Hormonal responses to cardiac tamponade: inhibition of release of atrial natriuretic factor despite elevation of atrial pressures


ABSTRACT Atrial distension, rather than change in intra-atrial pressure, has been suggested as a principal mediator of release of atrial natriuretic factor (ANF). During cardiac tamponade, atrial pressures rise whereas transmural pressures and atrial stretch may not be affected. The roles of atrial pressure and atrial distension were investigated in six open-chest dogs subjected to cardiac tamponade and rapid volume expansion as disparate means of affecting intra-atrial pressures and atrial stretch. Hemodynamic measurements, immunoreactive ANF (ir-ANF), plasma renin activity, antidiuretic hormone, epinephrine, and norepinephrine were monitored before, during, and after three interventions: (1) tamponade, (2) rapid volume loading followed by tamponade, and (3) volume loading during tamponade. Volume expansion increased right atrial pressure and caused a significant rise in ir-ANF. Elevations of right atrial pressure caused by tamponade were comparable to those induced by volume infusion, but an increase in ir-ANF was not elicited during tamponade, and the ir-ANF response to volume loading was abolished when performed during tamponade. The relation between the change in ANF concentration and change in right atrial pressure were highly significant in the absence of tamponade, when atrial stretch was freely responsive to volume expansion (r = .73, p < .0001), but not when stretch was inhibited (r = -.16, p = NS). These observations underscore the importance of considering the modulating effects of atrial compliance, transmural pressure, and atrial stretch on the relation between atrial pressures and ANF release.


ABUNDANT EVIDENCE suggests a prominent role for atrial distension as a major stimulus for secretion of atrial natriuretic factor (ANF). Indeed, reports of natriuretic and diuretic responses to experimental and pathophysiologic atrial distension predate discovery of the hormone by decades.1–4 Numerous recent studies have demonstrated a strong relationship between atrial pressure elevation and ANF secretion,5–11 but because both stretch and pressure changes occurred in these investigations it has not been possible to distinguish between the individual effects of these two variables.

Cardiac tamponade is a condition in which intra-atrial pressure is elevated but atrial stretch does not occur because of concomitant elevation of intrapericardial pressure. Clinical investigations from this laboratory12 in a patient with cardiac tamponade demonstrated low ANF levels during tamponade despite markedly elevated right atrial and pulmonary arterial wedge pressures. After pericardiocentesis, ANF levels rose dramatically, reflecting some persistent elevation of intracardiac filling pressures despite partial hemodynamic improvement after relief of tamponade. The initial suppression of immunoreactive ANF (ir-ANF) was postulated to result from reduced atrial stretch caused by elevated intrapericardial pressure. The current study was designed to assess further the hypothesis that the primary stimulus for ANF secretion is atrial stretch and that a dissociation between atrial pressure elevation and ANF release occurs in cardiac tamponade. This study also relates the ANF responses during tamponade to the responses of plasma renin activity, antidiuretic hormone (ADH), epinephrine, and norepinephrine.

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Methods

Six mongrel dogs of either sex (mean weight 29.3 kg, range 27.7 to 31.3) were anesthetized with 35 mg/kg iv sodium pentobarbital. The trachea was intubated and ventilation was maintained with room air (15 ml/kg) by a Harvard respirator. A left carotid arteriotomy and jugular venotomy were performed and vascular sheaths were inserted. High-fidelity micromanometers (Millar Instruments, Houston) were advanced through the sheaths into the left ventricle and right atrium. Pressures were calibrated using the fluid-filled lumen of these catheters connected to a Statham P50 pressure transducer (Gould Electronics, Cleveland) at the midpoint level. A left thoracotomy allowed access to the pericardium, through which a section of silicone rubber tubing was passed and tightly secured by means of a purse-string suture.

Left ventricular pressure, differentiated left ventricular pressure (dP/dt), and mean and phasic right atrial pressures were monitored continuously and recorded on a Gould recorder (Gould, Model 2800S).

