Cardiol Young 2002; 12: 253–259

ISSN 1047-9511

Original Article

Epidemiology of cardiomyopathies in children and adolescents: a retrospective study over the last 10 years

Ivan Malčić,[1] Marija Jelušić,[1] Hrvoje Kniewald,[1] Nina Barišić,[2] Dražen Jelašić,[3] Jadranka Božikov[4]

[1]Department of Paediatric Cardiology, [2]Department of Paediatric Neurology, [3]Department of Pathology, University Hospital Centre Zagreb; [4]School of Public Health "Andrija Štampar", Zagreb, Croatia

Abstract We conducted a retrospective study at the Department of Paediatric Cardiology of the University Hospital Centre Rebro, Zagreb, over the period from 1988 to 1998, so as to assess the epidemiology of childhood cardiomyopathies. The patients were categorized according to the guidelines of the Task Force on Cardiomyopathies of the World Health Organization and the International Society and Federation of Cardiology. We identified 121 infants, children and adolescents as having cardiomyopathy, giving an average occurrence for all cardiomyopathies of 38.81 for each 10,000 patients examined in our outpatient clinics for paediatric cardiology. Of the patients, 50 were female (41.3%) and 71 were male (58.7%). The cardiomyopathy was of the dilated variant in 52 patients (42.9%), with 43 patients (35.5%) having hypertrophic cardiomyopathy, and 6 patients (4.8%) identified with restrictive cardiomyopathy. We encountered no patients with arrhythmogenic right ventricular cardiomyopathy. In nine patients (7.4%), it proved impossible to classify the cardiomyopathy. We placed 11 patients (9.0%) in the group of specific cardiomyopathies. Most of those with dilated cardiomyopathy had been diagnosed prior to the age of 3 years (RR 1.9, 95% CI 1.4–2.47). There were no statistically significant differences in the incidences of dilated as compared to hypertrophic cardiomyopathy (Z 0.923, $p = 0.1779$), but we encountered a significantly lower occurrence of restrictive cardiomyopathy (Z 6.044, $p < 0.001$). Of those with hypertrophic cardiomyopathy, 15 patients (34.8%) had the asymmetric variant, while 28 patients (65.2%) exhibited the concentric form. During the period of follow-up, 10 patients died, 4 with dilated cardiomyopathy, 4 with hypertrophic cardiomyopathy, 1 with restrictive cardiomyopathy, and 1 with a specific cardiomyopathy. We encountered 12 (9.9%) patients who, besides cardiomyopathies, also suffered from neuromuscular disorders. Most of these had dilated cardiomyopathy. Mitochondrial disorders, in contrast, were more frequently found in patients with hypertrophic cardiomyopathy.

Keywords: Cardiomyopathies; childhood; epidemiology

CARDIOMYOPATHIES ARE A HETEROGENEOUS group of myocardial diseases associated with cardiac dysfunction.[1] According to the Task Force established by the World Health Organization and the International Society and Federation of Cardiology, they are classified either on the basis of the dominant pathophysiology or, if possible, by etiopathogenetic factors. The major varieties are the dilated, hypertrophic, and restrictive forms along with arrhythmogenic right ventricular cardiomyopathy. Unclassified cardiomyopathies include those cases which do not fit readily into these groups, such as fibroelastosis, noncompacted myocardium, systolic dysfunction with minimal dilation, and those with mitochondrial involvement. There are then a group of specific cardiomyopathies to account for myocardial diseases associated with specific cardiac or systemic disorders.[1] Numerous studies, performed in children and adults, have focused on the diagnosis and prognosis of cardiomyopathy. Only a few reports, in contrast, particularly in the era of

Correspondence to: Ivan Malčić, Department of Paediatrics, University Hospital Centre Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia. Tel: +385-1-2388-542; Fax: +395-1-2421-894; E-mail: ivanmalcic@hotmail.com

