

Online Data Supplement

Figure S1

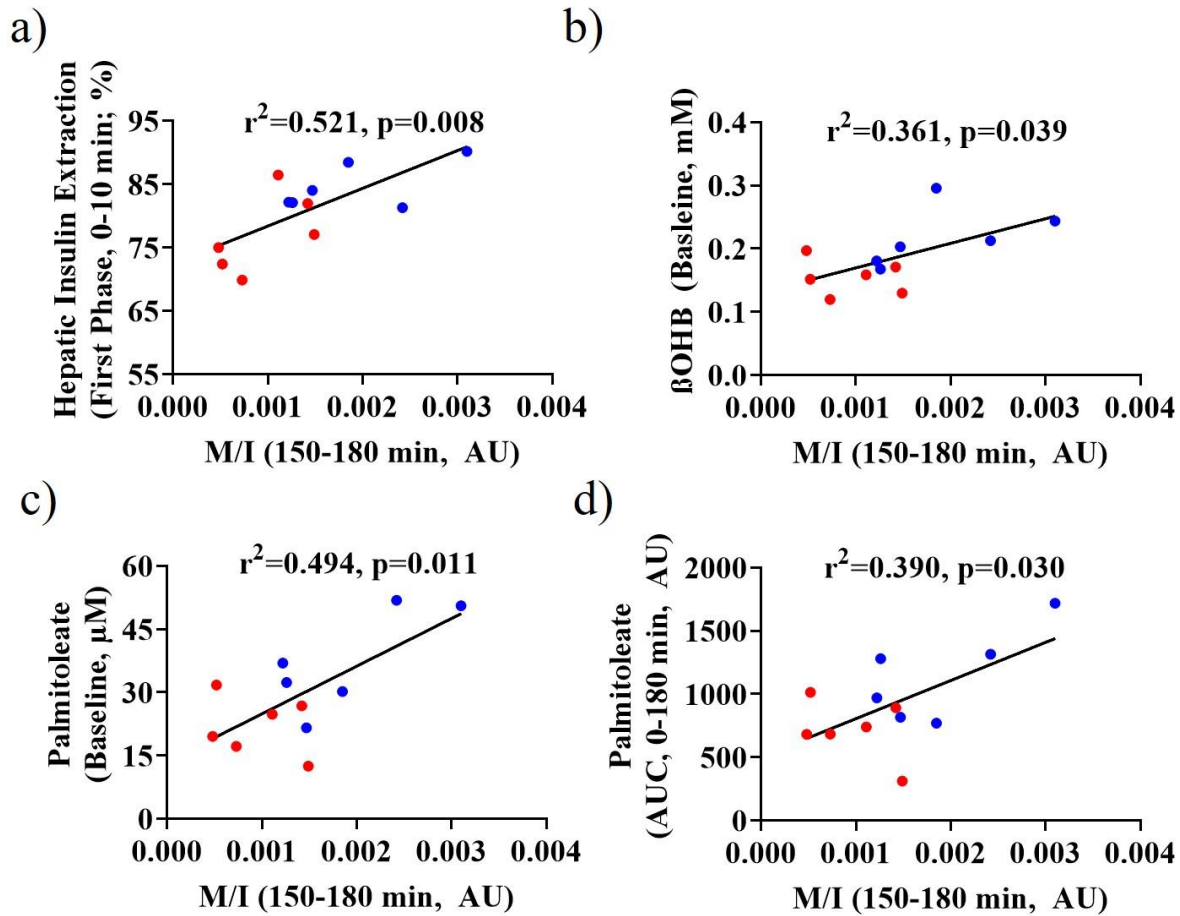


Figure S1. Metabolic Correlates with Insulin Sensitivity

a) M/I also correlated strongly with the hepatic insulin extraction during the 1st phase insulin secretion. b) and with β OHB at baseline. M/I correlated with palmitoleate at c) baseline and d) represented as AUC throughout the clamp. β OHB, β -hydroxybutyrate; M/I, mg glucose/kg body weight/min/ μ U insulin.ml.

