SUPPLEMENTARY DATA

Supplementary Table 1. Baseline subject characteristics

Parameter	
Age, years	64.00 (59.19 – 67.28)
Type 2 diabetes diagnosis, years	6.76 ± 0.96
Height, m	1.77 ± 0.01
Fat, %	25.87 ± 1.11
Oral glucose-lowering medication, n	16
Metformin + SUD, n	6
Metformin only, n	10
Diet only, n	1

Data are presented as means ± SEM when normally distributed, otherwise median and 95% CI (n=17). Medication use did not change during the study protocol. SUD, sulphonylurea derivatives.

SUPPLEMENTARY DATA

Supplementary Table 2. Insulin sensitivity and substrate kinetics assessed by hyperinsulinemic euglycemic clamp

		Placebo	Resveratrol	P-value
R_d glucose ($\mu mol.kg^{-1}$ body weight.min^{-1})				
	Basal	12.18 ± 0.72	12.60 ± 0.86	0.65
	Low insulin	9.98 ± 0.87	9.84 ± 0.53	0.89
	High insulin	21.10 ± 1.69	20.52 ± 1.92	0.66
	Delta (R_d low insulin - R_d basal)	-2.07 ± 0.96	-2.69 ± 0.78	0.56
	Delta (R_d high insulin - R_d basal)	9.23 ± 1.75	8.25 ± 1.95	0.52
EGP ($\mu mol.kg^{-1}$ body weight.min^{-1})				
	Basal	11.71 ± 0.77	12.49 ± 1.11	0.22
	Low insulin	6.73 ± 0.52	6.67 ± 0.66	0.84
	High insulin	0.77 ± 0.28	0.88 ± 0.38	0.74
	% suppression (low insulin)	39.79 ± 5.19	41.88 ± 6.93	0.64
	% suppression (high insulin)	92.45 ± 2.73	91.26 ± 3.90	0.73
Carbohydrate oxidation ($\mu mol.kg^{-1}$ body weight.min^{-1})				
	Basal	5.02 ± 0.62	5.19 ± 0.58	0.85
	Low insulin	7.27 (5.75 - 8.65)	7.23 (6.12 - 9.54)	0.51[a]
	High insulin	9.32 (8.27 - 11.55)	8.22 (7.77 - 12.30)	0.88[a]
Plasma insulin ($pmol.L^{-1}$)				
	Basal	97 (78 - 126)	94 (79 - 129)	0.68[a]
	Low insulin	212 (200 - 244)	223 (207 - 264)	0.59[a]
	High insulin	963 ± 28	945 ± 37	0.67
NOGD ($\mu mol.kg^{-1}$ body weight.min^{-1})				
	Basal	7.02 ± 0.86	7.39 ± 1.10	0.79
	Low insulin	3.06 (0.43 - 6.27)	2.40 (1.89 - 3.97)	0.70[a]
	High insulin	10.16 (7.61 - 14.76)	8.48 (5.63 - 14.05)	0.64[a]
	Delta (NOGD low insulin - NOGD basal)	-3.59 ± 1.58	-4.78 ± 1.30	0.53
	Delta (NOGD high insulin - NOGD basal)	5.15 (0.42 - 8.71)	1.44 (-2.73 - 8.76)	0.86[a]
FFA oxidation ($\mu mol.kg^{-1}$ body weight.min^{-1})				
	Basal	3.54 ± 0.19	3.63 ± 0.19	0.74
	Low insulin	2.90 ± 0.16	2.69 ± 0.12	0.31
	High insulin	2.42 ± 0.15	2.31 ± 0.21	0.57
Respiratory quotient				
	Basal	0.77 ± 0.01	0.78 ± 0.01	0.88
	Low insulin	0.81 ± 0.009	0.82 ± 0.009	0.35
	High insulin	0.86 (0.83 - 0.87)	0.84 (0.82 - 0.88)	0.78[a]

