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Atrial Natriuretic Peptide in Patent Ductus Arteriosus

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ABSTRACT. Plasma concentrations of atrial natriuretic peptide (ANP) were measured in nine infants (age 4 days–9 months) before and after closure of patent ductus arteriosus. Initially all patients had marked distention of the left atrium as indicated by a left atrium to aortic root ratio ≥ 1.3 on echocardiography. After closure of the ductus, operative in six and pharmacological in three patients, left atrial size normalized (left atrium to aortic root ratio < 1.3) in all patients, except in one treated surgically. Before closure the plasma concentration of ANP was 86–2224 pg/ml and after closure 44–1400 pg/ml. There was a significant correlation between the size of left atrium and plasma concentration of ANP ($r = 0.56$; $p = 0.01$). Our results suggest that in infants with patent ductus arteriosus the left atrium is the main source of ANP. The secretory rate of ANP decreases immediately after restoring left atrial size by closure of the ductus. (*Pediatr Res* 21: 396–398, 1987)

Abbreviations

ANP, atrial natriuretic peptide
LA/Ao, left atrium to aortic root

Mammalian atria contain peptides with potent diuretic, natriuretic, and vasorelaxing properties (1–5). These peptides are released in response to volume distention of the atria (6, 7). Plasma concentration of ANP is also increased in adult patients with congestive heart failure and supraventricular tachycardia (8, 9) and in children with different congenital heart and pulmonary diseases (10).

The ductus arteriosus closes postnatally within 12 h in 50% of full-term newborns and the closure is usually completed on the 3rd postnatal day (11). A delayed closure of the ductus increases the pulmonary flow, which leads to distention of the left atrium during systole when the mitral valve is closed preventing the pulmonary venous return to the left ventricle (12). The size of the left atrium can be estimated by echocardiography (Fig. 1) (12). Incomplete closure of the ductus is frequently seen in prematures and in newborns with respiratory distress syndrome (11). Therapeutical closure of the ductus, by indomethacin or by operation, may be needed because of symptoms due to the increased pulmonary circulation through the open ductus (13).

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The aim of the present work was to study the effect of distention of the left atrium on the plasma concentration of ANP in infants with patent ductus arteriosus and in response to restoration of the normal atrial size by closure of the ductus.

PATIENTS AND METHODS

Patients. Nine patients underwent therapeutic closure of patent ductus arteriosus as summarized in Table 1. The presence of a patent ductus arteriosus was diagnosed clinically, radiologically, and echocardiographically. The diagnosis was confirmed perioperatively in the patients who underwent surgery and by decrease in atrial size in the newborns treated with indomethacin. None of the patients had signs of other cardiac diseases. The six neonates all had some degree of respiratory distress and they were cared for in a respirator at the time of the study.

The ductus was closed surgically in six patients and intravenous administration of indomethacin was instituted in three patients. Patient 9 was anaesthetized with thiopentone, fentanyl, pancuronium, nitrous oxide, and enflurane. Isotonic glucose was infused at constant rate (2.3 ml/kg/h) throughout the operation. The external diameter of the ductus of this patient measured at the operation was 8 mm.

Echocardiography. All echocardiographic examinations were performed by the same cardiologist before and after the closure of the ductus. The size of the left atrium was estimated by two-dimensional echocardiography as measured at endsystole just before the opening of the mitral valve. Dilatation of the left atrium was determined as a LA/Ao ratio of 1.3 or more (Fig. 1) (12).

Blood samples and assay method. Blood samples (0.5–0.8 ml) for determination of plasma ANP concentrations were taken immediately after the echocardiographic examinations. Samples were drawn from peripheral veins or through umbilical artery catheters. The same route was used for pre- and posttherapeutic sampling with the exception of patient 9. From this patient peripheral venous blood was collected pre- and postoperatively after the echocardiographic examinations, while blood from a radial artery catheter inserted for peroperative monitoring was sampled during the operation and until 24 h postoperatively. The blood samples were collected in ice cold K_2 EDTA tubes which were immediately centrifuged and the plasma (0.2–0.4 ml) was stored at −20° C.

Radioimmunoassay of ANP was carried out as described previously (14). Linear regression was applied for statistical evaluation of the data. The study protocol was approved by the ethical committee of the Children's Hospital, University of Helsinki.

RESULTS

All patients had initially marked dilatation of the left atrium as determined by a LA/Ao ratio of more than 1.3. The six

youngest patients, *i.e.* numbers 1 to 6, whose ages at the first examination were 1 wk or less, all had LA/Ao ratios of more than 1.4 (mean 1.67). Accordingly the highest ANP concentrations (mean 1507 pg/ml) were observed in this group. The three older patients, *i.e.* numbers 7, 8, and 9, had initially both lower LA/Ao ratios (mean 1.33) and ANP concentrations (mean 217 pg/ml) (Table 1 and Fig. 2).

