

Heterogeneous Metabolic Response to Exercise Training in Heart Failure with Preserved Ejection Fraction - Suppl. Material - Bahls et al.

Suppl. Tables

Suppl. Table 1 – Feature selection parameters

physical parameters	sex
	age
	height
	weight
	BMI (kg/m <sup>2</sup> )
	BSA acc. Mosteller (m <sup>2</sup> )
	BP systolic
	BP diastolic
	waist circumference (cm)
	hip circumference (cm)
	menopause current
	smoking number of risk factors
	medical history
dyspnea at rest edema	
visible engorgement of the neck veins	
pulmonary rattling noises year of first HF diagnosis	
year of first HF diagnosis not known	
NYHA class	
age at first HF diagnosis	
time since first HF diagnosis	
diabetes mellitus	
Hypertension	
Hyperlipidemia	
Hyperuricemia	
alcohol consumption (drinks per week)	
coronary heart disease angina pectoris	
time since last myocardial infarction	
primary valve disease congenital	
heart disease cardiomyopathy	
primary cause for heart failure hepato-jugular reflux	
orthopnea	
paroxysmal dyspnoe at night nocturnal cough	
fatigue and performance problems	
nocturia	
nocturia - how often	
sleep apnoe smoking (pack-years)	
leukocytes	
cerebrovascular disease	

ECG parameters	PQ-time QRS-time QT-time AV-block left bundle branch block right bundle branch block 24h ECG HR (min) HR (max) HR (average) sNN50 sNN6% SDNN SDNNI SDANN RMSSD heart rate
lipids	total cholesterol LDL- cholesterol HDL-cholesterol
Biochemical parameters	Hemoglobin (mmol/L) creatinin ( $\mu\text{mol/L}$ ) uric acid ( $\mu\text{mol/L}$ ) sodium potassium creatinin clearance hematocrit platelets HbA1c (%) TSH date of blood analysis
echocardiography parameters	LVDD (mm) LVDS (mm) LA (mm) IV septal thickness (mm) posterior wall thickness (mm) LVEF (%) mitral valve insufficiency aorta insufficiency triscupid valve insufficiency end-diastolic LVV (Teichholz, mL) end- systolic LVV (Teichholz, mL) LVEF (Teichholz, %) Aorta diameter posterior wall thickness - end systolic end- diastolic left ventricular volume end-systolic left ventricular volume LV mass

left ventricular end-diastolic diameter (apical long axis)  
left ventricular end-diastolic diameter (apical short axis)  
left atrium end-systolic diameter (apical long axis) left  
atrium end-systolic diameter (apical short axis)

A1 LA-area (4 chamber view)

A2 LA-area (2 chamber view)

E-wave

A-wave

Mitral deceleration time

isovolumetric relaxation time (IVRT)

A-wave duration

Valsalva - E-wave

Valsalva - A-wave

Valsalva - deceleration time

Myocardial performance index (TEI)

a Myocardial performance index  
(TEI) b

tissue e'-wave (lateral) tissue

a'-wave (lateral) tissue e'-wave

(medial) tissue a'-wave

(medial) pulmonary valve

systolic flow pulmonary valve

diastolic flow pulmonary valve

atrial reversal duration of atrial  
reversal

Flow-Propagation-Time (Vp)

degree of diastolic dysfunction E/e'

medial

pulmonary valve

insufficiency tricuspidvalve

gradient stroke volume at

baseline cardiac output

CPET parameters	maximal watt maximal test duration BP systolic (rest) BP diastolic (rest) BP systolic (test) BP diastolic (test) HF (maximal) HF (rest) RQ (rest) RQ (max) RQ (max - post test) VE (rest) VE (max) peak VO2 watt @aerobic threshold <a href="#">VO2@AT</a> VE/VCO2 slope Borg score
strength test parameters	lat pull (1RM) arm pull (1RM) bench press (1RM) arm push (1RM) leg press - lying (1RM) leg press - sitting (1RM)
psychological parameters	total major depression acc. to PHQ-9 major/minor depression acc. to PHQ-9 SF-36 physical function SF-36 body role function SF-36 pain SF-36 overall health SF-36 vitality SF-36 social function SF-36 emotional role SF-36 physical health SF-36 physical SF-36 psychological health SF-12 physical SF-12 psychological health depression
Medication	ACE inhibitors AT1-antagonists beta blocker thiazide loop diuretics aldosterone antagonists other diuretics cardiac glycosides nitrate Calcium antagonists antiarrhythmic drugs statins

