Atrial Stretch, Not Pressure, Is the Principal Determinant Controlling the Acute Release of Atrial Natriuretic Factor


The current studies were designed to investigate the mechanisms in the intact anesthetized dog that control the release of atrial natriuretic factor (ANF). In vitro, mechanical stretch of atrial tissue produces an increased release of ANF. In vivo, changes in atrial pressure correlate positively with circulating ANF levels. The present investigations used 6 open-chest anesthetized dogs to evaluate the role of atrial pressure versus atrial stretch, the latter determined by atrial transmural pressure, in the release of ANF. In a paired design, animals underwent cardiac tamponade followed by constriction of the aorta and pulmonary artery. Tamponade produces a balanced increase in intra-atrial and pericardial pressures. Thus, despite an elevated atrial pressure, there is no increase in transmural pressure producing atrial stretch. Great artery constriction increases intra-atrial but not pericardial pressure, resulting in an increase in atrial transmural pressure and atrial stretch. Cardiac tamponade increased right atrial pressure (0.8 ± 0.3 to 7.6 ± 0.6 mm Hg, p < 0.001) and pulmonary capillary wedge pressure (3.7 ± 0.6 to 8.8 ± 0.6 mm Hg, p < 0.001). Constriction of the aorta and pulmonary artery also increased right atrial pressure (1.5 ± 0.8 to 6.3 ± 0.8 mm Hg, p < 0.05) and pulmonary capillary wedge pressure (4.6 ± 0.3 to 7.8 ± 1.0 mm Hg, p < 0.05). Atrial transmural pressure increased only during great artery constriction. ANF release increased only during great artery constriction from 73 ± 15 to 255 ± 53 pg/ml, p < 0.05, while there was no change in circulating ANF during tamponade, 51 ± 3 to 52 ± 11 pg/ml. These studies demonstrate that an increase in atrial transmural pressure with associated atrial stretch, not increased intra-atrial pressure, acts as the principal mediator controlling the acute release of ANF. (Circulation Research 1988;62:191–195)

Recent investigations have demonstrated the existence of a peptide hormone of cardiac origin known as atrial natriuretic factor (ANF). States of increased atrial pressure characteristically exhibit increased circulating levels of ANF. The hormone has been demonstrated to reside in membrane-bound granules of the atrial myocardial cells. In a model of hereditary cardiomyopathy with chronic volume and pressure overload, there exists an inverse relation between atrial content of ANF and the concentration of this hormone in the circulation. Humans with chronic congestive heart failure and increased atrial pressure consistently exhibit markedly elevated levels of ANF.

Deitz demonstrated in the isolated heart preparation that acute increases in atrial pressure resulted in an increase in secretion of a natriuretic substance thought to be ANF. Using isolated atria, it has been demonstrated that stretch produced by increasing tension applied to the atria results in an increased release of ANF into the suprafusion fluid. To date, the relative roles of atrial pressure versus atrial stretch as mediators of ANF release have not been addressed in the intact animal.

Goetz and colleagues reported that alterations in atrial transmural pressure, produced by atrial tamponade, may significantly influence atrial receptors and modulate renal function. These previous studies were performed prior to the recognition of the atrial endocrine system and, hence, the influence of intra-atrial versus transmural pressure on ANF release was not investigated.

We hypothesized that the principal stimulus for ANF release from the atria is mechanical stretch, not increased intracavitary atrial pressure. To test this hypothesis, we studied the effect of acute cardiac tamponade versus constriction of the great arteries in the intact dog. Cardiac tamponade represents a unique condition in which atrial pressure is acutely elevated; however, because of a balanced increase in both intra-atrial and pericardial pressures, transmural atrial pressure does not increase. By controlling transmural atrial pressure, stretch of the atria is inhibited. Great artery constriction results in an increase in both intra-atrial and transmural pressure. Thus, the current studies were designed to investigate in vivo whether the release of ANF is stimulated by elevated intra-atrial pressure or elevated transmural pressure and the associated atrial stretch.
**Materials and Methods**

