

SUPPLEMENTARY DATA

Impaired Amino acid and TCA Metabolism and Cardiovascular Autonomic Neuropathy Progression in Type 1 Diabetes

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Supplementary Table 1: Comparison of cardiovascular autonomic neuropathy parameters between groups with top quartile Insulin dose compared to the rest of the cohort.

Supplementary Table 2: Correlation of metabolites to baseline cardiovascular autonomic neuropathy measures

Supplementary Table 3: Correlation of metabolites to cardiovascular autonomic neuropathy measures at three year follow up.

Supplementary Table 4: Correlation of metabolites to change in cardiovascular autonomic neuropathy measures from baseline to three year follow up.

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Supplementary Table S1. Comparison of cardiovascular autonomic neuropathy parameters between groups with top quartile Insulin dose compared to the rest of the cohort.

Metabolite	High Insulin dose (N=10)		Others (N=30)		p-value
	Mean	SD	Mean	SD	
BMI	27.19	4.35	26.44	4.87	0.67
TG	76.78	51.32	68.41	26.24	0.52
B-SDNN	54.50	24.35	49.80	18.12	0.52
B-RMSSD	38.00	24.73	37.00	24.52	0.9
F-SDNN	51	31.97	41.25	18.16	0.26
F-RMSSD	38.2	36.61	33.1	29.12	0.67
D-SDNN	1.5	12.38	5.9	33.04	0.68
D-RMSSD	1.11	17.5	-2.9	16.6	0.53
Valine	224.84	97.39	261.76	65.32	0.29
Leucine	98.61	46.93	105.76	46.56	0.68
Isoleucine	66.77	20.48	73.76	25.71	0.44

B-baseline, F-three-year follow-up, D- change in CAN measure. SDNN: standard deviation of normal RR interval, RMSSD: root mean square difference of successive RR intervals, BMI: Body Mass Index, SD: standard deviation.

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Supplementary Table S2. Correlation of metabolites to baseline cardiovascular autonomic neuropathy measures

Metabolites	Variable	SDN N	RMS SD	pNN5 0	30:15	E:I Ratio	LF	HF	LF:H F ratio	Valsal -va ratio
Alanine	r	-0.16	-0.28	-.395*	-0.27	-0.23	0.06	-0.20	0.07	-0.02
	p-value	0.33	0.08	0.01	0.09	0.15	0.70	0.22	0.67	0.92
Glycine	r	0.02	-0.15	-0.20	0.10	-0.08	-0.03	-0.03	0.16	-0.08
	p-value	0.91	0.37	0.23	0.55	0.63	0.84	0.84	0.31	0.63
Alpha-aminoisobutyric acid	r	-0.29	-0.18	-.336*	.447*	-0.04	0.14	-0.11	-0.14	0.06
	p-value	0.07	0.28	0.03	0.00	0.81	0.40	0.49	0.38	0.73
Valine	r	-0.19	-0.22	-.374*	-0.30	-0.18	0.07	-0.17	-0.03	-0.03
	p-value	0.23	0.17	0.02	0.06	0.28	0.68	0.30	0.87	0.85
Leucine	r	-0.03	-0.01	-0.13	-0.17	-0.08	0.16	-0.09	.317*	0.04
	p-value	0.86	0.98	0.42	0.29	0.61	0.32	0.57	0.05	0.80
Isoleucine	r	-0.17	-0.08	-0.20	-0.29	-0.06	0.08	-0.18	0.10	-0.10
	p-value	0.30	0.64	0.21	0.07	0.70	0.64	0.28	0.53	0.54
Threonine	r	0.30	0.13	0.22	0.25	0.23	0.04	0.00	0.23	-0.02
	p-value	0.06	0.41	0.17	0.12	0.15	0.80	0.99	0.16	0.90
Serine	r	0.27	0.02	0.14	0.25	0.00	-0.09	0.01	0.10	-0.10
	p-value	0.09	0.91	0.40	0.12	1.00	0.58	0.98	0.53	0.55
Proline	r	-0.08	-0.17	-0.25	-0.14	-0.23	0.01	-0.18	-0.03	-0.02
	p-value	0.64	0.30	0.12	0.40	0.16	0.93	0.26	0.84	0.89
Asparagine	r	.436*	0.21	0.28	.317*	0.21	0.21	0.22	0.11	-0.06
	p-value	0.01	0.20	0.08	0.05	0.20	0.19	0.17	0.50	0.70
Aspartic acid	r	-0.01	-0.12	-0.16	-0.02	-0.01	0.04	-0.03	0.10	0.05
	p-value	0.94	0.46	0.32	0.91	0.97	0.80	0.87	0.53	0.78
Methionine	r	-0.06	-0.07	-0.01	0.09	0.01	-0.01	-0.13	0.25	0.01
	p-value	0.70	0.66	0.97	0.59	0.96	0.95	0.44	0.12	0.95
4-Hydroxyproline	r	0.27	0.15	0.22	0.03	0.03	-0.08	-0.10	0.05	0.03

