Surfactant Protein-B in Chronic Heart Failure: An Insight to the Alveolocapillary Barrier

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Chronic heart failure (CHF) is acknowledged as a modern and growing epidemic with an enormous social and economic burden.[1] Given that the cardinal clinical manifestation of CHF is dyspnea, it is remarkable that respiratory abnormalities in this complex clinical syndrome are so seldom the focus of attention by the cardiovascular research fraternity. A pulmonary based focus on CHF may yield important pathophysiologic information and pave the way for advances in the management of this common and complex condition. In their paper in this issue of *Revista Española de Cardiología* Pascual-Figal et al[2] take a step in this direction by confirming an increase in circulating surfactant protein-B (SP-B) in CHF and noting for the first time a relationship with ventilatory inefficiency.[2]

The alveolocapillary barrier separates alveolar gas from pulmonary blood. It is by necessity extremely thin and has a large surface area to allow sufficient and speedy gas diffusion. The alveolar epithelial cells form the external layer and the endothelial cells the internal layer. Both cell layers are supported by their respective basement membranes. Between the epithelial and endothelial basement membranes is the pulmonary interstitial space. This is only a potential space in the gas exchange regions. Type I alveolar epithelial cells are large, extremely flattened cells which cover 95% of the lung's surface area. These cells form a thin lining over the external interface (alveolar surface) and bind to adjacent cells via tight intercellular junctions. The type II alveolar epithelial cell is the more complex alveolar epithelial cell. It is a cuboidal highly metabolically active cell whose best-appreciated function is the synthesis and secretion of pulmonary surfactant. The pulmonary endothelial cells line the capillaries within the lung parenchyma (Figure).

SEE ARTICLE ON PAGES 136-42

Exposure of the fragile alveolocapillary barrier to raised pulmonary microvascular pressure as a consequence of heart failure (both acute and chronic) and the exposure of the components of the barrier to the hormonal and cytokine milieu of heart failure has multiple incompletely explored effects on its structure and function. These range from protein pore stretching to stress failure[3] and inflammatory damage[4] to fibrosis.[5]

SP-B is one of the 4 surfactant specific proteins. It is a quantitatively minor but physiologically critical component of pulmonary surfactant.[6,7] It is produced by the type II alveolar epithelial cell and has no other known or suspected side of synthesis.[6] Since there is a large concentration gradient of SP-B from the alveolar surfactant layer across the alveolocapillary barrier to the circulation where it is rapidly cleared, circulating levels are increased in conditions of alveolocapillary barrier damage.[6,7] The term pneumoproteinaemia has been coined to describe the abnormal presence of lung specific proteins (such as SP-B) in the circulation and their ability to reflect lung disorders by reflecting the health of the alveolocapillary barrier.[8] Circulating SP-B has been found to be elevated in acute respiratory distress syndrome,[9] acute cardiogenic pulmonary oedema[10] and chronic heart failure.[11] This SP-B work was performed using a competitive ELISA.

In their study Pascual-Figal et al have demonstrated an increase in circulating SP-B in CHF patients compared to healthy volunteers.[2] This is a noteworthy observation for 2 reasons. Firstly, it confirms the only other report of increased SP-B in CHF[11] and secondly it does so using a different measurement technique in a different laboratory (Western Blot). Given the known changes in the structure and function of the alveolocapillary barrier in CHF this observation might not have been expected. Like in mitral stenosis the chronic exposure of the fragile alveolocapillary barrier to high pulmonary microvascular pressure in CHF results in adaptive structural changes in order to

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Dr De Pasquale is a share holder in a company which has been set up to commercialize the use of surfactant protein-B as a biomarker.

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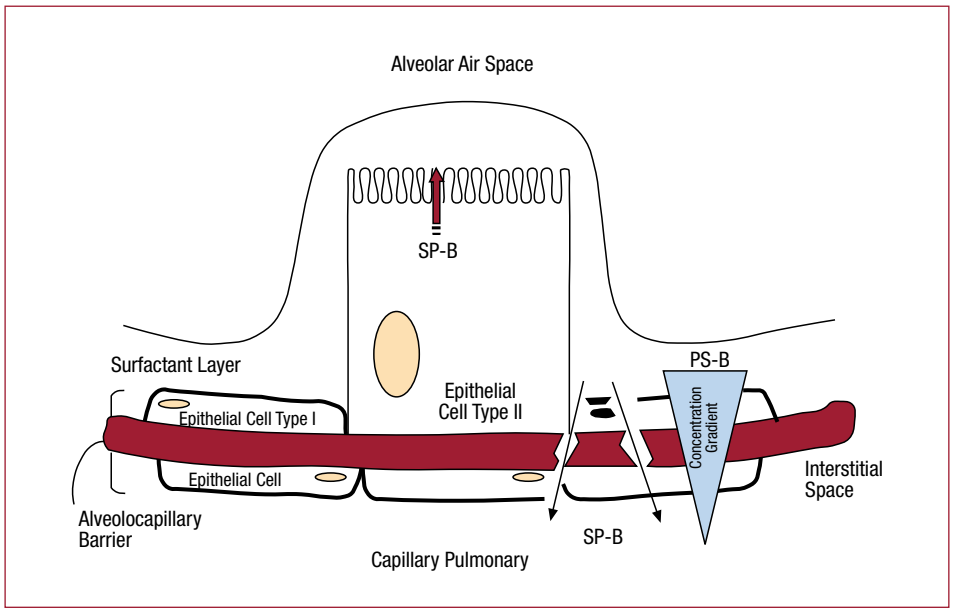

Figure. Surfactant protein-B (SP-B) and the alveolocapillary barrier.

protect the barrier from further vascular damage.[12] Such changes include a thickening of the barrier with more type II alveolar epithelial cells, thicker basement membranes and increased interstitial matrix.[13] This thickening of the alveolocapillary barrier is believed to be primarily responsible for the accepted and clinically important observation that gas exchange in reduced in CHF.[14] However why a thickened alveolar barrier might allow increased passage of SP-B from the alveolus into the circulation when the opposite might have been expected is perplexing. Although basic science work has demonstrated an increase in bidirectional alveolar capillary barrier protein permeability in CHF despite the thickened barrier,[15] clearly further research is needed to look at the effects of heart failure on the basic subunit of respiration the alveolocapillary barrier.

