Commentary

Cardiogenic Pulmonary Edema and Its Absence in Cardiac Tamponade and Constriction
A Role for Atrial Natriuretic Factor?

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Pulmonary edema may be anticipated in patients with cardiac failure and high central circulatory pressures as reflected in pulmonary artery wedge levels of 20 to 30 mm Hg,1 but does not occur at the same pressure levels with pericardial compression of the heart.2 Yet, in the systemic circulation, both right-sided cardiac failure and compressive pericardial disorders cause comparable venous congestion with sodium and fluid retention, and, in contrast to their strikingly different pulmonary parenchymal effects, both can provoke peripheral edema. The absence of pulmonary edema in cardiac tamponade and constriction remains unsatisfactorily explained. Indeed, the very rare patient developing pulmonary edema only upon relief of pericardial compression may have had acute cardiac failure due to underlying heart disease,3 or pulmonary parenchymal injury4 with or without volume overload from intravenous fluid therapy of tamponade.

Cardiac Failure and Cardiac Compression

Hemodynamic Comparison

If pericardial compression of the heart can be considered a kind of hemodynamic control state for the comparable pulmonary capillary pressures of left heart failure, it is clear that it requires more than an imbalance of Starling forces to account for cardiogenic pulmonary edema. Some factor or factors must permit the edema-producing Starling force imbalance to operate in cardiac disease or inhibit its operation during pericardial compression of the heart. Consequently, the answer is likely to reside in associated pathophysiologic differences between the two conditions. As currently understood, there are two such differences and they are interrelated: myocardial transmural pressure and myocardial (particularly atrial) stretch. Despite the comparably high intracavitary cardiac pressures, cardiac transmural pressure5 during cardiac tamponade falls toward zero, since intrapericardial pressure rises pari passu with intracardiac diastolic pressures.6 In contrast, cardiac transmural pressure rises progressively with chamber pressures in cardiac failure, since pericardial pressure in this circumstance changes relatively little from its customary near-zero level. Thus, the chamber distending force—transmural pressure—is radically different; correspondingly, myocardial stretch increases markedly in cardiac failure and plummets in cardiac tamponade. In constriction, myocardial stretch tends to be prevented or significantly buffered by the tough pericardial scar.7

A traditional explanation for the conspicuous absence of pulmonary edema in pericardial compression of the heart, despite systemic congestion like that of heart failure, has been the hemodynamic cause of the systemic congestion: right heart compression during tamponade supposedly denies the lung some critical level of blood flow. However, intravenous fluid administration that could catastrophically accentuate cardiac pulmonary edema tends to support cardiac output in cardiac tamponade without producing pulmonary edema.8

Nonhemodynamic Comparison

A conspicuous nonhemodynamic difference between cardiac failure and cardiac compression is the respective level of atrial natriuretic factor. Unlike patients with heart failure who have high atrial natriuretic factor production, those with cardiac tamponade have low levels and develop high levels comparable to those in cardiac failure only after relief of tamponade.8 Recently we reported a patient with constrictive pericarditis who had a comparably spectacular rise in serum atrial natriuretic factor immediately upon removal of the pericardium.7 These observations confirm that myocardial stretch, due to increased transmural pressure, stimulates atrial natriuretic factor production rather than the high intracavitary pressure alone, since pericardial constriction limits or prevents myocardial stretch or markedly buffers transmural pressures (or both) (Table 1). I subsequently hypothesized

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that the relatively low atrial natriuretic factor levels in tamponade and constriction could be a key element in the absence of pulmonary edema in pericardial compressive disorders. Indeed, apart from the marked differences in cardiac transmural pressures and atrial natriuretic factor levels, there are few, if any, known physiologic or metabolic differences between the congestive failure syndromes and the pericardial compression syndromes. Because the effects of circulating atrial natriuretic factor include alterations in vascular permeability causing increased transcapillary water shifts, this hypothesis requires that increased atrial natriuretic factor levels would constitute a "permissive" factor in the presence of excessive capillary hydrostatic forces due to high central pressures, both being necessary to produce pulmonary edema in left-sided myocardial and valvular diseases. Moreover, patients with liver and kidney diseases who have increased atrial natriuretic factor levels do not develop pulmonary edema, probably because they lack the other factor: elevated central circulatory pressures, as occur in congestive failure and the pericardial compressive syndromes. Therefore, for cardiogenic pulmonary edema to occur, it appears necessary to have sufficiently high levels of atrial natriuretic factor, as well as sufficiently high levels of central pressures.