Substrate metabolism assessed by a two-step hyperinsulinemic euglycemic clamp after 30 days of placebo and resveratrol supplementation. The glucose oxidation, lipid oxidation, and respiratory quotient were calculated by means of indirect calorimetry. Non-oxidative glucose disposal (NOGD) is calculated by subtracting the rate of glucose oxidation from the rate of disappearance of the glucose (R_d glucose). Data are presented as mean ± SEM when normally distributed, otherwise median and range are shown. Due to technical problems, the data is only available for 14 subjects (in one subject we had malfunctioning equipment, in another subject the line with D-[6,6-$^2H_2$]glucose tracer leaked, and in the last subject aspiration of the venous line was no longer possible in the late phase of the clamp, which is necessary for regular blood sampling). [a] P-value relates to non-parametric Wilcoxon Signed Rank test.
R_d, rate of disappearance; EGP, endogenous glucose production; NOGD, non-oxidative glucose disposal.

SUPPLEMENTARY DATA

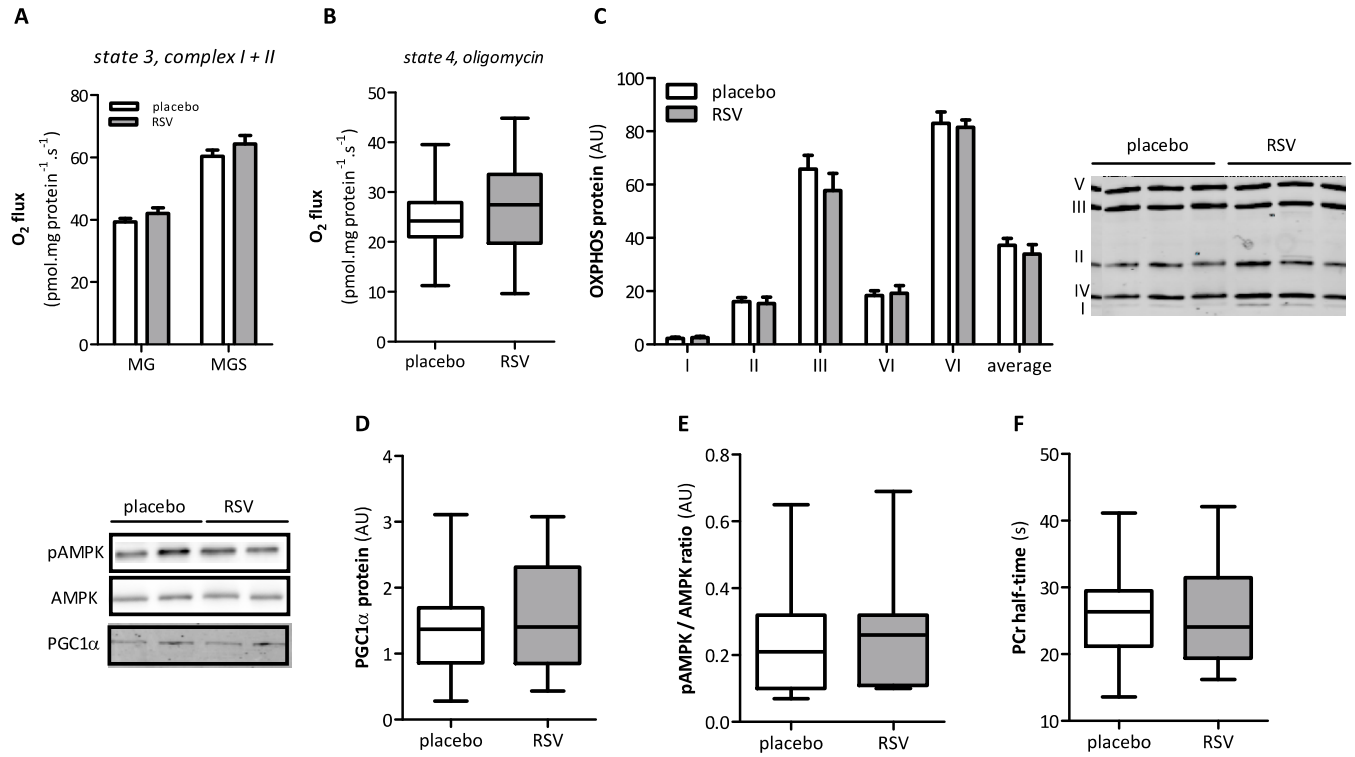
Supplementary Table 3. Subject characteristics before and after 30 days of resveratrol and placebo