Figure S2

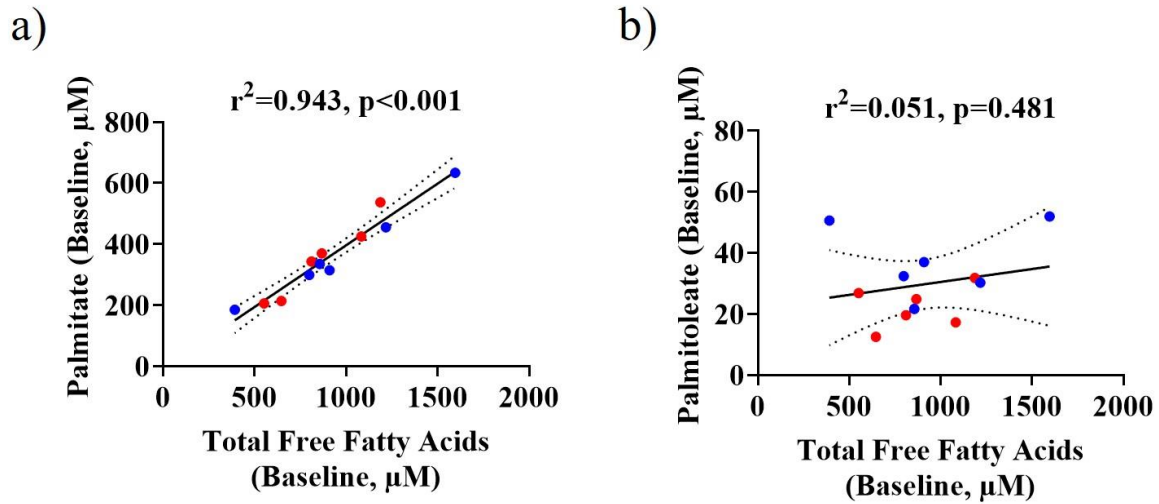


Figure S2. Free Fatty Acid Species Relationships with Total Free Fatty Acids

a) Baseline palmitoleate was strongly associated with ketone concentrations throughout the hyperglycemic clamp. b) Expectedly, complete fatty acid oxidation (acetylcarnitine) was associated with greater ketone concentrations throughout the hyperglycemic clamp. βOHB , β -hydroxybutyrate. AUC, area under the curve calculated by the trapezoidal method; AU, arbitrary units.

