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Insights into the Serum Metabolic Adaptations in Response to Inspiratory muscle training: A Metabolomics Approach Based on ^{1}H-NMR and UHPLC-HRMS/MS

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Supplementary Material

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Table S1 - Serum metabolites annotated by ^{1}H NMR spectroscopy and concentration values (mM) for the Sham, MI, and HI groups Pre and Post-inspiratory muscle training. Data are mean ± standard deviation.

Compound	Sham (n = 7)		MI (n = 10)		HI (n = 10)		p and q-values for LMM effects					
							G		T		*G*T*	
	Pre	Post	Pre	Post	Pre	Post	*p*	*q*	*p*	*q*	*p*	*q*
2-Hydroxybutyrate	0.031 ± 0.010	0.033 ± 0.014	0.043 ± 0.009	0.032 ± 0.008	0.045 ± 0.024	0.040 ± 0.012	0.080	0.013	**0.027**	0.035	0.038	0.035
2-Hydroxyisovalerate	0.012 ± 0.007	0.010 ± 0.003	0.015 ± 0.012	0.015 ± 0.016	0.011 ± 0.004	0.010 ± 0.002	0.256	0.052	0.313	0.117	0.842	0.174
2-Oxoisocaproate	0.007 ± 0.007	0.005 ± 0.002	0.004 ± 0.002	0.005 ± 0.004	0.005 ± 0.003	0.006 ± 0.002	0.248	0.043	0.705	0.178	0.112	0.043
3-Hydroxybutyrate	0.062 ± 0.100	0.022 ± 0.014	0.102 ± 0.125	0.025 ± 0.008	0.074 ± 0.086	0.036 ± 0.037	0.496	0.126	**0.001**	0.013	0.653	0.126
3-Hydroxyisobutyrate	0.017 ± 0.007	0.017 ± 0.007	0.017 ± 0.004	0.016 ± 0.004	0.021 ± 0.009	0.017 ± 0.006	0.853	0.174	0.286	0.100	0.676	0.130
3-Methyl-2-oxovalerate	0.009 ± 0.003	0.008 ± 0.002	0.008 ± 0.002	0.007 ± 0.001	0.008 ± 0.002	0.007 ± 0.002	0.375	0.100	0.043	0.039	0.861	0.187
Acetate	0.065 ± 0.025	0.056 ± 0.021	0.057 ± 0.017	0.060 ± 0.014	0.046 ± 0.015	0.046 ± 0.017	0.013	0.004	0.681	0.174	0.245	0.083
Acetoacetate	0.034 ± 0.050	0.028 ± 0.029	0.053 ± 0.049	0.019 ± 0.004	0.053 ± 0.047	0.031 ± 0.037	0.439	0.113	**0.001**	0.017	0.029	0.026
Acetone	0.184 ± 0.234	0.119 ± 0.119	0.131 ± 0.119	0.169 ± 0.175	0.238 ± 0.215	0.096 ± 0.113	0.883	0.183	**0.020**	0.030	0.025	0.017
Alanine	0.416 ± 0.123	0.367 ± 0.071	0.338 ± 0.097	0.359 ± 0.094	0.408 ± 0.179	0.390 ± 0.090	0.296	0.065	0.877	0.191	0.285	0.087
Ascorbate	0.042 ± 0.020	0.036 ± 0.021	0.043 ± 0.011	0.037 ± 0.016	0.034 ± 0.013	0.029 ± 0.009	0.311	0.074	0.053	0.048	0.966	0.196
Asparagine	0.045 ± 0.019	0.039 ± 0.017	0.032 ± 0.014	0.034 ± 0.018	0.034 ± 0.026	0.033 ± 0.017	0.290	0.061	0.733	0.183	0.502	0.113
Aspartate	0.030 ± 0.021	0.029 ± 0.015	0.023 ± 0.010	0.025 ± 0.008	0.029 ± 0.012	0.033 ± 0.012	0.182	0.026	0.226	0.087	0.698	0.152
Betaine	0.041 ± 0.022	0.046 ± 0.030	0.046 ± 0.017	0.047 ± 0.020	0.046 ± 0.017	0.046 ± 0.016	0.474	0.122	0.629	0.161	0.994	0.200
Choline	0.011 ± 0.006	0.012 ± 0.004	0.012 ± 0.006	0.011 ± 0.004	0.011 ± 0.004	0.011 ± 0.007	0.710	0.165	0.643	0.165	0.343	0.096
Citrate	0.064 ± 0.018	0.053 ± 0.014	0.064 ± 0.009	0.054 ± 0.009	0.066 ± 0.015	0.059 ± 0.013	0.533	0.143	**0.000**	0.009	0.555	0.117
Creatine	0.018 ± 0.013	0.016 ± 0.009	0.016 ± 0.008	0.019 ± 0.012	0.027 ± 0.023	0.025 ± 0.027	0.702	0.161	0.913	0.196	0.945	0.191
Creatinine	0.102 ± 0.051	0.085 ± 0.021	0.088 ± 0.010	0.085 ± 0.010	0.098 ± 0.041	0.086 ± 0.013	0.944	0.191	0.044	0.043	0.708	0.157
Dimethyl sulfone	0.006 ± 0.003	0.005 ± 0.002	0.007 ± 0.003	0.008 ± 0.002	0.007 ± 0.003	0.006 ± 0.003	0.170	0.022	0.618	0.157	0.170	0.052
Dimethylamine	0.004 ± 0.002	0.004 ± 0.003	0.003 ± 0.000	0.002 ± 0.001	0.004 ± 0.003	0.004 ± 0.003	0.407	0.109	0.165	0.074	0.422	0.109
Ethanol	0.104 ± 0.049	0.108 ± 0.043	0.110 ± 0.062	0.090 ± 0.020	0.149 ± 0.197	0.126 ± 0.059	0.497	0.130	0.474	0.139	0.289	0.091
Formate	0.027 ± 0.007	0.025 ± 0.010	0.024 ± 0.004	0.025 ± 0.005	0.021 ± 0.006	0.021 ± 0.005	0.037	0.009	0.610	0.152	0.194	0.057
Glucose	4.449 ± 1.291	3.718 ± 0.702	4.576 ± 1.420	4.073 ± 0.568	5.020 ± 2.290	4.431 ± 0.924	0.231	0.035	0.106	0.065	0.686	0.139
Glutamine	0.493 ± 0.169	0.475 ± 0.089	0.437 ± 0.053	0.403 ± 0.128	0.495 ± 0.149	0.477 ± 0.112	0.249	0.048	0.219	0.083	0.695	0.148
Glycerol	3.090 ± 2.442	2.683 ± 0.523	2.764 ± 0.608	2.685 ± 0.326	2.909 ± 0.960	2.949 ± 0.932	0.355	0.091	0.127	0.070	0.198	0.061

Histidine	0.091 ± 0.026	0.073 ± 0.012	0.081 ± 0.014	0.083 ± 0.013	0.090 ± 0.032	0.083 ± 0.017	0.678	0.152	0.170	0.078	0.218	0.074
Isoleucine	0.072 ± 0.027	0.062 ± 0.012	0.056 ± 0.010	0.058 ± 0.008	0.062 ± 0.016	0.059 ± 0.012	0.266	0.057	0.544	0.148	0.201	0.070
Isopropanol	0.009 ± 0.006	0.010 ± 0.005	0.009 ± 0.006	0.009 ± 0.005	0.010 ± 0.004	0.008 ± 0.003	0.986	0.200	0.384	0.126	0.345	0.100
Lactate	2.792 ± 1.316	2.477 ± 0.342	2.336 ± 0.542	2.408 ± 1.018	2.422 ± 0.873	2.090 ± 0.595	0.440	0.117	0.289	0.104	0.684	0.135
Leucine	0.094 ± 0.040	0.081 ± 0.011	0.084 ± 0.019	0.079 ± 0.018	0.094 ± 0.029	0.094 ± 0.020	0.236	0.039	0.520	0.143	0.805	0.165
Lysine	0.149 ± 0.063	0.138 ± 0.012	0.152 ± 0.023	0.158 ± 0.020	0.161 ± 0.064	0.149 ± 0.029	0.311	0.078	0.976	0.200	0.583	0.122
Methanol	0.413 ± 0.238	0.394 ± 0.176	0.365 ± 0.166	0.372 ± 0.161	0.516 ± 0.332	0.350 ± 0.122	0.726	0.170	0.312	0.109	0.201	0.065
Methionine	0.023 ± 0.004	0.030 ± 0.002	0.026 ± 0.005	0.026 ± 0.007	0.029 ± 0.007	0.028 ± 0.005	0.338	0.087	0.063	0.061	**0.007**	0.013
Methylamine	0.004 ± 0.004	0.002 ± 0.001	0.003 ± 0.001	0.002 ± 0.002	0.004 ± 0.003	0.002 ± 0.002	0.961	0.196	**0.009**	0.022	0.808	0.170
O-Acetylcarnitine	0.006 ± 0.007	0.008 ± 0.006	0.005 ± 0.002	0.005 ± 0.004	0.006 ± 0.003	0.008 ± 0.007	0.498	0.135	0.650	0.170	0.105	0.039
O-Acetylcholine	0.008 ± 0.002	0.005 ± 0.006	0.010 ± 0.004	0.004 ± 0.003	0.008 ± 0.006	0.006 ± 0.003	0.866	0.178	**0.000**	0.004	0.031	0.030
Ornithine	0.036 ± 0.022	0.031 ± 0.029	0.030 ± 0.025	0.020 ± 0.017	0.026 ± 0.015	0.025 ± 0.018	0.516	0.139	0.272	0.096	0.858	0.183
Phenylalanine	0.069 ± 0.019	0.059 ± 0.008	0.063 ± 0.009	0.061 ± 0.009	0.065 ± 0.023	0.062 ± 0.010	0.931	0.187	0.062	0.057	0.237	0.078
Proline	0.174 ± 0.143	0.107 ± 0.050	0.100 ± 0.046	0.123 ± 0.067	0.141 ± 0.052	0.176 ± 0.069	0.107	0.017	0.746	0.187	**0.006**	0.009
Propylene glycol	0.006 ± 0.004	0.004 ± 0.002	0.004 ± 0.002	0.003 ± 0.001	0.004 ± 0.002	0.003 ± 0.001	0.204	0.030	**0.013**	0.026	0.854	0.178
Pyruvate	0.034 ± 0.025	0.048 ± 0.041	0.059 ± 0.025	0.041 ± 0.025	0.060 ± 0.042	0.044 ± 0.015	0.338	0.083	0.229	0.091	0.025	0.022
Succinate	0.009 ± 0.004	0.005 ± 0.002	0.004 ± 0.001	0.006 ± 0.005	0.005 ± 0.002	0.006 ± 0.001	0.365	0.096	0.439	0.135	**0.000**	0.004
Threonine	0.099 ± 0.039	0.101 ± 0.044	0.086 ± 0.043	0.068 ± 0.049	0.101 ± 0.067	0.088 ± 0.051	0.388	0.104	0.330	0.122	0.687	0.143
Trimethylamine	0.002 ± 0.001	0.002 ± 0.001	0.002 ± 0.000	0.002 ± 0.001	0.002 ± 0.002	0.002 ± 0.001	0.700	0.157	0.313	0.113	0.150	0.048
Tyrosine	0.075 ± 0.029	0.065 ± 0.015	0.066 ± 0.009	0.066 ± 0.009	0.076 ± 0.034	0.074 ± 0.019	0.569	0.148	0.398	0.130	0.383	0.104
Valine	0.278 ± 0.113	0.232 ± 0.037	0.221 ± 0.028	0.216 ± 0.047	0.255 ± 0.079	0.239 ± 0.052	0.302	0.070	0.057	0.052	0.759	0.161

