experience angina during the exercise test, time to angina was estimated from Kaplan–Meier survival curves, and summarised as mean (SEM). All follow-up data were reported as mean (SEM) as we are interested in the precision of the mean estimates.

Next, with regards to the ischaemic burden during exercise tolerance test, this was not an a priori endpoint. As a generalization, one of our concerns regarding the literature in this field is the tendency of studies to report positive secondary outcomes when the primary outcome is negative. This is particularly the case when studies have not been adequately powered for such secondary endpoints. Nevertheless, following the comments of Dr de Vries and colleagues we have analysed these data and can report there is no significant difference between the two groups.

Finally, the SPIRIT acronym was the source of some mirth during the study as participants and workers alike struggled to find the meaning in its form. The origin may be found (with some imagination to be fair) in the Spinal cord stimulation vs. Percutaneous myocardial laser revascularization Randomised Trial.

We thank Dr de Vries and colleagues for their comments. In response, we would like to make the following points.

First, with regards to the study by Tio et al.,1 in our introduction, we did not intend to present a comprehensive review of all treatments for refractory angina, only to highlight the paucity of randomized trial data. Dr de Vries et al. correctly state that there are other randomized studies of spinal cord stimulation (SCS), apart from the ESBY study that we cited in our introduction, that fulfill accepted criteria to be deemed ‘trials.’ However, these other studies suffer from methodological issues that we felt were sufficiently important that their results should best be considered as hypothesis generating rather than supporting. Typically, these studies had small sample sizes (10–12 per group) and no sample size calculation, yet reported multiple outcomes (the study cited, for example, enrolled 12 patients in the SCS group and 13 controls). We should have been more explicit in our reasoning for proposing that the ESBY study was the only randomized trial to support SCS.

Secondly, this study was not powered for within group analyses and there are justifiable concerns that such findings may represent regression to the mean. These data were contained in original submissions but removed as a result of criticism from multiple reviewers.

Thirdly, baseline data were summarized as mean (SD) to enable the population from which these subjects were drawn to be characterized. As some patients did not

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Obstructive sleep apnoea: hypoapnoea syndrome reversibly depresses cardiac response to exercise

As a research team interested in both obstructive sleep apnoea syndrome (OSAS) and exercise physiology, we read with great interest the recent publication of Alonso-Fernandez et al.1 regarding the cardiac response of OSAS patients during exercise and its modification by continuous positive airway pressure (CPAP). We greatly appreciate the design of this study dealing with such a relevant subject. Indeed, metabolic and cardiovascular abnormalities encountered in OSAS may account for exercise intolerance and fatigability reported in these patients.2 Hence, physiological adaptations in OSAS patients at exercise deserve attention. However, we are greatly concerned with the stroke volume (SV) and cardiac output (Qc) values reported in this study. According to Figure 2, at 60% maximal workload, SV reached 200 mL and Qc reached 30 L min⁻¹ in the control group. Such values are surprising and in the same range as that measured in high-level endurance cyclists.3 Taking into account a Qc of 30 L min⁻¹ and assuming a mean oxygen extraction of 0.12 L min⁻¹ at 60% VO₂peak (direct Fick method) in healthy subjects, oxygen consumption recalculation leads to 41 mL min⁻¹ kg⁻¹ (3.6 L min⁻¹, average body weight of 88 kg), a value greater than VO₂peak measured in the control group i.e. an average of 25 mL min⁻¹ kg⁻¹. An extrapolation to maximal exercise intensity would lead to a VO₂peak of 60 mL min⁻¹ kg⁻¹. A part of the Qc and SV values determined in this study is not valid and may weaken the conclusions of this well-designed paper. At first, owing to the apparent overestimation of Qc in controls (but normal in OSAS as Qc = VO₂/(0.0572 + (0.001 shortly VO₂max))]³), the first conclusion stating OSAS is associated with a lower Qc and SV response during exercise may be disputed. Secondly, although the reproducibility of cardiac indexes between baseline and sham-CPAP is very reassuring, the Qc of at least nine subjects treated with CPAP seemed to be greatly overestimated (Figure 3). We cannot assert whether these overestimations would challenge the positive effect of CPAP on cardiac indexes. However, abnormally high Qc values obtained with CO₂ re-breathing method should be taken as indicative rather than definitive evidence that CPAP improved Qc in OSAS patients.

