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The neuroendocrinal system of the heart after construction of a Glenn anastomosis or the Fontan circulation

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MANY COMPLEX CARDIAC DEFECTS PRODUCE A functionally single ventricle, in which there is mixing of the systemic and pulmonary circulations. The output from the functionally single ventricle is divided between the two circulations: the proportion going to the systemic and pulmonary vascular beds being determined by the relative resistance to flows within the respective circulations.[1]

When systemic output is reduced, several compensatory mechanisms are activated to maintain the perfusion of vital organs. Most of these responses are due to the activation of the sympathetic nervous and the renin–angiotensin–aldosterone systems. Initially, there is an increase in the heart rate and myocardial contractility, with selective peripheral vasoconstriction, and retention of sodium and water. These systems are interrelated in maintaining cardiac output and systemic flow but, with time, they can become deleterious,[1] with the development of hypertrophy and cell death, which further contribute to cardiac contractile dysfunction (Fig. 1).

The myocardium responds to changes in loading conditions by ventricular remodelling. This involves not only the myocytic compartment, which responds by hypertrophy, but also the non-myocytic compartments, which respond to autocrinal and paracrinal signals. Increases in loading conditions are also associated with increased expression of natriuretic peptides.[1]

Natriuretic peptides are a family of four polypeptide hormones, which share a 17-amino acid disulphide ring structure with a highly conserved sequence. Each polypeptide is characterized by variable carboxy and amino end groups, giving rise to the atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide, and urodilatin.[2,3]

The atrial and brain peptides are primarily synthetized in the cardiac atriums and ventricles, respectively. They circulate in plasma, and directly modulate blood pressure and homoeostasis of body fluids and electrolytes. The C-type natriuretic peptide is mainly expressed in brain, but also in endothelium and other tissues. Its concentration in plasma is low, and it lacks a potent natriuretic action, but it possesses vasodilating and growth inhibiting actions. Urodilatin is produced in the distal tubules of the kidney and, when released, binds to luminal receptors in the collecting duct, resulting in a suppression of reabsorption of sodium.[2,3]

Three different receptors for the natriuretic peptides have also been identified, the A, B, C types. The receptor type-A seems to mediate many of the physiological effects of the atrial and brain peptides, while C-type natriuretic peptide is a potent selective activator of the receptor type-B. The receptor type-C has been thought to act as a clearance receptor.[4] The major determinant of secretion of the atrial natriuretic peptide is stretch of the atrial wall,[4] while it is the stretching of the ventricular myocytes that regulates the secretion of brain natriuretic peptide.[5]

The atrial and brain natriuretic peptides cause natriuresis, diuresis, and vasorelaxation. They inhibit the renin–angiotensin system, and secretion of endothelin and vasopressin. C-type natriuretic peptide, in contrast, may be a local regulator of vessel tone, and growth of vascular endothelial and smooth muscle cells.[4]

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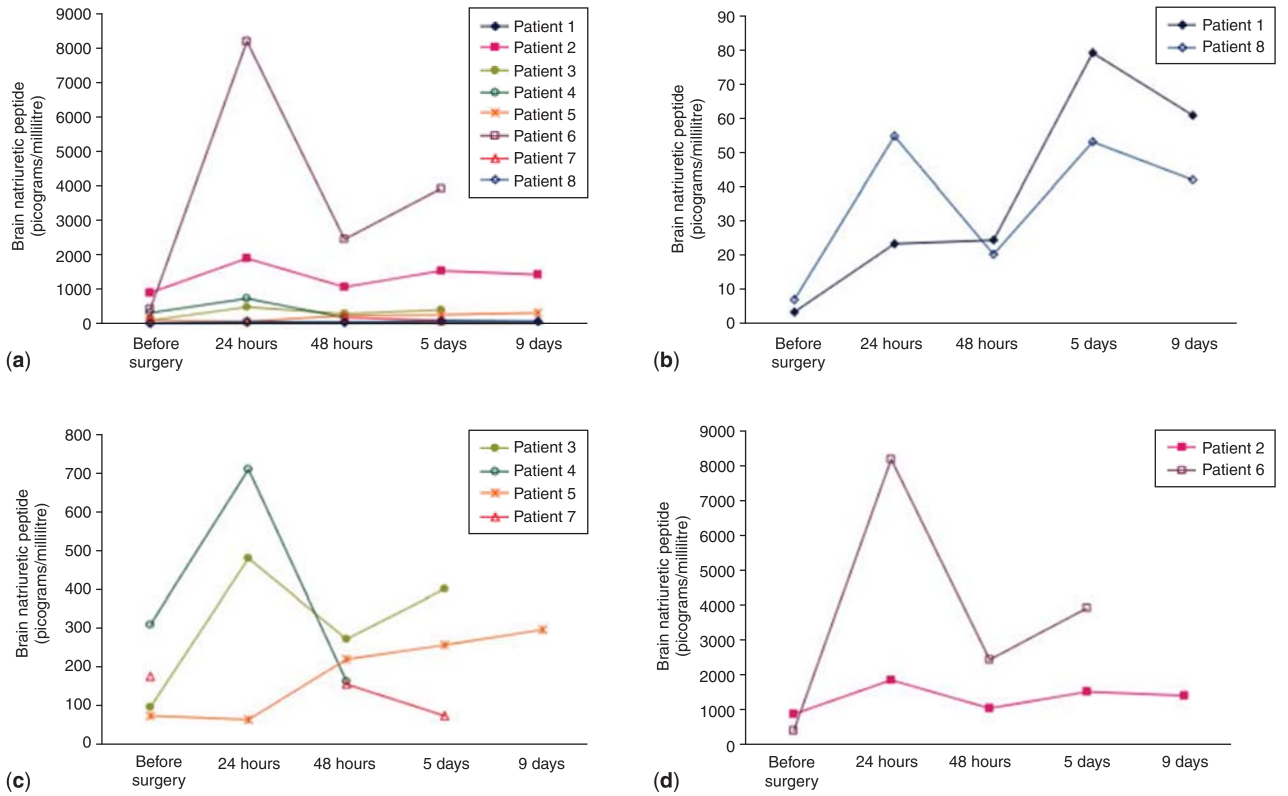