Data are mean ± standard deviation. MI: 60% maximal inspiratory pressure (MIP); HI: ~90% MIP; LMM: Linear Mixed Model; p: P-values for the LMM; q: Adjusted p-values for the false discovery rate (FDR); G: Group main effect; T: Time main effect; *G*T*: *Group*Time* interaction. Bold values indicate significant main effects adjusted for the FDR of 0.2 at the significance level of 5%. Data were transformed by Box and Cox procedure before analysis and presented in their original scale. Analyzes were conducted in the SPSS software, version 25.0.

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Table S2 - Serum compounds detected by UHPLC-HRMS/MS in positive ionization mode and peak intensities (u.a.) for the Sham, MI, and HI groups Pre and Post-inspiratory muscle training. Data are mean ± standard deviation.

Compound [retention time (min):mass-to-charge ratio (*m/z*)]	Sham (n = 7)		MI (n = 11)		HI (n = 10)		p and q-values for LMM effects					
							G		T		*G*T*	
	Pre	Post	Pre	Post	Pre	Post	*p*	*q*	*p*	*q*	*p*	*q*
1.69 : 146.030	1.098 ± 0.324	1.189 ± 0.341	1.231 ± 0.524	1.317 ± 0.295	1.269 ± 0.260	1.333 ± 0.330	0.303	0.095	0.064	0.044	0.681	0.163
1.90 : 120.066	1.053 ± 0.165	0.842 ± 0.204	0.889 ± 0.140	1.029 ± 0.395	0.993 ± 0.332	0.958 ± 0.250	0.965	0.200	0.425	0.117	**0.007**	0.012
1.97 : 162.113	0.915 ± 0.139	0.773 ± 0.386	0.916 ± 0.233	0.934 ± 0.198	1.069 ± 0.202	1.041 ± 0.244	0.163	0.068	0.441	0.120	0.672	0.159
2.07 : 203.054	0.951 ± 0.156	0.839 ± 0.400	0.972 ± 0.220	1.160 ± 0.188	0.985 ± 0.153	1.015 ± 0.172	0.104	0.049	0.053	0.037	**0.008**	0.015
2.09 : 104.077	0.969 ± 0.196	0.814 ± 0.426	0.871 ± 0.300	1.034 ± 0.397	1.009 ± 0.300	0.796 ± 0.346	0.837	0.185	0.461	0.129	0.166	0.088
2.13 : 116.070	0.879 ± 0.229	0.734 ± 0.322	0.741 ± 0.336	0.885 ± 0.548	0.885 ± 0.268	0.947 ± 0.488	0.693	0.163	0.851	0.178	0.284	0.102
2.31 : 169.039	1.035 ± 0.300	0.822 ± 0.387	1.084 ± 0.247	1.112 ± 0.312	1.100 ± 0.232	1.108 ± 0.125	0.218	0.080	0.177	0.071	0.066	0.056
3.05 : 182.087	0.920 ± 0.204	0.823 ± 0.418	1.007 ± 0.119	1.089 ± 0.206	0.971 ± 0.144	1.104 ± 0.192	0.086	0.041	0.090	0.056	0.064	0.054
3.25 : 136.067	0.943 ± 0.276	0.967 ± 0.335	1.097 ± 0.179	1.170 ± 0.286	1.003 ± 0.139	1.138 ± 0.237	0.100	0.044	0.082	0.054	0.502	0.146
3.41 : 86.096	1.074 ± 0.147	0.889 ± 0.409	0.975 ± 0.242	1.102 ± 0.181	0.945 ± 0.207	0.978 ± 0.141	0.410	0.112	0.804	0.173	**0.015**	0.024
3.42 : 132.096	1.061 ± 0.197	0.887 ± 0.422	0.983 ± 0.154	1.117 ± 0.199	0.976 ± 0.138	1.050 ± 0.190	0.775	0.173	0.217	0.078	**0.009**	0.017
3.88 : 153.054	0.946 ± 0.428	1.191 ± 0.563	0.943 ± 0.314	1.004 ± 0.390	0.982 ± 0.423	1.033 ± 0.362	0.904	0.195	0.296	0.090	0.777	0.185
3.90 : 137.046	1.100 ± 0.746	0.824 ± 0.414	0.970 ± 0.455	1.021 ± 0.326	0.995 ± 0.233	0.980 ± 0.256	0.801	0.176	0.251	0.080	0.107	0.080
5.97 : 100.093	0.599 ± 0.714	1.188 ± 1.150	0.898 ± 0.603	0.872 ± 0.584	1.509 ± 1.625	1.258 ± 1.143	0.588	0.149	0.206	0.076	0.080	0.063
6.64 : 120.081	0.963 ± 0.100	0.842 ± 0.406	0.977 ± 0.242	1.117 ± 0.258	0.937 ± 0.148	0.988 ± 0.109	0.171	0.071	0.313	0.098	**0.035**	0.037
6.80 : 166.086	0.975 ± 0.107	0.852 ± 0.396	0.982 ± 0.241	1.109 ± 0.263	0.935 ± 0.156	0.981 ± 0.115	0.205	0.076	0.419	0.115	0.047	0.044
7.22 : 209.101	0.872 ± 0.452	1.102 ± 0.426	0.852 ± 0.288	1.137 ± 0.314	0.886 ± 0.234	0.899 ± 0.174	0.554	0.144	**0.001**	0.005	0.052	0.049
7.47 : 253.126	0.984 ± 0.516	1.155 ± 0.606	0.972 ± 0.369	1.278 ± 0.638	0.887 ± 0.307	1.035 ± 0.559	0.590	0.151	0.031	0.027	0.664	0.156
7.71 : 185.128	0.926 ± 0.173	0.923 ± 0.500	1.153 ± 0.468	0.982 ± 0.294	0.947 ± 0.408	0.765 ± 0.256	0.210	0.078	0.025	0.022	0.886	0.190
7.75 : 472.683	0.956 ± 0.548	0.848 ± 0.315	0.955 ± 0.503	1.029 ± 0.429	0.852 ± 0.445	0.736 ± 0.192	0.432	0.117	0.948	0.190	0.776	0.183
8.09 : 239.148	0.980 ± 0.421	1.002 ± 0.550	0.939 ± 0.244	1.088 ± 0.419	0.870 ± 0.177	0.902 ± 0.367	0.534	0.132	0.795	0.171	0.392	0.122
8.14 : 181.072	1.091 ± 0.772	1.162 ± 1.187	0.920 ± 0.527	1.188 ± 0.914	0.756 ± 0.694	1.198 ± 1.147	0.837	0.188	0.365	0.100	0.462	0.129
8.14 : 205.097	1.074 ± 0.141	0.844 ± 0.388	0.827 ± 0.166	1.173 ± 0.271	0.859 ± 0.156	1.020 ± 0.289	0.685	0.161	0.021	0.017	**0.000**	0.002
8.24 : 247.137	0.474 ± 0.385	0.555 ± 0.216	1.207 ± 1.235	1.101 ± 1.234	0.886 ± 0.707	0.875 ± 0.655	0.120	0.056	0.526	0.139	0.077	0.061
8.70 : 114.089	0.298 ± 0.323	1.694 ± 3.334	0.285 ± 0.203	0.308 ± 0.262	0.468 ± 0.450	0.411 ± 0.305	0.539	0.134	**0.015**	0.015	**0.004**	0.010
8.82 : 155.152	0.867 ± 0.172	1.231 ± 0.574	1.093 ± 0.262	0.992 ± 0.278	0.753 ± 0.104	1.137 ± 0.350	0.450	0.120	**0.005**	0.012	**0.001**	0.005
9.70 : 113.059	0.995 ± 0.202	1.561 ± 1.576	1.004 ± 0.241	1.112 ± 0.371	0.887 ± 0.129	0.949 ± 0.255	0.373	0.105	0.311	0.095	0.979	0.200
10.23 : 134.057	0.995 ± 0.309	1.146 ± 0.366	1.141 ± 0.455	1.104 ± 0.376	0.984 ± 0.647	0.966 ± 0.434	0.546	0.139	0.486	0.137	0.708	0.168