other lipid lowering medications  
ASS  
other platelets inhibitors  
Vitamin K antagonists  
other anti-coagulation  
insulin  
oral antidepressive medication  
antidepressive medication hypnotic  
and/or sedative medication  
Allopurinol oral contraceptives  
postmenopausal hormone therapy  
inhalable medication  
antiphlogistics other  
medication  
ACE-inhibitors - active substance 1  
ACE-inhibitors - daily dose 1  
ACE-inhibitors - active substance 2  
ACE-inhibitors - daily dose 2  
AT1-receptor antagonists - active substance 1  
AT1-receptor antagonists - daily dose 1  
AT1-receptor antagonists - active substance 2  
AT1-receptor antagonists - daily dose 2 beta-  
blocker - active substance 1 beta-blocker -  
daily dose 1 beta-blocker - active substance  
2 beta-blocker - daily dose 2 thiazide  
diuretics - active substance 1 thiazide  
diuretics - daily dose 1 thiazide diuretics -  
active substance 2 thiazide diuretics - daily  
dose 2 loop diuretics - active substance 1  
loop diuretics - daily dose 1 loop diuretics -  
active substance 2 loop diuretics - daily dose  
2 aldosterone antagonists - active substance  
1 aldosterone antagonists - daily dose 1  
aldosterone antagonists - active substance 2  
aldosterone antagonists - daily dose 2  
Potassium-sparing diuretics  
Potassium-sparing diuretics - active substance 1  
Potassium-sparing diuretics - daily dose 1  
Potassium-sparing diuretics - active substance 2  
Potassium-sparing diuretics - daily dose 2 other  
diuretics - active substance 1 other diuretics - daily  
dose 1 other diuretics - active substance 2 other  
diuretics - daily dose 2 cardiac glycosides - active  
substance 1 cardiac glycosides - daily dose 1 cardiac  
glycosides - active substance 2 cardiac glycosides -  
daily dose 2 nitrates (continuous medication) - active  
substance 1 nitrates (continuous medication) - daily  
dose 1 nitrates (continuous medication) - active  
substance 2 nitrates (continuous medication) - daily  
dose 2  
Calcium-antagonists - active substance 1

Calcium-antagonists - daily dose 1  
Calcium-antagonists - active substance 2  
Calcium-antagonists - daily dose 2  
antiarrhythmic drugs - active substance 1  
antiarrhythmic drugs - daily dose 1  
antiarrhythmic drugs - active substance 2  
antiarrhythmic drugs - daily dose 2 statin  
- active substance 1 statin - daily dose 1  
statin - active substance 2 statin - daily  
dose 2  
other lipid lowering medication - active substance 1  
other lipid lowering medication - daily dose 1 other  
lipid lowering medication - active substance 2 other  
lipid lowering medication - daily dose 2  
ASS - daily dose  
other platelet inhibitors - active substance 1  
other platelet inhibitors - daily dose 1 other  
platelet inhibitors - active substance 2 other  
platelet inhibitors - daily dose 2  
Vitamin K antagonists - active substance 1  
Vitamin K antagonists - daily dose 1  
Vitamin K antagonists - active substance 2  
Vitamin K antagonists - daily dose 2 other  
anti-coagulants - active substance 1 other  
anti-coagulants - daily dose 1 other anti-  
coagulants - active substance 2 other anti-  
coagulants - daily dose 2 Insulin - active  
substance 1 insulin - daily dose 1 Insulin -  
active substance 2 insulin - daily dose 2  
oral anti-diabetics - active substance 1  
oral anti-diabetics - daily dose 1 oral anti-  
diabetics - active substance 2 oral anti-  
diabetics - daily dose 2 oral anti-diabetics  
- active substance 3 oral anti-diabetics -  
daily dose 3 oral anti-diabetics - active  
substance 4 oral anti-diabetics - daily  
dose 4  
oral substance - active substance 1 oral  
substance - daily dose 1 oral substance -  
active substance 2 oral substance - daily  
dose 2 inhalable medication - active  
substance 1 inhalable medication - daily  
dose 1 inhalable medication - active  
substance 2 inhalable medication - daily  
dose 2 anti-depressives - active substance  
1 anti-depressives - daily dose 1 anti-  
depressives - active substance 2 anti-  
depressives - daily dose 2  
hypnotic and/or sedative medication - active substance 1  
hypnotic and/or sedative medication - daily dose 1  
hypnotic and/or sedative medication - active substance 2






