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Systemic inflammation and progression of COPD

# Systemic inflammation and progression of COPD

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## The role of C-reactive protein

C-reactive protein (CRP) is considered one of the key markers of systemic inflammation in chronic obstructive pulmonary disease (COPD) and currently receives a lot of attention. In their systematic review of systemic inflammation in COPD, Gan *et al* showed that CRP was associated with the level of forced expiratory volume in 1 s (FEV<sub>1</sub>) in the five studies included in the review,<sup>1</sup> and two recent studies using fairly large populations of well-characterised patients with COPD have shown a strong association between increased CRP levels and prognosis.<sup>2,3</sup> Sin and Man have previously shown that raised levels of CRP were associated with cardiac injury in COPD<sup>4</sup> but, in the two recent studies, the association between CRP and mortality was not merely driven by an associated risk of cardiovascular deaths.<sup>2,3</sup>

In this issue of *Thorax* (see p 515) Fogarty *et al* examine the association between CRP and FEV<sub>1</sub> in more detail.<sup>5</sup> Using data on 2633 randomly selected adults from Nottingham in 1991 and followed up in 2000, they looked at both cross-sectional and longitudinal associations between CRP and FEV<sub>1</sub>. At both the 1991 and 2000 survey there was a clear inverse association between the level of FEV<sub>1</sub> and CRP, with a difference in FEV<sub>1</sub> between the highest and lowest deciles of CRP of 381 ml and 259 ml in 1991 and 2000, respectively. The association was strongest in underweight subjects, defined as those with a body mass index (BMI) <20 kg/m<sup>2</sup>. Data from 1343 subjects were available for analyses of FEV<sub>1</sub> decline and, in this population, there was no association between CRP at either time point and 9 year change in FEV<sub>1</sub>.

There are currently only limited data with which to compare these findings. In a smaller French study of 531 subjects, there was a tendency towards a steeper decline in FEV<sub>1</sub> over the 8.5 year follow-up in the

tertile with highest CRP at baseline (p = 0.14).<sup>6</sup> In this study by Shaaban *et al*, subjects with increasing CRP levels during follow-up had steeper declines in FEV<sub>1</sub> than those with stable or decreasing CRP levels, but it is not possible to imply causality from associations between parallel changes. Other markers of systemic inflammation do not seem to help us much. Dahl *et al*<sup>7</sup> looked at fibrinogen in a Danish cohort and found an association between fibrinogen level and level of FEV<sub>1</sub>, preceding decline in FEV<sub>1</sub> and subsequent hospital admission. In fact, based on these findings it would be tempting to look at systemic inflammation more as a consequence of COPD than an active component alongside inflammation in the airways and lung parenchyma. An indicator of an effect of systemic inflammation on decline in lung function comes from a clinical study of COPD patients with and without hepatitis C.<sup>8</sup> In this study, Kanazawa *et al* found a steeper decline in FEV<sub>1</sub> in patients with hepatitis C than in uninfected controls, independent of smoking habits. In addition, patients with hepatitis responding to interferon- $\alpha$  treatment had slower declines than those not responding, a response defined as disappearance of HCV RNA. Although the number of patients was very limited (59 in total), these findings leave open the possibility that systemic inflammation may be linked to progression of airflow limitation.

The systemic effects of COPD are more straightforward than the role of systemic inflammation on disease progression. In particular, weight loss and loss of fat-free mass become increasingly apparent with increasing severity of COPD, and both a low BMI and a low fat-free mass index have been shown to be strong predictors of mortality in COPD.<sup>9–11</sup> Studies have linked systemic inflammation with loss of both body mass and fat-free mass<sup>11–14</sup> but, in the largest study,<sup>11</sup> the association did

not seem impressive and it is likely that other factors also play a role for weight loss. Bolton *et al*<sup>15</sup> found a strong association between markers of systemic inflammation and loss of fat-free mass as well as bone density, but the severity of the patients studied (mean FEV<sub>1</sub> 1.0 litres) makes it difficult to determine whether the findings seen are anything but the consequences of disease progression. Whether the fact that fat-free mass depletion is seen even in early disease<sup>11</sup> indicates a role for systemic inflammation earlier than suggested above—at least in a subgroup of patients—remains to be seen.

In the most recent GOLD guidelines there has been more emphasis on extra-pulmonary effects as part of COPD, and systemic features are included in the chapter on pathology, pathogenesis and pathophysiology. It is very likely that systemic inflammation plays a key role in the development of systemic manifestations of COPD and that this should impact on our approach to the disease as suggested in a recent review.<sup>16</sup> However, as the study by Fogarty *et al* shows, we are still far from fully understanding the role of systemic inflammation in COPD.

