Cardiol Young 2001; 11: 498–504

ISSN 1047-9511

Original Article

The pathogenesis of heart failure in infants with congenital heart disease

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Abstract *Background:* The clinical symptoms of heart failure in infants with left-to-right shunts are thought to be explained by well-known hemodynamic disturbances such as pulmonary hypertension and overcirculation, but previous studies have not, thus far, found the expected correlations with hemodynamic and clinical parameters. Based on the neurohormonal model of heart failure, we hypothesised that the clinical symptoms of infants with left-to-right shunts are also related to neurohormonal disorders. *Methods:* We compared various neurohormonal and hemodynamic parameters measured invasively in 70 infants with left-to-right shunts to the respiratory rate and gain in weight over a corresponding period of time. Heart rate correlated significantly with respiratory rate ($r = 0.62^{***}$, $p < 0.001$) and gain in weight ($r = -0.31^{*}$, $p = 0.015$), but more conventional measures of severity, such as the ratio of pulmonary to systemic flows, failed to show comparable correlations with clinical symptoms. Respiratory rate was related to levels of norepinephrine ($r = 0.47^{***}$, $p < 0.001$) and plasma renin activity ($r = 0.65^{***}$, $p < 0.001$). The important impact of autonomic imbalance on respiratory rate was underlined by an analysis of variability of heart rate in 26 infants that showed significantly reduced values for the domains of time and frequency. We were not able to find a conclusive multiple regression model with which to explain the symptom "failure to thrive". *Conclusions:* A increased heart rate, reduced variability in heart rate, and elevated levels of norepinephrine and renin are significant predictors of clinical symptoms such as tachypnea in infants with congenital cardiac malformations. The neurohormonal hypothesis, in which heart failure is interpreted not only as a hemodynamic derangement but also as a neurohormonal disorder, may be valid for infants with congenital cardiac malformations.

Keywords: Failure to thrive; tachypnoea; left-to-right shunt; neurohormonal activity

TACHYPNEA AND FAILURE TO THRIVE ARE WELL recognised symptoms of cardiac failure in infants with congenital cardiac malformations, a phenomenon which is thought to be explained by the well-known hemodynamic disturbances such as pulmonary hypertension and overcirculation. The anticipated correlations between the hemodynamic and clinical parameters, however, have yet to be demonstrated.[1,2]

In the 1990s, physicians began to think about cardiac failure as a neurohormonal disorder in an attempt to explain the clinical symptoms and progression of the disease.[3] In this respect, at least in adults with chronic heart failure, an augmented peripheral chemosensitivity due to autonomic imbalance has provided a pathophysiological explanation of tachypnea. Such autonomic imbalance due to elevated sympathetic activity is manifest by elevated levels of norepinephrine levels and reduced variability in heart rate.[4,5] Similarly, in adults with congestive heart failure, cardiac cachexia is more closely associated with hormonal changes than with conventional measures of its severity.[6–8]

In infants with congenital cardiac malformations, significantly elevated levels of norepinephrine, renin, and aldosterone provide evidence for a comparable pathophysiology.[9] So as to explore further the

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Accepted for publication 4 April 2001

neurohormonal concept, we have performed extensive clinical, neurohormonal, and hemodynamic monitoring of infants with cardiac failure in our institution since 1996. Based on these results, we recently initiated betablockade for such infants with severe cardiac failure.[10]

On the basis of this different conceptual models for cardiac failure, we further hypothesise that the clinical symptoms of infants with left-to-right shunts are related to both neurohormonal and hemodynamic disorders. In this study, therefore, we aimed to assess the relationship between symptoms such as tachypnea and failure to thrive with neurohormonal and hemodynamic parameters in infants with left-to-right shunts.