hypnotic and/or sedative medication - daily dose 2  
Allopurinol - daily dose antiphlogistics - active substance  
1 antiphlogistics - daily dose 1 antiphlogistics - active  
substance 2 antiphlogistics - daily dose 2

change from Baseline to follow-up delta VO2peak  
delta LAVI  
delta E/e' delta  
VO2peak mean delta  
LAVI mean delta  
E/e' mean delta body  
weight delta BMI  
delta systolic BP  
delta diastolic BP  
delta resting heart  
rate delta  
hemoglobin delta  
creatinine delta uric  
acid delta cholesterol  
delta glomerular  
filtration rate delta  
resting heart rate  
(ecg) delta body  
surface area delta  
LVDD delta LDVS  
delta LVEF delta  
waist circumference  
delta hip  
circumference delta  
leukocytes delta  
hematocrit delta  
platelets delta LDL  
delta HDL delta  
LVEDD delta  
LVVES delta  
VO2@AT delta  
VE/VCO2 slope  
delta maximal HR  
delta stroke volume  
delta E/e' medial

Suppl. Table 2 – Metabolites associated with change in VO<sub>2</sub>peak

Class	Metabolite	Exercise		Overlap with other outcome parameters		
		Baseline	Follow-up	E/e'	VE/VCO <sub>2</sub> slope	LAVI
Amino Acid	Tryptophan	57.32 (52.89; 63.17)	54.15 (48.23; 61.40)			
Biogenic amines	Spermidine	0.2 (0.16; 0.24)	0.18 (0.15; 0.20)			
Glycerophospholipids	lysoPC a C16:0	95.52 (86.91; 102.98)	83.76 (72.60; 94.22)			
	lysoPC a C17:0	1.76 (1.45; 2.12)	1.6 (1.38; 1.91)			
	lysoPC a C26:1	0.06 (0.05; 0.07)	0.06 (0.05; 0.07)			
	PC aa C32:0	13.67 (11.32; 15.79)	13.83 (11.74; 15.51)			
	PC aa C36:0	1.87 (1.38; 2.42)	1.87 (1.50; 2.45)			
	PC aa C36:4	171.01 (154.43; 193.88)	167.99 (149.04; 193.58)			
	PC aa C36:5	26.38 (20.35; 36.74)	25.65 (19.52; 39.31)			
	PC aa C36:6	1.06 (0.85; 1.26)	1.06 (0.81; 1.39)			
	PC aa C38:0	2.25 (1.88; 2.95)	2.18 (2.82; 2.72)			
	PC aa C38:1	0.73 (0.46; 0.95)	0.64 (0.46; 0.98)			
	PC aa C38:4	96.64 (85.28; 113.56)	94.85 (82.42; 110.47)			
	PC aa C38:5	50.2 (44.62; 59.50)	50.62 (40.98; 62.20)			
	PC aa C38:6	80.43 (69.52; 103.25)	81.32 (61.76; 103.74)			
	PC aa C40:1	0.36 (0.34; 0.39)	0.36 (0.34; 0.45)			
	PC aa C40:3	0.45 (0.39; 0.55)	0.43 (0.36; 0.49)			
	PC aa C40:5	8.38 (7.28; 10.60)	8.19 (6.65; 9.79)			
	PC aa C40:6	25.95 (23.10; 31.66)	25.13 (19.22; 34.09)			
	PC aa C42:2	0.19 (0.16; 0.23)	0.19 (0.17; 0.23)			
	PC aa C42:5	0.29	0.26			



