Atrial natriuretic factor in hypovolemic tachycardia

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Summary. Atrial natriuretic factor (ANF) is released in response to many stimuli which increase right atrial pressure. Following hemorrhage pigs lowered their atrial pressures, developed a tachycardia and increased ANF levels. Electrical pacing increased heart rate and ANF levels. There is a stimulus to ANF release other than atrial stretch, probably heart rate.
Key words. Atrial natriuretic factor; hemorrhage; tachycardia.

A precurser to atrial natriuretic factor (ANF) is stored in granules in the atria of mammalian hearts and ANF is released by distention of the right atrium. As little as 1 mm Hg increase in right atrial pressure in the rat increases cardiac ANF release[1]. There is some evidence that distention of the left atrium can increase ANF levels in man[2] but few studies have measured the relationship between left atrial pressure and ANF. Congestive heart failure associated with elevated filling pressure of both right and left atria leads to very high ANF levels in man[3].

Many vasoconstrictor drugs raise blood pressure and ANF levels[3]. Although there is a relationship between the degree of arterial pressure elevation and ANF levels, vasoconstrictors act to decrease venous capacitance which increases atrial filling pressure.

Paroxysmal atrial tachycardia can raise heart rates to very high levels, and has been associated with elevated ANF levels[5] and polyuria[6]. However, in paroxysmal atrial tachycardia pressure in the atria increases[7]. All the physiological, pathological and pharmacological stimuli to ANF release previously reported have been associated with conditions that can increase atrial stretch, but it seemed possible that an increase in heart rate alone might stimulate ANF release independent of increased atrial pressure. Hemorrhage is a physiological stimulus to tachycardia which lowers atrial pressure. We induced a controlled hemorrhage in pigs and monitored heart rate, atrial pressures and ANF levels.

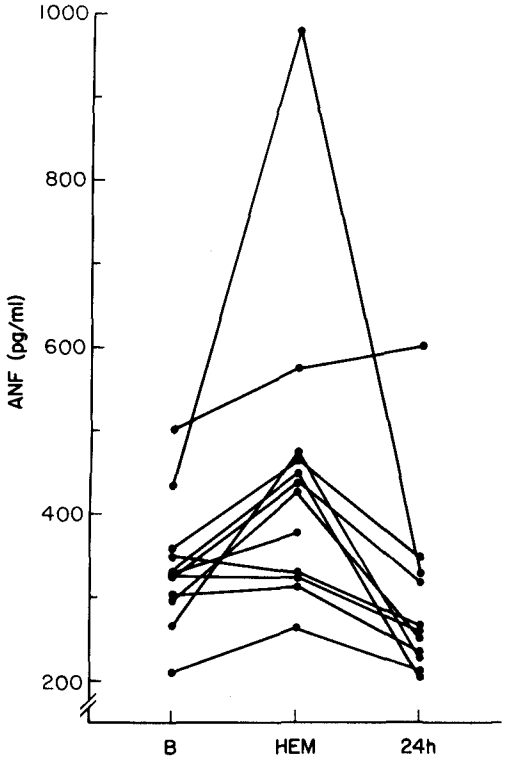

Figure 1. ANF levels in 12 pigs before hemorrhage (B), at the end of a 30-min period of hemorrhage (Hem) and 24 h later.

Anesthetized adult pigs weighing 28–34 kg had catheters placed to measure arterial and central venous pressure (CVP), pulmonary artery wedge pressure and to remove blood for sampling and hemorrhage. Twenty-four hours later the awake animals had baseline measurements made and underwent controlled hemorrhage. ANF was measured on unextracted plasma by the method of Gutkowska et al.[8]. 125 I ANF was prepared by the method of Napier[9]. Rabbit anti-human alpha ANF was purchased from Peninsula Labs, Belmont, California. The assay had a sensitivity of 40 pg/ml and within assay coefficient of variance of 5%. Rapid infusion of 2 l of fluid into a pig caused a 3.3-fold rise in ANF in response to a 3-fold rise in central venous pressure.

Twelve pigs were bled 40% of their calculated blood volume over 30 min and this decreased CVP from 4.0 to 0.4 mm Hg. Pulmonary artery wedge pressure did not change significantly but arterial pressure fell by half and heart rate increased from 113 to 187 beats per minute. ANF increased from 331 ± 20 pg/ml to 439 ± 51 pg/ml ($p = 0.02$) (fig. 1). Even if the 2 animals that attained the highest ANF levels are eliminated from the calculations, the increase in ANF is still statistically significant.

One hour after bleeding began the pigs were given either Ringer's lactate or hypertonic sodium lactate and 2 h after bleeding they were given their own red blood cells. Additional fluids were given hourly over 24 h to maintain CVP. Twenty-four hours after bleeding CVP was 3.4 ± 0.8 mm Hg (table), not significantly lower than control levels. Heart rate and blood pressure returned to control levels but ANF fell to 294 ± 34 pg/ml (fig. 1) lower than 30 min after bleeding ($p < 0.02$) and slightly lower than control levels ($p < 0.1$).

The finding of a borderline significant decrease in ANF levels at 24 h when there was a non-significant decrease in CVP was in accord with the many reports that ANF release is mediated by atrial distention. However, ANF levels rose during hypovolemic hypotension when CVP was one-tenth of control values. There are case reports of elevated ANF levels in man subsequent to paroxysmal atrial tachycardia. To investigate whether an increased heart rate alone might stimulate release of ANF we induced a tachycardia by electrical pacing in 2 animals and measured their ANF levels. Animals were anesthetized with halothane and pacing wires attached to the right atrium through a sternal incision. The animals were paced for 30 min at 150% of resting heart rate. This increased CVP by 5 and 12 mm Hg and more than doubled ANF levels (fig. 2).