Patients and methods

Population studied and clinical parameters measured

Between January 1996 and January 2000, we studied a group of 70 infants with congenital cardiac malformations. Patients were enrolled in the study if they were less than 1 year of age at presentation. All infants had left-to-right shunts caused by deficiencies of the atrial, ventricular or atrioventricular septums, patency of the arterial duct, or more complex cardiac anomalies (Table 1). All patients were evaluated for cardiac surgery during infancy. We excluded those patients undergoing surgery except those with persistent left-to-right shunts after palliative procedures such as banding of the pulmonary trunk or repair of aortic coarctation. We also excluded patients in intensive care who needed mechanical ventilation or intravenous inotropic drugs, as well as infants with cardiomyopathies. Informed consent of the parents was obtained.

In those patients entering the study, we assessed clinical, hemodynamic and neurohormonal parameters at presentation and during a period of 6 weeks follow up. Respiratory and heart rates were taken from the patient records, these parameters being documented in all patients 3 times a day, being counted whilst the infants were quiet for at least 1 minute. Gain in weight was determined during the same interval of 2–6 weeks. The clinical data were measured at the same time that neurohormonal and hemodynamic parameters were evaluated. In 63 children, these data concerning neurohormonal and hemodynamic parameters were obtained during a period of hospitalisation for cardiac catheterization. For the purposes of multiple regression analysis, we excluded data from 7 infants because of a longer interval of 6 weeks between the evaluation of neurohormonal and hemodynamic parameters.

In those infants with left-to-right shunts and moderate clinical signs of heart failure, we routinely perform cardiac catheterization and surgery at a mean age of 6 months. Patients with more pronounced clinical symptoms despite medical therapy undergo catheterization and surgery at an earlier time, and with lower body weight.

Neurohormonal measurements

For determination of neurohormonal levels in the plasma, venous blood was drawn from non-sedated infants by an experienced paediatrician during routine collection of blood. Levels of norepinephrine and epinephrine were measured by a high-performance liquid chromatography with detection of fluorescence.[11]

Concentrations of immunoreactive renin (Nichols Institute Diagnostika GmbH, Bad Nauheim, Germany, sensitivity $>1.4\,\mu U/ml$), and up to 1997, activity of renin in the plasma, (DiaSorin GmbH, Düsseldorf, Germany, sensitivity $>0.2\,ng/ml/h$) were determined using commercially available immunoradiometric assays and used separately for statistical analysis.

Hemodynamic evaluation

Hemodynamic data were derived from preoperative catheterizations performed under local anesthesia and sedation with low dose midazolam (0.1–0.5 mg/kg iv). Systemic and pulmonary flows were calculated using the Fick principle and, since 1998, consumption of oxygen was measured directly (Deltatrac™ II, HOYER Medizintechnik, Bremen, Germany).

Table 1. Diagnosis of study patients.

Diagnosis	N	Palliative surgery	Additional coarctation	Down's syndrome
ASD/VSD	28	1	4	3
PAD	4		1	1
AVSD	19		3	14
Complex cardiac anomaly	19	3	3	1

Abbreviations: ASD: atrial septal defect; VSD: ventricular septal defect; PAD: patent arterial duct; AVSD: atrio ventricular septal defect

https://doi.org/10.1017/S1047951101000725 Published online by Cambridge University Press

Right atrial, pulmonary arterial, and mean arterial pressures were measured invasively. Left atrial pressure was measured directly or estimated using the pulmonary capillary wedge pressure. The indexes of systemic and pulmonary vascular resistance were calculated from the differences in pressure and the specific flows in the corresponding compartments of the circulation. Ejection fractions were determined by bi-plane volumetric analysis of the systemic ventricle as visualised cineangiocardiographically.

Processing and analysis of 24-hour-Holter-recordings

24-hour-Holter-recordings were obtained using two-channel recorders. All recordings were analysed with use of a MARS 5000® system (Marquette Hellige Medical systems, Milwaukee, WI, USA) for QRS labelling and editing, considering only those RR intervals which differed less than 20 percent from the previous interval.