10.44 : 180.067	0.683 ± 0.215	0.719 ± 0.233	1.442 ± 0.823	1.261 ± 0.999	0.797 ± 0.905	0.961 ± 0.822	0.133	0.061	0.564	0.144	0.295	0.107
10.56 : 603.791	0.856 ± 0.550	0.643 ± 0.365	1.034 ± 0.315	0.963 ± 0.522	0.987 ± 0.449	1.153 ± 0.301	0.137	0.063	0.568	0.149	0.090	0.068
10.56 : 510.759	0.887 ± 0.305	0.879 ± 0.428	0.934 ± 0.380	0.891 ± 0.420	0.910 ± 0.335	1.192 ± 0.411	0.451	0.122	0.374	0.107	0.050	0.046
10.87 : 516.300	0.932 ± 0.186	0.925 ± 0.273	0.963 ± 0.222	1.068 ± 0.192	0.952 ± 0.118	0.901 ± 0.207	0.340	0.102	0.862	0.180	0.380	0.120
10.87 : 733.334	0.618 ± 0.407	0.698 ± 0.762	1.126 ± 0.796	1.176 ± 0.909	1.019 ± 0.694	1.236 ± 0.671	0.102	0.046	0.563	0.141	0.545	0.149
11.13 : 604.355	0.908 ± 0.319	1.021 ± 0.166	1.020 ± 0.198	1.050 ± 0.302	1.002 ± 0.185	0.908 ± 0.192	0.577	0.146	0.624	0.156	0.075	0.059
11.36 : 648.378	1.043 ± 0.185	1.050 ± 0.274	0.965 ± 0.295	1.093 ± 0.385	1.084 ± 0.236	0.827 ± 0.139	0.519	0.129	0.156	0.068	**0.002**	0.007
11.36 : 560.323	0.940 ± 0.198	0.870 ± 0.342	0.964 ± 0.200	1.140 ± 0.174	1.016 ± 0.066	1.039 ± 0.153	0.131	0.059	0.037	0.029	**0.009**	0.020
11.62 : 562.340	1.002 ± 0.292	1.181 ± 0.185	0.944 ± 0.135	1.021 ± 0.170	0.962 ± 0.291	0.963 ± 0.197	0.244	0.088	**0.004**	0.010	0.174	0.090
11.76 : 698.786	0.830 ± 0.391	0.790 ± 0.425	1.099 ± 0.436	0.899 ± 0.478	1.007 ± 0.531	1.207 ± 0.463	0.205	0.073	0.667	0.168	**0.039**	0.039
12.21 : 176.072	1.023 ± 0.277	0.824 ± 0.217	0.860 ± 0.398	0.875 ± 0.339	1.047 ± 0.290	1.162 ± 0.588	0.236	0.085	0.567	0.146	0.311	0.112
13.64 : 585.270	1.323 ± 1.041	1.045 ± 0.663	1.250 ± 0.517	1.024 ± 0.423	1.107 ± 0.692	0.962 ± 0.648	0.706	0.168	0.101	0.059	0.933	0.195
13.97 : 183.988	0.957 ± 0.601	1.155 ± 0.599	0.880 ± 0.274	0.913 ± 0.473	0.844 ± 0.289	0.892 ± 0.483	0.810	0.180	0.622	0.154	0.484	0.134
14.97 : 316.247	0.802 ± 0.522	0.705 ± 0.427	1.006 ± 0.517	0.773 ± 0.209	1.145 ± 1.192	1.337 ± 1.587	0.652	0.156	0.887	0.188	0.288	0.105
15.27 : 290.258	0.979 ± 0.212	1.330 ± 1.479	0.993 ± 0.305	1.207 ± 1.249	0.943 ± 0.262	0.917 ± 0.289	0.954	0.198	0.205	0.073	0.716	0.173
15.70 : 187.126	0.684 ± 0.748	0.626 ± 0.570	0.974 ± 0.560	1.193 ± 0.811	0.675 ± 0.456	0.888 ± 0.790	0.060	0.027	0.306	0.093	0.705	0.166
16.22 : 274.274	1.165 ± 0.503	0.804 ± 0.234	0.945 ± 0.310	0.836 ± 0.371	1.212 ± 0.688	0.976 ± 0.317	0.493	0.124	**0.002**	0.007	0.317	0.117
16.82 : 416.309	1.429 ± 0.667	1.300 ± 1.398	1.006 ± 0.625	1.635 ± 1.262	0.956 ± 0.518	0.945 ± 0.727	0.554	0.141	0.958	0.195	0.148	0.085
18.57 : 330.336	1.149 ± 0.593	0.938 ± 0.966	0.993 ± 0.443	0.787 ± 0.881	1.003 ± 0.583	0.905 ± 0.446	0.858	0.190	0.028	0.024	0.500	0.141
18.64 : 468.309	0.755 ± 0.405	0.944 ± 0.558	0.912 ± 0.453	1.109 ± 0.574	0.887 ± 0.386	1.182 ± 0.556	0.431	0.115	0.024	0.020	0.736	0.180
18.80 : 520.340	0.873 ± 0.165	0.764 ± 0.364	0.834 ± 0.139	0.889 ± 0.284	0.877 ± 0.145	0.771 ± 0.226	0.809	0.178	0.148	0.066	0.092	0.076
18.88 : 1039.673	0.865 ± 0.287	0.731 ± 0.389	0.770 ± 0.162	0.903 ± 0.425	0.851 ± 0.238	0.722 ± 0.302	0.865	0.193	0.382	0.110	**0.033**	0.034
19.26 : 400.353	0.784 ± 0.166	0.973 ± 0.339	1.314 ± 0.413	1.316 ± 0.537	1.198 ± 0.379	1.011 ± 0.461	0.025	0.010	0.986	0.198	0.083	0.066
19.28 : 494.332	0.709 ± 0.223	0.612 ± 0.380	1.041 ± 0.781	0.928 ± 0.385	0.941 ± 0.442	0.898 ± 0.315	0.112	0.051	0.271	0.088	0.501	0.144
19.45 : 496.340	0.941 ± 0.109	0.778 ± 0.345	0.974 ± 0.127	1.009 ± 0.179	0.958 ± 0.090	0.889 ± 0.100	0.068	0.029	0.072	0.051	**0.020**	0.029
19.57 : 991.674	0.966 ± 0.158	0.785 ± 0.354	1.020 ± 0.175	0.854 ± 0.354	1.000 ± 0.131	0.939 ± 0.111	0.542	0.137	**0.000**	0.002	0.498	0.139
19.66 : 480.321	0.928 ± 0.208	0.806 ± 0.372	0.989 ± 0.270	0.919 ± 0.398	0.896 ± 0.262	0.813 ± 0.208	0.513	0.127	0.056	0.039	0.905	0.193
19.69 : 522.356	0.906 ± 0.225	0.764 ± 0.378	0.954 ± 0.209	0.934 ± 0.321	0.858 ± 0.189	0.793 ± 0.195	0.266	0.093	0.067	0.049	0.493	0.137
19.72 : 428.373	0.750 ± 0.197	1.099 ± 0.490	1.203 ± 0.439	1.231 ± 0.490	1.071 ± 0.223	0.900 ± 0.313	0.030	0.012	0.647	0.161	0.054	0.051
20.02 : 482.336	0.911 ± 0.193	0.747 ± 0.338	1.097 ± 0.368	1.109 ± 0.576	0.873 ± 0.264	0.764 ± 0.222	0.034	0.017	0.138	0.063	0.445	0.124
22.11 : 524.371	0.905 ± 0.194	0.774 ± 0.348	1.051 ± 0.269	1.098 ± 0.286	0.972 ± 0.170	0.948 ± 0.308	0.048	0.022	0.400	0.112	0.255	0.098
22.46 : 870.561	0.825 ± 0.420	0.623 ± 0.370	0.973 ± 0.386	1.094 ± 0.616	1.095 ± 0.352	0.990 ± 0.321	0.079	0.039	0.365	0.102	0.136	0.083
22.80 : 550.382	0.916 ± 0.286	1.072 ± 0.716	0.949 ± 0.311	1.137 ± 0.493	0.872 ± 0.223	0.726 ± 0.208	0.073	0.032	0.826	0.176	**0.011**	0.022

