HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Atherosclerosis. 2016 May ; 248: 245–251. doi:10.1016/j.atherosclerosis.2016.02.013.

Relations of Circulating GDF-15, soluble ST2, and Troponin-I Concentrations with Vascular Function in the Community: The Framingham Heart Study

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Abstract

Background and aims—Growth differentiation factor-15 (GDF-15), soluble (s)ST2, and high-sensitivity troponin-I (hs-TnI) are associated with incident cardiovascular disease (CVD) including heart failure, yet the underlying mechanisms are not fully understood. We investigated if GDF-15, sST2, and hs-TnI are related to subclinical vascular dysfunction in the community, which may explain the relations of these biomarkers with CVD.

Methods—We evaluated 1,823 Framingham Study participants (mean age 61±10 years, 54% women) who underwent routine assessment of vascular function. We related circulating GDF-15, sST2, and hs-TnI concentrations to measures of arterial stiffness (carotid-femoral pulse wave

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velocity, CFPWV; augmentation index; and forward pressure wave amplitude, FW), endothelial-dependent vasodilation (flow-mediated dilation, FMD), and baseline and hyperemic brachial flow velocities using linear regression adjusting for standard risk factors.

Results—After multivariable adjustment, GDF-15 levels were positively associated with CFPWV (0.044 [95% confidence interval 0.007-0.081] standard deviation [SD] change per SD increase in $\log_e$[GDF-15], p=0.02) and FW (0.076 [0.026-0.126] SD change per SD increase in $\log_e$[GDF-15], p=0.003) and inversely related to FMD (-0.051 [-0.101--0.0003] SD change per SD increase in $\log_e$[GDF-15], p=0.048). sST2 was positively associated with CFPWV (0.032 [0.0005-0.063] SD change per SD increase in $\log_e$[sST2], p=0.046), and hs-TnI inversely associated with hyperemic flow velocity (-0.041 [-0.082--0.0004] SD change per SD increase in $\log_e$[hs-TnI], p=0.048).

Conclusion—In our community-based investigation, individual cardiac stress biomarkers were differentially related to select aspects of vascular function. These findings may contribute to the associations of circulating GDF-15, sST2, and hs-TnI with incident CVD and heart failure.

Keywords

Vascular stiffness; endothelial function; biomarkers; ST2; GDF-15; troponin I; general population

Introduction

Growth differentiation factor-15 (GDF-15), soluble ST2 (sST2), and high sensitivity troponin-I (hs-TnI) are novel biomarkers of cardiovascular stress that have been associated with incident cardiovascular disease (CVD), including heart failure.[1] Furthermore, GDF-15 and hs-TnI (but not sST2) have been associated with cardiac remodeling indices (i.e., left ventricular hypertrophy and a reduced ejection fraction), while sST2 has been linked to incident systolic arterial hypertension in the Framingham Heart Study.[2, 3] Higher arterial stiffness and endothelial dysfunction are known risk factors for exaggerated blood pressure responses during exercise, new-onset hypertension and incidence of CVD (including heart failure).[4-7] Given the relations between vascular dysfunction and risk of CVD, and the strong association between the novel cardiac stress biomarkers and CVD, we aimed to investigate if these cardiac stress biomarkers (GDF-15, sST2, and hs-TnI) are also associated with subclinical vascular dysfunction as assessed by vascular stiffness and brachial artery flow-mediated dilation. For this purpose, we evaluated the community-based Framingham Offspring cohort sample that has characterization of vascular function at multiple levels, including aortic stiffness (measured by carotid-femoral pulse wave velocity, CFPWV), stiffness in middle-sized muscular artery (measured by augmentation index and forward pressure wave amplitude), endothelial function in medium-sized muscular artery (measured by brachial artery flow-mediated dilation), and brachial artery baseline and hyperemic flow velocities (markers of shear stress).[8] We posited that higher circulating levels of the three cardiac stress biomarkers are associated with ‘pan-vascular’ dysfunction even after adjusting for other cardiac biomarkers that have previously been associated with vascular dysfunction, i.e., B-type natriuretic peptide (BNP), N terminal pro-atrial natriuretic peptide (NT-proANP), renin, and high-sensitivity C-reactive protein (hs-CRP).[9, 10]

Materials and methods

Sample

We evaluated Framingham Offspring cohort participants who attended both the sixth and seventh examination cycles (taking place in 1995-1998 and 1998-2001, respectively). Of the 3539 participants who attended the seventh examination cycle, participants were excluded for serum creatinine levels >2 mg/dL (n=23), missing covariates (n=677), missing vascular outcome measures (n=736), missing biomarker assessment at examination cycle 6 (n=274), and outlier values (n=8), resulting in a sample of 1823 participants for statistical analysis. The Boston University Medical Center Institutional Review Board approved the study protocol and all participants provided written informed consent.

