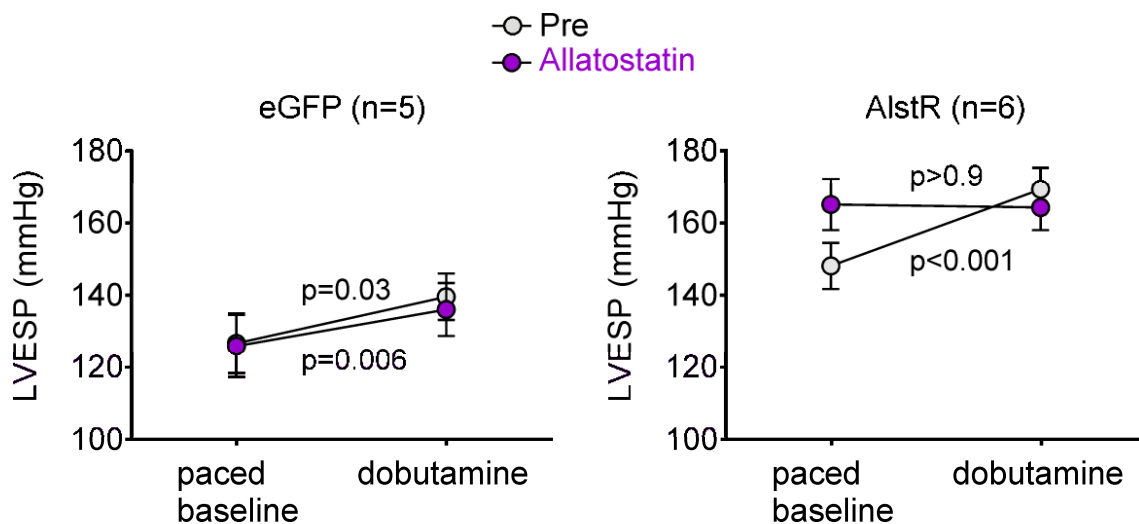
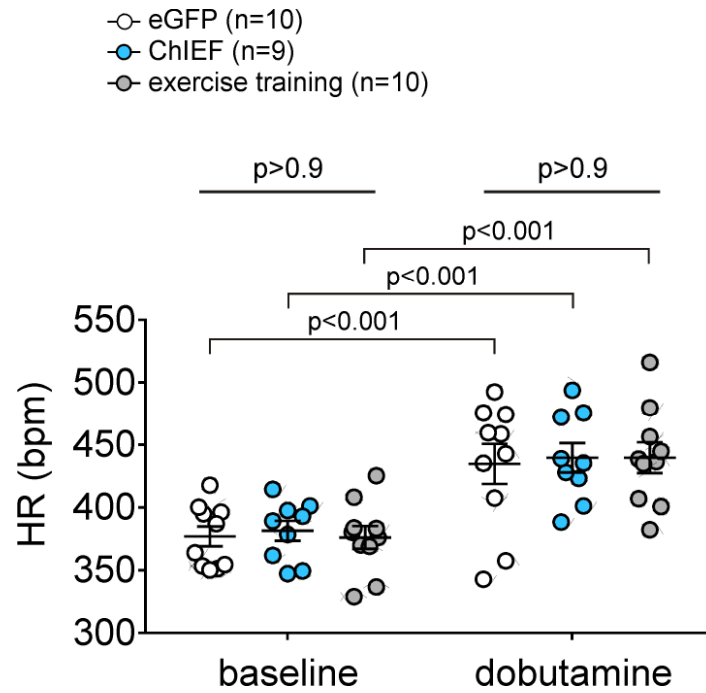


