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Atrial Natriuretic Factor in Patients With Congenital Heart Disease: Correlation With Hemodynamic Variables

INGRID OBERHÄNSLI, MD, BERNADETTE MERMILLOD, BSc, HERVÉ FAVRE, MD, BEAT FRIEDLI, MD, FACC, ERIC GIRARDIN, MD, LUC PAUNIER, MD

Geneva, Switzerland

To investigate the alpha-atrial natriuretic factor in congenital cardiac malformations, three groups of children, aged 7 months to 16 years, with different hemodynamic situations were studied during routine cardiac catheterization. Twenty-one (group I) had tetralogy of Fallot, 24 (group II) had a left to right shunt with pulmonary hypertension and 12 (control group) had a minor cardiac lesion. Alpha-atrial natriuretic factor levels were determined by a radioimmunoassay on blood samples from the inferior vena cava, right atrium, pulmonary artery, left atrium and aorta. To evaluate the effect of an acute volume load, measurements of hormone and pressures were repeated after right ventriculography.

Alpha-atrial natriuretic factor levels varied over a wide range in all groups and in all chambers investigated. Nevertheless, children with pulmonary hypertension had significantly higher levels of the hormone ($p < 0.01$) and were well separated from the control group, but less well from those with tetralogy of Fallot. A 50% increase of alpha-atrial natriuretic factor from the inferior vena cava to the right atrium occurred in patients with shunt lesions with pulmonary hypertension and in patients with tetralogy of Fallot ($p < 0.001$) and a further 30% increase from the right atrium to the pulmonary artery ($p < 0.05$). After right ventriculography, a 100% to 200% increase of alpha-atrial natriuretic factor was observed in the total sample ($p < 0.001$).

A positive correlation was observed between right atrial mean pressure and right atrial alpha-atrial natriuretic factor ($r = 0.63$) and between pulmonary artery mean pressure and pulmonary artery alpha-atrial natriuretic factor ($r = 0.61$).

Alpha-atrial natriuretic factor is thus only slightly increased in the presence of pressure overload (group I) but significantly increased in the presence of combined volume and pressure overload (group II). Temporary right ventricular volume overload with contrast medium is accompanied by temporary pressure increase in the right atrium and ventricle and acts as a further stimulus for alpha-atrial natriuretic factor release. The increase of the latter between the right atrium and pulmonary artery, statistically significant in group I and group II patients, suggests an intraventricular site for alpha-atrial natriuretic factor production and release.

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Atrial natriuretic hormone has been isolated from animals and humans (1–5). Increased levels occur in the presence of severe congestive heart failure of various origins (6–9) during the state of paroxysmal supraventricular tachycardia or atrial fibrillation (10,11) and in systemic hypertension (12–14). Alpha-atrial natriuretic factor in now recognized as an important regulator of blood pressure and water and electrolyte balance in humans (15–17). However, uncertainty still exists about the production centers of the hormone other than the right and left atria (18,19), especially in patients with congenital cardiac malformations.

In children with such malformations, limited information is available regarding alpha-atrial natriuretic factor secretion (20–31). We therefore evaluated levels of the hormone during cardiac catheterization in children with two congenital cardiac malformations with distinct hemodynamic features: tetralogy of Fallot presenting with right ventricular pressure overload (group I) and left to right shunt lesions with various degrees of pulmonary artery hypertension (group II). A third group with minor cardiac abnormalities served as the control group. The effect of right ventricular

From the Clinique de Pédiatrie, Centre d'Informatique Hospitalière and Division de Néphrologie, Hôpital Cantonal Universitaire, Geneva, Switzerland.

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Address for reprints: Ingrid Oberhänsli, MD, Hôpital Cantonal Universitaire, Clinique de Pédiatrie, 30 Boulevard de la Cluse, 1205 Geneva, Switzerland.

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Table 1. Description of Patients

	Group I (tetralogy of Fallot)	Group II (left to right shunt with pulmonary hypertension)	Control Group (minor cardiac lesions)
Number	21	24	12
Mean age (yr)*	6.8 (1.8 to 14.7)	5.0 (0.6 to 13.1)	6.2 (1.3 to 16.4)
Gender (F/M)	7/14	14/10	5/7
Mean weight (kg)	18.0 (9 to 37)	14.9 (5.5 to 33.8)	21.7 (8.4 to 45.5)
Mean height (cm)	109 (83 to 154)	103.4 (67 to 177)	112.2 (73 to 152)
Hematocrit (%)	57.9 (36.2 to 72.5)	40.8 (35.4 to 59)	39.2 (29 to 44)
Hemoglobin (g/100 ml)	16.6 (12.2 to 23.2)	13.4 (10.5 to 19.8)	13.4 (9.5 to 14.8)

*Values in parentheses are ranges. F = female; M = male.

angiography on the release of alpha-atrial natriuretic factor was also evaluated in these conditions.