Cardiac Stress Biomarkers

During the sixth examination cycle, circulating concentrations of GDF-15, sST2, and hs-TnI were measured along with a panel of other biomarkers, including BNP, NT-proANP, renin, and hs-CRP, as detailed previously.[1, 9, 10] In brief, all blood samples were drawn after an overnight fast and immediately centrifuged and frozen at -80°C until assays for various analyses were performed. sST2 concentrations were measured using an enzyme-linked immunosorbent assay with a detection limit of 2 ng/mL (Presage ST2; Critical Diagnostics, San Diego, CA), GDF-15 concentrations were obtained from a precommercial immunoassay on a Cobas e 411 analyzer (Roche Diagnostics, Switserland), and hsTnI was estimated by an ultra-sensitive immunoassay for cardiac TnI (Erenna hsTnI; Singulex, Alameda, CA). The intra-assay coefficients were <8% for low and high values of sST2, GDF-15, and hs-TnI, respectively.[11]

Vascular Function measures

At the seventh examination cycle all participants were investigated with applanation tonometry. Measurements were undertaken with the participant in a supine position after 5-10 minutes of rest using a commercially available tonometer (SPT-301, Millar Instruments, Houston, TX) and a standardized protocol.[12] All measures were digitally stored and subsequently analyzed in a core laboratory (Cardiovascular Engineering, Inc, Norwood, MA) blinded to clinical information.[12] Transit distances were measured from the suprasternal notch to each of the carotid and femoral sites. Carotid-femoral pulse-wave velocity (CFPWV) was measured as the difference in length from suprasternal notch to each of the two measurement sites divided by the time delay between the foot of the carotid and femoral waveforms.[13] The forward pressure wave amplitude was defined as the difference between pressure at the waveform foot and pressure at the first systolic inflection point or peak of the carotid pressure waveform.[12] Augmentation index was calculated as the difference between first systolic inflection point and peak waveform (i.e., the augmentation pressure) divided by the total pulse pressure and multiplied by 100. CFPWV, forward pressure wave amplitude, and augmentation index are frequently used as surrogate measures of arterial stiffness in epidemiological research. As reported previously, reproducibility of central hemodynamic measures using our protocol is high, with intraclass correlation coefficients of 0.93-0.95 for repeated measures of central hemodynamic variables, such as cardiac output and characteristic impedance.[14] Noninvasive central hemodynamic

measures correlate closely with invasive measures.[15] Similar high correlation coefficients have been reported for flow-mediated dilation (0.92).[16]

Baseline flow velocity, flow-mediated dilation, and peak hyperemic flow velocity were derived by ultrasound measures of the brachial artery using a Toshiba SSH-140A ultrasound system, as described in detail previously.[8, 16] In brief, after measuring the arterial flow velocity and diameter at baseline, a cuff placed at the proximal forearm was inflated to interrupt blood flow for 5 minutes. Flow was again measured during the initial 15 seconds after cuff deflation to derive the peak hyperemic flow velocity. Flow-mediated dilation was defined as the difference between the brachial artery dimension at 60 seconds post-deflation [D_{DF}] and dimension at baseline [D_{BL}] divided by baseline dimension (flow-mediated dilation %=[$D_{DF}-D_{BL}$]/D_{BL}). These measures have shown to reflect endothelial function previously.[8]

We a priori decided to study various measures reflecting arterial function at different levels of the vascular bed: elastic conduit artery stiffness was assessed by CFPWV (aorta), augmentation index (medium-sized artery), and forward pressure wave (medium-sized artery); medium-sized muscular artery endothelium-dependent vasodilation was evaluated with brachial artery flow-mediated dilation; and small vessel vasodilator response / shear stress was investigated with baseline and hyperemic flow velocities (after release of forearm occlusion; see above).

Statistical methods

All biomarkers were natural logarithmically transformed (to normalize their skewed distribution) and standardized. To reduce heteroscedasticity, CFPWV was inverse-transformed and multiplied by -1000 to restore directionality. To facilitate comparison of the magnitude of association between different biomarkers and vascular measures, vascular measures were standardized (so distributions had a mean=0 and a standard deviation=1). The correlation between different biomarkers and various vascular measures were estimated by Pearson correlation coefficients. Multivariable linear regression analysis was used to assess the relation between the different vascular measures (dependent variables) and individual biomarkers (independent variables). Separate analyses were performed for each biomarker in three steps. In a first model age, sex, and height were included as covariates. In a second model we incorporated the following variables additionally: weight, heart rate, mean arterial blood pressure, total/HDL cholesterol ratio, triglycerides, fasting blood glucose levels, diabetes (defined as fasting blood glucose ≥126 mg/dL or use of glucose-lowering medications), prevalent CVD (defined as coronary heart disease [myocardial infarction, coronary insufficiency, or angina], prior cerebrovascular disease [stroke or transient ischemic attack], peripheral artery disease [intermittent claudication], or heart failure), anti-hypertensive medications, lipid medications, smoking, and hormone replacement therapy. For the flow-mediated dilation analysis, hyperemic flow was additionally included as a variable in the second model, because these two measures have been shown to be associated.[8] The third model included all variables in the second model, and additionally all the biomarkers evaluated (GDF-15, sST2, hs-TnI, BNP, NT-proANP, renin, and hs-CRP). Except for the biomarkers, all variables used in the models were

