# ASYMMETRIC SEPTAL HYPERTROPHY (ASH): ECHOCARDIOGRAPHIC MANIFESTATIONS

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT TE ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. B. LEIJNSE
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATS VINDEN OP
WOENSDAG 7 JUNI 1978 DES NAMIDDAGS
TE 3.00 UUR PRECIES

DOOR

**FOLKERT JAN TEN CATE**

GEBOREN TE PONTIANAK (IND.)

1978
BRONDER-OFFSET B.V. – ROTTERDAM

| | | |
|---|---|---|
| PROMOTOR | : | PROF. P.G. HUGENHOLTZ |
| CO-REFERENTEN | : | PROF. DR. A.C. ARNTZENIUS |
| | | CELIA OAKLEY M.D., F.R.C.P., FACC |

Publication of this thesis was supported by The Dutch Heart Foundation

*Voor Marion en Tim,*

*Voor mijn ouders*

CONTENTS

# CHAPTER 1

# INTRODUCTION

## 1.1 Historical perspectives

In the late fifties and early sixties a distinct clinical entity has been recognized in clinical, hemodynamic and angiocardiographic studies. Since then a burst of information concerning this "cardiomyopathic" disorder has been forthcoming.
In this chapter most available information is condensed in a systematic fashion, as an introduction to the thesis itself.
Although various terms are currently still used to describe this condition, on clinical and hemodynamic grounds asymmetric septal hypertrophy, is considered in this study to be the common denominator and consequently this terminology is followed as a descriptor of the syndrome under discussion.
The earliest report available is from Dittrich[1], who, in 1852, described in a necropsy study a patient with typical asymmetric septal hypertrophy. "Das Septum ventriculorum fast 1.5 - 2 Zoll dick und von der Basis an unter den Aortaklappen bis zur Herzspitze herab mit dick gedrängten Muskelsubstanz durchsetzt".
Dilg[2] in 1883 reviewed 15 similar cases, five of these are now recognisable as muscular septal hypertrophy.
This author also noted that disease of the left ventricular outflow tract could coexist with other congenital abnormalities.

Zoll is 2:5 cm.

Schminke[3] described in 1907 two middle-aged females with a muscular stenosis of the left ventricular outflow tract; he surmised that the mechanism of muscular outflow tract stenosis could result in secundary hypertrophy of the left ventricular muscle. In fact, he postulated that this hypertrophy resulted in more stenosis and consequently in more hypertrophy by which a vicious cycle was generated. It was the introduction of cardiac catheterization and with it angiocardiography as well as cardiac surgery which led to the recognition of different types of myocardial hypertrophy during life.

When in 1957, Lord Brock[4] described two females with severe systemic hypertension and functional subaortic stenosis and was followed by Teare[5], who reported nine young adults who died suddenly and in whom a mass of muscle in the septum of the left ventricle was found during necropsy, the medical world again focussed attention on this disease.

In fact, Teare called this disease "Asymmetrical hypertrophy" of the heart, as Dittrich[1] had recognized one hundred years earlier.

The many patients reported in the early sixties by Goodwin[6], Braunwald[7] and Wigle[8] were described under different names. Although the anatomic appearance should have been the denominator of the disease, classification of many cases was based on descriptive terms derived from the angiocardiographic appearances. Goodwin employed the term hypertrophic obstructive cardiomyopathy (HOCM) to differentiate it from other cardiomyopathies.

On the other hand, Braunwald[7] and his group were struck by hemodynamic abnormalities: Idiopathic Hypertrophic Subaortic Stenosis (IHSS), was their choice. The same applied to Wigle who thought that the stenosis was mainly caused by the hypertrophied ventricular septum, although he suspected the role of the mitral valve to be important.

Thus, obstruction, hypertrophy and stenosis were common elements for the diagnosis of the disease. However, it took the last two decades before it became clear that both non-obstructive and obstructive forms exist and, indeed, can proceed from one to the other. This spectrum, already suspected on the basis of angiocardiograms became clarified with the advent of echocardiography[9-11]. Through this technic asymmetric septal hypertrophy (ASH) has become once again the crucial factor and today we can consider ASH again to be the denominator of the disease. In fact, echocardiographic studies have made it possible to enlarge the spectrum to those asymptomatic individuals who are family members of those with clinically evident forms of the disease[12-13]. Furthermore since asymmetric septal hypertrophy can coexist with other forms of cardiac disease such as mitral valve prolaps syndrome, coronary artery disease, fixed subaortic stenosis and valvular aortic stenosis, the echocardiogram has proved to be a most useful tool to extend the boundaries of this syndrome even further[14].

## 1.2 Purpose of the study

The purpose of this study is to describe the echocardiographic manifestations of all patients with asymmetric septal hypertrophy seen between 1970 and 1977 at the Thoraxcenter of the University Hospital in Rotterdam. Several previous publications have formed the backbone of these chapters. They are reprinted as originally published and provided with connecting text.
The first part of the study describes the echocardiographic examination method (both by single-element and multi-element echo techniques) (chapter 2) and the echocardiographic and clinical cardiologic aspects of ASH involved in diagnosis and treatment (chapter 3).

The latter part of the study relates to an echocardiographic analysis of the dynamic behaviour of the left ventricle in ASH (chapter 4) and to the echocardiographic criteria proposed for the assessment of the familial prevalence of ASH in unaffected family members (chapter 5 and 6).
In chapter 7 unexpected clinical findings are described and illustrated, when patients with ASH are followed over longer time periods by echocardiographic technique.
In chapter 8 the echocardiographic findings are described for patients with the fixed type of subvalvular aortic stenosis as a disease to be differentiated from ASH.
Chapter 9 includes a critique on the study and the dates and discusses future perspectives of the disease to be analyzed.
The final chapter contains a summary of the most relevant facts.

## 1.3 References


1. Dittrich F.: Ueber die Herzmuskelentzundung, Prager Vierteljahrschrift für Praktische Heilkunde 51:58, 1852.
2. Dilg J.: Ein Beitrag zur Kenntnis seltener Herzanomalien in Anschluss an einen Fall von angeborener linksseitiger Conusstenose. Archf. Path. Anat. 91:193, 1883.
3. Schminke A.: Ueber linksseitige muskellöse Conusstenosen. Deutsche Medizinische Wochenschrift 33:2082, 1907.
4. Brock R.: Functional obstruction of the left ventricle. Acquired aortic subvalvular stenosis. Guy's Hosp. Report 28:221, 1957.
5. Teare D.: Asymmetrical hypertrophy of the heart in young adults. British Heart Journal 20:1, 1958.
6. Goodwin J., Gordon H., Hollman A. and Bishop M.B.: Clinical aspects of Cardiomyopathies. Brit. Med. Journal 70:5219, 1961.
7. Braunwald E., Morrow A.G., Cornell W.P., Aygen M. and Hilbish T.: Idiopathic hypertrophic subaortic stenosis. Clinical, hemodynamic and angiographic manifestations. Amer. J. Medicine: 924, 1960.
8. Wigle E.D., Heimbecher R.O. and Gunton R.W.: Idiopathic ventricular septal hypertrophy causing muscular subaortic stenosis. Circulation 26:325, 1962.
9. Popp R.L. and Harrison D.C.: Ultrasound in diagnosis and evaluation of therapy of Idiopathic hypertrophic subaortic stenosis. Circulation 40:905, 1969.
10. Henry W.L., Clark C.E. and Epstein S.E.: Asymmetric septal hypertrophy (ASH): The unifying link in the IHSS disease spectrum. Observations regarding its pathogenesis, pathophysiology and course. Circulation: 47, 225, 1973.

11. Abassi A.S., Mc Alpin R.N., Eber L.M. and Pearce M.L.: Echocardiographic diagnosis of idiopathic hypertrophic cardiomyopathy without outflow obstruction.
Circulation 46:897, 1972.

12. Clark C.E., Henry W.L. and Epstein S.E.: Familiar prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis.
New Engl. J. Med. 289:709, 1973.

13. Epstein S.E., Henry W.L., Clark C.E., Roberts W.C., Maron B.J., Ferrans V.J., Redwood D.R. and Morrow A.G.: Asymmetric septal hypertrophy.
Annals of Int. Med. 81:650, 1974.

CHAPTER 2

METHODS

*British Heart Journal*, 1974, **36**, 737–746.

# Dimensions and volumes of left atrium and ventricle determined by single beam echocardiography

F. J. ten Cate, F. E. Kloster, W. G. van Dorp, G. T. Meester, and J. Roelandt

*From the Department of Clinical Echocardiography, Thoraxcenter, Erasmus University, Rotterdam, the Netherlands*

*This study further extends the clinical usefulness of the estimation of cardiac chamber size by means of single echocardiographic dimensions. In 24 patients left atrial size was calculated from an anteroposterior standard echographic dimension and correlates ($r=0{\cdot}88$) with the left atrial surface area measured from selective cineangiograms in the right anterior oblique position. For clinical use a left atrial aortic dimensional ratio was derived as a valid index for the separation of normal and enlarged atrial cavities. An excellent correlation between angiographic and echographic derived volumes was found for left ventricular volumes from single left ventricular echographic dimensions in the 35 patients studied. Correlation coefficients for end-systolic and end-diastolic volumes were $r=0{\cdot}96$ and $r=0{\cdot}97$, respectively. As might be expected, calculated stroke volumes and ejection fractions from echocardiograms and angiograms correlated less well ($r=0{\cdot}82$ and $r=0{\cdot}79$, respectively). From these results and from studies published by others, despite theoretical limitations and several assumptions in the use of single left ventricular dimensions, it is concluded that calculations can be used with confidence for volume determinations in the majority of patients, including those with coronary artery disease and over a wide range of left ventricular dimensions and sizes. It appears that, provided these observations are extended, derived variables such as stroke volume and ejection fractions, can be obtained for the assessment of left ventricular function by non-invasive means.*

