

SUPPLEMENTARY DATA

Supplementary Table S1. Characteristics of CON and NAFLD-IR mice in the 6h fasted state

	CON	NAFLD-IR	p value
Females (n)	6	6	NA
Age (days)	258 ± 2	255 ± 8	0.37
Body weight (g)	24.2 ± 1.4	29.3 ± 3.5	<0.01
Liver weight (g)	0.97 ± 0.09	1.84 ± 0.65	<0.01
Blood glucose (mg/dl)	120 ± 21	144 ± 12	0.03
Insulin (pmol/l)	81 ± 35	527 ± 285	<0.01
Triglycerides (mg/dl)	96 ± 7	94 ± 16	0.85
Free fatty acids (mmol/l)	0.73 ± 0.44	1.17 ± 0.54	0.18
Cholesterol (mg/dl)	97 ± 27	128 ± 37	0.15

Data are expressed as mean ± standard deviation, p values are calculated with unpaired two-tailed Student`s t-test. NA: not assessed.

SUPPLEMENTARY DATA

Supplementary Table S2. Patients characteristics based on their insulin sensitivity

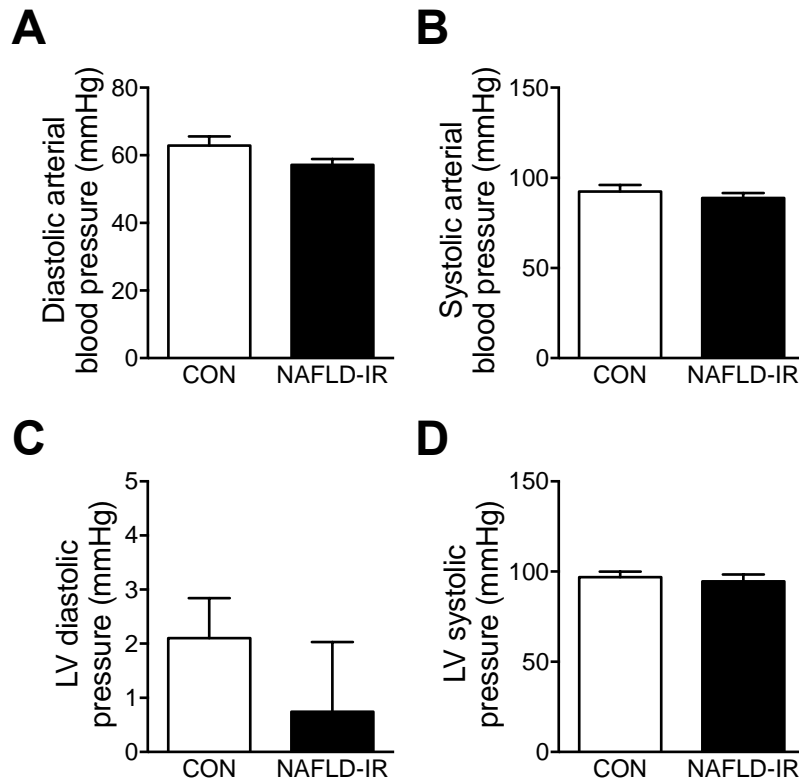
	All patients	Insulin sensitive	Insulin resistant	p value
Number of patients	35	17	18	
Age (years)	55 ± 12	58 ± 13	52 ± 12	0.07
Sex (n male; %)	26; 74.3	12; 70.6	14; 77.8	0.71
Body Mass Index (kg/m ²)	24 ± 2.5	24.2 ± 2.3	23.9 ± 2.7	0.71
Time since transplantation (months)	34 ± 53	48 ± 69	20 ± 25	0.20
<i>Hemodynamics</i>				
Left ventricular ejection fraction (%)	67 ± 7	68 ± 6	67 ± 8	0.69
Cardiac index (l/min/m ²)	2.9 ± 0.6	2.9 ± 0.7	2.9 ± 0.5	0.66
<i>Transplant rejection status</i>				
No histological allograft rejection (ISHLT 0R) (n; %)	28; 80	14; 82.3	14; 77.8	0.99
Mild histological allograft rejection (ISHLT 1R) (n; %)	7; 20	3; 17.6	4; 22.2	0.99
Suspected antibody-mediated rejection (n; %)	0; 0	0; 0	0; 0	1.0
<i>Medication</i>				
ACE inhibitor (n; %)	8; 22.9	5; 29.4	3; 16.7	0.44
Beta blocker (n; %)	10; 28.6	4; 23.5	6; 33.3	0.71
Loop diuretics or thiazids (n; %)	17; 48.6	7; 41.2	10; 55.6	0.51
Antimineralcorticoid (n; %)	5; 14.3	2; 11.8	3; 16.7	0.99
Ivabradine (n; %)	9; 25.7	4; 23.5	5; 27.8	0.71
Statin (n; %)	33; 94.3	16; 94.1	17; 94.4	0.99
Acetylsalicylic acid (n; %)	32; 91.4	16; 94.1	16; 88.9	0.99
Tacrolimus (n; %)	33; 94.3	16; 94.1	17; 94.4	0.99
Everolimus (n; %)	7; 20	3; 17.6	4; 22.2	0.99
Mycophenolate mofetil (n; %)	28; 80	13; 76.5	15; 83.3	0.69
Prednisolone (n; %)	32; 91.4	15; 88.2	17; 94.4	0.60
<i>Laboratory parameters</i>				
Fasting blood glucose (mg/dl)	82 ± 20	76 ± 12	88 ± 25	0.06
Fasting blood insulin (µU/ml)	10.1 ± 5.7	5.8 ± 1.7	14.1 ± 5.3	<0.001
Fasting C-peptide (ng/ml)	3.8 ± 3.0	2.6 ± 1.4	5.0 ± 3.6	<0.001
Hb _{A1c} (%)	5.6 ± 0.5	5.7 ± 0.4	5.6 ± 0.6	0.52
Hb _{A1c} (mmol/l)	37.8 ± 5.5	38.4 ± 4.4	37.3 ± 6.4	0.56
HOMA-IR	2.02 ± 1.16	1.08 ± 0.26	2.91 ± 0.95	<0.001
Free fatty acids (µmol/l)	509 ± 436	525 ± 245	494 ± 569	0.07
C-reactive protein (mg/dl)	0.35 ± 0.36	0.46 ± 0.43	0.24 ± 0.25	0.18
Creatine kinase (U/l)	68 ± 50	71 ± 49	66 ± 54	0.68
AST (U/l)	19 ± 5	20 ± 5	19 ± 5	0.49
ALT (U/l)	17 ± 8	16 ± 8	19 ± 8	0.15
GGT (U/l)	52 ± 52	40 ± 41	63 ± 60	0.18
AP (U/l)	63 ± 25	61 ± 29	65 ± 20	0.52
Triglycerides (mg/dl)	148 ± 60	144 ± 69	152 ± 52	0.40