Methods

Study patients (Table 1). The study comprised 57 children, aged 7 months to 16 years, undergoing elective preoperative cardiac catheterization for a congenital cardiac malformation. Twenty-one patients had tetralogy of Fallot (group I), 24 patients had a left to right shunt lesion (group II), with ventricular volume overload and various degrees of pulmonary hypertension in 21 and no or minimal elevation of pulmonary artery pressure in 3, and 12 patients had only minor cardiac abnormalities (the control group). This latter group included five children operated on for a ventricular or atrial septal defect several months or years earlier; four others had mild pulmonary or aortic stenosis and the other three were studied because of arrhythmias. The primary diagnosis was established by clinical investigation, two-dimensional echocardiography, Doppler evaluation and measurement of atrial, arterial and ventricular diameters by M-mode ultrasonography. Thirteen of the 21 group I patients were given beta-blocking medication (propranolol, 1 to 5 mg/kg body weight per day); 16 of the 24 children in group II were given digoxin (10 μg/kg per day) and 9 of the group II patients were also given furosemide (2 to 3 mg/kg per day). Creatinine, electrolyte and protein plasma concentrations were normal.

The study protocol was approved by the local Research Board and the Ethics Committee of the Pediatric Department of the University of Geneva. Informed consent was obtained from parents or tutors.

Cardiac catheterization. After a 6 to 12 h fasting period, patients were sedated in the morning, 60 min before cardiac catheterization, with a "cocktail" of dichlorpromazine, promethazine and pethidine. A complete right and left heart hemodynamic study was performed. Pressure measurements were obtained by a standardized method under baseline conditions and after right ventricular angiography with 1 ml/kg of contrast medium in patients with tetralogy of Fallot and control patients and 1.5 to 2 ml/kg in patients with a shunt and pulmonary hypertension. In addition, in seven patients a continuous right atrial mean pressure measurement was possible during angiography through a second venous catheter placed in the right atrium. The contrast medium used, iopamidol, is nonionic, low osmolar, hyperviscous and has an elimination half-life of 2 h.

Alpha-atrial natriuretic factor. Plasma concentrations of alpha-atrial natriuretic factor were determined before and after right ventricular angiography in the inferior vena cava, right atrium, pulmonary artery, aorta and left atrium when entered. For ethical reasons, blood sampling of a maximum of 16 ml blood was accepted for the study in children weighing >10 kg. Blood samples of 2 ml were obtained in a rapid sequence at the sites mentioned for measurements of alpha-atrial natriuretic factor and oxygen saturation; 1.5 ml of each sample was transferred into chilled, siliconized disposable tubes containing Trasylol (aprotinin) and ethylenediaminetetraacetic acid (EDTA), then immediately placed on ice and promptly centrifuged. The plasma was adjusted to a pH of 4 and immediately frozen at −20°C. After extraction, a radioimmunoassay using the iodine-125–labeled alpha-atrial natriuretic factor (produced by Amersham International), and the antibody (supplied by Peninsula Laboratories) was performed for alpha-atrial natriuretic factor determination, as described elsewhere (32). The number of samples analyzed for each group appears in Figure 1. For our laboratory, the intra- and interassay variation coefficients were 10.9% and 13.5%, respectively. The recovery of alpha-atrial natriuretic factor after the extraction procedure was 79%.

Statistical analysis. A log transformation of alpha-atrial natriuretic factor values was used to stabilize the variances and to normalize the distribution. One-way analysis of variance was used to compare the three groups with use of Welch's test when the variances were considered to be different by the Levene test. In case of significant differences among groups, pairwise comparison of means with the Bonferroni criterion were performed. Two-sided p values <0.05 were considered significant. With the clinical and

