SUPPLEMENTAL MATERIAL

Supplemental Table 1. Univariate Predictors of Exercise Oscillatory Ventilation

Variable	Beta-Coefficient	P-Value
Age	-0.04	0.105
Sex	0.04	0.952
Ischemic	-0.64	0.245
Weight	0.01	0.475
LVEF	-0.052	0.264
RVEF	-0.078	0.014
Beta Blocker	-0.11	0.680
ACE Inhibitor	0.693	0.245
Diuretic	1.75	0.117
ARB	1.01	0.078
Digoxin	0.435	0.421
CRT	0.482	0.448
RER	1.63	0.372
Ventilatory Efficiency	0.048	0.088
Peak VO_2	-0.169	0.045
Heart Rate (Rest)	0.012	0.531
RAP (Rest)	0.158	0.053
PAP (Rest)	0.097	0.010
PCWP (Rest)	0.127	0.004
SBP (Rest)	-0.016	0.170
DBP (Rest)	0.018	0.444
MAP (Rest)	-0.008	0.684
$C(a\text{-}v)O_2$ (Rest)	0.637	0.005
Cardiac Index (Rest)	-2.20	0.007
PaO_2 (Rest)	0.015	0.488
$PaCO_2$ (Rest)	0.022	0.669
pH (Rest)	10.96	0.171
RAP (exercise)	0.02	0.029
PAP (exercise)	0.009	0.053
PCWP (exercise)	0.014	0.027
SBP (exercise)	-0.005	0.020
DBP (exercise)	-0.0004	0.910
MAP (exercise)	0.005	0.132
$C(a\text{-}v)O_2$ (exercise)	0.077	0.006
Cardiac Index (exercise)	-0.33	0.001
PaO_2 (exercise)	0.006	0.066
$PaCO_2$ (exercise)	-0.006	0.460
pH (exercise)	-2.85	0.029

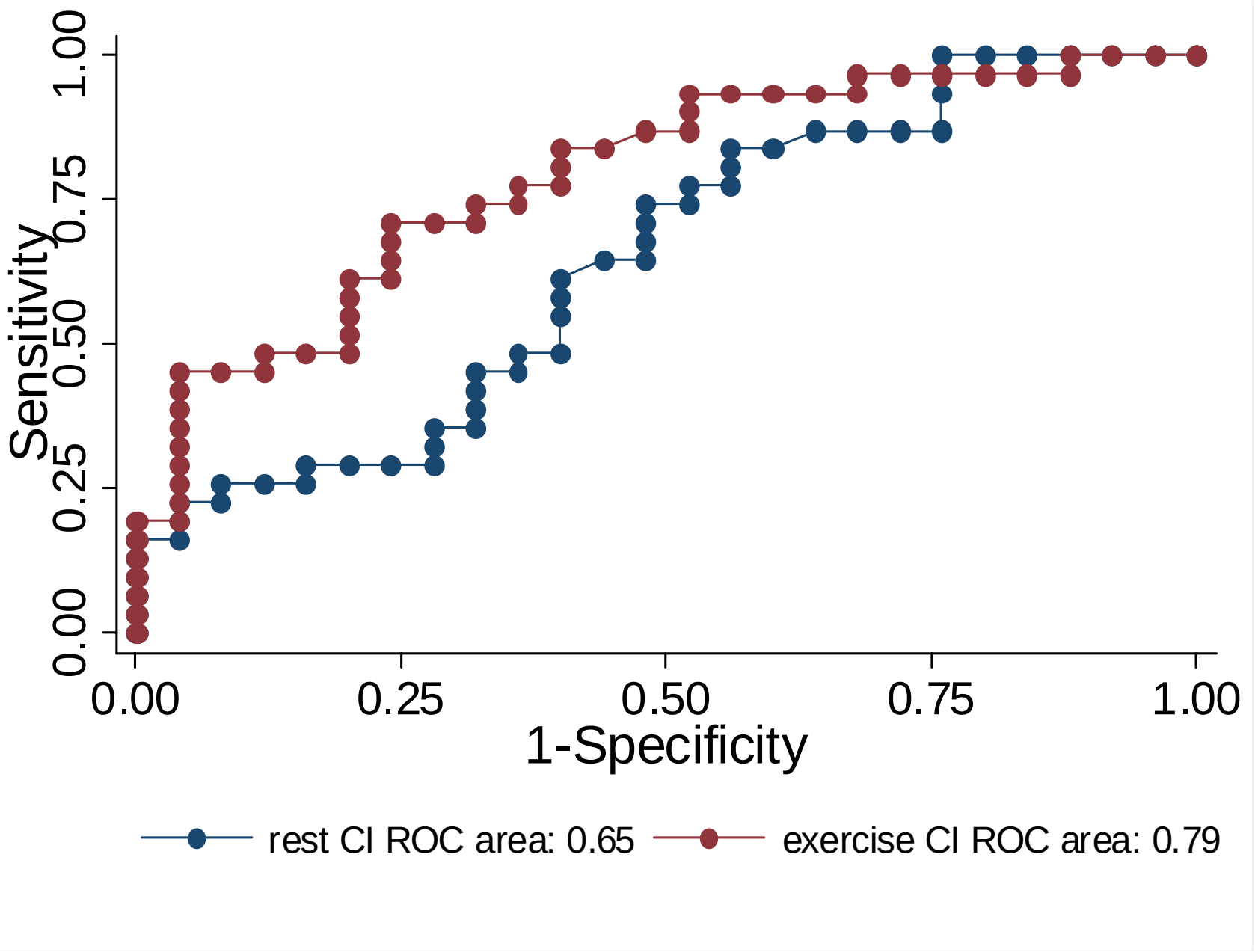
MAP indicates mean systemic arterial pressure; RAP indicates mean right atrial pressure; PAP indicates mean pulmonary arterial pressure; $C(a\text{-}v)O_2$ indicates arterio-venous difference in oxygen content (i.e. oxygen extraction).

