracking echocardiography in type 2 diabetes patients relates to complications of microangiopathy. *J Cardiol*. 2016;68(4):282-7.
11. Liu X, Yang ZG, Gao Y, Xie LJ, Jiang L, Hu BY, et al. Left ventricular subclinical myocardial dysfunction in uncomplicated type 2 diabetes mellitus is associated with impaired myocardial perfusion: a contrast-enhanced cardiovascular magnetic resonance study. *Cardiovasc Diabetol*. 2018;17(1):139.

12. D'Andrea A, Nistri S, Castaldo F, Galderisi M, Mele D, Agricola E, et al. The relationship between early left ventricular myocardial alterations and reduced coronary flow reserve in non-insulin-dependent diabetic patients with microvascular angina. *Int J Cardiol.* 2012;154(3):250-5.
13. Sakuragi S, Ichikawa K, Yamada K, Tanimoto M, Miki T, Otsuka H, et al. An increase in the coronary calcification score is associated with an increased risk of heart failure in patients without a history of coronary artery disease. *J Cardiol.* 2016;67(4):358-64.
14. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *J Am Soc Echocardiogr.* 2011;24(3):277-313.
15. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging.* 2009;2(5):356-64.
16. Ernande L, Audureau E, Jellis CL, Bergerot C, Henegar C, Sawaki D, et al. Clinical Implications of Echocardiographic Phenotypes of Patients With Diabetes Mellitus. *J Am Coll Cardiol.* 2017;70(14):1704-16.
17. Leong DP, Joseph PG, McKee M, Anand SS, Teo KK, Schwalm JD, et al. Reducing the Global Burden of Cardiovascular Disease, Part 2: Prevention and Treatment of Cardiovascular Disease. *Circ Res.* 2017;121(6):695-710.
18. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* 2017;14(10):591-602.
19. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC, Jr., et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation.* 2007;115(12):1563-70.
20. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA.* 2013;310(1):66-74.
21. Yang H, Wang Y, Nolan M, Negishi K, Okin PM, Marwick TH. Community Screening for Nonischemic Cardiomyopathy in Asymptomatic Subjects ≥ 65 Years With Stage B Heart Failure. *Am J Cardiol.* 2016;117(12):1959-65.
22. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019.

23. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. 2015;131(6):550-9.
24. Michelsen MM, Pena A, Mygind ND, Bech J, Gustafsson I, Kastrup J, et al. Coronary microvascular dysfunction and myocardial contractile reserve in women with angina and no obstructive coronary artery disease. *Echocardiography*. 2018;35(2):196-203.
25. Srivaratharajah K, Coutinho T, deKemp R, Liu P, Haddad H, Stadnick E, et al. Reduced Myocardial Flow in Heart Failure Patients With Preserved Ejection Fraction. *Circ Heart Fail*. 2016;9(7).
26. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary Calcium Score and Cardiovascular Risk. *J Am Coll Cardiol*. 2018;72(4):434-47.
27. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62(4):263-71.
28. Tromp J, Westenbrink BD, Ouwerkerk W, van Veldhuisen DJ, Samani NJ, Ponikowski P, et al. Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction. *J Am Coll Cardiol*. 2018;72(10):1081-90.
29. Marwick TH, Ritchie R, Shaw JE, Kaye D. Implications of Underlying Mechanisms for the Recognition and Management of Diabetic Cardiomyopathy. *J Am Coll Cardiol*. 2018;71(3):339-51.
30. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. *J Am Coll Cardiol*. 1998;31(1):126-33.

Table I Baseline characteristics according the presence of subclinical coronary artery calcification.

	CCS = 0 N = 71	CCS > 0 N = 85	P
Age, years	56.5 ± 7	59.8 ± 6.5	<0.05
Sex, male (%)	24, (33.8)	46, (54.1)	0.02
Total cholesterol, mean (mmol/L)	5.4 (0.65)	5.4 (0.72)	0.89
High Density Lipoprotein, mmol/L	1.48 (0.42)	1.58 (0.51)	0.15
Smoker: n, (%)			
- Never	32 (45)	48 (56)	

