Recovery pathway of post-SARS patients

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The recovery pathway of SARS survivors mirrors that of ARDS patients in several respects

The article by Hui *et al* in this issue of *Thorax*[1] and an earlier article in *Thorax* by Ng *et al*[2] on the longer term functional state of patients who have recovered from severe acute respiratory syndrome (SARS) have arrived in a timely fashion for two reasons. Firstly, as survivors of the global epidemic which shocked the world in 2003, patients who have recovered from SARS are certainly an important source of world knowledge on the longer term impact of the illness on the health of those affected. Secondly, there has recently been renewed interest in the long term outcome of patients who have survived acute respiratory distress syndrome (ARDS), as evidenced by seven studies published since 2000 on patient outcome following an episode of ARDS.[3–9]

WHY IS SARS PUT IN THE SAME LIGHT AS ARDS?

The question of whether SARS is just ARDS has been asked since the 2003 outbreak.[10] Indeed, the more severe form of SARS does resemble ARDS, with both being a process of acute lung injury extensively involving the lungs, causing severe gas exchange impairment and requiring intensive care and ventilatory support. The recovery potential of the lungs in SARS patients may closely follow the recovery potential of ARDS patients. However, one needs to keep in mind that only about 30% of SARS patients in the cohorts reported by Hui *et al* and Ng *et al* had spent time in the intensive care unit (ICU), ventilated or otherwise. Any fair comparison of the lung recovery pattern between the two diseases should theoretically be restricted to a comparison between ventilated ARDS patients and ventilated SARS patients, both preferably having been subjected to similar ventilatory strategies to minimise the confounding effect of the well described phenomenon of ventilator-associated lung injury (VALI).

RECOVERY OF LUNG FUNCTION

It is therefore reassuring to see in the study by Hui *et al* that, at 6 months, there was no difference in the lung function parameters between the ICU non-intubated SARS patients and the ICU intubated SARS patients, suggesting either that VALI did not contribute to pulmonary outcome at 6 months or that the present day practice of lung protective strategy was effective in preventing VALI. However, one should be cautioned against reading too much into these data as the numbers of subjects in each arm were small (six and 25, respectively). Indeed, there was a subtle (albeit insignificant) difference in the carbon monoxide transfer factor (TLCO) between the non-intubated ICU group and the intubated group, with a lower median TLCO in the latter. The latter group also had a significantly higher peak level of lactate dehydrogenase which has been reported to be a marker of SARS severity,[11] rendering a more severe disease as the more likely explanation for the relatively low TLCO at 6 months. VALI did not appear to have any detectable impact on lung recovery potential in the cohort studied by Hui *et al*.

Based on the lung function findings reported by Hui *et al*, what is currently known about pulmonary morbidity following ARDS can be applicable to post-SARS patients: ''pulmonary function returns to normal or is nearly normal by 6 months to 1 year, with the exception of a persistent reduction in carbon monoxide diffusion capacity''.[3] Hui *et al* reported that 15.5% of their patients had impaired TLCO and a 7.3% reduction in lung volumes at 6 months. In the same study about a quarter of the patients were found to have respiratory muscle weakness at 3 months, suggesting extrapulmonary pathology for the reduction in lung volumes. Ng *et al*, however, reported a higher proportion of post-SARS patients with pulmonary function impairment at 6 months, with 35% having impaired TLCO and 28.1% having a reduction in lung volumes. It is not clear why the patients studied by Ng *et al* had more pulmonary sequelae than those studied by Hui *et al*. A detailed comparison of the two cohorts in terms of severity of illness during the SARS episode, the proportion of ventilated patients, the issue (or non-issue) of VALI, the different reference ranges used for the pulmonary function parameters*, as well as the proportion of patients with respiratory muscle weakness may render a crude comparison of the provided figures not advisable. All in all, it does appear that most post-SARS patients had a favourable pulmonary outcome similar to post-ARDS patients.

