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Cellular Adhesion Molecules in Young Adulthood and Cardiac Function in Later Life

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Abstract

Background—E-selectin and intercellular adhesion molecule-1 (ICAM-1) are biomarkers of endothelial activation, which has been implicated in the pathogenesis of heart failure (HF) with preserved ejection fraction (HFpEF). However, the temporal associations between E-selectin and ICAM-1 with subclinical cardiac dysfunction are unclear.

Objectives—To assess the longitudinal associations of E-selectin and ICAM-1 with subclinical alterations in cardiac function.

Methods—In the Coronary Artery Disease Risk Development in Young Adults study, a cohort of black and white young adults, we evaluated the associations of E-selectin and ICAM-1, obtained at year 7 (Y7) and Y15 examinations, with cardiac function assessed at Y30 after adjustment for key covariates.

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Results—Higher E-selectin (n=1,810) and ICAM-1 (n=1,548) at Y7 were associated with black race, smoking, hypertension, and higher BMI. After multivariable adjustment, higher E-selectin at Y7 (β-coefficient per 1-SD higher: 0.22, SE: 0.06, P<0.001) and Y15 (β-coefficient per 1-SD higher: 0.19, SE: 0.06, P=0.002) was associated with worse left ventricular (LV) global longitudinal strain (GLS). Additionally, higher Y15 ICAM-1 (β-coefficient per 1-SD higher: 0.18, SE: 0.06, P=0.004) and its increase from Y7 to Y15 (β-coefficient per 1-SD higher: 0.16, SE: 0.07, P=0.03) were also independently associated with worse LV GLS. E-selectin and ICAM-1 partially mediated the associations between higher BMI and black race with worse GLS. Neither E-selectin nor ICAM-1 were associated with measures of LV diastolic function after multivariable adjustment.

Conclusion—Circulating levels of E-selectin and ICAM-1 and increases in ICAM-1 over the course of young adulthood are associated with worse indices of LV systolic function in midlife. These findings suggest associations of endothelial activation with subclinical HFpEF.

Condensed Abstract

Endothelial activation has been implicated in the pathogenesis of heart failure with preserved ejection fraction (HFpEF). The temporal relationships between E-selectin and intercellular adhesion molecule-1 (ICAM-1), which represent biomarkers of endothelial activation, and subclinical cardiac dysfunction are unclear. We evaluated associations between E-selectin and ICAM-1 in young adulthood with cardiac function in later life. E-selectin, ICAM-1, and increases in ICAM-1 were independently associated with worse left ventricular global longitudinal strain (GLS). E-selectin and ICAM-1 mediated associations between BMI and black race with worse GLS. Biomarkers of endothelial activation are associated with subclinical HFpEF.

Keywords

cellular adhesion molecules; heart failure with preserved ejection fraction; cardiac mechanics; pathogenesis; subclinical

Normal vascular endothelial function is integral to the maintenance of adequate cardiovascular performance. Recently, endothelial cell activation and subsequent coronary microvascular dysfunction have been implicated in the pathogenesis of heart failure (HF) with preserved ejection fraction (HFpEF) (1–3). Cellular adhesion molecules (CAMs), including E-selectin and intercellular adhesion molecule-1 (ICAM-1), are biomarkers of endothelial activation and play important roles in initiation of the inflammatory response (4). CAMs expressed on vascular endothelium participate in the recruitment of leukocytes to activated endothelial cells (5), and higher CAM levels are associated with impaired microvascular vasodilation (6). As such, higher circulating levels of CAM may reflect endothelial activation (7). Various cardiovascular (CV) risk factors trigger a systemic inflammatory response mediated by E-selectin and ICAM-1, which has been specifically implicated as a central mechanism of HFpEF (8). Indeed, expression of E-selectin and ICAM-1 is upregulated in myocardial tissue of both HFpEF patients and murine models of HFpEF (3,9,10).

While CAMs have been associated with prevalent HFpEF (3), the temporal relationship between CAMs and the onset of HFpEF is not well known. Notably, the associations between CAMs and subclinical alterations in myocardial function among individuals without prevalent HF are less clear and may provide insight into the longitudinal relationship between endothelial activation and overt HFpEF. Indeed, recent evidence has demonstrated that HFpEF is associated with abnormalities in both systolic and diastolic myocardial function, which may precede its development. Furthermore, sensitive measures of cardiac systolic dysfunction are strongly associated with poor outcomes in HFpEF (11,12). As such, we evaluated the associations between endothelial activation, as measured by E-selectin and ICAM-1, in early adulthood and indices of cardiac systolic and diastolic function later in life in the Coronary Artery Risk Development in Young Adults (CARDIA) study.