Accepted for publication 4 May 2001

modern diagnosis, and using the currently accepted definitions, have been concerned with epidemiology. Those which have been carried out[2–4] studied the epidemiology of so-called "idiopathic" cardiomyopathy.[2–4] The term "idiopathic", however, has fallen from grace in recent years, since the striking development of molecular biology and molecular genetics has provided new insights into the pathogenesis of the cardiomyopathies.[5–7] In the light of these considerations, using strict criterions for inclusion and exclusion, we have examined the occurrence of the various cardiomyopathies in a well-defined population. We sought to obtain information on the average occurrence of all cardiomyopathies relative to other cardiac diseases, the occurrences of special types of cardiomyopathy, age and sex-specific occurrences of the various types of cardiomyopathy, their relation with other conditions, and the outcome of the disease.

Patients and methods

All patients aged from birth to 20 years and diagnosed during the period 1988–1998 as having cardiomyopathy were entered into the study, following strict criterions for inclusion and exclusion. To ensure maximum certainty about the identification of all cases, we reviewed the records not only of all patients given the diagnosis of cardiomyopathy, but also those of all patients diagnosed as having undefined arrhythmia, heart failure of unknown origin, unspecified pathologic cardiac condition such as cardiac enlargement, and myocarditis. The evaluation included a thorough medical history, physical examination, standard chemical analysis of blood, hematologic measurements, protein electrophoresis, electrocardiography, X-ray, echocardiography and, in some cases, cardiac catheterisation and endomyocardial biopsy. During the physical examination, we followed carefully the guidelines of the New York Heart Association[8] with regard to congestive lung disease, positive venous pulse, apical and parasternal cardiac impulses, systolic murmurs, heart rate, hepatomegaly, splenomegaly and signs of protein losing enteropathy. The initial diagnosis was based on echocardiographic features. Hypertrophic cardiomyopathy was recognised by hypertrophy of the septum and/or the left ventricular free wall. We required the absolute thickness of these structures to surpass by at least 2 standard deviations the normal values regarding to the age and wieght. In those with the obstructive variant, we observed systolic anterior motion of the leaflets of the mitral valve.[9–12]

Dilated cardiomyopathy was recognised on the basis of enlargement of the cardiac chambers, especially the left atrium and left ventricle. The left ventricular end-diastolic and end-systolic dimensions exceeded by at least 2 standard deviations the normal values regarding to the age and weight. The left ventricular ejection fraction was decreased by at least 2 standard deviations from the normal values, and occasionally we noted reduced thickness of the left ventricular free wall and septum. The right ventricle, in contrast, was often not obviously dilated or dysfunctional.[9,11–13] In those with restrictive cardiomyopathy, we observed symmetrical hypertrophy with reduced diastolic dimensions of the left ventricle, occasionally also with right ventricular involvement.[9,11,12,14]

There were 12 patients who, besides their cardiomyopathy, also suffered from neuromuscular disorders. In these patients, the neurologic and cardiologic diagnoses were established by routine methods, but myocardial biopsy was performed in some. In all patients, we followed the outcome of disease with regard to mortality, improvement, worsening, and resolution of the disease. Statistical analysis of incidence was performed using the hypothesis test for two proportions from one group (mutually exclusive categories). For testing the specific incidence of dilated and hypertrophic cardiomyopathy in different age groups, we established the relative risk with 95% confidence intervals.

Results

Our study contains data obtained during inpatient and outpatient examinations. Using hospital and outpatients records, we identified 121 patients as having cardiomyopathy amongst 31,167 infants, children and adolescents examined in the period between 1988 and 1998. There were 117 newly diagnosed cases, with 4 of the patients having been diagnosed before 1988. The average occurrence of all cardiomyopathies was 38.81 for each 10,000 patients examined in our outpatient clinics for paediatric cardiology. The average occurence of dilated cardiomyopathy was 16.68 per 10,000, while that for hypertrophic cardiomyopathy was 13.80 per 10,000, and that for restrictive cardiomyopathy was 1.93 per 10,000 examined patients (Table 1). The occurrence tended to increase with age in those with hypertrophic cardiomyopathy. Thus, 16 patients (37%) were over the age of 10 years, giving an annual occurrence of 5.13 for each 10,000 patients seen in the outpatient clinic (Table 1).