23.25 : 760.505	0.845 ± 0.313	0.868 ± 0.687	0.928 ± 0.373	1.135 ± 0.943	0.979 ± 0.337	0.919 ± 0.300	0.702	0.166	0.877	0.185	0.723	0.178
23.32 : 826.545	0.809 ± 0.317	0.524 ± 0.347	0.898 ± 0.342	0.949 ± 0.600	0.993 ± 0.337	0.845 ± 0.300	0.141	0.066	0.048	0.034	0.101	0.078
23.32 : 738.492	0.821 ± 0.326	0.830 ± 0.539	0.893 ± 0.340	1.022 ± 0.643	1.001 ± 0.342	0.976 ± 0.336	0.672	0.159	0.661	0.166	0.709	0.171
23.34 : 694.464	0.834 ± 0.237	0.950 ± 0.662	0.920 ± 0.297	0.917 ± 0.514	0.970 ± 0.299	1.018 ± 0.315	0.757	0.171	0.864	0.183	0.831	0.188
23.58 : 256.262	0.723 ± 0.314	0.790 ± 0.409	1.004 ± 0.186	0.907 ± 0.236	0.961 ± 0.209	0.934 ± 0.267	0.073	0.034	0.654	0.163	0.312	0.115
23.75 : 650.441	0.773 ± 0.164	0.695 ± 0.396	0.829 ± 0.260	0.796 ± 0.375	0.881 ± 0.231	0.897 ± 0.221	0.319	0.100	0.486	0.134	0.719	0.176
23.83 : 737.438	0.970 ± 0.074	1.476 ± 1.233	0.977 ± 0.124	1.440 ± 1.644	1.035 ± 0.125	1.122 ± 0.611	0.827	0.183	0.990	0.200	0.180	0.093
24.15 : 666.469	1.101 ± 0.683	1.284 ± 1.111	1.128 ± 0.579	1.060 ± 0.412	1.019 ± 0.276	0.848 ± 0.569	0.385	0.107	0.457	0.124	0.212	0.095
24.23 : 912.627	0.825 ± 0.421	0.752 ± 0.551	0.921 ± 0.434	1.112 ± 1.052	1.064 ± 0.627	1.128 ± 0.664	0.392	0.110	0.602	0.151	0.584	0.151
24.41 : 597.407	0.783 ± 0.576	0.459 ± 0.310	0.871 ± 0.460	1.163 ± 1.082	1.066 ± 0.620	1.102 ± 0.698	0.304	0.098	0.370	0.105	0.460	0.127
24.63 : 553.381	0.791 ± 0.588	0.448 ± 0.365	0.931 ± 0.421	1.183 ± 1.005	1.072 ± 0.661	1.121 ± 0.711	0.057	0.024	0.107	0.061	0.092	0.073
24.66 : 956.641	0.742 ± 0.398	0.923 ± 1.213	0.879 ± 0.392	1.100 ± 1.019	1.058 ± 0.613	1.051 ± 0.634	0.625	0.154	0.955	0.193	0.954	0.198
24.91 : 531.371	0.742 ± 0.580	0.494 ± 0.372	0.965 ± 0.500	1.107 ± 1.004	1.050 ± 0.653	1.215 ± 0.826	0.077	0.037	0.268	0.085	0.304	0.110
25.15 : 1000.672	0.754 ± 0.470	0.423 ± 0.344	0.921 ± 0.428	1.152 ± 1.063	1.044 ± 0.560	1.085 ± 0.566	0.016	0.002	0.041	0.032	**0.018**	0.027
25.35 : 916.648	0.706 ± 0.425	0.427 ± 0.344	0.853 ± 0.403	1.136 ± 1.137	1.036 ± 0.578	0.979 ± 0.537	0.022	0.007	0.057	0.041	**0.039**	0.041
25.48 : 740.550	0.692 ± 0.217	0.732 ± 0.533	0.813 ± 0.382	1.101 ± 1.082	0.973 ± 0.449	1.033 ± 0.431	0.233	0.083	0.466	0.132	0.476	0.132
25.54 : 652.493	0.808 ± 0.338	0.603 ± 0.375	0.958 ± 0.335	1.237 ± 1.158	0.938 ± 0.376	1.104 ± 0.449	0.031	0.015	0.263	0.083	**0.022**	0.032
25.74 : 564.439	0.835 ± 0.373	0.651 ± 0.451	0.973 ± 0.234	1.195 ± 0.887	0.916 ± 0.325	1.024 ± 0.320	0.047	0.020	0.626	0.159	0.284	0.100
25.99 : 476.394	0.806 ± 0.264	0.892 ± 0.308	0.965 ± 0.204	1.151 ± 0.707	0.898 ± 0.285	1.022 ± 0.273	0.259	0.090	0.065	0.046	0.652	0.154
26.44 : 284.295	0.747 ± 0.299	0.724 ± 0.375	0.960 ± 0.229	1.036 ± 0.327	0.979 ± 0.194	0.821 ± 0.267	0.115	0.054	0.452	0.122	0.090	0.071
27.04 : 310.309	0.706 ± 0.308	0.729 ± 0.391	0.975 ± 0.144	0.931 ± 0.332	0.954 ± 0.220	0.868 ± 0.305	0.017	0.005	0.460	0.127	0.680	0.161

MI: 60% maximal inspiratory pressure (MIP); HI: ~90% MIP; LMM: Linear Mixed Model; p: p-values for the LMM; q: Adjusted p-values for the false discovery rate (FDR); G: Group main effect; T: Time main effect; *G*T*: *Group*Time* interaction. Bold values indicate significant main effects adjusted for the FDR of 0.2 at the significance level of 5%. Data were transformed by Box and Cox procedure before analysis and presented in their original scale. Analyzes were conducted in the SPSS software, version 25.0.

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Table S3 - Serum compounds detected by UHPLC-HRMS/MS in negative ionization mode and peak intensities (u.a.) for the Sham, MI, and HI groups Pre and Post-inspiratory muscle training. Data are mean ± standard deviation.

Compound [retention time (min):mass-to-charge ratio (*m*/*z*)]	Sham (n = 7)		MI (n = 11)		HI (n = 10)		p and q-values for LMM effects					
							G		T		*G*T*	
	Pre	Post	Pre	Post	Pre	Post	*p*	*q*	*p*	*q*	*p*	*q*
1.07 : 154.062	1.005 ± 0.267	0.984 ± 0.287	1.084 ± 0.196	1.281 ± 0.305	1.267 ± 0.463	0.867 ± 0.338	0.201	0.050	0.324	0.093	0.018	0.022
1.07 : 96.922	0.989 ± 0.121	0.972 ± 0.095	0.996 ± 0.106	1.012 ± 0.098	1.046 ± 0.110	0.990 ± 0.085	0.525	0.123	0.381	0.110	0.172	0.078
1.08 : 94.925	1.002 ± 0.089	0.972 ± 0.099	0.997 ± 0.119	1.028 ± 0.078	1.057 ± 0.088	0.992 ± 0.125	0.339	0.086	0.402	0.116	0.134	0.063
1.09 : 92.928	1.003 ± 0.088	0.984 ± 0.097	1.010 ± 0.103	1.039 ± 0.087	1.076 ± 0.104	1.015 ± 0.122	0.763	0.161	0.835	0.179	0.088	0.054
1.09 : 150.886	1.003 ± 0.101	0.941 ± 0.162	0.976 ± 0.076	0.935 ± 0.073	0.932 ± 0.100	1.010 ± 0.103	0.723	0.153	0.164	0.056	0.010	0.013
1.09 : 152.884	0.996 ± 0.135	0.973 ± 0.135	0.975 ± 0.086	0.971 ± 0.109	0.950 ± 0.103	1.053 ± 0.119	0.823	0.172	0.696	0.159	0.490	0.135
1.13 : 146.046	1.077 ± 0.837	1.112 ± 0.519	0.974 ± 0.324	1.153 ± 0.720	1.048 ± 0.590	0.862 ± 0.436	0.355	0.092	**0.523**	0.133	0.773	0.174
1.14 : 145.062	1.092 ± 0.143	1.064 ± 0.629	0.886 ± 0.296	0.987 ± 0.111	0.955 ± 0.094	1.021 ± 0.120	0.525	0.125	0.678	0.155	0.017	0.020
1.17 : 112.986	0.918 ± 0.284	0.896 ± 0.291	0.926 ± 0.274	0.800 ± 0.236	0.864 ± 0.314	1.085 ± 0.299	0.886	0.189	0.009	0.026	0.023	0.024
1.18 : 195.811	1.047 ± 0.263	0.992 ± 0.334	0.983 ± 0.266	0.970 ± 0.206	1.145 ± 0.263	0.874 ± 0.284	0.033	0.013	0.501	0.129	0.000	0.002
1.18 : 154.919	0.905 ± 0.345	1.143 ± 0.243	1.017 ± 0.249	0.642 ± 0.297	1.063 ± 0.258	1.077 ± 0.190	0.064	0.024	0.662	0.148	0.151	0.072
1.23 : 217.030	0.908 ± 0.134	0.859 ± 0.263	0.978 ± 0.117	1.020 ± 0.134	1.038 ± 0.127	0.988 ± 0.125	0.246	0.061	0.303	0.090	0.814	0.178
1.46 : 119.035	0.798 ± 0.410	0.784 ± 0.405	1.214 ± 0.492	1.058 ± 0.506	1.077 ± 0.483	0.972 ± 0.408	0.664	0.146	0.380	0.108	0.000	0.004
1.46 : 116.072	0.999 ± 0.329	0.785 ± 0.383	0.842 ± 0.217	1.123 ± 0.208	0.938 ± 0.358	0.995 ± 0.275	0.728	0.157	0.517	0.131	0.540	0.137
1.55 : 135.030	0.854 ± 0.470	0.782 ± 0.602	0.852 ± 0.415	0.919 ± 0.374	0.892 ± 0.348	0.681 ± 0.228	0.864	0.181	0.005	0.017	0.184	0.080
1.58 : 96.960	0.890 ± 0.285	1.053 ± 0.225	0.907 ± 0.211	0.956 ± 0.278	0.856 ± 0.133	0.962 ± 0.279	0.426	0.107	0.961	0.200	0.944	0.196
1.60 : 162.839	0.967 ± 0.146	0.949 ± 0.196	1.027 ± 0.150	1.031 ± 0.206	0.968 ± 0.130	0.983 ± 0.128	0.416	0.103	0.391	0.112	0.934	0.194
1.60 : 164.836	1.003 ± 0.328	0.941 ± 0.157	0.949 ± 0.161	0.922 ± 0.152	1.055 ± 0.124	0.992 ± 0.270	0.399	0.101	0.896	0.193	0.473	0.131
1.61 : 160.842	0.925 ± 0.181	0.874 ± 0.192	0.963 ± 0.166	0.975 ± 0.311	0.972 ± 0.103	1.026 ± 0.190	0.110	0.035	0.236	0.077	0.841	0.181
1.71 : 201.038	0.981 ± 0.073	1.024 ± 0.078	0.979 ± 0.132	1.007 ± 0.188	0.919 ± 0.128	0.927 ± 0.098	0.209	0.052	0.705	0.166	0.700	0.164
1.71 : 89.024	0.998 ± 0.213	1.009 ± 0.331	0.979 ± 0.189	1.036 ± 0.329	0.888 ± 0.229	0.867 ± 0.208	0.549	0.127	0.674	0.151	0.160	0.074
1.77 : 335.050	1.030 ± 0.205	0.873 ± 0.380	1.016 ± 0.300	1.125 ± 0.357	0.992 ± 0.210	0.972 ± 0.152	0.631	0.142	0.946	0.196	0.267	0.096
1.78 : 167.021	1.011 ± 0.116	0.924 ± 0.281	1.004 ± 0.156	1.043 ± 0.236	0.994 ± 0.128	1.006 ± 0.099	0.268	0.070	0.179	0.060	0.083	0.050
1.86 : 191.020	0.774 ± 0.180	0.880 ± 0.364	1.065 ± 0.200	0.904 ± 0.286	0.958 ± 0.382	0.840 ± 0.270	0.057	0.022	0.879	0.187	**0.331**	0.109
1.87 : 128.035	0.689 ± 0.099	0.714 ± 0.211	0.729 ± 0.342	0.796 ± 0.349	0.580 ± 0.114	0.556 ± 0.166	0.869	0.185	**0.331**	0.095	0.364	0.113
2.26 : 151.026	0.827 ± 0.318	1.013 ± 0.426	0.957 ± 0.239	1.000 ± 0.285	1.012 ± 0.343	0.968 ± 0.346	0.869	0.187	0.331	0.097	0.364	0.115
2.49 : 117.019	0.821 ± 0.158	0.798 ± 0.204	0.880 ± 0.226	1.073 ± 0.498	0.779 ± 0.121	0.751 ± 0.084	0.075	0.028	**0.996**	0.202	0.145	0.065
2.55 : 281.036	0.979 ± 0.133	1.019 ± 0.207	1.075 ± 0.255	1.147 ± 0.281	0.952 ± 0.344	0.994 ± 0.173	0.184	0.046	0.161	0.052	0.932	0.193