The use of reflected ultrasound from external transducers to determine cardiac chamber size is a relatively recent development. The assessment of left atrial size was first attempted by Hirata *et al.* (1969). He found a good correlation between a single left atrial echo dimension and its area measured from cineangiograms in the right anterior oblique position. Left ventricular end-systolic and end-diastolic volumes estimated from single left ventricular echo dimensions and measured from left ventricular angiograms have been compared in many studies. The good agreement between both methods that has been demonstrated by many authors (Popp *et al.*, 1969; Pombo, Troy, and Russell, 1971a; Murray, Johnston, and Reid, 1972; Feigenbaum and Chang, 1972; Fortuin *et al.*, 1971; Gibson, 1973; Ratshin *et al.*, 1973) is surprising when one considers the geometry and the mathematics that are involved. Results obtained by other methods such as the Fick technique (Feigenbaum, Zaky, and Nasser, 1967; Popp and Harrison, 1970, 1970) and the indicator dilution technique (Pombo *et al.*, 1971b) have also been used as a reference and again good correlations have been found. More recent echographic studies employ standardized techniques to obtain echoes both from the left side of the septum and from the endocardium of the left ventricular posterior wall. This standardization refers to the patient position, transducer position, control of gain settings, and the use of stripchart recorders (Feigenbaum and Chang, 1972; Popp and Harrison, 1973), and has added validity to many dimensional measurements. The purpose of the present study is to investigate further the role of echocardiography in the derivation of left atrial and ventricular size by comparing the results with those obtained with quantitative angiocardiography in a variety of clinical conditions.

Received 21 February 1974.

## Subjects

### Left atrial dimensional study

Studies were made on 24 patients, 12 male and 12 female, aged 12 to 65 years. The patients (Table 1) included 6 with coronary artery disease, 12 with valvular heart disease, 3 with asymmetrical septal

TABLE 1 *Results of left atrial dimension studies*

| *Case no.* | *Age and sex* | *Diagnosis* | *Body surface ($m^2$)* | *Angiogram Left atrial area* | | *Echocardiographic data* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Left atrium* | | *Aorta* | | *LA/Ao ratio* |
| | | | | *$mm^2$* | *$mm^2$ per $m^2$* | *mm* | *mm per $m^2$* | *mm* | *mm per $m^2$* | |
| 1 | 50 M | IHSS | 1·58 | 3616 | 1910 | 33 | 17 | 30 | 16 | 1·1 |
| 2 | 39 M | MR | 1·99 | 5880 | 2955 | 64 | 32 | 28 | 14 | 2·1 |
| 3 | 64 F | MS | 1·71 | 6570 | 3842 | 75 | 44 | 28 | 16 | 2·7 |
| 4 | 45 M | CAD | 1·86 | 3300 | 1780 | 34 | 18 | 34 | 18 | 1·0 |
| 5 | 57 F | MS | 1·86 | 6000 | 3226 | 45 | 24 | 29 | 16 | 1·6 |
| 6 | 55 M | CAD | 1·86 | 3020 | 1624 | 32 | 17 | 38 | 20 | 0·9 |
| 7 | 55 F | MS | 1·73 | 4330 | 2503 | 40 | 23 | 29 | 17 | 1·4 |
| 8 | 60 M | MR | 1·71 | 6700 | 3918 | 80 | 47 | 35 | 20 | 2·4 |
| 9 | 50 F | CAD | 1·29 | 3190 | 2473 | 32 | 25 | 30 | 23 | 1·1 |
| 10 | 31 M | CAD | 1·75 | 2890 | 1651 | 27 | 15 | 25 | 14 | 1·1 |
| 11 | 62 F | MS | 1·49 | 5600 | 3758 | 56 | 38 | 29 | 19 | 2·0 |
| 12 | 26 F | IHSS | 1·59 | 4050 | 2547 | 35 | 22 | 26 | 16 | 1·4 |
| 13 | 46 F | MS | 1·68 | 5310 | 3161 | 61 | 36 | 30 | 18 | 2·0 |
| 14 | 21 M | COCM | 1·90 | 6440 | 3400 | 50 | 26 | 29 | 15 | 1·7 |
| 15 | 12 M | Normal | 1·30 | 2050 | 1580 | 27 | 21 | 27 | 21 | 1·0 |
| 16 | 12 F | PS | 1·30 | 1060 | 820 | 14 | 11 | 14 | 11 | 1·0 |
| 17 | 61 M | CAD | 1·84 | 3550 | 1929 | 37 | 20 | 24 | 13 | 1·5 |
| 18 | 45 M | CAD | 1·71 | 3040 | 1778 | 32 | 19 | 44 | 27 | 0·7 |
| 19 | 49 M | MS | 1·83 | 5400 | 2951 | 61 | 33 | 28 | 15 | 2·2 |
| 20 | 12 M | IHSS | 1·60 | 2200 | 1376 | 27 | 17 | 20 | 13 | 1·3 |
| 21 | 65 F | MR/AR | 1·59 | 4350 | 2736 | 34 | 21 | 24 | 15 | 1·4 |
| 22 | 36 F | MS/AR | 1·83 | 5850 | 3197 | 48 | 26 | 24 | 13 | 2·0 |
| 23 | 47 F | MS/MR | 1·58 | 3090 | 1956 | 37 | 23 | 19 | 12 | 1·9 |
| 24 | 46 F | MR | 1·73 | 5590 | 3231 | 50 | 29 | 30 | 17 | 1·7 |
| Mean | 41·5 | | | 4294·8 | 2512·6 | 43·0 | 25·1 | 28·5 | 16·5 | 1·55 |
| Standard deviation ± | | | | 1599·4 | 861·8 | 16·3 | 9·1 | 5·2 | 3·7 | 0·52 |

$r = 0{\cdot}88$

$y = 0{\cdot}009x + 1{\cdot}7$

$Sy.x = 4{\cdot}3$

$r = 0{\cdot}82$

$y = 0{\cdot}005x + 0{\cdot}3$

$Sy.x = 0{\cdot}3$

Abbreviations: Ao, aorta; AR, aortic regurgitation; CAD, coronary artery disease, COCM: congestive cardiomyopathy, IHSS: idiopathic hypertrophic subaortic stenosis, LA: left atrium, MR: mitral regurgitation, MS: mitral stenosis, PS: pulmonary stenosis.

hypertrophy, one with cardiomyopathy, one with pulmonary stenosis and one with no demonstrable heart disease (functional murmur). All underwent routine diagnostic cardiac catheterization and quantitative angiocardiography. The echocardiographic examination was performed within 24 hours before or after the catheterization procedure and patient selection was only on the basis of the quality of the left atrial cineangiograms. Left atrial and aortic root dimensions were also measured in 25 normal subjects. The absence of heart disease was based on their history, the normal clinical cardiac examination, electrocardiogram, and chest *x*-ray. The same measurements were also made in the last 27 patients presenting at the outpatient clinic with mitral stenosis. All had the typical auscultatory findings of mitral stenosis, further confirmed by other non-invasive methods; of these the abnormal mitral valve motion pattern on the echocardiogram was the most consistent one.

## Left ventricular dimensional study

Of 50 consecutive patients undergoing diagnostic heart catheterization, 42 had suitable echocardiograms (84%). In 35 both the echocardiograms and angiocardiograms permitted left ventricular volume calculations (70%). These 35 patients, 32 male and 3 female, aged 16 to 64 years presented with a wide spectrum of cardiac diseases (Table 2). They include 19 with coronary artery disease; 14 with valvular disease; one with asymmetrical septal hypertrophy, and one with Ebstein's disease. Their echocardiographic study was performed within a 24-hour period before or after the catheterization procedure.

