

Table S1. Final multivariable regression models assessing the association between principal components loads, individual metabolites and adverse cardiac characteristics and outcomes.

O₂ saturation < 95%					
<i>Variable</i>	<i>Rel</i>	<i>OR</i>	<i>LCL</i>	<i>UCL</i>	<i>p-value</i>
Single ventricle	.	16.36	4.40	60.75	<0.001
GCDCA	98.4%	1.33	0.99	1.79	0.06
Serotonin/tryptophan	64.4%	0.86	0.78	0.94	0.002
ADMA/Arg	95.8%	1.32	1.03	1.68	0.03
Betaine	61.8%	1.06	1.01	1.11	0.02
Cardiac Dysfunction					
<i>Variable</i>	<i>Rel</i>	<i>OR</i>	<i>LCL</i>	<i>UCL</i>	<i>p-value</i>
PC2	77.4%	0.89	0.82	0.97	0.01
PC5	61.4%	1.15	1.02	1.29	0.02
Citrulline	89.2%	1.09	1.02	1.16	0.02
Cystine	65.6%	1.01	1.00	1.03	0.04
1-Methylhistidine	60.2%	1.15	1.02	1.29	0.02
RV Dysfunction					
<i>Variable</i>	<i>Rel</i>	<i>OR</i>	<i>LCL</i>	<i>UCL</i>	<i>p-value</i>
TGA	.	9.65	2.40	38.8	0.001
PC4	94.0%	0.85	0.76	0.96	0.01
DHEAS	59.0%	0.64	0.41	1.00	0.05
Arrhythmia History					
<i>Variable</i>	<i>Rel</i>	<i>OR</i>	<i>LCL</i>	<i>UCL</i>	<i>p-value</i>
TGA	.	5.96	1.54	23.1	0.01
Single ventricle	.	39.6	3.38	463	0.003
Age at assessment	.	1.06	1.01	1.10	0.01
PC2	97.2%	1.09	1.02	1.16	0.01
TMCA	100.0%	1.46	1.00	2.13	0.05
Orn/Arg	100.0%	1.22	1.05	1.43	0.01
Arrhythmia History					
<i>Variable</i>	<i>Rel</i>	<i>OR</i>	<i>LCL</i>	<i>UCL</i>	<i>p-value</i>
TGA	.	6.23	1.89	20.6	0.003
Single ventricle	.	20.1	1.61	251	0.02
Age at assessment	.	1.04	1.00	1.08	0.08
PC2	98.0%	1.08	1.01	1.15	0.02
TCA	99.8%	1.28	1.02	1.60	0.03
Orn/Arg	95.0%	1.19	1.01	1.41	0.03
Shortness of Breath					
<i>Variable</i>	<i>Rel</i>	<i>OR</i>	<i>LCL</i>	<i>UCL</i>	<i>p-value</i>
Ornithine	98.8%	1.05	1.02	1.08	<0.001
Homo-L-Arginine	95.8%	0.07	0.02	0.30	<0.001
SDMA/Arg	80.4%	1.15	1.03	1.29	0.01
Exertional SOB					
<i>Variable</i>	<i>Rel</i>	<i>OR</i>	<i>LCL</i>	<i>UCL</i>	<i>p-value</i>
Hypertension	.	2.64	1.15	6.05	0.02
PC1	89.6%	0.96	0.93	0.98	0.003
PC4	94.8%	0.90	0.82	0.98	0.02

Abbreviations: ADMA—asymmetric dimethylarginine; Arg—arginine; DHEAS—dehydroepiandrosterone sulfate; GCA—glycolic acid; LCL—lower confidence limit; mets—metabolites; O₂—oxygen; OR—odds ratio; Orn—ornithine; PC—principal component; Rel—reliability in bootstrap resampling analysis; RV—right ventricular; SDMA—symmetric

dimethylarginine; SOB—shortness of breath; TGA—transposition of the great arteries; TMCA—taumuricholic acid; UCL—upper confidence limit.

Table S2. Patient clinical status at the time of sample collection (number of patients = 99; number of assessments = 167) *.