Of the total, dilated cardiomyopathy was the most common form, being diagnosed in 52 patients (42.9%). Of the remainder, 43 (35.5%) had hypertrophic cardiomyopathy. Of these, 15 patients (12.3%) had the asymmetric variant, while 28 patients (23.1%) had the concentric form. Only 6 patients (4.9%) were identified as having restrictive cardiomyopathy. There were no patients with

https://doi.org/10.1017/S1047951102000550 Published online by Cambridge University Press

Table 1. Occurrence of firmly established cases of cardiomyopathy in infants, children and adolescents seen in Department of Pediatrics, University Hospital Centre Rebro, Zagreb, Croatia, over the period 1988–1998.

Type of cardiomyopathy and age (years)	Number of males	Number/ 10,000[1]	Number of females	Number/ 10,000[1]	Total number	Total number/ 10,000[1]	Total number/ 1000[2]
Dilated cardiomyopathy							
<1	7	2.25	6	1.93	13	4.17	2.44
1–2	6	1.93	6	1.93	12	3.85	4.17
3–5	2	0.64	3	0.96	5	1.60	0.83
6–10	6	1.93	2	0.64	8	2.57	1.11
11–15	5	1.60	6	1.93	11	3.53	1.25
16–20	1	0.32	2	0.64	3	0.96	1.39
Total	27	8.66	25	8.02	52	16.68	
Hypertrophic cardiomyopathy							
<1	4	1.28	2	0.64	6	1.93	1.13
1–2	4	1.28	2	0.64	6	1.93	2.08
3–5	1	0.32	1	0.32	2	0.64	0.33
6–10	7	2.25	2	0.64	9	2.89	1.25
11–15	12	3.85	4	1.28	16	5.13	1.82
16–20	3	0.96	1	0.32	4	1.28	1.85
Total	31	9.95	12	3.85	43	13.80	
Restrictive cardiomyopathy							
<1							
1–2			1	0.32	1	0.32	0.35
3–5			1	0.32	1	0.32	0.17
6–10	1	0.32			1	0.32	0.14
11–15	2	0.64			2	0.64	0.23
16–20	1	0.32			1	0.32	0.46
Total	4	1.28	2	0.64	6	1.93	
All cardiomyopathy[3]							
<1	14	4.49	9	2.89	23	7.38	4.32
1–2	13	4.17	12	3.85	25	8.02	8.68
3–5	2	0.64	7	2.24	9	2.88	1.48
6–10	10	3.21	8	2.56	18	5.77	2.50
11–15	26	8.34	11	3.53	37	11.87	4.21
16–20	6	1.93	3	0.96	9	2.89	4.17
Total	**71**	**22.78**	**50**	**16.03**	**121**	**38.81**	

[1]Age- and sex-specific occurrences shown as absolute numbers of cases for each 10,000 patients examined in the outpatient clinics for paediatric cardiology; [2]Absolute number of cases in each age group per 1000 patients examined of equivalent age in the outpatient clinics for paediatric cardiology; [3]Includes patients with dilated, hypertrophic or restrictive cardiomyopathy, along with 11 patients with specific cardiomyopathies and 9 with unclassified cardiomyopathy

arrhythmogenic right ventricular cardiomyopathy. Dominant inheritance was strongly suggested on the basis of family history in a group of 8 patients with hypertrophic cardiomyopathy, with maternal inheritance suggested in three. None of the patients with hypertrophic cardiomyopathy had Noonan's syndrome, Friedreich's ataxia or Leopard syndrome.

The incidence of dilated cardiomyopathy, when compared to the hypertrophic form, did not show any statistical significance (Z 0.923, $p = 0.1779$), but there was a significantly lower occurrence of restrictive cardiomyopathy (Z 6.044, $p < 0.001$).