The investigation consisted of three randomized protocols, each concluding with a 30 min recovery phase. Protocol 1 consisted of 30 min of stable cardiac tamponade, induced by means of air insufflation into the pericardial space via the rubber tubing, in sufficient volume (usually 150 to 250 ml) to raise right atrial pressure (RAP) and left ventricular end-diastolic pressure (LVEDP) while maintaining systolic pressure above 100 mm Hg. Protocol 2 began with an infusion of 1 liter of Ringer’s solution through the jugular sheath, administered over 5 min, followed at 30 min (T = 30) by 30 min of tamponade. Protocol 3 began with 60 min of tamponade, interposed at T = 30 by a 5 minute infusion of 1 liter of Ringer’s solution. These procedures are displayed graphically in figures 1 to 3.

Arterial blood samples for plasma ir-ANF activity were taken during basal conditions and every 15 min during each intervention and recovery. Additionally, in five of six dogs, an ir-ANF sample was drawn 5 min after the initiation of each rapid infusion of Ringer’s solution. Arterial samples for measurement of plasma renin activity, ADH, epinephrine, and norepinephrine were taken during basal conditions and every 30 min during each intervention and recovery. All samples were drawn from the carotid access sheath. Samples for ir-ANF were collected in iced EDTA tubes and separated within 1 hr. Plasma samples were then stored at -70°C until processed. Determination of ir-ANF concentration was done with a previously described radioimmunossay. Plasma ADH and renin activity were also determined by radioimmunoassay. Simultaneous radioenzymatic assays for epinephrine and norepinephrine were performed with the technique of Peuler and Johnson.

Hemodynamic and hormonal variables were assessed by repeated measures analysis of variance. When significance was noted, a Dunnett’s multiple comparison test was used to disclose times at which each variable differed from either basal levels, T = 30 or T = 35, as appropriate. Differences were considered statistically significant when p < .05. A Hartley test was used to test equality of variances between factor levels for renin, ADH, epinephrine, and norepinephrine, as indicated by the considerable range in error values for these variables. If significant differences between variances were indicated by this test, data were log-transformed to account for these differences. Unless otherwise stated, all p values discussed below refer to differences from basal levels. Changes in LVEDP and RAP were considered covariates and were compared with ir-ANF as an independent variable by an analysis of covariance. This was used to account for both variability among dogs and the fact that repeated observations were made in individual dogs.

Results

Protocol 1: cardiac tamponade. Induction of tamponade in the non-volume loaded preparation (figure 1) resulted in the expected significant rise in LVEDP and mean RAP (each p < .01 at T = 15 and T = 30). Systolic blood pressure (SBP) was reduced at T = 15 (p < .05), but by T = 30 the decrease was no longer significant. Despite significant elevations of RAP and LVEDP, concentrations of plasma ir-ANF showed no significant change throughout the intervention or recovery. ADH and norepinephrine concentrations (table 1), however, showed significant increases (p < .05 and p < .01, respectively). After release of tamponade, hemodynamics, hormone concentrations, and plasma renin activity returned to control levels.

Protocol 2: volume loading followed by cardiac tamponade. Rapid volume loading resulted in prompt elevations in LVEDP and RAP at T = 5 (each p < .01) and T = 15 (p < .05 and p < .01, respectively) (figure 2). SBP was unaffected, as were all measured hormones with the exception of ANF. Here, the intravascular expansion resulted in an immediate and significant (p < .05) rise in plasma ir-ANF concentration at T = 5 and T = 15. Subsequently, induction of tamponade caused a fall in SBP and an elevation in RAP (each p < .01 at T = 45 and T = 60 vs control, and p < .05 and p < .01, respectively, vs the T = 30 values) (see table 1.) LVEDP remained slightly elevated after volume loading and the subsequent rise in LVEDP during tamponade was not statistically significant, although it was identical to the RAP, as expected with tamponade. Despite these elevations, ir-ANF levels did not rise. In