2.66 : 180.067	0.934 ± 0.228	0.869 ± 0.205	0.911 ± 0.199	1.092 ± 0.246	0.925 ± 0.204	1.056 ± 0.160	0.351	0.090	0.016	0.031	0.013	0.017
2.70 : 130.087	0.993 ± 0.309	0.968 ± 0.294	0.936 ± 0.235	1.062 ± 0.202	0.895 ± 0.244	0.926 ± 0.170	0.458	0.112	**0.252**	0.080	0.258	0.094
2.95 : 103.040	0.779 ± 0.648	0.603 ± 0.318	1.391 ± 0.740	0.840 ± 0.356	0.910 ± 0.337	0.711 ± 0.280	0.012	0.006	0.000	0.007	0.281	0.102
4.28 : 115.040	0.899 ± 0.146	0.846 ± 0.232	1.018 ± 0.326	1.070 ± 0.292	0.927 ± 0.183	0.934 ± 0.183	0.210	0.054	0.960	0.198	0.570	0.146
5.70 : 147.045	0.918 ± 0.214	0.887 ± 0.281	0.960 ± 0.219	1.076 ± 0.218	0.908 ± 0.133	0.923 ± 0.112	0.155	0.043	**0.292**	0.088	0.147	0.070
5.84 : 164.072	0.905 ± 0.147	0.822 ± 0.288	0.916 ± 0.248	1.030 ± 0.237	0.897 ± 0.156	0.878 ± 0.100	0.388	0.097	0.919	0.194	0.116	0.059
6.25 : 117.056	0.688 ± 0.195	0.600 ± 0.291	1.219 ± 0.934	1.282 ± 1.264	0.738 ± 0.273	0.742 ± 0.217	0.051	0.020	0.263	0.086	0.464	0.130
6.34 : 188.986	1.383 ± 1.031	0.878 ± 0.551	0.816 ± 0.485	0.947 ± 0.679	0.730 ± 0.355	0.671 ± 0.339	0.441	0.110	0.253	0.082	0.211	0.083
7.27 : 172.991	0.949 ± 0.991	1.091 ± 0.801	1.189 ± 1.302	0.965 ± 0.680	0.844 ± 0.351	0.869 ± 0.401	0.949	0.198	**0.482**	0.125	0.622	0.156
7.61 : 203.083	1.026 ± 0.209	0.887 ± 0.304	0.953 ± 0.172	1.072 ± 0.222	0.965 ± 0.153	0.944 ± 0.141	0.625	0.140	**0.676**	0.153	0.007	0.009
8.47 : 291.030	1.278 ± 0.137	1.049 ± 0.328	1.192 ± 0.261	1.195 ± 0.308	1.265 ± 0.239	1.068 ± 0.360	0.935	0.194	0.008	0.022	0.086	0.052
8.48 : 212.002	0.926 ± 0.399	0.974 ± 0.539	1.173 ± 0.471	1.152 ± 0.585	0.922 ± 0.700	0.835 ± 0.462	0.316	0.080	0.893	0.191	0.969	0.202
8.50 : 254.928	1.077 ± 0.309	0.958 ± 0.308	1.140 ± 0.321	1.078 ± 0.257	0.945 ± 0.284	1.011 ± 0.212	0.272	0.072	0.218	0.073	0.233	0.089
8.66 : 129.056	0.957 ± 0.139	0.838 ± 0.220	1.059 ± 0.169	1.110 ± 0.417	0.878 ± 0.210	0.883 ± 0.241	0.032	0.011	0.200	0.064	0.221	0.085
8.94 : 178.051	0.695 ± 0.269	0.553 ± 0.328	1.133 ± 0.753	1.008 ± 0.773	0.680 ± 0.619	0.742 ± 0.638	0.231	0.059	0.402	0.118	0.274	0.098
8.98 : 263.103	0.747 ± 0.409	0.854 ± 0.850	1.349 ± 0.675	0.950 ± 0.440	0.925 ± 1.001	0.684 ± 0.329	0.074	0.026	0.225	0.075	0.403	0.120
9.57 : 187.008	1.060 ± 1.086	0.901 ± 1.352	1.019 ± 0.604	0.919 ± 0.562	0.797 ± 0.896	0.667 ± 0.529	0.420	0.105	**0.245**	0.079	0.606	0.154
11.19 : 171.066	1.037 ± 0.416	1.010 ± 0.402	0.975 ± 0.335	1.001 ± 0.232	1.086 ± 0.221	1.214 ± 0.370	0.272	0.074	0.422	0.121	0.481	0.133
11.73 : 617.738	0.877 ± 0.448	0.932 ± 0.359	0.980 ± 0.578	1.063 ± 0.652	0.760 ± 0.245	0.909 ± 0.497	0.719	0.151	0.376	0.107	0.928	0.191
11.97 : 187.097	0.863 ± 0.173	0.966 ± 0.365	0.780 ± 0.192	0.964 ± 0.185	0.818 ± 0.144	0.849 ± 0.241	0.675	0.150	0.009	0.024	0.116	0.061
12.16 : 383.153	1.153 ± 0.700	1.248 ± 0.886	0.866 ± 0.426	0.875 ± 0.354	0.848 ± 0.320	0.897 ± 0.394	0.473	0.116	0.555	0.138	0.959	0.200
12.89 : 159.103	0.775 ± 0.237	0.971 ± 0.263	0.884 ± 0.430	1.006 ± 0.379	0.895 ± 0.278	0.805 ± 0.252	0.734	0.159	0.113	0.049	0.053	0.041
13.08 : 413.200	0.905 ± 0.424	0.959 ± 0.223	1.036 ± 0.337	1.104 ± 0.470	1.047 ± 0.539	0.976 ± 0.441	0.794	0.170	0.578	0.142	0.562	0.144
14.72 : 369.174	0.767 ± 0.665	0.776 ± 0.449	1.088 ± 0.655	1.097 ± 0.748	0.823 ± 0.483	0.884 ± 0.318	0.567	0.129	0.671	0.150	0.693	0.163
14.79 : 367.158	1.042 ± 0.435	1.155 ± 0.488	1.055 ± 0.534	1.006 ± 0.471	0.986 ± 0.421	0.982 ± 0.380	0.889	0.191	0.532	0.136	0.276	0.100
14.82 : 510.253	0.972 ± 0.144	0.945 ± 0.187	0.887 ± 0.279	0.927 ± 0.566	1.111 ± 0.472	1.154 ± 0.601	0.217	0.056	0.869	0.185	0.914	0.189
14.88 : 397.205	0.912 ± 0.308	0.894 ± 0.245	0.871 ± 0.399	0.952 ± 0.303	1.068 ± 0.599	0.929 ± 0.389	0.835	0.176	0.600	0.144	0.145	0.067
15.84 : 512.268	1.253 ± 0.507	0.816 ± 0.751	0.874 ± 0.499	1.165 ± 0.821	0.849 ± 0.464	0.726 ± 0.502	0.598	0.131	0.195	0.062	0.051	0.033
16.39 : 185.118	1.039 ± 0.469	1.137 ± 0.874	0.798 ± 0.473	0.919 ± 0.425	0.845 ± 0.332	0.719 ± 0.209	0.295	0.079	0.791	0.170	0.226	0.087
16.64 : 221.118	0.964 ± 0.045	1.002 ± 0.084	0.956 ± 0.039	0.962 ± 0.110	0.990 ± 0.102	0.971 ± 0.066	0.606	0.135	0.699	0.163	0.600	0.152
17.09 : 187.134	0.771 ± 0.408	0.746 ± 0.230	1.162 ± 0.726	0.942 ± 0.378	0.909 ± 0.411	0.732 ± 0.271	0.247	0.063	0.437	0.123	0.586	0.148
17.16 : 376.225	0.871 ± 0.234	0.888 ± 0.229	1.018 ± 0.218	1.081 ± 0.246	1.007 ± 0.311	0.848 ± 0.163	0.075	0.031	0.563	0.140	0.052	0.037
18.19 : 512.299	0.712 ± 0.324	0.896 ± 0.254	0.866 ± 0.513	1.047 ± 0.545	0.771 ± 0.271	0.930 ± 0.499	0.829	0.174	0.013	0.030	0.748	0.170