Most patients with dilated cardiomyopathy were diagnosed before the age of 3 years (RR 1.9, 95% CI 1.4–2.47). We did not find any relative risk for any specific age of those having hypertrophic cardiomyopathy (no statistical significance). Age specific incidences are presented as the number of diagnostic cases for each 1000 patients examined in a matched age group. Among the age groups, the highest total incidence is between 1 and 2 years of age (8.68), predominantly in children having the diagnosis of dilated cardiomyopathy (4.16), while the incidences of hypertrophic and restrictive cardiomyopathies are distributed equally in all agegroups.

The median age at diagnosis for those with dilated cardiomyopathy was 6 years, with a range from 1 day to 20 years. In those with hypertrophic cardiomyopathy, the comparable figure was 10 years, with a range from 10 days to 20 years, while for those with restrictive cardiomyopathy the number was 9 years, with a range from 1 month to 16 years.

https://doi.org/10.1017/S1047951102000550 Published online by Cambridge University Press

Of the total number of patients, 50 were female (41.3%) and 71 were male (58.7%), giving a ratio of 1 to 1.42. There were no significant differences between males (25 patients) and females (27 patients) amongst those with dilated cardiomyopathy, but in those with hypertrophic cardiomyopathy, males predominated, in the ratio 7 to 3. Of the six patients with restrictive cardiomyopathy, four were male and two female. No differences were found in sex-linked incidence.

Of those with dilated cardiomyopathy at presentation, 23 were asymptomatic, 21 had dyspnea during ordinary physical activity, and 8 had severe dyspnea, being in functional class III or IV of the gradings of the New York Heart Association, and also having signs of heart failure (Table 2). The most common preceding symptoms in infants were feeding difficulties, abnormal sweating, and poor weight gain, whereas older children and adolescents had a cardiac murmur and identified a gradual loss of capacity for physical performance. At the time of diagnosis, a systolic murmur over the apex had been noticed in 12 patients (23.1%), 19 (36.5%) had hepatomegaly, 3 (5.8%) splenomegaly, 9 (17.3%) had abnormal electrocardiographic signs, and 27 (51.9%) borderline electrocardiographic features.

Most patients with hypertrophic cardiomyopathy were asymptomatic at presentation (Table 2). The primary reason for cardiac examination was a previously heard systolic murmur. The most common presenting complaint was dyspnea. All patients had abnormal electrocardiographic findings, with signs of left ventricular hypertrophy, abnormal Q-waves, and marked T-wave inversion. None of the patients had hepatomegaly or splenomegaly.

In those with restrictive cardiomyopathy, two patients were presented with congestive heart failure while the other four had dyspnea during ordinary physical activities (Table 2). Three patients had a systolic murmur of mitral regurgitation, while two had hepatomegaly and splenomegaly. All patients had abnormal electrocardiographic findings.

Of the patients with dilated cardiomyopathy, twelve were catheterised, with myocardial biopsy performed in seven. Focal myonecrosis was identified in 4, probably due to chronic myocarditis. The biopsied material was analysed at light microscopic level following the Dallas criterions,[15] subsequently using also immunohistology, immunohistochemistry, and electron microscopy. We catheterised 6 patients with hypertrophic cardiomyopathy, obtaining myocardial biopsies in 4.

In 9 patients (7.4%) fibroelastosis was diagnosed. They were in a group of unclassified cardiomyopathies. Eleven patients (9.0%) were in a group of specific cardiomyopathies. Five of them had metabolic cardiomyopathy (1 patient had hemochromatosis, 3 had selenium deficiency and 1 had adrenal cortical insufficiency), 2 patients had hypertensive cardiomyopathy, 3 had valvular cardiomyopathy (with ventricular dysfunction that is out of proportion to the normal loading conditions) and 1 had toxic reactions to catecholamines.