FIGURE 1. Hemodynamic and hormonal responses to cardiac tamponade, (protocol 1). Despite significant elevations in mean RAP and LVEDP, there was no increase of ANF. All values are mean ± SE.
contrast, ADH, epinephrine, and norepinephrine levels rose (each \( p < .01 \)), as did renin (\( p < .05 \)) (table 1). Levels of ir-ANF showed significant depression compared with those 30 minutes after volume infusion (\( p < .05 \) for \( T = 30 \) vs \( T = 45 \) and \( p < .01 \) for \( T = 30 \) vs \( T = 60 \)), although these values were not different from control. Hormone concentrations and hemodynamics returned to basal levels during the recovery phase.

Protocol 3: volume loading during cardiac tamponade. During tamponade, SBP fell (\( p < .05 \) at \( T = 15 \) and \( p < .01 \) at \( T = 30 \)), and RAP (\( p < .01 \)) and LVEDP (\( p < .05 \)) were elevated to an equivalent level at \( T = 15 \) through \( T = 30 \). Directional changes in all hormone levels were the same as those seen in response to tamponade in protocol 2. Significant elevations in ADH (\( p < .01 \)), renin (\( p < .01 \)), norepinephrine (\( p < .05 \)), and epinephrine (\( p < .01 \)) were noted. ANF was unaffected.

Volume infusion was superimposed on tamponade at \( T = 30 \), resulting in elevations at \( T = 35 \) in LVEDP and RAP (each \( p < .01 \)). Upon completion of tamponade, \( T = 60 \), LVEDP and RAP remained elevated from control (each \( p < .01 \)). In contrast to the brisk ir-ANF elevations after volume infusion in protocol 2, no elevation of ir-ANF occurred in the presence of tamponade.

The relationship between changes from control in ir-ANF and RAP or LVEDP, respectively, in the presence and absence of cardiac tamponade are shown in figures 4 and 5. Significant relations between ir-ANF changes and both changes in RAP (\( r = .73, p < .0001 \)) and LVEDP (\( r = .68, p < .0001 \)) were noted. No increase in ANF release was noted in response to volume loading with concurrent tamponade.
and changes in LVEDP ($r = .34, p < .02$) in the absence of tamponade were found. In the presence of tamponade, analysis of covariance demonstrated no significant relationships (for changes in RAP, $r = -.16, p = NS$; for changes in LVEDP, $r = .27, p = NS$).

**Discussion**

Clinical observations from this institution prompted this more detailed investigation into the roles of atrial pressure and atrial stretch as mediators of ANF release during cardiac tamponade. The results demonstrate a dissociation between ANF release and atrial pressure elevations in the presence of tamponade in keeping with the hypothesis that atrial stretch is the primary stimulus for ANF secretion. This observation is consistent with preliminary data presented by Edwards et al. and Mathias et al. Moreover, this study demonstrates that the systemic hemodynamic sequelae induced by tamponade elicit the expected activation of the renin-angiotensin system and release of catecholamines and ADH.

As clearly demonstrated in each intervention, the onset of tamponade produced stable and reproducible hemodynamic alterations that in no case resulted in an ANF response. This lack of response to significant increases in RAP and LVEDP discounts the role of intra-atrial pressure as a release mechanism for the hormone, a conclusion further emphasized by a comparison of these results with the ANF response to acute volume loading. Unrestricted volume expansion (figure 2, $T = 5$) caused a significant increase in ir-ANF secretion concomitant with elevations in RAP and LVEDP, a phenomenon originally interpreted only in terms of intra-atrial pressure. Recent echocardiographic studies have quantified a relationship between short-term changes in atrial pressure and size and the correlation of these changes with ANF release, but the implicit stimulus for ANF secretion was not discernible because both atrial pressure and size were affected concomitantly. Since RAP and LVEDP increases were similar during volume expansion and tamponade in this study, the impairment of stretch in cardiac tamponade explains the lack of ANF response in the face of increased intra-atrial pressure.