TABLE 2 *Results of left ventricular volume studies*

| *Case no.* | *Age and sex* | *Diagnosis* | *Body surface area* ($m^2$) | *Systolic diameter* (*mm*) | *Diastolic diameter* (*mm*) | *End-diastolic volume* ($ml/m^2$) | | *End-systolic volume* ($ml/m^2$) | | *Stroke volume volume* ($ml/m^2$) | | *Ejection fraction* (%) | | *Heart rate* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Echo* | *Angio* | *Echo* | *Angio* | *Echo* | *Angio* | *Echo* | *Angio* | *Echo* | *Angio* |
| 1 | 21 M | Ebstein | 1·6 | 37 | 53 | 94 | 97 | 32 | 34 | 64 | 63 | 66 | 67 | 80 | 108 |
| 2 | 31 M | CAD | 1·75 | 40 | 54 | 94 | 91 | 38 | 37 | 56 | 54 | 60 | 59 | 75 | 62 |
| 3 | 43 M | AS/AR | 1·72 | 43 | 54 | 97 | 103 | 49 | 58 | 48 | 45 | 50 | 44 | 90 | 122 |
| 4 | 37 M | CAD | 1·75 | 44 | 56 | 104 | 97 | 50 | 40 | 54 | 57 | 52 | 59 | 60 | 66 |
| 5 | 55 M | CAD | 1·9 | 40 | 52 | 75 | 82 | 36 | 38 | 39 | 44 | 51 | 54 | 60 | 66 |
| 6 | 40 M | CAD | 1·9 | 37 | 50 | 76 | 83 | 23 | 29 | 53 | 54 | 70 | 65 | 70 | 80 |
| 7 | 42 M | MS/MR/AS/AR | 1·64 | 50 | 56 | 113 | 100 | 79 | 57 | 34 | 43 | 29 | 33 | 70 | 97 |
| 8 | 46 M | CAD | 1·73 | 40 | 53 | 89 | 112 | 38 | 45 | 51 | 67 | 57 | 60 | 60 | 73 |
| 9 | 51 F | CAD | 1·47 | 36 | 46 | 70 | 77 | 32 | 41 | 38 | 36 | 56 | 47 | 60 | 75 |
| 10 | 61 M | MS/MR | 1·84 | 30 | 43 | 45 | 49 | 16 | 16 | 29 | 33 | 65 | 66 | 60 | 57 |
| 11 | 50 F | MS | 1·54 | 43 | 50 | 84 | 87 | 55 | 48 | 29 | 39 | 36 | 45 | 65 | 84 |
| 12 | 61 M | CAD | 1·84 | 57 | 64 | 150 | 162 | 107 | 97 | 43 | 65 | 27 | 40 | 65 | 54 |
| 13 | 43 M | CAD | 1·74 | 45 | 49 | 72 | 89 | 50 | 46 | 22 | 43 | 31 | 48 | 80 | 121 |
| 14 | 46 M | CAD | 1·9 | 37 | 53 | 79 | 86 | 27 | 34 | 52 | 52 | 66 | 61 | 70 | 64 |
| 15 | 52 M | CAD | 1·97 | 43 | 53 | 77 | 97 | 43 | 37 | 34 | 60 | 45 | 62 | 70 | 64 |
| 16 | 42 M | AR | 1·83 | 63 | 79 | 288 | 280 | 150 | 187 | 138 | 93 | 46 | 33 | 80 | 107 |
| 17 | 46 M | CAD | 1·92 | 34 | 51 | 72 | 65 | 21 | 24 | 51 | 41 | 71 | 63 | 80 | 89 |
| 18 | 64 F | MS | 1·70 | 37 | 55 | 100 | 84 | 31 | 29 | 69 | 55 | 70 | 65 | 90 | 123 |
| 19 | 43 M | CAD | 1·89 | 41 | 53 | 80 | 79 | 39 | 40 | 41 | 39 | 51 | 49 | 80 | 82 |
| 20 | 51 F | MS/MR | 1·69 | 40 | 48 | 67 | 67 | 39 | 38 | 28 | 29 | 42 | 44 | 70 | 76 |
| 21 | 62 F | MS/MR | 1·49 | 46 | 56 | 122 | 117 | 67 | 68 | 55 | 49 | 45 | 42 | 70 | 80 |
| 22 | 50 M | AR | 1·82 | 37 | 58 | 109 | 107 | 28 | 33 | 81 | 74 | 74 | 69 | 70 | 70 |
| 23 | 49 M | MS | 1·83 | 45 | 56 | 99 | 108 | 52 | 52 | 47 | 56 | 48 | 52 | 70 | 82 |
| 24 | 50 M | CAD | 2·02 | 43 | 58 | 99 | 101 | 42 | 45 | 57 | 56 | 57 | 56 | 60 | 58 |
| 25 | 12 M | IHSS | 1·60 | 32 | 44 | 57 | 66 | 21 | 20 | 36 | 46 | 64 | 70 | 70 | 80 |
| 26 | 42 M | CAD | 1·7 | 31 | 42 | 45 | 55 | 18 | 15 | 27 | 40 | 59 | 72 | 70 | 85 |
| 27 | 29 M | TR | 1·9 | 29 | 43 | 44 | 46 | 13 | 15 | 31 | 31 | 71 | 68 | 70 | 77 |
| 28 | 52 M | CAD | 1·78 | 39 | 51 | 77 | 71 | 34 | 22 | 43 | 49 | 57 | 69 | 70 | 78 |
| 29 | 47 M | MR/TR | 1·84 | 45 | 59 | 117 | 115 | 51 | 46 | 66 | 69 | 57 | 60 | 70 | 83 |
| 30 | 38 M | CAD | 2·0 | 40 | 58 | 99 | 107 | 34 | 48 | 65 | 59 | 67 | 56 | 60 | 65 |
| 31 | 45 M | CAD | 1·71 | 33 | 45 | 56 | 64 | 21 | 20 | 35 | 44 | 62 | 68 | 70 | 80 |
| 32 | 16 M | AS/VSD | 1·75 | 37 | 51 | 79 | 101 | 31 | 37 | 48 | 64 | 62 | 63 | 70 | 79 |
| 33 | 40 M | CAD | 1·8 | 40 | 55 | 96 | 86 | 39 | 34 | 58 | 52 | 60 | 60 | 70 | 72 |
| 34 | 49 F | MR | 1·69 | 55 | 62 | 150 | 183 | 100 | 134 | 50 | 49 | 33 | 27 | 70 | 80 |
| 35 | 44 M | CAD | 1·83 | 40 | 50 | 69 | 82 | 34 | 32 | 35 | 50 | 48 | 61 | 70 | 97 |
| | | Mean | | 51·6 | 40·8 | 92·6 | 97·0 | 44·3 | 45·6 | 48·5 | 51·4 | 54·3 | 55·9 | 70 | 76 |
| | | Standard deviation ± | | 11·04 | 7·29 | 42·3 | 41·9 | 29·0 | 33·5 | 19·5 | 13·2 | 13·08 | 11·7 | 7 | 24 |
| | | | | | | r = 0·97 | | 0·96 | | 0·82 | | 0·79 | | | |
| | | | | | | y = 0·98x − 2·22 | | y = 0·83x + 6·30 | | y = 1·21x − 14·02 | | y = 0·88x + 4·94 | | | |
| | | | | | | Sy.x = 10·6 | | Sy.x = 8·3 | | Sy.x = 11·07 | | Sy.x = 7·98 | | | |

AS, aortic stenosis; VSD, ventricular septal defect; TR, tricuspid regurgitation.
For other abbreviations, see footnote to Table 1.

## Methods

### Echocardiographic studies

Echocardiographic studies were done with the ECHO-cardioVISOR, an instrument that has both the conventional single element and the multiscan facility (Bom *et al.*, 1973; Roelandt *et al.*, 1973). All studies were performed using a 1·9 cm diameter, 2·25 mHz, and 7·5 cm focused transducer. The transducer is pulsed for 1 msec and receives during a period of 200 $\mu$sec. The repetition rate is 1024 impulses per second. The echo signals were recorded in the M-mode using a Honeywell Linescanrecorder (Visicorder 1856) on Kodak light sensitive paper (Linagraph type 1895).

Patients were examined in the supine position. Turning the patient slightly on his left side sometimes allows better visualization of the interventricular septum and left ventricular posterior wall simultaneously. The standard position of the transducer is in that intercostal space where the characteristic rapid anterior mitral leaflet motion is recorded while the transducer is held perpendicularly on the chest and as close as possible

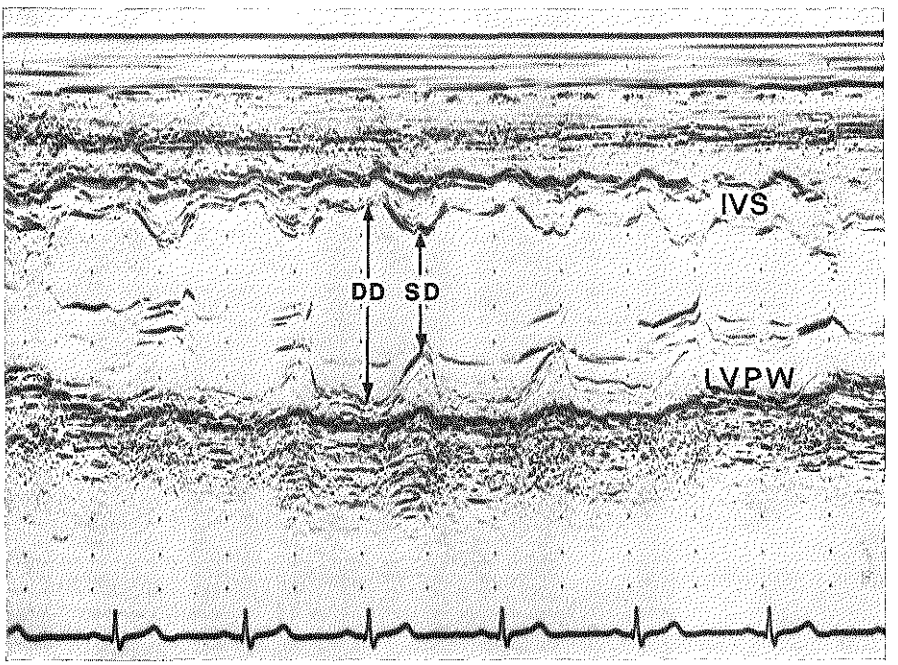



FIG. 1 *Transverse scan perpendicular to the long axis of the left ventricle. The left ventricular end-diastolic (DD) and end-systolic dimensions (SD) are measured where the left ventricular cavity is largest and at their respective times in the cycle as indicated by the electrocardiogram. Calibration points are 1 cm apart. (Abbreviations: IVS = interventricular septum; LVPW = left ventricular posterior wall.)*

to the left sternal border. The long-axis plane of the heart is then defined by reorienting the transducer from this position slightly to the aortic root (medial-superior direction) and to the apex of the heart (lateral-inferior direction). A continuous sectorscan through this plane is then performed and recorded (Feigenbaum and Chang, 1972; Popp and Harrison, 1973). Subsequently, selective recordings of the aorta and left atrium are made. The transducer is then aimed at a point just below the tip of the mitral valve leaflets. From this position, the transducer is angled so as to be perpendicular to the plane of the long axis. This is referred to as the transverse, or T-scan (Henry, Clark, and Epstein, 1973). Several T-scans are performed and the largest left ventricular diameter defined (Fig. 1). Recordings of the left ventricular dimensions are then made during several cardiac cycles, with the transducer in this position. Different time-sensitive gain settings are used to obtain the highest quality echocardiograms. Representative time-motion recordings are shown in Fig. 2. Panel A shows echocardiographic traces from the anterior and posterior aortic root and left atrial dimensions. An example of left ventricular echocardiogram, where both the endocardium of the left side of the interventricular septum and of the left ventricular posterior wall are seen is shown in panel B.