Figure 1.
In Figure 1a, we show the time course for levels of brain natriuretic peptide, in picograms per millilitre, in the plasma for all patients. Figure 1b shows the time courses of patients #1 and #8, in whom the value, before surgery, was less than 10 picograms per millilitre. Data from patients #3, #4, #5, and #7 with a value between 72.9 and 308.7 picograms per millilitre, are shown in Figure 1c. Figure 1d shows the time courses of patients #2 and #6, who had the highest initial values, at 886.9 picograms per millilitre and 429.1 picograms per millilitre, respectively.

In adults, the level of brain natriuretic peptide in the plasma has been demonstrated to be a useful biochemical marker of left ventricular dysfunction, acute myocardial infarction, and dilated cardiomyopathy Moreover it is also used for screening for cardiac function in primary care.[6]

To our current knowledge, there are relatively few studies, in children, in which the levels of brain natriuretic peptide in the plasma have been studied in the setting of congenital cardiac disease.[6–12] A small number have also been carried out in children with either a Glenn anastomosis or the Fontan circulation.[13–15] Our study is designed to evaluate the relationship between the levels of brain natriuretic peptide in the plasma and the outcome of children with either a Glenn anastomosis or a Fontan circulation. Our main intent was to establish if the levels of the peptide could be a useful prognostic marker after surgery.

Materials and methods

We studied eight patients, aged from 1 year to 8 years and 2 months, three of whom were male, undergoing either construction of the Fontan circulation or a Glenn anastomosis at our institution from March 2004 to July 2004 (Table 1). The study was approved by the Ethics Committee of the "G. Pasquinucci Hospital", and of the "Institute of Clinical Physiology" of the Italian National Research Council. Informed consent was obtained from all patients.

Collection and analysis of blood samples

Blood samples for the measurements of brain natriuretic peptide were obtained from all patients at admission, and 24 hours, 48 hours, five days, and nine days postoperatively. All the samples were collected in ethylene diamine tetracetic acid vacutainers, immediately chilled in ice, centrifuged, and frozen at −20 degrees Celsius. All samples from the same patient were analysed in the same session, so as to minimize the error between assays.

The measurements were performed using the AxSYM® platform (Abbott Laboratories, Diagnostic Division, Abbott Park, USA); in particular, by a Microparticle Enzyme Immuno-Assay. The reference intervals for our laboratory are 0 to 110 picograms per millilitre.

Table 1. Intra- and post-operative characteristics of patients.

Patients	Sex	Age	Intervention	Cardiopulmonary by-pass time (minutes)	Clamp time (minutes)	Cardioplegia (doses)	Intensive care unit stay (days)	Complications (numbers)	Inotropics drugs (administration days)
1	Female	3 years and 6 months	Fontan (fenestrated)	95	No	No	3	1	2
2	Male	1 year and 3 months	Glenn	122	44	2	15	7	4
3	Female	8 years and 2 months	Glenn	54	No	No	1	2	2
4	Female	1 year	Glenn	52	No	No	1	0	2
5	Male	7 years and 11 months	Fontan	81	No	No	2	0	2
6	Female	2 years	Fontan (fenestrated)	208	28	3	10	4	7
7	Female	5 years and 10 months	Fontan	113	No	No	2	1	2
8	Male	5 years	Fontan (fenestrated)	139	85	3	5	1	2

All statistical analysis was performed using Statview 5.0 (SAS Institute Inc, Cary, NC). The statistical difference between mean concentrations of the peptide at different time points were assessed by the Sheffè post hoc test after repeated measures analysis of variance. The continuous variables are expressed in the Tables as mean values plus or minus the standard deviation. A p-value of less than 0.05 was considered significant.

