Arterial stiffness by pulse wave velocity in COPD: reliability and reproducibility

To the Editor:

Cardiovascular diseases are the most common cause of mortality in chronic obstructive pulmonary disease (COPD) [1]. Arterial stiffness certainly plays a role in the increased cardiovascular risk of these patients [2, 3]. Arterial pulse wave velocity (PWV) constitutes a useful and safe non-invasive method [4] for assessing central arterial stiffness. The carotid-femoral PWV is considered as the gold standard method by the European Society of Hypertension/European Society of Cardiology [5] and is a strong predictor of future cardiovascular events and all-cause mortality, supporting its implementation into clinical research and daily practice [6]. In patients with COPD, feasibility and validity of this marker of arterial stiffness have been confirmed [2] and PWV is now used in studies evaluating cardiovascular risk and/or the efficacy of new bronchodilators and rehabilitation programmes [3, 7, 8]. However, little is known about its variability and reproducibility studies are lacking in the COPD population.

Here we report on the variability of PWV measurements between baseline, day 15 and day 42 in stable COPD patients. The carotid-femoral PWV was assessed using the Complior device (Alam Medical, Vincennes, France) and pulmonary function, blood pressure, metabolic and inflammatory markers were systematically measured at each evaluation. Pearson or Spearman correlation coefficients and intraclass correlation coefficient (ICC) allowed comparison of PWV at day 0 *versus* day 15 (short-term) and day 42 (middle-term reproducibility). From 62 stable patients enrolled in the study, four patients dropped out (withdrawal of study participation) and 20 patients were excluded from the analysis due to exacerbations during the follow-up evaluations (day 15 and day 42) or absence of at least one of the datasets at day 0, day 15 and day 42. Among the remaining patients, the majority were in Global Initiative for Chronic Obstructive Lung Disease stage II and III, but three patients were in stage I and two patients in stage IV at baseline. 18 (47%) patients presented with a history of at least one cardiovascular risk factor and nine (24%) patients had two or more cardiovascular risk factors.

At baseline (day 0), mean±SD PWV was 11.10±1.91 $m \cdot s^{-1}$, ranging from 7.0 to 14.9 $m \cdot s^{-1}$, with 79% of patients exhibiting abnormal PWV >9.3 $m \cdot s^{-1}$ [6]. During the following evaluations, mean±SD PWV was 11.05±2.17 and 11.24±2.25 $m \cdot s^{-1}$ at day 15 and day 42, respectively. Figure 1 shows Bland–Altman analysis and the correlation analysis of PWV values for short-term (fig. 1a and c, respectively) and middle-term (fig. 1b and d, respectively) variability. For short-term reproducibility, the mean bias was -0.046 $m \cdot s^{-1}$ (fig. 1a), the spearman coefficient was 0.78 ($p<0.0001$) and the ICC was 0.790 (range 0.632–0.885) (fig. 1c), suggesting good reproducibility. For middle-term reproducibility, the mean bias was +0.142 $m \cdot s^{-1}$ (fig. 1b), the Pearson coefficient was 0.76 ($p<0.0001$) and the ICC was 0.749 (range 0.567–0.861) (fig. 1d), also suggesting good reproducibility. Furthermore, no significant differences were found between day 0, day 15 and day 42 in metabolic, inflammatory or oxidative stress biomarkers, suggesting that patients were stable during the three evaluation sessions. At baseline, significant correlations were found between PWV and fasting glucose ($r=0.43$, $p=0.01$), interleukin-6 ($r=0.43$, $p=0.01$) and tumour necrosis factor-α ($r=0.37$, $p=0.02$).

