Cardiology in the Young (2013), **23**, 174–180
doi:10.1017/S1047951112000613

Original Article

Evaluation of cardiac functions with Doppler echocardiography in children with Down syndrome and anatomically normal heart

Mohammed Al-Biltagi,[1] Amany R. Serag,[2] Mohammed M. Hefidah,[3] Maaly M. Mabrouk[4]

[1]*Cardiology Unit, Department of Paediatric, Faculty of Medicine, Tanta University, Tanta;* [2]*Department of Cardiology, Faculty of Medicine, Menoufyia University, Egypt;* [3]*Department of Diagnostic Radiology, Faculty of Medicine, Tanta University;* [4]*Department of Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt*

Abstract *Objective:* To study the cardiac functions in Down syndrome children who did not have structural cardiac lesion by conventional and tissue Doppler echocardiography. *Materials and methods:* A total of 85 children with Down syndrome without anatomic heart disease and 50 normal control children were subjected to the assessment of right and left ventricular functions by both two-dimensional and tissue Doppler echocardiography. *Results:* Children with Down syndrome had significantly higher left ventricular ejection fraction detected by two-dimensional echocardiography and left ventricular diastolic dysfunction detected by tissue Doppler than observed in the controls. In addition, children with Down syndrome also had right ventricular systolic and diastolic dysfunctions. Children with Down syndrome had significantly higher pulmonary artery systolic pressure than the control children. There was no significant difference in the cardiac functions between children with non-disjunction Down syndrome and those with the translocation type. *Conclusion:* Despite an apparently normal heart, children with Down syndrome may have silent disturbed cardiac functions, which may be detected by two-dimensional or tissue Doppler echocardiography. This may have an important clinical implication, especially before involving Down syndrome children in surgery or strenuous exercise.

Keywords: Tissue Doppler; echocardiography; cardiac function; Down syndrome

Received: 14 May 2011; Accepted: 26 March 2012; First published online: 26 April 2012

DOWN SYNDROME IS THE MOST FREQUENT AUTOSOMAL aneuploidy that is compatible with postnatal life. It is characterised by a complex phenotype in which over 80 features occur with various degrees of expression and frequency.[1] It is not uncommon to be associated with congenital heart disease and it can provide an important model to link certain genes to the pathways controlling heart development. Congenital heart disease occurs in 40–50% of cases with Down syndrome and about 30% of patients have several cardiac defects.[2,3] The severity of the underlying congenital heart disease adversely affects survival. People with Down syndrome without congenital heart disease survive relatively longer than those with congenital heart disease especially with complexity of the defects.[4] Despite that, the newer surgical techniques have significantly improved the 1-year survival for those who have early surgical correction. Recent studies have mainly focused on congenital heart disease in patients with Down syndrome. However, data on cardiac functions in Down syndrome children with structurally normal hearts are rare. Owing to the fact that life expectancy of individuals with Down syndrome is increasing and most of them now reach

Correspondence to: Dr M. Al-Biltagi, MD, PhD, Associate Professor of Pediatrics and Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Egypt. Tel: +20102209797; Fax: +20402213543; E-mail: mbelrem@hotmail.com

adulthood in the developed countries, and they are actively engaged in various exercises and sports, information about cardiac dysfunction in this patient group is clinically important. This is especially important to find an explanation for exercise intolerance, decreased work capacity, and increased morbidity and mortality rate among the Down syndrome population. The purpose of this study was to evaluate the cardiac functions by two-dimensional and tissue Doppler echocardiography in Down syndrome children without structurally heart disease.

Materials and methods

The study was conducted as a case–control study. A group of 85 children with Down syndrome between 7 and 13 years of age with clinically and anatomically normal heart were included in the study from March, 2006 to April, 2009 in the Cardiology Unit of the Pediatric Department. An age- and sex-matched cohort of 50 healthy children was studied as the control group. The control group inclusion criteria were the absence of a history of any cardiac or significant systemic disease, as well as the absence of any family history of chromosomal disorders.