18.28 : 378.241	0.825 ± 0.266	0.957 ± 0.144	1.069 ± 0.220	0.969 ± 0.150	0.995 ± 0.201	0.875 ± 0.145	0.118	0.039	0.524	0.135	**0.001**	0.007
18.37 : 586.315	0.433 ± 0.168	0.596 ± 0.272	0.655 ± 0.270	0.826 ± 0.618	0.609 ± 0.537	0.478 ± 0.260	0.193	0.048	**0.403**	0.120	0.208	0.081
18.63 : 538.315	0.682 ± 0.201	0.773 ± 0.164	1.020 ± 0.697	0.909 ± 0.485	0.761 ± 0.290	0.922 ± 0.293	0.476	0.118	0.079	0.044	0.060	0.044
18.87 : 194.082	0.998 ± 0.114	0.906 ± 0.151	0.948 ± 0.174	0.970 ± 0.155	1.051 ± 0.201	0.994 ± 0.128	0.343	0.088	**0.335**	0.099	0.545	0.139
18.97 : 500.278	1.027 ± 0.280	0.936 ± 0.203	1.192 ± 0.444	1.104 ± 0.387	1.315 ± 0.302	1.138 ± 0.381	0.285	0.076	0.090	0.046	0.653	0.159
18.98 : 476.278	1.211 ± 0.669	1.065 ± 0.334	0.997 ± 0.486	1.083 ± 0.461	1.302 ± 0.475	1.199 ± 0.522	0.399	0.099	0.849	0.183	0.441	0.122
19.00 : 612.331	0.508 ± 0.254	0.686 ± 0.339	0.815 ± 0.480	0.736 ± 0.370	0.543 ± 0.258	0.456 ± 0.173	0.075	0.030	**0.800**	0.172	0.078	0.048
19.06 : 588.331	0.649 ± 0.244	0.648 ± 0.289	0.796 ± 0.198	0.760 ± 0.249	0.699 ± 0.211	0.604 ± 0.187	0.134	0.041	**0.173**	0.058	0.645	0.157
19.17 : 564.331	0.802 ± 0.177	0.852 ± 0.188	0.842 ± 0.187	0.869 ± 0.240	0.809 ± 0.167	0.723 ± 0.170	0.440	0.108	0.815	0.176	0.331	0.107
19.50 : 452.278	0.936 ± 0.173	0.980 ± 0.221	1.072 ± 0.293	1.044 ± 0.348	1.039 ± 0.355	1.005 ± 0.371	0.768	0.163	0.699	0.161	0.701	0.166
19.61 : 590.346	0.470 ± 0.128	0.597 ± 0.279	0.750 ± 0.350	0.719 ± 0.413	0.532 ± 0.141	0.509 ± 0.269	0.092	0.033	0.815	0.174	0.283	0.104
19.71 : 311.222	1.008 ± 0.585	1.164 ± 0.514	1.224 ± 0.605	1.154 ± 0.850	1.131 ± 0.530	1.168 ± 0.616	0.965	0.202	0.783	0.168	0.552	0.141
19.76 : 540.331	0.926 ± 0.108	0.932 ± 0.117	0.970 ± 0.102	0.980 ± 0.151	0.963 ± 0.064	0.887 ± 0.059	0.373	0.093	0.123	0.050	0.059	0.043
19.93 : 478.294	1.087 ± 0.449	1.312 ± 0.487	1.037 ± 0.519	1.054 ± 0.472	1.106 ± 0.417	1.168 ± 0.413	0.487	0.121	0.161	0.054	0.460	0.128
20.04 : 566.347	0.756 ± 0.136	0.855 ± 0.229	0.925 ± 0.192	0.897 ± 0.231	0.784 ± 0.163	0.718 ± 0.194	0.043	0.017	**0.883**	0.189	0.108	0.057
20.10 : 436.283	0.701 ± 0.207	0.729 ± 0.271	0.763 ± 0.262	0.775 ± 0.350	0.737 ± 0.347	0.493 ± 0.203	0.117	0.037	0.049	0.041	0.015	0.019
20.28 : 524.335	0.661 ± 0.122	0.708 ± 0.190	0.869 ± 0.230	0.951 ± 0.553	0.634 ± 0.201	0.522 ± 0.184	0.001	0.002	0.338	0.101	0.095	0.056
20.33 : 526.350	0.642 ± 0.116	0.708 ± 0.209	0.803 ± 0.246	0.957 ± 0.669	0.662 ± 0.131	0.581 ± 0.143	0.046	0.019	0.396	0.114	0.147	0.069
20.37 : 305.187	0.996 ± 0.182	0.986 ± 0.166	0.962 ± 0.211	0.917 ± 0.137	1.016 ± 0.158	0.966 ± 0.163	0.672	0.148	0.206	0.067	0.840	0.179
20.43 : 233.154	0.899 ± 0.120	0.957 ± 0.169	0.950 ± 0.180	0.930 ± 0.189	0.803 ± 0.169	0.975 ± 0.115	0.646	0.144	0.010	0.028	0.008	0.011
20.60 : 554.346	0.771 ± 0.309	0.751 ± 0.244	1.141 ± 0.377	1.028 ± 0.359	0.910 ± 0.147	0.874 ± 0.315	0.009	0.004	0.202	0.065	0.795	0.176
20.61 : 592.361	0.595 ± 0.122	0.762 ± 0.331	0.770 ± 0.308	0.808 ± 0.389	0.641 ± 0.192	0.558 ± 0.217	0.173	0.044	0.817	0.178	0.078	0.046
20.80 : 552.366	0.626 ± 0.162	0.727 ± 0.272	0.754 ± 0.214	0.838 ± 0.464	0.577 ± 0.164	0.533 ± 0.170	0.019	0.007	0.687	0.157	0.333	0.111
20.94 : 235.170	1.008 ± 0.171	1.089 ± 0.170	1.023 ± 0.186	1.031 ± 0.169	1.028 ± 0.159	1.041 ± 0.149	0.930	0.193	0.210	0.071	0.455	0.126
21.15 : 480.309	1.303 ± 0.409	0.853 ± 0.429	1.267 ± 0.506	1.141 ± 0.222	1.343 ± 0.399	1.135 ± 0.382	0.328	0.084	0.000	0.004	0.033	0.026
21.83 : 483.368	1.309 ± 0.385	1.211 ± 0.436	1.181 ± 0.532	1.117 ± 0.482	1.261 ± 0.448	1.184 ± 0.438	0.610	0.136	0.258	0.084	0.950	0.198
21.85 : 568.362	0.883 ± 0.169	0.904 ± 0.121	1.001 ± 0.208	1.026 ± 0.256	0.987 ± 0.163	0.867 ± 0.188	0.228	0.057	0.309	0.092	0.040	0.031
21.98 : 612.387	1.232 ± 0.607	1.017 ± 0.137	1.041 ± 0.159	1.050 ± 0.146	1.244 ± 0.504	0.941 ± 0.118	0.961	0.200	0.021	0.033	0.012	0.015
21.99 : 585.352	1.270 ± 0.404	1.018 ± 0.174	1.034 ± 0.219	1.024 ± 0.123	1.233 ± 0.356	0.947 ± 0.107	0.791	0.168	0.032	0.037	0.169	0.076
22.00 : 652.323	1.073 ± 0.269	0.941 ± 0.401	1.070 ± 0.084	1.009 ± 0.155	1.312 ± 0.358	0.900 ± 0.116	0.465	0.114	0.000	0.002	0.001	0.006
22.01 : 560.331	1.216 ± 0.375	0.997 ± 0.239	1.080 ± 0.214	1.040 ± 0.137	1.164 ± 0.212	0.944 ± 0.185	0.938	0.196	0.000	0.006	0.034	0.028
22.18 : 464.314	0.709 ± 0.154	0.691 ± 0.187	0.820 ± 0.163	0.839 ± 0.392	0.722 ± 0.380	0.551 ± 0.173	0.039	0.015	0.060	0.043	**0.245**	0.093
22.67 : 271.228	0.837 ± 0.130	0.799 ± 0.208	1.033 ± 0.241	0.909 ± 0.290	0.930 ± 0.255	0.755 ± 0.167	0.247	0.065	**0.004**	0.015	0.558	0.143

