The strength of EPC is its holistic approach. This means that this palliative hour is run not only by the pulmonologist but also by a palliative care physician, a psychologist, a social worker, a palliative nurse and a thoracic oncology nurse. Each team member has their own specific domain to discuss. For example, the palliative nurse will empower the patient to talk about the EoL and give more practical information about the different possibilities, such as home care, hospice care, palliative sedation, *etc.* Since this palliative hour is implemented in our standard oncology care, short-notice, unplanned appointments are always possible. Specific problems needing another profession are planned in the patients' ambulatory service (*e.g.* neurologist) and information exchange is linked with the weekly patient discussions.

As mentioned before, the first appointment is always planned with the pulmonologist. This way, we make a clear statement that EPC is integrated into our standard oncology care. The second appointment is with the palliative care physician to discuss topics that have not been covered yet and to check if palliative home care has already started. When making follow-up appointments, we make sure that each team member attends the patient once, to assure better psychosocial support.

In conclusion, we have developed tools for the pulmonologist to implement EPC in daily practice. These tasks mainly consist of assuring adequate symptom control, and transparent communication with patients, relatives and team members. As EPC needs a holistic approach, collaboration with other members of the palliative team is necessary.

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Pulmonologists need to be involved in early palliative care for patients with metastatic lung cancer http://ow.ly/U3oXg

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References

1 Blum T, Schönfeld N. The lung cancer patient, the pneumologist and palliative care: a developing alliance. *Eur Respir J* 2015; 45: 211–226.
2 Temel JS, Greer JA, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; 363: 733–742.
3 Janssens A, Teugels L, Kohl S, *et al.* Integrating early palliative care (EPC) in the management of lung cancer: the role of the thoracic oncologist. *Lung Cancer* 2015; 90: 135–138.
4 Levin TT, Coyle N. A communication training perspective on AND *versus* DNR directives. *Palliat Support Care* 2014; 28: 1–3.

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Paradoxical decrease in isoprostane and increase in superoxide dismutase following CPAP withdrawal in OSA

To the Editor:

Stradling *et al.* [1] have recently published an interesting, unprecedented study assessing the effects of a continuous positive airway pressure (CPAP) withdrawal on oxidative stress in patients already treated for moderate-to-severe obstructive sleep apnoea (OSA). Based on a combination of two different studies, the authors showed that stopping CPAP for 2 weeks ("sham-CPAP" group) significantly decreased the urinary F2-isoprostane concentration, while it increased the activity of the blood superoxide dismutase (SOD),

compared with uninterrupted treatment ("CPAP" group). The fall in urinary F2-isoprostane concentration observed in patients who returned to OSA was contrary to the hypothesis tested by the authors, *i.e.* an increase in oxidative stress when the disease returns. Interestingly, these paradoxical results are corroborated by the strong negative correlation they found between the re-increased oxygen desaturation index values after 2 weeks of CPAP withdrawal and the fall in urinary F2-isoprostane concentration. The authors advanced the hypothesis that intermittent hypoxia for 2 weeks of CPAP withdrawal may have caused a preconditioning protection against oxidative stress.