All children were evaluated by a paediatric cardiologist. Any anatomic cardiac lesions – congenital and acquired – were excluded by clinical and echocardiographic examination. A thorough clinical examination, as well as assessment of thyroid functions and complete blood pictures, were performed. Exclusion of upper airway obstruction was performed by an otolaryngologist and lateral neck radiograph was performed to exclude adenoid hypertrophy. Chest X-ray post-anterior and lateral views were done in some cases to exclude chronic lung diseases. Chromosomal studies were conducted to confirm diagnosis and to know the karyotype of the Down syndrome children: non-disjunction or translocation types. Exclusion criteria were the presence of any anatomical cardiac defect – congenital or acquired – hypothyroidism, severe anaemia, upper airway obstruction, obstructive sleep apnoea, recurrent or chronic lung disease, or any significant systemic disease.

Echocardiography

Echocardiographic examination was done using Hewlett-Packard/Phillips SONOS 5500 systems – Palo Alto, Calfornia, USA – equipped with 2.5–5 megahertz transducers. M-mode and two-dimensional echocardiography – to assess left ventricular internal dimensions, ejection fraction, and fractional shortening – were done according to the recommendation of the American Society of Echocardiography.[5] The ejection fraction was measured by the Teichholz formula based on short-axis measurements of the left ventricle inner diameter by M-mode.[6] To avoid intra-observer variability, two examinations were performed by the same operator for each patient within 1 week. All children were examined in a semi-supine, left lateral position. Pulmonary arterial flow was recorded with pulsed-wave Doppler, placing the sample volume centrally between the leaflets of the pulmonary valve in a short-axis view at the base of the heart. The mitral and tricuspid Doppler signals were recorded in the apical four-chamber view, with the Doppler sample volume placed at the tip of the mitral or tricuspid valve. Colour Doppler study for the cardiac valves was conducted to assess the severity of regurgitation. The pulmonary artery systolic pressure was estimated in some cases from the tricuspid regurgitation jet using the Bernoulli equation. Pulmonary artery systolic pressure was considered abnormal when it was greater than 30 millimetres of mercury.[7]

Tissue Doppler image

Using pulsed-wave angle-corrected colour-coded Doppler tissue imaging filters, the baseline was adjusted to low velocity range (−20 to 20 centimetres per second) with minimal gain setting to minimise background noise and to obtain the highest quality images. The sample volume was placed within the myocardium equidistant from the endocardial and epicardial borders. From the apical four-chamber planes, using pulsed-wave Doppler tissue imaging, the myocardial velocity curves of septal mitral valve annulus, lateral mitral valve annulus, and lateral tricuspid valve annulus were recorded. The electrocardiogram was connected and traced simultaneously to define the timing of cardiac cycle events. The beginning of QRS complex was used as a reference point.

Velocities and interval measurements. The systolic wave reflects the systolic function of either right or left ventricle. The early′/atrial′ ratio of tricuspid and mitral valve annulus reflects the diastolic function of the right and left ventricle, respectively. Isometric contraction time was defined as the time duration between the beginning of QRS complex in the electrocardiogram to the beginning of Doppler tissue imaging systolic wave. The isometric relaxation time was defined as the interval between the end of systolic wave and the beginning of the early′ wave. At least 10 cardiac cycles were recorded at a speed of 100 millimetres per second and the images were stored electronically. The Doppler tissue imaging measurements were indexed for children's heart size.[8]

All parents signed a written informed consent before enrolment into the study. The local Institutional

https://doi.org/10.1017/S1047951112000613 Published online by Cambridge University Press

Research Review and Ethics Committee reviewed and approved the study protocol.

Statistical analysis. The power level of the number of cases in the study was more than 90%. Data are presented as mean (±standard deviation) values. The two-way analysis of variance with repeated measures was used to identify statistically significant differences in the different parameters among the groups. For all analyses, a statistical significance of p-value less than 0.05 was used. Wilcoxon's signed-rank test was used to assess the normality of distributions of the data. The Bonferroni correction/adjustment procedure was performed to avoid "significance" due to chance only, in multiple comparisons with echocardiographic parameters. The analysis was performed using TexaSoft, WINKS SDA Software, Sixth Edition, Cedar Hill, Texas, 2007.