	Placebo	Resveratrol	P-value
Weight, kg	n = 17	n =17	
0 days	95.31 ± 2.36	95.57 ± 2.24	0.86
30 days	93.61 ± 2.32	93.98 ± 2.24	
BMI, kg/m^2	n = 17	n = 17	
0 days	30.52 ± 0.60[a]	30.48 ± 0.56[a]	0.53
30 days	29.96 ± 0.57[a]	30.06 ± 0.58[a]	
Systolic blood pressure, mmHg	n = 17	n = 17	
0 days	142 ± 3.9	139 ± 4.2	0.96
30 days	141 ± 2.8	138 ± 2.9	
Diastolic blood pressure, mmHg	n = 17	n = 17	
0 days	87 ± 2.7	85 ± 2.7	0.13
30 days	86 ± 1.9	86 ± 1.9	
Glucose, mmol/l	n = 17	n = 17	
0 days	8.29 ± 0.37	8.11 ± 0.37[a]	0.28
30 days	7.70 ± 0.41	7.80 ± 0.39	
HbA1$_c$, %	n = 17	n = 17	
0 days	6.78 ± 0.21	6.77 ± 0.19	0.12
30 days	6.61 ± 0.19	6.80 ± 0.21	
HbA1$_c$, mmol/mol	n =17	n = 17	
0 days	50.59 ± 2.33	50.53 ± 2.06	0.12
30 days	48.12 ± 2.06	50.35 ± 2.23	
Insulin, pmol/l	n = 16	n = 16	
0 days	87.29 ± 6.30	99.53 ± 12.70	0.31
30 days	90.61 ± 10.99	90.45 ± 9.41	
Creatinine, µmol/l	n = 16	n = 16	
0 days	86.09 ± 3.41	90.69 ± 4.98	0.64
30 days	80.88 ± 3.50	83.68 ± 4.07	
Gamma-GT, U/l	n = 17	n = 17	
0 days	31.97 ± 2.43	33.29 ± 2.22	0.99
30 days	30.59 ± 3.50	31.94 ± 2.57	
AST, U/l	n = 17	n = 17	
0 days	26.78 ± 1.66	26.29 ± 1.72	0.62
30 days	26.94 ± 1.91	27.41 ± 1.51	
ALT, U/l	n = 17	n = 17	
0 days	34.54 ± 2.94	32.53 ± 2.42	0.07
30 days	32.18 ± 3.56	34.71 ± 2.55	
Bilirubin, µmol/l	n = 15	n = 15	
0 days	10.15 ± 1.65	9.52 ± 1.55	0.79
30 days	10.34 ± 1.62	9.89 ± 1.26	
Cholesterol, mmol/l	n = 17	n = 17	
0 days	4.15 ± 0.19	4.15 ± 0.17[a]	0.32
30 days	3.87 ± 0.18	4.05 ± 0.19[a]	
HDL-cholesterol, mmol/l	n = 17	n = 17	
0 days	1.18 ± 0.08[a]	1.18 ± 0.10[a]	0.41
30 days	1.06 ± 0.07	1.09 ± 0.07[a]	
LDL-cholesterol, mmol/l	n = 17	n = 17	
0 days	2.17 ± 0.19	2.16 ± 0.18	0.37
30 days	1.93 ± 0.15	2.05 ± 0.16	
Triglycerides, mmol/l	n = 17	n = 17	
0 days	2.04 ± 0.40[a]	2.18 ± 0.41[a]	0.49
30 days	2.07 ± 0.35	2.09 ± 0.26	

Data are mean ± SEM. P-value reflects time*treatment effect by two-way repeated measures ANOVA. Plasma values are obtained after an overnight fast. [a] Data is not normally distributed but residuals from the ANOVA fit are normally distributed. n.d., not detectable.