obtained from examination cycle seven when vascular function was assessed. Analyses were performed in SAS version 9.3 (SAS institute, NC). A two-sided p-value <0.05 was considered statistically significant for all analyses. Given the hypothesis generating nature of this study, no formal adjustment was made for the numbers of statistical tests performed.

Results

In total 1,823 participants (mean age 61±10 years, 54% women) were included in our analyses. A total of 31% of the study sample had hypertension, 21% were on lipid-lowering medications, 12% had diabetes, and 12% had prevalent CVD (Table 1).

Pearson correlation coefficients between the circulating levels of the different biomarkers and the various vascular measures were in general weak (r<0.3) and are presented in online Supplemental Table 1.

Unadjusted means of different vascular measures by tertiles of GDF-15, sST2, and hs-TnI are presented in Figure 1 A-C. Higher levels of biomarkers were observed for increasing tertiles of forward wave amplitude and carotid-femoral pulse wave velocity, and for decreasing tertiles of baseline and hyperemic flow velocities and flow-mediated dilation.

Results from linear regression models relating biomarkers to measures of vascular function are presented in Figure 2. Upon multivariable adjustment, higher levels of GDF-15 remained statistically significantly associated with greater CFPWV (estimate 0.044 [95% confidence interval 0.007-0.081] standard deviation [SD] change per SD increase in $\log_e$[GDF-15], p=0.02) and forward pressure wave amplitude (estimate 0.076 [0.026-0.126] SD change per SD increase in $\log_e$[GDF-15], p=0.003). Higher GDF-15 concentrations were also associated with lower flow-mediated dilation in the multivariable-adjusted model (estimate -0.051 [-0.101--0.0003] SD change per SD increase in $\log_e$[GDF-15], p=0.048). Higher levels of sST2 were associated with greater CFPWV (estimate 0.032 [0.0005-0.063] SD change per SD increase in $\log_e$[sST2], p=0.046), and higher levels of hs-TnI were associated with lower hyperemic flow velocity after multivariable adjustment (estimate -0.041 [-0.082--0.0004] SD change per SD increase in $\log_e$[hs-TnI], p=0.048). In addition, higher levels of hs-TnI were associated with greater forward pressure wave amplitude in model 1 and 2, but the association was attenuated becoming statistically non-significant after adjustment for other biomarkers, Figure 2. The magnitude of association between a SD increment in different log-biomarkers and vascular measures corresponded to the effect of an increment in age of 0.5-2.5 years on different vascular function measures (online supplemental Table 2 shows the association between age and different vascular measures). There was no evidence of differential strengths of associations between biomarkers and vascular function measures by gender, age, diabetes, hypertension, or prevalent CVD, online supplemental Table 3.

Discussion

In our sample of middle-aged and older adults from the Framingham Offspring Study cohort, we observed that higher circulating levels of GDF-15 and sST2 were associated with greater aortic stiffness (measured by CFPWV). Higher levels of GDF-15 were also

associated with greater medium-sized artery stiffness (reflected by higher forward pressure wave amplitude), and worse endothelial function (in terms of lower flow-mediated dilation). Higher concentrations of hs-TnI were associated with lower hyperemic flow velocity that correlates with shear stress during hyperemia after release of brachial artery occlusion. These associations persisted after adjustment for standard CVD risk factors, potential confounders, and additionally for circulating biomarkers of cardiac load (BNP and NT-proANP), inflammation (hs-CRP), and neurohumoral activation (BNP, NT-proANP, and renin) that have been previously related to vascular function in Framingham. Given the exploratory nature of the present work we did not adjust for the numbers of statistical tests performed; however, if a Bonferroni correction (0.05/18 = 0.0028, for 6 vascular function tests related to 3 stress biomarkers) were to be applied, a majority of the observed associations would have turned statistically non-significant. The results should, therefore, be regarded as hypothesis generating only.