- Former	37 (52)	35 (41)	0.34
- Current	2 (3)	2 (3)	
Systolic blood pressure, mean;sd (mmHg)	125.8 (14)	130.2 (15)	0.06
Hypertension Rx, n (%)	16, (22.5)	27, (32.5)	0.16
Diabetes Mellitus, n (%)	2, (2.8)	4, (4.7)	0.54
IRSAD, mean	1045 (53)	1043 (55)	0.83
Relative CAD Age	51.2 (7)	52.0 (7)	0.48
Body mass index, kg/m ²	26.7 (4)	27.5 (5)	0.27
Pooled Cohort Equation Risk	4.8 +/- 4.8	7.7 +/- 6.2	<0.05
GLS	-19.2 +/- 2	-19.5 +/- 2	0.14
E/e'	7.2 +/- 1.5	7.5 +/- 2.1	0.33
LAVi	31.9 +/- 8.7	32.4 +/- 7.9	0.75
LVMi	75.8 +/- 20	76.3 +/- 17	0.86
LVEDVi	57.4 +/- 11	60.3 +/- 13	0.13
LVEF (Biplane)	59.2 +/- 6.9	60.5 +/- 5.9	0.23
S-LVD	5 (7%)	10 (12%)	0.32
Abnormal TTE	37 (64%)	38 (72%)	0.32

Note:

Abbreviations: CCS = coronary calcium score; IRSAD = Index of relative socioeconomic advantage and disadvantage; CAD = coronary artery disease; GLS = average global longitudinal strain; LAVi = left atrial volume indexed; LVMi = left ventricular mass indexed; LVEDVi = left ventricular end-diastolic volume indexed; LVEF = left ventricular ejection fraction; S-LVD = subclinical left ventricular dysfunction.

TABLE II. Association of risk factors with coronary calcium score > 0 and subclinical left ventricular dysfunction. CS>0 is expressed as subclinical atherosclerosis and any abnormalities of any LV marker are expressed as LV dysfunction.

Risk Factor	CCS > 0 OR (95% CI)	p	S-LVD OR (95% CI)	p
Age	1.08 (1.06, 1.10)	0.01	1.04 (0.96,1.13)	0.38
Sex, male	2.31 (1.21, 4.47)	0.01	1.47 (0.50, 4.36)	0.49
PCE	1.14 (1.05, 1.25)	<0.01	1.03 (0.94,1.10)	0.46
BMI, kg/m ²	1.04 (0.97, 1.12)	0.28	0.98 (0.86,1.10)	0.81
Alcohol ≥ 4 standard drinks	1.74 (0.90, 3.37)	0.10	0.99 (0.33, 2.90)	0.98

Hypertension	1.68 (0.83, 3.51)	0.16	1.66 (0.53,4.91)	0.37
Smoking				
- Never smoker	REF		REF	
- Ex-smoker	0.63 (0.33-1.19)	0.16	1.12 (0.36, 3.45)	0.84
- current	0.67 (0.07, 5.79)	0.69	3.48 (0.16, 31.7)	0.31
Diabetes Mellitus	1.70 (0.32,12.6)	0.55	n/a	0.99
Heart Rate	0.95 (0.91, 0.99)	0.01	0.98 (0.92,1.04)	0.50
IRSAD	1.00 (0.99,1.00)	0.82	1.00 (0.99,1.01)	0.61
Age of onset of CAD in relative	1.01 (0.97,1.07)	0.48	0.98 (0.91,1.06)	0.53

Table III: Associations of risk factors with tertiles of LV dysfunction parameters

