Cardiac dimensions and myocardial function of infants with congenital hypothyroidism

An echocardiographic study

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SUMMARY This study was undertaken to evaluate the cardiac dimensions and various indices of myocardial function, determined by echocardiography, in a group of 12 infants with congenital hypothyroidism. Left ventricular systolic and diastolic dimensions, posterior wall thickness, end-diastolic and systolic volumes were all significantly lower in the hypothyroid infants compared with 25 normal infants of the same age. No pericardial effusion was found. Hypothyroid infants had a lower heart rate with a reduced cardiac output. The mean velocity of circumferential fibre shortening and the shortening fraction of the left ventricle were normal. The pre-ejection period of the left ventricle (PEP), however, was abnormally prolonged as well as the ratio PEP over left ventricular ejection time (PEP/ET). This ratio correlated inversely with the end-diastolic volume, suggesting that the increased PEP/ET could be partly the result of decreased preload.

Several screening programmes have indicated that congenital hypothyroidism can be successfully detected during the first weeks of life, preventing irreversible cerebral damage.¹ To our knowledge, no data are available concerning the cardiac size and myocardial function of these infants. Because of the structural and functional differences between neonatal and adult myocardial tissue,^{2,3} extrapolations from studies carried out in adults⁴ or older children⁵ must be made with great caution. Furthermore, the possibility that early diagnosis and treatment could minimise myocardial involvement and be an added benefit to the screening programme deserved investigation. We wish to report the cardiac dimensions and various indices of myocardial function, determined by echocardiography, in a group of newborn infants with congenital hypothyroidism. For comparison, the same echocardiographic study was performed on 25 normal infants of the same age.

Subjects and methods

The procedure according to which patients are screened and recalled in the Quebec screening programme for neonatal hypothyroidism has previously

been described.^{6,7} Twelve infants aged 3 to 9 weeks (mean age 5.4 weeks) detected by this network were included in the study. The study procedure, applied to all patients on the day of the first visit, has also been published⁷ and includes the establishment of a clinical hypothyroid index (Table 1), chest and lower limbs x-rays (to evaluate the surface area of distal femoral ossification centres), and analysis of plasma T3, T4, and TSH. To this routine evaluation was added the recording of an echocardiogram.

Echocardiograms were recorded on an Ekoline model 20A ultrasonoscope interfaced with a Honeywell Cambridge fiberoptic recorder. An electrocardiogram with a well-defined Q wave was simultaneously recorded. A 5 MHz unfocused transducer was used in all patients. The following left ventricular systolic time intervals were measured⁸: the pre-ejection period (PEP) from the onset of the QRS complex to the opening of the aortic valve; the ejection time (ET) from the opening to closure of aortic valves; and the ratio PEP/ET. Posterior wall and septal thickness in diastole, and systolic (LVIDS) and diastolic (LVIDD) internal dimensions of the left ventricular cavity were also measured. These measurements were made according to the recommendations of the American Society of Echocardiography.⁹ From the left ventricular internal dimensions, the following indices

Table 1 Clinical signs and symptoms used for the hypothyroid clinical index score (for details see Reference 6)

Hernia
Feeding problems
Hypotonia
Constipation
Tongue
Inactivity
Skin mottling
Dry skin
Fontanelle
post. <0.5 cm
Typical facies

were calculated: the shortening fraction of the LV ($SF = (LVIDd - LVIDs) / LVIDd$), and mean velocity of circumferential fibre shortening (mean $VCF = (LVIDd - LVIDs) / (LVIDd \times ET)$), expressed in circumferences per second. Systolic and diastolic volumes of the left ventricle were calculated according to the cube formula,¹⁰ allowing evaluation of cardiac output and stroke volume. All measurements were made to the nearest 5 ms at a paper speed of 100 mm/s. In all patients, at least five different measurements were made for each value. In order to establish a control group, the same echocardiographic study was carried out in 25 normal infants aged 4 to 8 weeks. In this group, ejection time but not pre-ejection period strongly correlated with heart rate ($r = -0.76$). The difference between the ejection time observed in the hypothyroid group and that predicted by the regression equation calculated from our normal data for the appropriate heart rate was expressed as the change in this interval in milliseconds (ΔET). (Predicted $LVET = 331.4 - 0.933 HR$, $p < 0.05$.)