		(0.25; 0.34)	(0.24; 0.34)	
	PC aa C42:6	0.41	0.43	
		(0.35; 0.48)	(0.37; 0.50)	
	PC ae C30:2	0.11	0.1	
		(0.08; 0.13)	(0.08; 0.13)	
	PC ae C32:2	0.63	0.64	
		(0.50; 0.80)	(0.52; 0.81)	
	PC ae C34:0	1.36	1.48	
		(1.04; 1.88)	(1.08; 1.73)	
	PC ae C36:0	0.71	0.71	
		(0.63; 0.90)	(0.61; 0.85)	
	PC ae C36:5	9.84	9.98	
		(8.53; 11.54)	(7.98; 11.73)	
	PC ae C38:0	1.97	1.88	
		(1.59; 2.36)	(1.55; 2.39)	
	PC ae C38:6	6.13	6.26	
		(5.47; 7.95)	(5.41; 7.69)	
	PC ae C40:1	1.06	1.01	
		(0.88; 1.28)	(0.85; 1.19)	
	PC ae C40:2	1.7	1.54	
		(0.88; 1.28)	(1.25; 2.10)	
	PC ae C40:5	2.99	2.93	
		(2.64; 3.57)	(2.42; 3.35)	
	PC ae C40:6	3.9	3.75	
		(3.45; 5.04)	(3.32; 4.82)	
	PC ae C42:2	0.5	0.49	
		(0.42; 0.62)	(0.40; 0.57)	
	PC ae C42:3	0.67	0.66	
		(0.58; 0.81)	(0.55; 0.78)	
	PC ae C44:3	0.14	0.13	
		(0.12; 0.15)	(0.11; 0.14)	
	PC ae C44:6	0.81	0.77	
		(0.66; 0.95)	(0.64; 0.98)	
<hr/>				
sphingolipids	SM OH C16:1	2.66	2.64	
		(2.09; 3.28)	(2.03; 3.24)	
	SM C18:0	17.59	17.22	
		(14.73; 21.29)	(14.02; 20.03)	
	SM C24:1	29.96	26.62	
		(25.41; 33.74)	(23.91; 31.00)	
	SM C26:0	0.11	0.11	
		(0.09; 0.13)	(0.09; 0.13)	
	SM C26:1	0.24	0.21	
		(0.20; 0.30)	(0.18; 0.28)	

Suppl. Table 3 – Metabolites associated with change in VE/VCO<sub>2</sub> slope

Class	Metabolite	Exercise		Overlap with other outcome parameters		
		Baseline	Follow-up	E/e'	VO2peak	LAVI
Amino Acid	Leucine	134.25 (117.00; 150.00)	129.5 (113.87; 143.55)			
Biogenic amines	ADMA	0.41 (0.36; 0.47)	0.35 (0.30; 0.44)			
	Serotonin	0.1 (0.05; 0.14)	0.09 (0.05; 0.12)			
	Taurine	48.97 (41.22; 58.07)	47.15 (37.69; 55.97)			
Glycerophospholipids	lysoPC aa C24:0	0.1 (0.09; 0.11)	0.1 (0.08; 0.11)			
	PC aa C24:0	0.09 (0.09; 0.10)	0.09 (0.09; 0.09)			
	PC aa C38:0	2.25 (1.88; 2.95)	2.18 (2.82; 2.72)			
	PC aa C38:1	0.73 (0.46; 0.95)	0.64 (0.46; 0.98)			
	PC aa C40:2	0.24 (0.22; 0.30)	0.23 (0.19; 0.28)			
	PC aa C40:3	0.45 (0.39; 0.55)	0.43 (0.36; 0.49)			
	PC aa C42:0	0.41 (0.34; 0.52)	0.43 (0.36; 0.51)			
	PC aa C42:1	0.2 (0.18; 0.26)	0.22 (0.18; 0.26)			
	PC aa C42:2	0.19 (0.16; 0.23)	0.19 (0.17; 0.23)			
	PC ae C32:1	2.43 (2.09; 3.15)	2.6 (2.08; 2.95)			
	PC ae C34:2	9.83 (8.12; 13.13)	10.18 (8.54; 13.09)			
	PC ae C34:3	6.77 (5.27; 8.28)	6.79 (5.42; 8.36)			
	PC ae C36:3	6.33 (5.61; 8.12)	6.9 (5.53; 7.86)			
	PC ae C36:4	14.34 (12.91; 17.07)	15.1 (11.86; 18.44)			
	PC ae C36:5	9.84 (8.53; 11.54)	9.98 (7.98; 11.73)			
	PC ae C38:2	1.65 (1.32; 2.03)	1.54 (1.31; 1.87)			
	PC ae C38:4	11.21 (9.89; 13.10)	10.97 (10.03; 13.73)			
	PC ae C38:6	6.13 (5.47; 7.95)	6.26 (5.41; 7.69)			
	PC ae C40:1	1.06	1.01			

