Supplemental Data

Endothelin-1, cardiac morphology, and heart failure: The MESA Angiogenesis Study

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Figure E1. Polynomial smoothed function of the UNADJUSTED relationship between ET1 and cardiac morphology. Only presented in the range from the 10th to 90th percentile given the limitations of performing a polynomial smoothing algorithm where variables are sparse.

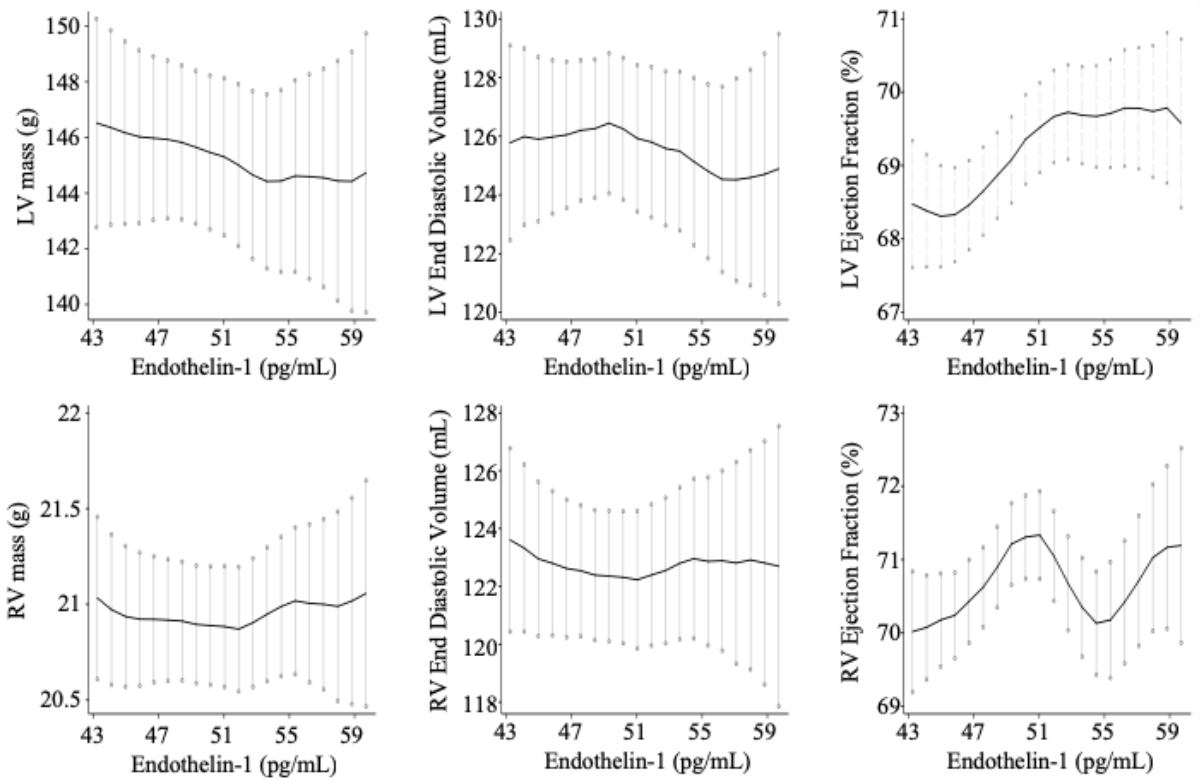

Figure E2. Predicted linear fit over the range of observed endothelin-1 values for the ADJUSTED relationship between ET1 and cardiac morphology.