Measurement and physiological interpretation of parameters of variability in heart rate were performed according to the standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[12] Normal values for such variability during infancy were taken from a previous study performed in healthy infants.[13]

Statistical analysis

Data were expressed as means plus and minus the standard deviation. For analysing the clinical symptoms of tachypnea and gain in weight, the population studied was divided into three groups according to the severity of the symptoms. The corresponding intervals for respiratory rate and gain in weight, used in the tables were determined on the basis of previously published scores for heart failure in infants.[10,14] To compare the differences between the subgroups, we used One-Way-ANOVA. Because we cannot assume a Gaussian distribution for variability in heart rate and the neurohormonal data, we used a Kruskal-Wallis test for this analysis.

For calculating correlations between the clinical, hemodynamic, and neurohormonal data, we used univariate regression analysis. Significant correlations were expected if the p-value was below 0.05. Data with significant correlations were used for multiple regression analysis. Within this analysis, we excluded in stepwise fashion all parameters with p-values above 0.3 in order to find a conclusive model explaining the clinical symptoms of tachypnea and failure to thrive. We expected to consider the model as appropriate if the r^2-value exceeded 0.5.

Results

Tachypnea

As shown in Table 2, higher heart rate, lower mean arterial pressure, and decreased systemic cardiac index were significant hemodynamic risk factors for tachypnea. The trend to higher ratios of pulmonary to systemic flows in those infants with tachypnea did not reach statistical significance. Arterial oxygen saturation, uptake of oxygen, mean pulmonary

Table 2. Oxygen consumption, ejection fraction and hemodynamics in infants with left-to-right shunts.

Respiratory rate (min^{-1}):	**<50**		**50–60**		**>60**			
	N	**mean ± SD**	**N**	**mean ± SD**	**N**	**mean ± SD**	**Significance**	**p-Wert**
Heart rate (min^{-1})	30	122 ± 11	18	127 ± 8	22	137 ± 10	***	<0.001
Ejection fraction (%)	27	64 ± 7	15	65 ± 7	16	68 ± 9	ns	0.17
LVedP (mmHg)	27	8.9 ± 2.4	23	8.9 ± 3.0	16	9.7 ± 3.2	ns	0.63
VO_2 (ml/min/m^2)	16	129 ± 19	7	139 ± 19	8	125 ± 33	ns	0.49
Qp/Qs	30	3.0 ± 1.7	18	3.9 ± 2.5	22	4.4 ± 2.5	ns	0.07
Qp (l/min/m^2)	30	7.2 ± 3.3	18	9.4 ± 4.4	21	8.6 ± 3.5	ns	0.11
Qs (l/min/m^2)	30	2.7 ± 1.0	18	2.6 ± 0.6	21	2.1 ± 0.5	*	0.02
RAP (mmHg)	30	5 ± 2	18	5 ± 2	21	6 ± 2	ns	0.16
LAP (mmHg)	27	10 ± 4	14	8 ± 3	18	8 ± 2	ns	0.36
PAP (mmHg)	30	33 ± 13	18	38 ± 15	18	31 ± 8	ns	0.2
MAP (mmHg)	30	63 ± 9	18	60 ± 8	21	54 ± 9	**	0.004
SVRI (WE x m^2)	30	23.2 ± 6.5	18	22.8 ± 6.9	21	24.4 ± 7.4	ns	0.76
PVRI (WE x m^2)	27	3.8 ± 1.8	14	3.6 ± 2.7	16	2.7 ± 1.2	ns	0.17
SaO_2 (%)	30	94 ± 7	18	94 ± 5	21	92 ± 5	ns	0.33

Results of One-Way-ANOVA: ***p < 0.001; **p = 0.001 to < 0.01; *p = 0.01–0.05; ns = not significant

Abbreviations: LVedP: left ventricular enddiastolic pressure; VO_2: oxygen consumption; Qp/Qs: ratio of pulmonary to systemic flow; Qp: pulmonary flow; Qs: systemic flow; RAP: mean right atrial pressure; LAP: mean left atrial pressure; PAP: mean pulmonary artery pressure; MAP: mean arterial pressure; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index; SaO_2: systemic oxygen saturation

https://doi.org/10.1017/S1047951101000725 Published online by Cambridge University Press

pressure, and systemic and pulmonary vascular resistances were not significantly different between the groups. Normal ejection fractions, end-diastolic left ventricular pressures, and mean averaged atrial pressures were evidence for normal ventricular function in all groups of patients.