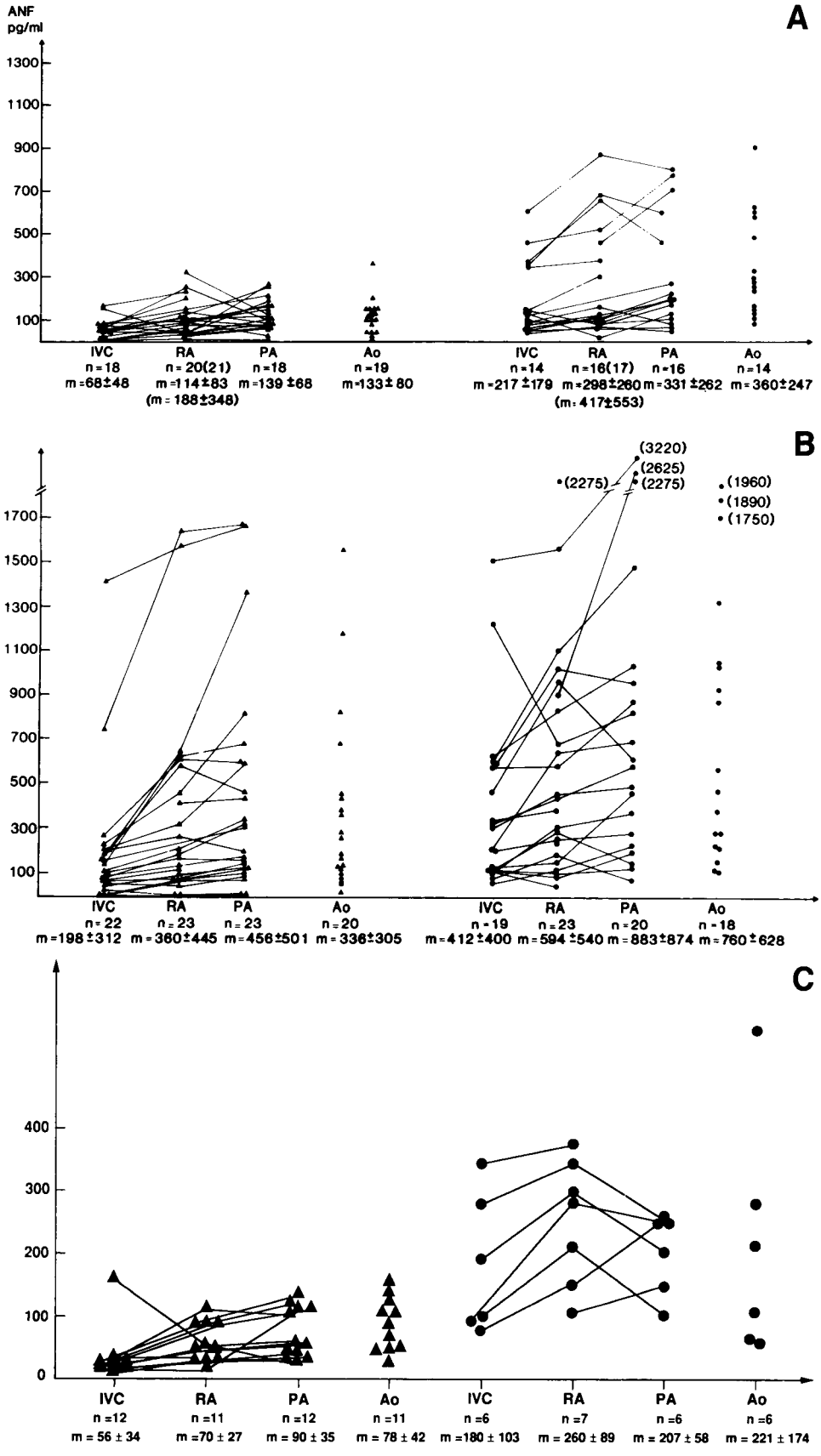

Figure 1. Concentrations of atrial natriuretic factor (ANF) (pg/ml) (**A**) in children with tetralogy of Fallot (group I); (**B**) in children with a left to right shunt lesion and pulmonary hypertension (group II); and (**C**) in children with minor cardiac lesions (control group). Note the increase of alpha-atrial natriuretic factor concentrations from the inferior vena cava (IVC) to the right atrium (RA) and to the pulmonary artery (PA) and the aorta (Ao), before (**triangles**) and after (**circles**) right ventriculography (angio). A rather wide dispersion of individual values exists within the three groups. The number of plasma measurements obtained, the mean values (m) and the standard deviations are shown below each graphic presentation.

Table 2. Hemodynamic Variables and Plasma Concentration of Immunoreactive Alpha-atrial Natriuretic Factor in 57 Children

	Group I		Group II		Control Group	
	Before A	After A	Before A	After A	Before A	After A
No. of measurements	21	19	24	23	12	5
QP/QS	0.7 (0.1 to 1.2)		2.8 (1 to 7.2)		1.0 (1.0 to 1.2)	
Pressures (mm Hg)						
Mean						
RA	6 (1 to 22)	9 (3 to 27)	4 (1 to 10)	7 (2 to 12)	2.5 (1 to 4)	6 (3 to 12)
RV S	107 (40 to 200)	112 (83 to 190)	64 (26 to 105)	72 (32 to 120)	29 (16 to 55)	38 (20 to 65)
RV D	9 (4 to 24)	11 (6 to 30)	7 (3 to 12)	9 (4 to 18)	5 (4 to 8)	8 (4 to 14)
PA	13 (6 to 20)	15 (10 to 20)	42 (14 to 73)	50 (19 to 84)	14 (9 to 21)	23 (11 to 42)
LA	7 (3 to 12)	9 (6 to 13)	12 (6 to 22)	12 (11 to 14)	7 (4 to 10)	10 (10)
AO	80 (60 to 120)	87 (62 to 132)	74 (60 to 85)	77 (63 to 90)	76 (66 to 90)	77 (56 to 92)
α-ANF (pg/ml)						
Mean						
IVC	68 (10 to 169)	217 (42 to 612)	198 (10 to 1,417)	412 (63 to 1,568)	56 (28 to 162)	181 (70 to 346)
RA	114 (10 to 308) [*188 (10 to 1,662)	298 (21 to 875) 417 (21 to 2,310)]	360 (10 to 1,655)	594 (45 to 2,275)	70 (35 to 122)	260 (122 to 378)
PA	139 (10 to 262)	331 (49 to 805)	456 (10 to 1,697)	883 (74 to 3,220)	90 (46 to 147)	207 (105 to 266)
LA	128 (24 to 210)	228 (77 to 525)				
AO	133 (10 to 365)	360 (95 to 910)	336 (10 to 1,190)	760 (116 to 1,960)	78 (38 to 168)	221 (66 to 567)
M-mode echo						
Ratio LA/AO diameter	1.0 (0.73 to 1.5)		1.5 (1.0 to 2.1)		1.1 (1.0 to 1.2)	