Circulating GDF-15 levels and vascular function measures

At the molecular level, GDF-15 is known to be a stress-responsive cytokine that is produced by a variety of cells, including cardiomyocytes, macrophages, and endothelial cells in response to inflammation, injury, pressure overload, and oxidative stress.[17-20] It is thought to have anti-inflammatory and anti-apoptotic effects on cells, including cardiomyocytes.[20] GDF-15 may also promote angiogenesis and may play a role in the adaptation to ischemia.[20] Our study demonstrating that higher levels of GDF-15 were associated with impaired endothelial function and higher arterial stiffness in central and medium-sized arteries fits well with the pan-vascular biological function of GDF-15 noted in the literature. In a prior study, higher circulating GDF-15 levels were associated with greater plaque burden in the common carotid, the carotid bulb, and the internal carotid artery among elderly people in the community.[21] These prior observations support our findings because carotid plaque burden is correlated positively with CFPWV.[22] Higher GDF-15 levels have also previously been associated with higher coronary artery calcium scores in the Dallas Heart Study,[23] and with endothelial vasodilation in resistance vessels, but not with brachial flow-mediated vasodilation in a community-based cohort of older people.[21] The latter finding is in contrast to our observations.[21] The reason for these divergent findings is unclear, but may relate to inherent differences in the study samples and also to methodological differences across the two studies. Notably, we defined flow-mediated dilation as the difference between the brachial diameter measured 60 seconds post-deflation and baseline, whereas the prior study defined flow-mediated dilation as the difference between the maximal brachial diameter obtained at any time between 30 and 90 seconds post-deflation and baseline diameter.[21]

Circulating sST2 concentrations and vascular function

At the molecular level, sST2 exists as soluble and membrane-bound components. The membrane bound component is present in various cells, including cardiomyocytes. In response to binding the ligand interleukin 33 (IL-33), the membrane-bound part of sST2 exerts antihypertrophic effects on cardiomyocytes and reduces myocardial fibrosis.[24] Circulating levels of sST2 act antagonistically to the membrane-bound sST2 component by binding circulating IL-33.[25] Experimental studies have suggested that IL-33 is a potent

endothelial activator, and abnormalities of the ST2 system may contribute to the development of atherosclerosis.[26] In our study we observed no association of sST2 levels with brachial artery endothelial function; however, given the temporal distance between obtainment of biomarkers and vascular measures it cannot be excluded that a true association between sST2 levels and measurements of endothelial function may have been missed.

In our study, which to the best of our knowledge is the first to investigate the association of sST2 with vascular function in a community based sample, we observed a direct relation between higher sST2 levels and greater aortic stiffness. Interestingly, sST2 has previously been demonstrated to be a significant predictor of incident hypertension (even after adjustment for traditional risk factors) in the Framingham Heart Study.[3] Given the direct association of sST2 with CFPWV, one mechanism linking sST2 with incident hypertension could perhaps be through its association with higher vascular stiffness, given that CFPWV is a strong risk factor for incident hypertension.[6]

Circulating hs-TnI concentrations and vascular function measures

Circulating concentrations of high-sensitivity troponins reflect cardiac strain and subclinical myocardial injury and are strongly associated with structural heart disease, risk of heart failure, and mortality in the general population.[27, 28] hs-TnI has previously shown to be associated with high left ventricular mass and reduced ejection fraction, as well as incident heart failure and cardiovascular and all-cause mortality in the Framingham Offspring cohort.[1, 2] Contrary to what might be expected based on these prior associations, we observed that hs-TnI was not associated with arterial stiffness. In contrast to our findings, a previous study of community-dwelling individuals in China reported a positive association of circulating hs-TnT with CFPWV, and another Chinese case-control study demonstrated a positive association of CFPWV and hs-TnI in patients with type 2 diabetes.[29, 30] The relation was, however, reported to be present only among people aged ≥60 years in the previous community-based study, which may explain the discrepancy with our study.[29] It is also possible that the temporal discrepancy between vascular and biomarker measures may have lead to our missing a true association. We, however, observed that hs-TnI was inversely associated with hyperemic flow velocity, which to the best of our knowledge has not been reported previously. Hyperemic flow is related to the vasodilator function of forearm resistance vessels and is impaired in individuals with a greater burden of cardiovascular risk factors and prevalent cardiovascular disease; this inverse relation of hyperemic flow velocity to risk factors may translate also into an inverse relation to circulating TnI that is elevated in people with a greater burden of risk factors.