Those infants without tachypnea, breathing less than 50 times per minute, all had normal age-specific levels of renin- and norepinephrine levels,[15,16] despite of a mean ratio of pulmonary to systemic flow of 3.0 ± 1.7 (Table 3). Compared to this group, infants with respiratory rates greater than 60 per minute had, on average, 8.8-fold higher activity of renin in the plasma, 5.1-fold higher concentrations of renin, and 2.3-fold higher levels of norepinephrine. In contrast, levels of epinephrine were not significantly different between the groups (Table 3).

For weighting the influence of the different parameters on respiratory rate, we performed multiple regression based on those parameters with significant results in univariate analysis (Table 4). Such univariate analysis showed heart rate as the most significant predictor for tachypnea ($r = 0.62^{***}$, $p < 0.001$), along with concomitantly elevated levels of norepinephrine ($r = 0.47^{***}$, $p < 0.001$). The activity of renin in the plasma correlated well with respiratory rate ($r = 0.65^{***}$, $p < 0.001$), but had to be excluded from multiple regression analysis because of the two different methods used in this study for its measurement. Hemodynamic predictors, such as mean arterial pressure ($r = -0.42^{**}$, $p = 0.001$), the ratio of pulmonary to systemic flows ($r = 0.27^{*}$, $p = 0.03$) and systemic cardiac index ($r = -0.32^{*}$, $p = 0.01$) showed lower correlation coefficients with respiratory rate. We found a significant but paradoxical correlation between respiratory rate and ejection fraction ($r = 0.3^{*}$, $p = 0.03$), with higher values in infants with pronounced tachypnea.

Table 3. Group characteristics, medication and neurohormonal activity in infants with left-to-right shunts.

Respiratory rate (min^{-1}):	**<50**		**50–60**		**>60**			
	N	**mean ± SD**	**N**	**mean ± SD**	**N**	**mean ± SD**	**Significance**	**p-Wert**
Age (month)	30	6 ± 2	18	4 ± 2	22	3 ± 2	***	<0.001
Bodyweight (kg)	30	5.7 ± 0.9	18	5.1 ± 1.2	22	3.9 ± 0.8	***	<0.001
Weight gain (g/week)	30	388 ± 158	18	357 ± 219	22	211 ± 270	*	0.018
Medication:								
Furosemide (mg/kg/day)	8	1.5 ± 0.6	6	1.5 ± 0.4	17	2.5 ± 1.4	ns	0.12
Spironolactone (mg/kg/day)	10	2.6 ± 1.4	12	2.6 ± 0.5	18	2.8 ± 0.6	ns	0.23
Digoxin (nmol/l)	13	0.8 ± 0.5	11	1.3 ± 0.5	17	1.2 ± 0.7	ns	0.12
Propranolol (mg/kg/day)	4	1.8 ± 0.6	4	1.7 ± 0.3	2	2.1 ± 0.4	ns	0.58
Captopril (mg/kg/day)	0		0		2	0.7 ± 0.5		
Neurohormonal activity:								
Plasma renin activity (ng/ml/h)	10	10 ± 7	7	35 ± 40	10	88 ± 64	**	0.005
Renin concentration (µU/ml)	16	177 ± 227	9	373 ± 677	9	907 ± 654	**	0.003
Norepinephrine (ng/l)	24	362 ± 219	14	420 ± 268	14	1041 ± 622	***	<0.001
Epinephrine (ng/l)	24	85 ± 157	14	112 ± 98	15	108 ± 125	ns	0.16

Results of Kruskal-Wallis-test: ***p < 0.001; **p = 0.001 to < 0.01; *p = 0.01–0.05; ns = not significant

Table 4. Univariate and multiple regression analysis considering hemodynamic and neurohormonal parameters as potential determinants of tachypnea in 63 infants with congenital heart disease. R-value for multiple regression analysis: $r^2 = 0.60$; $r = 0.78$.