There were 12 (9.9%) patients who, besides their cardiomyopathies, also suffered from neuromuscular disorders. Myogenic or neurogenic muscle disorders were found in seven patients with dilated cardiomyopathy, with progressive muscular dystrophy found in 3, two with congenital myopathy, one with Friedreich's ataxia and Charcot-Marie-Tooth disease, and one with spinal scapuloperoneal amyotrophy. Mitochondrial disorders were found in three patients with hypertrophic cardiomyopathy. Two of them had mitochondrial encephalomyoneuropathy, while the other had mitochondrial encephalopathy with myoclonic epilepsy. Myocardial biopsy was performed in two children with restrictive cardiomyopathy. Using electron microscopy, we found collections of mitochondrions in one. In the other, using polarised-light microscopy, we noticed birefringency typical for amyloid. Thus, this child with a clinical diagnosis of restrictive cardiomyopathy had primary cardiac amyloidosis, a very rare finding.

The great number of patients with dilated cardiomyopathy were treated with digoxin and diuretics, or the combination of digoxin, diuretics and vasodilators. Most of our patients with hypertrophic

Table 2. Distribution of patients according to the classification of the New York Heart Association (NYHA) at time of diagnosis.

	NYHA I		NYHA II		NYHA III		NYHA IV	
	No.	%*	No.	%*	No.	%*	No.	%*
Dilated cardiomyopathy	23/52	44.2	21/52	40.4	6/52	11.5	2/52	3.9
Hypertrophic cardiomyopathy	30/43	69.8	12/43	27.9	1/43	2.3		
Restrictive cardiomyopathy			4/6	66.7			2/6	33.3
Other cardiomyopathies	12/20	60.0	8/20	40.0				
Total no. %**	65/121	53.8	45/121	37.2	7/121	5.7	4/121	3.3

*Percentage in separate group of cardiomyopathy, **percentage in separate group of New York Heart Association classification

https://doi.org/10.1017/S1047951102000550 Published online by Cambridge University Press

cardiomyopathy received β-adrenergic blockade. In three patients, we performed myectomy.

In recent years, 7 to 8 new cases of cardiomyopathy have been diagnosed annually in our department. The majority of patients with dilated cardiomyopathy improved during the study, with 6 of 52 (11%) being cured, improvement noted in 31 (60%), worsening in 11 (21%), and death occurring in 4 (7%). In the group with hypertrophic cardiomyopathy, the condition remained stable, apart from 5 of the 43 (11.6%) who died. In 4 patients, arrhythmias were seen on electrocardiography, and two of these four patients died suddenly. Both had exhibited nonsustained ventricular tachycardia during Holter monitoring. One of the six patients with restrictive cardiomyopathy died during the study (16.6%).

Discussion

Today, the cardiomyopathies represent a field of great interest in cardiology. Many clinical and molecular genetic studies have shown that genetic alterations play a significant role in their pathogenesis.[5–7,16–31] Unfortunately, the major advances in the cause and disease mechanism have not yet resulted in therapeutic improvements.

This study, using the criterions established by the Task Force of the World Health Organization and the International Society and Federation of Cardiology, and employing modern diagnostic methods, offers reasonable estimates of the occurrence of cardiomyopathy in infants, children and adolescents. The average annual occurrence of all forms over the period of 10 years was 38.81 for each 10,000 patients examined. Just over one third of the patients were diagnosed under the age of 3 years, giving an average occurence of 15.4 per 10,000 patients, while in the age period from 11 to 15 years, the average occurrence was 11.87 per 10,000 examined patients. Hospitalized patients represent only a fraction of all patients with cardiomyopathy. Most patients were diagnosed and observed exclusively on an outpatient basis. At presentation, the great number of patients were asymptomatic, the diagnosis being established due to the higher index of suspicion among clinicians and the increased use of echocardiography. The majority of patients with hypertrophic cardiomyopathy were asymptomatic at presentation, with severe dyspnea found in only one patient. Most patients with dilated cardiomyopathy were in classes I and II of the grading of the New York Heart Association, with only eight in class III or IV. Four patients with hypertrophic cardiomyopathy died, but three of them were asymptomatic at presentation. In contrast, of four patients with dilated cardiomyopathy who died, none were asymptomatic at presentation, all being in classes III and IV.