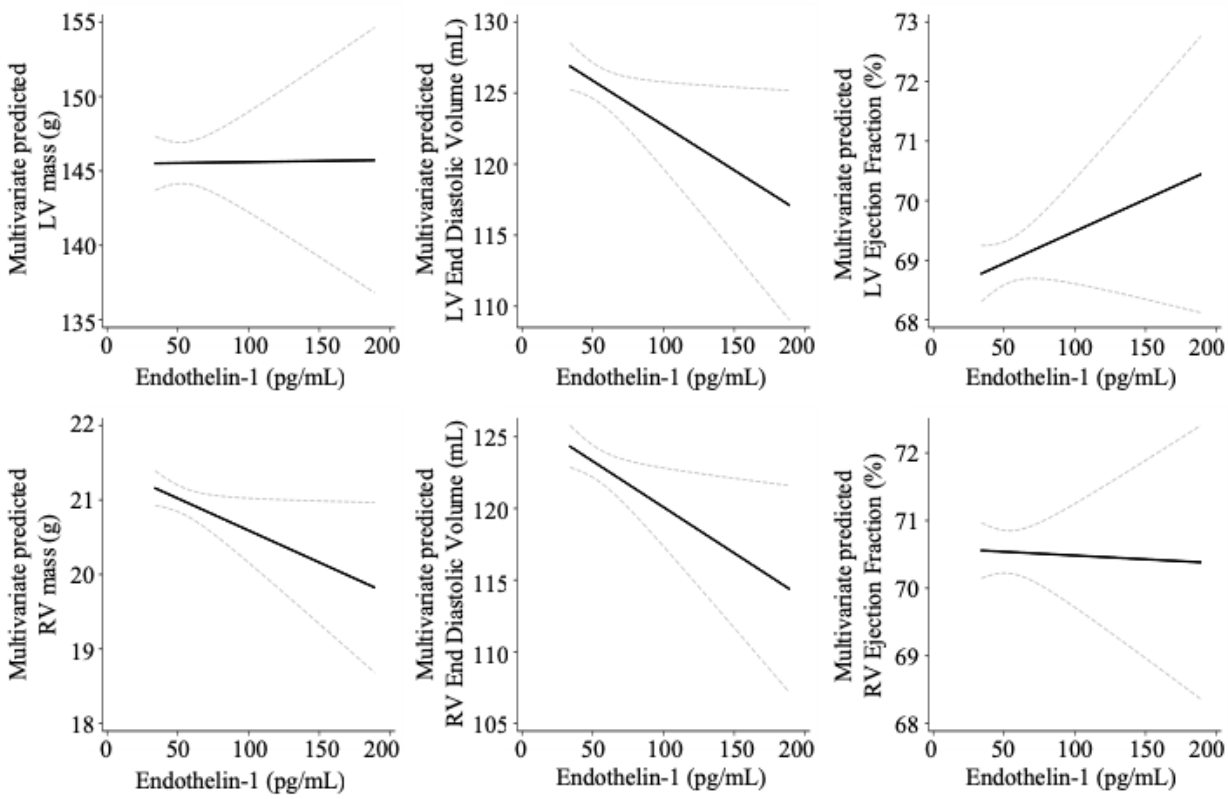

Table E1. Characteristics of the MESA Angiogenesis Cohort (n=1,383)

	Lowest Endothelin-1	Low-Medium Endothelin-1	High-Medium Endothelin-1	Highest Endothelin-1
Number of participants	184	548	385	264
Mean Endothelin-1 (pg/mL)	41.7 ± 1.9	47.1 ± 1.7	52.7 ± 1.6	68.8 ± 45.0
Endothelin-1 range (pg/mL)	34.6 – 43.8	44.1 – 49.9	50.0 – 55.9	56.0 – 189.1
Age (years)	63 ± 10	62 ± 10	61 ± 10	59 ± 10
Female (%)	45	52	52	58
Race (%)				
White	46	39	39	41
Chinese	13	12	14	8
African-American	26	29	25	27
Hispanic	15	21	22	24
Height (cm)	167 ± 9	166 ± 10	167 ± 10	166 ± 9
Weight (kg)	77 ± 14	78 ± 17	77 ± 17	77 ± 14
Body mass index (kg/m^2)	28 ± 5	28 ± 5	28 ± 5	28 ± 5
Educational attainment (%)				
No high school degree	16	15	15	19
High school degree	17	19	18	20
Some college	15	16	15	16
Bachelor's Degree	21	19	14	16
Higher than bachelor's degree	22	19	22	17
Insurance Status (%)				
No insurance	4	6	9	7
Medicare	40	36	30	26
Private insurance	69	73	73	76
Cigarette smoking status (%)				
Never	48	51	53	58
Former	43	36	35	34
Current	9	13	12	8
Pack-years	14 ± 26	12 ± 24	9 ± 16	7 ± 16
Metabolic Syndrome (%)	34	35	33	29
Hypertension (%)	47	43	43	40
Systolic blood pressure (mmHg)	128 ± 20	126 ± 22	124 ± 21	123 ± 21
Diabetes mellitus (%)	15	12	13	10
Cholesterol (mg/dL)	192 ± 32	194 ± 34	194 ± 34	194 ± 32
Glucose (mg/dL)	99 ± 31	98 ± 32	96 ± 30	93 ± 27
NT-ProBNP (pg/mL)	97 ± 170	94 ± 157	99 ± 170	87 ± 115
Medications (%)				
NSAIDs	48	44	40	39
Beta-blockers	13	9	7	9
ACE-inhibitors/ARBs	18	17	17	16
Any diuretic	11	13	13	9