	Univariate regression		**Multiple regression**	
	Coefficient of correlation	**p-value**	**Coefficient of regression**	**p-value**
Heart rate	0.62***	<0.001	0.41	0.002
Norepinephrine	0.47***	<0.001	0.18	0.16
Mean arterial pressure	−0.42**	0.001	−0.23	0.08
Ejection fraction	0.3*	0.03	0.27	0.25
Qp/Qs	0.27*	0.03	0.27	0.04
Qs	−0.32*	0.01	0.15	0.30

Abbreviations: Qp/Qs: ratio of pulmonary to systemic flow; Qp: pulmonary flow; Qs: systemic flow

https://doi.org/10.1017/S1047951101000725 Published online by Cambridge University Press

Table 5. Tachypnea and heart rate variability.[$]

Respiratory rate (min^{-1}):	<50 (N = 7)	50–60 (N = 8)	>60 (N = 11)	Significance	P-value
Baseline characteristics					
Mean NN (msec)	470 ± 41	469 ± 40	438 ± 32	ns	0.12
Time domain measures					
SDNN (ms)	55.4 ± 16.9	55.5 ± 16.0	33.6 ± 7.6	**	0.002
SDANN (ms)	47.0 ± 13.1	44.9 ± 12.5	27.1 ± 6.8	**	0.001
pNN50 (%)	4.1 ± 5.3	3.3 ± 3.9	2.0 ± 2.9	ns	0.6
rMSSD (ms)	19.6 ± 8.9	18.5 ± 9.4	14.9 ± 6.6	ns	0.58
Frequency domain measures					
Total power (ms)	23.6 ± 12.8	18.9 ± 7.1	13.8 ± 6.3	ns	0.06
VLF (ms)	14.4 ± 5.5	13.4 ± 4.6	8.8 ± 5.5	*	0.02
LF (ms)	14.5 ± 9.9	10.1 ± 4.5	6.1 ± 3.5	*	0.01
HF (ms)	8.4 ± 6.6	6.1 ± 2.5	4.7 ± 3.5	ns	0.18
LF/HF	1.9 ± 0.5	1.7 ± 0.4	1.5 ± 0.7	ns	0.22

[$]Plus-minus values are means ± SD; Results of Kruskal-Wallis-test: * p = 0.05–0.01; ** p = 0.001–0.01; *** p < 0.001; ns = not significant
Abbreviations: Mean NN: mean value of all normal RR intervals during 24 h; SDNN: standard deviation of all NN intervals; SDANN: standard deviation of the averages of NN intervals in all 5-minute segments; pNN50: number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; rMSSD: the square root of the mean of the sum of the squares of differences between adjacent NN intervals; Total power: heart rate power spectrum between 0.003 and 0.4 Hz; VLF: very low frequency power spectrum between 0.003 and 0.04 Hz; LF: low frequency power spectrum between 0.04 and 0.15 Hz; HF: high frequency power spectrum between 0.15 and 0.4 Hz; LF/HF ratio: ratio of low to high frequency power

Table 6. Bodyweight, weight gain and nutrition disorders.

Weight gain (g/month):	>400 (N = 29)	200–400 (N = 24)	<200 (N = 16)
Age (month)	4.5 ± 1.9	4.9 ± 2.5	3.6 ± 2.4
Birthweight (g)	3015 ± 578	3279 ± 520	3094 ± 614
Bodyweight (g)	5387 ± 187	5027 ± 1140	4290 ± 1470
Weight gain (g/month)	516 ± 109	304 ± 60	17 ± 165
Caloric intake (kcal/kg/day)	93 ± 16	107 ± 24	90 ± 25
<3% percentile (%/group)	34	67	57
3 to <10% percentile (%/group)	34	17	25
Vomiting (%/group)	24	21	38
Nasogastric tube (%/group)	14	21	50

The influence of sympathetic activation on respiratory rate was confirmed by an analysis variability in heart rate in a subgroup of 26 infants (Table 5). Significantly lower values for several parameters for heart rate in infants with tachypnea have been presumed to be due to autonomic imbalance caused by high sympathetic and concomitantly low vagal activity.[12]

Gain in weight

Failure to thrive was related neither to a lower caloric intake or birth weight, but we frequently observed disorders such as vomiting in infants with severe heart failure (Table 6).