The effect of increased atrial pressure on release of ANF was studied in 6 volume-replete, pentobarbital-anesthetized (30 mg/kg i.v.) mongrel dogs. After induction of anesthesia, animals were prepared by selective cannulation of the femoral artery and the femoral vein. The right external jugular vein was isolated, and a 7.5 French balloon-tipped thermodilution pulmonary artery catheter with right atrial port (American Edwards Laboratory, Santa Ana, Calif.) was advanced into the pulmonary artery. The trachea was intubated using a 9.5-mm endotracheal tube, and the animal was mechanically ventilated (Harvard Apparatus, Millis, Mass.).

The pericardium was approached by a right thoracotomy made between the 4th and 5th intercostal space. A small incision was made in the parietal pericardium, and a catheter (PE240, Clay Adams, Parsippany, N.J.) was advanced toward the cardiac apex. The pericardial incision was closed around the catheter with purse-string sutures. This catheter allowed for instillation of saline into the pericardial space and monitoring of intrapericardial pressure (Gould pressure transducer, Rolling Meadows, Ill.). Following completion of the tamponade portion of the protocol, the pericardium was incised and reflected. The great arteries were dissected to allow placement of two Blalock clamps, one around the ascending aorta and one around the pulmonary trunk.

These studies consisted of 6 periods. Following surgical preparation as detailed above, and a 1-hour equilibration period, data were collected during a 15-minute control period. Cardiac tamponade was created by instillation of normal saline into the pericardial space and was considered sufficient when mean right atrial pressure had increased by approximately 5–7 mm Hg. Data were collected after 15 minutes of stable tamponade. Following release of the tamponade, the animal was allowed to recover for 45 minutes after which repeat data were obtained during a 15-minute recovery period. Constriction of the great arteries was performed following reequilibration in a 15-minute control period. The pulmonary trunk and aorta were constricted simultaneously while atrial pressure was monitored. Constriction was considered suitable when stable right atrial pressure had increased by approximately 5–7 mm Hg. Data were collected after 15 minutes of great artery constriction. The clamps were then removed, and the animal was allowed to recover for 45 minutes prior to the final recovery period.

During each period, the following hemodynamic pressures were measured: systemic arterial pressure, pulmonary artery pressure, right atrial pressure, pulmonary capillary wedge pressure, and pericardial space pressure. Cardiac output was determined in triplicate by thermodilution (cardiac output computer, model 9510A, American Edwards Laboratory). At the midpoint of each period, arterial blood was collected for determination of circulating immunoreactive ANF. An equal volume of normal saline was infused to replace the volume of blood sampled. ANF was determined by radioimmunoassay as previously described. The intra-assay variability was ±6%, and the interassay variability was ±9%. The lower limit of detection was 3 pg/ml.

Systemic vascular resistance (SVR) and transmural right and left atrial pressure (TRAP and TLAP, respectively) were calculated using the following formulas:

\[
\text{SVR} = \frac{\text{mean arterial pressure} - \text{right atrial pressure}}{\text{cardiac output}} \times 80
\]

\[
\text{TRAP} = \text{right atrial pressure} - \text{pericardial pressure}
\]

\[
\text{TLAP} = \text{pulmonary capillary wedge pressure} - \text{pericardial pressure}
\]

Data were analyzed using the Student’s paired t test and reported as mean ± SEM. Level of significance was \(p<0.05\).