Strengths and limitations

The strengths of our investigation include the comprehensive measures of vascular function and a panel of circulating biomarkers in a large cohort of ambulatory individuals in the community. The present study has, however, some important limitations to consider. We studied a predominantly white middle-aged cohort and the study sample was comprised of participants who attended both examination cycles 6 and 7, which may have resulted in a relatively healthier sample of attendees. The results may, therefore, not be generalizable to

younger cohorts or to individuals of different ethnicity. Also, the blood samples were drawn approximately 3 years prior to the vascular measures, which may have weakened some of the observed associations. Further, although we adjusted for multiple variables, residual confounding cannot be excluded and causality of the observed associations cannot be proven. For the flow-mediated dilation analyses, we measured the hyperemic diameter 60 seconds after occlusion; however we acknowledge that the peak diameter may have occurred at other points in some individuals, which may have weakened our associations. Finally, albeit statistically significant, some associations may not always be clinically relevant.

Perspectives

In this community-based cohort, we observed complex relations of circulating biomarkers of cardiac stress to measures of vascular function. These observations may be relevant to the associations of these biomarkers of cardiovascular stress with incident hypertension, CVD and heart failure;[1] however, more research is needed to establish the exact mechanisms underlying the associations and to assess their role as initial screening tools for subclinical vascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank Dr. Kai C. Wollert, Hannover Medical School, Germany, for measuring some of the biomarkers.

Conflicts of Interest and Source of Funding: This study was funded by the NIH Heart, Lung and Blood Institute (Contract #N01-HC-25195, and R01 HL107385, PI Vasan) and (1R01HL60040; 1RO1HL70100) with additional support from Evans Scholar award from the department of Medicine, Boston University School of Medicine (PI, Vasan). Dr. Januzzi is supported in part by the Desanctis Clinical Scholar Endowment and the Hutter Family Professorship. Dr. Andersson was supported by a grant from the Danish Research Council.

Dr. Mitchell is the owner of Cardiovascular Engineering Inc., a company that develops and manufactures devices to measure vascular stiffness. He has also served as consultant for and received honoraria from Merck and Novartis.

References

1. Wang TJ, Wollert KC, Larson MG, Coglianese E, McCabe EL, Cheng S, et al. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. Circulation. 2012; 126(13): 1596–604. [PubMed: 22907935]
2. Xanthakis V, Larson MG, Wollert KC, Aragam J, Cheng S, Ho J, et al. Association of novel biomarkers of cardiovascular stress with left ventricular hypertrophy and dysfunction: implications for screening. J Am Heart Assoc. 2013; 2(6):e000399. [PubMed: 24200688]
3. Ho JE, Larson MG, Ghorbani A, Cheng S, Vasan RS, Wang TJ, et al. Soluble ST2 predicts elevated SBP in the community. J Hypertens. 2013; 31(7):1431–6. discussion 6. [PubMed: 23615326]
4. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. Journal of the American College of Cardiology. 2012; 60(16):1455–69. [PubMed: 22999723]
5. Thanassoulis G, Lyass A, Benjamin EJ, Larson MG, Vita JA, Levy D, et al. Relations of exercise blood pressure response to cardiovascular risk factors and vascular function in the Framingham Heart Study. Circulation. 2012; 125(23):2836–43. [PubMed: 22572915]

6. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. Jama. 2012; 308(9):875–81. [PubMed: 22948697]
7. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation. 2010; 121(4):505–11. [PubMed: 20083680]
8. Mitchell GF, Parise H, Vita JA, Larson MG, Warner E, Keaney JF Jr, et al. Local shear stress and brachial artery flow-mediated dilation: the Framingham Heart Study. Hypertension. 2004; 44(2): 134–9. [PubMed: 15249547]
9. Kathiresan S, Gona P, Larson MG, Vita JA, Mitchell GF, Tofler GH, et al. Cross-sectional relations of multiple biomarkers from distinct biological pathways to brachial artery endothelial function. Circulation. 2006; 113(7):938–45. [PubMed: 16476848]
10. Lieb W, Larson MG, Benjamin EJ, Yin X, Tofler GH, Selhub J, et al. Multimarker approach to evaluate correlates of vascular stiffness: the Framingham Heart Study. Circulation. 2009; 119(1): 37–43. [PubMed: 19103986]
11. Rienstra M, Yin X, Larson MG, Fontes JD, Magnani JW, McManus DD, et al. Relation between soluble ST2, growth differentiation factor-15, and high-sensitivity troponin I and incident atrial fibrillation. Am Heart J. 2014; 167(1):109–15. e2. [PubMed: 24332149]
12. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004; 43(6):1239–45. [PubMed: 15123572]
13. Mitchell GF, Izzo JL Jr, Lacourciere Y, Ouellet JP, Neutel J, Qian C, et al. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. Circulation. 2002; 105(25): 2955–61. [PubMed: 12081987]
14. Mitchell GF, Lacourciere Y, Ouellet JP, Izzo JL Jr, Neutel J, Kerwin LJ, et al. Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. Circulation. 2003; 108(13):1592–8. [PubMed: 12975261]
15. Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. Journal of the American College of Cardiology. 1992; 20(4):952–63. [PubMed: 1527307]
16. Benjamin EJ, Larson MG, Keyes MJ, Mitchell GF, Vasan RS, Keaney JF Jr, et al. Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. Circulation. 2004; 109(5):613–9. [PubMed: 14769683]
17. Kempf T, Zarbock A, Widera C, Butz S, Stadtmann A, Rossaint J, et al. GDF-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. Nature medicine. 2011; 17(5):581–8.
18. Nickel N, Jonigk D, Kempf T, Bockmeyer CL, Maegel L, Rische J, et al. GDF-15 is abundantly expressed in plexiform lesions in patients with pulmonary arterial hypertension and affects proliferation and apoptosis of pulmonary endothelial cells. Respiratory research. 2011; 12:62. [PubMed: 21548946]
19. Schlittenhardt D, Schober A, Strelau J, Bonaterra GA, Schmiedt W, Unsicker K, et al. Involvement of growth differentiation factor-15/macrophage inhibitory cytokine-1 (GDF-15/MIC-1) in oxLDL-induced apoptosis of human macrophages in vitro and in arteriosclerotic lesions. Cell and tissue research. 2004; 318(2):325–33. [PubMed: 15459768]
20. Ago T, Sadoshima J. GDF15, a cardioprotective TGF-beta superfamily protein. Circ Res. 2006; 98(3):294–7. [PubMed: 16484622]
21. Lind L, Wallentin L, Kempf T, Tapken H, Quint A, Lindahl B, et al. Growth-differentiation factor-15 is an independent marker of cardiovascular dysfunction and disease in the elderly: results from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study. Eur Heart J. 2009; 30(19):2346–53. [PubMed: 19561023]
22. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. Stroke. 2001; 32(2):454–60. [PubMed: 11157182]