Results

The demographic and clinical characteristics of children with Down syndrome and the control group are shown in Tables 1 and 2. The presence of Down syndrome was confirmed in all cases by chromosomal examination, which revealed 78 children with non-disjunction type of Down syndrome and seven children with Translocation type. There were no significant differences between Down syndrome children and the controls with regard to age and sex. The body mass index and pulse and respiratory rates were significantly higher in Down syndrome children than in the controls ($p < 0.001$), whereas systolic and diastolic blood pressure were significantly lower in Down syndrome children than in controls ($p < 0.001$). There were no significant differences in demographic and clinical data between children with Down syndrome due to non-disjunction and those with Down syndrome due to translocation.

Echocardiography

Echocardiographic data of children with Down syndrome and the controls are shown in Table 3. The intra-observer agreement of echocardiographic measurements is shown in Table 4. The left ventricular ejection fraction, which reflects left ventricular systolic function, was significantly higher in Down syndrome children than the controls ($p < 0.001$). There were no significant differences in systolic wave and isometric contraction time measured at mitral valve annulus by tissue Doppler ($p > 0.05$ for both).

The early/atrial of mitral valve showed no significant difference between the two groups, but the tissue Doppler derived early′/atrial′ ratio was significantly reduced and the isometric relaxation time was significantly prolonged in Down syndrome children than in controls ($p < 0.001$). For right ventricle, the systolic wave measured at the tricuspid valve annulus showed significant reduction ($p < 0.001$), whereas isometric contraction time showed significant lengthening ($p < 0.001$)

Table 1. Comparison of demographic data in Down syndrome children and control group.

	Down syndrome children (n = 85)	Control group (n = 50)	t	p-value
Age	9.1 (1.5)	8.7 (2.4)	0.9	>0.355
Body mass index	21.6 (2.5)	18.2 (1.9)	9.93698	<0.001*
Systolic blood pressure	92.6 (5.6)	100.0 (6.3)	7.02896	<0.001*
Diastolic blood pressure	50.8 (5.7)	57.8 (5.7)	23.78583	<0.001*
Heart rate	85.28 (7.9)	80.9 (7.3)	16.90585	<0.001*
Respiratory rate	21.6 (2.5)	20.2 (2.3)	10.44684	<0.001*
Sex (male:female ratio)	1.3:1	01:01	0.48	>0.05

*Means that p-value is significant

Table 2. Demographic data of children with both types of Down syndrome.

	Down syndrome children non-disjunction (n = 78)	Down syndrome children translocation (n = 7)	t	p-value
Age	6.4 (1.3)	6.3 (1.9)	0.05	>0.96
Body mass index	20.4 (2.7)	20.7 (2.4)	0.29	>0.05
Systolic blood pressure	87.7 (6.2)	89 (5.03)	0.42	>0.05
Diastolic blood pressure	45.85 (5.01)	47.7 (5.03)	0.6	>0.05
Heart rate	87 (6.7)	84 (5.6)	0.67	>0.05
Respiratory rate	22.4 (3.4)	21.3 (1.7)	0.6	>0.05
Sex (male:female ratio)	1.3:1	2.5:1		

https://doi.org/10.1017/S1047951112000613 Published online by Cambridge University Press

Table 3. Comparison of echocardiographic features in Down syndrome children and control group.