Pulmonary vascular resistance index was the only hemodynamic parameter that showed significant differences in infants with left-to-right shunts grouped according to their gain in weight (Table 7). Levels of norepinephrine level ($r = -0.48^{***}$, $p < 0.001$), plasma renin activity ($r = -0.43^{*}$, $p = 0.028$), and heart rate ($r = -0.31^{*}$, $p = 0.015$) showed significant inverse correlations with gain in weight.

Discussion

Our major finding is that tachypnea in infants with congenital cardiac malformations is associated not only with conventional measures for the severity of hemodynamic disturbance, like the ratio of pulmonary to systemic flows, but also to hormonal changes. These results were confirmed by both univariate and multiple regression analysis, showing significant correlations between respiratory rates and levels of norepinephrine, as well as the ratio of pulmonary to systemic flows (Table 4). We conclude that, in infants with congenital cardiac malformations, neurohormonal changes parallel the hemodynamic status. We were not able to find, however, an appropriate model using multiple regression to

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Table 7. Hemodynamic data of infants with left-to-right shunts, differentiated according to their weight gain.

Weight gain (g/month):	>400		200–400		<200			
	N	mean ± SD	N	mean ± SD	N	mean ± SD	Significance	p-Wert
Heart rate (min^{-1})	29	126 ± 10	24	126 ± 14	16	133 ± 12	ns	0.100
Ejection fraction (%)	24	63.4 ± 7.9	18	68.2 ± 6.4	16	65.4 ± 7.4	ns	0.110
LVedP (mmHg)	27	8.9 ± 2.4	23	8.9 ± 3.0	16	9.7 ± 3.2	ns	0.635
VO_2 (ml/min/m^2)	14	129.8 ± 24.8	11	132.4 ± 21.2	6	127.5 ± 26.9	ns	0.918
Qp/Qs	29	3.4 ± 1.7	24	4.3 ± 3.2	16	3.0 ± 1.0	ns	0.173
Qp (l/min/m^2)	28	7.8 ± 3.3	24	9.4 ± 4.7	16	7.1 ± 2.4	ns	0.132
Qs (l/min/m^2)	28	2.5 ± 0.8	24	2.6 ± 1.1	16	2.4 ± 0.5	ns	0.598
RAP (mmHg)	28	4.9 ± 2.2	24	5.2 ± 2.5	16	5.7 ± 2.0	ns	0.477
LAP (mmHg)	23	9.2 ± 2.8	20	8.9 ± 3.8	16	8.5 ± 2.8	ns	0.798
PAP (mmHg)	27	33.8 ± 12.9	23	33.2 ± 11.9	15	35.4 ± 14.6	ns	0.876
MAP (mmHg)	28	59.4 ± 6.9	24	62.3 ± 11.2	16	56.7 ± 9.5	ns	0.169
SVRI (WE × m^2)	28	23.7 ± 6.1	24	24.2 ± 8.3	16	22.4 ± 5.8	ns	0.728
PVRI (WE × m^2)	23	3.6 ± 1.6	19	2.6 ± 1.2	15	4.3 ± 2.6	*	0.035
SaO_2 (%)	28	94.5 ± 4.8	24	92.6 ± 7.4	16	92.5 ± 6.2	ns	0.446

Results of One-Way-ANOVA: ***p < 0.001; **p = 0.001 to <0.01; *p = 0.01–0.05; ns = not significant
Abbreviations: LVedP: left ventricular enddiastolic pressure; VO_2: oxygen consumption; Qp/Qs: ratio of pulmonary to systemic flow; Qp: pulmonary flow; Qs: systemic flow; RAP: mean right atrial pressure; LAP: mean left atrial pressure; PAP: mean pulmonary artery pressure; MAP: mean arterial pressure; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index; SaO_2: systemic oxygen saturation

explain the symptom 'failure to thrive' with a r^2-value of more than 0.36.

