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Statement of Interest: None declared.

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DOI: 10.1183/09031936.00147111

From the authors:

P. Castiglioni and co-workers suggest that residual excessive sleepiness (RES) in patients with obstructive sleep apnoea (OSA) who are adequately treated with nasal positive airway

pressure may be caused by a concomitant, untreated hypercapnia (if OSA overlaps with obesity hypoventilation syndrome or with chronic obstructive pulmonary disease) or by persistent autonomic subcortical arousals. We examined with interest both hypotheses, but neither fits our series [1]. Concomitant chronic obstructive pulmonary disease was a criterion for exclusion (as was any medical disease that could cause sleepiness *per se*), after reviewing the clinical history and respiratory function tests. As for obesity hypoventilation syndrome, all patients with a body mass index $<30 \text{ kg}\cdot\text{m}^{-2}$ (which represents only half of the sample in the RES group) had arterial blood gases and functional respiratory tests, and none had any hypercapnia (arterial carbon dioxide tension $>45 \text{ mmHg}$) (table 1). In addition, we noted that the patients with RES were thinner, as a mean, than those without sleepiness.

As for autonomic activity, we performed a spectral analysis of the R–R cardiac interval (low and high frequencies) in the three groups of the sample, as suggested. Heart rate spectrograms were obtained by computing R–R interval power spectra over a running data window of 110 s. Spectral powers were calculated in the low- (LF; 0.04–0.14 Hz) and high-frequency (HF; 0.15–0.40 Hz) bands. The ratio between the LF and HF powers of the R–R interval (LF/HF) was taken as an indirect measure of cardiac sympathetic/vagal balance [2]. The LF and HF powers and LF/HF power ratio were averaged over the whole recording. None of these measurements were different between treated OSA patients with and without RES or between patients and controls (table 1). In addition, the autonomic activation index (LF/HF ratio) did not significantly correlate with the residual Epworth sleepiness score (Pearson correlation $r=0.25$, $p=0.17$), residual mean sleep latency in the multiple sleep latency test ($r=-0.16$, $p=0.37$) or fatigue score ($r=-0.07$, $p=0.69$) in the apnoeic groups. Therefore, the association between high LF/HF ratios (indicating high sympathetic activity during the night) and sleepiness (measured by the multiple sleep latency test) previously found in untreated OSA patients [3] was probably related to untreated respiratory events. When respiratory events are efficaciously treated, as in our sample, the LF/HF ratios are similar to those of controls and do not correlate with any measure of sleepiness or fatigue. This new result provides additional evidence to support the concept that residual sleepiness (and in our study, the feeling of nonrestorative sleep) is not the

TABLE 1 Measurements of arterial carbon dioxide tension (PaCO_2) and spectral analysis of the R–R cardiac interval in patients with obstructive sleep apnoea (OSA) with and without residual excessive sleepiness (RES) despite adequate positive airway pressure, and healthy controls

Patients	OSA with RES	OSA without RES	Healthy controls	p-value
Subjects n	20	20	20	
BMI $\text{kg}\cdot\text{m}^{-2}$	$31.3\pm 5.4^*$	$35.4\pm 9.2^\ddagger$	25.2 ± 3.5	<0.001
PaCO_2 mmHg (range)	39.7 ± 4.9 (34–43)	40.3 ± 2.5 (36.6–45)	ND	0.86
LF ms^2	369 ± 291	458 ± 577	379 ± 277	0.80
HF ms^2	366 ± 687	504 ± 774	290 ± 260	0.62
LF/HF	2.47 ± 2.13	1.5 ± 1.18	2.38 ± 1.85	0.21

Data are presented as mean $\pm$ SD, unless otherwise stated. BMI: body mass index; LF: low-frequency power for R–R interval; HF: high-frequency power for R–R interval; ND: not determined. *: $p<0.05$ for OSA patients with versus without RES; ‡ : $p=0.05$ for OSA patients without RES versus healthy controls.

consequence of a subtle alteration of the sleep structure by an abnormally high sympathetic activity.

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Statement of Interest: Statements of interest for V. Attali, E. Frija-Orvoen and M. Pottier can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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DOI: 10.1183/09031936.00153311

Viral wheezing is virus specific and not just host specific

To the Editors:

In a recent issue of the *European Respiratory Journal*, STRIPPOLI *et al.* [1] reported their interesting findings on exclusive viral wheezing *versus* allergic wheezing in a large population-based, prospectively followed cohort including 4,102 children at 1 yr and 1,858 children at 9 yrs of age. The parents reported current wheezing in 36, 20, 16 and 16% of the children at age 1, 4, 6 and 9 yrs, respectively. The study showed considerable age-related, parent-reported changes in the relative importance of triggers for wheezing in children. The proportion of infection decreased constantly from 94.1% (at age 1 yr) to 81.0% (at age 9 yrs) and the proportion of allergic wheeze increased constantly from 7.5% (at age 1 yr) to 62.4% (at age 9 yrs). The proportion of exercise as a trigger for wheezing was rather similar at all ages, being lowest (35.5%) at age 1 yr and highest (48.6%) at age 6 yrs.

The association between exercise and allergens as triggers for wheezing was significant at age 1, 4 and 6 yrs, and between exercise and infection at age 1, 6 and 9 yrs. Conversely, allergens and infection were not associated at any age; the association was even negative (OR 0.54; $p=0.051$) at age 6 yrs. Thus, the authors confirmed positive associations between exercise and allergens, and between exercise and infection as triggers for wheezing, but there were no positive associations between allergens and infection at any age. The authors concluded that exclusive viral wheezing and allergen-induced, multiple-trigger wheezing are distinct disease entities presenting in genetically different children [1].

The findings are in agreement with those from post-bronchiolitis studies [2], and with clinical experience as well. If bronchiolitis is defined as wheezing-associated respiratory infection at age <24 months, post-bronchiolitis wheezing during subsequent viral infections is common. In long-term, prospective post-bronchiolitis studies, 60% of the former bronchiolitis patients

have wheezed at age 2–3 yrs and 15–40% have had doctor-diagnosed asthma at school age [2]. However, if bronchiolitis has been caused by respiratory syncytial virus (RSV) [2], or has taken place at age <6 months when RSV is the predominant causative agent [3], later asthma seems not to be substantially more common than in the non-selected population. Doctor-diagnosed asthma was present at age 6.5 yrs in 12.7% of the 166 children hospitalised for bronchiolitis at age <6 months. The figure was 8.2% in the former RSV patients *versus* 24% in the former non-RSV patients [3].

Asthma in parents and atopy in infants are the most strong and consistently documented risk factors for later chronic asthma after bronchiolitis or early-life wheezing [2]. In addition, the virus that is associated with the first wheezing episode may play an important role, either by modifying the course or outcome of early-life wheezing, or by picking up those who are prone to asthma and actually have their first asthma episode in infancy. Rhinovirus-induced wheezing, in particular, seems to be associated with atopy, eosinophilia and later asthma [4]. Bocavirus is nearly equally as common as RSV and rhinovirus in wheezing infants and young children, but its role as an independent aetiological agent in children with respiratory infection and its association with later outcomes are still unknown [5]. Thus, children with viral wheezing, even those with exclusively viral wheezing, merely form a genetically heterogeneous, rather than a genetically homogenous, group. In future studies, the group of children with viral wheezing should be analysed as stratified into virus-specific categories allowing the evaluation of the interaction between viral and genetic factors, such as atopy or components of innate immunity.

The observation of STRIPPOLI *et al.* [1] that there was no association between allergens and symptomatic infections as triggers for wheezing in children is important and provides evidence that exclusive viral wheezing is its own disease entity