Data presented as mean ± standard deviation or percentage as appropriate
Abbreviations: cm=centimeters, kg=kilograms, m^2=meters squared, mmHg=millimeters of mercury, mg=milligram, dL=deciliter, pg=picogram, mL=milliliter, NT-ProBNP=amino-terminal fragment of pro-B-type natriuretic peptide NSAIDs=non-steroidal anti-inflammatory medications, ACE-inhibitors=angiotensin converting enzyme inhibitors, ARBs=angiotensin II receptor blockers

Table E2. Exploratory multivariable regression estimating associations between endothelin-1 level and cardiac morphology or heart failure and cardiovascular death when accounting for estimated glomerular filtration rate or co-medication use (n=1,361)

	Per log increase in Endothelin-1		
	Difference	(95% CI)	p-value
Right Ventricle			
RV mass, g (Full Model† + estimated GFR)	-0.8	(-2.0, 0.3)	0.16
RV mass, g (Full Model† + Co-medication use‡)	-0.8	(-2.0, 0.3)	0.16
RV mass, g (Full Model† + intentional exercise)	-0.8	(-2.0, 0.3)	0.16
RVEDV, mL (Full Model + estimated GFR)	-7.1	(-14.3, 0.1)	0.05
RVEDV, mL (Full Model + Co-medication use)	-6.5	(-13.8, 0.8)	0.08
RVEDV, mL (Full Model + intentional exercise)	-7.0	(-14.2, 0.2)	0.06
RVEF, % (Full Model + estimated GFR)	0.2	(-1.9, 2.3)	0.86
RVEF, % (Full Model + Co-medication use)	0.2	(-1.9, 2.4)	0.83
RVEF, % (Full Model + intentional exercise)	0.1	(-2.0, 2.2)	0.90
Left Ventricle			
LV mass, g (Full Model† + estimated GFR)	-2.1	(-11.2, 6.9)	0.65
LV mass, g (Full Model† + Co-medication use‡)	-1.3	(-10.5, 8.0)	0.79
LV mass, g (Full Model† + intentional exercise)	-2.4	(-11.5, 6.6)	0.60
LVEDV, mL (Full Model + estimated GFR)	-8.9	(-17.1, -0.7)	0.03
LVEDV, mL (Full Model + Co-medication use)	-8.1	(-16.4, 0.3)	0.06
LVEDV, mL (Full Model + intentional exercise)	-9.2	(-17.4, -0.9)	0.03
LVEF, % (Full Model + estimated GFR)	2.8	(0.4, 5.2)	0.02
LVEF, % (Full Model + Co-medication use)	2.9	(0.5, 5.3)	0.02
LVEF, % (Full Model + intentional exercise)	2.9	(0.5, 5.2)	0.02

Abbreviations: SD=standard deviation, CI=confidence interval, RV=right ventricular, GFR=glomerular filtration rate, EDV=end-diastolic volume, and EF=ejection fraction, LV=left ventricular, g=grams, mL=milliliters

**Limited model: age, sex, race/ethnicity, height and weight, study site*

†Full model: Limited + education, smoking status, pack-years, hypertension, systolic blood pressure, diabetes, and cholesterol

‡Co-Medication use included: ace-inhibitor use (± diuretic), angiotensin-II-receptor blocker use (± diuretic), beta-blocker use (± diuretic), digoxin use, oral steroid use, non-steroidal anti-inflammatory use (including aspirin, COX-2 inhibitors and other non-steroidal anti-inflammatory medications) and leukotriene antagonist use

Table E3. Multivariable linear regression estimating associations between endothelin-1 level and cardiac structure and function including influential outliers (n=1,364)

	Per log increase in Endothelin-1		
	Difference	(95% CI)	p-value
Right Ventricle			
RV mass, g (Unadjusted)	0.1	(-1.2, 1.4)	0.88
RV mass, g (Limited model*)	-0.9	(-1.9, 0.0)	0.06
RV mass, g (Full Model†)	-1.0	(-1.9, 0.0)	0.05
RVEDV, mL (Unadjusted)	-0.1	(-8.9, 8.7)	0.98
RVEDV, mL (Limited model)	-6.9	(-12.8, -0.9)	0.02
RVEDV, mL (Full Model)	-8.0	(-14.0, -2.0)	0.009
RVEF, % (Unadjusted)	-0.3	(-2.2, 1.6)	0.74
RVEF, % (Limited model)	-0.1	(-1.8, 1.7)	0.96
RVEF, % (Full Model)	-0.1	(-1.9, 1.6)	0.87
Left Ventricle			
LV mass, g (Unadjusted)	-0.1	(-11.3, 11.4)	0.99
LV mass, g (Limited model*)	-3.7	(-11.6, 4.2)	0.36
LV mass, g (Full Model†)	-1.8	(-9.3, 5.7)	0.64
LVEDV, mL (Unadjusted)	-1.6	(-10.6, 7.3)	0.72
LVEDV, mL (Limited model)	-8.2	(-15.0, -1.4)	0.02
LVEDV, mL (Full Model)	-8.8	(-15.6, -2.0)	0.01
LVEF, % (Unadjusted)	1.9	(-0.3, 4.0)	0.08
LVEF, % (Limited model)	2.2	(0.3, 4.2)	0.03
LVEF, % (Full Model)	2.1	(0.2, 4.1)	0.03