Methods

Study Population

The CARDIA study is a prospective cohort of 5,115 black and white young adults, aged 18–30 years at baseline, who were initially recruited across 4 U.S. urban sites (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) between March 1985 to June 1986. Complete information regarding the CARDIA study design, recruitment, and protocol for in-person examinations has been published previously (13). Briefly, CARDIA participants have been followed for over 30 years with in-person examinations at baseline (year 0: Y0) and at Y2, Y5, Y7, Y10, Y15, Y20, Y25, and Y30. Various evaluations, including demographic, clinical, laboratory, and imaging measures are performed at each examination, as outlined previously (13). Diabetes was defined as fasting glucose ≥126 mg/dL or use of diabetes medications. Retention rates among surviving participants at each in-person examination were: 90.5%, 85.7%, 80.6%, 78.5%, 73.6%, 71.9%, 72.1%, and 71.0%, respectively (14). Through telephone, mail, or email, contact is maintained with participants every 6 months. Additionally, interim medical history ascertainment is performed annually. Over the last 5 years, more than 90% of living cohort members have been directly contacted. Vital status follow-up is virtually complete through related contacts and periodic National Death Index searches.

For the present analysis, participants with (1) echocardiography obtained at Y30 and (2) CAMs at Y7 or Y15 were included in the analysis. Of the 5115 CARDIA participants, 2830 were initially excluded: 1756 did not attend Y30 examination, 342 did not attend Y7 exam, 273 did not attend Y15 exam, 1 withdrew consent, 108 were missing all CAM measurements at Y7 and Y15, and 229 were missing covariate data at Y7 or Y15. Additionally, 108 were missing echocardiographic quality control measures and 13 were missing all echocardiography variables. Of the remaining 2285 participants, the final analytic cohorts for subsequent analyses varied based on availability of CAMs at each exam (Y7 E-selectin [n=1810], Y7 I-CAM1 [n=1548], Y15 E-selectin [n=1912], Y15 I-CAM1 [n=2002]). The study was approved by institutional review boards at each site and all participants provided written informed consent.

Measurement of E-selectin and ICAM-1

Fasting blood samples were obtained from participants at Y7 and Y15 exams. Participants were asked to avoid physical activity and abstain from smoking for at least 2 hours before blood draw. Blood samples were processed and stored at −70°C and were shipped on dry ice to the central laboratory (Minneapolis, Minnesota). Soluble CAMs were assayed with sandwich ELISA methods (R&D systems) at the central laboratory (University of Minnesota, Minneapolis, Minnesota) as previously described (15). The inter-assay coefficients of variation were 7.7% for E-selectin and <10% for ICAM-1. Due to length of time between performing assays for ICAM-1 (Y15 ICAM-1 was performed in 2003 while Y7 was performed in 2012), we recalibrated Y7 ICAM-1 levels for compatibility with early assays as previously described (15).

Echocardiography

Comprehensive 2-dimensional, M-mode, and Doppler echocardiography was performed as a part of the CARDIA Y30 examination protocol. Cardiac sonographers from the 4 field centers participated in centralized training for image acquisition and used standard machines at each site (Apilo Artida scanner; Toshiba Medical Systems) (16). Additionally, quality control procedures assessed intrasonographer and intersonographer reliability intermittently throughout the Y30 examination (16). Studies were digitized, sonographers made measurements using standard software (Digisonics), and studies were subsequently sent electronically to the echocardiography core reading laboratory (Johns Hopkins University, Baltimore, Maryland). All echocardiograms were given an image quality score (0–3) in both the apical and short-axis views based on visualization of cardiac structures. Protocol for the assessment of cardiac structure and function has been previously described. Briefly, left atrial (LA) volume and left ventricular (LV) ejection fraction were measured using the apical 2-chamber and 4-chamber views as outlined by the American Society of Echocardiography guidelines (17). LV mass was assessed using the Devereux formula (18). LV end diastolic dimension was measured in the parasternal long-axis view. E wave and A wave velocities were measured during diastole using pulse-wave Doppler of mitral inflow. Tissue doppler at the lateral and septal LV walls measured early peak diastolic mitral annular velocities (e') and were averaged. E/e' was defined as the E wave divided by the average of e' velocities.

Speckle-tracking echocardiography was performed using dedicated semiautomated software (Toshiba Medical Systems). LV strain curves were generated using 3 consecutive cardiac cycles. LV longitudinal strain curves were generated in the apical 4-, 3-, and 2- chamber views. In each view, 6 LV segments were identified, and the average peak longitudinal strain of the 6 segments was obtained. LV global longitudinal strain (GLS) was subsequently calculated by averaging the peak longitudinal strain values from all 3 apical views. LV circumferential strain was assessed in the mid-LV cavity short axis view and was defined as the average peak systolic strain from the 6 segments.

For this analysis, the primary echocardiographic variables of cardiac function of interest were those of LV systolic function (LV GLS, and LV circumferential strain) and LV diastolic function (average e' and E/e').