	N	Septal Defects	N	Single Ventricle	N	TGA	N	TOF/RVOT	N	Other
Age (years)	33	43 ± 15	16	33 ± 8	45	37 ± 13	54	38 ± 14	19	33 ± 10
Systolic pressure (mmHg)	33	114 ± 17	16	117 ± 10	44	115 ± 18	54	127 ± 17	19	123 ± 19
Heart rate (bpm)	33	74 ± 14	16	76 ± 11	43	72 ± 11	54	76 ± 14	19	77 ± 13
O2 saturation < 95%	33	5 (15%)	16	12 (75%)	44	2 (5%)	54	2 (4%)	19	2 (11%)
Current arrhythmia	33	7 (21%)	16	13 (81%)	45	30 (67%)	54	7 (13%)	19	2 (11%)
Any cardiac dysfunction	15	7 (47%)	8	2 (25%)	19	12 (63%)	36	18 (50%)	12	0 (0%)
Any RV dysfunction	15	4 (27%)	6	2 (33%)	19	11 (58%)	35	16 (46%)	12	0 (0%)
RV volume overload	15	0 (0%)	5	0 (0%)	19	0 (0%)	35	13 (37%)	11	0 (0%)
Any LV dysfunction	15	6 (40%)	8	0 (0%)	18	2 (11%)	36	3 (8%)	12	0 (0%)
Shortness of breath	31	3 (10%)	16	5 (31%)	43	9 (21%)	51	10 (20%)	18	4 (22%)
Exertional SOB	32	10 (31%)	16	8 (50%)	43	20 (47%)	52	14 (27%)	18	3 (17%)
Anxiety/depression score	32	88 ± 13	16	71 ± 18	44	69 ± 24	53	83 ± 17	18	82 ± 16
Arrhythmia score	31	83 ± 17	16	68 ± 34	44	76 ± 26	52	82 ± 17	18	73 ± 20
Physical limitations score	32	64 ± 22	16	52 ± 25	44	57 ± 30	52	67 ± 24	18	68 ± 24
Quality of life score	32	76 ± 20	16	56 ± 20	44	63 ± 27	53	71 ± 23	18	74 ± 18
Symptoms score	32	80 ± 17	16	62 ± 26	44	69 ± 22	53	77 ± 18	18	74 ± 22
Total score	32	80 ± 15	16	63 ± 20	44	66 ± 23	53	77 ± 17	18	76 ± 17
Worsening quality of life	23	2 (9%)	14	1 (7%)	36	11 (31%)	39	4 (10%)	12	1 (8%)

N = Number of Assessments; RV volume overload—moderate or greater mitral or pulmonary regurgitation. Abbreviations: O2—oxygen; LV—left ventricular; RV—right ventricular. *Certain patients had more than one assessment during the study period.

Table S3. Non-cardiac diagnoses. Each space includes all non-cardiac diagnoses for each of the 71 patients in whom a non-cardiac diagnosis was present.

Types of Non-Cardiac Diagnoses
Patellar instability; Hypothyroid; Zoster; Hypercholesterolemia
Asthma
Obesity; Stenosis of R subclavian
Exercise induced asthma
Focal segmental glomerulosclerosis; Joint hypermobility; Recurrent pneumonias; Guillain barre history; Scoliosis
Hx of pancreatitis; Deep vein thrombosis; Seizure disorder; Stroke; Restrictive ventilatory defect; Hypothyroidism;
Ashtma; Depression
Leukemia; Obstructive sleep apnea; Obesity; Down's Syndrome
Radial-ulnar synostoses
Anxiety; Attention deficit disorder; Large facial teratoma; Dysarthria likely due to deficient palate; Disequilibrium;
Developmental delay; Menorrhagia
Psoriasis; Psoriatic arthritis; Essential thrombocytosis; Asthma; Obstructive sleep apnea; Obesity
Hypercholesterolemia
Pulmonary hypertension
Hypertension; Vascular disease involving the celiac axis and carotid arteries; Pulmonary hypertension
Asthma; Migraine; Fibromyalgia; Irritable Bowel Syndrome; Hepatitis C; Hypothyroidism
22q11 deletion syndrome; Acne vulgaris; Gingival hyperplasia
Hypertriglyceridemia; Allergic rhinitis
Cataracts; Depression; Cardiac cirrhosis; Obstructive sleep apnea
Raynauds; Seasonal allergies; Back pain
Paralyzed vocal cord; Alcoholism; Anxiety/depression; Obstructive sleep apnea; Chronically decreased vision in the
left eye; Status post surgery to remove a supernumerary digit from his left thumb in infancy
Allergic rhinitis; Diverticulosis coli; Anxiety; Panic disorder; Pulmonary hypertension; Obesity; Snoring without
sleep apnea; Non-alcoholic steatohepatitis; Thyroid nodules; Osteoarthritis

