Reply to the letter: Particular challenges in the use of pulmonary vasodilating therapy for patients with pulmonary hypertension secondary to left heart disease. Letter regarding the article 'Effects of sildenafil on symptoms and exercise capacity for heart failure with reduced ejection fraction and pulmonary hypertension (the SilHF study): a randomized placebo-controlled multicentre trial'

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We thank Drs Dandel and Hetzer for their interest in our paper[1]. They make several important points and elegantly outline the complexities and controversies of treating patients with pulmonary hypertension secondary to left heart disease (PHT-LHD) with phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil[2]. In our study[1], use of sildenafil for patients with heart failure with reduced ejection fraction (HFrEF) and echocardiographic evidence of PHT, was not associated with improvement in symptoms, quality of life or exercise capacity.

PHD-LHD is a complex entity, characterized by adverse pulmonary vascular remodeling, which might become irreversible and eventually lead to right ventricular dysfunction, aggravating heart failure. We acknowledge that the population enrolled in the SilHF study was highly heterogeneous. In our study, we did not perform right heart catheterisation with measurement of pulmonary resistance but based on the high tricuspid regurgitation velocities measured by Doppler, the high prevalence of atrial fibrillation, the raised natriuretic peptide levels and the reduced ejection fractions of the populations enrolled, it is likely that most had chronically elevated right atrial pressures and post capillary pulmonary hypertension.

A large proportion of patients (56 %) enrolled in SilHF had moderate to severe breathlessness on exertion (NYHA III), usually required treatment with a loop diuretic, and were likely to have a poor prognosis [3-5]. Dandel and Hetzer hypothesise that these patients might have had a different response to sildenafil, compared to those with milder symptoms, as the use of pulmonary vasodilatory therapy, with potential improvements in right ventricular function, could have compounded lung congestion related to the failing left ventricle. As a result, this could be a potential explanation for lack of treatment effect and the high rate of temporary discontinuation of the study medication.

We now compared study outcomes according to NYHA function class. (See table I). There were 30 patients in the NYHA II group and 36 patients in the NYHA III group. We did not find any difference in symptoms as measured by the patient global assessment, quality of life as measured by the Kansas City Cardiomyopathy Questionnaire, exercise capacity as measured by the six-minute walk distance, or pulmonary artery systolic pressure for patients in NYHA class II assigned to sildenafil as compared to those receiving placebo, at 8 and at 24 weeks. Further, we found no interaction between NYHA functional class on outcomes.

There were no differences in temporary withdrawals between patients in NYHA II (n=5, 17%) and patients in NYHA III (n=5, 14%). Three patients in NYHA III died (8%) vs one (3%) of those in NYHA II class.

In conclusion, we found no evidence that patients in NYHA II demonstrated a different response to sildenafil compared to those with more severe symptoms, in terms of treatment effect or tolerability. However, it is important to emphasise that the sample sizes were small and the study was underpowered to detect small changes. Current evidence suggests that chronic treatment with sildenafil in patients with HFrEF[1], preserved left ventricular ejection fraction (HFpEF)[6] or valve disease[7] is not likely to improve clinical status. Whether a subset of those with PHD-LHD might benefit from this treatment remains to be demonstrated.

References

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Table I NYHA II subgroup analysis on outcome measures

Outcome	8 weeks			24 weeks		
	Placebo	Sildenafil	p-value	Placebo	Sildenafil	p-value
VAS						
NYHA II	70.0 (57.5 - 75.0)	75.0 (50.0 - 80.0)	0.37	68.0 (63.8 - 71.2)	70.0 (50.0 - 84.8)	0.67
NYHA III	60.0 (48.8 - 66.2)	60.0 (45.0 - 61.0)	0.97	60.0 (50.0 - 67.5)	59.0 (50.0 - 70.0)	0.88
6MWT						
NYHA II	450.0 (439.0 - 505.5)	400.0 (370.8 - 442.3)	0.51	455.5 (416.5 - 523.0)	435.0 (338.0 - 465.5)	0.85
NYHA III	356.4 (291.0 - 406.4)	375.0 (299.2 - 446.0)	0.30	405.0 (298.1 - 421.6)	375.2 (260.8 - 468.5)	0.54
KCCQ						
NYHA II	75.5 (70.7 - 83.9)	74.7 (66.0 - 91.7)	0.21	74.7 (64.9 - 82.9)	84.4 (55.1 - 96.1)	0.66
NYHA III	66.3 (59.4 - 77.3)	62.5 (35.4 - 71.1)	0.51	75.3 (65.6 - 83.5)	60.0 (40.4 - 74.2)	0.13
PASP						
NYHA II	37.0 (30.0 - 48.0)	38.5 (35.0 - 49.2)	0.53	37.0 (30.0 - 39.0)	42.0 (35.0 - 50.0)	0.12
NYHA III	52.5 (48.5 - 61.8)	41.0 (39.0 - 53.0)	1.00	48.0 (41.5 - 64.0)	40.0 (29.8 - 47.2)	0.42

VAS – Visual Analogue Scale, 6MWT – six-minute walk test, KCCQ-O – Kansas City Cardiomyopathy Questionnaire Overall score, PASP = pulmonary artery systolic pressure, Measurements are presented using the median with the 25^{th} and 75^{th} percentiles.