Abbreviations: SD=standard deviation, CI=confidence interval, RV=right ventricular, GFR=glomerular filtration rate, EDV=end-diastolic volume, and EF=ejection fraction, LV=left ventricular, g=grams, mL=milliliters

**Limited model: age, sex, race/ethnicity, height and weight, study site*

†Full model: Limited + education, smoking status, pack-years, hypertension, systolic blood pressure, diabetes, and cholesterol

Table E4. Cox proportional hazard regression estimating the relationship of log of endothelin-1 level at the baseline exam with clinical outcomes including influential endothelin-1 outliers (n=1,364)

Hazard Ratio per log increase in endothelin-1 level		(95% CI)	p-value
Hazard of heart failure or cardiovascular death			
Unadjusted	0.02	(0.00, 0.49)	0.02
Limited model*	0.08	(0.01, 1.06)	0.06
Full Model†	0.09	(0.00, 1.42)	0.09
Hazard of heart failure			
Unadjusted	0.04	(0.00, 1.17)	0.06
Limited model*	0.11	(0.01, 1.75)	0.12
Full Model†	0.14	(0.01, 2.73)	0.20
Hazard cardiovascular death			
Unadjusted	0.03	(0.00, 2.07)	0.10
Limited model*	0.09	(0.00, 2.73)	0.17
Full Model†	0.09	(0.00, 2.98)	0.18
Hazard of non-cardiovascular death			
Unadjusted	0.36	(0.03, 5.23)	0.46
Limited model*	0.51	(0.13, 2.01)	0.34
Full Model†	0.57	(0.14, 2.42)	0.45

Definition of abbreviations: CI-confidence interval

Because initial models suggested a non-proportional hazard, all models accounted included a term accounting for the possibility of a time-varying relationship between endothelin-1 and the hazard of heart failure or death. Three influential endothelin-1 outliers were excluded from the primary analysis. Inclusion of these outlier strengthened the association with mortality

**Limited model: age, sex, race/ethnicity, height and weight, study site*

†Full model: Limited + education, smoking status, pack-years, hypertension, systolic blood pressure, diabetes, and cholesterol

Table E5. Parsimonious models using backward elimination (threshold for significance, p=0.05) for all adjusted regression analyses

	Hazard Ratio	(95% CI)	p-value
Hazard of heart failure or cardiovascular death			
Parsimonious Model (included age, weight, site, and smoking status)	0.08	(0.00, 1.37)	0.08
Hazard of heart failure			
Parsimonious Model (included age, weight, and site)	0.11	(0.01, 2.18)	0.15
Hazard cardiovascular death			
Parsimonious Model (included age, pack-years, and diabetes)	0.08	(0.00, 3.92)	0.20
Hazard of non-cardiovascular death			
Parsimonious Model (included age, smoking status, pack-years, and cholesterol)	0.75	(0.08, 7.03)	0.80
	Difference	**(95% CI)**	**p-value**
RV mass			
Parsimonious Model (included age, gender, height, weight, study site, and systolic blood pressure)	-0.7	(-1.8, 0.4)	0.23
RV End Diastolic Volume			
Parsimonious Model (included age, gender, height, weight, study site, and pack-years)	-6.4	(-13.6, 0.8)	0.08
RV Ejection Fraction			
Parsimonious Model (included age, gender, weight, study site, systolic blood pressure, and cholesterol)	0.2	(-1.9, 2.3)	0.85
LV Mass			
Parsimonious Model (included age, gender, race, height, weight, study site, smoking status, hypertension and systolic blood pressure)	-1.9	(-10.9, 7.1)	0.68
LV End Diastolic Volume			
Parsimonious Model (included age, gender, race, height, weight, study site, and systolic blood pressure)	-7.8	(-16.0, 0.3)	0.06
LV Ejection Fraction			
Parsimonious Model (included age, gender, race, and study site)	2.8	(0.5, 5.2)	0.02