At a clinical level it has only been relatively recently acknowledged that a significant part of the reduction in exercise performance in CHF reflects reduced gas exchange. This physiological abnormality is reflected in the reduction in peak oxygen consumption (VO_2) and the increase in the slope of the linear relationship between ventilation (VE) and the production of carbon dioxide (VCO_2); VE/VCO_2 slope. These 2 physiologic variables are prognostically important in CHF.[16] It follows that a relationship between a circulating biomarker which reflects the health of the alveolocapillary barrier (SP-B) and cardio-respiratory variables which reflects the function of the alveolocapillary barrier (VO_{2max} and VE/VCO_2 slope) would be of interest both clinically and from a pathophysiologic viewpoint. Pascual-Figal et al have for the first time demonstrated that ventilatory inefficiency as measured by the VE/VCO_2 slope is related to circulating SP-B levels thereby linking these 2 markers of abnormal alveolocapillary barrier function in CHF.[2] They point out that the relationship between brain natriuretic peptide levels and VO_{2max} is intuitive given their close relationship to cardiac output while the SP-B and the VE/VCO_2 slope relationship reflects a different fundamental abnormality in CHF; the state of the alveolocapillary barrier.

Much work is still required at both the basic science and clinical science level in exploring the respiratory consequences of CHF. It is a fertile field of potential research as it tends to lie between cardiac researchers who focus on the heart and vasculature in CHF and pulmonary researchers who tend to focus on the lungs in what are traditionally considered "pulmonary diseases," which CHF is not. The observations of Pascual-Figal et al remind us that in the complex clinical syndrome of CHF there are pulmonary consequences of cardiac disease.

REFERENCES

1. Guía de Práctica Clínica de la Sociedad Europea de Cardiología (ESC) para el diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica. Rev Esp Cardiol. 2008;61:1329.e1-e70.
2. Pascual-Figal DA, Sánchez-Más J, de la Morena G, Casas T, Garrido IP, Ruipérez JA, et al. Proteína surfactante pulmonar tipo B en circulación periférica y deterioro funcional en pacientes con insuficiencia cardiaca crónica. Rev Esp Cardiol. 2009;62:136-42.

3. West JB, Mathieu-Costello O. Vulnerability of pulmonary capillaries in heart disease. Circulation. 1995;92:622-31.
4. Pugin J, Verghese G, Widmer MC, Matthay M. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med. 1999;27:304-12.
5. Townsley MI, Snell KS, Ivey CL, Culberson DE, Liu DC, Reed RK, et al. Remodeling of lung interstitium but not resistance vessels in canine pacing-induced heart failure. J Appl Physiol. 1999;87:1823-30.
6. Hermans C, Bernard A. Lung epithelium-specific proteins. Characteristics and potential applications as markers. Am J Respir Crit Care Med. 1999;159:646-78.
7. Doyle IR, Nicholas TE, Bersten AD. Partitioning lung and plasma proteins: circulating surfactant proteins as biomarkers of alveolocapillary permeability. Clin Exp Pharmacol Physiol. 1999;26:185-97.
8. Hermans C, Bernard A. Pneumoproteinaemia: a new perspective in the assessment of lung disorders. Eur Respir J. 1998;11:801-3.
9. Doyle IR, TE Nicholas, Bersten AD. Surfactant proteins A and B are elevated in plasma of patients with acute respiratory failure. Am J Respir Crit Care Med. 1997;156:1217-29.
10. De Pasquale CG, Arnolda LF, Doyle IR, Grant RL, Aylward PE, Bersten AD. Prolonged alveolocapillary barrier damage following acute cardiogenic pulmonary edema. Crit Care Med. 2003;31:1060-7.
11. De Pasquale CG, Arnolda LF, Doyle IR, Aylward PE, Chew DP, Bersten AD. Plasma surfactant protein-B: a novel biomarker in chronic heart failure. Circulation. 2004;110:1091-6.
12. Townsley MI, Fu Z, Mathieu-Costello O, West JB. Pulmonary microvascular permeability. Responses to high vascular pressure after induction of pacing-induced heart failure in dogs. Circ Res. 1995;77:317-25.
13. Lee YS. Electron microscopic studies of the alveolar-capillary barrier in the patients of chronic pulmonary edema. Jpn Circ J. 1979;43:945-54.
14. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, et al. Lung function and exercise gas exchange in chronic heart failure. Circulation. 1997;96:2221-7.
15. De Pasquale CG, Bersten AD, Doyle IR, Aylward PE, Arnolda LF. Infarct-induced chronic heart failure increases bi-directional protein movement across the alveolocapillary barrier. Am J Physiol (Heart Circ Physiol). 2003;284:H2136-45.
16. Francis DP, Shamin W, Ceri Davis L, Piepoli MF, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in heart failure: continuous and independent prognostic values from VE/VCO2 slope and peak VO2. Eur Heart J. 2000;21:154-61.