		(0.88; 1.28)	(0.85; 1.19)	
		0.97	0.88	
	PC ae C40:3	(0.83; 1.14)	(0.75; 1.10)	
		1.84	1.7	
	PC ae C40:4	(1.61; 2.08)	(1.50; 2.00)	
		2.99	2.93	
	PC ae C40:5	(2.64; 3.57)	(2.42; 3.35)	
		0.3	0.31	
	PC ae C42:1	(0.25; 0.35)	(0.26; 0.33)	
		0.67	0.66	
	PC ae C42:3	(0.58; 0.81)	(0.55; 0.78)	
		0.62	0.6	
	PC ae C42:4	(0.51; 0.72)	(0.49; 0.70)	
		0.14	0.13	
	PC ae C44:3	(0.12; 0.15)	(0.11; 0.14)	
		0.29	0.29	
	PC ae C44:4	(0.25; 0.33)	(0.24; 0.32)	
		1.13	1.08	
	PC ae C44:5	(0.92; 1.39)	(0.93; 1.42)	
		0.81	0.77	
	PC ae C44:6	(0.66; 0.95)	(0.64; 0.98)	
Sugars	H1	5281	5400	
		(4990; 5894)	(4850; 5721)	

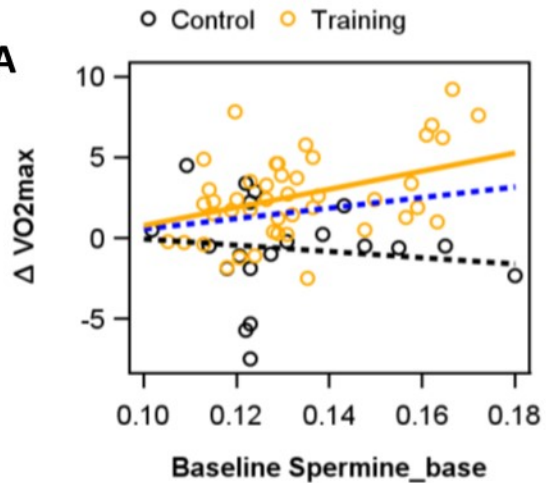
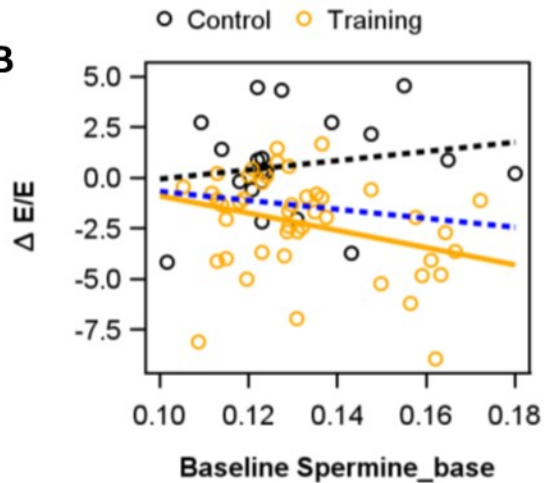
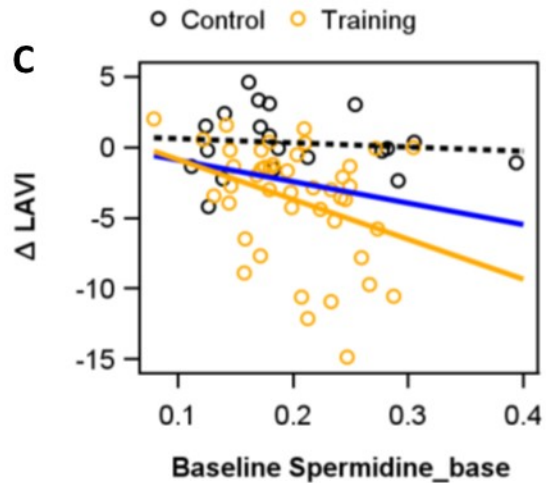
Suppl. Table 4 – Metabolites associated with change in E/e'