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	p-value	0.10	0.35	0.18	0.87	0.85	0.63	0.54	0.74	0.84
Glutamic acid	r	0.14	0.22	0.28	0.19	0.06	0.10	0.14	0.09	0.01
	p-value	0.38	0.18	0.08	0.25	0.72	0.53	0.41	0.59	0.97
Phenylalanine	r	0.16	0.00	0.10	0.01	0.00	-0.04	-0.08	0.27	0.06
	p-value	0.31	0.99	0.54	0.97	0.98	0.81	0.64	0.09	0.72
Glutamine	r	.516*	0.26	.433*	.472*	0.31	0.10	.409*	-0.18	-0.09
	p-value	0.00	0.11	0.01	0.00	0.05	0.54	0.01	0.27	0.59
Ornithine	r	0.11	0.24	0.17	0.08	0.06	0.27	.326*	0.23	-0.11
	p-value	0.49	0.14	0.29	0.63	0.70	0.09	0.04	0.16	0.49
Lysine	r	0.05	-0.03	0.02	-0.08	-0.02	-0.04	-0.11	0.31	0.09
	p-value	0.74	0.84	0.91	0.63	0.93	0.82	0.52	0.06	0.60
Histidine	r	0.11	0.02	0.15	0.09	0.08	-0.06	0.11	-0.11	0.05
	p-value	0.51	0.92	0.35	0.57	0.64	0.70	0.51	0.49	0.77
Tyrosine	r	0.28	0.09	0.15	-0.07	-0.06	0.07	-0.03	0.31	0.26
	p-value	0.08	0.59	0.35	0.69	0.72	0.68	0.88	0.06	0.11
Tryptophan	r	0.19	0.20	.327*	0.07	0.07	-0.01	0.04	0.12	0.21
	p-value	0.24	0.21	0.04	0.65	0.65	0.97	0.81	0.47	0.20

Metabolites	Variable	SDN N	RMS SD	pNN5 0	30:15	E:I Ratio	LF	HF	LF:H F ratio	Valsal -va ratio
α-ketoglutarate	r	-0.26	-0.14	-0.22	-0.22	-0.14	-0.06	-0.21	-0.01	0.05
	p-value	0.10	0.38	0.18	0.17	0.38	0.73	0.20	0.95	0.75
Fumarate	r	-.379*	-.322*	-.479*	-.391*	-0.29	0.08	-.317*	0.24	-0.10
	p-value	0.02	0.04	0.00	0.01	0.07	0.61	0.05	0.14	0.54
Lactate	r	-0.16	-0.12	-0.11	-0.16	-0.23	0.02	-0.02	0.15	-0.14
	p-value	0.34	0.47	0.52	0.34	0.16	0.92	0.90	0.36	0.41
Pyruvate	r	-.336*	-0.31	-0.31	-0.19	-0.29	-0.18	-0.24	0.12	-0.15