Although the reproducibility of PWV in a 1-day session had already been reported before in healthy subjects or other patient populations [9, 10], between-session variability of aortic PWV measurements was poorly described in the literature. The present study is the first to investigate specifically the reproducibility of aortic PWV over short- and middle-term durations, showing a consistency in carotid-femoral PWV values in COPD patients with stable inflammatory and metabolic status. We found good reproducibility of aortic PWV, with a higher dispersion in patients with an initially high value of PWV (>11 $m \cdot s^{-1}$) in a cone shape, as shown graphically for both periods (fig. 1c and 1d), suggesting that the higher PWV is, the lower reproducibility and, inversely, a very good reproducibility of PWV may be expected when PWV was initially <11 $m \cdot s^{-1}$. Variability of PWV measurements may be indirectly calculated from previous data in already published studies investigating the effects of different interventions (*i.e.* bronchodilators and rehabilitation) on arterial stiffness. In COPD patients, one study aimed at comparing the benefit of fluticasone propionate or salmeterol to a placebo control group on arterial stiffness [7]. Between baseline and 8 weeks, a mean variability in the PWV measurement of +0.13 $m \cdot s^{-1}$ can be estimated from the control group. This is close to our findings for middle-term reproducibility (+0.14 $m \cdot s^{-1}$), suggesting that our measurements are in the same range of variability as the other available data.