Values in parentheses are ranges. Groups are defined as in Table 1. * = with inclusion of the patient in right heart failure. A = angiography; α-ANF = plasma alpha-atrial natriuretic factor; AO = aorta; D = diastole; echo = echocardiography; IVC = inferior vena cava; LA = left atrium; PA = pulmonary artery; QP = pulmonary flow; QS = systemic flow; RA = right atrium; RV = right ventricle; S = systole.

laboratory data and the hemodynamic variables, we performed a stepwise discriminant analysis. Linear regression analyses were carried out between hemodynamic variables and alpha-atrial natriuretic factor values.

Results

Hemodynamic findings (Table 2). The hemodynamic variables differ significantly among groups but are rather similar within each study group. All patients with tetralogy of Fallot (group I) had very low pulmonary artery mean, systolic and diastolic pressures, systemic pressures in the right ventricle and a dominant right to left shunt. Only one patient in this group was in right heart failure with a mean right atrial pressure of 22 mm Hg at cardiac catheterization.

Pulmonary artery pressure varied among the patients with a left to right shunt (group II). Pulmonary hypertension was severe in three patients who had developed a bidirectional shunt, whereas three had normal pulmonary artery pressures. All patients except the three with Eisenmenger syndrome had a very high pulmonary artery flow rate and a pulmonary to systemic flow ratio >2.

In the control group, 4 of the 12 patients still had mildly increased pulmonary artery pressures, although their shunt lesion had been surgically closed >6 months earlier; the other 8 patients had no shunt and had normal hemodynamic variables.

Plasma alpha-atrial natriuretic factor concentrations (Table 3). *Group I. Patients with tetralogy of Fallot malformation.* Mean plasma values in these patients were slightly but insignificantly higher than in the control group and compared with reported values in children with tetralogy of Fallot malformation (20–22,24,29). Alpha-atrial natriuretic factor concentrations varied within the groups over a wide range (Fig. 1). There was one patient with extremely high plasma values (1,662 pg/ml) presenting with right heart failure (as mentioned earlier). A stepwise increase in plasma values

Table 3. Atrial Natriuretic Factor: Ratio of Means With 95% Confidence Intervals

	Group I	Group II	Control Group
RA/IVC	1.62 (1.21 to 2.16)	1.60 (1.23 to 2.08)	1.41 (0.97 to 2.04)
PA/RA	1.36 (1.05 to 1.76)	1.29 (1.01 to 1.64)	1.18 (0.84 to 1.67)
PA/IVC	2.05 (1.50 to 2.80)	2.07 (1.55 to 2.77)	1.69 (1.15 to 2.48)
AO/PA	0.94 (0.72 to 1.22)	0.92 (0.72 to 1.18)	0.78 (0.56 to 1.09)
AO/IVC	1.84 (1.42 to 2.38)	1.88 (1.47 to 2.41)	1.43 (1.03 to 1.99)

*Differences of atrial natriuretic factor concentration between chambers in log scale were "back"-transformed to present the ratio of ANF means together with the 95% confidence levels by use of Bonferroni criteria. Groups are as defined in Table 1; abbreviations as in Table 2.