Echocardiography has proved important in monitoring the development of dilated cardiomyopathy, not only because of a good estimate of contractility and the level of mitral insufficiency, but also because of its ability to estimate the size of septum and left ventricular wall. In children where the improvement is clearly visible, by using echocardiography one can clearly identify a gradual thickening of these walls towards normal size.

Echocardiography also permits subaortic stenosis to be assessed in those with hypertrophic cardiomyopathy, this being the indication for myectomy. Partial asymmetric hypertrophy of the left ventricle, however, showed no tendency towards arrhythmias, this being the main reason of sudden death. A long lasting subaortic stenosis primarly caused by asymmetric hypertrophic cardiomyopathy can result in concentric hypertrophy of the left ventricle, for which it is essential to consider individual signs such as systolic anterior motion of the mitral valve and mitral insufficiency.

Our therapeutic approach to patients with dilated cardiomyopathy, particularly when we suspected preexisting myocarditis, was to use drugs to reduce preload and afterload, specifically diuretics and inhibitors of angiotensin-converting enzyme, in the first phase of the disease. We then used digoxin subsequent to resolution of acute phase in children who had clinical signs of heart failure so as to improve contractility. When the child had no more than a reduction in ejection fraction, without hepatomegaly, we used digoxin and diuretics. Inhibitors of angiotensin-converting enzyme were reserved for those children who developed severe mitral insufficiency and hepatomegaly.

It is well established that many patients with dilated cardiomyopathy die suddenly, most frequently secondary to ventricular arrhythmia, with a smaller number due to bradyarrhythmia.[32–34] In our study, four patients with dilated cardiomyopathy died. Of the four, three died suddenly, secondary to ventricular arrhythmia. They had been treated with inhibitors of angiotensin-converting enzyme. The presence and severity of ventricular ectopy may predict the risk for sudden death in such patients, but the role of electrophysiologic studies, along with signal-averaged electrocardiography, in stratifying risk remains uncertain. Currently, inhibitors of angiotensin-converting enzyme along with antagonists of beta-receptors are the major agents used in attempts to reduce the incidence of sudden death. Other measures still under investigation include amiodarone, the implantable cardioverter-defibrillator, and dual chamber-pacing.[32–34]

During our study, we also lost 5 patients with hypertrophic cardiomyopathy. Myectomy had been performed in three patients of our overall group. All

https://doi.org/10.1017/S1047951102000550 Published online by Cambridge University Press

continued to have symptoms after surgery, and two of those dying had undergone myectomy. In these two patients, we had observed nonsustained ventricular tachycardia during Holter monitoring, but we did not insert implantable defibrillators, which have been shown to be highly effective in terminating such arrhythmias.[35,36] Like others, we are anxious to avoid sudden death. Our current algorithm contains five steps for patients with hypertrophic cardiomyopathy. The steps are, first, genetic analysis, followed by 24-hour ambulatory Holter monitoring, scintigraphy of the myocardium, cardiac catheterization, and electrophysiologic study. Now, if we find positive results to any of these tests, such as a "malignant" mutation in one of nine genes, ventricular tachycardia during Holter monitoring, or worrisome family history, we will insert an implantable defibrillator.[35–40]

With the ever increasing understanding of the molecular defects, it is to be expected that hypertrophic cardiomyopathy will soon become diagnosed and prevented by molecular techniques, as with other genetically determined disorders. It is also to be anticipated that the rapid advances in the field of molecular medicine will eventually offer the possibility of genetic molecular treatment. Until then, the cardiomyopathies will continue to be a challenging problem for all investigators.[5–7,16–31,41–44]

