From the authors:

S. Andreas asks two questions about dysfunction of the autonomic nervous system in chronic obstructive pulmonary disease (COPD). Does it occur? And if it does, why? To clarify our response, we add a third question: what are the clinical implications of autonomic dysfunction in COPD?

Regarding the question whether autonomic dysfunction occurs in COPD, there is accumulating evidence for sympathetic activation and sympathovagal imbalance in COPD [1, 2]. There is also growing support for the presence of sympathetic [3, 4] and parasympathetic neuropathy [5] in COPD.

Why does sympathetic activation occur [1, 2]? Potential mechanisms include activation of the limbic system by the perception of respiratory discomfort, muscle metaboreflexes and altered lung inflation reflexes [1, 2, 6]. Another possible mechanism is right atrial distension [6].

Why does autonomic neuropathy occur? In the most severe cases of COPD, we agree with S. Andreas that autonomic neuropathy might be caused by intraneural hypoxaemia [5]. We also agree that it is difficult to postulate a mechanistic role of hypoxaemia in the development of autonomic imbalance in patients who are normoxic [1, 3], unless decreased oxygenation during exercise and sleep [2] are sufficient to cause critical levels of intraneural hypoxaemia. If not hypoxaemia, what other factors could cause autonomic neuropathy? In patients with cardiac disease [7], type 1 diabetes mellitus [8] and cirrhosis-hepatic encephalopathy [9], a link between low-grade inflammation and autonomic neuropathy has been proposed. These observations raise the possibility that low-grade inflammation [10] could be linked to autonomic neuropathy in COPD.

What are the implications of autonomic dysfunction in COPD? Parasympathetic neuropathy can increase vasopressin and thus increase tubular reabsorption of solute-free water [10]. Sympathetic neuropathy could explain why hypercapnia can cause a (direct) decrease in peripheral vascular resistance rather than an (indirect) increase secondary to sympathetic stimulation [10]. Autonomic dysfunction may thus contribute to the fluid retention seen in patients with COPD and associated with a poor prognosis [10]. In addition, heightened sympathetic activity, through the stimulation of the renin–angiotensin–aldosterone system, can participate in sodium reabsorption [11]. Heightened sympathetic activity might also contribute to dyspnoea, exercise intolerance and increased cardiovascular morbidity and mortality [2]. Autonomic neuropathy has been suggested as an independent risk factor for sudden cardiac death in diabetic patients [12]. Whether the same is true for patients with COPD is unknown. Should attempts to modulate autonomic tone be a goal of therapy in COPD? The current understanding of autonomic dysfunction is not sufficient to formulate any recommendation.

F. Laghi*,#, N. Adiguzel¶ and M.J. Tobin*,#
*Division of Pulmonary and Critical Care Medicine, Edward Hines Jr VA Hospital, Hines, and #Loyola University Stritch School of Medicine, Maywood, IL, USA. ¶SB Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey.

Correspondence: F. Laghi, Pulmonary and Critical Care, Loyola University Chicago, Building 54 Room 131A, 2160 South First Ave, Maywood, IL, USA. E-mail: flaghi@lumc.edu

Statement of Interest: None declared.

REFERENCES

1 Raupach T, Bahr F, Herrmann P, *et al.* Slow breathing reduces sympathoexcitation in COPD. *Eur Respir J* 2008; 32: 387–392.
2 Andreas S, Anker SD, Scanlon PD, *et al.* Neurohumoral activation as a link to systemic manifestations of chronic lung disease. *Chest* 2005; 128: 3618–3624.
3 Chhabra SK, De S. Cardiovascular autonomic neuropathy in chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 126–133.
4 Chen WL, Chen GY, Kuo CD. Hypoxemia and autonomic nervous dysfunction in patients with chronic obstructive pulmonary disease. *Respir Med* 2006; 100: 1547–1553.
5 Stewart AG, Waterhouse JC, Howard P. Cardiovascular autonomic nerve function in patients with hypoxaemic chronic obstructive pulmonary disease. *Eur Respir J* 1991; 4: 1207–1214.
6 Naeije R, van de Borne P. Clinical relevance of autonomic nervous system disturbances in pulmonary arterial hypertension. *Eur Respir J* 2009; 34: 792–794.
7 Janszky I, Ericson M, Lekander M, *et al.* Inflammatory markers and heart rate variability in women with coronary heart disease. *J Intern Med* 2004; 256: 421–428.
8 Gonzalez-Clemente JM, Vilardell C, Broch M, *et al.* Lower heart rate variability is associated with higher plasma concentrations of IL-6 in type 1 diabetes. *Eur J Endocrinol* 2007; 157: 31–38.
9 Mani AR, Montagnese S, Jackson CD, *et al.* Decreased heart rate variability in patients with cirrhosis relates to the presence and degree of hepatic encephalopathy. *Am J Physiol Gastrointest Liver Physiol* 2009; 296: G330–G338.
10 Laghi F, Adiguzel N, Tobin MJ. Endocrinological derangements in COPD. *Eur Respir J* 2009; 34: 975–996.
11 de Leeuw PW, Dees A. Fluid homeostasis in chronic obstructive lung disease. *Eur Respir J* 2003; 22: Suppl. 46, 33s–40s.
12 Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; 115: 387–397.

DOI: 10.1183/09031936.00181509