**Results**

The relations between intra-atrial pressure, transmural atrial pressure, and circulating ANF are illustrated in Figures 1 and 2. Acute cardiac tamponade resulted in an increase in right atrial pressure from 0.8 ± 0.3 to 7.6 ± 0.6 mm Hg \((p<0.001)\) and in pulmonary capillary wedge pressure from 3.7 ± 0.6 to 8.8 ± 0.6 mm Hg \((p<0.001)\). Constriction of the great arteries increased right atrial pressure from 1.5 ± 0.8 to 6.3 ± 0.8 mm Hg \((p<0.05)\) and pulmonary capillary wedge pressure from 4.6 ± 0.3 to 7.8 ± 1.0 mm Hg \((p<0.05)\). The right atrial and pulmonary capillary wedge pressures achieved during tamponade did not differ significantly from those achieved with aortic and pulmonary artery constriction. Right and left atrial transmural pressures did not change significantly with tamponade \((0.8 ± 0.6 to 0.2 ± 0.9 \text{ mm Hg})\) and 3.7 ± 0.7 to 1.3 ± 0.8 mm Hg, respectively). However, both right atrial transmural pressure \((1.5 ± 0.8 \text{ to} 6.3 ± 0.8 \text{ mm Hg})\) and pulmonary capillary wedge pressure \((3.7 ± 0.7 \text{ to} 7.8 ± 1.0 \text{ mm Hg})\) increased significantly with tamponade.

**Figure 1.** Right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), right (RA) and left atrial (LA) transmural pressures, and plasma levels of atrial natriuretic factor (ANF) during tamponade and combined aortic (Ao) pulmonary artery (PA) constriction. \(*p<0.05\) control, vs. tamponade; \(\dagger p<0.05\) control, vs. Ao PA constriction.
mechanisms that control the release of atrial natriuretic factor by examining in vivo the relative role of arterial levels of atrial natriuretic factor did not change during cardiac tamponade (51 ± 3 to 52 ± 11 pg/ml) but increased significantly in association with great artery constriction (73 ± 15 to 255 ± 53 pg/ml, p < 0.05).

Mean systemic arterial pressure decreased during tamponade from 105 ± 7 to 71 ± 9 mm Hg (p < 0.001) and declined with great artery constriction from 87 ± 8 to 57 ± 7 mm Hg (p < 0.01). The arterial pressure observed during tamponade did not differ significantly from that observed with great artery constriction. Cardiac output was reduced by tamponade (3.7 ± 0.3 to 1.6 ± 0.2 l/min, p < 0.001) but not by great artery constriction (2.8 ± 0.3 to 2.1 ± 0.4 l/min). The level of cardiac output was not significantly different during tamponade compared to great artery constriction. Heart rate did not change significantly with tamponade (151 ± 5 to 150 ± 6 beats/min) or great artery constriction (144 ± 10 to 152 ± 9 beats/min). Systemic vascular resistance increased significantly during tamponade (2,320 ± 198 to 3,250 ± 431 pg/ml, p < 0.05) but not during great artery constriction (2,390 ± 329 to 2,486 ± 691 pg/ml).

Discussion
The present studies were designed to investigate the mechanisms that control the release of atrial natriuretic factor by examining in vivo the relative role of intra-atrial pressure versus transmural atrial pressure in the control of ANF release. Although cardiac tamponade and great artery constriction represent dissimilar experimental models, these two techniques do result in similar hemodynamic alterations and allow for the clear dissociation of increased atrial pressure from ANF release. These studies demonstrate that atrial transmural pressure, not intracavity pressure, acts as the principal stimulus for the acute release of ANF.

Lang and colleagues' first reported that increases in atrial pressure resulted in enhanced release of ANF. Thus, this early study demonstrated an important link between atrial pressure and ANF release. Subsequent studies in intact animals, as well as in humans, employing ventricular pacing, positional change, and hemorrhage have established a positive correlation between atrial pressure and circulating ANF. Further, a positive relation between atrial pressure and atrial endocrine function has also been observed in states of chronic atrial pressure overload such as in congestive heart failure. Despite these important earlier studies, it was not clear whether the release of ANF, a hormone principally located in the atrial subendocardial region, was increased by intra-atrial pressure or actual mechanical stretch of the atria.