References

1. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. Circulation 1996; 93: 841–842.
2. Arola A, Jokinen E, Ruuskanen O, Saraste M, Pesonen E, Kuusela AL, Tikanoja T, Paavilainen T, Simell O. Epidemiology of idiopathic cardiomyopathies in children and adolescents. Am J Epidemiol 1997; 146: 385–393.
3. Codd MB, Sugrue DD, Gersh BJ, Melton LJ. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy: a population-based study in Olmested County, Minnesota, 1975–1984. Circulation 1989; 80: 564–572.
4. Bagger JP, Baandrup U, Rasmussen K, Moller M, Vesterlund T. Cardiomyopathy in western Denmark. Br Heart J 1984; 52: 327–331.
5. Schwartz K, Mercadier JJ. Molecular and cellular biology of heart failure. Curr Opin Cardiol 1996; 11: 227–236.
6. Pathak SK, Kukreja RC, Hess ML. Molecular pathology of dilated cardiomyopathies. Curr Probl Cardiol 1996; 21: 99–144.
7. Mestroni L, Rocco C, Vatta M, Miocic S, Giacca M. Advances in molecular genetics of dilated cardiomyopathy. Cardiol Clin 1998; 16: 611–621.
8. New York Heart Criteria Committee: Nomenclature and Criteria for Diagnosis of Disease of the Heart and Great Vessels, 8th edn. Little, Brown and Co, 1979.
9. The Normal Echocardiographic Examination. In: Goldberg SJ, Allen HD, Sahn DJ. Pediatric and Adolescent Echocardiography, 2nd edn. Year Book Medical Publishers, Inc. Chicago, London, 1980, pp 61–126.
10. Maron BJ. Hypertrophic cardiomyopathy. In: Emmanouilides GC, Riemenschneider TA, Gutgesell HP (eds). Heart Disease in Infants, Children, and Adolescents, 5th edn. Williams & Wilkins, Baltimore, 1995, pp 1337–1361.
11. Dubourg O, Bourddaris JP. Doppler echocardiographic investigation of cardiomyopathies. Arch Mal Coeur Vaiss 1996; 2: 39–45.
12. Dubourg O, Pellerin D, Coisne D, Beauvais F, Jondeau G, Bourdarias JP. The echocardiographic examination in adult cardiomyopathy. Arch Mal Coeur Vaiss 1998; 91: 35–42.
13. Chan DP, Allen HD. Dilated congestive cardiomyopathy. In: Emmanouilides GC, Riemenschneider TA, Gutgesell HP (eds). Heart Disease in Infants, Children, and Adolescents, 5th edn. Williams & Wilkins, Baltimore, 1995, pp 1365–1381.
14. Langlard JM. Restrictive cardiomyopathy. Arch Mal Coeur Vaiss 1998; 91: 59–64.
15. Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol 1987; 18: 619–624.
16. Vosberg HP, Uhl WK, Schulz O, Trojani A, Schlepper M, McKeown P, Nauheim B. Molecular diagnosis of causes of dominantly hypertrophic cardiomyopathies. In: Sauer U, Schumacher G. Herzfehler und Genetik. Wissenschaftliche Verlagsgesellschaft mbH. Stuttgart, 1999, pp 237–259.
17. Fananapazir L. Advances in molecular genetics and management of hypertrophic cardiomyopathy. JAMA 1999; 281: 1746–1752.
18. Dausse E, Komajda M, Fetler L, et al. Familial hypertrophic cardiomyopathy. Microsatellite haplotyping and indentification of a hot spot for mutations in the β-myosin heavy chain gene. J Clin Invest 1993; 92: 2807–2813.
19. Burch M, Blair E. The inheritance of hypertrophic cardiomyopathy. Pediatr Cardiol 1999; 20: 313–316.
20. Mogensen J, Klausen IC, Pedersen AK, et al. Alfa-cardiac actin is a novel disease gene in familial hypertrophic cardiomyopathy. J Clin Invest 1999; 103: 39–43.
21. Satoh M, Takahashi M, Sakamoto T, Hiroe M, Marumo F, Kimura A. Structural analysis of the titin gene in hypertrophic cardiomyopathy: identification of a novel disease gene. Biochem Biophys Res Commun 1999; 262: 411–417.
22. Seidman CE, Seidman JG. Molecular genetic studies of familial hypertrophic cardiomyopathy. Basic Res Cardiol 1998; 93 (Suppl 3): 13–16.
23. Baschinski LL, Roberts R. New theories. Causes of dilated Cardiomyopathy. Cardiol Clin 1998; 16: 603–610.
24. Watkins H, Conner D, Thierfelder L, et al. Mutation in the cardiac myosin binding protein-C gene on chromosome 11 cause familial hypertrophic cardiomyopathy. Nat Genet 1995; 11: 434–437.
25. Maron BJ, Moller JH, Seidman CE, et al. Impact of laboratory molecular diagnosis on contemporary diagnostic criteria for genetically transmitted cardiovascular diseases: hypertrophic cardiomyopathy, long-QT syndrome, and Marfan syndrome. Circulation 1998; 98: 1460–1471.
26. Anan R, Greve G, Thierfelder L, et al. Prognostic impications of novel β cardiac myosin heavy chain gene mutations that cause familial hypertrophic cardiomyopathy. J Clin Invest 1994; 93: 280–285.
27. Charron P, Dubourg O, Desnos M, et al. Genotype-phenotype correlations in familial cardiomyopathy. A comparison between mutations in the cardiac protein-C and beta-myosin haevy chain genes. Eur Heart J 1998; 19: 139–145.
28. Fananapazir L, Epstein ND. Genotype-phenotype correlations in hypertrophic cardiomyopathy: insights provided by comparisons of kindreds with distinct and indetical β-heavy chain gene mutations. Circulation 1994; 89: 22–32.
29. Rayment I, Holden HM, Sellers JR, Fananapazir L, Epstein ND. Structural interpretation of the mutations in the β-cardiac myosin that have been implicated in familial hypertrophic cardiomyopathy. Proc Natl Acad Sci USA 1995; 92: 38–64.