Supplemental Figure Legends

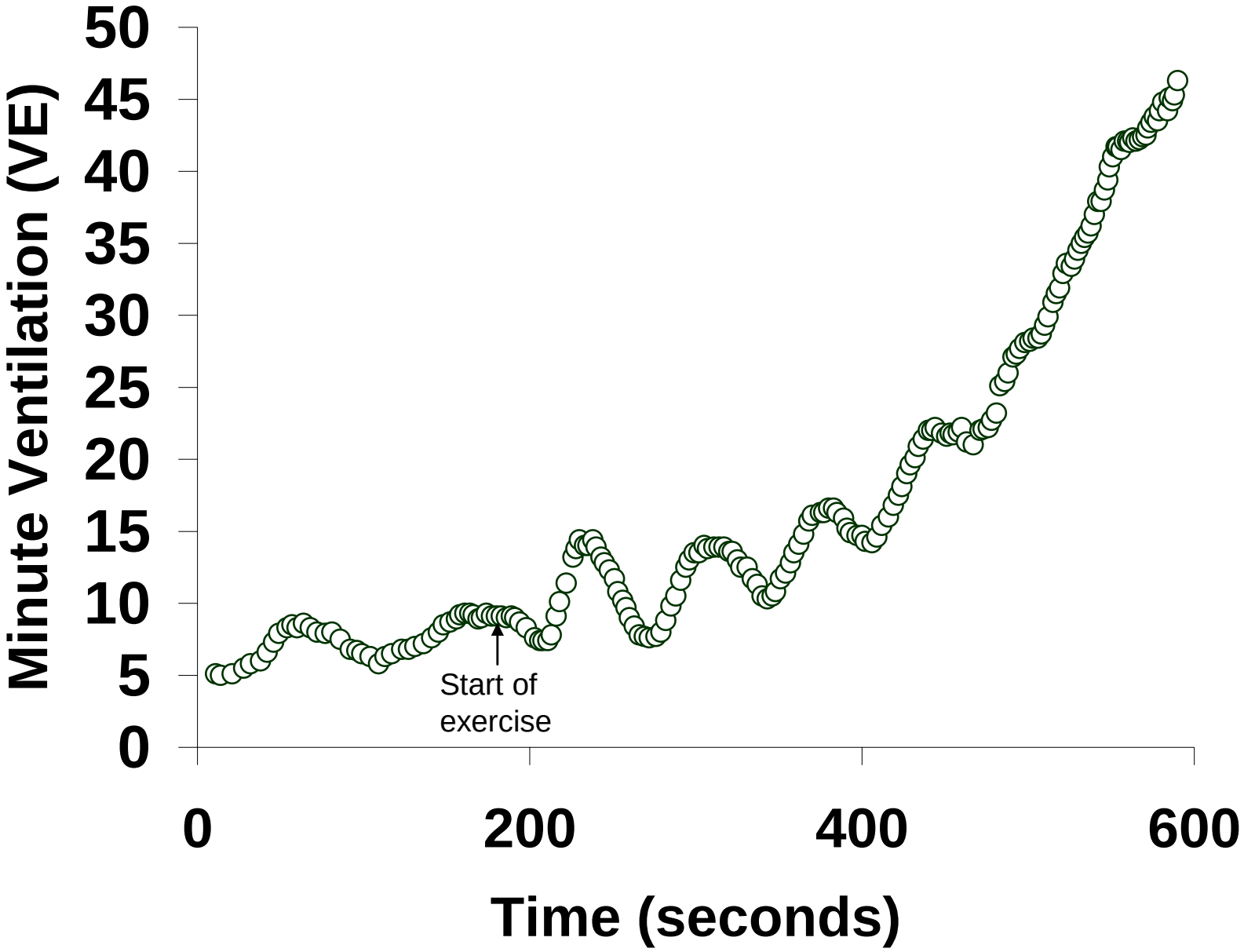
Supplemental Figure 1. Receiver operator characteristic analysis of the relationship between the presence of exercise oscillatory ventilation and cardiac index at rest (blue line) and during exercise (red line).

Supplemental Figure 2. Graphical depiction of resolution of exercise oscillatory ventilation during late exercise in a representative patient.

Supplemental Figure 1



Supplemental Figure 2



Cyclic fluctuations in minute ventilation during exercise, termed exercise oscillatory ventilation (EOV), have been observed in 19-51% of patients with systolic heart failure. When present, EOV potently predicts adverse outcomes in heart failure patients. However, mechanistic insights into EOV have been limited by the absence of studies relating EOV to invasive hemodynamic measurements and blood gases performed during exercise. EOV was present in 45% of HF subjects in this study and was closely related to elevated filling cardiac filling pressures and reduced cardiac index during exercise but not to $PaCO_2$ or PaO_2. Multivariate logistic regression identified that low exercise cardiac index is the strongest predictor of EOV (odds ratio 1.39, for each 1.0 $L/min/m^2$ decrement in exercise CI, 95% confidence interval 1.14-1.70, P=0.001). Among HF patients with EOV, exercise CI was also inversely related to the cycle length (R=-0.71) and amplitude (R=-0.60) of oscillations (both $P<0.001$). EOV cycle length and amplitude decreased proportionate to increases in cardiac index in 11 heart failure patients with EOV who were treated with 12 weeks of sildenafil. Because EOV is an easily recognized, reproducible, non-invasive measurement than can be measured during submaximal exercise testing, it represents an attractive surrogate for exercise hemodynamic measurements, which are invasive and challenging to perform. By indicating an inadequate hemodynamic response to exercise (i.e. impaired cardiac index augmentation, increased filling pressures) independent of left ventricular ejection fraction, EOV may provide not only prognostic information but also an impetus to intensify therapy to optimize cardiac hemodynamics in HF subjects.