We have confirmed the results of Gidding et al.,[1] who identified increased heart rate as an important hemodynamic correlate of clinical severity in infants with deficient ventricular septation, but we found no evidence to support their pathophysiological interpretation based on deficiency of oxygen. As has been demonstrated previously,[17] extraction of oxygen rises if the systemic cardiac index falls, but uptake of oxygen remains normal.

In our study, we found severe hormonal changes in infants with clinical signs of heart failure consistent with activation of the renin-angiotensin-aldosterone pathways and activation of the sympathetic nervous system. Elevated levels of norepinephrine, and reduced variability in heart rate, are evidence for sympathetic activation in infants with tachypnea. We demonstrated recently that autonomic imbalance in infants with congenital heart disease could be demonstrated with high diagnostic sensitivity by the finding of reduced values for the domain of frequency in heart rate variability.[18] These changes in the variability of heart rate correlate inversely with the activity of the peripheral chemoreflex.[19,20] In adults with cardiac failure, it is postulated that overactivity of peripheral chemoreceptors may lead to an increased ventilatory response and tachypnea.[4,5]

In addition, significant correlations between levels of norepinephrine and gain in weight were evidence for an influence of an autonomic imbalance on cardiac cachexia, also comparable to results in adults.[6] Activation of the immune system as a further important factor for cardiac cachexia,[21] however, was not measured in our study. As shown in Table 7, a normal caloric intake was guaranteed by using feeding tubes in infants with severe cardiac failure, but the gain in weight remained unsatisfactory in many infants.[22] Nutritional problems such as vomiting frequently restricted higher caloric intake, possibly caused by impaired gastric emptying known to occur in infants with cardiac failure.[23,24]

In contrast to adults with heart failure, we found no evidence of an impaired ventricular function in our infants with congenital cardiac malformations,[25] as measured by ejection fraction and end-diastolic left ventricular pressure. Moreover, higher ejection fractions, possibly due to sympathetic activation, correlated positively with respiratory rates.

We conclude that the morphology of the congenital malformations within the heart is the pathophysiological cause of the well-known hemodynamic disturbances, but cannot explain clinical symptoms such as tachypnea and failure to thrive. Thus, the neurohormonal hypothesis,[26] which regards cardiac failure not only as a hemodynamic derangement, but also as a neurohormonal disorder, may be valid in infants with left-to-right shunts.[27]

Limitations of the study

If neurohormonal levels were estimated from samples drawn from non-sedated infants, an influence of activity on the levels of norepinephrine levels cannot be excluded. Acute release of catecholamines during the collection of the blood specimens, however, should

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increase the levels of both norepinephrine and epinephrine, but only the levels of norepinephrine were enhanced in our infants with tachypnea (Table 3). The low levels of norepinephrine (362 ± 219 ng/l) and renin (177 ± 227 µU/ml) measured in 24 infants without tachypnea (Table 3) are further evidence for the minimal influence of activity on the neurohormonal parameters measured in this setting.

Cardiac catheterization in infants has to be undertaken under sedation and local anaesthesia. This may have impacted on the hemodynamic data obtained in our study, particularly by decreasing systemic vascular resistance and mean arterial pressure.

Consumption of oxygen was measured in only 31 infants, this method not being available in our institution before 1998. The mean values for consumption of oxygen as shown in Table 2, however, are in accordance with the assumed consumptions[28] were used up to 1998.

Acknowledgements

We wish to thank S. D. Anker, MD, National Heart and Lung Institute, London, for evaluating the manuscript.

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