### Angiocardiographic studies

Selective single plane left atrial cinenagiograms were made at 80 frames per second in the right anterior oblique position. Urografin 60 per cent (0·75 ml/kg body weight) was injected either in the left atrium or in the pulmonary artery. Quantitative single plane left ventricular cineangiograms were all done in the right anterior oblique position at 80 frames per second. The same amount of Urografin was injected into the left ventricle through a retrograde catheter properly positioned in the left ventricle. An electrocardiographic lead, cineframe markers, and the timing of the contrast injection were recorded on a multichannel recorder.

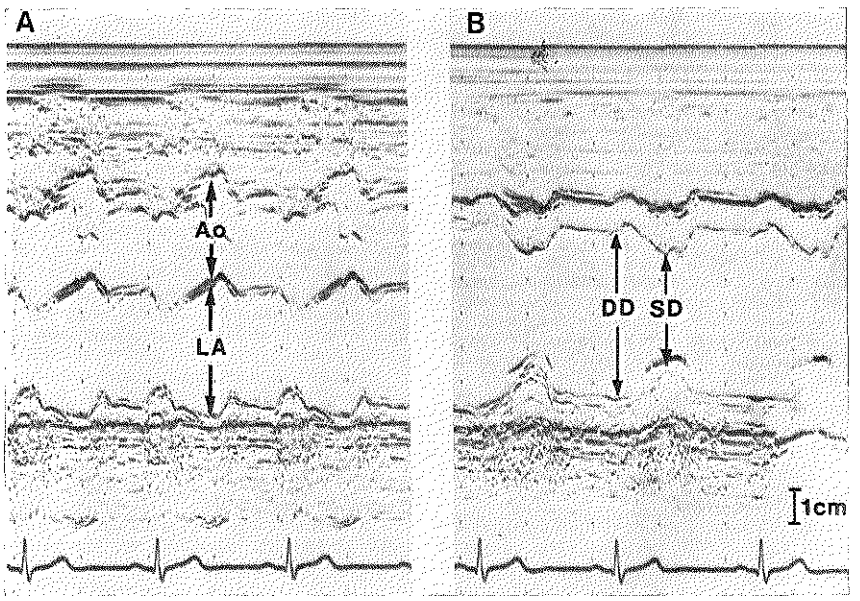



FIG. 2 *Panel A shows a standard echocardiogram used for left atrial dimensional measurements. The aortic walls and the left atrial posterior wall are visualized. Arrows indicate the internal dimensions of both the aortic root (Ao) and left atrium (LA). Calibration points are 1 cm apart. A standard left ventricular echocardiogram is represented in panel B. Left ventricular dimensions at end-diastole (DD) and at end-systole (SD) are indicated by arrows. The diastolic dimension (DD) is measured at the R peak of the simultaneously recorded electrocardiogram.*

## Echocardiographic and angiocardiographic data analysis

**Echo data** Only the best quality tracings of each patient were selected for this study. For left atrial dimensional measurements, echocardiographic recordings were used where the anterior and posterior aortic wall and left atrial posterior wall were seen during several cardiac cycles. The typical motion patterns of these structures have been described elsewhere (Hirata *et al.*, 1969; Feigenbaum and Chang, 1972; Popp and Harrison, 1973). Arbitrarily the distance between the anterior surfaces of the anterior and posterior aortic walls was considered to be the dimension of the aortic root, and the distance between the posterior aortic wall and the anterior echoes of the left atrial posterior wall was taken as the left atrial standard anteroposterior dimension (Popp and Harrison, 1973). All measurements were done at end-systole at which time the largest left atrial diameter was considered to be present. Measurements during 3 to 5 consecutive cardiac cycles were made and expressed in mm (see Fig. 2A). For analysis of the left ventricular dimensions, tracings were selected where the endocardium of both the interventricular septum and left ventricular posterior wall were clearly seen simultaneously (Fig. 2B). Measurements were done at the peak of the R wave for the end-diastolic dimensions, while the smallest distance between the interventricular septum and left ventricular posterior wall was considered as the end-systolic dimension. End-systolic volumes were calculated as $1{\cdot}047\ SD^3$ (where SD is the end-systolic dimension in cm) and end-diastolic volume as $1{\cdot}047\ DD^3$ (where DD is the end-diastolic dimension in cm). Indeed, the volume of a prolate ellipse is $(\pi/6)\ LD^2$, where L is the long and D the minor axis. If one assumes $L=2D$, the formula becomes $(2\pi/6)\ D^3$ or $1{\cdot}047\ D^3$. Stroke volumes were calculated as the difference between end-diastolic and end-systolic volumes. Ejection fraction is stroke volume divided by end-diastolic volume. All the volumes were corrected for body surface area and expressed in $ml/m^2$.

**Angiocardiographic data** The left atrial area visualized on the right anterior oblique cineangiograms was measured by planimetry using a special projecting table (Autotrol Corp-model 3400 Curve Tracer). The largest left atrial area-curve was used for comparison with the left atrial echo dimension. The areas were corrected for *x*-ray magnification using a filmed standard grid at the mid-level of the heart. The left atrial area is expressed in $mm^2$. Left ventricular volumes were calculated from the area and length of the left ventricle measured on the same projecting table and corrected for *x*-ray magnification by means of the area-length method for volume calculation for films taken in the right antero-oblique position as described by Greene *et al.* (1967). The cine-frame at the R-peak of the electrocardiogram was taken as the end-diastolic volume and the smallest volume as the end-systolic volume. Stroke volume of the left ventricle is end-diastolic minus end-systolic volume. Ejection fraction is the ratio of systolic volume to end-diastolic volume.

**Statistical analysis** Data were analysed by a statistical programme on a PDP 9 computer, using standard regression techniques (Fisher, 1970).

## Results

### Left atrial size studies

The diagnosis and the results of the 24 patients are given in Table 1. The left atrial areas calculated from angiographic and the left atrial and aortic echographic dimensions are listed with and without adjustment for body surface area. The mean angiographic left atrial area was 4294 $mm^2$ (2512·6 $mm^2/m^2$ body surface area), with a standard deviation (SD) of 1599 $mm^2$ (861 $mm^2/m^2$ body surface area). The mean left atrial echocardiographic dimension was 43·0 mm with a SD of 16·3 mm, after adjustment for variation in body surface area it was 25·1 mm with a SD of 9·1 mm. Fig. 3A shows the relation between the body surface area adjusted angiographic left atrial areas and left atrial echographic dimensions. The correlation coefficient r is 0·88. The calculated regression equation was left atrial dimension = 0·009 x (angiographic) + 1·7 with a standard error of the estimate (Sy.x) of 4·3 $mm/m^2$. The left atrial dimensions of patients with valvular heart disease and the one with cardiomyopathy (mean: 54·3 mm ± 14·8) were clearly different from the left atrial dimensions in the other 11 patients (mean 30·0 mm ± 6·2). The range of the left atrial dimensions is large, and it is impossible to separate normals from those with left atrial enlargement. In an attempt to standardize and to improve the reliability of the estimation of left atrial enlargement, the ratio of left atrial to aortic dimension was calculated in all patients. Fig. 3B shows the correlation between this ratio and the left atrial area (r = 0·82). This ratio was found to be higher than 1·0 in only 2 of 25 normal subjects (mean 0·90 with a SD of 0·13), while in 27 patients with mitral stenosis the ratio was considerably higher (mean 1·93 with a SD of 0·48). It appears, therefore, that the ratio left atrium to aorta allowed separation of patients in whom left atrial enlargement was present from those in whom it was considered to be absent (Fig. 4). Absolute left atrial size in the same patients yielded values that fell in the normal range in 20 per cent of patients with long-standing and chronic atrial fibrillation (18–40 mm; Hirata *et al.*, 1969).

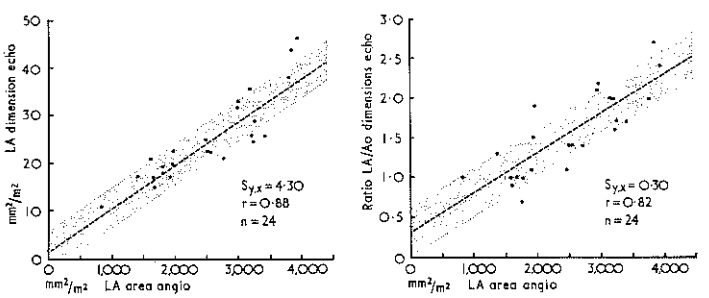



FIG. 3 *The left panel shows the correlation between the echocardiographic left atrial dimension and left atrial area as determined by cineangiography. Both values for left atrial size are corrected for body surface area. Right panel: Correlation between the ratio of left atrial and aortic root dimensions by echocardiography and the left atrial area as determined by angiocardiography. The broken lines represent the calculated regression lines and the stippled area the standard error of the estimate (Sy.x).*

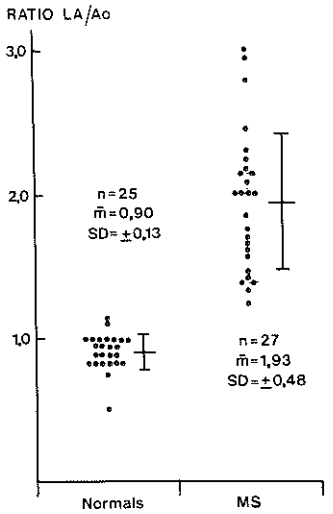



FIG. 4 *The LA/Ao dimensional ratios are shown for 25 normal subjects and 27 patients with mitral stenosis. Note that all normals centre around 1 and that there is a clear separation from patients with mitral senosis.*

### Left ventricular volume studies

Tables 2 summarizes the results in the 35 patients. The uncorrected mean values for the echographic determined DD and SD were 51·6 and 40·8 mm. Standard deviations from the mean were 10·04 and 7·29 mm, respectively. Mean values for echocardiographic and angiographic calculated end-diastolic volumes were 92·6 and 97·0 ml/m$^2$. Standard deviation is 42·3 and 41·9 ml/m$^2$. The correlation coefficient is 0·97 and the calculated regression equation: echocardiogram (EDV) = 0·98 angiogram (EDV) − 2·22. The standard error of the estimate (Sy.x) is 10·63 ml/m$^2$.