23. Rohatgi A, Patel P, Das SR, Ayers CR, Khera A, Martinez-Rumayor A, et al. Association of growth differentiation factor-15 with coronary atherosclerosis and mortality in a young, multiethnic population: observations from the Dallas Heart Study. Clin Chem. 2012; 58(1):172–82. [PubMed: 22065155]

24. Sanada S, Hakuno D, Higgins LJ, Schreiter ER, McKenzie AN, Lee RT. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. The Journal of clinical investigation. 2007; 117(6):1538–49. [PubMed: 17492053]

25. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov. 2008; 7(10):827–40. [PubMed: 18827826]

26. Choi YS, Choi HJ, Min JK, Pyun BJ, Maeng YS, Park H, et al. Interleukin-33 induces angiogenesis and vascular permeability through ST2/TRAF6-mediated endothelial nitric oxide production. Blood. 2009; 114(14):3117–26. [PubMed: 19661270]

27. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA : the journal of the American Medical Association. 2010; 304(22): 2503–12. [PubMed: 21139111]

28. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. Jama. 2010; 304(22):2494–502. [PubMed: 21078811]

29. Bai Y, Ye P, Luo L, Xiao W, Xu R, Wu H, et al. Arterial stiffness is associated with minimally elevated high-sensitivity cardiac, troponin T levels in a community-dwelling population. Atherosclerosis. 2011; 218(2):493–8. [PubMed: 21784424]

30. Yiu KH, Zhao CT, Chen Y, Siu CW, Chan YH, Lau KK, et al. Association of subclinical myocardial injury with arterial stiffness in patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2013; 12:94. [PubMed: 23799879]

Highlights

- Growth differentiation factor-15 (GDF-15), soluble (s)ST2, and high-sensitivity troponin-I (hs-TnI) are associated with incident cardiovascular disease (CVD) including heart failure, yet the underlying mechanisms are not fully understood.
- We showed that GDF-15, sST2, and hs-TnI are related to several measures indicative of subclinical vascular dysfunction in the community.
- These findings may contribute to our understanding of the associations between circulating GDF-15, sST2, and hs-TnI and incident CVD and heart failure.