**FURTHER DEVELOPMENT OF HYPOTHESIS**

Since formulation of the hypothesis linking atrial natriuretic factor and pulmonary edema, new supportive evidence has been published from experiments with animals and a unique human case. Zimmerman and colleagues demonstrated differing effects of atrial natriuretic factor at different serum levels. High "pharmacologic" levels of atrial natriuretic factor (achieved at moderate infusion rates), like "physiologic" levels, appear to protect the lung by preventing increased pulmonary albumin escape, while at high infusion rates, described as achieving "pathophysiologic levels ... levels seen in heart failure," atrial natriuretic factor shifted protein and fluid out of the circulation into the lungs. This implies that atrial production of natriuretic factor must not only increase, but must reach some high threshold level and combine with high pulmonary capillary pressure to provoke pulmonary edema. In our patient with constrictive pericarditis, the atrial natriuretic factor level rose threefold immediately upon pericardiectomy, but without provoking edema, probably because central circulatory pressures fell simultaneously.

In a patient with what is categorized as unequal pericardial constriction, Svanegaard and colleagues observed tight compression of all cardiac chambers except a dilated left atrium. Atrial natriuretic factor production was predominantly in the left atrium with a high level in the peripheral circulation, but a low level in the pulmonary circulation and no pulmonary edema. They concluded that atrial natriuretic factor circulating in the arterial system was "used and/or degraded" before reaching the pulmonary circulation.

In this connection, my hypothesis would predict pulmonary edema in an animal model of unequal constriction sparing only the right atrium or in a comparable patient, since high central pressures would be accompanied by high atrial natriuretic factor in the pulmonary circulation.

Table 1 summarizes the hypothesis of interaction between very high atrial natriuretic factor levels and central pressures in pulmonary edema and the corresponding cardiac-pericardial relationships affecting myocardial transmural pressures and stretch. However, further complexity is implied by the nature of atrial natriuretic factor, a polypeptide released mainly from atrial myocytes with a range of recognized actions and interactions in addition to natriuresis: increased glomerular filtration rate and diuresis, inhibition of renin-angiotensin-aldosterone release and activity, vasodilation and modulation of baroreceptor function in cardiac failure. Clearly, further investigation is required to substantiate or refute the hypothesis.

**ADDENDUM**

Since this manuscript was submitted, Anand and colleagues have described the pathogenesis of edema in constrictive pericarditis and contrasted it with that in congestive heart failure, noting the differences in ANF levels despite comparable hemodynamic abnormalities, concluding: "Spodick hypothesized a role of low circulating ANP in preventing transcapillary fluid


**Table 1 — Cardiac Pathophysiology Related to Atrial Natriuretic Factor (ANF) in Pulmonary Edema and Its Absence**

<table>
<thead>
<tr>
<th>Cardiac: Mean pressures</th>
<th>Pulmonary edema</th>
<th>Failure</th>
<th>Tamponade</th>
<th>Constriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial</td>
<td>+ + + +</td>
<td>+ + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial</td>
<td>0</td>
<td>+ + + +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac transmural</td>
<td>+ + + + 0 to -</td>
<td>Buffered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial/Myocardial stretch</td>
<td></td>
<td>+ + + +</td>
<td>0 or limited by scar</td>
<td></td>
</tr>
<tr>
<td>ANF change before treatment</td>
<td></td>
<td>+ + + +</td>
<td>0 to +</td>
<td></td>
</tr>
<tr>
<td>ANF change after treatment</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

+ to + + + + = relative increase over normal levels. - to -- -- -- = relative decrease over normal levels. 0 = absence.
movement in these patients. This needs to be investigated further."

REFERENCES

2 Shabetai R, Fowler NO, Guntheroth WG. The hemodynamics of cardiac tamponade and constrictive pericarditis. Am J Cardiol 1970; 26:480-89
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10 Spodick DH. Low atrial natriuretic factor levels and absent pulmonary edema in pericardial compression of the heart. Am J Cardiol 1989; 63:1271-72