After closure of the ductus the ANP level decreased in all patients and the LA/Ao ratio was normalized in all patients except in patient 7. This patient also showed one of the smallest changes of ANP concentration. There was a statistically significant correlation ($r = 0.56$; $p = 0.01$) between the size of the left atrium measured by the LA/Ao ratio and the plasma concentration of ANP (Fig. 2).

Operation of patient 9. The plasma level of ANP was not affected by anaesthesia or thoracotomy (Fig. 3). After ligation of the ductus the plasma concentration of ANP decreased instantly. Ten minutes after the ligation the concentration of ANP was 158 pg/ml which is 36% of the value (440 pg/ml) immediately before the ligation.

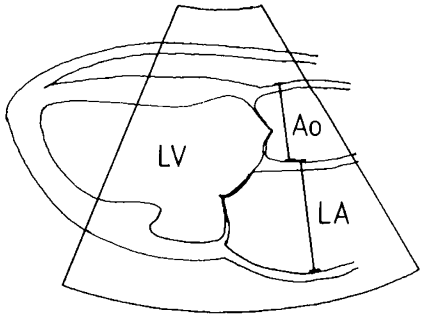

Fig. 1. Echocardiographic measurement of the LA/Ao ratio. *LA*, left atrium; *Ao*, aorta; *LV*, left ventricle.

DISCUSSION

In our investigation the initial ANP concentrations were higher in all patients than those measured in healthy adults (3, 8). The degree of distention of the left atrium correlated with plasma concentrations of ANP. The highest LA/Ao ratios were observed in the prematures and in this group both the posttherapeutic decrease in size of the left atrium and in plasma level of ANP were also most marked. It is possible that the great compliance of the atrium of the newborn, and especially of the premature,

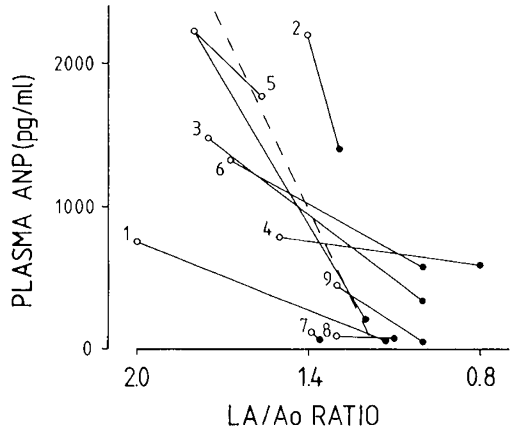

Fig. 2. Dependance of plasma ANP concentration on the left atrial size. Plasma ANP concentration is given as pg/ml and left atrial size as LA/Ao ratio. *Open circles* represent pretherapeutic and *closed circles* posttherapeutic measurements. Note that patient 5 was examined twice before closure of the ductus. The correlation ($r = 0.56$; $p = 0.01$) between plasma ANP concentration and LA/Ao ratio is indicated by the broken line ($y = -1030.8 \pm 1334.8 \times X$). Numbers of the patients are as in Table 1.

Table 1. *Patient data; measurement of LA/Ao ratio and plasma ANP*

Patient	Sex, gestational age, birth wt/length (g/cm) Apgar score 1/5 min	Initial examination			Posttherapeutic examination		
		Age	LA/Ao ratio	Plasma ANP (pg/ml)	Age	LA/Ao Ratio	Plasma ANP (pg/ml)
1	M, 25 + 0 wk, 760/32, 4/5	7 day	2.00	756	9 day (2 day)*	1.13	52
2	F, 24 + 6 wk, 760/33, 3/6	5 day	1.40	2200	8 day (0 day)	1.29	1400
3	M, 31 + 4 wk, 1790/44, 8/9	7 day	1.75	1480	9 day (2 day)	1.00	340
4	M, 28 + 6 wk, 1320/41, 2/8	6 day	1.50	784	9 day (2 day)	0.80	584
5	M, 31 + 0 wk, 1300/39, 8/9	4 day	1.56	1774			
		6 day†	1.80	2224	9 day (2 day)	1.20	204
6	F, 29 + 5 wk, 560/32, 1/7	4 day	1.67	1330	7 day (3 day)	1.00	574
7	M, 35 + 4 wk, 1930/45, 8/8	2.5 mo	1.39	114	2.5 mo (6 day)	1.36	64
8	F, 29 + 4 wk, 1555/38, 7/8	3 wk	1.30	86	3 wk (2 day)	1.10	72
9	F, 38 + 0 wk, 3130/51, 9/10	9 mo	1.31	450	9 mo (4 day)	1.00	44

* Time after therapy (indomethacin in patient 2, 3, and 4; operative in all the others).