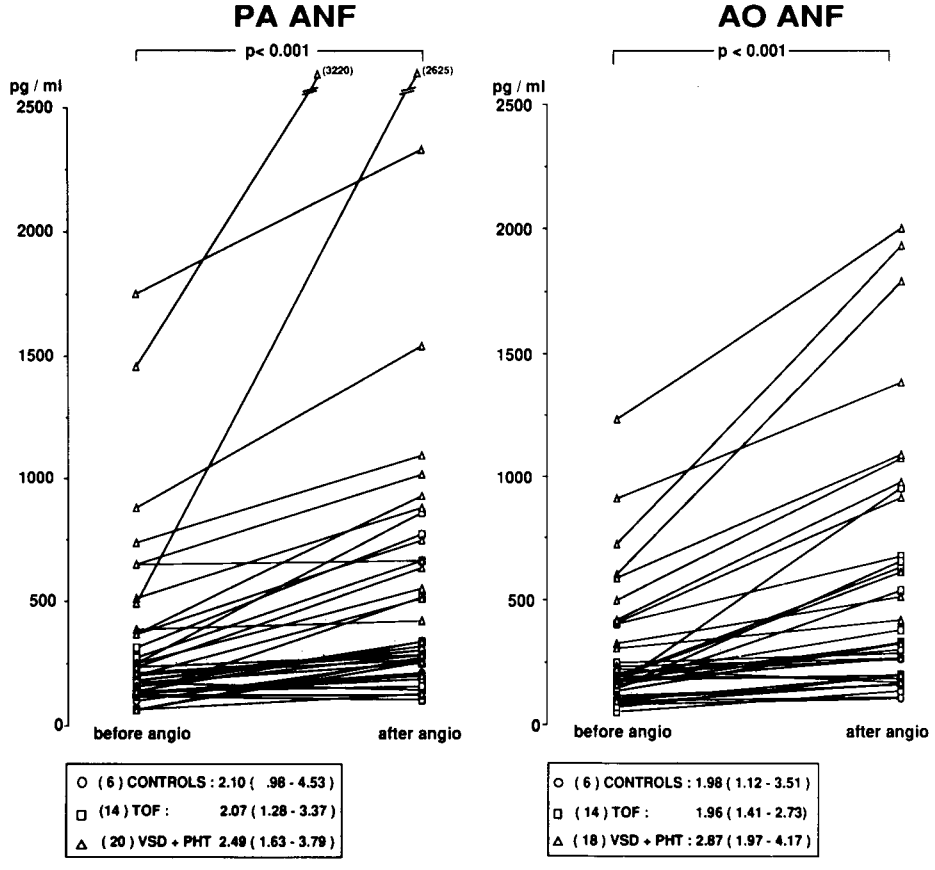

Figure 2. Right ventriculography (angio) with 1 to 2 ml/kg of contrast medium produces a very significant increase in alpha-atrial natriuretic factor (pg/ml) in the aorta (AO ANF) and pulmonary artery (PA ANF) in 14 patients with tetralogy of Fallot (TOF) (group I), 20 with ventricular septal defect with pulmonary hypertension (VSD + PHT) (group II) and in 6 control patients. The ratio of changes between chambers and the confidence limits are indicated in the boxes below each graph (see Table 3).

occurred from the inferior vena cava to the pulmonary artery and to the aorta ($p < 0.001$) (Table 3). No significant differences existed between plasma alpha-atrial natriuretic factor concentrations in patients receiving a beta-adrenergic blocking agent or in those without medication.

Group II. Patients with left to right shunt and pulmonary hypertension. Plasma alpha-atrial natriuretic factor concentrations in these patients were significantly higher than in the control group except in the inferior vena cava. No clear separation was possible between groups I and II as a result of the marked variations of individual values within groups and an important overlap: the three children who had a left to right shunt and normal pulmonary artery pressure had the lowest alpha-atrial natriuretic factor values. A significant and similar increase in plasma concentration occurred before and after angiography between the inferior vena cava and the right atrium ($p < 0.001$) but also between the right atrium and the pulmonary artery ($p < 0.03$) (Table 3). No significant difference was observed for alpha-atrial natriuretic factor values among children treated with digoxin or diuretics, or both, and untreated patients.

Angiography (Fig. 2). Right ventriculography produced a similar increase in alpha-atrial natriuretic factor excretion in all chambers in all three groups. This increase in plasma concentration was paralleled by a temporary increase in mean right atrial and right ventricular diastolic pressures.

Regression analyses (Fig. 3). For the total group, a positive correlation was found between right atrial mean pressure and right atrial alpha-atrial natriuretic factor concentration ($r = 0.63$, $p < 0.01$) and between right atrial and pulmonary artery mean pressures and pulmonary alpha-atrial natriuretic factor values ($r = 0.61$, $p < 0.01$). A stepwise linear regression analysis for the total group selected mean pulmonary artery pressure, left atrial to aortic diameter ratio and mean right atrial pressure as independent predictors for right atrial ($R^2 = 0.79$) and pulmonary artery ($R^2 = 0.84$) alpha-atrial natriuretic factor values, respectively.

Discussion

In the present study, we determined alpha-atrial natriuretic factor excretion in three age-matched groups of children with very different congenital cardiac diseases and distinct and typical hemodynamic conditions. We also tried to characterize these cardiac conditions on the basis of alpha-atrial natriuretic factor concentrations.