Mean end-systolic volumes by echocardiogram and angiogram are 44·3 and 45·6 ml/m$^2$ (standard deviation ± 29·0 and 35·5 ml/m$^2$). The correlation coefficient is 0·96. The regression equation is echogram (ESV) = 0·83 angiogram (ESV) + 6·30 with Sy.x = 8.30 ml/m$^2$. Fig. 5a and b show the relations between the angiographic and echocardiographic end-diastolic and end-systolic volumes, respectively. Mean stroke volume by echocardiography and angiography is 48·5 and 51·4 ml/m$^2$ (standard deviation ± 19·5 and 13·2 ml/m$^2$). Both methods correlate with r = 0·82 and r = 0·79, respectively. The regression equation is: echogram (SV) = 1·21 angiogram (SV) − 14·02 and Sy.x = 11·07 ml/m$^2$.

Mean ejection fraction is 54·3 and 44·9 per cent by echocardiography and angiography, respectively, with standard deviation ± 13·08 and 11·7 per cent. The regression equation is echocardiography (EF) = 0·88, angiography (EF) + 4·94 with Sy.x = 7·9 per cent. Fig. 6a and b show diagrammatically the relations between both by angiogram and echocardiogram calculated stroke volume and ejection fraction.

### Discussion

Only one previous study deals with the feasibility of assessing the left atrial size from a single anteroposterior echocardiogram dimension (Hirata *et al.*,

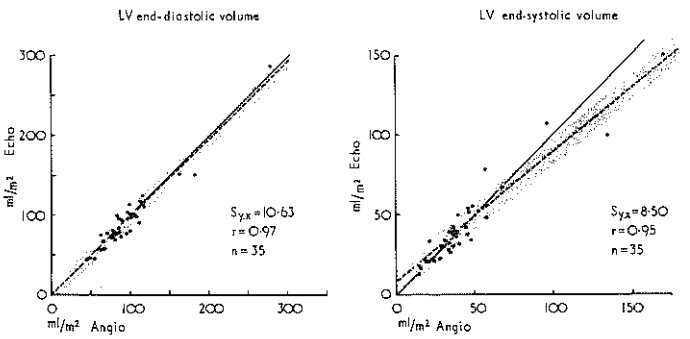



FIG. 5 *The left panel shows the correlation between end-diastolic volumes calculated from echocardiography (ordinate) and angiography (abscissa). The right panel shows a plot of the end-systolic echographic volumes against the angiographic end-systolic volumes. Solid line is line of identity, broken line the regression line, and the stippled area represents the standard error of the estimate (Sy.x).*

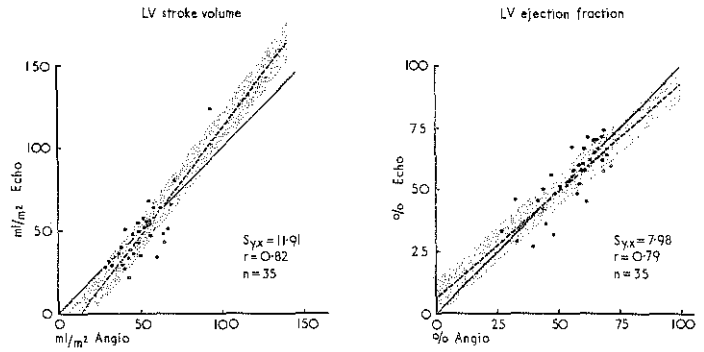



FIG. 6 *Comparison of total left ventricular stroke volumes (left panel) and ejection fractions (right panel) by echocardiogram and angiogram. The line of identity is the solid line, the regression line the broken line and the stippled area the standard error of the estimate.*

1969). These investigators found a good correlation with the left atrial area measured from selective left atrial cineangiograms in the right anterior oblique position (r = 0·91). Shortly after this study the walls of the left atrial chamber were also identified echocardiographically by means of Cardiogreen dye injections (Gramiak, Shah, and Kramer, 1969; Feigenbaum *et al.*, 1970) which, by the added contrast (echoes from the blood containing the dye), permitted the validation of the accuracy of the echographic mesurements. The left atrial size has also been assessed from the suprasternal transducer position (Goldberg, 1971). The dimensions obtained in that study are about 30 per cent larger but the number of cases reported was not very large. The present study confirms the validity of estimating the left atrial size from a single anteroposterior standard dimension since the correlation coefficient (r = 0·88) was high and standard deviation small. The assumption made in the present study and in that by Hirata *et al.* (1969) was that the cineangiographic left atrial area in the right anterior oblique position is representative of the left atrial chamber size or volume. This is a questionable assumption for a normal left atrium but may well apply to enlarged left atria where the angiographic evidence shows that the shape becomes more globular. The problem in the use of left atrial dimensions is that there is a large variation in the normal left atrial dimension while correction for body surface area will restrict the range of normal values (Hirata *et al.*, 1969). The late atrium/aorta ratio was found to be a useful empirical index in the individual patient at the bedside and gave better separation between the normal left atrium and left atrial enlargement than the absolute left atrial size. It is known from surgical experience that the sinuses of Valsalva, where echocardiographic dimensions are measured, rarely dilate in chronic aortic valve disease (poststenotic dilatation is always above the sinuses of Valsalva so that aortic dilatation should not invalidate this ratio). The application of echocardiography and its clinical usefulness in the estimation of left ventricular volumes has been shown in many recent studies (Popp *et al.*, 1969; Popp and Harrison, 1970; Pombo *et al.*, 1971a, b; Fortuin *et al.*, 1971; Feigenbaum *et al.*, 1972; Murray *et al.*, 1972; Belenkie *et al.*, 1973; Gibson, 1973; Ratshin *et al.*, 1973). Correlation coefficients in these studies for end-diastolic volumes ranged from r = 0·84 to 0·97. Values ranging from r = 0·85 to 0·97 have been found for end-systolic volumes. In addition to the estimation of left ventricular volumes, its pump function has been assessed from derived parameters such as stroke volume and ejection fraction (Pombo *et al.*, 1971a; Fortuin *et al.*, 1971; Fortuin, Hood, and Craige, 1972; Feigenbaum *et al.*, 1972). Correlation coefficients for ejection fraction in the different reports are consistently less than for end-diastolic and end-systolic volumes and varied from r = 0·69 to 0·81.

The major problem in the calculation of left ventricular volumes by the conventional ultrasound method is that only one single dimension is employed to calculate the volume of the three-dimensional left ventricular chamber. With the assumption that the left ventricular chamber approximates the shape of an ellipsoid of revolution, the measured

echogram dimension is assumed to represent the anatomical (or angiographic) minor left ventricular axis. It also implies that the measured dimension has a constant relation to the axis of the left ventricle at both end-systole and end-diastole and that this minor axis is indeed half as long as the long axis. It has been shown in experimental studies that major information about left ventricular volume and its change can indeed be obtained from its minor axis alone (Rushmer, Crystal and Wagner, 1953; Hawthorne, 1961; Lynch and Bove, 1969).

Two questions arise in the clinical situation where hearts may assume different shapes: 1) should the same formula which is applied to a small (normal) heart be used for an enlarged (diseased) heart, and 2) what errors are introduced by localized disorders in wall motion? 1) It is known that the minor axis becomes relatively larger as compared to the long axis in dilated ventricles (Fortuin *et al.*, 1971; Teichholz *et al.*, 1972; Popp and Harrison, 1973). Though there are only a few patients with larger left ventricular volumes included in this series from which to draw any conclusions, it was found that no systematic overestimation of the larger volumes occurred, though this could have been expected particularly when the left ventricular shape was more spherical. In addition other recent studies demonstrate that echocardiography allows reliable quantitation of end-diastolic and end-systolic volumes over a wide range of left ventricular sizes (Ratshin *et al.*, 1973) by applying the volume formula of a prolate ellipse. 2) Since coronary artery disease presently represents the largest group of patients in cardiological practice, the second question is more important. While the majority of these patients do not have pronounced dilatation of their left ventricle, most of them do have abnormally contracting segments. Thus, the use of the echographic minor axis should be reasonably accurate in the calculation of end-diastolic volume but the estimation of end-systolic volume might not be satisfactory. It was indeed found that angiographic and echocardiographic end-systolic volumes did not correlate as well as did end-diastolic volumes. Furthermore the accuracy of the echographic estimated end-systolic volumes appeared to be related to the location of the dyskinetic or akinetic segment and not to its extent (Ratshin *et al.*, 1973). These observations seem to invalidate the derived stroke volumes and ejection fractions, particularly in this group of patients where the non-invasive continuous assessment of the left ventricular function is most desired. However, good semi-quantitative estimates of left ventricular volumes and function can be obtained from echographic measurements. Its non-invasive nature and the potential of serial determinations (Redwood, Henry, and Epstein, 1973), even in the critically ill, stimulate continuing research in this field.

We are grateful to Mrs. I. Tiggelaar – de Widt and Mrs. S. Leenheer for their technical assistance.

## References

Belenkie, I., Nutter, D. O., Clark, D. W., McCraw, D. B., and Raizner, A. E. (1973). Assessment of left ventricular dimensions and function by echocardiography. *American Journal of Cardiology*, **31**, 755.

Bom, N., Lancée, C. T., van Zwieten, G., Kloster, F. E., and Roelandt, J. (1973). Multiscan echocardiography I. Technical description. *Circulation*, **48**, 1066.

Feigenbaum, H., and Chang, S. (1972). *Echocardiography*. Lea and Febiger, Philadelphia.

Feigenbaum, H., Popp, R. L., Wolfe, S. B., Troy, B. L., Pombo, J. F., Haine, C. L., and Dodge, H. T. (1972). Ultrasound measurements of the left ventricle. A correlative study with angiocardiography. *Archives of Internal Medicine*, **129**, 461.