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	p-value	0.03	0.05	0.05	0.23	0.07	0.28	0.13	0.47	0.36
Citrate/ Isocitrate	r	-0.28	-.427*	-.480*	-.330*	-0.14	-0.03	-0.30	0.16	-0.21
	p-value	0.09	0.01	0.00	0.04	0.41	0.87	0.06	0.33	0.20
Flavin Adenine Nucleotide	r	0.23	0.06	0.08	-0.13	0.05	-0.13	-0.03	-0.19	0.31
	p-value	0.16	0.71	0.62	0.42	0.77	0.41	0.84	0.25	0.05
Hexose-6- Phosphate	r	0.08	-0.06	-0.03	0.16	0.04	0.10	.323*	0.01	-0.20
	p-value	0.64	0.73	0.86	0.34	0.79	0.55	0.04	0.95	0.21
Malate	r	-0.18	-0.19	-0.23	-0.17	-0.21	0.08	-0.13	0.01	-0.18
	p-value	0.27	0.24	0.16	0.30	0.19	0.64	0.43	0.96	0.27
Succinate	r	0.15	0.10	0.07	0.20	-0.02	0.22	0.14	0.04	-0.06
	p-value	0.36	0.54	0.66	0.22	0.90	0.18	0.38	0.81	0.71

N=40 patients; r- pearson Correlation Coefficient; yellow cells are significant negative correlation; orange cells are significant positive correlation. ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed). LF: low-frequency power, HF: high-frequency power, E:I expiration inspiration ratio, SDNN: standard deviation of normal RR interval, RMSSD: root mean square of difference of successive normal RR interval.

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Supplementary Table S3. Correlation of metabolites to cardiovascular autonomic neuropathy measures at three year follow up.

Baseline Metabolites	Variables	SDN N	RMS SD	pNN5 0	30-15	E:I Ratio	LF power	HF power	LF:H F ratio	Valsalva ratio
Alanine	r	-0.30	-0.26	-.346*	-0.12	-0.20	-0.16	-0.12	0.07	-0.25
	p-value	0.07	0.12	0.03	0.48	0.23	0.35	0.46	0.67	0.12
Glycine	r	-0.05	-0.07	-0.12	-0.05	-0.06	-0.07	0.00	-0.15	0.18
	p-value	0.78	0.69	0.46	0.76	0.74	0.70	1.00	0.39	0.29
Alpha-aminoisobutyric acid	r	-0.17	0.03	-0.17	0.07	-0.03	0.08	0.13	-0.02	-0.19
	p-value	0.32	0.85	0.32	0.69	0.86	0.63	0.45	0.88	0.26
Valine	r	-0.24	-0.20	-.325*	-0.02	-0.10	-0.02	-0.02	0.11	-0.08
	p-value	0.16	0.22	0.05	0.89	0.55	0.89	0.89	0.53	0.63
Leucine	r	0.03	0.05	-0.14	0.19	0.12	0.15	0.11	0.03	0.20
	p-value	0.84	0.79	0.39	0.26	0.47	0.38	0.52	0.86	0.23
Isoleucine	r	-0.05	-0.02	-0.18	0.08	0.10	0.10	0.08	0.27	-0.04
	p-value	0.79	0.89	0.29	0.62	0.54	0.54	0.65	0.11	0.83
Threonine	r	0.23	0.08	0.15	-0.05	0.24	-0.01	-0.04	0.31	0.29
	p-value	0.16	0.62	0.38	0.75	0.14	0.96	0.80	0.06	0.08
Serine	r	0.18	-0.02	0.06	-0.17	0.04	-0.11	-0.09	.425*	.378*
	p-value	0.28	0.91	0.71	0.32	0.83	0.51	0.59	0.01	0.02
Proline	r	-0.06	-0.18	-0.23	-0.15	-0.19	-0.11	-0.13	.389*	-0.04
	p-value	0.75	0.29	0.17	0.37	0.26	0.50	0.44	0.02	0.79
Asparagine	r	0.30	0.19	0.22	0.08	0.27	0.08	0.06	0.19	0.15
	p-value	0.07	0.25	0.19	0.64	0.11	0.65	0.73	0.25	0.38
Aspartic acid	r	0.18	0.06	-0.10	0.12	0.15	0.19	0.05	0.01	0.06
	p-value	0.28	0.72	0.55	0.47	0.39	0.27	0.76	0.97	0.70
Methionine	r	0.15	-0.05	-0.07	-0.08	0.07	-0.04	-0.11	0.03	0.11
	p-value	0.39	0.79	0.67	0.62	0.66	0.80	0.52	0.86	0.51
4-Hydroxypr	r	0.17	0.05	-0.01	-0.06	0.03	0.06	0.04	.330*	.512*

