plasm, left-sided heart failure, or ischemic heart disease did more poorly over 1 year if they had PE than if they did not have PE. Was the COPD more severe in the patients with PE? The data do not indicate the results of pulmonary function tests or values of the PaO2 before the PE or on follow-up among patients having PE compared with patients who did not have PE. Were the associated diseases (neoplasms, heart failure, ischemic heart disease) more severe in patients with PE? Was pulmonary function so impaired that even a slight residual perfusion defect in patients with PE may have contributed to their deaths when they had associated pulmonary abnormality? Did the patients with PE have residual deep venous thrombosis? Could silent PE have contributed to the death of these patients with impaired cardiorespiratory reserve? Clearly the data are not available to answer all of these questions, but perhaps the records of these patients may suggest some answers.

The article by Carson and coworkers is one of many useful articles that have resulted from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). Hopefully, information related to unanswered questions will be forthcoming.

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REFERENCES

The Natriuretic Peptides

Clinical Applications in Patients With COPD

It was only 15 years ago that De Bold and colleagues discovered atrial natriuretic factor (ANF), opening the door to a flood of investigative work and to a new concept that the heart has an endocrine system that plays an active role in responding to changes in its workload. Initial investigations were concerned with the role of ANF in regulating vascular tone and volume in the systemic circulation. The high concentration of ANF in the right atrium soon led other investigators to consider its effect on the pulmonary circulation. With the discoveries that ANF dilates constricted pulmonary vessels and that chronic hypoxia increases circulating ANF levels, attention was shifted to the role of ANF in regulating pulmonary vascular tone.

At the same time, it became evident that ANF was only one member of a closely related family of compounds, now referred to as the natriuretic peptides: atrial, brain (BNP), and C-type natriuretic peptide (CNP). Despite their names, BNP is probably no more a brain peptide than CNP is a natriuretic peptide. Rather, ANP, BNP, and CNP are peptides that interact with a set of membrane-bound guanylate cyclase-linked receptors (natriuretic peptide receptors A [NPR-A] and B [NPR-B]) to elevate intracellular cGMP levels. A third receptor (NPR-C) is not linked to a known second messenger and appears to function primarily as a clearance receptor that regulates circulating levels of all three peptides. The importance of these peptides is inferred by their tightly conserved amino acid sequences throughout most species of mammals, reptiles, and fish, but their physiologic function is just beginning to be understood.

The vasodilating and natriuretic properties of ANP led investigators to consider that ANP might play a role in regulating pulmonary vascular tone and intravascular volume in patients with chronic hypoxic lung diseases. In particular, patients with advanced COPD often have hypoxic pulmonary hypertension and impairments in sodium excretion that result in volume overload and cor pulmonale. Early studies found that patients with COPD had elevated plasma ANP levels that correlated with pulmonary artery pressure (Ppa) and were higher in the right atrium and pulmonary artery than in the systemic arterial or venous circulation.

Infusion of ANP into patients with COPD partially reversed hypoxic pulmonary vasoconstriction, lowered Ppa, and decreased plasma aldosterone levels. Additional studies found that exercise increased plasma ANP in COPD patients with normal Ppa, but not in patients with pulmonary hypertension, suggesting that a blunted ANP response may contribute to the development of hypoxic pulmonary hypertension.

The role of the other natriuretic peptides in modulating pulmonary vascular responses to chronic hypoxia has received less attention. Increases in plasma levels of both BNP and CNP have been demonstrated in patients with COPD, however, the hemodynamic and natriuretic effects of these peptides are no more potent than those of ANP, and their circulating levels are considerably lower. Furthermore, the biologic actions of ANP and BNP are mediated, for the most part, by the same guanylate cyclase-linked receptor, and its affinity for BNP is less than that for ANP. These findings have led some investigators to consider BNP as a redundant and less important signaling system for the NPR-A receptor.

Recent studies have changed this view. Unlike ANP
that is synthesized and secreted primarily in atrial tissue, BNP appears to be a peptide primarily of ventricular origin. Although the concentrations of BNP and its mRNA transcripts are highest in the atria, the total quantity of BNP mRNA transcripts are greater in the ventricle than in the atria when the larger mass of the ventricle is considered. In isolated perfused heart preparations, 95% of total cardiac ANP release is of atrial origin, whereas 60% of BNP release is supplied by the ventricles. Ventricular BNP synthesis increases in response to elevated ventricular end diastolic volume, and in patients with severe congestive heart failure, plasma BNP levels can exceed those of ANP.

BNP also differs from ANP in the transcriptional and posttranscriptional regulation of its gene expression. Studies in cardiac myocytes and intact rats demonstrate that BNP expression is upregulated as much as eightfold more quickly than ANP, suggesting that BNP transcripts are stabilized in response to hypertrophic stimuli. In fact, the rapidity of the BNP gene response earned it the description of “emergency cardiac hormone against ventricular overload.” Also, BNP is metabolized at a slower rate than ANP. In one study, BNP binding to NPR-C was less than one fourteenth that of ANP. These unique features of BNP have led to the concept that the heart has a “dual” natriuretic peptide response to increases in end diastolic volume and afterload.