Feigenbaum, H., Stone, J. M., Lee, D. A., Nasser, W. K., and Chang, S. (1970). Identification of ultrasound echoes from the left ventricle by use of intracardiac injections of indocyanine green. *Circulation*, **41**, 615.

Feigenbaum, H., Zaky, A., and Nasser, W. K. (1967). Use of ultrasound to measure left ventricular stroke volume. *Circulation*, **35**, 1092.

Fisher, R. A. (1970). *Statistical Methods for Research Workers*, 14th ed. Oliver and Boyd, Edinburgh.

Fortuin, N. J., Hood, W. P., Jr., and Craige, E. (1972). Evaluation of left ventricular function by echocardiography. *Circulation*, **46**, 26.

Fortuin, N. J., Hood, W. P., Jr., Sherman, M. E., and Craige, E. (1971). Determination of left ventricular volumes by ultrasound. *Circulation*, **44**, 575.

Gibson, D. G. (1973). Estimation of left ventricular size by echocardiography. *British Heart Journal*, **35**, 128.

Goldberg, B. B. (1971). Suprasternal ultrasonography. *Journal of the American Medical Association*, **215**, 245.

Gramiak, R., Shah, P. M., and Kramer, D. H. (1969). Ultrasound cardiography: contrast studies in anatomy and function. *Radiology*, **92**, 939.

Greene, D. G., Carlisle, R., Grant, C., and Bunnell, I. L. (1967). Estimation of left ventricular volume by one-plane cineangiography. *Circulation*, **35**, 61.

Hawthorne, E. W. (1961). Instantaneous dimensional changes of the left ventricle in dogs. *Circulation Research*, **9**, 110.

Henry, W. L., Clark, C. E., and Epstein, S. E. (1973). Asymmetric septal hypertrophy. Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation*, **47**, 225.

Hirata, T., Wolfe, S. B., Popp, R. L., Helman, C. H., and Feigenbaum, H. (1969). Estimation of left atrial size using ultrasound. *American Heart Journal*, **78**, 43.

Lynch, P. R., and Bove, A. A. (1969). Geometry of the left ventricle as studied by a high-speed cineradiographic technique. *Federation Proceedings*, **28**, 1330.

Murray, J. A., Johnston, W., and Reid, J. M. (1972). Echocardiographic determination of left ventricular dimensions, volumes and performance. *American Journal of Cardiology*, **30**, 252.

Pombo, J. F., Russell, R. O., Jr., Rackley, C. E., and Foster, G. L. (1971b). Comparison of stroke volume and cardiac output determination by ultrasound and dye dilution in acute myocardial infarction. *American Journal of Cardiology*, **27**, 630.

Pombo, J. F., Troy, B. L., and Russell, R. O., Jr. (1971a). Left ventricular volumes and ejection fraction by echocardiography. *Circulation*, **43**, 480.

Popp, R. L., and Harrison, D. C. (1970). Ultrasonic cardiac echocardiography for determining stroke volume and valvular regurgitation. *Circulation*, **41**, 493.

Popp, R. L., and Harrison, D. C. (1973). The use of ultrasound in cardiac diagnosis. In *Non-invasive Technics in Cardiac Evaluation*, p. 149. Ed. by A. M. Weissler. Grune and Stratton, New York.

Popp, R. L., Wolfe, S. B., Hirata, T., and Feigenbaum, H. (1969). Estimation of right and left ventricular size by ultrasound. *American Journal of Cardiology*, **24**, 523.

Ratshin, R. A., Boyd, C. N. Jr., Rackley, C. E., Moraski, R. E., and Russell, R. O. (1973). Quantitative echocardiography: correlations with ventricular volumes by angiocardiography in patients with coronary artery disease with and without wall motion abnormalities. *Circulation*, **48**, Suppl. IV, 48.

Redwood, D. R., Henry, W. L., and Epstein, S. E. (1973). Evaluation of the ability of echocardiography to measure alterations in left ventricular volume. *Circulation*, **48**, Suppl. IV, 206.

Roelandt, J., Kloster, F., ten Cate, F. J., Born, N., Lancée, C. T., and Hugenholtz, P. G. (1973). Multiscan echo cardiography: description of the system and initial results in 100 patients. *Heart Bulletin*, **4**, 51.

Rushmer, R. F., Crystal, D. K., and Wagner, C. (1953). Funcrional anatomy of ventricular contraction. *Circulation Research*, **1**, 162.

Teichholz, L. E., Kreulen, T. H., Herman, M. V., and Gorlin, R. (1972). Problems in echocardiographic volume determinations: echo-angiographic correlations. *Circulation*, **46** (Suppl. II), II, 51.

Requests for reprints to Professor J. Roelandt, Department of Clinical Echocardiography, Thoraxcenter, P.O. Box 1738, Rotterdam, The Netherlands.

*British Heart Journal*, 1974, **36**, 29–43.

# Multidimensional echocardiography
## *An appraisal of its clinical usefulness*

J. Roelandt, F. E. Kloster, F. J. ten Cate, W. G. van Dorp, J. Honkoop, N. Bom, and P. G. Hugenholtz

*From the Department of Clinical Echocardiography, Thoraxcenter, Erasmus University, Rotterdam, Netherlands*

*Multiscan is a new concept in echocardiography providing instantaneous cross-sections of the heart in motion without distortion. The examination technique and the present display and recording methods are described and discussed in some detail.*

*Multiscan provides important anatomical and functional information in the non-invasive diagnosis of congenital malformations and of valvular heart disease. The size, shape, and overall function of the left ventricle can be assessed.*

*Localized disorders of wall motion are also detected, making the instrument useful for the study and follow-up of patients with coronary artery disease.*

*Quantitative measurements of cardiac dimensions and calculation of left ventricular volumes using the area-length method can be obtained. From the results presented in this paper one may conclude that the concept of Multi-element echocardiography is a valuable extension of the now widely accepted single element technique and offers vast possibilities for the screening, study, and follow-up of patients with cardiac disease.*

Echocardiography is now established as a unique non-invasive diagnostic aid for many congenital and acquired cardiac diseases (Gramiak and Shah, 1971; Feigenbaum, 1972; Meyer and Kaplan, 1973; Popp and Harrison, 1973). However, in most studies where single element probes are used, only a selected, narrow, portion of the heart is explored in depth and recorded as a function of time (time-motion or M-mode). Therefore, no direct information about the anatomical relations of specific cardiac structures or about the activity of the heart as a whole is available. Yet, the importance of and the need for a multi-dimensional echographic display of cardiac structures has been demonstrated by the many attempts over the last few years to visualize the entire cardiac configuration with its true anatomical relations (Åsberg, 1967; Ebina *et al.*, 1967; King, 1973; Kikuchi and Okuyama, 1970; Hertz and Lündström, 1972; Gramiak, Waag, and Simon, 1972). Such a cross-sectional image should afford great advantages in the study of patients with valvular and congenital malformations. In addition, it would allow determination of the ventricular volumes and wall motion. Techniques described so far, however, produce 'frozen' images of the heart (Ebina *et al.*, 1967; King, 1973; Kikuchi and Okuyama, 1970) or have limited frame rates (Åsberg, 1967; Hertz and Lündström, 1972; Gramiak *et al.*, 1972). In fact, real time information about the dynamic function of the heart cannot be obtained with these techniques.

Received 31 August 1973.

The present study provides the first clinical evaluation of a system with which two-dimensional cross-sections of the heart were recorded in real time with good resolution at 80 frames a second. Cardiac structures are visualized in their true anatomical relations and important functional information is obtained. In this paper, the examination techniques and the clinical applications of the system will be described in more detail.

### Methods

The technical aspects of the multiple element echo system[1] have been described in detail in previous papers (Bom *et al.*, 1971, 1973a; Bom, 1972; Roelandt *et al.*, 1973). The core of the system consists of an 8 cm linear array of 20 fixed ultrasound elements. From each element,

[1] ECHOcardioVISOR 01, Organon Teknika, Oss, The Netherlands.

the video signal of the returning echoes is converted to intensity or brightness dots (B-mode) and displayed on the horizontal axis of the oscilloscope. The anterior chest wall is always to the left on the display. The location of the signal from each element on the vertical axis of the oscilloscope corresponds to the position of the element in the transducer. Rapid electronic scanning of all elements and appropriate display of the echoes results in the instantaneous display of moving structures. Presently a 40 line oscilloscope image is produced by an 'interlacing' technique (alternating shift of 2 mm of the image) to provide a more pleasing image. This reduces the effective frame rate to 80 frames a second or half the original repetition rate. Patient identification symbols, the continuous electrocardiogram, and the cross-sectional image are displayed simultaneously on the oscilloscope face. By means of display of the electrocardiogram of the three preceding seconds at the bottom of each frame, the exact correlation with the cardiac cycle is achieved.

Depth calibration can easily be performed in the same way as with conventional echo systems using a calibrated perspex block. Markings on the oscilloscope screen allow adjustment to the approximate $8 \times 16$ cm viewing area. For the figures shown in this paper, a correction factor can be calculated, as the height of a frame always corresponds to 8 cm in the original recordings. The energy levels of the ultrasound in the system were measured in a water tank. Ultrasonic intensity is usually expressed as average intensity in watts per $cm^2$; the average acoustic intensity was found to be 0·6 mwatts/$cm^2$ at 2·25 MHz. At 4·5 MHz it was 2 mwatts/$cm^2$. Both were measured 6 cm in front of the centre of the transducer in a water tank. Peak intensity was measured to be 0·7 watts/$cm^2$ and 3·6 watts/$cm^2$, respectively. These intensities are well within recognized limits of safety (Woodward, Pond, and Warwick, 1970; Ulrich, 1971).

## Recording techniques

While the best images are those directly available on the oscilloscope display at the time of study, permanent records are required for subsequent analysis. However, production of a 'hard copy' of the same quality as the original study poses serious problems. In our laboratory, several recording methods are used and have been assessed for specific applications.