Statistical comparison between the echocardiographic data of the hypothyroid patients and that of the normal group was made by unpaired *t* test. Regression analysis was utilised to evaluate the correlations between the indices of myocardial function which were altered and the clinical index and the thyroid function tests. Normal biochemical values for thyroid function have already been published.⁶

Results

THYROID FUNCTION

Clinical, radiological, and biochemical data for the 12 patients are summarised in Table 2.

CARDIAC DIMENSIONS

Echocardiographic measurements of the minor axis of the left ventricle and the volumes calculated for the hypothyroid and the normal groups are shown in Table 3. Ventricular systolic and diastolic echocardiographic dimensions of hypothyroid patients were significantly lower than those of the normal group ($p < 0.05$). This was also true for ventricular volumes

Table 2 Clinical, radiological, and biochemical characteristics of hypothyroid patients

	No of patients	Mean	SD
Clinical index*	12	8.1	3.2
T4 (ng/dl)*	12	1.8	1.74
T3 (μ g/dl)*	10	81	43
TSH (μ U/ml)*	12	468	261
Bone maturation delay (wk)			
Distal femoral	12	9.34	2.62
Proximal tibial	12	10.37	2.25

*Normal values. ^a Clinical index: 0.6 ± 0.1 , T4 (plasma thyroxine): 5–14 ng/dl, T3 (plasma triiodothyronine): 70–220 μ g/dl, TSH (thyrotropin-stimulating hormone): less than 20 μ U/ml. Abbreviation: SD, one standard deviation.

Table 3 Comparison between ventricular dimensions of hypothyroid patients and control group

	Hypothyroid		Control		<i>p</i>
	Mean	SD	Mean	SD	
LVIDd (mm)	19	2	20	2	<0.05
LVIDs (mm)	13	2	14	2	<0.05
EDV (cm^3)	7.1	2.1	8.7	2.5	<0.1
ESV (cm^3)	2.3	0.9	3.1	1.1	<0.05
LVPWd (mm)	2.9	0.34	3.3	0.48	<0.05
IVSDd (mm)	3.5	0.9	3.4	0.5	NS

Abbreviations: LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; EDV, end-diastolic volume; ESV, end-systolic volume; LVPWd, left ventricular posterior wall thickness in diastole; IVSDd, interventricular septal dimension in diastole.

and left posterior wall thickness. No difference was found for septal thickness. No patient had echocardiographic evidence of pericardial effusion.

MYOCARDIAL PERFORMANCE

Mean velocity of circumferential fibre shortening (mean VCF) as well as shortening fraction and stroke volume of the hypothyroid infants were normal (Table 4). The pre-ejection period, however, was prolonged ($p < 0.02$) as well as the ratio PEP/ET ($p < 0.001$). The ejection time measured was consistently shorter than that predicted for the appropriate heart rate (average ΔET of 24 ms). Heart rate was also significantly lower ($p < 0.001$) and cardiac output was decreased when compared with normal ($p < 0.02$) (Table 4).

CORRELATION STUDIES

The correlation coefficients between abnormal echocardiographic variables and biological data are shown in Table 5. The clinical index of hypothyroidism was the only variable which correlated not only with systolic time intervals but also with ventricular

Table 4 Comparison between myocardial performance of hypothyroid patients and control group

	Hypothyroid (No.12)		Control (No.25)		p
	Mean	SD	Mean	SD	
Heart rate	132	19	153	16	0.001
SF	0.31	0.08	0.30	0.06	NS
Mean VCF (circ/s)	1.69	0.42	1.6	0.36	NS
PEP (ms)	66	11	57	7	0.02
PEP/ET	0.36	0.06	0.31	0.02	0.001
CO (l/min)	0.63	0.27	0.87	0.26	0.02
EF	0.66	0.11	0.64	0.09	NS
SV (ml)	4.8	1.8	5.6	1.8	NS

Abbreviations: SD, one standard deviation; SF, shortening fraction of the left ventricle; mean VCF, mean velocity of circumferential fibre shortening; PEP, pre-ejection period; ET, ejection time; CO, cardiac output; EF, ejection fraction; SV, stroke volume; NS, not significant.