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	p-value	0.31	0.78	0.97	0.71	0.85	0.73	0.82	0.04	0.00
Glutamic acid	r	0.29	0.19	0.14	0.18	0.07	0.21	0.17	0.21	0.23
	p-value	0.09	0.25	0.40	0.27	0.68	0.22	0.31	0.21	0.17
Phenylalanine	r	0.18	-0.03	-0.08	0.02	0.01	-0.01	-0.09	0.29	0.27
	p-value	0.29	0.87	0.63	0.89	0.97	0.95	0.60	0.08	0.10
Glutamine	r	.598*	0.24	.407*	0.14	0.26	0.08	0.04	.334*	0.18
	p-value	0.00	0.14	0.01	0.40	0.11	0.62	0.81	0.04	0.28
Ornithine	r	.451*	.442*	0.29	.508*	.332*	.448*	.429*	0.11	0.08
	p-value	0.01	0.01	0.08	0.00	0.04	0.01	0.01	0.49	0.62
Lysine	r	0.17	-0.01	-0.11	0.08	0.04	0.00	-0.04	0.03	0.22
	p-value	0.32	0.95	0.50	0.62	0.79	0.99	0.80	0.86	0.18
Histidine	r	.328*	0.07	0.12	0.09	-0.01	-0.01	-0.08	0.15	0.16
	p-value	0.05	0.69	0.46	0.60	0.95	0.96	0.64	0.36	0.35
Tyrosine	r	0.27	0.02	0.05	0.00	-0.03	-0.13	-0.13	0.09	0.24
	p-value	0.11	0.92	0.79	0.99	0.88	0.45	0.43	0.58	0.15
Tryptophan	r	.363*	0.10	0.20	-0.08	0.07	-0.11	-0.08	0.09	0.30
	p-value	0.03	0.57	0.23	0.62	0.69	0.53	0.62	0.60	0.07
Baseline Metabolites	Variables	SDN N	RMS SD	pNN5 0	30-15	E:I Ratio	LF power	HF power	LF:H F ratio	Valsalva ratio
α -ketoglutarate	r	-0.09	-0.04	-0.11	-0.08	-0.10	-0.02	-0.02	0.04	-0.17
	p-value	0.59	0.81	0.50	0.63	0.55	0.93	0.93	0.82	0.30
Fumarate	r	-0.18	-0.20	-.346*	-0.11	-0.09	-0.06	-0.07	0.13	-0.16
	p-value	0.28	0.23	0.03	0.52	0.60	0.71	0.68	0.45	0.35
Lactate	r	0.07	-0.06	-0.06	-0.12	-0.03	-0.03	0.00	.473*	-0.16
	p-value	0.69	0.73	0.70	0.48	0.84	0.85	1.00	0.00	0.35
Pyruvate	r	-0.19	-0.19	-0.15	-0.15	-0.22	-0.13	-0.14	0.21	-0.32
	p-value	0.26	0.25	0.37	0.39	0.19	0.44	0.41	0.20	0.05

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Citrate/ Isocitrate	value									
	r	-0.06	-0.24	-.323*	-0.04	-0.02	-0.04	-0.15	.463*	-0.19
	p-value	0.71	0.15	0.05	0.82	0.91	0.82	0.38	0.00	0.25
Flavin Adenine Nucleotide	r	-0.01	-0.13	-0.07	-0.15	-0.06	-0.29	-0.25	0.07	-0.04
	p-value	0.97	0.44	0.69	0.36	0.71	0.08	0.13	0.69	0.84
Hexose-6- Phosphate	r	0.26	0.14	0.09	.382*	0.20	.325*	0.18	-0.08	-0.17
	p-value	0.12	0.40	0.59	0.02	0.22	0.05	0.29	0.65	0.32
Malate	r	0.10	-0.08	-0.12	-0.01	-0.05	0.06	-0.03	.573*	-0.28
	p-value	0.54	0.63	0.49	0.94	0.76	0.71	0.84	0.00	0.10
Succinate	r	0.15	0.11	0.07	0.10	0.08	0.12	0.08	0.07	-0.15
	p-value	0.38	0.52	0.66	0.57	0.65	0.46	0.65	0.66	0.38