Statistical Analysis

Clinical characteristics at Y7 examination by quartile of CAM were compared using χ^2 tests or Fisher's exact tests for categorical variables and univariate general linear models for continuous variables. Due to their skewed distributions, levels of E-selectin and ICAM-1 at both Y7 and Y15 were log-transformed and standardized (per SD) for all regression models. Multivariable general linear models were used to evaluate the associations of Y7 and Y15 log-transformed CAMs (E-selectin or ICAM-1) with the following echocardiographic indices of function at Y30: systolic (LV GLS, LV circumferential strain) and diastolic (average e' velocity and average E/e'). Models were adjusted for the following covariates obtained at the exam corresponding to that of CAM measurement (either Y7 or Y15): age, race, sex, number of cigarettes per day, body mass index (BMI), average systolic blood pressure (SBP), anti-hypertensive medication use, diabetes, plasma total cholesterol, serum creatinine, CARDIA field center, and image quality scores. Of note, as creatinine levels were not obtained at Y7, Y10 creatinine levels were used in models assessing Y7 CAMs. We also evaluated the association of change in CAMs from Y7 to Y15 and indices of cardiac function using general linear models which further adjusted for Y7 CAM level. In sensitivity analyses, we evaluated associations of Y7/Y15 CAMs with Y30 indices of cardiac function after adjustment for covariates that were significantly associated with E-selectin or ICAM-1 on crude analysis. Given that BMI can affect circulating levels of CAMs as well as LV GLS (19,20), we assessed interaction by BMI on the association of Y15 CAMs and LV GLS using an interaction term for BMI (continuous) in the fully adjusted models. We also assessed interaction by sex on the association of Y15 CAMs and LV GLS because of pathophysiologic differences in HFpEF by sex (21,22). Given that endothelial dysfunction is a potential mechanism underlying the association between cardiovascular (CV) risk factors and HFpEF, we performed a formal mediation analyses of Y15 E-selectin or Y15 ICAM-1 on the association between CV risk factors (BMI, average SBP, black race, cigarette smoking, diabetes, and total cholesterol level) and low GLS using the *mediation* package in R (R Foundation for Statistical Computing). Mediation analyses estimate the proportional effects of potential mediators (i.e., CAMs) on the total effect of exposure (CV risk factors) and outcome (GLS) (23). First, regression models were performed to determine the independent associations between 1) each CV risk factor (independent variable) and CAMs and 2) CAMs (independent variable) and GLS. If these associations were significant, mediation analyses were performed for specific CV risk factors and CAMs. Multivariable-adjusted direct and indirect effects (i.e. mediation effect) were reported, with calculation of 95% confidence intervals (CIs) using bootstrapping with 1000 resamples. Statistically significant mediation was determined if the indirect effect was significantly different from zero. Analyses were carried out using R version 3.5.1 (R Foundation for Statistical Computing) and SAS version 9.4 (Cary, NC). Two-tailed p-values <0.05 were considering statistically significant.

Results

Participant Characteristics

The characteristics of the analytic cohort stratified by quartile of Y7 E-selectin and ICAM-1 are shown in Table 1 and Supplemental Table 1, respectively. While participants with higher

E-selectin levels were of similar age, they were more likely male, of black race, and current smokers compared with those with lower E-selectin levels. Additionally, participants with higher E-selectin levels had higher BMI, systolic and diastolic blood pressures, total cholesterol, low-density lipoprotein cholesterol, and creatinine levels along with lower high-density lipoprotein cholesterol compared with participants with lower E-selectin levels. There was a significant correlation between Y7 E-selectin and Y7 ICAM-1 (r_p = 0.36, P<0.001). Participants with higher Y7 ICAM-1 shared similar clinical characteristics to participants with higher Y7 E-selectin levels (Supplemental Table 1). Compared with participants in the final analytic cohort, those who were excluded were more likely younger, black race, current smokers, and had lower education levels (Supplemental Table 2).

CAMs and Left Ventricular Function

In unadjusted analysis, participants with higher Y7 E-selectin levels had significantly higher LV mass, smaller LV dimension, worse LV GLS, worse LV circumferential strain, and lower e' velocities measured at Y30 compared to participants with lower Y7 E-selectin levels (Table 2). Similar findings were noted when participants were stratified by quartile of ICAM-1.

After covariate adjustment, higher E-selectin levels at both Y7 and Y15 were independently associated with worse LV GLS at Y30 (Table 3; Figure 1). While higher E-selectin was associated with worse LV circumferential strain, lower e' tissue velocities, and higher E/e' ratio in unadjusted analyses, these associations were attenuated after adjustment for clinical characteristics. Higher ICAM-1 at Y15, but not Y7, was independently associated with worse LV GLS at Y30 (Table 4). In addition, higher ICAM-1 at Y7 and Y15 were independently associated with worse LV circumferential strain at Y30. There were no significant associations of ICAM-1 with indices of diastolic function after multivariable adjustment. There was no interaction by BMI with the association between Y15 E-selectin and Y30 GLS ($P_{interaction}$ = 0.92) or Y15 ICAM-1 and Y30 GLS ($P_{interaction}$= 0.51). There was no interaction by sex with the association between Y15 E-selectin and Y30 GLS ($P_{interaction}$ = 0.20) or Y15 ICAM-1 and Y30 GLS ($P_{interaction}$ = 0.84).