30. Bonne G, Carrier L, Richard P, Hainque B, Schwartz K. Familial hypertrophic cardiomyopathy: from mutations to functional defects. Circ Res 1998; 83: 580–593.
31. Epstein ND, Cohn GM, Cyran F, Fananapazir L. Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the β-myosin heavy chain gene: a 908Leu-Val mutation and a 403Arg-Gln mutation. Circulation 1992; 86: 345–352.
32. Hayes DL. Evolving indications for permanent pacing. Am J Cardiol 1999; 83: 161D–165D.
33. Symanski JD, Nishimura RA. The use of pacemakers in the treatment of cardiomyopathies. Curr Probl Cardiol 1996; 21: 385–444.
34. Wu AH, Das SK. Sudden death in dilated cardiomyopathy. Clin Cardiol 1999; 22: 267–272.
35. Maron BJ, Shen WK, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000; 342: 365–373.
36. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000; 342: 1778–1785.
37. Sadoul N, de Chillou C, Aliot E, McKenna WJ. Evaluation of the risk of sudden death in hypertrophic cardiomyopathy. Arch Mal Coeur Vaiss 1999; 92: 65–73.
38. Fananapazir L, McAreaveay D. Hypertrophic cardiomyopathy: evaluation and treatment of patients at high risk for sudden death. Pacing Clin Electrophysiol 1997; 20: 478–501.
39. Fananapazir L, Chang AC, Epstein SE, McAreaveay D. Prognostic determinants in hypertrophic cardiomyopathy: prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiologic findings. Circulation 1992; 86: 730–740.
40. Schulte HD, Gramsch-Zabel H, Schwartzkopff B, Gams E. Hypertrophic cardiomyopathy. Surgical versus drug therapy. Z Kardiol 1999; 88: 163–172.
41. Thierfelder L. Genetics of dilated cardiomyopathy. Med Klin 1998; 93: 210–214.
42. Ferlini A, Sewry C, Melis MA, Mateddu A, Mutoni F. X-linked dilated cardiomyopathy and the dystrophin gene. Neuromuscul Disord 1999; 9: 339–346.
43. Towbin JA. The role of cytoskeletal proteins in cardiomyopathies. Curr Opin Cell Biol 1998; 10: 131–139.
44. Thierfelder L. Genetic screening of cardiomyopathies. Z Kardiol 2000; 89: 638–640.