Levels of ANF, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP) and pulmonary wedge pressure (PWP) in response to volume depletion and 24 h after volume depletion. *$p < 0.05$ by 2-tailed paired t-test when compared with control values.

	Control	Volume depletion	24 h Recovery
ANF pg/ml	331 ± 20	439 ± 51*	294 ± 34
HR beats/min	113 ± 11	187 ± 13*	120 ± 8
MAP mm Hg	106 ± 2	53 ± 6*	102 ± 4
CVP mm Hg	4 ± 0.9	0.4 ± 1.2*	3.4 ± 0.8
PWP mm Hg	9.3 ± 0.8	7.2 ± 1.2	8.9 ± 0.7

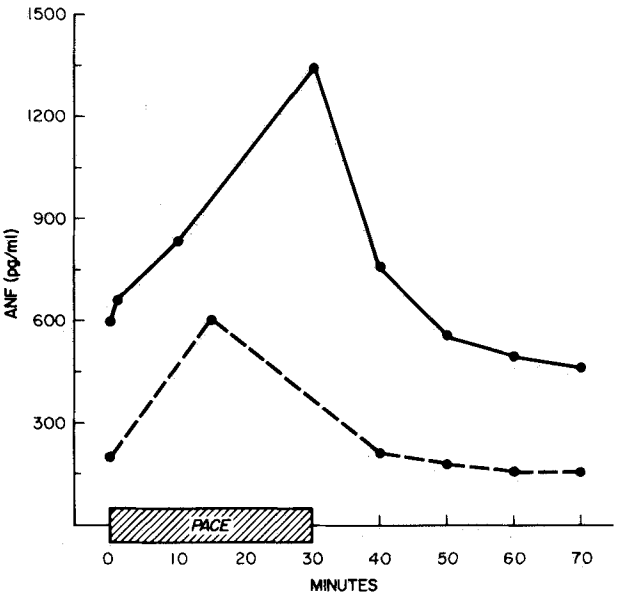

Figure 2. ANF levels of 2 pigs electrically paced at 150% of their basal heart rate for 30 min (pace). ANF levels returned to baseline over the following 40 min.

Atrial distention increases ANF levels. The many pharmacological and pathological stimuli associated with high ANF levels all increase right atrial pressure. During hemorrhage, however, right atrial pressure showed a significant and left atrial pressure, a non-significant decrease while ANF levels rose. These animals were capable of decreasing ANF levels from control values, and would be expected to do so following hemorrhage, based on their right atrial pressures. They instead increased ANF levels, so there is a physiologic mechanism for ANF release other than atrial stretch. Tachycardia seems the likely mediator of ANF release. Paroxysmal atrial tachycardia has been reported to increase ANF levels[5,6] and cardiac pacing markedly increased ANF levels (fig. 2). Hemorrhage and pacing both lower blood pressure, so they can both stimulate release of catecholamines, vasopressin and renin. Pacing is a lesser stimulus to release of these hormones but was associated with greater ANF levels, so stress hormones would not seem likely mediators of the ANF response. ANF levels can be increased by atrial distention and another mechanism, probably tachycardia.

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Detection of high concentration of Mg and Ca in the nematocysts of various cnidarians[1]

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Summary. An X-ray spectral analysis (EDAX) of isolated undischarged nematocysts of various cnidarians *(Hydrozoa, Scyphozoa, Anthozoa)* revealed the presence of extremely high concentrations of divalent cations. In *Hydra* nematocysts both Ca^{2+} (conc. 0.36 µmole/mg dry cysts) and Mg^{2+} (conc. 0.80 µmole/mg dry cysts) ions add up to a total in situ concentration of 0.5 to 1.0 M. More than 85% of the cations, which are believed to be involved in cyst discharge, are contained in the soluble fraction of the cysts, where they must be bound to high molecular weight molecules.
Key words. Calcium; magnesium; nematocysts; *Hydra; Cnidaria.*

The stinging cells (nematocytes, cnidocytes) of the *Cnidaria (Hydrozoa, Cubozoa, Scyphozoa, Anthozoa)* are undoubtedly the most complex cells found in the animal kingdom[3]. The prominent organelle of these cells is a spherical or oblong capsule (nematocyst, cnidocyst, fig. 1) which upon adequate triggering[4] ejects its tubular content by a process of evagination[5–7]. There are about 30 different types of cysts and, accordingly, of nematocytes[4,8,9]. Their function is associated mainly with prey capture and/or defense. The majority of cysts contain toxins and enzymes[10–13], which when introduced into the target by the exploding cyst paralyze and kill the prey or the potential aggressor[5,7]. Some of these toxins can even be fatal for man[12,14].

The violent discharge of the cyst is an extremely rapid event in the course of which the cyst's tubule and its associated structures, such as spines, stylets, barbs etc. are ejected by evagination from the interior of the capsule. In the stenoteles of *Hydra* it is completed within 3 ms[6].

Neither the magnitude nor the nature of the forces enacting and sustaining this process are known. However, various theories dealing with this phenomenon have been proposed[4,7]. There is increasing evidence that the intracapsular pressure required for the cyst's explosion is, at least partly, built up osmotically. The discharge of triggered anthozoan cysts is accompanied by a rapid uptake of water by the latter. Simultaneously the cysts release Ca-ions into the surrounding medium[15–17]. In fact, the undischarged nematocysts of *Anthozoa* have been found to contain large amounts of calcium[16,18,19]. The causal relationship between Ca release and water uptake, however, is still not understood.

In the course of investigations concerned with the morphodynamics and energetics of nematocyst discharge in *Hydra*[5–7]