SUPPLEMENTARY DATA

Supplementary Figure 1. Effect of resveratrol on *in vivo* and *ex vivo* mitochondrial function
After 30 days of resveratrol and placebo, a muscle biopsy was obtained from the vastus lateralis muscle. Part of the muscle biopsy was used for evaluation of *ex vivo* mitochondrial function (n=17). (A) ADP-stimulated respiration (state 3) upon parallel electron input into complex I and II. (B) Mitochondrial respiration uncoupled from ATP synthesis (state4o). The other part of the biopsy was used for Western blotting. Total protein extracts were made from the vastus lateralis muscle as previously described (1), and 50 µg of protein was used to determine protein expression of important mitochondrial proteins (n=15). Representative subsets for all mitochondrial proteins are shown. (C) Protein content of the individual complexes of the mitochondrial respiratory chain was quantified by using an antibody cocktail that detects all five complexes (MS601, MitoSciences, Eugene, OR). (D) PGC1α protein content was measured using a polyclonal antibody (Santa Cruz, Heidelberg, Germany). (E) Total and the phosphorylated subunit α of AMPK (#2531 and #2532 Cell Signalling Technology, Inc., Beverly MA, USA) were detected as described (2). The relative expression of actin was used as loading control for the Western blotting (n=15). (F) Muscle oxidative capacity expressed as PCr half-time measured by ^{31}P-MRS after 29 days of resveratrol and placebo supplementation (n=13). Data are presented as means ± SEM. * P <0.05. M, malate; G, glutamate; S, succinate.



SUPPLEMENTARY DATA

Supplementary Table 4. Cardiac function with echocardiography

		Placebo	Resveratrol	P-value
Characteristics				
	HR, bpm	70.00 ± 2.30	74.31 ± 3.14	0.11
	Systolic blood pressure, mmHg	140 ± 2.84	138 ± 2.87	0.09
	Diastolic blood pressure, mmHg	86 ± 1.87	86 ± 1.86	1.00
LV systolic function				
	SV, ml	78.35 (76.88 – 102.02)	78.35 (72.79 – 92.61)	0.14[a]
	CO, L/min	5.90 ± 0.28	5.81 ± 0.37	0.85
	LVEDD, mm	50.00 (48.78 – 52.85)	48.50 (46.95 – 51.17)	0.08[a]
	LVESD, mm	34.88 ± 0.82	33.13 ± 0.93	0.04
	LVFS, %	30.94 ± 0.82	32.41 ± 0.80	0.19
	LVEF, %	58.81 ± 1.29	60.25 ± 1.17	0.35
LV diastolic function				
	E top, cm/s	63.19 ± 3.48	61.06 ± 2.11	0.41
	A top, cm/s	78.63 ± 3.55	80.69 ± 3.79	0.53
	E/A	0.80 (0.71 – 0.89)	0.75 (0.67 – 0.87)	0.36[a]
	E/E'	8.32 ± 0.48	8.23 ± 0.55	0.84
Structure				
	LPVW, mm	9.00 (8.71 – 9.92)	10.00 (9.11 – 9.89)	0.64[a]
	LV mass, gram	181.29 ± 10.50	175.57 ± 8.43	0.50
	LV mass index, gram/m^2	85.07 ± 4.53	82.36 ± 4.00	0.49

Left ventricular systolic and diastolic function measured at day 29 of the placebo and resveratrol intervention (n=16). Data are presented as means ± SEM. [a] P-value relates to non-parametric Wilcoxon Signed Rank test.

HR, heart rate; SV, stroke volume; CO, cardiac output; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; LPVW, left ventricular posterior wall thickness; LV mass, Left ventricular mass.

SUPPLEMENTARY DATA

Supplementary References

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