The median change in E-selectin from Y7 to Y15 was 1.28 ng/mL (interquartile range [IQR]: −4.16, 6.29 ng/mL). There were no associations between change in E-selectin from Y7 to Y15 and indices of cardiac systolic or diastolic function (Supplemental Table 3). The median change in ICAM-1 from Y7 to Y15 was 10.97 ng/mL (IQR: −6.58, 28.25). Increase in ICAM-1 from Y7 to Y15 was independently associated with worse LV GLS (β coefficient: 0.16, SE: 0.07; P=0.03). Increase in ICAM-1 was not associated with other indices of cardiac function (Supplemental Table 3). In sensitivity analyses adjusting for covariates significantly associated with E-selectin or ICAM-1 on crude analyses, findings were consistent (Supplemental Tables 4 and 5).

CAMs as Mediators of Associations between Risk Factors and Global Longitudinal Strain

Results of mediation analyses of CV risk factors, CAMs, and GLS are displayed in Figure 2. After multivariable adjustment, BMI, SBP, and black race were the only clinical characteristics that were independently associated with both the potential mediators (i.e., E-

selectin and ICAM-1) and with the outcome of interest (GLS) and were thus included in the mediation analysis. E-selectin was a partial mediator of the relationships between 1) BMI and GLS, 2) SBP and GLS, and 3) black race and GLS. Specifically, E-selectin appeared to mediate 17% (95% CI: 5–47%) of the association between BMI and GLS, 8% (95% CI: 2–22%) of the association between SBP and GLS, and 9% (95% CI: 2–27%) of the association between black race and GLS. ICAM-1 was a partial mediator of the relationships between 1) BMI and GLS and 2) black race and GLS. Specifically, ICAM-1 appeared to mediate 17% (95% CI: 5–47%) of the association between BMI and GLS and 13% (95% CI 4–33%) of the association between black race and GLS. ICAM-1 was not a significant mediator of the relationship between SBP and GLS.

Discussion

In a diverse cohort of adults, we characterized the clinical profile of participants by degree of endothelial activation in young adulthood as measured by circulating E-selectin and ICAM-1, and evaluated the association of indices of endothelial activation with subclinical cardiac dysfunction in mid-life. Participants in CARDIA with higher levels of E-selectin and ICAM-1 carried a distinct demographic profile, highlighted by increased male sex and black race, and had higher blood pressure, BMI, smoking rates, and cholesterol levels. Higher levels of E-selectin, ICAM-1, and changes in ICAM-1 through young adulthood were independently associated with adverse LV systolic function, but not diastolic function, in later life. Finally, both E-selectin and ICAM-1 appeared to be partial mediators of the associations between BMI and black race with worse LV GLS.

Several evolving lines of evidence have revealed that HFpEF is not simply a disease of diastolic dysfunction, but rather represents a syndrome of systemic inflammation within multiple organ beds (8,24). Due to cumulative comorbidity exposure, an inflammatory cascade ensues leading to endothelial activation and endothelial expression of CAMs. Such signaling triggers transmigration of infiltrating leukocytes, which in turn promotes vascular and myocardial interstitial collagen deposition along with oxidative stress and decreased nitric oxide bioavailability (25). These converging pathways ultimately may result in coronary microvascular dysfunction (CMD) (26). Indeed, recent studies have demonstrated a high prevalence of CMD in HFpEF (2), further substantiating the role of systemic inflammation in this heterogeneous syndrome. E-selectin and ICAM-1 have been implicated specifically in the pathogenesis of HFpEF, as both CAMs are upregulated in myocardial samples of HFpEF patients compared with those with HF with reduced ejection fraction (HFrEF) or states of pressure overload (i.e., aortic stenosis) (3). Additionally, murine models of HFpEF that were deficient in ICAM-1 had less proinflammatory monocyte infiltration and did not develop cardiac fibrosis (10). Despite current understanding of endothelial activation in HFpEF, *in vivo* human studies to date have largely explored associations through cross-sectional analyses of CAMs in prevalent HFpEF, which limits understanding of temporal associations. In our study, we further substantiate the role of CAMs in subclinical HFpEF through detailed descriptions of the longitudinal associations between clinical risk factors, endothelial activation, and subclinical cardiac dysfunction among those at risk for HFpEF.

Both E-selectin and ICAM-1 in young adulthood were independently associated with worse LV GLS in midlife, providing insight into the role of endothelial activation in subclinical HF. LV GLS is a sensitive measure of LV systolic function, and is specifically most reflective of endocardial systolic function (27). The LV endocardium is the most susceptible myocardial layer to CMD due to endothelial activation, as the endocardium is most reliant upon the coronary microvasculature for its blood supply (28). Given the independent associations of E-selectin at 2 timepoints (Y7 and Y15), ICAM-1 at Y15, and increases in ICAM-1 from Y7 to Y15 with worse LV GLS, our findings suggest that endothelial activation is associated with worse endocardial systolic function, potentially due to CMD. While increases in ICAM-1 were associated with worse LV GLS, no association was noted between changes in E-selectin and LV GLS. These findings are likely explained by the relative stability in E-selectin levels across Y7 and Y15 exams.