The fact that a CPAP withdrawal decreased this urinary biomarker of lipid peroxidation is quite unexpected and somewhat questionable. Indeed, on the whole, isoprostane production has been shown to be positively associated with sleep apnoea severity and degree of nocturnal hypoxia, even if some studies did not show such links. Whatever the biological fluid, most studies have shown increased concentrations of isoprostanes in OSA patients compared with control subjects. Above all, CPAP treatment for at least 2 months is effective in decreasing isoprostane concentration in urine, serum, plasma or exhaled breath condensate [2–4]. Consequently, because of their counterintuitive results, STRADLING *et al.* [1] should provide some additional information to reinforce the advanced hypothesis. The first point is about the expression of the urinary F2-isoprostane results. Since renal dysfunction may impact the urinary concentration of biomarkers, urinary F2-isoprostane results should be expressed as pg per mg of urinary creatinine, as usually done [2], and the statistical tests should be reassessed. Furthermore, since intra- and inter-individual variations are known to be consequential for mean concentrations of urinary F2-isoprostane [5] and given the wide standard deviations reported by STRADLING *et al.* [1] it would be more appropriate to show the new results graphically, ideally using a dot-and-line graph detailing each patient. Similarly, superoxide quenching by SOD results from its enzymatic activity, thus SOD measurement in Units·L^{-1} would have been preferable, as usually expressed, and since mass concentration does not augur enzymatic activity [6]. The second point is about the method used for urinary F2-isoprostane quantification, *i.e.* the ELISA kit. Indeed, even if used in many clinical studies, the ELISA method is not the most reliable approach since different kits may give discrepant results [7]. Moreover, the results cannot be compared with those obtained by mass spectrometry, which remains the reference method. The last point is about the pathophysiological mechanism. It has been well-demonstrated in many cell models, animal studies and human diseases that SOD is activated under hyperoxic conditions rather than hypoxia, to counteract superoxide production [8, 9]. Nevertheless, the hypothesis that intermittent hypoxic preconditioning may protect from subsequent ischaemia by increasing antioxidant defence cannot be ruled out. To our knowledge, even if such preconditioning has been demonstrated for SOD activity in cell models, or in renal tissues from rats as cited by the authors [10], it has never yet been shown at a circulating level in human studies. It should be noted that in this reference cited as support, lipid peroxidation was not decreased after such preconditioning, as precisely assessed by renal isoprostane and malonedialdehyde concentrations [10]. Moreover, studies evaluating circulating SOD before and after CPAP in OSA patients are too rare and conflicting, perhaps due to the differences between the subtype of assayed SODs (cytosolic or extracellular Cu, Zn-SOD, and mitochondrial Mn-SOD), or because of pre-analytical and analytical biases regarding SOD measurements. Thus, as with the fall in urinary F2-isoprostane concentration, an increase in SOD activity after 2 weeks of intermittent hypoxia is also debatable. Isoprostanes are oxidised compounds formed *in vivo via* a non-enzymatic mechanism involving the peroxidation of arachidonic acid by overproduction of reactive oxygen species, whereas SOD acts as a major antioxidant by catalysing superoxide transformation into oxygen plus hydrogen peroxide through a dismutation reaction. Thus, given the fall in urinary F2-isoprostane concentrations (∼30%) and the rise in SOD ones (∼30%) one may expect concentrations of both biomarkers to be inversely correlated, which should be analysed by the authors.

To conclude, the deleterious role of oxidative stress in the cardiovascular consequences of OSA has been well-demonstrated. Most studies seem to indicate that CPAP enables lowering of this phenomenon. Consequently, the paradoxical decrease of lipid peroxidation and the rise in antioxidant enzymatic defence observed after a 2-week CPAP withdrawal period are quite unexpected results. This deserves to be reinforced before being reinvestigated in further studies using such interesting approach of treatment withdrawal.

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A comment about the paradoxical variations in oxidative stress biomarkers following CPAP withdrawal in OSA http://ow.ly/Uc33R