N=40 patients; r- pearson Correlation Coefficient; yellow cells are significant negative correlation; orange cells are significant positive correlation. ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed). LF: low-frequency power, HF: high-frequency power, E:I expiration inspiration ratio, SDNN: standard deviation of normal RR interval, RMSSD: root mean square of difference of successive normal RR interval.

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Supplementary Table S4. Correlation of metabolites to change in cardiovascular autonomic neuropathy measures from baseline to three year follow up.

Baseline Metabolite	Variable	SDNN	RMSD	PNN50	LF Power	HF Power	LF:HF ratio	30:15 Ratio	E:I Ratio	Valsalva ratio
Alanine	r	-0.21	-0.12	-0.09	-0.23	-0.01	0.04	0.11	-0.02	-0.06
	p-value	0.22	0.48	0.59	0.17	0.94	0.80	0.49	0.89	0.75
Glycine	r	-0.05	0.06	0.01	-0.01	0.03	-0.20	-0.09	-0.03	-0.20
	p-value	0.77	0.72	0.97	0.97	0.85	0.24	0.59	0.85	0.25
Alpha-aminoisobutyric acid	r	0.07	0.26	0.17	-0.01	0.24	0.06	.363*	-0.02	-0.14
	p-value	0.69	0.11	0.31	0.96	0.15	0.72	0.03	0.90	0.41
Valine	r	-0.08	-0.06	-0.01	-0.08	0.08	0.11	0.19	0.04	-0.13
	p-value	0.65	0.71	0.95	0.65	0.65	0.50	0.25	0.79	0.47
Leucine	r	0.03	0.09	-0.03	0.02	0.19	-0.13	0.26	0.26	-0.07
	p-value	0.84	0.58	0.85	0.93	0.26	0.43	0.11	0.11	0.67
Isoleucine	r	0.11	0.10	0.08	0.03	0.19	0.17	0.25	0.23	-0.09
	p-value	0.52	0.57	0.64	0.85	0.26	0.30	0.13	0.16	0.62
Threonine	r	-0.02	0.00	-0.04	-0.08	-0.06	0.15	-0.22	0.05	-0.01
	p-value	0.92	0.98	0.83	0.61	0.72	0.37	0.19	0.78	0.96
Serine	r	0.04	-0.01	-0.07	-0.05	-0.12	0.31	-0.30	0.02	-0.15
	p-value	0.83	0.93	0.68	0.77	0.48	0.06	0.07	0.92	0.40
Proline	r	0.00	-0.12	-0.09	-0.13	-0.04	.363*	-0.02	0.00	0.00
	p-value	0.99	0.47	0.60	0.43	0.81	0.03	0.92	0.98	1.00
Asparagine	r	-0.04	0.10	0.01	-0.16	-0.07	0.10	-0.15	0.06	-0.17
	p-value	0.83	0.54	0.96	0.34	0.69	0.55	0.36	0.72	0.33
Aspartic acid	r	0.31	0.31	0.11	0.22	0.08	-0.04	0.12	0.16	-0.09
	p-value	0.07	0.06	0.53	0.19	0.62	0.79	0.48	0.35	0.60
Methionine	r	0.22	0.04	-0.07	-0.07	-0.07	-0.11	-0.14	0.13	-0.10
	p-value	0.18	0.83	0.67	0.66	0.68	0.52	0.41	0.43	0.55
4-Hydroxyproline	r	0.04	0.03	-0.06	0.08	0.08	0.22	-0.10	0.05	0.00
	p-value	0.84	0.86	0.71	0.61	0.62	0.19	0.53	0.76	0.98
Glutamic acid	r	0.13	0.05	-0.15	0.12	0.12	0.13	0.01	0.08	0.00
	p-value	0.43	0.77	0.38	0.47	0.47	0.45	0.97	0.64	0.99
Phenylalanine	r	0.09	0.05	-0.12	-0.03	-0.08	0.09	-0.01	0.08	-0.09
	p-value	0.61	0.77	0.46	0.85	0.62	0.59	0.97	0.64	0.61