Obesity; Post traumatic stress disorder; Anxiety
 Chronic sinusitis; Obesity; Hypothyroidism
 Headaches; Endometriosis
 Hyperlipidemia; Acne; Depression/anxiety; MTHFR gene mutation; Anemia; Lipomas
 Carpal tunnel syndrome on left; Hepatitis C; Lymphadenopathy
 Cohen's syndrome; Hypothyroidism; Seizures; Obesity
 Pectus excavatum; Scoliosis; Obesity; Synostosis (cranial); Amenorrhea
 Chronic osteoarthritis
 Anemia; Depression; Gastroesophageal reflux disease; Hiatal hernia; History of kidney stones; Hyperlipidemia;
 Obesity; Obstructive sleep apnea
 Obesity; Hyperlipidemia
 Mild persistent asthma
 Plantar fascial fibromatosis; Osteoporosis
 Hyperlipidemia
 Gastroesophageal reflux disease; Gout; Iron deficiency; Obstructive sleep apnea; Pulmonary embolism; Transient
 ischemic attack
 Rheumatoid arthritis
 Gastroesophageal reflux disease; Psychotic affective disorder; Developmental delay; Sleep apnea; Hyperlipidemia;
 Obesity
 Attention-deficit disorder; Down's syndrome; Hypothyroidism; Obesity; Obstructive sleep apnea; Pulmonary
 hypertension; Refractive amblyopia; Thyrotoxicosis history
 Depression; Pulmonary hypertension
 Nephrolithiasis
 Hyperlipidemia; Thyroid disease; Migraine aura without headache
 Obesity; Depression
 Tracheal stenosis
 Attention deficit disorder; Acne vulgaris
 Obstructive sleep apnea
 Sjogren's syndrome; Parenchymal lung disease; Migraine headache; Iron deficiency anemia; Gastroesophageal reflux
 disease; Mixed connective tissue disease; Pectus excavatum; Scoliosis
 Fracture of shaft of clavicle
 Anxiety; Asthma; Down's syndrome; Eczema; Hypothyroidism; Obstructive sleep apnea
 C7 spinal cord injury; Calculus of kidney; Chronic cystitis; Edema; Endometriosis; Hyperlipidemia; Osteoporosis;
 Pressure ulcer; Restrictive lung disease; Pressure sore on head
 Congenital coxa vara; Pectus excavatum; Anxiety disorder; Dorsalgia
 Hearing impairment; Cyanosis; Mental disability;
 Interstitial lung disease; Pulmonary hypertension; Obstructive sleep apnea; Pulmonary tuberculosis; Hyperlipidemia
 Obstructive sleep apnea; Epilepsy; Gastroesophageal reflux disease; Anoxic brain injury; Dysphagia; Psoriasis;
 Pulmonary hypertension; Seizures
 Malignant neoplasm of prostate
 Hyperlipidemia
 Benign prostatic hyperplasia; Gastroesophageal reflux disease; Hernia; Hyperlipidemia; Hypertension; Nonalcoholic
 steatohepatitis; Chronic obstructive lung disease
 Pulmonary hypertension
 Anemia; Asthma; Congenital malrotation of intestine; Dysplasia of vocal cord; Dyspnea; History of omphalocele;
 History of small bowel obstruction; Nontoxic single thyroid nodule
 Anxiety; Hyperlipidemia
 Anxiety; Gout; Hypertrophy tonsils; Obesity
 Attention deficit disorder; Asthma; Chronic depression; Hypersomnia; Nicotine dependence; Obesity
 Anxiety; Fibroid; Gastroesophageal reflux disease; Hiatal hernia; viral pneumonia; Hypothyroidism