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## Unsuspected pulmonary embolism on CT scans

# Unsuspected pulmonary embolism on CT scanning: yet another headache for clinicians?

Sujal R Desai

## Arguments for and against treatment of small unsuspected pulmonary emboli

Clinicians have long known that the symptoms and signs of pulmonary embolism are non-specific and that, unless the index of suspicion is reasonably high, the diagnosis is frequently overlooked. Against this background, clinically unsuspected pulmonary emboli are increasingly being spotted by radiologists on CT scans. Clinicians not only need to be aware of this, but also need to know how to deal with such serendipity. The quality of CT examinations has improved unimaginably; image acquisition, particularly with the new generations of multidetector CT (MDCT) machines, is now astonishingly fast and access to CT scanning has increased. The entire thorax can now be covered in a single breath-hold, and image degradation due to respiratory and cardiac motion is no longer a major issue. Furthermore, because of narrow collimation, images with exquisite spatial resolution are almost the norm and visualisation of opacified peripheral pulmonary arteries (down to fifth order branches) is now possible.<sup>1,2</sup>

The detection of unsuspected pulmonary emboli by CT scanning has been the subject of a number of previous reports.<sup>3–8</sup> The prevalence of incidental emboli in these studies has varied from 0.6% to 5% and has depended to a large degree on the tests used for detection (single-slice CT vs MDCT vs echocardiography), the manner in which images were reviewed (hard copy vs workstation analysis) and the

demographics of the study population (cancer vs non-cancer or inpatient vs outpatient).<sup>3–9</sup>

In the current issue of *Thorax* (see p 536), another study documents the prevalence of incidental pulmonary emboli in consecutive inpatients undergoing MDCT scanning.<sup>10</sup> Most patients were imaged on a 16-channel CT machine and, following the routine report, all studies were reviewed by an experienced thoracic radiologist unaware of the original findings. In nine out of 28 studies judged positive by the expert reviewer, filling defects were overlooked by the initial reporting radiologist but, in these patients, emboli were localised to the segmental (n=6) and subsegmental (n=3) vessels. Overall, emboli unsuspected at the time of referral were found in 28 of 487 (5.7%) scans. This figure is broadly comparable to the inpatient prevalence of unsuspected emboli in previous CT studies: in two reports comprising 634 inpatients the prevalence of unsuspected filling defects was 4.3%.<sup>7,8</sup> An interesting aspect of the present study, implied but not stressed in earlier series, was the significant relationship between the likelihood of unsuspected pulmonary embolism and age. Unsuspected emboli were not detected in any of the patients aged below 50 years (n=47), whereas incidental filling defects were present in almost 17% of those aged over 80 years (n=66). The authors suggest that age may have been a

surrogate for other relevant risk factors. However, an alternative explanation is that pulmonary emboli might simply be missed in the elderly because of the tendency to ascribe symptoms to age-related comorbidity.

The links between cancer and venous thromboembolism are widely acknowledged and one theme of earlier publications on incidental pulmonary emboli has been the emphasis on a background of malignancy. In the studies reported by Gosselin *et al*<sup>7</sup> and Storto *et al*<sup>8</sup> there was a history of malignant disease in 70% and 83% of patients, respectively. At first sight these results seem to imply that radiologists should be on the lookout for clinically unsuspected pulmonary emboli in patients with cancer. However, the published data warrant closer scrutiny for there is an intrinsic bias: patients with cancer are just more likely than those without to have a CT examination because of the need for pretreatment staging, to say nothing of the further surveillance CT studies needed to monitor treatment response or detect relapse. It is therefore perhaps unsurprising that patients with malignancy account for a larger proportion of those with unsuspected pulmonary embolism on CT scans. It is noteworthy that clinically unsuspected emboli were seen in fewer than 10% of the 81 patients with cancer in the study by Gosselin *et al*.<sup>7</sup> The experience at tertiary cancer centres is similar: the prevalence of non-suspected pulmonary embolism was only 4% (16/403 patients) in a recent study published from the M D Anderson hospital.<sup>11</sup> Importantly, the results presented by Ritchie and colleagues show, for the first time, that there are no significant differences in the prevalence of incidental pulmonary embolism between patients with and without malignancy (18/343 (5.2%) vs 10/144 (6.9%)). Thus, two points emerge: (1) despite the high prevalence of malignancy in patients with incidental pulmonary embolism, the converse scenario (that patients with cancer are more likely to have unsuspected pulmonary emboli) does not necessarily follow; and (2) the demonstration of incidental emboli