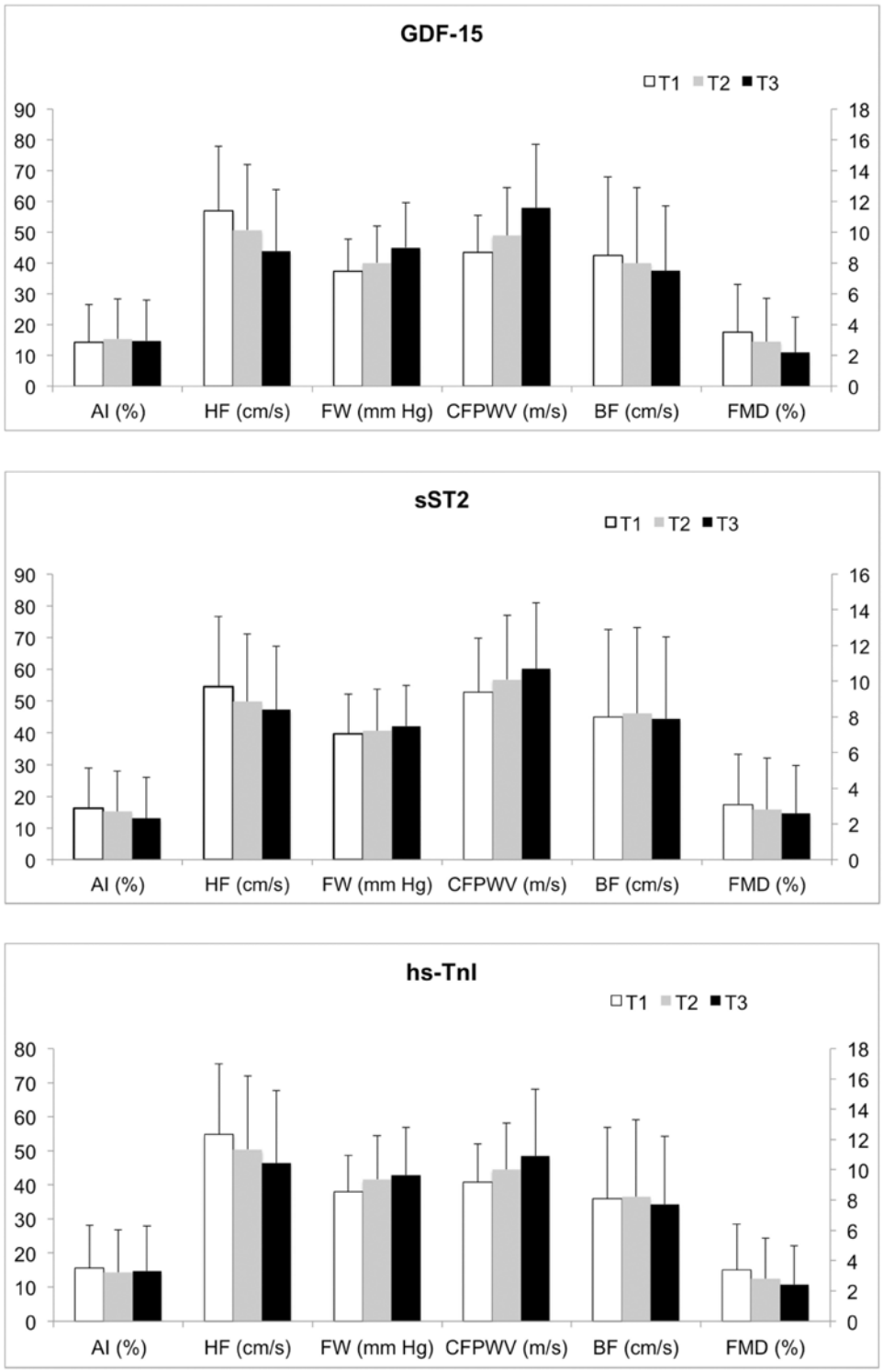

Figure 1. A-C – Unadjusted means of different vascular measures according to tertiles of biomarkers

Legend: Unadjusted means with standard deviations (error bar) for various vascular measures by tertiles of biomarker (T1-T3). AI=augmentation index, HF=hyperemic flow, FW=forward pressure wave amplitude, CFPWV=carotid-femoral pulse wave velocity,

BF=baseline flow velocity, FMD=flow-mediated dilation. AI, HF, and FW values refer to the left hand Y-axis, and CFPWV, BF, and FMD refer to the right hand Y-axis.

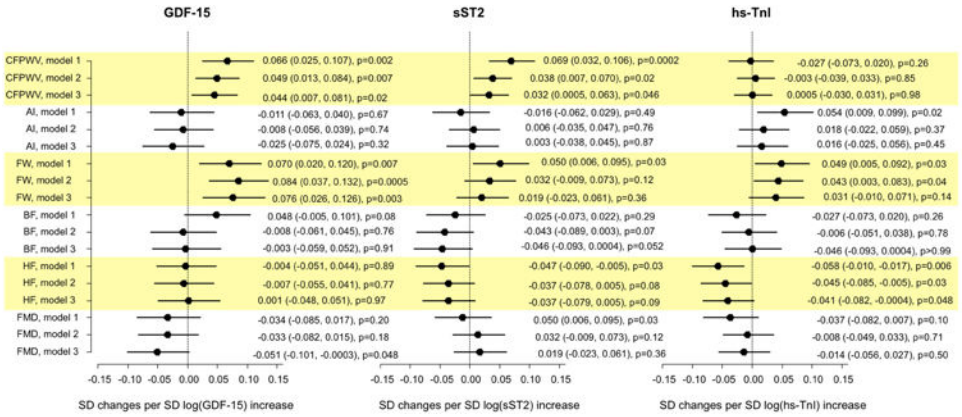

Figure 2. Association of various vascular measures with biomarkers based on multivariable linear regression