22.67 : 277.217	0.798 ± 0.380	0.740 ± 0.677	0.955 ± 0.707	0.700 ± 0.311	1.445 ± 1.565	1.003 ± 0.998	0.382	0.095	0.022	0.035	0.848	0.183
23.17 : 227.201	0.806 ± 0.331	0.988 ± 0.571	1.224 ± 0.665	0.678 ± 0.193	1.155 ± 0.684	0.885 ± 0.392	0.863	0.179	**0.042**	0.039	0.038	0.030
23.44 : 303.233	1.006 ± 0.371	0.884 ± 0.349	1.092 ± 0.371	0.852 ± 0.353	1.038 ± 0.403	0.797 ± 0.366	0.844	0.178	0.001	0.011	0.596	0.150
23.68 : 485.282	1.044 ± 0.378	1.039 ± 0.393	1.020 ± 0.373	0.886 ± 0.231	1.092 ± 0.301	1.087 ± 0.527	0.623	0.138	0.366	0.105	0.757	0.172
23.80 : 421.332	1.254 ± 0.718	1.053 ± 0.471	1.039 ± 0.343	0.988 ± 0.411	1.097 ± 0.381	1.130 ± 0.282	0.724	0.155	**0.348**	0.103	0.399	0.119
23.84 : 559.473	0.824 ± 0.483	0.842 ± 0.676	1.211 ± 0.801	0.708 ± 0.251	1.342 ± 1.102	0.952 ± 0.892	0.788	0.166	0.008	0.020	0.446	0.124
23.88 : 279.233	0.873 ± 0.310	0.764 ± 0.461	1.124 ± 0.531	0.784 ± 0.222	1.161 ± 0.645	0.904 ± 0.582	0.604	0.133	0.001	0.013	0.896	0.187
23.91 : 375.275	1.578 ± 1.207	1.253 ± 0.763	1.219 ± 1.113	1.118 ± 0.484	1.295 ± 0.870	1.483 ± 1.139	0.788	0.164	**0.846**	0.181	0.725	0.168
24.23 : 445.332	1.215 ± 0.609	1.267 ± 0.544	0.923 ± 0.470	0.890 ± 0.429	0.992 ± 0.310	0.895 ± 0.255	0.263	0.069	0.647	0.146	0.299	0.106
24.58 : 473.282	1.061 ± 0.314	0.989 ± 0.106	0.984 ± 0.225	1.111 ± 0.221	1.020 ± 0.140	0.995 ± 0.257	0.867	0.183	0.703	0.164	0.052	0.039
24.71 : 537.416	1.289 ± 0.617	1.113 ± 0.305	0.973 ± 0.390	1.008 ± 0.438	1.138 ± 0.424	0.965 ± 0.262	0.476	0.120	0.208	0.069	0.391	0.117
24.80 : 299.259	0.917 ± 0.289	0.903 ± 0.239	1.314 ± 0.423	1.233 ± 0.547	1.009 ± 0.540	0.917 ± 0.198	0.022	0.009	**0.497**	0.127	0.886	0.185
25.31 : 255.233	0.723 ± 0.329	0.783 ± 0.425	1.208 ± 0.691	0.727 ± 0.127	1.034 ± 0.418	0.845 ± 0.379	0.251	0.067	**0.006**	0.019	0.051	0.035
25.64 : 281.249	0.846 ± 0.384	0.757 ± 0.417	1.212 ± 0.513	0.784 ± 0.166	1.122 ± 0.517	0.841 ± 0.397	0.321	0.082	0.000	0.009	0.234	0.091

MI: 60% maximal inspiratory pressure (MIP); HI: ~90% MIP; LMM: Linear Mixed Model; p: p-values for the LMM; q: Adjusted p-values for the false discovery rate (FDR); G: Group main effect; T: Time main effect; *G*T*: *Group*Time* interaction. Bold values indicate significant main effects adjusted for the FDR of 0.2 at the significance level of 5%. Data were transformed by Box and Cox procedure before analysis and presented in their original scale. Analyzes were conducted in the SPSS software, version 25.0.

Table S4. Annotation parameters of the compound significantly different between or within-groups obtained by UHPLC-HRMS-based metabolomics.

Compound	LMM effects	HMDB ID	Chemical Formula	Monoisotopic Mass	Ion	*m/z*	Matched fragments (*m/z*) and mass error (ppm)
3-Methylsuberic acid	Time	HMDB0059783	C9H16O4	188.1049	$[M-H]^-$	187.0973	97.0660 (1); 125.0975 (2); 187.0986 (5); 123.0825 (8); 169.0886 (9).
Arachidonic acid	Time	HMDB0001043	C20H32O2	304.2402	$[M-H]^-$	303.2331	59.0136 (5); 205.1957 (0); 231.2111 (0); 259.2435 (4); 285.2233 (5); 303.2323 (2).
Valine	Interaction	HMDB0000883 HMDB0250806	C5H11NO2	117.0790	$[M-H]^-$	116.0712	116.0732 (8).
Hydroxyhexadecanoic acid*	Time	HMDB0112184 HMDB0112186 HMDB0112188 HMDB0112189	C16H32O3	272.2351	$[M-H]^-$	271.2274	55.0185 (7); 225.2217 (3); 253.2193 (8); 271.2273 (2).
Linoleic acid	Time	HMDB0000673	C18H32O2	280.2402	$[M-H]^-$	279.2330	279.2325 (1); 280.2359 (2); 281.2375 (1).
Linolenelaidic acid	Time	HMDB0030964	C18H30O2	278.2246	$[M-H]^-$	277.2170	241.1966 (0); 259.2021 (0); 277.2165 (0).
LysoPC(0:0/16:0)	Interaction	HMDB0240262	C24H50NO7P	495.3325	$[M+H]^+$	496.3404	57.0703 (7); 60.0811 (5); 71.0861 (8); 81.0693 (7); 86.0969 (6); 95.0855 (0); 97.1017 (5); 98.9843 (1); 104.1073 (3); 125.1321 (3); 184.074 (4); 258.1098 (1); 313.2727 (3); 478.3293 (0); 496.3403 (1).
LysoPC(14:0/0:0)	Time	HMDB0010379	C22H46NO7P	467.3012	$[M+HCOO]^-$	512.2996	224.0686 (3); 227.2012 (2); 452.2783 (0).
LysoPC(16:0/0:0)	Time	HMDB0010382	C24H50NO7P	495.3325	$[2M+H]^+$	991.6728	184.0736 (1); 496.3407 (1).
LysoPC(18:2/0:0)	Interaction	HMDB0010386	C26H50NO7P	519.3325	$[2M+H]^+$	1039.6728	86.0970 (7); 104.1069 (1); 124.999 (6); 146.9823 (3); 184.0735 (1); 258.1117 (6); 502.3304 (2); 520.3396 (0); 542.3205 (2).
LysoPC(P-16:0/0:0)	Group	HMDB0010407	C24H50NO6P	479.3376	$[M+HCOO]^-$	524.3358	78.9590 (1); 168.043 (1); 224.0694 (0); 239.237 (4); 464.3135 (2).
LysoPE(18:0/0:0)	Interaction	HMDB0011130	C23H48NO7P	481.3168	$[M-H]^-$	480.3094	152.9957 (1); 214.0497 (5); 283.2638 (2); 480.3107 (2).

LysoPE(P-16:0/0:0)	Interaction	HMDB0011152	C21H44NO6P	437.2906	$[M-H]^-$	436.2821	78.9591 (1); 122.0007 (4); 122.9858 (5); 137.0016 (5); 140.012 (1); 152.9957 (1); 196.0365 (8); 375.2289 (5); 436.2824 (2).
Oleic acid	Time	HMDB0000207	C18H34O2	282.2559	$[M-H]^-$	281.2489	281.2485 (0); 282.2520 (0).
o-Tyrosine	Time/Interaction	HMDB0006050	C9H11NO3	181.0739	$[M-H]^-$	180.0667	72.0091 (0); 74.0255 (9); 93.0340 (3); 107.0500 (2); 119.0501 (1); 134.0609 (1); 136.0771 (2); 163.0403 (1); 180.0660 (3).
Palmitic acid	Time	HMDB0000220	C16H32O2	256.2402	$[M-H]^-$	255.2331	237.2239 (10); 255.2328 (1); 256.2354 (1).
Sphingosine 1-phosphate	Interaction	HMDB0000277	C18H38NO5P	379.2488	$[M-H]^-$	378.2411	78.9590 (1); 378.2403 (3).
Tryptophan	Interaction	HMDB0000929 HMDB0013609	C11H12N2O2	204.0899	$[M+H]^+$	205.0971	91.0541 (2); 115.0548 (10); 117.0576 (7); 118.0654 (3); 130.0652 (5); 132.0813 (1); 140.0488 (3); 142.0653 (2); 143.0725 (7); 144.081 (3); 146.0605 (5); 147.0637 (5); 159.0917 (2); 188.0713 (1).
Tryptophan	Interaction	HMDB0013609 HMDB0000929	C11H12N2O2	204.0899	$[M-H]^-$	203.0828	116.0505 (1); 117.0536 (5); 142.0661 (6); 159.0917 (8); 186.0567 (2); 204.0859 (0).
Unknown	Interação	-	-	-	Positive	Unfragmented	-
Unknown	Interação	-	-	-	Positive	Unfragmented	-
Unknown	Interação	-	-	-	Positive	Unfragmented	-
Unknown	Interação	-	-	-	Positive	550.3883	-
Unknown	Interação	-	-	-	Positive	Unfragmented	-
Unknown	Interaction	-	-	-	Negative	Unfragmented	-
Unknown	Interaction	-	-	-	Negative	152.8837	-
Unknown	Interaction	-	-	-	Negative	112.9856	-
Unknown	Interaction	-	-	-	Negative	Unfragmented	-
Unknown	Interaction	-	-	-	Positive	Unfragmented	-
Unknown	Interaction	-	-	-	Positive	Unfragmented	-