Class	Metabolite	Exercise		Overlap with other outcome parameters		
		Baseline	Follow-up	VE/VCO2 slope	VO2peak	LAVI
Amino Acid	Glycine	190.6 (166.6; 235.9)	176.5 (154.1; 209.2)			
	Serine	91.6 (83.4; 107.3)	95.1 (90.6; 103.8)			
Biogenic amines	Spermine	0.13 (0.12; 0.14)	0.12 (0.12; 0.13)			
Sphingolipids	SM C18:0	17.59 (14.72; 21.29)	17.22 (14.02; 20.03)			
	SM C22:3	1.07 (0.92; 1.27)	1.19 (0.85; 1.31)			
Glycerophospholipids	PC aa C38:5	50.2 (44.6; 59.5)	50.6 (41.0; 62.2)			
	PC aa C40:5	8.38 (7.28; 10.60)	8.19 (6.65; 9.79)			
	PC ae C30:1	0.08 (0.03; 0.12)	0.06 (0.02; 0.09)			
	PC ae C44:5	1.13 (0.92; 1.39)	1.08 (0.93; 1.42)			
Acetylcarnitine	Propionylcarnitine (C3)	0.37 (0.31; 0.44)	0.34 (0.29; 0.45)			
	Valeryl carnitine (C5)	0.14 (0.11; 0.16)	0.14 (0.11; 0.17)			
Sugars	H1	5281 (4990; 5894)	5400 (4850; 5721)			

Suppl. Table 5 – Metabolites associated with change in LAVI

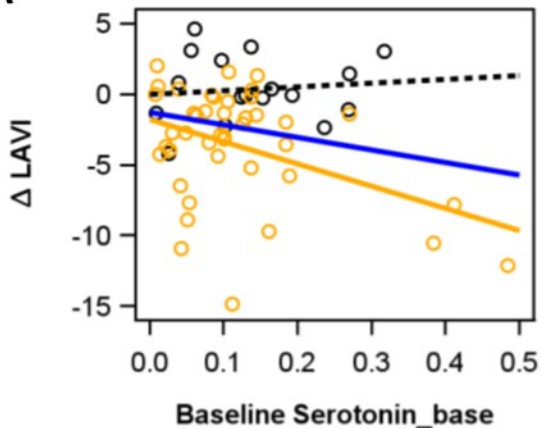
Class	Metabolite	Exercise		Overlap with other outcome parameters		
		Baseline	Follow-up	E/e'	VO <sub>2</sub> peak	VE/VCO <sub>2</sub> slope
Acetylcarnitine	Tetradecadienylcarnitine (C14:2)	0.04 (0.04; 0.05)	0.04 (0.04; 0.05)			
Amino Acid	Lysine	174.5 (156.8; 193.0)	172.5 (157.7; 188.4)			
Biogenic amines	Serotonin	0.1 (0.05; 0.14)	0.09 (0.05; 0.12)			
	Spermidine	0.2 (0.16; 0.24)	0.18 (0.15; 0.20)			
Glycerophospholipids	PC aa C36:2	197.8 (166.9; 219.2)	193.1 (155.1; 228.3)			
	PC aa C38:4	96.6 (85.3; 113.6)	94.9 (82.4; 110.5)			
	PC ae C34:2	9.83 (8.12; 13.1)	10.2 (8.5; 13.1)			
	PC ae C34:3	6.77 (5.27; 8.28)	6.79 (5.42; 8.36)			
	PC ae C36:3	6.34 (5.61; 8.12)	6.9 (5.53; 7.86)			



**A****B****C**

**A**

○ Control    ○ Training

**B**

○ Control    ○ Training