With their article in this issue of CHEST (see page 1220), Cargill and Lipworth have swung the ANP spotlight over to the second member of this dual peptide response. Their findings that BNP is as effective as ANP at reducing Ppa and pulmonary vascular resistance in patients with COPD and cor pulmonale support the hypothesis that both peptides play important roles in regulating pulmonary hemodynamics and volume homeostasis in these patients. Although the number of patients in their study was small and non-invasive techniques were used to measure cardiac output and hemodynamics, their results with ANP infusion are in accordance with those of previous studies using larger numbers of catheterized patients. Recent data demonstrating that circulating BNP levels are elevated in patients with primary pulmonary hypertension and that right ventricular BNP synthesis is markedly upregulated in rats exposed to chronic hypoxia add further support to the hypothesis that BNP is part of a dual peptide response aimed at mitigating the pulmonary hypertensive response to chronic hypoxic lung disease.

The authors purposely selected patients that demonstrated partial reversibility of their pulmonary hypertension in response to oxygen and studied them while they were breathing room air. It would be of great interest to see if the beneficial effects of BNP could be demonstrated in COPD patients with more fixed pulmonary hypertension and if the effects of BNP infusion were additive to that of supplemental oxygen. Although there are insufficient data to suggest that BNP had a greater pulmonary vasodilator effect than ANP, in a previous study, Cargill and Lipworth found that BNP was a more potent pulmonary vasodilator than ANP in normal volunteers, and we have recently found that BNP had a greater effect than ANP in inhibiting pulmonary vascular remodeling in rats exposed to chronic hypoxia (unpublished data, 1996).

Future studies of natriuretic peptides in patients with COPD will have to consider the effects of this dual peptide system as has been done by many investigators studying congestive heart failure. In fact, increased BNP synthesis and release may have been responsible for the unimpressive results obtained in studies that attempted to exacerbate hypoxic pulmonary hypertension by administering ANP neutralizing antibodies.

Despite the efficacy and apparent short-term safety of the natriuretic peptides, the therapeutic potential of these agents will take a long time to realize. The only route of administration is continuous infusion, and the large quantity of peptide required to sustain increases in circulating levels would make long-term therapy prohibitively expensive. Rather, future efforts may be better spent on increasing the potency of endogenous natriuretic peptides by delaying their metabolism. This strategy has proven to be effective in blunting the development of hypoxic pulmonary hypertension in rats but remains untested in patients with established pulmonary hypertension or cor pulmonale.

Nonetheless, the natriuretic peptides have pharmaceutical potential that should not be overlooked. In addition to their vasodilating properties, they facilitate sodium excretion, inhibit pulmonary vascular remodeling, and increase minute ventilation in patients with COPD. While we await the development of more practical therapeutic applications, the natriuretic peptides should be considered a multiple peptide system that protects against the development of pulmonary hypertensive disease states. In addition to ANP, the role of BNP and possibly CNP in modulating the pulmonary vascular response to hypoxia should not be forgotten. We await the results of future studies of these peptides with great interest.

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Asthma Pathogenesis and the Peripatetic Polymorphonuclear Granulocyte

The Phlogistic Plot Thickens

The complexity of clinical asthma is matched by the heterogeneous nature of its inflammatory cellular response, which is associated with increased bronchial hyperresponsiveness. Soon after the techniques of bronchoalveolar lavage (BAL) and bronchial biopsy were deemed to be clinically safe, investigation of the asthmatic inflammatory cascade was intensified, particularly after laboratory challenge protocols with both allergens and pollutants. The majority of these earlier studies focused on the activation of mast cells and release of mediators, some of which were chemoattractants for eosinophils to sites of bronchial allergic inflammation.1 Tissue damage in the bronchial conducting airway was thought to be mediated by eosinophil-derived toxic products.2 More recently, the role of the T-lymphocyte in orchestration of inflammatory events via cytokine networks has also been explored and espoused as a major component of allergic inflammation.3 Because neutrophils have not been regularly demonstrated after allergen-induced bronchial challenge protocols, the overall significance of this cell in the chronic inflammatory response of asthma generally has been deemphasized. However, in this issue of CHEST (see page 1236), Frangova et al reported significant increase in neutrophils and a neutrophil granule product, myeloperoxidase, in BAL from nonsmoking allergic and nonallergic asthmatics. The patients in this study were sampled under baseline conditions at a time when they were free of respiratory infections for at least 1 month preceding the BAL procedure; the allergic patients were investigated out of their respective pollen seasons. The number of BAL eosinophils and lymphocytes, but not epithelial cells, also correlated significantly with the number of BAL neutrophils. The degree of methacholine hyperresponsiveness in these patients did not correlate with any of the cellular components, including eosinophils. Equivalent results were obtained in allergic and nonallergic patients.

Although a single cross-sectional study such as this requires confirmation, the results are of sufficient interest to revisit the role of the neutrophil in the asthmatic inflammatory process. First, it has been demonstrated that the neutrophil is the dominant cell after both in vitro and in vivo exposure to ozone in both animals and humans.4,5 Under these experimental conditions, a number of cytokines [interleukin-6 (IL-6), the α-family of chemokines (IL-8, Gro-α, Gro-γ) and GM-CSF] derived from bronchial epithelium act as potent chemoattractants for polymorphonuclear cells, which may exert toxic effects by release of elastase, toxic oxygen metabolites, and/or serine neutral proteases (cathepsin G, trypsin, and chymotrypsin). Recent in vitro investigations demonstrated that the latter group of proteolytic enzymes are involved in the detachment of epithelial cells from the basement membranes.6 In addition, neutrophil products are known to increase the induction of both histamine and