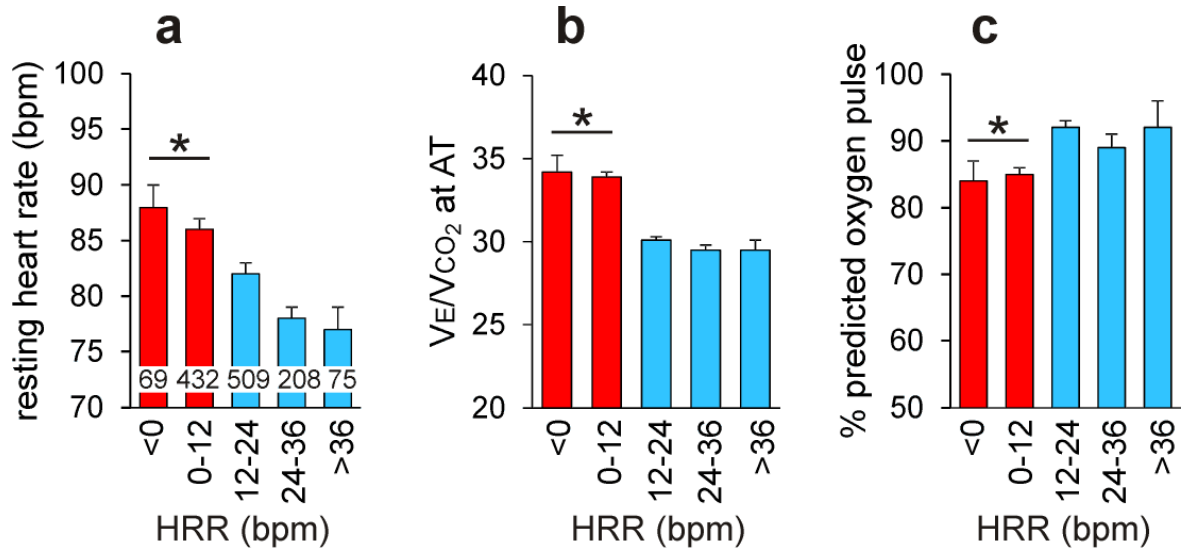
## Supplementary Information



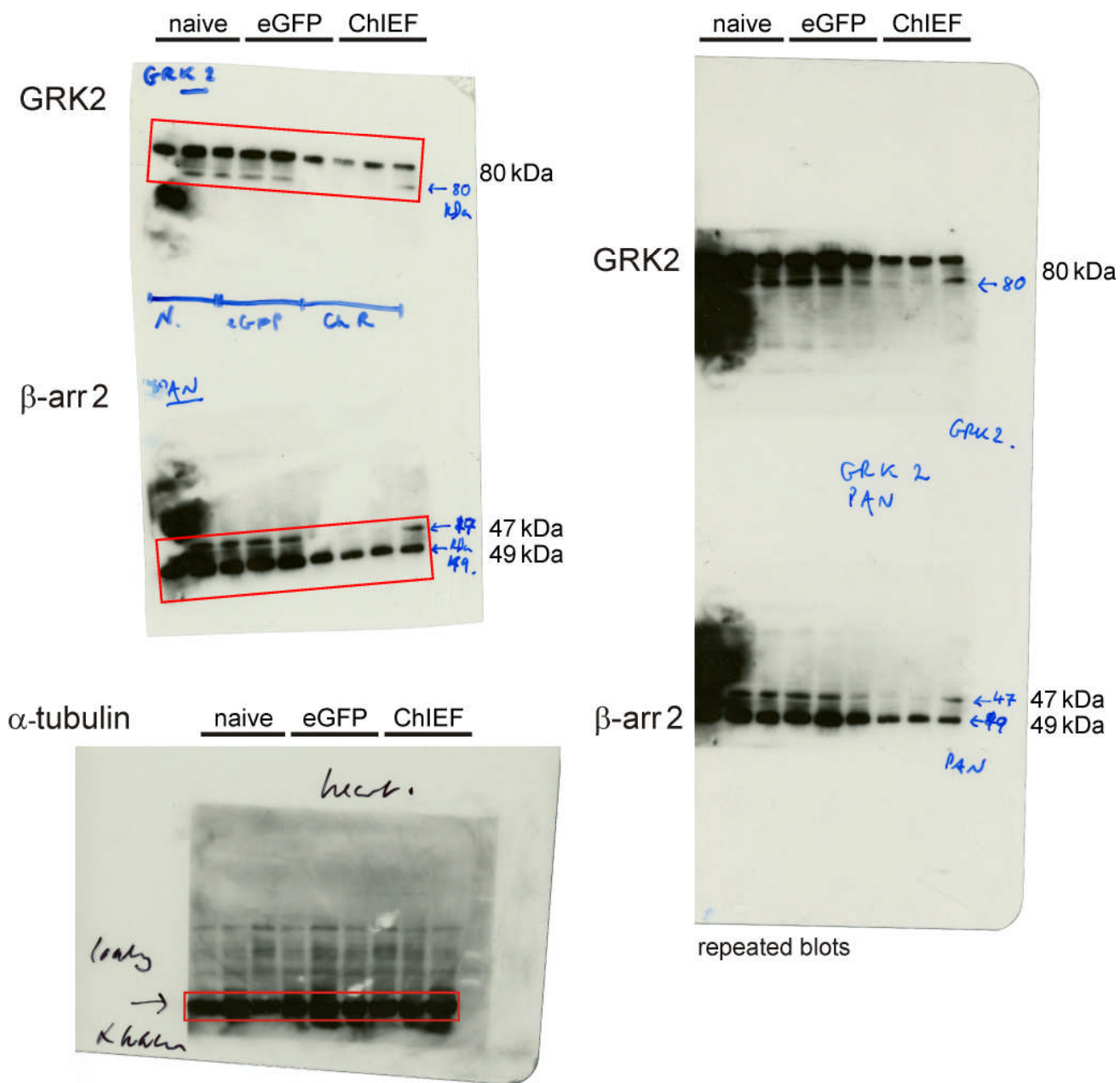
**Supplementary Figure 1** | Summary data illustrating changes in left ventricular end-systolic pressure (LVESP) in response to  $\beta$ -adrenoceptor stimulation (administration of dobutamine) at baseline (paced at 20% above the resting heart rate) and 15 min after allatostatin infusion into the *cisterna magna* in rats transduced to express enhanced green fluorescent protein (eGFP, n=5) or allatostatin receptor (AlstR)/eGFP (n=6) by the DVMN neurons. Data are presented as means $\pm$ s.e.m. Comparisons are made using ANOVA.