In aggregate, our findings provide evidence for the role of endothelial activation in subclinical HFpEF via reduced systolic function. While E-selectin and ICAM-1 were associated with worse diastolic function, these relationships were attenuated after covariate adjustment, suggesting the associations of CAMs with diastolic function are explained by comorbidity burden. Although its name implies relative preservation of systolic function, HFpEF is now recognized as a syndrome of both systolic and diastolic cardiac mechanical dysfunction. Indeed, in the Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, over half of trial participants had abnormal LV longitudinal strain values at baseline and LV longitudinal strain was significantly worse in HFpEF compared with high-risk community-based controls (12). LV longitudinal strain was also significantly worse in HFpEF compared to patients with hypertension and evidence of diastolic dysfunction in the Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) Trial (11). Furthermore, LV longitudinal strain was independently associated with CV death and represented the strongest echocardiographic predictor of the primary composite outcome of the TOPCAT trial (12). Systolic dysfunction in HFpEF as measured by LV longitudinal strain likely occurs as a result to cardiomyocyte T-tubule disruption and abnormal calcium cycling (29). As such, our findings suggest an association between endothelial activation in young adulthood with subclinical cardiac systolic dysfunction, a finding that is common in overt HFpEF, carries important prognostic implications, and has a molecular basis in HFpEF development. Further, long-term prospective studies are required to evaluate if measures of endothelial activation and subsequent subclinical alterations in systolic function are associated with incident HFpEF.

The current mechanistic paradigm of HFpEF suggests that chronic CV risk factors induce a systemic inflammatory state, triggering endothelial activation and subsequent cardiac dysfunction. However, temporal understanding of this relationship has remained unclear. Through our mediation analysis, we were able to understand potential direct and indirect relationships between several CV risk factors, endothelial activation, and abnormal cardiac mechanics. Among a variety of CV risk factors, the associations between BMI and black race with low LV GLS were both partly mediated by higher levels of both E-selectin and ICAM-1. Additionally, the association of SBP with low LV GLS was partly mediated by E-selectin. Indeed, we noted similar patterns and degree of mediation effect by both CAMs on

LV GLS. As such, our findings provide further evidence for the role of endothelial activation in facilitating the relationship between these CV risk factors and subclinical cardiac dysfunction, which may ultimately drive HFpEF to exist (**Central Illustration**).

Limitations

Our study has strengths and limitations. The CARDIA study has recruited and followed a large, diverse cohort of black and white young adults, allowing for investigation of associations between risk factors and subclinical CV disease. Given the age at baseline of CARDIA participants, rates of incident HF events or overt dyspneic episodes have been low to date despite long-term follow-up, and thus we were unable to evaluate associations of CAMs with incident HFpEF. A number of CARDIA participants were excluded from this analysis due to lack of CAM and/or echocardiographic data. Excluded participants were more likely younger, current smokers, less educated, and black race (Supplemental Table 2). Despite this, our analytic sample was reflective of a diverse cohort and the exclusion of these generally higher-risk participants would tend to bias our results to the null, suggesting the association of CAMs with cardiac function may be underestimated. Further, it remains uncertain whether circulating CAM levels are reflective of activity at the level of the coronary microvasculature. Serial measurements of natriuretic peptides and certain speckle-tracking indices of cardiac function were not available for analysis. Although the *a priori* statistical plan did not account for multiple testing and is thus subject to type I error, our primary findings would remain significant even after traditional Bonferroni correction. While we chose multiple prespecified covariates in models given concern for confounding, it is possible that our fully adjusted models led to over-adjustment bias (30). Variability in echocardiographic image quality may have been present due to acquisition of images across the 4 field centers, which may have confounded the association between CAMs and cardiac function. However, we adjusted for field center and image quality scores in all analyses.

In this investigation of a diverse cohort of young adults, biomarkers of endothelial activation identified participants more likely male, of black race, along with higher BMI, blood pressure, and smoking rates. Circulating levels of E-selectin, ICAM-1, and increases in ICAM-1 over the course of young adulthood were independently associated with adverse LV systolic function in midlife as measured by LV GLS. E-selectin and ICAM-1 significantly appeared to mediate the associations of BMI and black race with worse systolic function, further suggesting that certain cardiovascular risk factors may drive subclinical HFpEF through endothelial activation. Collectively, our findings suggest that endothelial activation is associated with the development of a specific subclinical HFpEF phenotype, characterized by inflammatory cardiovascular risk factors and adverse systolic function. Interventions aimed to decrease endothelial activation among this high-risk cohort may prevent worsening of cardiac function and progression to overt HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation List

BMI	body mass index
CAM	cellular adhesion molecule
CARDIA	Coronary Artery Risk Development in Young Adults
GLS	global longitudinal strain
HFpEF	heart failure with preserved ejection fraction
ICAM-1	intercellular adhesion molecule-1
LV	left ventricular
SBP	systolic blood pressure