SUPPLEMENTARY DATA

Total Cholesterol (mg/dl)	173 ± 49	183 ± 64	163 ± 26	0.07
LDL (mg/dl)	100 ± 36	111 ± 46	90 ± 21	0.13
HDL (mg/dl)	55 ± 15	60 ± 13	51 ± 16	0.01

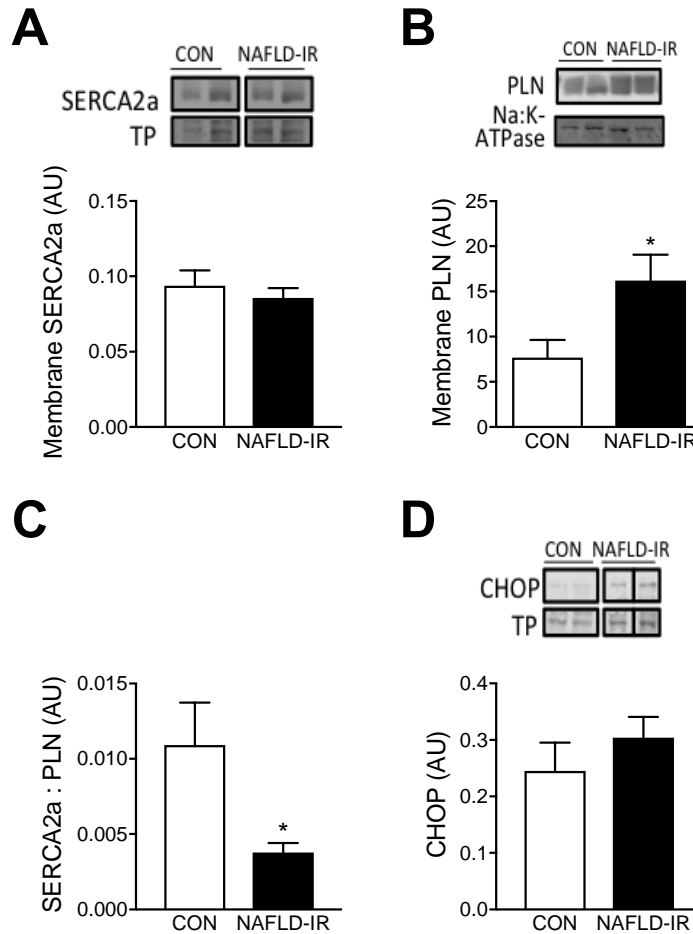
Patients were grouped to insulin sensitive and insulin resistant groups by a median split of the HOMA-IR index. Data are expressed as mean ± standard deviation, p values are calculated with Mann-Whitney U test between insulin sensitive and resistant patients. ACE inhibitor: angiotensin-converting-enzyme inhibitor; ALT: alanine transaminase; AP: alkaline phosphatase; AST: aspartat transaminase; GGT: gamma-glutamyltransferase; HDL: high-density lipoprotein; ISHLT: International society for heart & lung transplantation; LDL: low-density lipoprotein.

Supplementary Figure S1. Arterial and left ventricular (LV) blood pressure in diastole and systole. All data are presented as mean±SEM and groups (n=8-9) were compared with t-test.



SUPPLEMENTARY DATA

Supplementary Figure S2. Molecular markers of contractility and endoplasmic reticulum in the heart of NAFLD-IR mice at baseline. **A-B**, Relative protein expression of the sarco/endoplasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a) and phospholamban (PLN) assessed with Western blots and normalized to total protein (TP) (n=5 per group). **C**, Ratio of SERCA2a to PLN protein levels (n=5 per group). **D**, Relative protein expression of the CCAAT-enhancer-binding protein homologous protein (CHOP) assessed with Western blots and normalized to total protein (TP) (n=5 per group). All data are presented as mean \pm SEM. *p < 0.05, t-test.



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Supplementary Figure S3. Association of myocardial mitochondrial function with insulin resistance and myocardial integrity in humans. **A, D, G,** Mitochondrial respiration linked to electron transfer flavoprotein complex (CETF; octanoyl-carnitine) at state 3 (adp). **B, E, H,** Mitochondrial respiration linked to CETF, complex I (glutamate) and complex II (succinate) at state 3. **C, F, I,** Maximal mitochondrial respiration linked to CETF, complex I (glutamate) and complex II (succinate) at state u. HOMA-IR: homeostatic model assessment insulin resistance index. Spearman two-tailed correlation test n=35 (A-F) and n=26 (G-I). Logarithm to the base two of troponin T was calculated for better visualization, without affecting Spearman's rank correlation coefficient.