A primary role for atrial stretch in the ANF release mechanism is further supported by the lack of ANF response to volume expansion with concurrent tamponade (figure 3, $T = 35$). Highly significant elevations of RAP and LVEDP, resulting from both altered compliance and volume expansion, were incapable of eliciting the ANF response seen with volume expansion alone. This was also confirmed by analysis of change in plasma ir-ANF concentration against change in RAP and change in LVEDP in the presence and absence of tamponade (figures 4 and 5). The correlations of change in ANF and change in RAP or LVEDP were significant only in the absence of tamponade and consistent with a stretch-dependent mechanism of ANF release.

Increased plasma renin activity reflected the systemic hypotension induced by tamponade. The directional change was the same in all tamponade interventions but was statistically significant only in protocol 2. Volume expansion in the presence of tamponade (protocol 3, $T = 35$) would be expected to compensate partially for induced hypotension, leading to decreased plasma renin activity. This was perhaps not seen because of continued hemodynamic embarrassment by
TABLE 1
Summary of hemodynamic and hormonal responses induced by cardiac tamponade and rapid volume loading (mean ± SD)

<table>
<thead>
<tr>
<th>Time/intervention (min)</th>
<th>SBP (mm Hg)</th>
<th>Peak + dP/dt (mm Hg/sec)</th>
<th>Peak − dP/dt (mm Hg/sec)</th>
<th>LVEDP (mm Hg)</th>
<th>Mean RAP (mm Hg)</th>
<th>Mean ANF (pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol 1</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>0 Control</td>
<td>141.2 ± 18.4</td>
<td>2016 ± 567</td>
<td>2916 ± 668</td>
<td>8.4 ± 2.9</td>
<td>6.9 ± 1.1</td>
<td>17.7 ± 7.6</td>
</tr>
<tr>
<td>15 Tamponade</td>
<td>120.3 ± 37.1</td>
<td>1866 ± 758</td>
<td>2667 ± 1349</td>
<td>13.3 ± 4.5</td>
<td>12.2 ± 1.8</td>
<td>20.8 ± 13.5</td>
</tr>
<tr>
<td>30 Tamponade</td>
<td>124.0 ± 36.4</td>
<td>1833 ± 907</td>
<td>2966 ± 1253</td>
<td>13.8 ± 5.3</td>
<td>12.1 ± 1.4</td>
<td>20.3 ± 17.3</td>
</tr>
<tr>
<td>45 Recovery</td>
<td>139.5 ± 24.8</td>
<td>1780 ± 864</td>
<td>3100 ± 875</td>
<td>9.5 ± 4.5</td>
<td>7.5 ± 1.9</td>
<td>18.7 ± 10.1</td>
</tr>
<tr>
<td>60 Recovery</td>
<td>137.3 ± 24.1</td>
<td>1870 ± 800</td>
<td>3160 ± 856</td>
<td>9.7 ± 5.2</td>
<td>7.4 ± 1.7</td>
<td>17.8 ± 8.2</td>
</tr>
<tr>
<td>Protocol 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Control</td>
<td>135.5 ± 25.2</td>
<td>1900 ± 822</td>
<td>3000 ± 922</td>
<td>10.3 ± 5.5</td>
<td>7.2 ± 2.3</td>