Asthma; Depression; Endometriosis; Hepatitis C; Hypercholesteremia; Migraine; Spondylosis, lumbar region; Intervertebral disc degeneration, lumbar region; Insomnia; Gastroesophageal reflux disease without esophagitis; Acute stress reaction
Hypothyroidism
Blindness; Brain cyst; Chronic obstructive pulmonary disease; Gastroesophageal reflux disease; Head trauma in child; Migraines; Seizures
Thyroid disease; Cerebral vascular accident; Obstructive sleep apnea; Hyperlipidemia; Lung disease; Cervical cancer
Chronic kidney disease; Gout; Liver fibrosis; Obesity; Obstructive sleep apnea; Thyroid disease; Transient ischemic attack
Anxiety; Asthma; Thrombophlebitis
Asthma; Obesity; Obstructive sleep apnea
Malignant neoplasm of uterus
Anemia, iron deficiency; Breast cancer; Dysthymic disorder; Gastroesophageal reflux disease; Obstructive sleep apnea; Tracheal stenosis; Vasodepressor syncope; and Vocal cord paralysis; Hyperlipidemia
Anemia; Anxiety; Migraines; Spastic hemiparesis of left dominant side; Gastroesophageal reflux disease

Table S4. Significantly impacted pathways stratified by diagnoses (** FDR $0.01 < p < 0.05$, * FDR $0.05 < p < 0.10$, no * FDR > 0.10).

Significantly Impacted Pathways	
Any cardiac dysfunction	Arrhythmia
Arginine biosynthesis *	Valine, leucine and isoleucine biosynthesis*
Histidine metabolism *	Glutathione metabolism*
Butanoate metabolism *	Arginine biosynthesis
D-Glutamine and D-glutamate metabolism	Primary bile acid biosynthesis
Glutathione metabolism	Aminoacyl-tRNA biosynthesis
Alanine, aspartate and glutamate metabolism	Taurine and hypotaurine metabolism
Cysteine and methionine metabolism	Arginine and proline metabolism
Arginine and proline metabolism	
Aminoacyl-tRNA biosynthesis	
RV dysfunction	Worsened QOL
Arginine biosynthesis *	Aminoacyl-tRNA biosynthesis
Butanoate metabolism *	Biosynthesis of unsaturated fatty acids
Histidine metabolism *	Histidine metabolism
D-Glutamine and D-glutamate metabolism *	Sphingolipid metabolism
Glutathione metabolism	
Alanine, aspartate and glutamate metabolism	
Glycine, serine and threonine metabolism	
Cysteine and methionine metabolism	
Arginine and proline metabolism	
Aminoacyl-tRNA biosynthesis	
Sphingolipid metabolism	
Shortness of breath	
Glycine, serine and threonine metabolism	
Glycerophospholipid metabolism	
Arginine biosynthesis	
Histidine metabolism	
Citrate cycle (TCA cycle)	
Exertional shortness of breath	
Valine, leucine and isoleucine biosynthesis **	
Butanoate metabolism *	
D-Glutamine and D-glutamate metabolism	

Aminoacyl-tRNA biosynthesis
 Alanine, aspartate and glutamate metabolism
 Valine, leucine and isoleucine degradation
 Citrate cycle (TCA cycle)
Low oxygen saturation
 Primary bile acid biosynthesis **
 D-Arginine and D-ornithine metabolism
 Arginine and proline metabolism
 Taurine and hypotaurine metabolism
 Arginine biosynthesis
 Butanoate metabolism

Abbreviations: FDR—false discovery rate; TCA—tricarboxylic acid cycle.