**Supplementary Figure 2** | Summary data illustrating baseline heart rate and chronotropic responses to  $\beta$ -adrenoceptor stimulation (administration of dobutamine) in rats transduced to express eGFP (n=10) or ChIEFtdTomato (n=9) by the DVMN neurons after 4 days of 445 nm light stimulation of the dorsal brainstem and in a group of naïve animals (n=10) following 4 daily sessions of treadmill exercise training. Data are presented as individual values and means  $\pm$  s.e.m. Comparisons are made using ANOVA.



**Supplementary Figure 3|** Exercise capacity is reduced in subjects with cardiac vagal dysfunction. (a) Resting heart rate in subjects (n=1293), stratified by heart rate recovery (HRR) 1 minute after cessation of cardiopulmonary exercise testing. Numbers of subjects represented within bars. Resting heart rate is higher in the participants with reduced HRR following exercise. (b) Minute ventilation-carbon dioxide production relationship ( $V_E/V_{CO_2}$  slope) is higher in subjects with lower HRR. (c) Percentage of predicted oxygen pulse achieved is reduced in conditions of vagal dysfunction. Data are presented as means $\pm$ s.e.m. \* $p < 0.001$  (ANCOVA/ANOVA, with post-hoc Tukey-Kramer testing).



Supplementary Figure 4 | Uncropped images of the western blots.

## Supplementary Table 1

### Characteristics of population undergoing cardiopulmonary exercise testing (1293 human participants)

Age: 63±14

Gender: 67% male

Body-mass index: 26.9±5.3

Cardiovascular disease: 45%

Diabetes mellitus: 11.7%

Resting heart rate: 83±16 beats.min<sup>-1</sup>

Peak heart rate: 135±24 beats.min<sup>-1</sup>

% predicted peak VO<sub>2</sub>: 74.7±23.8%

% predicted oxygen pulse: 88.7±28.0%

Ventilatory equivalents, CO<sub>2</sub> at anaerobic threshold: 31.5±5.8

Anaerobic threshold: 11.3±3.2 ml.kg<sup>-1</sup>

ST segment depression during exercise, lead II: -0.6 (-0.3 to -1.1) mm

Borg exertion scale: 15 (14-17)

Duke activity score: 43 (27-54)

## Supplementary Table 2

**Multivariate logistic regression analysis of factors associated with delayed HRR.** On multivariate logistic regression analysis, the only factors associated with delayed HRR were age and diabetes mellitus. Multivariable logistic regression analysis showed no association with any cardiovascular medication.

<b>Independent variable</b>	<b>Regression Coefficient</b>	<b>Standard Error</b>	<b>Wald Z-Value</b>	<b>Wald P-Value</b>	<b>Odds ratio</b>
Intercept	-2.14	0.55	-3.88	0.00	0.12 (0.04-0.35)
Age	0.02	0.01	3.71	<0.001	1.02 (1.01-1.04)
Body-mass index	0.02	0.02	1.00	0.32	1.02 (0.99-1.05)
Female gender	0.23	0.17	1.37	0.17	1.26 (0.90-1.76)
Beta-blocker	0.26	0.25	1.04	0.30	1.30 (0.79-2.12)
ACE inhibitor/ARB	0.12	0.23	0.50	0.62	1.12 (0.71-1.77)
Statins	0.00	0.21	0.01	0.99	1.00 (0.67-1.51)
Diabetes mellitus	0.60	0.25	2.43	0.01	1.82 (1.12-2.94)
Cardiovascular disease	0.13	0.22	0.60	0.55	1.14 (0.74-1.76)