### Magnetic videotape

For routine studies, all data are stored on magnetic videotape which allows playback for motion studies later. It was found that about 30 per cent of the quality of the original image is lost in the process. This is chiefly because of the rather slow frame speed of the video system as compared to the multiscan frame rate and the time-constant and limited sensitivity of the video camera. Motion, however, is preserved though the details of finer structures, such as valve cusps, may be lost.

### Cinematographic film

The original oscilloscope image can be recorded on 16 mm and 35 mm cine film. However, since the camera speed is less than the frame rate of the multiscan, the echo dots are superimposed on one film frame. This results in smearing. Increasing the film speed to 80 frames per second creates problems with film exposure time and synchronization. The quality of the images is good when viewed in motion but the quality of each individual frame is poor. However, interpretation and qualitative assessment of left ventricular dynamics is quite possible with the cine film recordings.

### Polaroid photographs

Single frame photographs can be made from the oscilloscope screen by Polaroid camera. Their quality is reasonably good for quantitative measurements. Triggering from the QRS complex allows the recording of frames at selected moments in the cardiac cycle, such as end-systole and end-diastole. Polaroids are presently used for outlining the left ventricle and calculation of volumes. Furthermore, they are quite suitable for documentation of specific anatomical abnormalities but, with this recording technique, motion is not preserved. Most of the figures included in this paper are Polaroid photographs.

### Individual element recording

The signal from any selected element of the multiscan transducer can be recorded on the line scan recorder[1] in the M-mode. This combines the two-dimensional orientation facility of the multiscan with single element recording and facilitates measurements on selected lines of which the position through cardiac structures is known. The resolution and definition of specific echoes is comparable to conventional single element M-mode recordings.

### Line scan records

Complete frames can be recorded on the line scan recorder.[1] The format of these images is small ($19 \times 40$ mm), being limited by the recorder paper speed. An increase in size of the images by a factor of 2 would call for increase of recorder paper speed from 500 to 1000 mm/sec in order to keep the cross-sectional geometry correct. However, definition of the echoes is good and this recording technique is most promising. These 'postage stamp size' pictures are recorded at 25 frames a second simultaneously with the electrocardiogram.

## Examination technique

### Position of patient

Patients are examined in the supine position, with the head of the bed raised about 20° to 30°. A change in the position of the patient occasionally enhances the images. In our experience, turning the patient slightly on his left side allows better visualization of the interventricular septum and left ventricular posterior wall simultaneously. This is especially important for dimensional measurements and the outline of the left ventricle for the calculation of left ventricular volumes.

[1] Honeywell 1856 Visicorder.

## Transducer positions

The transducer can either be held in a fixed position on the chest or a scanning movement can be performed. It is clear that the exact position and direction of the probe will differ from patient to patient and the described technique is only applicable when no significant changes in the configuration or position of the heart are present. A routine multielement echographic examination should always consist of displaying the long-axis cross-section first, followed by a transverse cross-section through the left ventricular cavity and a transverse scan.

**Long-axis or oblique position** In this position, the transducer is placed obliquely to the left of the sternum with the upper end at the costosternal border. The lower end is angulated laterally about 25° from the midline. This produces a cross-section through the long axis of the heart in a sagittal plane from the base of the heart toward the apex (Roelandt *et al.*, 1973; Kloster *et al.*, 1973a). When the probe is pointed straight posteriorly, the aortic root is the first structure identified in the upper part of the screen. Slight tilting of the probe to the right or left establishes that position in which both the aortic root and the cusps are seen. In this position the left atrium is posterior and part of the right ventricular cavity and/or pulmonary outflow tract are anterior to the aorta. The anterior leaflet of the mitral valve can be seen as it extends downward in direct continuity with the posterior aortic wall (mitral-aortic continuity). The interventricular septum is usually less clearly identified as the structure which extends directly from the anterior aortic wall (septal-aortic continuity) into an anterior direction. Improved definition of the wall of the left atrium and the posterior wall of the left ventricle can be obtained when the transducer is aimed to the patient's left. When the probe is slightly directed to the right of the patient, the interventricular septum, right ventricular cavity, and pulmonary outflow tract can be better seen.

**Transverse position and scan** In the transverse position the transducer is placed to the left of the sternum perpendicular to the long-axis position and approximately along the 3rd or 4th intercostal space. The upper end of the transducer is to the patient's right and forms the top of the image on the oscilloscope. The resulting image is a transverse cross-section through both the right and left ventricle at a ±90° angle with the long axis of the heart (Roelandt *et al.*, 1973; Kloster *et al.*, 1973a). The left ventricle is posterior to the right ventricle with the interventricular septum at a slight angle from the upper right to the lower left. By tilting the transducer in a superior or an inferior direction, a two-dimensional transverse scan of the heart along the long axis can be performed (Fig. 1). A tilt in a superior direction establishes that position where the cross-sections of the right and left ventricles are largest and where the interventricular septum is best defined (Fig. 2A). The anterior leaflet of the mitral valve can be identified by its movement in the left ventricular cavity. Directing the probe slowly superiorly shows the interventricular septum merging into the anterior aortic wall (septal-aortic continuity) and the anterior leaflet of the mitral valve into the posterior aortic wall (mitral-aortic continuity). In the transverse cross-section when the base of the aorta is seen, the left atrium is sometimes clearly outlined posterior to the aorta (Fig. 2B). During this scan, the anterior tricupsid valve often becomes visible in the cross-section just below the aorta. In infants, where calcified structures in the anterior chest give no impediment to sound transmission, it is actually possible to displace the transducer stepwise from the apex towards the base and the great vessels, resulting in successive parallel cross-sections. The transverse scan and/or stepwise displacement of the transducer is very important for the diagnosis of congenital malformations, as cross-sectional anatomy can be assessed without any distortion.

## Results

Up to the time of writing, 296 patients have been studied with the system. In the first 100 patients,

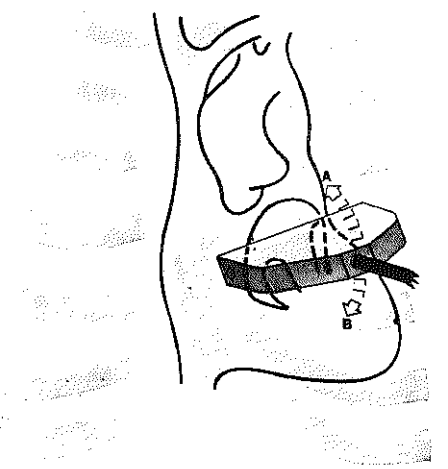



FIG. 1 *A schematic drawing of the transducer in the transverse position on the chest. The upper end of the transducer is to the patient's right and is the top of the cross-section displayed on the oscilloscope. By tilting the transducer a two-dimensional transverse scan along the long axis of the left ventricle is performed. The resulting image in position A is a transverse cross-section through both the right and left ventricle. In position B, the root of the aorta is visualized with the right ventricular outflow tract anterior and the left atrium posterior to it (see Fig. 2). During this scan a large part of the left ventricle can be studied and the septal-aortic and mitral-aortic continuity can be examined.*

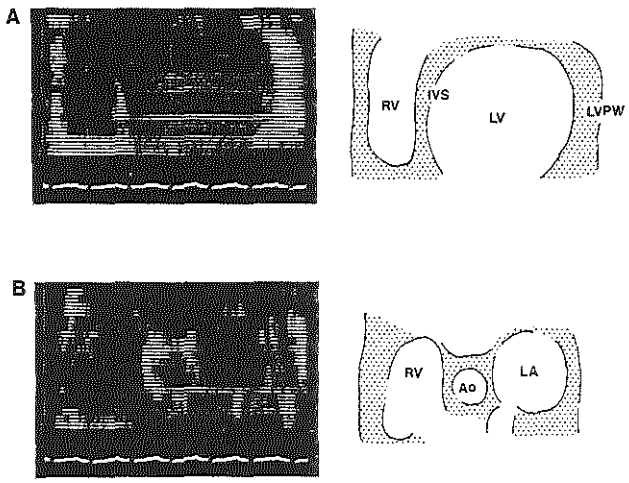



FIG. 2 *Two transverse cross-sections are shown with the transducer in positions A and B as shown in Fig. 1. The anterior chest wall is to the left. The resulting cross-section in position A is seen in panel A. The left ventricle (LV) is posterior to the right ventricle (RV) with the interventricular septum (IVS) at a slight angle from the upper right to the lower left. (LVPW = left ventricular posterior wall.) The lower cross-section is obtained with the transducer in position B (Fig. 1). The root of the aorta (Ao) is clearly delineated with the left atrium (LA) posterior and part of the right ventricle (RV) anterior to it. The cross-sections were obtained in a patient with cardiomyopathy. The size of the left ventricle is enlarged and there is also left atrial enlargement due to mitral incompetence.*

efforts were directed to develop the most efficient examination technique and to establish standard views for rapid recognition of the different cardiac structures and cavities, as described above. Clinical evaluation forms were used to determine the capabilities of the system, including the overall quality of the study, the frequency and quality of recognition of specific structures, and the possibility of making a clinical diagnosis from the oscilloscope display. The results are described in detail elsewhere (Roelandt *et al.*, 1973; Kloster *et al.*, 1973a; Bom *et al.*, 1973b). In brief, good or excellent studies with satisfactory recognition of the mitral and aortic valves and left ventricular walls were possible in over two-thirds of all adults and in nearly all infants and children. Specific cardiac diagnoses could be made in about 40 per cent of patients.

