Editorials

Pulmonary diffusion capacity as prognostic marker in chronic heart failure

See page 467, doi:10.1053/euhj.2001.2803 for the article to which this Editorial refers

In chronic heart failure not only the cardiovascular system, but several organ systems including the respiratory system, skeletal muscles, distribution of blood flow, the hormonal and neural feedback control systems for breathing and cytokine activation are affected indirectly by the failing myocardial function.

Dyspnoea is one of the cardinal symptoms of chronic heart failure. The cause of dyspnoea in heart failure is multifactorial. In acute heart failure pulmonary capillary wedge pressure is related to the degree of dyspnoea, whereas no such relationship is found in chronic heart failure[1]. In chronic heart failure other factors, such as the excessive ventilatory response, limited possibility of increasing perfusion to respiratory muscles and respiratory muscle weakness may contribute to the sensation of dyspnoea. After cardiac transplantation, dyspnoea is improved at submaximal levels, but not normalized[2].

Pulmonary abnormalities in chronic heart failure are well known features and include both restrictive, obstructive and diffusion abnormalities. Obstructive and restrictive changes occur early in the course of heart failure, whereas diffusion capacity can be normal or even increased[3]. The preserved diffusion capacity may result from an increased alveolar capillary blood volume. Interstitial oedema, progressive fibrosis and impaired alveolar perfusion occur in chronic heart failure as a result of pulmonary venous congestion[4]. Structural changes of the alveolar–capillary membrane develop as the disease progresses, which leads to an impaired diffusion capacity[5].

The blood–gas barrier consists of a thinner and a thicker part. The thinner side, with a thickness of 0·2–0·3 mm, comprises about half of the surface area of the alveolar wall[6] and is important for pulmonary gas exchange. The interstitium of the thin side is composed of two fused basement membranes, the endothelium and the epithelium. This offers a high resistance to the penetration of fluid from the capillary, and substantial interstitial oedema of the lung can occur with no change to the thin side[7]. The collagen fibres of the thick side of the blood–gas barrier provide an important prop to the lung[8]. Interstitial cells, such as fibroblasts and pericytes, which are probably important for the fluid exchange across the pulmonary capillary are also part of the thicker side. In the early stages of interstitial oedema of the lung, accumulations of fluid are seen on the thick side[9].

Pulmonary capillaries are exposed to three forces[10], the circumferential tension, the longitudinal tension in tissue elements of the alveolar wall associated with lung inflation, and the surface tension of the alveolar lining layer. The tension of the tissue elements of the alveolar wall depends on lung volume. Although extremely resistant, disruptions of the blood–gas barrier occur under extreme physiological conditions and in several pathophysiological conditions. Disruption of the capillary endothelium occurs at high transmural pressures, but its basement membrane, the basement membrane of the alveolar epithelial layer and the epithelial layer itself remain intact. Most of the disruptions are reversible when the capillary transmural pressure is reduced[11].

Patients with long-standing pulmonary venous hypertension caused, for example, by mitral stenosis and pulmonary venous occlusive disease, develop marked thickening of the basement membrane of pulmonary capillaries[12–14]. In both conditions capillary pressure is raised over long periods, as it may be in patients with chronic heart failure. It is reasonable to assume that the thickening of the basement membrane occurs in response to increased capillary wall stress. Most of the thickening of the basement membrane is associated with the capillary endothelial cell rather than the alveolar epithelial cell.

Circulating bradykinin is inactivated mainly during its passage through the lungs by angiotensin converting enzyme (ACE), which is highly concentrated on the luminal surface of the lung microvessels[15]. Blockade of this enzyme may increase the local kinin concentration, leading to the enhanced and sustained formation of NO and vasodilator prostaglandins,

Published online 10 January 2002.
mainly prostacyclin. Guazzi and co-workers investigated the effect of enalapril, enalapril with aspirin, aspirin and placebo in 16 patients with chronic heart failure and 16 controls during a 2-week period. Enalapril induced significant improvements in carbon monoxide diffusion capacity (DlCO), peak oxygen consumption and exercise tolerance[16]. These results were confirmed in a 1-year prospective follow-up study performed in a similar patient population showing that enalapril-mediated changes in DlCO were reproducible and persist over time[17]. This shows that inhibition of ACE has a favourable modulatory activity on lung diffusing properties of patients with chronic heart failure.