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Baseline Metabolite	Variable	SDNN	RMSD	PNN50	LF Power	HF Power	LF:HF ratio	30:15 Ratio	E:I Ratio	Valsalva ratio
Glutamine	r	0.16	0.09	0.08	-0.04	-0.20	.368*	-0.22	0.01	-0.03
	p-value	0.35	0.59	0.64	0.79	0.22	0.02	0.18	0.96	0.86
Ornithine	r	.371*	.466**	0.25	0.30	.342*	-0.02	.353*	.365*	-0.04
	p-value	0.02	0.00	0.14	0.07	0.04	0.92	0.03	0.02	0.84
Lysine	r	0.12	0.07	-0.13	-0.01	0.00	-0.14	0.10	0.16	-0.01
	p-value	0.47	0.68	0.44	0.94	0.98	0.39	0.55	0.35	0.94
Histidine	r	0.26	0.11	0.02	0.02	-0.17	0.18	-0.01	-0.04	-0.05
	p-value	0.12	0.53	0.92	0.91	0.30	0.27	0.96	0.82	0.79
Tyrosine	r	0.08	-0.07	-0.13	-0.25	-0.15	-0.07	0.04	0.04	0.20
	p-value	0.66	0.67	0.44	0.12	0.36	0.66	0.80	0.82	0.26
Tryptophan	r	0.21	-0.12	-0.15	-0.17	-0.14	0.01	-0.13	0.05	0.12
	p-value	0.21	0.47	0.38	0.30	0.41	0.96	0.43	0.75	0.48
α-ketoglutarate	r	0.21	0.09	0.03	0.11	0.12	0.05	0.11	-0.02	-0.04
	p-value	0.22	0.61	0.86	0.53	0.46	0.75	0.51	0.91	0.84
Fumarate	r	0.20	0.06	0.06	-0.11	0.13	0.00	0.21	0.19	-0.11
	p-value	0.24	0.71	0.72	0.50	0.43	1.00	0.20	0.25	0.55
Lactate	r	0.28	0.03	-0.04	-0.02	0.02	.344*	0.02	0.19	-0.09
	p-value	0.09	0.86	0.83	0.89	0.88	0.03	0.89	0.25	0.59
Pyruvate	r	0.19	0.08	0.15	0.08	-0.01	0.13	0.03	0.02	-0.04
	p-value	0.26	0.64	0.37	0.65	0.94	0.42	0.85	0.89	0.82
Citrate/ Isocitrate	r	0.30	0.20	0.19	0.01	0.00	.327*	0.20	0.09	-0.13
	p-value	0.07	0.22	0.25	0.94	0.98	0.04	0.22	0.60	0.47
Flavin Adenine Nucleotide	r	-0.04	-0.24	-0.18	-0.20	-0.29	0.16	-0.01	-0.25	0.06
	p-value	0.82	0.15	0.29	0.23	0.08	0.33	0.97	0.14	0.73
Hexose-6-Phosphate	r	0.31	.368*	0.24	.335*	0.03	-0.07	0.21	0.19	-0.06
	p-value	0.07	0.02	0.14	0.04	0.86	0.67	0.21	0.27	0.74
Malate	r	.412*	0.15	0.16	0.02	0.04	.495**	0.11	0.14	-0.07
	p-value	0.01	0.36	0.34	0.88	0.81	0.00	0.49	0.39	0.68
Succinate	r	0.13	0.07	0.01	-0.06	0.02	0.05	-0.04	0.05	-0.23
	p-value	0.46	0.66	0.95	0.72	0.93	0.78	0.79	0.76	0.18

N=40 patients; r- pearson Correlation Coefficient; yellow cells are significant negative correlation; orange cells are significant positive correlation. ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed). LF: low-frequency power, HF: high-frequency power, E:I expiration inspiration ratio, SDNN: standard deviation of normal RR interval, RMSD: root mean square of difference of successive normal RR interval.