	Patient group (n = 85)	Control (n = 50)	Mean between groups	95% CI		t	p-value
				Lower	Upper		
E/A ratio mitral valve	1.57 (0.3)	1.63 (0.2)	−0.054	−0.148	−0.04	1.15	0.225
Left ventricle ejection fraction	68.1 (4.7)	60.2 (5.2)	7.94	6.6	9.27	11.9	<0.001*
E/A ratio tricuspid valve	1.57 (0.3)	1.7 (0.2)	−0.126	−0.2445	−0.0075	2.13713	<0.05*
Pulmonary R–R	118.6 (4.7)	105.1 (5.4)	13.42	11.92	14.92	18	<0.001*
Pulmonary systolic pressure	20.9 (3.7)	12.7 (2.2)	8.16	7	9.3	14	<0.001*
E′/A′ wave mitral annulus	1.35 (0.22)	2.49 (0.1)	−1.18	−1.21	−1.06	31	<0.001*
S wave mitral annulus	8.4 (0.8)	8.56 (0.7)	−0.16	−0.33	0.015	1.83	>0.05
Isometric contraction time of mitral valve	86.6 (8.8)	84.2 (4.5)	2.4	−0.52	5.3	1.64	>0.05
Isometric relaxation time of mitral valve	79.8 (5.5)	66.7 (3.4)	13.1	11.66	14.53	18.38	<0.001*
E′/A′ wave tricuspid annulus	1.04 (0.2)	1.6 (0.1)	−0.57	−0.62	−0.52	23.08	<0.001*
S wave tricuspid annulus	9.9 (1.04)	13.3 (0.5)	−3.34	−3.64	−3.04	22.37	<0.001*
Isometric contraction time of tricuspid annulus	94 (3.3)	82.7 (2.2)	11.34	10.54	12.13	28.67	<0.001*
Isometric relaxation Time of tricuspid annulus	73.24 (4.1)	62.9 (1.04)	10.38	10.08	10.68	70.06	<0.001*

E/A = early/atrial; E′/A′ = early′/atrial′; S = systolic
*Means that p-value is significant

in children with Down syndrome than in the controls. Both early/atrial and early′/atrial′ ratios at the tricuspid valve annulus showed significant reduction ($p < 0.05$ and 0.001, respectively), whereas the isometric relaxation time showed significant lengthening ($p < 0.001$) in children with Down syndrome than in the controls.

For pulmonary pressure, the pulmonary acceleration time (pulmonary R–R) was significantly prolonged in Down syndrome children than in the control group ($p < 0.001$). The pulmonary arterial systolic pressure was significantly higher in Down syndrome children than the controls. Table 5 showed no significant difference in any of the echocardiographic parameters in children with non-disjunction or translocation types of Down syndrome.

Discussion

Congenital heart diseases are a common problem in children with Down syndrome. However, despite being structurally normal, the heart may be affected in those children. They are more liable to the common cardiovascular risk factors – sedentary life, obesity, and hypertension – than those without Down syndrome.[9] Therefore, the aim of this study was to assess the presence of any significant echocardiographic changes in the cardiac function in a subset group of children with Down syndrome and structurally normal heart.

This study showed that children with Down syndrome had statistically but not clinically significant lower systolic and diastolic blood pressure than control children. This was in agreement with the results of Morrison et al[10] who found lower blood pressure in Down syndrome adults than in controls. They considered it as a feature of the disease rather than due to the protected surrounding environment. The low blood pressure noted in children with Down syndrome may be due to trisomy of type-1-angiotensin II receptor gene, resulting in its underexpression.[11,12]

Our study showed that children with Down syndrome had statistically but not clinically significant higher respiratory and heart rates than the control children, which was in agreement with the work of Pastore et al who found higher heart rates in Down syndrome children than controls.[5] The differences in respiratory and pulse rate, as well as the blood pressure, may be related to autonomic cardiac dysregulation in Down syndrome, which may be due to the autonomic dysfunction occurring at a central, brain stem, site as a result of the genetic disorder.[13]

This study showed that the left ventricle ejection fraction by conventional echocardiography was significantly higher in Down syndrome children

https://doi.org/10.1017/S1047951112000613 Published online by Cambridge University Press

Table 4. The intra-observer agreement of echocardiographic measurements between children with Down syndrome and control group.