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An open label, single-centre, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris: the SPIRIT trial: reply

We thank Dr de Vries and colleagues for their comments. In response, we would like to make the following points.

First, with regards to the study by Tio et al.,1 in our introduction, we did not intend to present a comprehensive review of all treatments for refractory angina, only to highlight the paucity of randomized trial data. Dr de Vries et al. correctly state that there are other randomized studies of spinal cord stimulation (SCS), apart from the ESBY study that we cited in our introduction, that fulfill accepted criteria to be deemed 'trials.' However, these other studies suffer from methodological issues that we felt were sufficiently important that their results should best be considered as hypothesis generating rather than supporting. Typically, these studies had small sample sizes (10–12 per group) and no sample size calculation, yet reported multiple outcomes (the study cited, for example, enrolled 12 patients in the SCS group and 13 controls). We should have been more explicit in our reasoning for proposing that the ESBY study was the only randomized trial to support SCS.

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We appreciate the comments by Patrice et al. regarding our recent article. As we pointed out, the CO2 rebreathing manoeuvre is an indirect and reliable method to measure Qt, but it may overestimate its values. However, although the agreement interval of Qt during incremental exercise between non-invasive techniques and direct Fick method is ±2-10 L/min, the inaccuracy of the CO2 rebreathing method seems acceptable in previous studies, and it is not higher than that in other indirect procedures.

In our study, we asked the subjects to rebreathe CO2 for ~20 s. The CO2 concentration was ~15% in the last determinations, which is poorly tolerated and it may lead to an increase in the stress level. Thus, the intensity of exercise might be >60% of the theoretical maximum work intensity (W), and it could be comparable with a peak assessment. In fact, VO2 at 60% of W (Figure 2) was actually close to the theoretical VO2 peak (Table 2). Under such conditions, a Qt of 28 L/min is lower than that obtained from the well-trained subjects (36 L/min), and it is only slightly higher than that of sedentary subjects when the direct Fick method is used.

We agree with Patrice et al. that there is a clear relationship between Qt and VO2 during exercise; however, their recalculations should be interpreted cautiously. Predicting Qt from a cardiopulmonary exercise test, i.e. the percentage of predicted VO2 max values, could lead to inaccuracies. In addition, it has been demonstrated that Qt is a non-linear function of VO2 during incremental exercise, and assuming a mean oxygen extraction of 0.12 L/min, VO2 recalculation (41 mL/min/kg) would be concordant with typical values for VO2max recorded in male subjects (40–50 mL/kg/min). However, these values are quite different from the mean VO2 peak of our control subjects (Table 2). We must take into account that the test could have ended prematurely, because the rebreathing of CO2 is uncomfortable to perform during heavier stages of exercise and therefore VO2 peak may be lower than that could be achieved without applying this technique. We also must remember that we used the slope of the relationship between Qt and stroke volume with VO2 and W (instead of absolute values) in order to reduce all these potential limitations.

Finally, it is difficult to accept (in the context of a randomized crossover double-blind-controlled trial) that Qt was overestimated in nine patients only during the CPAP period. Furthermore, on successive studies, we have tried to define who would have a better response to CPAP, and preliminary data suggest that they would be subjects with variable grades of left ventricular diastolic dysfunction.

We thank Patrice et al. for their observations, and we cannot rule out absolutely an overestimation of Qt with a non-invasive method, but we believe that our data are robust enough to maintain the main conclusions of the study.

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