Figure S3

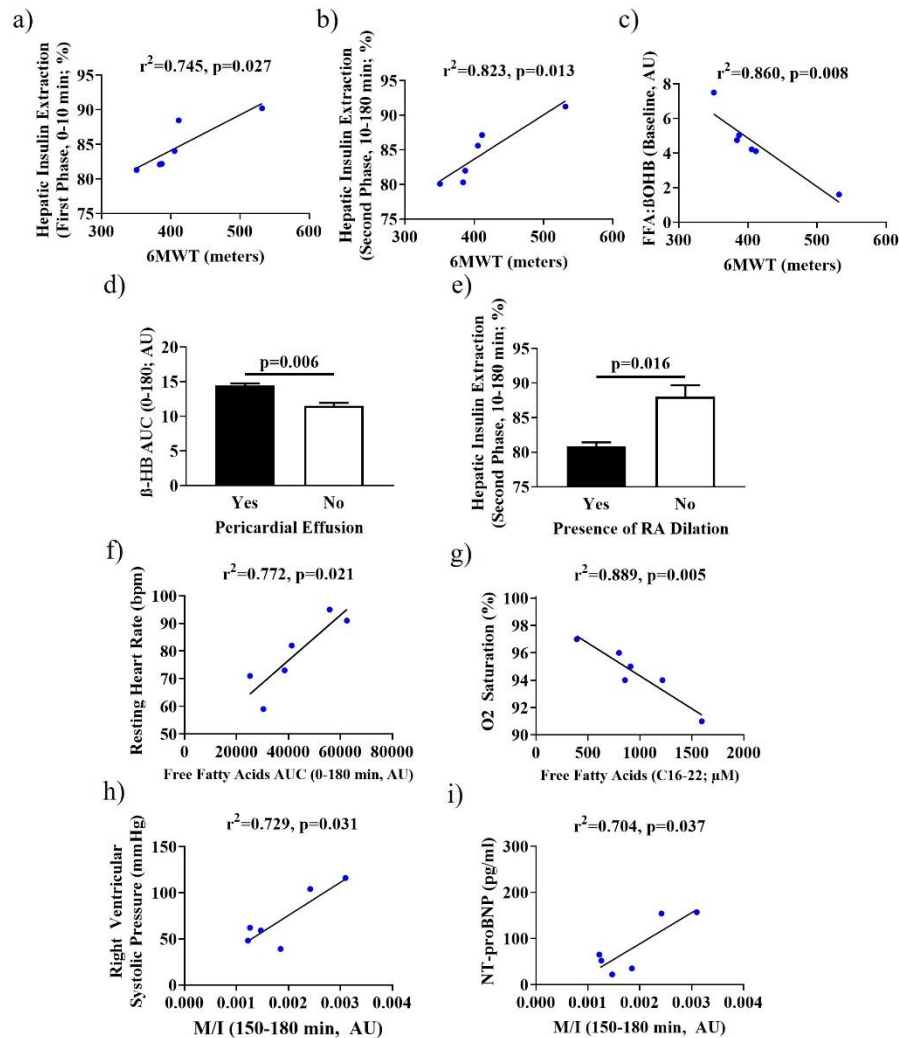


Figure S3. Clinical Correlates with Nutrient Metabolism

Greater distance walked during a 6MWT was related to greater a) 1st phase and b) 2nd phase hepatic insulin extraction along with c) a lower FFA:βOHB ratio. d) Presence of pericardial effusion was associated with greater βOHB during the hyperglycemic clamp. e) Presence of right arterial dilation was associated with lower hepatic insulin extraction. f) FFAs during the hyperglycemic clamp was related to higher resting heart rate. g) Fasting FFAs were related to lower O₂ saturation. h) M/I was increased with greater RVSP and i) greater NTpro-BNP. 6MWT, 6-minute walk test; FFA, free fatty acids; βOHB, β-hydroxybutyrate; RVSP, right ventricular systolic pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; M/I, mg glucose/kg body weight/min/μU insulin.ml.