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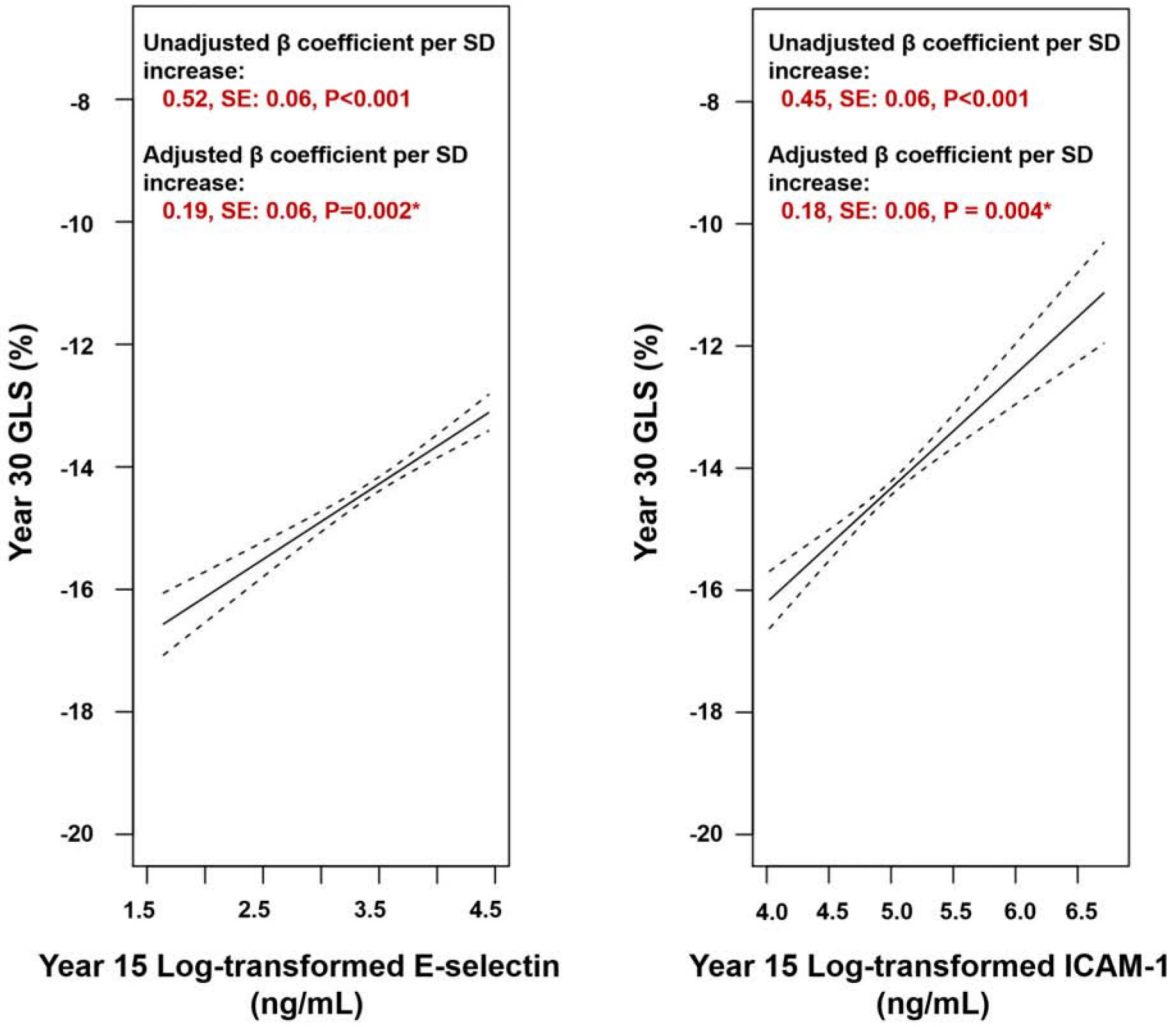
CLINICAL PERSPECTIVES

Competency in Medical Knowledge

Biomarkers of endothelial dysfunction in young adulthood are independently associated with endocardial systolic dysfunction and heart failure preserved ejection fraction (HFpEF) later in life.

Translational Outlook

Future studies should assess the efficacy and safety of targeting endothelial activation to prevent progression to HFpEF in patients at risk.



*Adjusted for Y15 covariates: age, sex, race, systolic blood pressure, anti-hypertensive medication use, total cholesterol, diabetes, number of cigarettes per day, body mass index, creatinine, field center, and image quality score.

Figure 1. Association of Year 15 Circulating Cellular Adhesion Molecules and Global Longitudinal Strain at Year 30.

Shown are generalized additive models displaying the unadjusted relationships between E-selectin/ICAM-1 and GLS. β coefficients are based on linear regression models. GLS = global longitudinal strain; ICAM-1 = intercellular adhesion molecule-1.