5-yr Risk	Average GLS OR (95% CI)	P- value	E' (cm/s) OR (95% CI)	P-value	LV Mass Indexed OR (95% CI)		LA ESV Indexed OR (95% CI)	p-value
Age	0.97 (0.93, 1.01)	0.13	1.07 (1.02, 1.11)	0.004	0.97 (0.93, 1.02)	0.19	1.01 (0.97, 1.06)	0.59
CCS category	0.90 (0.60,1.36)	0.88	1.16 (0.79, 1.74)	0.44	1.15 (0.77, 1.71)	0.49	1.15 (0.77, 1.70)	0.49
Sex, male	3.96 (2.15, 7.45)	<0.01	1.18 (0.66, 2.13)	0.57	2.49 (1.38, 4.55)	0.004	0.82 (0.45, 1.47)	0.50
PCE	1.00 (0.95, 1.07)	0.82	1.06 (1.00,1.14)	0.03	1.01 (0.96, 1.07)	0.63	0.99 (0.93, 1.04)	0.66
BMI, kg/m ²	1.02 (0.96, 1.09)	0.50	1.04 (0.98,1.11)	0.19	1.00 (0.93, 1.07)	0.98	0.98 (0.92, 1.04)	0.51
Alc $\geq$ 4 s.d	1.35 (0.75, 2.45)	0.32	1.50 (0.83, 2.76)	0.18	1.02 (0.56, 1.85)	0.93	1.03 (0.57, 1.87)	0.91
Hypertension	0.95 (0.50, 1.81)	0.87	1.19 (0.63, 2.25)	0.58	1.29 (0.68, 2.43)	0.44	0.87 (0.45, 1.65)	0.66
Smoking	1.02 (0.60, 1.74)	0.94	1.07 (0.63, 1.83)	0.78	1.37 (0.81,2.35)	0.24	1.12 (0.66,1.90)	0.66
Diabetes	2.48 (0.44,18.8)	0.28	0.92 (0.22, 3.82)	0.90	0.09 (0.01, 0.57)*	0.03	0.25 (0.05, 1.3)	0.15
Heart Rate	1.02 (0.97, 1.08)	0.36	1.03 (0.97,1.09)	0.25	1.01 (0.96, 1.07)	0.56	0.97 (0.91, 1.03)	0.35
IRSAD, tert	0.88 (0.61,1.25)	0.48	0.98 (0.68,1.39)	0.89	0.84 (0.59, 1.20)	0.34	0.78 (0.54, 1.12)	0.18
Relative GAD Age	0.98 (0.93,1.02)	0.33	0.95 (0.91, 0.99)	0.02	0.99 (0.95, 1.03)	0.66	1.03 (0.99, 1.07)	0.19

(*) likely reflects sampling error in the setting of low absolute numbers of diabetic participants.

Figure 1: Boxplot of average GLS values according CCS = 0, 0-100 and > 100

Figure 2: Longitudinal Strain measurements in a 17 segment model of the LV, mitral inflow by pulse wave Doppler tissue Doppler velocities from the septal annulus in a participant with a) subclinical systolic dysfunction and b) subclinical diastolic dysfunction

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Appendix Table AI

Association of risk factors with echocardiographic parameters as a univariate linear regression model

5-yr Risk	Average GLS β (95% CI)	P- value	E' (cm/s) β (95% CI)	P-value	LV Mass Indexed β (95% CI)	P value
Age	0.05 (0.003-0.942)	0.04	-0.086 (-0.124 -0.048)	<0.01	-0.216 (-0.636, 0.204)	0.31
Log(CCS+1)	0.061 (-0.0893, 0.211)	0.43	-0.077 (-0.208, 0.054)	0.25	0.360 (-1.01, 1.73)	0.61
Sex, male	-1.22 (-1.83, -0.606)	<0.05	-0.109 (-0.671, 0.452)	0.70	6.96 (1.21, 12.6)	0.02
PCE	0.015 (-0.040, 0.070)	0.59	-0.073 (-0.121—0.026)	<0.01	0.098 (-0.408, 0.604)	0.70
BMI, kg/m ²	-0.043 (-0.111, 0.025)	0.22	-0.040 (-0.102, 0.021)	0.2	-0.325 (-0.967, 0.316)	0.32
Hypertension	-0.291 (-0.991, 0.410)	0.41	-0.174 (-0.790, 0.442)	0.58	2.3 (-4.17, 8.63)	0.50
sbp	-0.012 (-0.0337, 0.0103)	0.30	-0.017 (-0.036, 0.001)	0.08	0.076 (-0.125, 0.278)	0.46
dbp	-0.031	0.09	-0.027	0.08	0.373	0.01

	(-0.066, 0.004)		(-0.057, 0.002)		(0.088, 0.657)	
Smoking	0.632 (-1.38, 2.64)	0.54	0.928 (-0.835, 2.69)	0.30	1.66 (-16.6, 20.0)	0.86
Diabetes	-0.227 (-1.88, 1.43)	0.79	-0.187 (-1.640, 1.267)	0.80	-19 (-33, -4)	0.02
Heart Rate	-0.052 (-0.088, -0.15)	0.01	-0.014 (-0.045, 0.017)	0.40	-0.414 (-0.708, -0.120)	0.01
IRSAD	-0.004 (-0.010, 0.002)	0.20	-0.004 (-0.009, 9.046)	0.11	0.017 (-0.037, 0.072)	0.53
Relative CAD Age	0.044 (-0.002, 0.089)	0.06	0.034 (-0.006, 0.076)	0.09	-0.01 (-0.442, 0.418)	0.95