<td>23.3 ± 22.4</td>
</tr>
<tr>
<td>5 Postinfusion</td>
<td>140.8 ± 24.0</td>
<td>1667 ± 473</td>
<td>2767 ± 208</td>
<td>19.0 ± 6.7</td>
<td>11.8 ± 2.2</td>
<td>37.8 ± 40.9</td>
</tr>
<tr>
<td>15 Postinfusion</td>
<td>141.0 ± 19.2</td>
<td>2000 ± 837</td>
<td>3025 ± 465</td>
<td>13.8 ± 6.7</td>
<td>9.8 ± 2.2</td>
<td>35.0 ± 26.4</td>
</tr>
<tr>
<td>30 Postinfusion</td>
<td>136.5 ± 19.8</td>
<td>2000 ± 976</td>
<td>3025 ± 568</td>
<td>10.8 ± 7.1</td>
<td>8.4 ± 2.1</td>
<td>32.2 ± 23.5</td>
</tr>
<tr>
<td>45 Tamponade</td>
<td>114.8 ± 18.9</td>
<td>1380 ± 409</td>
<td>1960 ± 416</td>
<td>13.3 ± 5.1</td>
<td>13.5 ± 1.6</td>
<td>25.0 ± 19.3</td>
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<td>60 Tamponade</td>
<td>114.5 ± 12.1</td>
<td>1420 ± 363</td>
<td>2060 ± 288</td>
<td>13.7 ± 5.1</td>
<td>14.2 ± 2.1</td>
<td>21.7 ± 15.7</td>
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<tr>
<td>75 Recovery</td>
<td>136.0 ± 16.6</td>
<td>1840 ± 623</td>
<td>2700 ± 600</td>
<td>11.0 ± 7.6</td>
<td>7.8 ± 1.5</td>
<td>22.3 ± 19.8</td>
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<td>90 Recovery</td>
<td>133.3 ± 17.3</td>
<td>1890 ± 658</td>
<td>2810 ± 609</td>
<td>10.3 ± 7.9</td>
<td>7.5 ± 1.6</td>
<td>24.3 ± 19.0</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0 Control</td>
<td>134.8 ± 16.6</td>
<td>1975 ± 498</td>
<td>2950 ± 327</td>
<td>10.0 ± 6.8</td>
<td>7.4 ± 1.0</td>
<td>19.0 ± 11.5</td>
</tr>
<tr>
<td>15 Tamponade</td>
<td>113.8 ± 27.0</td>
<td>1683 ± 646</td>
<td>2467 ± 833</td>
<td>13.5 ± 4.8</td>
<td>13.3 ± 1.6</td>
<td>16.3 ± 9.5</td>
</tr>
<tr>
<td>30 Tamponade</td>
<td>111.2 ± 23.2</td>
<td>1617 ± 531</td>
<td>2250 ± 972</td>
<td>13.6 ± 4.3</td>
<td>13.1 ± 1.2</td>
<td>14.0 ± 10.5</td>
</tr>
<tr>
<td>35 Postinfusion</td>
<td>126.2 ± 17.4</td>
<td>1680 ± 476</td>
<td>2480 ± 415</td>
<td>16.8 ± 5.5</td>
<td>15.6 ± 1.4</td>
<td>13.4 ± 10.2</td>
</tr>
<tr>
<td>45 Postinfusion</td>
<td>129.0 ± 10.5</td>
<td>1917 ± 571</td>
<td>2433 ± 361</td>
<td>15.3 ± 5.0</td>
<td>14.3 ± 2.1</td>
<td>17.5 ± 16.1</td>
</tr>
<tr>
<td>60 Postinfusion</td>
<td>129.3 ± 15.3</td>
<td>1950 ± 606</td>
<td>2450 ± 446</td>
<td>14.7 ± 4.8</td>
<td>13.3 ± 2.4</td>
<td>17.5 ± 14.5</td>
</tr>
<tr>
<td>75 Recovery</td>
<td>138.0 ± 11.6</td>
<td>2017 ± 488</td>
<td>2767 ± 197</td>
<td>10.9 ± 6.3</td>
<td>7.5 ± 1.8</td>
<td>21.7 ± 17.8</td>
</tr>
<tr>
<td>90 Recovery</td>
<td>134.3 ± 12.5</td>
<td>1880 ± 427</td>
<td>2840 ± 207</td>
<td>10.3 ± 6.4</td>
<td>7.3 ± 1.8</td>
<td>20.5 ± 15.0</td>
</tr>
</tbody>
</table>

EPI = epinephrine; NOR = norepinephrine.