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References

1 Stradling JR, Schwarz EI, Schlatzer C, *et al.* Biomarkers of oxidative stress following continuous positive airway pressure withdrawal: data from two randomised trials. *Eur Respir J* 2015; 46: 1065–1071.
2 Del Ben M, Fabiani M, Loffredo L, *et al.* Oxidative stress mediated arterial dysfunction in patients with obstructive sleep apnoea and the effect of continuous positive airway pressure treatment. *BMC Pulm Med* 2012; 12: 36.
3 Alonso-Fernández A, García-Río F, Arias MA, *et al.* Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: a randomised trial. *Thorax* 2009; 64: 581–586.
4 Minoguchi K, Yokoe T, Tanaka A, *et al.* Association between lipid peroxidation and inflammation in obstructive sleep apnoea. *Eur Respir J* 2006; 28: 378–385.
5 Monneret D. Isoprostane as oxidative stress biomarker in the VARIAFIT study: analytical and methodological considerations. *Diabetes Metab* 2014; 40: 316–317.
6 Mamo LB, Suliman HB, Giles BL, *et al.* Discordant extracellular superoxide dismutase expression and activity in neonatal hyperoxic lung. *Am J Respir Crit Care Med* 2004; 170: 313–318.
7 Klawitter J, Haschke M, Shokati T, *et al.* Quantification of 15-F2t-isoprostane in human plasma and urine: results from enzyme-linked immunoassay and liquid chromatography/tandem mass spectrometry cannot be compared. *Rapid Commun Mass Spectrom* 2011; 25: 463–468.
8 Arab A, Wang J, Bausch K, *et al.* Transient hyperoxic reoxygenation reduces cytochrome C oxidase activity by increasing superoxide dismutase and nitric oxide. *J Biol Chem* 2010; 285: 11172–11177.
9 Kinnula VL, Crapo JD. Superoxide dismutases in the lung and human lung diseases. *Am J Respir Crit Care Med* 2003; 167: 1600–1619.
10 Chen CF, Tsai SY, Ma MC, *et al.* Hypoxic preconditioning enhances renal superoxide dismutase levels in rats. *J Physiol* 2003; 552: 561–569.

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From the authors:

We thank Monneret and Bonnefont-Rousselot for their commentary. Our controlled trial design overcomes most of their concerns; any failure of assay techniques would not have produced a biased result, but in fact would have decreased the chances of finding any between-group effects. In our study we observed a statistically significant decrease in urinary F2-isoprostanes following the withdrawal of continuous positive airway pressure (CPAP) treatment in patients with obstructive sleep apnoea (OSA), in a randomised, 2-week trial, where those involved in the assays were entirely blind to group allocation [1]. In addition to this unexpected result, we observed no significant change in any plasma marker of oxidative stress we measured in this population (malondialdehyde and lipid hydroperoxides) or even the production of superoxide radicals by peripheral blood mononuclear cells. It is important to note that these were morning measurements.

Regarding the methods of F2-isoprostane analysis, we used ELISA to measure F2-isoprostane because immunoassays are a widely used alternative for isoprostane analysis. The assay we chose for this measurement (Oxford Biomedical, Oxford, UK) is validated against gas chromatography–mass spectrometry (GC-MS), and shows high correlation between the two methods [2]. Further, measurement by GC-MS is not required, particularly in the setting of interventional controlled clinical trials where paired samples are analysed.

Regarding the correction of F2-isoprostanes for urinary creatinine excretion this is important in measurements of 24 h (or overnight) urine collections to account for dehydration of the participants, and it is less relevant in spot urine measurement of F2-isoprostanes, where measurement of creatinine could on its own introduce further variability. To date, relatively few studies have evaluated biomarker performance by both absolute and normalised concentration, and there is no consensus on how data should be reported [3]. It has also been shown that normalising to creatinine may briefly amplify the biomarker signal soon after a reduction in glomerular filtration rate [4]. Non-urinary creatinine-corrected F2-isoprostane levels are also reported in the literature, as highlighted by another randomised clinical trial which also measured F2-isoprostane in serial urine samples [5].

Regarding the estimation of superoxide dismutase (SOD), this can be derived from the measurement of its enzymatic activity (which is a highly variable assay and it is preferred when assessing acute interventions) or from the measurement of its total concentration (when testing the effects of non-acute interventions that modulate gene expression, such as in our study). In any case, SOD protein levels in plasma may be more reflective of the protein levels in the tissues of interest, rather than its enzymatic activity in the plasma.

The hypoxic/hyperoxic preconditioning mechanism we propose is only advanced as a hypothesis, as this study was not designed to specifically answer this question. As detailed in the paper, this was an exploratory analysis