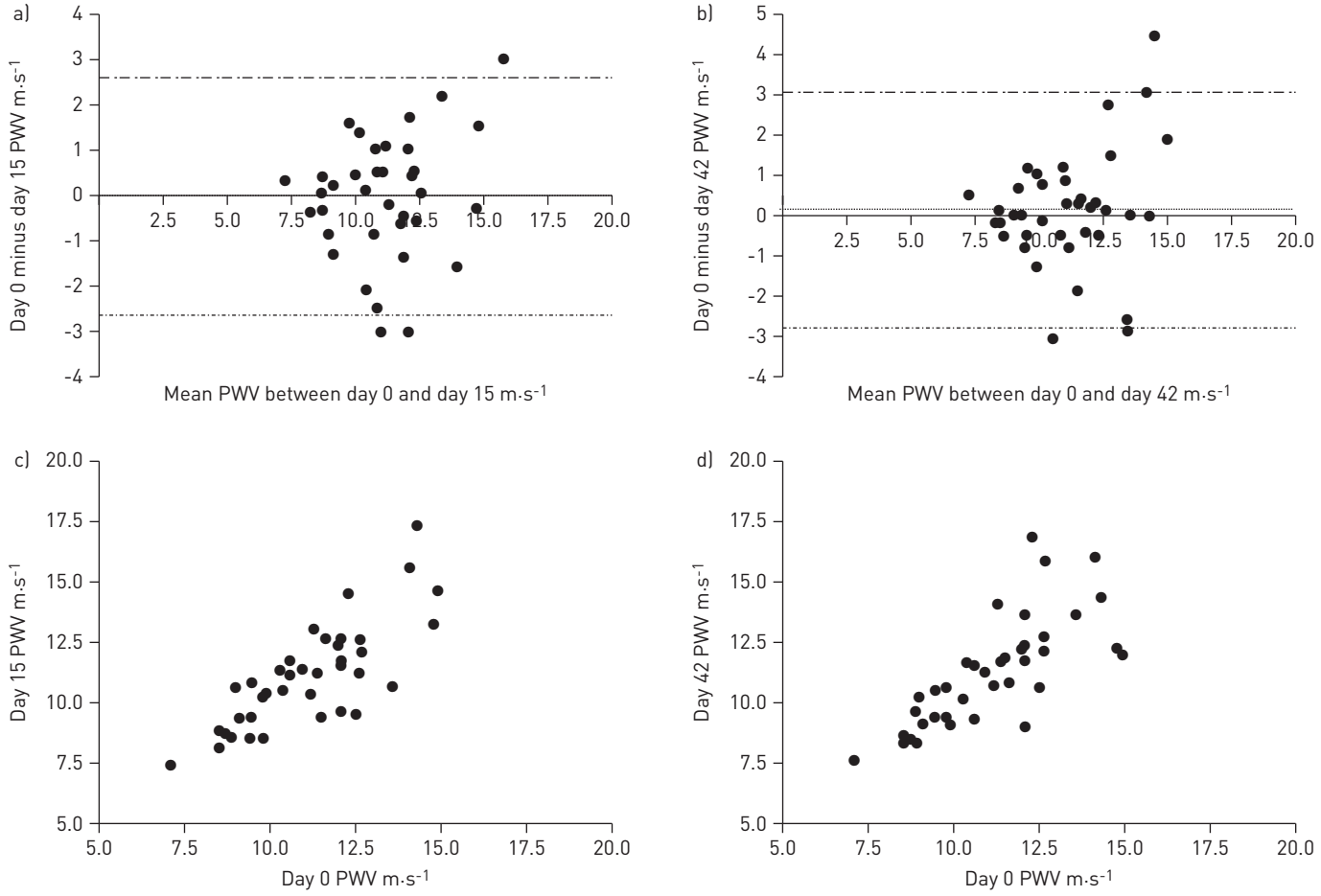

FIGURE 1 a) Bland–Altman comparison of day 0 and day 15 pulse wave velocity (PWV) measurements (short-term reproducibility). Limit of agreement (reference range of differences) were -2.67 and 2.57 $m \cdot s^{-1}$. The mean ± SD bias was -0.046 ± 1.336 $m \cdot s^{-1}$. b) Bland–Altman comparison of day 0 and day 42 PWV measurements (middle-term reproducibility). Limit of agreement (reference range of differences) were -2.77 and 3.06 $m \cdot s^{-1}$. The mean ± SD bias was +0.142 ± 1.488 $m \cdot s^{-1}$. c) Correlation between day 0 and day 15 PWV measurements. Spearman coefficient correlation was r=0.78, p<0.0001. d) Correlation between day 0 and day 42 PWV measurements. Spearman coefficient correlation was r=0.76, p<0.0001.

Considering the link between arterial stiffness and systemic inflammation, one strength of the present study is the assessment of inflammatory parameters at each evaluation session in order to check for any variation. The absence of significant changes in inflammatory biomarkers, antioxidant status and metabolic status between day 0, day 15 and day 42 showed the stability of these parameters during the test-retest period. The 15- and 42-day periods were chosen to mimic the control period of drug treatment as well as short-term rehabilitation programmes.

From a clinical point of view, the present results confirm the reliability of carotid-femoral PWV for comparison of arterial stiffness values before and after a short- to middle-term intervention in COPD. We found a very low mean bias of -0.04 $m \cdot s^{-1}$ for two measurements performed in a 2-week period and moderate mean bias of +0.14 $m \cdot s^{-1}$ for two measurements performed in a 6-week period, in COPD patients in a stable condition. These data constitute a basis for sample size calculation in further COPD studies including arterial stiffness as an outcome.

In conclusion, using the Complior System (Alam Medical), we reported significant reproducibility of measurements of carotid-femoral PWV over time, in stable COPD patients for a 15- and 42-day period. Such assessment of arterial stiffness can be properly used as an objective outcome for randomised trials.

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Significant reproducibility of measurements of carotid-femoral PWV over time, in stable COPD patients http://ow.ly/nsDaV

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No TWEAK for COPD

To the Editor:

The therapy with the greatest functional benefit in chronic obstructive pulmonary disease (COPD) is pulmonary rehabilitation [1]; while the mode of action is probably multifactorial the functional benefit of pulmonary rehabilitation is associated with strength gain in the quadriceps [2]. This suggests that muscle hypertrophy, or countering atrophy, could be at least one of the mechanisms through which pulmonary rehabilitation is beneficial. However, despite the success of pulmonary rehabilitation, there are several occasions in which an effective adjunctive drug therapy might have a place in clinical practice; for example in patients who are too unwell to exercise, in patients unwilling or unable to complete pulmonary rehabilitation, or indeed to magnify or extend benefit in those who do.

In order to conduct stratified medicine studies of future novel anabolic agents for skeletal muscle dysfunction in COPD, biomarkers to identify potential responders will be required. In particular, it is likely that such therapies may be aimed at subsets of patients with COPD rather than, as is the case with most current therapies, targeted at all patients with the condition. In the case of a novel anabolic agent, it is likely that those with skeletal muscle weakness, which is present in ~30% of patients [3, 4], would benefit most and, therefore, should be the subgroup in which a study would be conducted [5].

TNF-like weak inducer of apoptosis (TWEAK, TNFSF12) is an inflammatory cytokine which is a member of the tumour necrosis factor (TNF) superfamily. When chronically overexpressed in a murine model, TWEAK has been reported to cause skeletal muscle wasting through upregulation of E3 ubiquitin ligases [6]. Few data in