*p < .05 vs control; "p < .01 vs control. "p < .05 vs T = 30; "p < .01 vs T = 30; "p < .01 vs T = 35.

the persistent tamponade. There was a small decrease in plasma renin activity in response to volume expansion unconstrained by tamponade (protocol 2), consistent with several studies that have implicated atrial distension as a mode of suppressing secretion of this enzyme.\textsuperscript{20, 21} These opposite responses of ir-ANF and plasma renin activity are in keeping with the previously reported negative correlation between them.\textsuperscript{13} The decrease in plasma renin activity from control to T = 30 (5.6 ± 2.4 to 2.8 ± 0.6 ng/ml/hr) strongly implies such a relationship but was not statistically significant in this study.

Similar to renin, ADH secretion is regulated by both arterial and atrial pressure receptor mechanisms.\textsuperscript{22} Acute cardiac tamponade is a strong stimulus for ADH release, via both arterial and atrial baroreceptors,\textsuperscript{23} and a significant increase in plasma ADH secretion occurred during each episode of tamponade. Significant decreases in plasma ADH during atrial distension have been reported.\textsuperscript{24} ADH levels decreased 50% (table 1) with volume expansion in this study (6.2 ± 1.9 to 3.1 ± 1.1 pg/ml). Decreased levels of ADH were also observed when tamponade precluded atrial dis-
tension during volume expansion (figure 3, T = 30-60), most likely because of the concomitant rise in SBP.

Epinephrine and norepinephrine levels consistently increased in response to the hemodynamic impairments caused by tamponade. The increase in norepinephrine was significant in each intervention; epinephrine paralleled this without always reaching statistical significance. Volume expansion during tamponade effectively reduced both catecholamines to control levels (protocol 3), suggesting that systemic perfusion was compensated for by this infusion. Volume loading capable of eliciting an ANF response had no effect on either epinephrine or norepinephrine levels.

This study is limited by a lack of actual transmural pressure measurements. Controversy continues regarding the most accurate and appropriate measurement of intrapericardial pressure for the calculation of transmural pressure. The observations of Smiseth et al.\textsuperscript{25} point out the difficulty in measuring intrapericardial pressures with traditional fluid-filled manometers in the absence of substantial fluid within the pericardium, as was the case in this preparation. Thus potentially inac-

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accurate measurements of intrapericardial pressure were not performed. Although unexpected changes in transmural pressure or wall stress cannot be excluded in this study, the elevation of intracardiac pressures by insufflation of air into the pericardium is still most likely to have been associated only with decreased transmural pressures. Therefore these observations in a relatively uncomplicated experimental preparation clearly demonstrate the apparent dissociation between elevation of intracardiac filling pressures and ir-ANF release during tamponade.

An atrial stretch–dependent mechanism of ANF release is consistent with reports of increased ANF levels in patients with several cardiovascular disease states. The long-term increase in atrial pressure and size seen in congestive heart failure is associated with elevated ANF levels. 8, 10, 13 The natriuresis present in supraventricular tachycardia has recently been correlated with ANF release, 11 and atrial distension is a correlate of the increased atrial pressure seen in this condition. Essential hypertension and chronic renal failure likewise promote ANF release and are associated with atrial distension secondary to increased preload. 26, 27 The use of tamponade in this study demonstrates the secondary importance of pressure elevation as compared with stretch-mediated ANF release in each of these conditions and suggests that studies relating hemodynamic data to ANF release should attempt to take into account effects that may modulate changes in actual atrial stretch. In addition, the observations in this study suggest that the response of ANF to volume loading in the presence of pericardial effusion or thickening of varying etiology may form the basis of an adjunctive, hormonal test for determining whether the pericardial disease is hemodynamically important.

References

Hormonal responses to cardiac tamponade: inhibition of release of atrial natriuretic factor despite elevation of atrial pressures.

G B Mancini, M J McGillem, E R Bates, A B Weder, S F DeBoe and R J Grekin

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