Unknown	Interaction	-	-	-	Positive	Unfragmented	-
Unknown	Interaction	-	-	-	Positive	Unfragmented	-
Unknown	Interaction	-	-	-	Positive	Unfragmented	-
Unknown	Interaction	-	-	-	Positive	Unfragmented	-
Unknown	Interaction	-	-	-	Positive	Unfragmented	-
Unknown	Time	-	-	-	Negative	96.9600	-
Unknown	Time	-	-	-	Negative	103.0398	-
Unknown	Time	-	-	-	Negative	585.3508	-
Unknown	Time	-	-	-	Negative	Unfragmented	-
Unknown	Time	-	-	-	Negative	559.4726	-
Unknown	Time	-	-	-	Negative	291.0310	-
Unknown	Time	-	-	-	Positive	Unfragmented	-
Unknown	Time	-	-	-	Positive	274.2742	-
Unknown	Time	-	-	-	Positive	209.1022	-
Unknown	Time	-	-	-	Positive	Unfragmented	-
Unknown	Time/Interaction	-	-	-	Positive	Unfragmented	-
Unknown	Time/Interaction	-	-	-	Negative	154.9180	-
Unknown	Time/Interaction	-	-	-	Negative	233.1538	-
Unknown	Time/Interaction	-	-	-	Negative	612.3843	-
Unknown	Time/Interaction	-	-	-	Negative	652.3241	-

LMM: Linear mixed model effects; *Hydroxylated isomers.

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Table S5. Summary of the Metabolite Set Enrichment Analysis and altered pathways Pre to Post-inspiratory muscle training.

Pathway	Library	Total	Expected	Hits	P-value	FDR	Decision	Enrichment ratio*
Biosynthesis of unsaturated fatty acids	KEGG	36	0.328	4	0.0002	0.0063	SIG	12.20
Aminoacyl-tRNA biosynthesis	KEGG	48	0.438	4	0.0007	0.0125	SIG	9.13
Ketone body metabolism	SMPDB	13	0.241	3	0.0014	0.0188	SIG	12.45
Butanoate metabolism	KEGG	15	0.137	2	0.0076	0.0250	SIG	14.60
Citrate cycle	KEGG	20	0.182	2	0.0134	0.0313	SIG	10.99
Propanoate metabolism	KEGG	23	0.21	2	0.0175	0.0375	SIG	9.52
Fatty acid biosynthesis	SMPDB	35	0.649	3	0.0244	0.0438	SIG	4.62
Alanine, aspartate and glutamate metabolism	KEGG	28	0.255	2	0.0255	0.0500	SIG	7.84
Alpha linolenic acid and linoleic acid metabolism	SMPDB	19	0.353	2	0.0462	0.0563	SIG	5.67
Butyrate metabolism	SMPDB	19	0.353	2	0.0462	0.0625	SIG	5.67
Valine, Leucine and Isoleucine Degradation	SMPDB	60	1.11	3	0.0949	0.0688	NS	2.70
Phospholipid biosynthesis	SMPDB	29	0.538	2	0.0984	0.0750	NS	3.72
Arginine and Proline Metabolism	SMPDB	53	0.983	2	0.2580	0.0813	NS	2.03
Warburg effect	SMPDB	58	1.08	2	0.2930	0.0875	NS	1.85
Arachidonic acid metabolism	SMPDB	69	1.28	2	0.3700	0.0938	NS	1.56
Tyrosine metabolism	SMPDB	72	1.34	2	0.3910	0.1000	NS	1.49

*Pathway enrichment ratio is computed by Hits/Expected hits; FDR: False discovery rate of 0.1.

Table S6 - Metabolite-metabolite networks sub-information table.

KEGG ID	Label	Degree of centrality	Betweenness	Technique
C00002	Adenosine triphosphate	12	32.73	Not annotated
C00007	Oxygen	10	25.99	Not annotated
C00158	Citrate	10	23.83	^{1}H NMR
C00073	Methionine	10	15.83	^{1}H NMR
C00004	NADH	9	19.60	Not annotated
C00219	Arachidonic acid	9	16.09	UHPLC-HRMS/MS
C03878	Beta-N-Acetylglucosamine	9	13.73	Not annotated
C00042	Succinate	8	21.58	^{1}H NMR
C00078	Tryptophan	8	14.15	UHPLC-HRMS/MS
C00249	Palmitic acid	8	9.14	UHPLC-HRMS/MS
C00183	Valine	8	2.31	UHPLC-HRMS/MS
C00712	Oleic acid	7	3.30	UHPLC-HRMS/MS
C00148	Proline	7	1.15	^{1}H NMR
C01595	Linoleic acid	6	1.20	UHPLC-HRMS/MS
C00218	Methylamine	5	10.19	^{1}H NMR
C00027	Hydrogen peroxide	5	4.96	Not annotated
C01996	O-acetylcholine	5	0.48	^{1}H NMR
C00166	Phenylpyruvic acid	4	21.14	Not annotated
C00207	Acetone	3	4.48	^{1}H NMR
C00356	3-Hydroxy-3-methylglutaryl-CoA	3	1.47	Not annotated
C01089	3-Hydroxybutyrate	3	1.40	^{1}H NMR
C08262	Isovaleric acid	2	0.28	Not annotated
C05984	2-Hydroxybutyrate	1	0.00	^{1}H NMR

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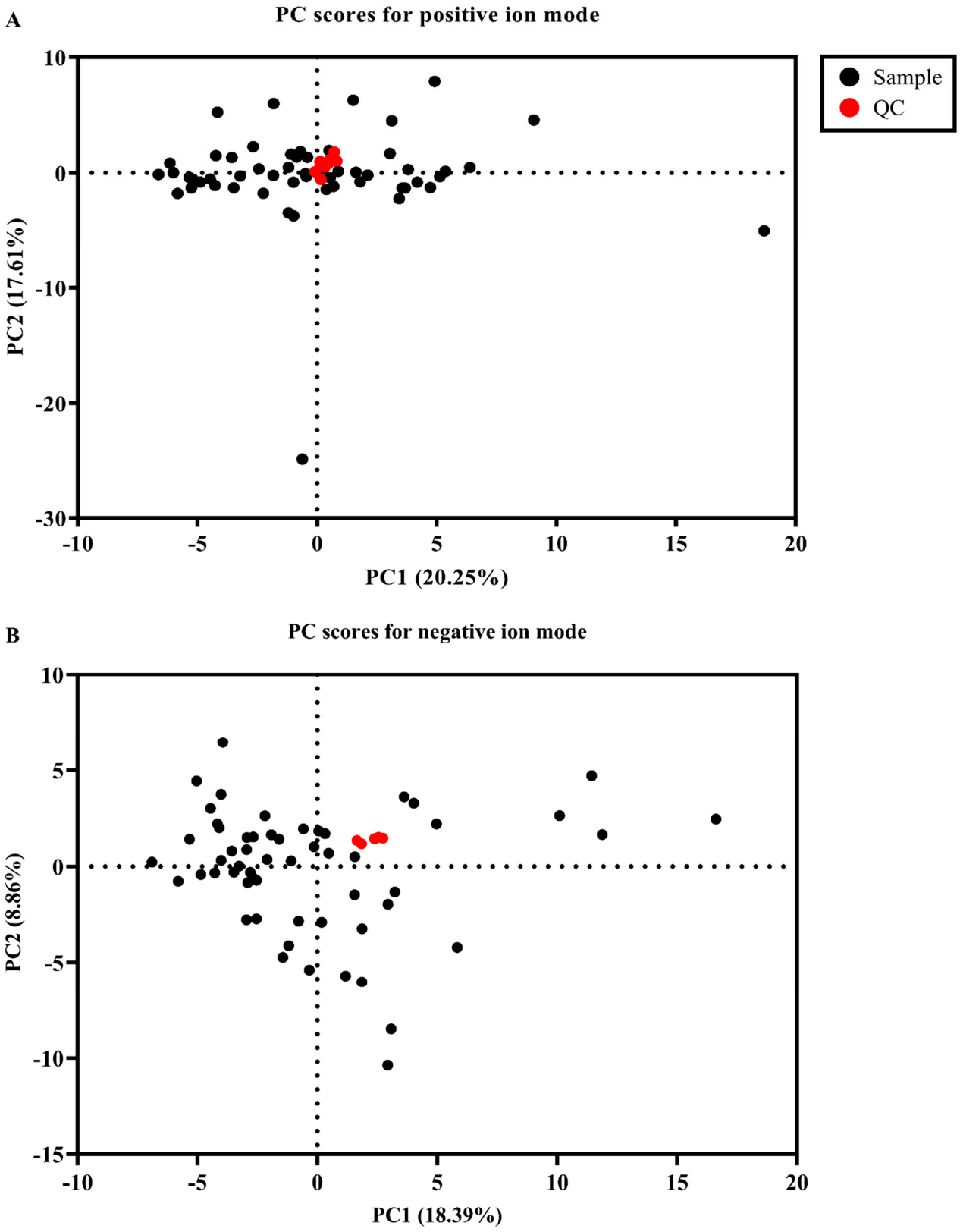

Figure S1. Instrumental stability assessed through quality control samples for the data obtained by UHPLC-HRMS/MS in positive (**A**) and negative (**B**) ionization mode.