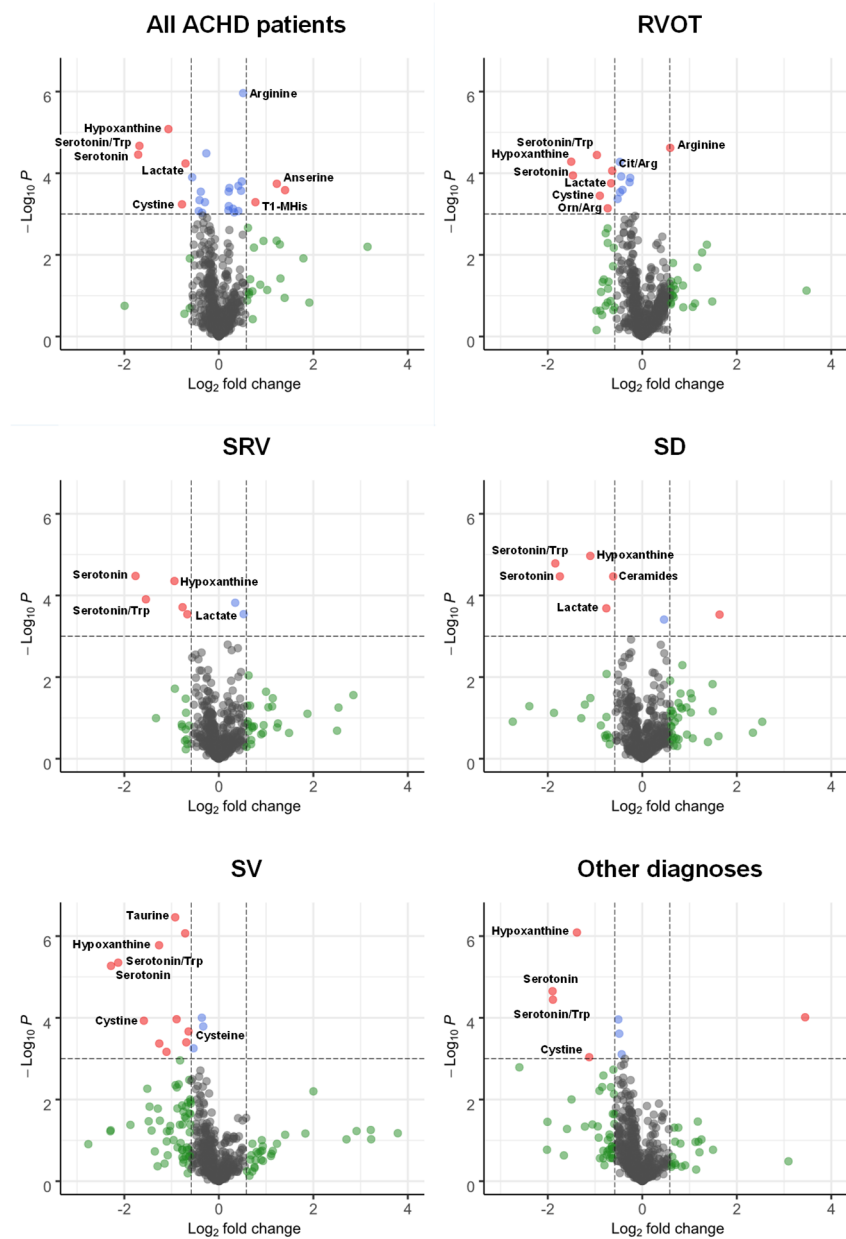


Figure S1. Volcano plots for differential expression of metabolites between controls and patients with ACHD, stratified by type of diagnosis (fold difference cutoff: 0.67/1.50, p -value cutoff: 0.001). Note:

Unlabelled red circles represent generic lipid-derived metabolites. Abbreviations: Arg—arginine; Cit—citrulline; Orn—ornithine; RVOT—right ventricular outflow stenosis; T1-MHis—1-Methylhistidine; TGA—transposition of the great arteries; TOF—Tetralogy of Fallot; Trp—tryptophan.

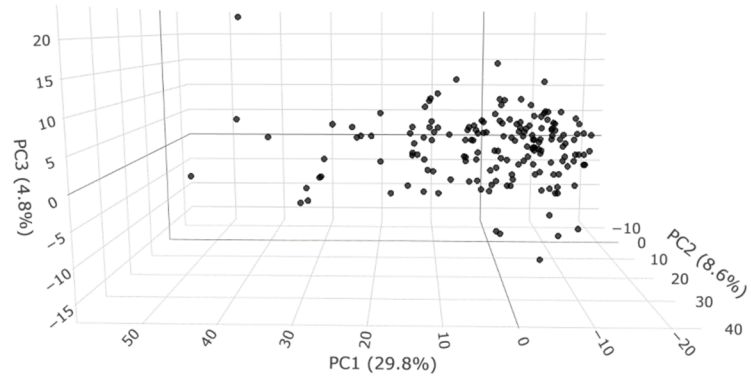


Figure S2. Principal cluster analysis plot in 3 dimensions.