	Down syndrome children (n = 85)	Control children (n = 50)
E/A ratio mitral valve	κ = 0.86	κ = 0.86
Left ventricle ejection fraction	κ = 0.69	κ = 0.87
E/A ratio tricuspid valve	κ = 0.76	κ = 0.78
Pulmonary R–R	κ = 0.88	κ = 0.86
Pulmonary systolic pressure	κ = 0.78	κ = 0.87
E′/A′ wave mitral annulus	κ = 0.82	κ = 0.82
S wave mitral annulus	κ = 0.88	κ = 0.84
Isometric contraction time of mitral valve	κ = 0.78	κ = 0.86
Isometric relaxation time of mitral valve	κ = 0.88	κ = 0.75
E′/A′ wave tricuspid annulus	κ = 0.78	κ = 0.72
S wave tricuspid annulus	κ = 0.89	κ = 0.89
Isometric contraction time of tricuspid annulus	κ = 0.84	κ = 0.85
Isometric relaxation time of tricuspid annulus	κ = 0.76	κ = 0.81

E/A = early/atrial; E′/A′ = early′/atrial′; S = systolic
κ = Cohen Kappa; agreement is poor if κ ≤ 0.20, fair if κ 0.20 ≤ 0.40, moderate if κ 0.41 ≤ 0.60, substantial if κ 0.61 ≤ 0.80, and good if κ > 0.80

Table 5. Comparison of echocardiographic features in Down syndrome children with non-disjunction type and translocation type.

	Non-disjunction group (n = 78)	Translocation group (n = 7)	Mean between groups	95% CI		t	p-value
				Lower	Upper		
E/A ratio mitral valve	1.57 (0.2)	1.41 (0.2)	0.15	−0.17	0.48	1.17	>0.05
Left ventricle ejection fraction	67.7 (1.9)	69.3 (93.8)	−1.57	−6.41	3.26	0.79	>0.05
E/A ratio tricuspid valve	1.9 (0.11)	1.7 (0.2)	0.17	−0.07	0.41	1.72	>0.05
Pulmonary R–R	117.3 (6.9)	119.6 (4.2)	−28	−10.08	5.51	0.72	>0.05
Pulmonary systolic pressure	18 (2.9)	21 (3.1)	−3	−7.11	1.11	1.79	>0.05
E′/A′ wave mitral annulus	1.09 (0.3)	1.16 (0.14)	0.07	−0.44	0.29	0.51	>0.05
S wave mitral annulus	8.2 (1.1)	8.7 (0.6)	−0.45	−1.34	0.43	1.26	>0.05
Isometric contraction time of mitral valve	82.7 (9.5)	80 (6.5)	2.71	−3.46	8.89	1.07	>0.05
Isometric relaxation time of mitral valve	76.2 (5.2)	75.1 (4.8)	1.07	−6.31	8.46	0.35	>0.05
E′/A′ wave tricuspid annulus	0.97 (0.16)	1.1 (0.2)	−0.11	−0.34	0.21	0.85	>0.05
S wave tricuspid annulus	9.6 (1.0)	9.7 (1.7)	−0.1	−2.33	2.13	0.11	>0.05
Isometric contraction time of tricuspid annulus	92.7 (1.9)	95.7 (3.3)	−3	−6.21	0.21	2.29	>0.05
Isometric relaxation time of tricuspid annulus	70.4 (3.4)	74.1 (4.3)	−3.71	−8.69	1.26	1.83	>0.05

E/A = early/atrial; E′/A′ = early′/atrial′; S = systolic

than the controls ($p < 0.001$), which is similar to the findings of Russo et al who studied 22 Down syndrome patients without congenital heart disease and found evident left ventricular hyperkinesia. They attributed these hyperkinesias to the reduced afterload and not to intrinsic abnormalities of the myocardium.[14]

The absence of intrinsic myocardial abnormalities of left ventricle in the current study was supported by a lack of significant difference between systolic wave and isometric contraction time of the mitral valve annulus measured by tissue Doppler between Down syndrome children and the controls. The systolic wave, which reflects the longitudinal systolic function, is positively correlated with measurements of left ventricle ejection fraction. It is less load dependent, whereas the isometric contraction time is inversely correlated with myocardial contractility.