RECOVERY OF FUNCTIONAL CAPACITY AND QUALITY OF LIFE

Aside from pulmonary considerations, SARS resembles ARDS in yet another important dimension. In a study by Herridge *et al*[3] of post-ARDS patients, the median 6 minute walk distance improved steadily during the 12 months but did not reach normal values, and the median score for the physical role domain in a quality of life survey revealed a level one third that of the normal population at 12 months; both these findings suggest generalised muscle weakness. The investigators went on to postulate that the observed muscle wasting and weakness in ARDS survivors is multifactorial and may be due in part to corticosteroid-induced and critical illness-associated polyneuromyopathy. In the cohort of SARS survivors studied by Hui *et al* the mean 6 minute walk distance, although improved from 3 to 6 months, remained lower than the normal range across all ages at 6 months. The measured SF36 scores were also lower than normal at 6 months. The pattern of residual functional impairment in post-SARS patients at 6 months therefore appears to follow that seen in post-ARDS patients. Although SARS patients might not have suffered from critical illness-associated polyneuromyopathy, other factors such as corticosteroid-induced myopathy, prolonged confinement and/or immobilisation and SARS-induced myositis, as postulated by Hui *et al*, are likely contributors to post-SARS generalised muscle weakness. It is worthwhile emphasising that SARS is a multisystem disease involving not only the lungs but also the gastrointestinal tract, liver, blood clotting system,[12] and the muscles; the pathogenesis may be by direct viral attack and/or by cytokine mediation. Muscle involvement is evidenced by myalgia reported in 50.8% of

*Ng *et al*[2] adopted a European reference range for their lung function laboratory, unlike the Singaporean reference range adopted by Hui *et al*[1] (personal communication with Dr Johnny Chan, Queen Elizabeth Hospital, Hong Kong, December 2004).

the Hong Kong SARS cohort[13] and by raised creatinine kinase levels found in 32.1% of the patients studied by Hui *et al*.[11] A much rarer but more severe form of muscle involvement in SARS—rhabdomyolysis—has also been reported.[14] The multifactorial generalised muscle weakness found at 6 months, extrapolated from the ARDS experience, will probably persist beyond 6 months but most patients will eventually be able to resume full time work.[8]

PSYCHOLOGICAL RECOVERY

Not only should we consider the functional recovery pathway of post-SARS patients, we should also be concerned with their psychological recovery pathway. In a recent review of the long term outcomes after critical illness, Herridge described not only physical dysfunction in ARDS survivors but also psychological dysfunction following ARDS, including both neurocognitive impairment such as memory deficit and impaired attention and concentration, and psychological impairment such as depression and post-traumatic stress disorder.[15 16] Patients with SARS during the 2003 outbreak no doubt went through a highly stressful experience, including their close encounter with a then mysterious infectious disease which, in a minority of patients, could be fatal, and the physical and social isolation mandated by the authority. The psychological impact of the SARS episode may mirror that of a critical illness in many ways.

The efforts of Hui *et al* and Ng *et al* in systematically following up post-SARS patients are laudable and will serve as a nucleus for the body of knowledge on the functional and psychological recovery pathway of post-SARS patients.

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Lung repair

Circulating endothelial progenitor cells in pulmonary inflammation

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Do endothelial progenitor cells contribute to lung repair and, if so, how?

Understanding how circulating stem cells released from the haematopoietic compartment accumulate and differentiate into the parenchymal cells of organs has become an exciting, thought provoking, and intriguing forefront of medical science. Many investigators have begun to address the ability of various populations of stem cells to aid in the repair of nearly every organ including the lungs,[1–19] either through recruitment and differentiation into parenchymal cells or through facilitating proliferation and differentiation of cells already present to mediate the repair. Numerous questions remain about if and how stem cells can facilitate organ repair.

ROLE OF ENDOTHELIAL PROGENITOR CELLS IN LUNG REPAIR

The studies presented by Yamada and colleagues[1] in this issue of *Thorax* address an important aspect about endothelial progenitor cells (EPC) in lung repair. They show that patients with pneumonia confined to one lobe and no other illnesses have circulating EPC in their blood within the first day of illness, and that this number is decreased 8 weeks after treatment and recovery. Their data provide strong evidence that inflammation in the lungs induces release of progenitor cells from the bone marrow that are capable of differentiating toward endothelial cell phenotypes upon culturing in appropriate growth media. Most curiously, the patients who had fibrotic changes persisting at 8 weeks were the ones with low numbers of circulating EPC within the first 28 hours of pneumonia. These data raise the possibility that circulating EPC may contribute to normal lung repair.

As with all good clinical studies, these results raise more questions than they answer. Are these circulating EPC retained within the lungs and what is their fate? Do they participate in the repair of the lungs and, if so, what role do they play? Studies examining the lungs of patients with transplanted haematopoietic stem cells from a donor of a different sex than the recipient have proved to be helpful in showing that donor-derived endothelial and epithelial cells are present within the lungs, and many studies in other species have also supported this concept.[20 21] In healthy lungs there may be little need for stem cells to contribute to the turnover rates