Figure S4

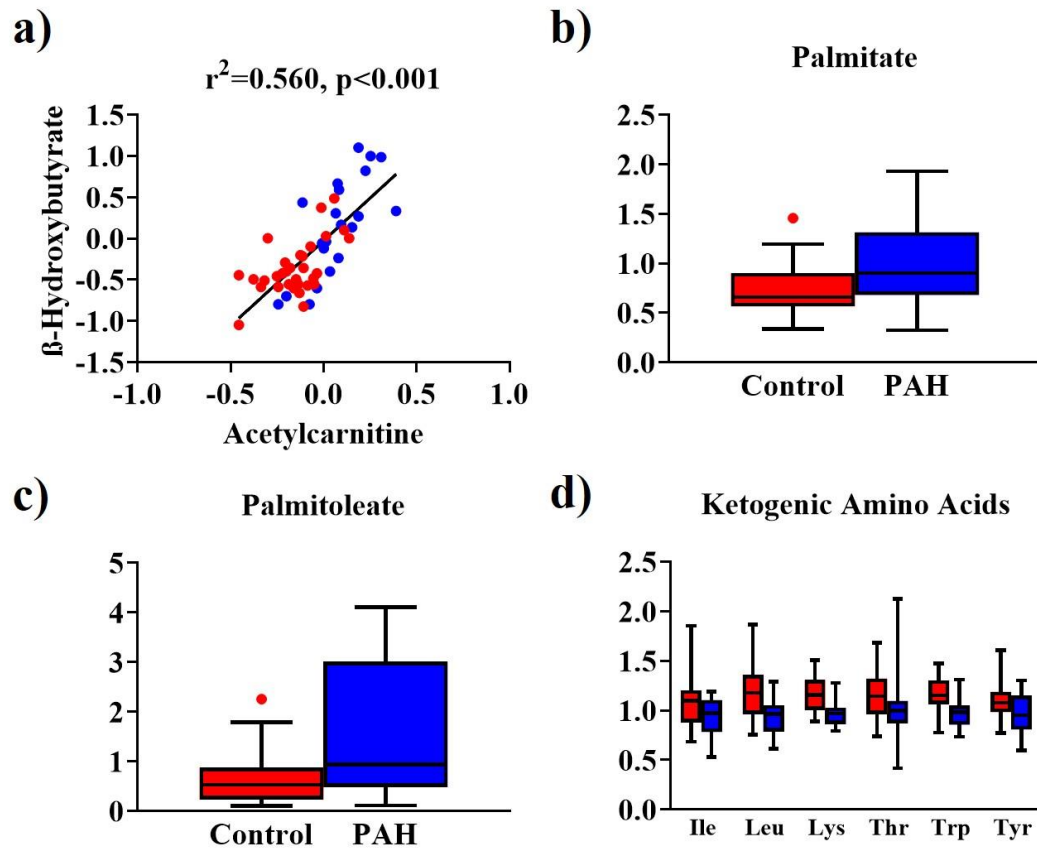


Figure S4. Additional Metabolomic Data

a) β OHB and acetylcarnitine are highly correlated. The fatty acids b) palmitate (1.4-fold, $q=0.019$) and c) palmitoleate (2.2-fold, $q=0.010$) were elevated in PAH. d) Ketogenic amino acids were significantly reduced in PAH. *, $q<0.01$. PAH, pulmonary arterial hypertension; β OHB, β -hydroxybutyrate; Ile, isoleucine; Leu, leucine; Lys, lysine; Thr, threonine; Trp, tryptophan; Tyr, tyrosine.

Figure S5

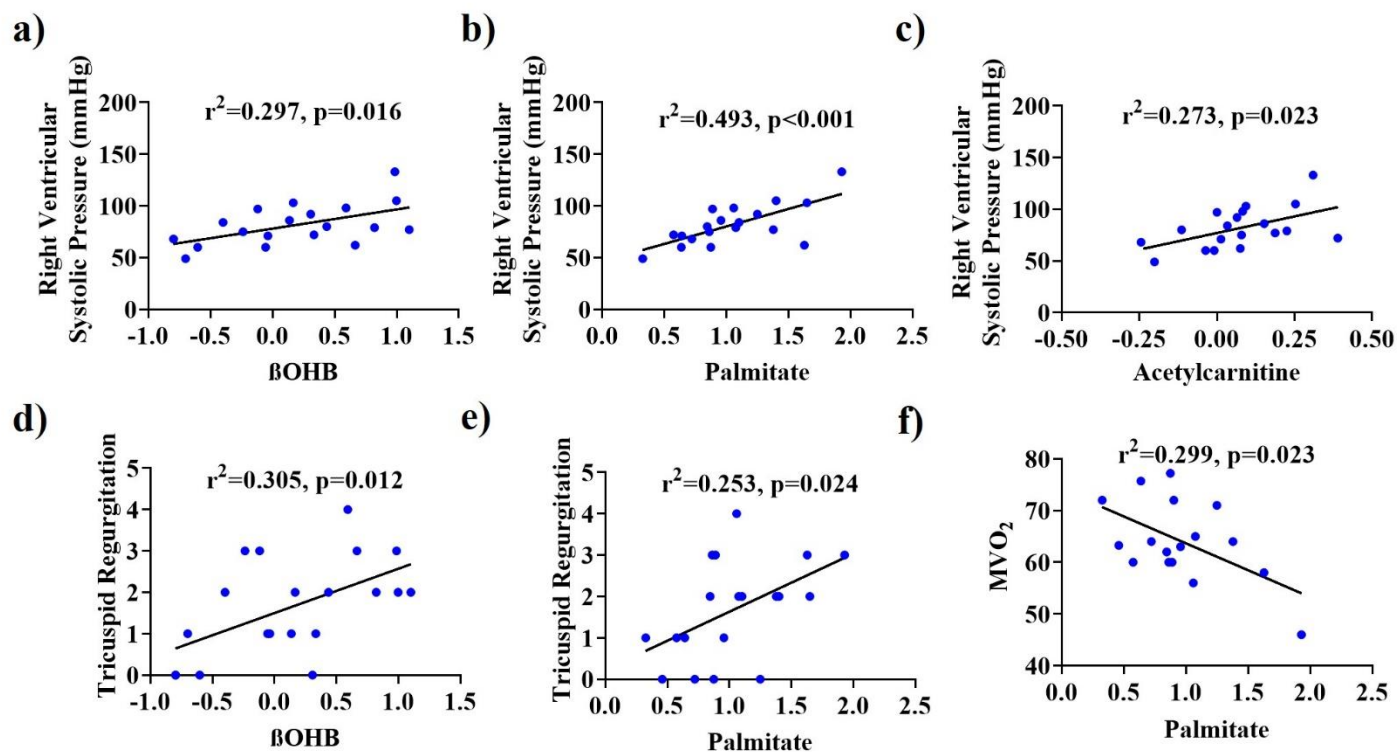


Figure S5. Clinical Correlates with Select Plasma Metabolites

RVSP was associated with higher a) BOHB, b) palmitate and c) acetylcarnitine. The grade of tricuspid regurgitation was associated with d) BOHB and e) palmitate. f) Palmitate was further associated with lower MVO₂. RVSP, right ventricular systolic pressure; BOHB, β -hydroxybutyrate.