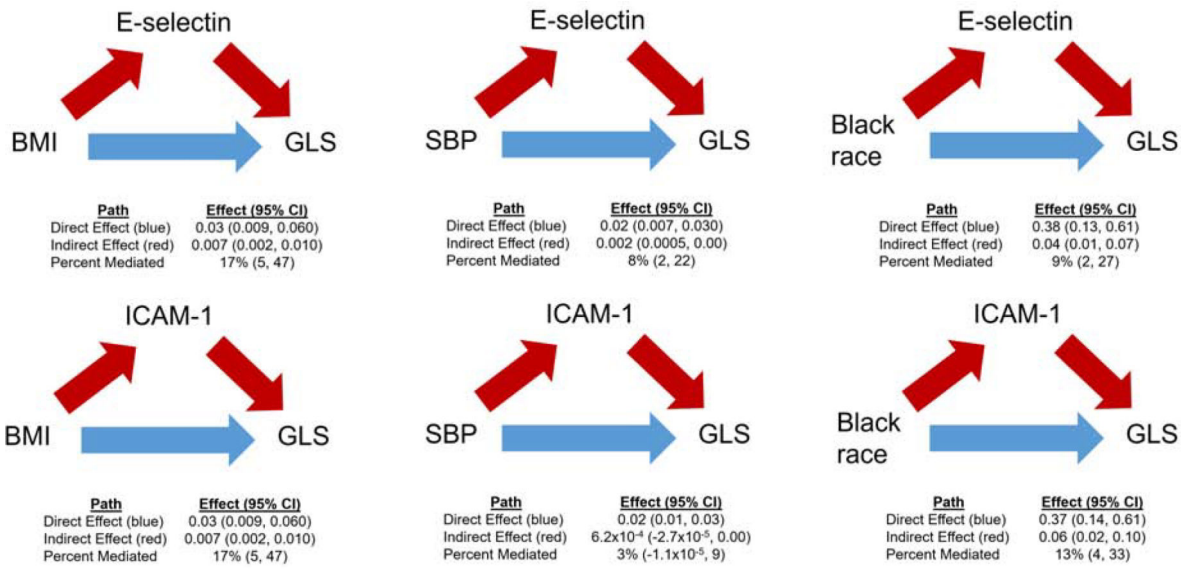


Figure 2. Mediation Analysis of Risk Factors, CAMs, and GLS.

The path model and mediation analysis describing mediation of the relationship between CV risk factors and GLS by E-selectin and ICAM-1 are displayed. CV = cardiovascular; GLS = global longitudinal strain; ICAM-1 = intercellular adhesion molecule-1.

Table 1.

Characteristics at Year 7 Exam By Quartile of Year 7 Circulating E-Selectin.

Characteristic	Quartile of Y7 E selectin				
	1 (n=452)	2 (n=453)	3 (n=453)	4 (n=452)	P value
Age, y, mean ± SD	32.2±3.7	32.2±3.4	32.2±3.5	32.3±3.4	0.92
Female, n (%)	326 (72.1)	265 (58.5)	228 (50.3)	192 (42.5)	<0.001
Black, n (%)	147 (32.5)	179 (39.5)	214 (47.2)	234 (51.8)	<0.001
Body mass index, kg/m2	24.5±4.6	25.6±4.9	26.9±5.8	28.7±6.3	<0.001
Systolic blood pressure, mmHg, mean ± SD	105.0±11.2	105.8±10.6	109.0±11.7	112.0±12.3	<0.001
Diastolic blood pressure, mmHg, mean ± SD	66.7±8.8	67.4±8.5	69.6±10.4	71.1±10.2	<0.001
Anti-hypertensive medication, n (%)	8 (1.8)	1 (0.2)	7 (1.6)	11 (2.4)	0.05
Diabetes mellitus, n (%)	4 (0.9)	0 (0)	7 (1.6)	13 (2.9)	0.002
Smoking Status					<0.001
Current smoker, n (%)	83 (18.4)	90 (19.9)	107 (23.6)	141 (31.2)	
Former smoker, n (%)	92 (20.4)	82 (18.1)	62 (13.7)	66 (14.6)	
Never smoker, n (%)	277 (61.3)	281 (62.0)	284 (62.7)	245 (54.2)	
Years of Education, mean±SD	15.4±2.4	15.0±2.5	14.8±2.4	14.2±2.3	<0.001
Total cholesterol, mg/dL, mean ± SD	170.9±29.8	177.0±32.3	174.5±33.7	181.3±33.3	<0.001
LDL cholesterol, mg/dL, mean ± SD	101.1±27.6	108.6±30.8	107.3±30.7	110.4±30.6	<0.001
HDL cholesterol, mg/dL, mean ± SD	56.0±13.1	53.4±13.4	50.2±12.7	49.8±16.1	<0.001
Creatinine, mg/dL, mean ± SD	0.80±0.16	0.84±0.16	0.86±0.17	0.87±0.17	<0.001
E-selectin, ng/mL, mean ± SD	16.3±4.0	26.6±2.7	36.7±3.3	53.5±8.5	<0.001

HDL = high-density lipoprotein; LDL = low-density lipoprotein

Table 2.

Echocardiographic Parameters at Year 30 Stratified by Quartile of E-selectin or ICAM-1.