† Patient 5 was examined twice before the therapy.

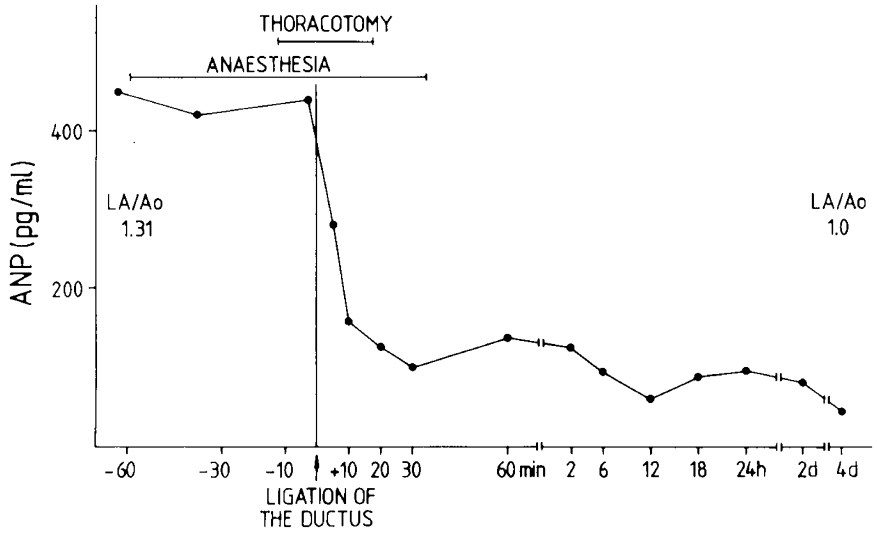

Fig. 3. Operative closure of the ductus of patient number 9. The ligation of the ductus, indicated by *arrow*, represent the zero time. Plasma ANP concentration is given as in Figure 2. The half-life of ANP is 4.0 min as estimated on the concentrations measured immediately before and 5 and 10 min after the ligation.

causes prominent strain on the atrial wall in the presence of a patent ductus arteriosus. Another factor responsible for the high ANP concentrations in the neonates may be the acute postnatal onset of the dilation of the atrium compared to the more chronic situation in the older children. In newborns there is a physiological increase of plasma ANP concentrations to a mean of 227 pg/ml 2–4 days postnatally (17). After the 4th day of life the normal values are 53–159 pg/ml (17). All neonates of our study were older than 4 days at the first examination and their initial ANP concentrations were 756–2224 pg/ml. Thus, developmental changes of ANP levels have negligible effects on our results.

Increased levels of circulating ANP have been measured in experimental animals with increased stretch of the left (15) or the right (7) atrium. Because the patent ductus arteriosus does not affect the size of the right atrium (13) the present results indicate that the distended left atrium is the most important source of ANP in infants with patent ductus arteriosus. This possibility is further confirmed by the instant decrease of ANP concentration after operative closure of the ductus in patient 9. The estimated half-life of ANP of 4 min in this patient also corroborates the short half-life of ANP in man as has been determined previously (16). This result is in accordance with the observation of the rapid decrease in ANP concentration after cessation of supraventricular tachycardia in adult patients (9). The differences in ANP levels measured after closure of the ductus may be caused by factors acting on the right atrium. There may also still be some strain on the left atrial wall, the left atrial size being at the upper limit of the normal at the time of the measurement. Moreover, because of the wide normal variation of the LA/Ao ratio, the obtained numerical values only semiquantitatively indicate the size of the left atrium of one individual, whereas in a group of patients the increased left atrial size, measured as a high mean LA/Ao ratio, reflects left atrial strain. However, small variations of the stretch of the left atrial wall that may affect the release of ANP are not measurable by noninvasive techniques.

In conclusion, infants with distended left atrium due to patent ductus arteriosus have markedly elevated plasma concentrations of ANP. The size of the left atrium is significantly correlated to the level of ANP. In this condition, high plasma ANP may be considered a marker of mainly left atrial wall strain. Reduction of plasma ANP may serve as an indicator of successful therapeutic closure of patent ductus arteriosus in infants. In view of the potent vasorelaxing properties of ANP (3), possible hemodynamic consequences of exaggerated ANP release in this condition should be considered and further explored.

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