Figure S6

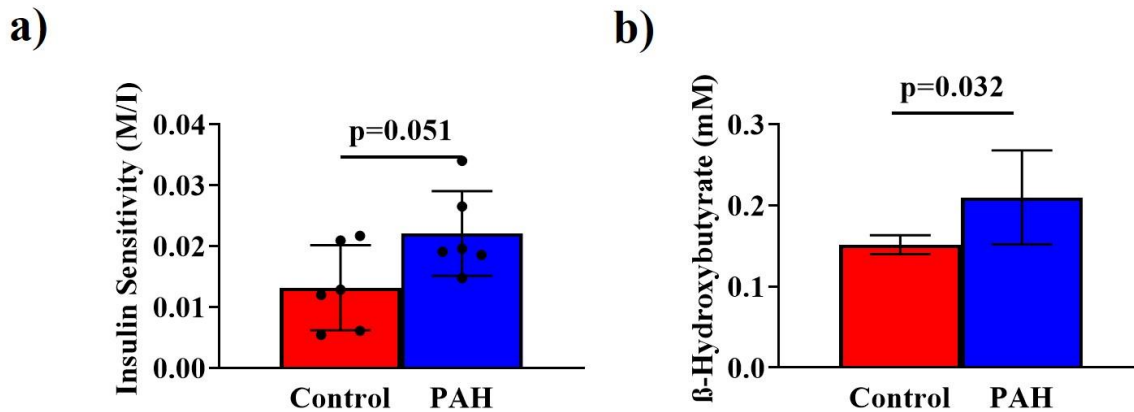


Figure S6. Controlling Nutrient Metabolism Data for Basal Metabolic Rate

Given the differences in BMR, we have thus performed an additional analysis to control for BMR, showing a) M/I remains elevated to a similar extent as our original data presented (original data: (M/I, 150-180 minute; PAH: 0.02451 ± 0.0070 , Control: 0.01323 ± 0.0077 , $p=0.024$) vs (M/I, 150-180 minutes normalized to BMR (kcal/min): Control: 0.01316 ± 0.0070 , PAH: 0.02209 ± 0.0070 , $p=0.051$). The differences in ketogenesis remain similar as well (original data: β OHb; Control: $0.155 \text{mM} \pm 0.03$, PAH: 0.217 ± 0.05 , $p=0.018$) vs (β OHb: Control: $0.151 \text{mM} \pm 0.01$, PAH: 0.210 ± 0.06 , $p=0.032$). M/I and ketogenesis were unchanged after normalizing to BMR. PAH, pulmonary arterial hypertension; BMR, basal metabolic rate; β OHb, β -hydroxybutyrate; M/I, mg glucose/kg body weight/min/ μ U insulin.ml.

TABLE S1. Subject Characteristics (male participants removed)

	Control	PAH	<i>p</i>-value
<i>N</i> (sex)	5 (5 F)	5 (5 F)	-
Age (years)	35±11	52±9	0.03
BMI (kg/m²)	30±4	32±5	0.52
Baseline Glucose (mg/dl)	88±12	85±4	0.62
Baseline Insulin (μU/ml)	16±8	12±3	0.28
Baseline C-peptide (ng/ml)	2.2±0.6	2.1±0.6	0.76
Baseline βOHB (mM)	0.15±0.02	0.22±0.05	0.02
Baseline FFA (μM)	867±273	982±453	0.64
HOMA-IR	3.7±2.2	2.5±0.6	0.29
BMR (kcal/day)	1367±153	1519±88	0.09
O₂ Saturation (%)	99.2±1.3	94.6±2.3	<0.01
M/I (150-180 min)	0.0011±0.0004	0.0020±0.0008	<0.05
Hepatic Extraction, 2nd phase (%)	74.0±4.9	84.2±2.2	0.096
Baseline Palmitoleate (μM)	22.6±7.7	40.4±10.2	0.014
Baseline Acetylcarnitine (μM)	7.8±1.4	10.2±1.8	0.045

Data represent mean±SD.

PAH, subjects with pulmonary arterial hypertension; BMI, body mass index; βOHB, β-hydroxybutyrate; FFA, free fatty acids; HOMA-IR, homeostatic model assessment of insulin resistance; BMR, basal metabolic rate; O₂ Saturation; oxygen saturated hemoglobin relative to total hemoglobin; M/I, mg glucose/kg body weight/min/μU insulin.ml.