Concentration of alpha-atrial natriuretic factor in different cardiac malformations. Plasma concentration measurements in all three groups were higher than reported values in normal children (20–24,29–31). In our study, a clear-cut separation of groups on the basis of alpha-atrial natriuretic

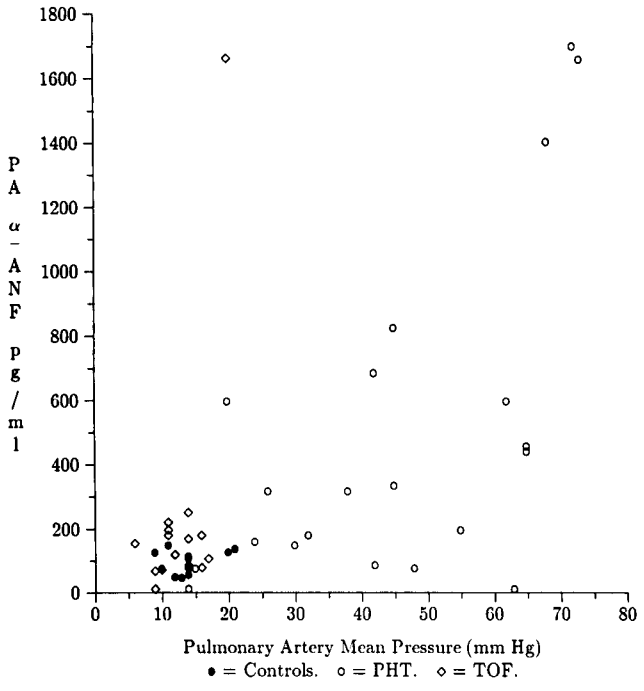

Figure 3. A positive correlation is shown between pulmonary artery mean pressure (mm Hg) and pulmonary artery (PA) alpha-atrial natriuretic factor (α-ANF) (pg/ml) for the total study group ($y = 16,5, \times -105$; $r = 0.61$; $p < 0.001$). Abbreviations as in Figure 2.

factor values was possible only between control patients and those with pulmonary hypertension (group II). Children with a shunt and with pulmonary hypertension, although receiving digitalis or a diuretic, or both, had higher plasma values than did patients with tetralogy of Fallot (group I) and control patients in the various sampling sites, thus confirming some of the previously reported observations when only peripheral venous blood samples were analyzed (20,24,26–28). As a result of very important variations within groups, the differences were statistically significant only between control patients and group II patients; the overlap among groups was especially important between control patients and those with tetralogy of Fallot, but it was also present among the other groups. Unfortunately, our study is lacking an entirely normal reference group, but for ethical reasons such a study in normal children is not possible.

Release of alpha-atrial natriuretic factor in atria and ventricles. Plasma values increased from the inferior vena cava to the right atrium and pulmonary artery in the total study group. Such findings were reported in some earlier studies in adults with congestive cardiomyopathy. In this condition there is a hypocontractile ventricle in contrast to the hypercontractile ventricle in children with a left to right shunt or tetralogy of Fallot. Except for two studies (29,30), the reported plasma alpha-atrial natriuretic factor values in children with congenital cardiac malformations have relied on determinations in peripheral venous blood samples only (20–24,26,27), whereas we studied serial concentrations in various intracardiac sites.

The increase from the inferior vena cava to the right atrium and from the right atrium to the pulmonary artery in our group I and group II patients suggests that an important alpha-atrial natriuretic factor release occurs not only in the right and left atria but also in the ventricles. Indeed, production centers other than the atria have been found in animal studies (8,19,33–35), in human fetuses and recently also in human adults (18,35–37). Cardiocytes containing increased levels of immunoreactive alpha-atrial natriuretic factor were isolated in ventricles of different species (35), and the hormone released from ventricular cardiocytes was shown to reach cardiac cavities partially through the great cardiac veins that drain into the coronary sinus (37) and it is probably also released directly into the ventricles. Because production of alpha-atrial natriuretic factor exists in fetal ventricles, we can only assume that an embryonic expression of hormone production centers in the ventricular cardiocytes that regresses under normal conditions by the end of pregnancy and after birth (20,38) is preserved in children with congenital cardiac malformations. Alternatively, this expression may be reinitiated when acquired heart diseases occur in children and adults, especially in association with heart failure. In our present study group, no significant age-related variations were observed, but neonates, infants and very young children were, for ethical reasons, not included in this protocol. The significant decrease of alpha-atrial natriuretic factor concentration from the aorta to the inferior vena cava is probably related to a high number of alpha-atrial natriuretic factor receptors all over the body and to rapid catabolism of the hormone.

Angiography and the release of alpha-atrial natriuretic factor. An acute volume load with a temporary pressure increase in the right atrium and ventricle resulting from right ventriculography induced a 100% to 200% increase in alpha-atrial natriuretic factor levels in the total study group; no significant difference occurred among the three subgroups. The contrast injection thus produced a stimulus for the release of atrial natriuretic factor whether the initial levels under baseline conditions were high or not. Because we used iopamidol, a nonionic, low osmolar but hyperviscous contrast medium, a chemical stimulus for the release of alpha-atrial natriuretic factor seems unlikely; thus, a combined stretch and pressure effect is probably the mechanism for the release of this hormone (Table 2, Fig. 1). This observation also suggests large reserves and additional production capacities.