The present studies importantly extend previous in vivo as well as in vitro investigations. The current investigations provide a unique model that is capable of testing the alternative mechanism of atrial stretch versus atrial pressure in regulating ANF release. Employing a modification of the model of tamponade used by Goetz et al to examine the role of atrial transmural pressure in the activation of atrial receptors, the present studies confirm the hypothesis that increased atrial transmural pressure and associated atrial stretch increase ANF. In contrast, an increase in atrial cavity pressure produced by tamponade without an associated increase in atrial transmural pressure was not associated with ANF release. For atrial stretch to occur, there must be a pressure gradient across the atrial wall. In states of tamponade, no such gradient exists, and therefore, the driving force for atrial stretch does not exist.

The present studies were designed to better define the mechanism controlling the release of ANF and not primarily to investigate the physiologic actions of the hormone. It is of interest to note, however, that during great artery constriction with the associated elevated ANF, systemic vascular resistance did not increase, while during cardiac tamponade with no increase in ANF, systemic vascular resistance increased significantly. One cannot exclude the possibility that vasodilatory properties of ANF may be responsible for the apparent difference in the systemic vascular response between tamponade and constriction.

The present findings may have important clinical implications and provide insight into the pathophysiology of cardiac tamponade and constrictive pericarditis, two conditions characterized by avid retention. Subjects with cardiac tamponade or chronic constrictive pericarditis may have near normal levels of ANF.
in spite of markedly elevated atrial pressures. Koller and associates\textsuperscript{19} have recently observed an inappropriately low level of ANF in an individual with elevated atrial pressure secondary to cardiac tamponade. Following pericardiocentesis, atrial dimensions increased as did plasma ANF. While transmural atrial pressure was not measured, they conclude, "atrial distention produced by changes in the pressure gradient across the atrial wall is the major determinant of ANF [ANF] release." We believe that the present studies, by documenting transmural atrial pressure, validate the speculation of the prior case report. The failure of ANF to increase in response to the elevated atrial pressure associated with cardiac tamponade may in part contribute to the acute sodium retention known to occur.

These studies did not assess total coronary or atrial blood flow, which may in themselves modulate ANF release. However, we have observed preservation of normal atrial endocrine function in humans with the artificial heart.\textsuperscript{16} In these individuals, much native atria remains intact, and the atrium responds to elevated atrial pressure by increasing plasma ANF. This occurs despite surgical ligation of the coronary sinus and absence of coronary arteries.

The present studies were performed in the anesthetized animal, and one cannot completely exclude modulating actions of anesthesia on ANF release. However, a similar dissociation between intra-atrial pressure and plasma ANF has recently been observed in the unanesthetized conscious human.\textsuperscript{17} Further, we have observed that general anesthesia does not significantly alter plasma ANF values or atrial pressure.\textsuperscript{18}

The activity of the adrenergic nervous system was not fully characterized in the current studies. However, the similar heart rates observed during tamponade and great artery constriction suggest similar levels of adrenergic stimulation. While some investigators have speculated that adrenergic stimulation may alter ANF release, studies using \( \alpha - \) and \( \beta - \)blockade with propranolol and phentolamines have failed to demonstrate any modulating actions of adrenergic receptor stimulation on ANF release.\textsuperscript{19} Further studies in the conscious dog have demonstrated that surgical denervation of the heart does not alter basal or stimulated-ANF release.\textsuperscript{18}

In vitro studies by Bilder and associates\textsuperscript{20} have demonstrated that ANF release may be modulated by the rate of atrial stretch. In the present studies, cardiac rates were comparable during tamponade and great artery constriction suggest similar levels of adrenergic stimulation. While some investigators have speculated that adrenergic stimulation may alter ANF release, studies using \( \alpha - \) and \( \beta - \)blockade with propranolol and phentolamines have failed to demonstrate any modulating actions of adrenergic receptor stimulation on ANF release.\textsuperscript{19} Further studies in the conscious dog have demonstrated that surgical denervation of the heart does not alter basal or stimulated-ANF release.\textsuperscript{18}

Aorta, however, resulted in increases in atrial transmural pressure, allowing atrial stretch and increased release of ANF. Thus, the present studies demonstrate that atrial stretch is the principal stimulus for release of ANF.

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B S Edwards, R S Zimmerman, T R Schwab, D M Heublein and J C Burnett, Jr

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