Legend: Association of biomarkers with different vascular measures. The units on the x-axis refer to changes in standard deviations for each standard deviation increase in $\log_e$(biomarker). CFPWV= carotid-femoral pulse wave velocity (ms/m), AI=augmentation index (%), FW=forward pressure wave amplitude (mm Hg), BF=baseline flow velocity (mm Hg), HF=hyperemic flow velocity (cm/s), FMD=flow-mediated dilation (%). Model 1 was adjusted for age, height, and sex; model 2 was adjusted for model 1 plus weight, heart rate, mean arterial blood pressure, total/HDL cholesterol ratio, triglycerides, glucose, diabetes, prevalent CVD, anti-hypertensive medication, lipid lowering medication, smoking, and hormone replacement therapy; Model 3 was adjusted for model 2 plus $\log_e$(BNP), $\log_e$(NT-proANP), $\log_e$(renin), $\log_e$(hs-CRP), $\log_e$(GDF-15), $\log_e$(sST2), and $\log_e$(hs-TnI).

Table 1

Sample Characteristics

	Total sample	Women	Men
	n=1823	n=985	n=838
Age, years	61 (10)	61 (9)	61 (10)
Height, cm		161 (6)	178 (7)
Weight, kg		69 (12)	86 (14)
Current cigarette smoking	233 (13%)	130 (13%)	103 (12%)
Prior cardiovascular disease	218 (12%)	81 (8%)	137 (16%)
Mean arterial blood pressure, mmHg	88 (12)	88 (12)	95 (11)
Hypertension, on medications	574 (31%)	275 (28%)	299 (36%)
Heart rate, bpm	65 (11)	66 (10)	63 (11)
Serum total /HDL cholesterol ratio	4.0 (1.3)	3.6 (1.2)	4.5 (1.4)
Serum triglycerides, mg/dL	132 (84)	126 (73)	139 (94)
Dyslipidemia, on medications	381 (21%)	178 (18%)	203 (24%)
Blood glucose, mg/dL	103 (26)	99 (23)	108 (29)
Diabetes mellitus	222 (12%)	90 (9%)	132 (16%)
Use of hormone replacement therapy	358 (36%)	358 (36%)	NA
Vascular measures			
Augmentation index (%)	14.8 (12.9)	18.5 (12.1)	10.5 (12.4)
Carotid-femoral pulse wave velocity *, ms/m	10.0 (3.5)	9.7 (3.4)	10.4 (3.6)
Forward pressure wave amplitude, mmHg	40.8 (12.8)	41.1 (13.1)	40.4 (12.5)
Flow-mediated dilation (%)	2.8 (2.8)	3.3 (3.0)	2.3 (2.4)
Baseline flow velocity, cm/s	8.0 (4.8)	7.5 (4.5)	8.6 (5.0)
Hyperemic flow velocity, cm/s	51 (21)	53 (22)	47 (20)
Vascular biomarkers †			
GDF-15, ng/L	1005 (800-1284)	996 (802-1260)	1021 (798-1333)
sST2, ng/mL	20.7 (16.4-25.6)	18.5 (15.1-22.8)	23.4 (19.0-28.9)
hs-TnI, pg/mL	1.32 (0.85-2.15)	1.14 (0.78-1.79)	1.59 (1.00-2.52)
BNP, pg/mL	7.9 (4.0-17.3)	9.4 (4.0-18.8)	6.0 (4.0-14.8)
hs-CRP, mg/L	1.8 (0.9-4.3)	2.0 (0.9-4.9)	1.6 (0.8-3.3)
Renin, mU/L	12 (7-21)	10.0 (6.0-18.0)	14.0 (8.0-24.0)
NT-proANP, pmol/L	321 (227-459)	351 (259-488)	280 (197-423)

Baseline characteristics and vascular measures were derived from examination cycle 7, whereas the vascular biomarkers were measured at examination cycle 6.

* To reduce heteroscedasticity, CFPWV was inverse-transformed and multiplied by -1000 to restore directionality. For Characteristics and vascular measures, numbers in parenthesis are standard deviations [for continuous variables] or percentages [for discrete variables]) unless specified.

† Biomarkers are presented as median (quartiles 1, 3). GDF-15=growth differentiation factor 15, hs-TnI= high-sensitivity troponin-I, BNP= B-type natriuretic peptide, hs-CRP= high-sensitivity C-reactive protein, NT-proANP= N terminal pro-atrial natriuretic peptide.