The current study showed no significant difference in the left ventricular diastolic function in Down syndrome children compared with the controls by the conventional pulsed Doppler (early/atrial ratio $p > 0.05$), but tissue Doppler showed a significant decrease in the early′/atrial′ ratio of mitral valve annulus and prolongation of left ventricle isometric relaxation time in the Down syndrome children than in the controls ($p < 0.001$). This may be due to the higher sensitivity of the tissue Doppler to detect

https://doi.org/10.1017/S1047951112000613 Published online by Cambridge University Press

diastolic dysfunction than the conventional Doppler. The prolonged isometric relaxation time, which is inversely correlated to myocardial relaxation, may indicate that the diastolic dysfunction, which observed in Down syndrome children, is due to impaired cardiac muscle relaxation. However, the difference in left ventricle Doppler echocardiographic findings between Down syndrome children and control group was of no clinical significance.

The right side of the heart showed a significant reduction of the early/atrial ratio at the tricuspid valve measured by pulsed Doppler and reduction of systolic wave and early′/atrial′ ratio measured by tissue Doppler, with significant prolongation of right ventricle isometric relaxation time in children with Down syndrome than observed in the controls. The reduction of the systolic and diastolic cardiac functions in children with Down syndrome observed in this study may be explained by autonomic cardiac control dysregulation,[15,16] abnormality in the cardiac muscle fibres with increased cardiac muscle fibre size and reduced cell number,[17] or overexpression of calcineurin.[18–21] Overexpression of calcineurin may lead to cardiac muscle hypertrophy.

Children with Down syndrome are at increased risk of developing pulmonary arterial hypertension even without structural heart lesion. Pulmonary arterial hypertension may develop in Down syndrome children secondary to chronic upper airway obstruction, abnormal pulmonary vasculature growth, alveolar hypoventilation, and recurrent pulmonary infections.[1] In the current study; the pulmonary R–R was significantly shorter and the pulmonary arterial systolic pressure was significantly higher in children with Down syndrome than in the controls. We excluded cases with congenital or acquired cardiac disease and cases with chronic upper airway obstruction, as well as chronic or recurrent lung problems that may affect pulmonary pressure. This may indicate that the cause of the higher pulmonary arterial systolic pressure may be intrinsic factors inside the lung rather than extrinsic factors. In an autopsy study of six patients with Down syndrome; Schloo et al[22] found reduction in the alveolar count, persistence of the foetal double capillary network in the lung, and reduction in the cross-sectional area of the vascular bed. All these factors are important in the pathogenesis of pulmonary hypertension. It may also result from abnormal nitrous oxide production owing to impaired vascular endothelial function, which is possibly related to increased oxidative stress.[23]

In this study, there was no significant difference in the echocardiographic findings in children with the dysjunction or translocation type of Down syndrome. However, the small number of children with translocation type of Down syndrome may give rise to inaccurate statistical results. Therefore, we advise including more cases in a further study.

Limitation of the study

Although there were statistical differences in many of the data examined between normal and Down syndrome children, the values in both groups in many of the data examined are within normal limits. This may make the findings of limited clinical significance. However, these findings may help to understand why children with Down syndrome have limited physical fitness and are more liable to many cardiovascular risks.

Conclusion

Despite having an apparently normal heart, children with Down syndrome may have silent disturbed cardiac functions, which may be discovered by two-dimensional or tissue Doppler echocardiography. This may have an important clinical implication, especially before involving Down syndrome children in surgery or strenuous exercise.

Acknowledgements

The authors greatly appreciate the generous support of Professor Osama A. Tolba, the Head of Pediatric Department, Tanta University, for his critical reading and drafting the manuscript. This study was performed in the Cardiology Unit, Pediatric Department, Faculty of Medicine, Tanta University, Egypt, a non-profit organisation, without any commercial support.