Ewert and co-workers investigated 642 patients 1–11 years after heart transplantation[18]. The restrictive and obstructive ventilatory abnormalities, acquired in the course of chronic heart failure, improved in the first year after transplantation, whereas no subsequent improvement was seen after the first year. The pulmonary diffusion capacity, as measured by lung transfer factor for carbon monoxide and transfer coefficient for carbon monoxide was markedly decreased in 83% and 90% of the patients. In a subgroup of patients investigated before and after orthotopic cardiac transplantation, the diffusion capacity decreased markedly after transplantation with a slight restoration 1 year post-operatively.

Despite improved therapies for patients with chronic heart failure, mortality and morbidity remain high. Cardiac transplantation has evolved into an important treatment option for patients with severe heart failure, but this option remains limited to a relatively small number of patients with end-stage disease because there continues to be a severe shortage of donor hearts. The high mortality rate and widening gap between patients listed for transplantation and available donor hearts have magnified the need for reliable prognostic markers in chronic heart failure.

Pulmonary function tests have until now had little value in the diagnosis of chronic heart failure, whereas it is a useful tool in the differential diagnosis to pulmonary diseases[19].

Guazzi and co-workers[20] have investigated cardio-pulmonary exercise capacity, lung function and pulmonary diffusion capacity in 106 patients with moderate chronic heart failure. Seventeen patients died during the follow-up period of a mean of 17 months. The non-survivors had lower peak oxygen consumption and a steeper ventilation/carbon dioxide production (VE/VCO2) slope. They also had impaired pulmonary function tests compared with the survivors; this was especially clear for the membrane diffusing capacity Dm. However, the non-survivors were older, more often male, and were on more medication such as digoxin, diuretics, angiotensin receptor blockers, nitrates and amiodarone, whereas fewer were on ACE-inhibitors and beta-blockers, which indicates that they were more severely ill than the survivors. In multivariate Cox regression analysis, ACE-inhibition and Dm were the only independent predictors of mortality. However, two well known prognostic indicators, peak oxygen consumption and VE/VCO2 slope, were not included in the multivariate analysis.

This paper adds prognostic information to the already known fact that pulmonary function is impaired in chronic heart failure patients. If Dm is a better tool than established prognostic indicators, such as peak oxygen consumption or VE/VCO2 slope, this still has to be tested. On the other hand, a pulmonary function test is easier for the patient to perform and needs just standard equipment. This makes it a useful complement to cardiopulmonary exercise testing.

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References


Atrial fibrillation: one more sporting inconvenience?

See page 477, doi:10.1053/euhj.2001.2802 for the article to which this Editorial refers

In a paper I submitted some years ago, I stated that every arrhythmia had something to do with the autonomic nervous system. Then I was asked by the reviewer to withdraw such a statement unless I could produce evidence of its reality. I asked, respectfully, for the referee to provide the evidence of a single arrhythmia that was free of any autonomic influence. Apparently the referee could not satisfy my request and, as a result, the initial statement was left in the final version. The philosophy of the story is that one cannot always provide evidence of a statement but we can stick to any theory as long as it does not contradict experiments or observations.

An arrhythmogenic substrate must be responsible for an arrhythmia even though its very existence cannot be demonstrated. There is no spontaneous arrhythmogenesis, and only transient substrates are conceivably undetectable. This leads to an analysis of the relationships between the two essential ingredients of any arrhythmia, the substrate and its modulating factors. As to the third ingredient, namely the initiating factor, it also depends on the autonomic nervous system, but not necessarily according to the same rules.

Every time an equilibrium exists between two factors, one should consider the situation created by the extremes of an imbalance, a scenario in which the role of one of the two factors largely predominates over the other. This leads to a discussion of the notion of a substrate’s sensitivity to autonomic influences, as opposed to its strength. A curious paradox can then occur. It consists of the fact that the more visible one of the two factors the less important it is in arrhythmia determinism. A corollary is that the less easily detectable one factor, the more important it may be for the patient in terms of therapeutic consequences. As an example, what we called the adrenergic paradox[1] supposes that any clinical arrhythmia triggered by strenuous exercise should correspond to an arrhythmogenic substrate relatively insensitive to adrenergic stimulation: the adrenergic stimulation must be strong to produce an effect. On the other hand, any clinical arrhythmia preceded by a limited heart rate increase should be suspected of being very sensitive to sympathetic stimulation.

These theoretical notions have practical consequences; for instance beta-blockade is indicated much more in the latter case compared to the former. The adrenergic paradox explains why rhythmologists have overlooked the therapeutic aspects of beta-blockade: a large body of evidence now indicates that adrenergic-dependent tachyarrhythmias must be more common in heart failure than in the absence of...