Results

Levels of brain natriuretic peptide in the plasma (Fig. 1a, Table 2)

We identified three clinical groups according to the value of brain natriuretic peptide measured prior to surgery. In our first group (Fig. 1b), we included our first and eighth patients, who had values before surgery of less than 10 picograms per millilitre. Their profiles are similar, showing an increase at 24 hours after surgery, higher in the eighth than the first patient. In the first patient, the value remained the same until 48 hours, increased to the fifth day after surgery, and finally decreased during the ninth day. In the eighth patient, a reduction was noted between 24 hours and 48 hours, a new increase on the fifth day, and a final decrement nine days after surgery. In both patients, the level of the peptide never exceeded 61 picograms per millilitre.

We placed the third, fourth, fifth and seventh children in the second group (Fig. 1c), with the initial value of peptide ranging between 72.9 and 308.7 picograms per millilitre. In the third patient, there was an increase at 24 hours, a decrease over the following 24 hours and, in the fifth day, a further increase. The value on the ninth day was not available. Our fourth patient also showed an increase 24 hours after surgery, but it diminished rapidly over the following 24 hours, falling to levels below those obtained prior to surgery by the fifth day. In the fifth patient, the level did not change in the first 24 hours after surgery, but subsequently increased slowly until the ninth day. For the seventh patient, for whom values at 24 hours and 9 days were unavailable, the value remained constant until 48 hours after surgery, and then decreased slowly until the fifth day.

We placed our second and sixth patients into a third group (Fig. 1d), these having the highest levels measured, specifically 886.9 picograms per millilitre in the second patient, and 429.1 picograms per millilitre in the sixth. In the second patient, the measured levels did not vary significantly during the monitoring. The sixth patient showed a high increment in the first 24 hours after surgery, which decreased at 48 hours, only to increase again 5 days after surgery.

Table 2. Time course of levels of brain natriuretic peptide in the plasma.

	Brain natriuretic peptide (picograms/millilitre)						
Patients	Before surgery	24 hours after surgery	48 hours after surgery	5 days after surgery	9 days after surgery	Mean value	Standard deviation
1	3.1	23.2	24.2	79.2	60.7	38.1	31.0
2	886.9	1876.8	1048.4	1533.1	1416.3	1352.3	394.0
3	94.3	479.4	271.4	400.7	XXX	311.5	168.3
4	308.7	711.3	161.5	XXX	XXX	393.8	284.6
5	72.9	63.3	218.8	256.8	295.2	181.4	106.9
6	429.1	8181.6	2450.2	3920.0	XXX	3745.2	3285.6
7	173.5	XXX	153.7	72.3	XXX	133.2	53.6
8	6.8	54.7	20.1	53.0	41.9	35.3	21.1

Table 3. Statistical data.

Univariate analysis		
Brain natriuretic peptide versus complications (numbers)	$R^2 = 0.473$	$p < 0.04$
Brain natriuretic peptide versus cardiopulmonary by-pass time (minutes)	$R^2 = 0.492$	$p < 0.04$
Brain natriuretic peptide versus intensive care unit time (days)	$R^2 = 0.563$	$p < 0.02$
Brain natriuretic peptide versus inotropic drugs (days)	$R^2 = 0.971$	$p < 0.0001$
Multivariate analysis		
Brain natriuretic peptide versus complications (numbers)	$p < 0.0001$	$p < 0.0001$
Brain natriuretic peptide versus inotropic drugs (days)	$p < 0.0001$	$p < 0.0001$

Univariate and multivariate analysis (Table 3)

Univariate analysis showed the levels of peptide to be correlated with the number of complications (p less than 0.04), with the duration of cardiopulmonary by-pass (p less than 0.04), with days spent in the intensive cure unit (p less than 0.02), and with the number of days in which an inotropic drug was administered (p less than 0.0001). Multivariate analysis revealed significant correlations with the number of complications, and the days of administration of inotropic drugs.

Discussion

Our preliminary study shows that the levels of brain natriuretic peptide in the plasma can, indeed, serve as a marker of cardiac performance in children undergoing cardiac surgery. Patients with lower values before surgery are those with better follow-up, taking into account the number of post-operative complications and the days requiring administration of inotropic drugs as markers of prognosis after surgery. Our two patients with the highest values of peptide prior to surgery had the worse post-operative courses. They needed a longer time in the intensive care unit, at fifteen and ten days, respectively, with a relevant number of complications, and also needed several days of inotropic support.

Irrespective of the absolute concentrations of the peptide, the time course was quite similar in all patients. Levels were at their maximum at 24 hours after surgery, while they had returned close to the initial values 48 hours postoperatively. The indication of a better prognosis, however, is correlated to the levels of the peptide. When the initial value is less than 300 picograms per millilitre, and the maximum value at 24 hours is lower than 720 picograms per millilitre, the patients had a better follow-up. Our preliminary study suggests that at least two measurement of the levels of brain natriuretic peptide in the plasma, at admission and either 24 or 48 hours after surgery, could be useful in monitoring the post-operative prognosis. Further studies, involving a much larger number of patients, are needed to confirm our initial findings.

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