References

1. Banjar HH. Down's syndrome and pulmonary arterial hypertension. PVRI Review 2009; 1: 213–216.
2. Barlow GM, Chen XN, Shi ZY, et al. Down syndrome congenital heart disease: a narrowed region and a candidate gene. Genet Med 2001; 3: 91–101.
3. Frid C, Drott P, Lundell B, Rasmussen F, Anneren G. Mortality in Down's syndrome in relation to congenital malformations. J Intellect Disabil Res 1999; 43: 234–241.
4. Marino B. Patterns of congenital heart disease and associated cardiac anomalies in children with Down syndrome. In: Marino B, Pueschel SM (eds). Heart Disease in Persons with Down Syndrome. Paul H Brookes Publishing, Baltimore, 1996: 133–140.
5. Picard MH, Adams D, Bierig SM, et al. American society of echocardiography recommendations for quality echocardiography laboratory operations. J Am Soc Echocardiogr 2011; 24: 1–10.
6. Cevik Y, Değertekin M, Başaran Y, Turan F, Pektaş O. A new echocardiographic formula to calculate ejection fraction by using systolic excursion of mitral annulus. Angiology 1995; 46: 157–163.
7. Giardini A. Limitations inherent to the simplified Bernoulli equation explain the inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension. Chest 2011; 140: 270–271.
8. Ng AC, Thomas L, Leung DY. Tissue Doppler echocardiography. Minerva Cardioangiol 2010; 58: 357–378.

9. Pastore E, Marino B, Calzolari A, Digilio M, Giannotti A, Turchetta A. Clinical and cardiorespiratory assessment in children with Down syndrome without congenital heart disease. Arch Pediatr Adolesc Med 2000; 154: 408–410.
10. Morrison R, McGrath A, Davidson G, Brown JJ, Murray GD, Lever AF. Low blood pressure in Down's syndrome. A link with Alzheimer's disease? Hypertension 1996; 28: 569–575.
11. Sethupathy P, Borel C, Gagnebin M, et al. Human microRNA-155 on chromosome 21 differentially interacts with its polymorphic target in the AGTR1 3′ untranslated region: a mechanism for functional single-nucleotide polymorphisms related to phenotypes. Am J Hum Genet 2007; 81: 405–413.
12. Wiseman FK, Alford KA, Tybulewicz VL, Fisher EM. Down syndrome – recent progress and future prospects. Hum Mol Genet 2009; 18: R75–R83.
13. Iellamo F, Galante A, Legramante J, et al. Altered autonomic cardiac regulation in individuals with Down syndrome. Am J Physiol Heart Circ Physiol 2005; 289: H2387–H2391.
14. Russo MG, Pacileo G, Marino B, et al. Echocardiographic evaluation of left ventricular systolic function in the Down syndrome. Am J Cardiol 1998; 81: 1215–1217.
15. Goulopoulou S, Baynard T, Collier S, et al. Cardiac autonomic control in individuals with Down syndrome. Am J Ment Retard 2006; 111: 27–34.
16. Fernhall B, Otterstetter M. Attenuated responses to sympathoexcitation in individuals with Down syndrome. J Appl Physiol 2003; 94: 2158–2165.
17. Recalde AL, Landing BH, Lipsey AI. Increased cardiac muscle fiber size and reduced cell number in Down syndrome. Pediatr Pathol 1986; 6: 47–53.
18. Molkentin JD, Lu JR, Antos CL, et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell 1998; 93: 215–228.
19. Rothermel BA, Vega RB, Yang J, Wu H, Bassel-Duby R, Williams RS. A protein encoded within the Down syndrome critical region is enriched in striated muscles and inhibits calcineurin signaling. J Biol Chem 2000; 275: 8719–8725.
20. Tandan S, Wang Y, Wang TT, et al. Physical and functional interaction between calcineurin and the cardiac L-type Ca^{2+} channel. Circ Res 2009; 105: 51–60.
21. Arron JR, Winslow MM, Polleri A, et al. NFAT dysregulation by increased dosage of DSCR1 and DYRK1A on chromosome 21. Nature 2006; 441: 595–600.
22. Schloo BL, Vawter GF, Reid LM. Down syndrome: patterns of disturbed lung growth. Hum Pathol 1991; 22: 919–923.
23. Cappelli-Bigazzi M, Santoro G, Battaglia C, et al. Endothelial cell function in patients with Down's syndrome. Am J Cardiol 2004; 94: 392–395.