Table 5 Correlation coefficients between echocardiographic variables, plasma T4, T3, and clinical index at time of diagnosis

Variables	T4	T3	Index
Heart rate	0.34	0.21	-0.57
PEP	-0.52	-0.49	0.59
PEP/ET	-0.65	-0.71	0.57
LVIDd	0.41	0.39	-0.62
LVIDs	0.14	0.41	-0.59
LVPWd	-0.34	-0.54	0.76
EDV	0.40	0.32	-0.57
ESV	0.19	0.51	-0.60
CO	0.54	0.35	-0.58

Abbreviations: as in Tables 3 and 4.

A positive or negative coefficient of 0.58 is significant at a p value of 0.05.

dimensions and cardiac output. There was also a significant correlation between the thyroid hormone plasma levels and the PEP/ET ratio.

Discussion

Severe hypothyroidism has long been known to produce abnormalities of cardiac structure and function in adults and children. In typical cases the myocardium is oedematous and basophilic with accumulation of mucopolysaccharides disrupting myocardial integrity.^{11,12} Clinically, bradycardia, reduced cardiac output,¹³ pericardial effusion,¹⁴ cardiomegaly, and diminished myocardial contractility¹⁵⁻¹⁷ are classical features. The effect, however, of decreased thyroid activity *in utero* on the cardiovascular condition of the newborn has never been specifically studied. Since the placenta is not permeable to TSH and T4, the fetus is completely autonomous as far as the hypothalamic-pituitary-thyroid axis is concerned. Recent studies have suggested that this system is functionally mature at the end of the last trimester of gestation (phase III of fetal thyroid-system ontogenesis).¹⁸ To assess the

influence of lack of thyroid hormone on the circulatory system during the first weeks of life, a non-invasive approach has been adopted in this study. The validity of echocardiography for myocardial function study and ventricular cavity measurements is now well established.¹⁹

Infants in this study had left ventricular cavities smaller than normal with no echocardiographic evidence of pericardial effusion. This finding is particularly significant in the presence of bradycardia that normally would tend to increase the end-diastolic volume. This suggests that the drop in the cardiac output and of the venous return is severe enough to counterbalance the increase in diastolic filling caused by lowering of the heart rate.

Results of myocardial function study of our hypothyroid patients seem to be contradictory. On one hand, PEP and PEP/ET have been found abnormally prolonged. This has been a consistent finding in all previous studies on hypothyroidism and interpreted as a sign of decreased myocardial contractility.^{16,17,20} On the other hand, the ejection phase indices of ventricular performance such as mean VCF and shortening fraction were both within normal limits. This apparent contradiction can perhaps be explained by the fact that systolic time intervals (PEP, PEP/ET) are influenced not only by intrinsic myocardial contractility but also by changes in preload and/or afterload of the ventricles.²¹ In this study, cardiac output has been reduced. It has previously been shown that this low blood flow is essentially the result of the depressed metabolic requirements of the body.^{13,22} A low cardiac output is necessarily associated with a fall in the venous return to the heart and consequently a decrease in the preload of the ventricle. This decrease in preload could, at least partly, explain the lengthening of the pre-ejection period and the abnormal PEP/ET ratio which were observed in our group of patients. To verify this hypothesis, we have studied the correlation between the PEP/ET ratio and the diastolic volume of the left ventricle, which is a reliable reflection of its preload. Though the number of patients is too small to allow any definitive conclusion, the results presented in the Figure show that left ventricular volume is inversely related to PEP/ET ratio. A completely different situation would be observed in primary myocardial dysfunction, where the pre-ejection period would indeed be prolonged but the cardiac chambers would also be enlarged. In contrast to the PEP/ET ratios, VCF and the shortening fraction are relatively unaffected by either an acute,²³ or chronic²⁴ alteration of the preload.

Definite signs of myocardial dysfunction are therefore not present in the hypothyroid neonate. This may be because of the different structural and functional characteristics of the neonatal myocardium.

Fig. Relation between left ventricular pre-ejection period (PEP)/left ventricular ejection time (ET) and left ventricular end-diastolic volume (expressed in ml).

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