5-yr Risk	LA ESV Indexed β	p-value	LV EDV Indexed β (95% CI)	P	E/e' β	P
Age	0.116 (-0.07, 0.305)	0.23	-0.225 (-0.499, 0.050)	0.11	0.043 (0.00,0.08)	0.05
Log(CCS+1)	0.077 (-0.54, 0.697)	0.805	0.726 (-0.169, 1.62)	0.11	0.003 (-0.138, 0.146)	0.96
Sex, male	0.710 (-3.34, 1.92)	0.60	8.78 (5.20, 12.4)	<0.01	-1.10 (-1.68, -0.515)	<0.01

PCE	0.041 (-0.18, 0.27)	0.72	0.20 (-0.128, 0.534)	0.23	-0.004 (-0.056, 0.048)	0.87
BMI, kg/m ²	-0.087 (-0.377, 0.202)	0.55	-0.37 (-0.785, 0.053)	0.09	0.021 (-0.045, 0.088)	0.53
Hypertension	0.018 (-2.87, 2.91)	0.99	1.11 (-3.10, 5.31)	0.60	0.315 (-0.348, 0.978)	0.35
sbp	-0.020 (-0.11, 0.07)	0.66	0.09 (-0.044, 0.219)	0.19	0.010 (-0.011, 0.030)	0.36
dbp	-0.041 (-0.19, 0.11)	0.60	0.17 (-0.051, 0.390)	0.13	-0.009 (-0.043, 0.025)	0.62
Smoking	-1.65 (-9.92, 6.63)	0.69	3.07 (-8.98, 15.1)	0.62	0.772 (-1.13, 2.67)	0.42
Diabetes	-6.49 (-13.2, 0.237)	0.06	-10.1 (-20, -0.30)	0.04	0.375 (-1.19, 1.94)	0.64
Heart Rate	-0.326 (-0.47, -0.178)	<0.01	-0.473 (-0.690, -0.256)	<0.01	-0.006 (-0.041, 0.030)	0.76
IRSAD	0.013 (-0.012, 0.037)	0.31	0.014 (-0.022, 0.049)	0.47	-0.003 (-0.008, 0.002)	0.26
Relative CAD Age	0.094 (-0.10, 0.288)	0.34	-0.035 (-0.319, 0.248)	0.81	-0.012 (-0.057, 0.033)	0.60

Table All**Risk factor associations with subclinical diastolic and systolic dysfunction**

Risk Factor	Subclinical Diastolic Dysfunction OR (95% CI)	p	Subclinical Systolic Dysfunction OR (95% CI)	p
Age	1.15 (0.99, 1.32)	0.06	0.97 (0.87,1.07)	0.50
Sex, male	0.48 (0.07, 2.29)	0.39	3.94 (0.87,27.49)	0.10
PCE	1.05 (0.94, 1.14)	0.25	0.99 (0.83, 1.10)	0.91
BMI, kg/m ²	0.96 (0.79, 1.13)	0.71	1.00 (0.84,1.15)	0.99
Alcohol ≥ 4 standard drinks	2.96 (0.62, 21.2)	0.20	0.36 (0.05, 1.61)	0.22
Hypertension	3.51 (0.75, 18.5)	0.11	0.81 (0.12, 3.69)	0.81
Smoking				
- Never smoker	REF		REF	
- Ex-smoker	0.54 (0.07, 2.87)	0.48	1.92 (0.45, 9.6)	0.40
- current	6.33 (0.29, 65.1)	0.15	0.00	1
Diabetes Mellitus	NA	1	NA	1
Heart Rate	0.91 (0.81, 1.00)	0.07	1.02 (0.94, 1.10)	0.62
IRSAD	1.00 (0.99, 1.02)	0.45	1.00 (0.99, 1.01)	0.98
Age of onset of CAD in relative	1.07 (0.95, 1.26)	0.31	0.92 (0.84, 1.01)	0.08

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Author/s:

Venkataraman, P;Wright, L;Huynh, Q;Marwick, TH

Title:

Independence of coronary artery disease to subclinical left ventricular dysfunction

Date:

2020-04-21

Citation:

Venkataraman, P., Wright, L., Huynh, Q. & Marwick, T. H. (2020). Independence of coronary artery disease to subclinical left ventricular dysfunction. ECHOCARDIOGRAPHY-A JOURNAL OF CARDIOVASCULAR ULTRASOUND AND ALLIED TECHNIQUES, 37 (5), pp.678-687. <https://doi.org/10.1111/echo.14657>.

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