	Quartile of Y7 E-selectin					Quartile of Y7 ICAM-1				
Echocardiographic Variable	**1**	**2**	**3**	**4**	**P value**	**1**	**2**	**3**	**4**	**P value**
Myocardial Structure										
Left ventricular mass indexed, g/m^2, mean ± SD	77.5±18.9	79.7±21.4	82.6±22.3	83.9±22.4	<0.001	77.2±17.6	81.4±22.0	82.2±21.2	82.5±22.0	0.001
LVIDDi, cm/m^2, mean ± SD	2.56±0.28	2.52±0.32	2.47±0.31	2.44±0.31	<0.001	2.61±0.28	2.52±0.29	2.45±0.31	2.44±0.31	<0.001
LAVI, mL/m^2, mean ± SD	25.2±7.0	25.5±7.0	25.3±7.2	26.1±8.3	0.31	26.0±7.7	25.5±7.0	25.3±7.4	25.4±7.4	0.55
Myocardial Systolic Function										
LVEF, %, mean ± SD	60.3±5.2	59.8±5.9	59.5±6.1	59.4±5.7	0.07	60.2±5.6	59.7±5.7	59.8±6.2	59.4±5.8	0.30
LV GLS, %, mean ± SD	−15.1±2.6	−14.7±2.5	−14.1±2.5	−13.8±2.5	<0.001	−14.9±2.5	−14.6±2.6	−14.3±2.5	−14.1±2.7	<0.001
LV circumferential strain, %	−14.9±3.6	−14.8±4.0	−14.2±3.7	−14.1±3.5	0.002	−14.9±3.8	−14.7±3.7	−14.4±3.8	−14.1±3.7	0.02
Myocardial Diastolic Function										
E/A, mean ± SD	1.24±0.36	1.19±0.35	1.17±0.34	1.14±0.33	<0.001	1.22±0.34	1.18±0.33	1.18±0.35	1.13±0.35	0.01
Average e', cm/s, mean ± SD	10.3±2.2	10.3±2.2	10.1±2.3	9.8±2.4	0.01	10.5±2.1	10.0±2.2	10.2±2.3	10.0±2.5	0.03
E/e', mean ± SD	8.0±2.0	7.9±2.3	7.9±2.3	8.3±2.7	0.06	7.6±2.0	8.0±2.3	7.9±2.3	8.3±2.4	0.003

LAVI = left atrial volume indexed; LV= left ventricular; LVIDDi = left ventricular diastolic dimension indexed; LVEF = left ventricular ejection fraction

Table 3.

Association of Circulating E-Selectin with Indices of Systolic and Diastolic Function at Year 30.

	Log-transformed Year 7 E-selectin			Log-transformed Year 15 E-selectin		
Echocardiographic Variable (Dependent Variable)	**N**	**β coefficient per SD increase (SE)**	**P value**	**N**	**β coefficient per SD increase (SE)**	**P value**
Systolic Function						
GLS	1680			1778		
Unadjusted		0.50 (0.06)	<0.001		0.52 (0.06)	<0001
Model 1 *		0.22 (0.06)	<0.001		0.19 (0.06)	0.002
Circumferential Strain	1619			1713		
Unadjusted		0.35 (0.09)	<0.001		0.31 (0.09)	<0.001
Model 1 *		0.19 (0.10)	0.05		0.09 (0.09)	0.35
Diastolic Function						
e' average	1751			1849		
Unadjusted		−0.18 (0.05)	<0.001		−0.18 (0.05)	<0.001
Model 1 *		−0.08 (0.05)	0.14		−0.03 (0.05)	0.53
E/e'	1719			1819		
Unadjusted		0.08 (0.06)	0.17		0.13 (0.05)	0.02
Model 1 *		0.03 (0.06)	0.64		0.01 (0.05)	0.81

GLS = global longitudinal strain

*Adjusted for age, sex, race, systolic blood pressure, anti-hypertensive medication use, total cholesterol, diabetes, number of cigarettes per day, body mass index, creatinine, field center, and image quality score. Covariates obtained at the corresponding exam as E-selectin measurements were used for analyses.

Table 4.

Association of Circulating ICAM-1 and Indices of Systolic and Diastolic Function at Year 30.

	Log transformed Year 7 ICAM-1			Log-transformed Year 15 ICAM-1		
Echocardiographic Variable (Dependent Variable)	**N**	**β coefficient per SD increase (SE)**	**P value**	**N**	**β coefficient per SD increase (SE)**	**P value**
Systolic Function						
GLS	1434			1863		
Unadjusted		0.29 (0.07)	<0.001		0.45 (0.06)	<0.001
Model 1 *		0.06 (0.08)	0.41		0.18 (0.06)	0.004
Circumferential Strain	1383			1794		
Unadjusted		0.29 (0.10)	0.005		0.49 (0.09)	<0.001
Model 1 *		0.24 (0.12)	0.04		0.31 (0.10)	0.001
Diastolic Function						
e' average	1495			1934		
Unadjusted		−0.09 (0.06)	0.12		−0.17 (0.05)	<0.001
Model 1 *		0.04 (0.06)	0.51		−0.02 (0.05)	0.63
E/e'	1472			1903		
Unadjusted		0.15 (0.06)	0.02		0.26 (0.05)	<0.001
Model 1 *		−0.04 (0.07)	0.59		0.07 (0.06)	0.20

GLS = global longitudinal strain; ICAM-1 = intercellular adhesion molecule-1.

*Adjusted for age, sex, race, systolic blood pressure, anti-hypertensive medication use, total cholesterol, diabetes, number of cigarettes per day, body mass index, creatinine, field center, and image quality score. Covariates obtained at the corresponding exam as ICAM-1 measurements were used for analyses.