Correlation of plasma alpha-atrial natriuretic factor and hemodynamic variables. In children with congenital cardiac malformations, the influence of the different hemodynamic variables on release of alpha-atrial natriuretic factor is mostly unknown (20,23–30). It has been speculated that increased hormone levels are directly related to elevated

pulmonary artery pressure at birth (20). We tried to correlate several variables (including echocardiographically determined left atrial to aortic diameter ratio, pulmonary artery pressure, right atrial mean pressure, pulmonary to systemic flow ratio) with the corresponding values of atrial natriuretic factor. Correlations were obtained in all these analyses with the best results obtained between right atrial and pulmonary artery mean pressures and alpha-atrial natriuretic factor plasma levels in the corresponding location ($r = 0.63$ and $r = 0.61$, respectively) (Fig. 3). A multivariate analysis for the total study group suggests that pulmonary artery pressure is as important as right atrial pressure and right atrial dimension for the prediction of alpha-atrial natriuretic factor concentration in the pulmonary artery and aorta; the large variations in concentrations within groups are still not completely explained by the individual hemodynamic variables. However, the different degrees of pressure or volume overload, or both, with different degrees of congestive heart failure do play an important role. Digitalis and diuretic treatment in most of our patients with a shunt lesion could have influenced this correlation, but the limited number of patients does not allow detailed analyses in this study. Indeed, 16 of the 24 patients were receiving digitalis and 9 of them were receiving both digitalis and a diuretic.

Conclusions. Our results show that different congenital cardiac malformations present with different plasma concentrations of atrial natriuretic factor. The differences in hormone levels within groups are probably related to the very specific hemodynamic status of each patient. In congenital cardiac malformations with volume or pressure overload, or both, the hormone release occurs probably not only in the atria but also in the ventricles. An adequate stimulus liberates further alpha-atrial natriuretic factor even when initial levels at baseline conditions are already markedly increased. To evaluate the influence of digoxin and diuretics on alpha-atrial natriuretic factor production, further studies with a large number of patients will be necessary. In congenital heart disease, the postulated release of atrial natriuretic factor in the ventricles needs further investigation on ventricular biopsy material, with emphasis on histochemical and histopathologic aspects.

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References

1. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981;28:89–94.
2. de Bold AJ. Atrial natriuretic factor: a hormone produced by the heart. Science 1985;230:767–70.
3. Atlas SA, Kleinert HD, Camargo MJ, et al. Purification, sequencing and synthesis of natriuretic and vasoactive rat atrial peptide. Nature 1984;309: 717–9.
4. Kangawa K, Matsuo H. Purification and complete amino acid sequence of α-human atrial polypeptide (α-hANP). Biochem Biophys Res Commun 1984;118:131–9.
5. Yandle TG, Espiner EA, Nicholls G, Duff H. Radioimmunoassay and characterization of atrial natriuretic peptide in human plasma. J Clin Endocrinol Metab 1986;63:72–9.
6. Raine AEG, Erne P, Bürgisser E, et al. Atrial natriuretic peptide and atrial pressure in patients with congestive heart failure. N Engl J Med 1986;315:533–7.
7. Hirata Y, Ishii M, Mastuoka H, et al. Plasma concentrations of α-human atrial natriuretic polypeptide and cyclic GMP in patients with heart disease. Am Heart J 1987;113:1463–9.
8. Riegger GA, Elsner G, Kromer EP, et al. Atrial natriuretic peptide in congestive heart failure in the dog: plasma levels, cyclic guanosine monophosphate, ultrastructure of atrial myoendocrine cells, and hemodynamic, hormonal, and renal effects. Circulation 1988;77:398–406.
9. Sugawara A, Nakao K, Morii N, et al. Synthesis of atrial natriuretic polypeptide in human failing hearts. J Clin Invest 1988;81:1962–70.
10. Roy D, Paillard F, Cassidy D, et al. Atrial natriuretic factor during atrial fibrillation and supraventricular tachycardia. J Am Coll Cardiol 1987;9: 509–14.
11. Tsai RC, Yamaji T, Ishibashi M, et al. Atrial natriuretic peptide during supraventricular tachycardia and relation to hemodynamic changes and renal function. Am J Cardiol 1988;61:1260–4.
12. Hamet P. Effect of natural and synthetic atrial natriuretic factor on atrial blood pressure, natriuresis and cyclic GMP excretion in spontaneously hypertensive rats. Clin Sci 1985;69:721–6.
13. Needleman P, Greenwald JE. Atriopeptin: a cardiac hormone intimately involved in fluid electrolyte and blood pressure homeostasis. N Engl J Med 1986;314:828–34.
14. Bolli P, Muller FB, Linder L, et al. Greater vasodilator responsiveness to atrial natriuretic peptide in low-renin essential hypertensives. J Hypertens 1987;5:S55–8.
15. Saxenhofer H, Weidmann P. Pharmakologische Effekte des atrialen natriuretischen Peptids beim Mechen. Z Kardiol 1988;77:6–10.
16. Indolfi C, Piscione F, Volpe M, et al. Cardiac effects of atrial natriuretic peptide in subjects with normal left ventricular function. Am J Cardiol 1989;63:353–7.
17. Roy LF, Ogilvie RI, Larochelle P, Hamet P, Leenen F. Cardiac and vascular effects of atrial natriuretic factor and sodium nitroprusside in healthy men. Circulation 1989;79:383–92.
18. Tsuchimochi H, Kurimoto F, Ieki K, et al. Atrial natriuretic peptide distribution in fetal and failed adult human hearts. Circulation 1988;78: 920–7.
19. Ding J, Thibault G, Gutkowska J, et al. Cardiac and plasma atrial natriuretic factor in experimental congestive heart failure. Endocrinology 1987;121:248–57.
20. Weil J, Bidlingmaier F, Döhlemann C, Kuhnle U, Strom T, Lang RE. Comparison of plasma atrial natriuretic peptide levels in healthy children from birth to adolescence and in children with cardiac diseases. Pediatr Res 1986;20:1328–31.
21. Kikuchi K, Shiomi M, Horie K, et al. Plasma atrial natriuretic polypeptide concentration in healthy children from birth to adolescence. Acta Paediatr Scand 1988;77:380–4.
22. Weil J, Strom TM, Heim JM, et al. Influence of diurnal rhythm, posture and right atrial size of plasma atrial natriuretic peptide levels. Z Kardiol 1988;77:36–40.
23. Rascher W, Tulassay T, Lang RE. Atrial natriuretic peptide in plasma of volume-overloaded children with chronic renal failure. Lancet 1985;2: 303–5.