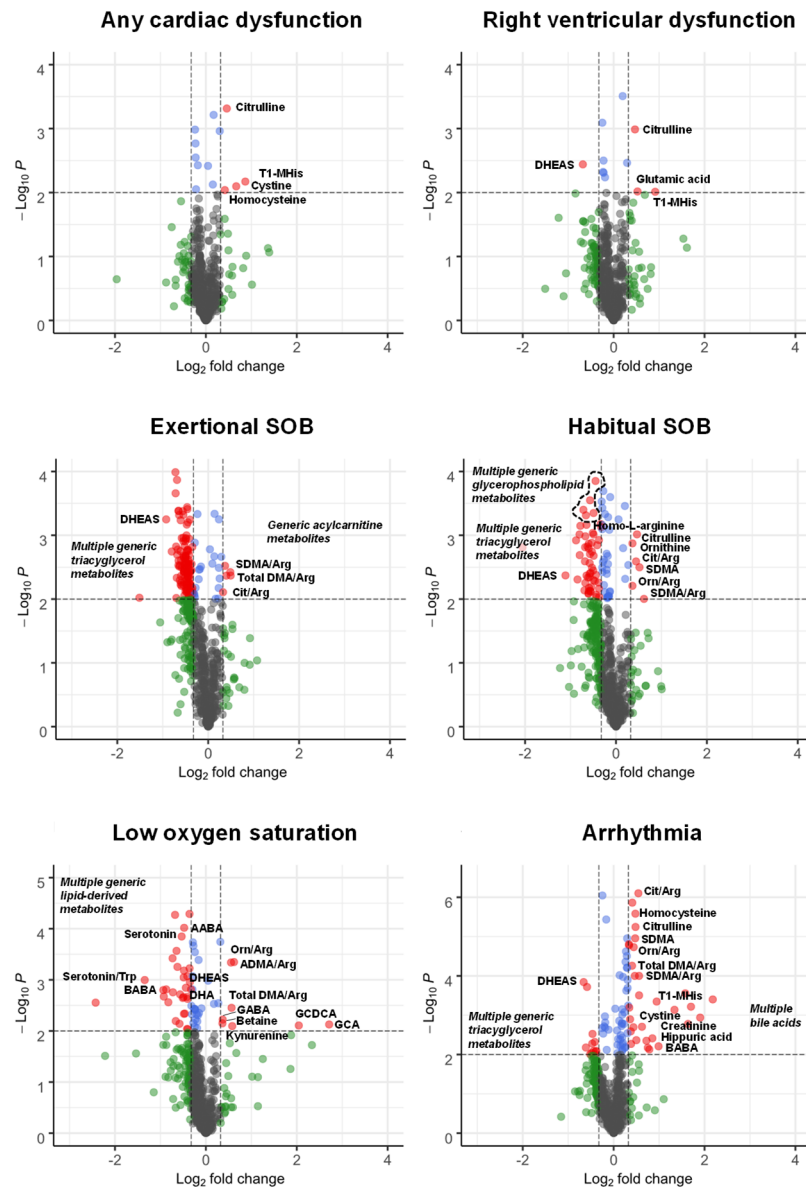


Figure S3. Volcano plots for differential expression of metabolites between patients with and without various clinical characteristics and outcomes (fold difference cutoff: 0.80/1.25, *p*-value cutoff: 0.01). Notes: For each graphs/areas, label in *italic* applies to all red circles that are unlabelled. In the habitual SOB panel, metabolites circles in dotted black line represent the generic glycerophospholipids metabolites, all other non-labelled metabolites in this area are generic triaglycerol metabolites. Habitual SOB—SOB not associated with exertion; Arrhythmia—history of arrhythmia. Abbreviations: ADMA— asymmetric dimethylarginine; ABBA—3-aminobutanoic acid; BABA—L- α -aminobutyric acid; Arg—arginine; Cit—citrulline; DHA—dosaheanoic acid; DHEAS—dehydroepiandrosterone sulfate; DMA—dimethylarginine; GABA—gamma aminobutyric acid; GCA—glycocholic acid; GCDCA—chenodeoxycholic acid glycine conjugate; Orn—ornithine; SDMA—symmetric dimethylarginine; SOB—shortness of breath; T1-MHis—1-Methylhistidine; Trp—tryptophan.