24. Kikuchi K, Nishioka K, Ueda T, et al. Relationship between plasma atrial natriuretic polypeptide concentration and hemodynamic measurements in children with congenital heart diseases. J Pediatr 1987;111:335–42.

25. Oberhänsli I, Favre H, Friedli B, Girardin E, Paunier L. Atrial natriuretic factor in congenital heart disease before and after angiography (abstr). Eur Heart J 1988;9:251.

26. Matsuoka S, Karahashi Y, Tomimatsu H, et al. Plasma atrial natriuretic peptide levels in patients with ventricular septal defects. J Pediatr 1987;110:578–80.

27. Andersson S, Tikkanen I, Pesonen E, Meretoja O, Hynynen M, Fyhrquist F. Atrial natriuretic peptide in patent ductus arteriosus. Pediatr Res 1987;21:396–8.

28. Andersson S, Tikkanen I, Pesonen E, Wallgren EI, Fyhrquist F. Atrial natriuretic peptide and atrial pressures in newborns with transposition of the great arteries. Acta Paediatr Scand 1988;77:72–5.

29. Matsuoka S, Kurahashi Y, Miki Y, et al. Plasma atrial natriuretic peptide in patients with congenital heart diseases. Pediatrics 1988;82:639–43.

30. Ross RD, Daniels SR, Dolan LM, Young CA, Meyer RA. Determinants of plasma atrial natriuretic factor concentrations in congenital heart disease. Am J Cardiol 1988;62:785–8.

31. Schmidt KG, Cloez JL, Rascher W, Lange RE. Atrial natriuretic peptide in congenital heart defects with right heart volume overload (abstr). J Am Coll Cardiol 1988;11(suppl A):137A.

32. Larose P, Meloche S, Du Souich P, Delean A, Ong H. Radioimmunoassay of atrial natriuretic factor: human plasma levels. Biochem Biophys Res Commun 1985;130:553–8.

33. Nemer M, Lavigne JP, Drouin J, Thibault G. Expression of atrial natriuretic factor gene in heart ventricular tissue. Peptides 1986;7:1147–52.

34. Wei H, Rodi CP, Day MD, et al. Developmental changes in the rat atriopeptin hormonal system. J Clin Invest 1987;79:1325–9.

35. Seidman CE. Expression of atrial natriuretic factor in the normal and hypertrophied heart. Heart Failure 1989;5:130–4.

36. Kikuchi K, Nakao K, Hayashi K, et al. Ontogeny of atrial natriuretic polypeptide in the human heart. Acta Endocrinol 1987;115:211–7.

37. Yasue H, Obata K, Okumura K, et al. Increased secretion of atrial natriuretic polypeptide from the left ventricle in patients with dilated cardiomyopathy. J Clin Invest 1989;83:46–51.

38. Tulassay T, Rascher W, Seyberth HW, Lang RE, Toth M, Sulyok E. Role of atrial natriuretic peptide in sodium homeostasis in premature infants. J Pediatr 1986;109:1023–7.