**Applications of system in diagnostic cardiology**

**Normal cardiac cross-sections** The cross-section of the heart obtained by the multiscan with the probe in the oblique position is the same as that plane through which the single element is rocked when one performs a sector scan from the apex towards the base of the heart (Feigenbaum, 1972). However, these structures are now visualized two-dimensionally in their true anatomical relations and in real time motion. Such a cross-section is shown in Fig. 3 in diastole and systole. The anterior and posterior aortic walls present as two parallel echoes which move anteriorly during systole and posteriorly during diastole. The sinuses of Valsalva can usually be outlined and the cusps are seen centred in the aortic root in diastole. In the best studies they can be followed during opening and throughout systole as well. As the left atrium is posterior to the aorta and its dimension normally never exceeds that of the aorta, confusion with this structure is impossible. The anterior leaflet of mitral valve is a direct continuation of the posterior aortic wall (mitral-aortic continuity) and terminates in the region of the posterior papillary muscle. Therefore, the anterior leaflet of the mitral valve is usually best seen with the probe in the long axis position. It

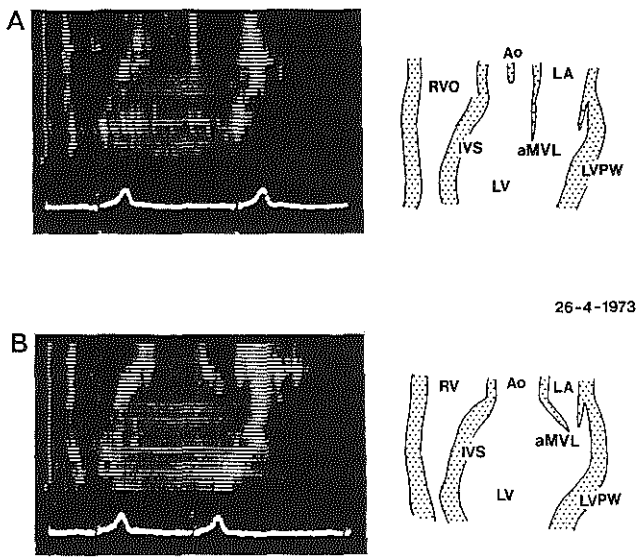



FIG. 3 *End-diastolic (A) and early systolic (B) long-axis cross-sections are shown. For orientation see diagrams. The aortic root (Ao) is seen in the upper centre with the cusps visible in diastole. The right ventricular outflow tract (RVO) is anterior to the aorta and the left atrium (LA) posterior to it. The interventricular septum (IVS) is in continuity with the anterior aortic wall (septal-aortic continuity) and the anterior mitral valve leaflet (aMVL) with the posterior aortic wall (mitral-aortic continuity). The anterior mitral valve (aMVL) in diastole is in an open anterior position and in a posterior and superior position when closed in systole. The right end of the electrocardiographic tracing indicates the position of the cross-section in the cardiac cycle. (LV = left ventricle; LVPW = left ventricular posterior wall.)*

appears as a thin, freely moving structure which travels anteriorly in early diastole, closes partially, then reopens during atrial contraction. During systole, closure of the mitral valve takes place primarily by a posterior and superior movement of the anterior leaflet of the mitral valve against the posterior leaflet. It is difficult to define the free edge of the anterior leaflet as it often appears as a continuous structure from the posterior aortic wall to the posterior papillary muscle, including the chordae. The motion of the posterior leaflet of the mitral valve varies between individuals, but is always much shorter, less mobile, and moves in the opposite direction from the anterior leaflet in diastole. The interventricular septum is in continuity with the anterior aortic wall (septal-aortic continuity). In general, the left side of the interventricular septum is clearly seen whereas the right side may only be definable when some right ventricular enlargement is present. The left ventricular epicardium and pericardium are the best reflectors for ultrasound of the heart and the left ventricular posterior wall is clearly delineated posteriorly by these echoes. Anterior to these, multiple echoes are seen which represent myocardium and endocardium. This was verified by recording the echoes of each line of the multiscan in time-motion on the line scan recorder.

The cavity of the right ventricle and the pulmonary outflow tract are only well delineated when right ventricular hypertrophy or dilatation is present. Of great importance is the study of the movement of the left ventricular wall. The long-axis cross-section closely resembles the outline of the left ventricular cavity as seen on the left ventricular angiograms in the right anterior oblique position. Therefore, it is possible to analyse the contraction

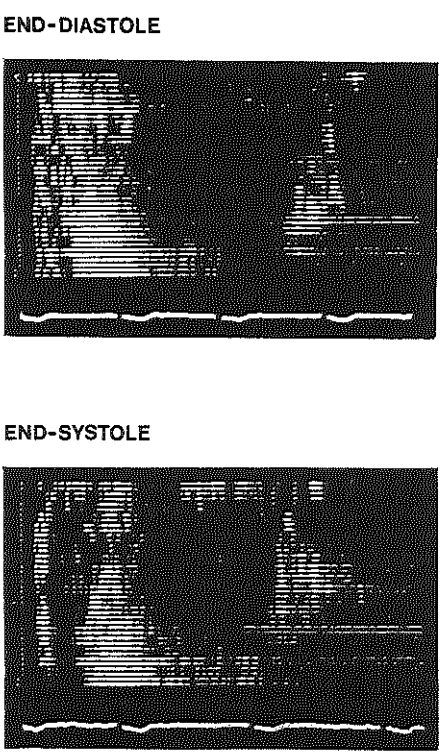



FIG. 4 *Transverse cross-sections in end-diastole and end-systole in a normal individual are shown. The left ventricular cavity is clearly outlined. Motion of the ventricular walls in this cross-section was symmetrical and this could easily be assessed on the oscilloscope display.*

pattern and motion of the septum and posterior left ventricular walls. Furthermore, with the transverse scan, the contraction of the left ventricular myocardium can be studied in different cross-sections and a greater percentage of the left ventricle is accessible for wall motion analysis than with conventional angiographic techniques. By way of example, Fig. 4 shows a diastolic and systolic transverse cross-section of the left ventricle. Though in this single frame representation real-time motion is lacking, the symmetrical contraction of the left ventricle is clearly shown.

**Valvular heart disease** In mitral stenosis alterations are seen in mobility and thickness of the anterior leaflet of the mitral valve. In mild mitral stenosis the anterior leaflet appears stiff, and motion is jerky and decreased in amplitude. There may even be anterior diastolic bulging. With severe stenosis the leaflets are fixed and the entire valve moves as a unit (Fig. 5, 6, and 7). Except for some cases with mild mitral stenosis, one sees the posterior leaflet of the mitral valve moving in the same direction with the anterior leaflet in diastole instead of in the opposite direction, as occurs, normally. A fibrotic and/or a calcific valve is indicated by dense, thickened echoes most apparent in the anterior leaflet (Fig. 5, 6, and 7). The enlarged left atrial cavity is usually well delineated; its cross-sectional dimension is larger than the aortic diameter and the increase is proportional to the degree of enlargement (higher LA/Ao ratio) (see Fig. 5, 6, and 7). With pulmonary hypertension, the right ventricular cavity is enlarged and the tricuspid valve becomes visible. The presence of concomitant mitral regurgitation in patients with mitral stenosis cannot be diagnosed with the multiscan system. However, in some cases with predominant mitral regurgitation, an increased excursion of the anterior leaflet of mitral valve is seen. The presence of an enlarged left atrium together with an increased left ventricular volume supports further the diagnosis of mitral regurgitation.

An exaggerated movement of the amplitude of the anterior leaflet of the mitral valve is seen in patients with prolapsing mitral valve syndrome during diastole. Actual prolapse in systole of the anterior leaflet past the posterior leaflet has been seen in two patients. The posterior leaflet of the mitral valve rarely shows this excessive movement. Thickening, calcification, and decreased mobility of the cusps can readily be seen in aortic valve disease (Fig. 5, 6, and 7). In severe calcific aortic stenosis, the valve appears as a series of dense, thick echoes in diastole which separate incompletely during systole. In mild aortic stenosis, either an immobile anterior (right coronary) cusp or posterior cusp can be seen (Fig. 7). Concomitant features are poststenotic dilatation of the aorta and increased left ventricular wall thickness.

**Coronary artery disease** A general qualitative assessment of the state of left ventricular function can be made immediately from cardiac size, shape, and wall motion. In general an enlarged left ventricle has a more round geometric shape while its dimensions are increased. The motion pattern can be studied, and localized or generalized disorders of contraction detected. The sagittal long-axis cross-section shows the interventricular septum and the

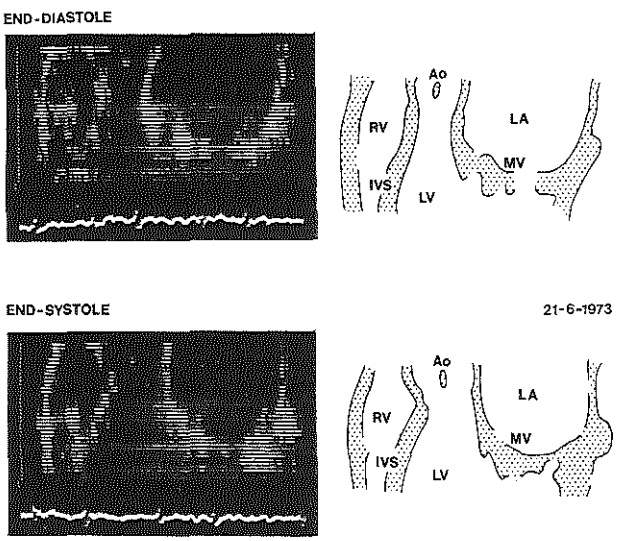



FIG. 5 *End-diastolic and end-systolic frames in a patient with severe calcific aortic and mitral stenosis. Both the anterior and posterior mitral valve leaflets are fixed and the entire valve (MV) moves as a unit, anteriorly in end-diastole, and posteriorly in end-systole. The immobilized calcified aortic valve remains visible during the whole cardiac cycle in the middle of the aortic (Ao) root. (RV = right ventricle; LV = left ventricle; IVS = interventricular septum.) The left atrium is extremely large.*

left ventricular posterior wall. By transverse scanning along the long axis, extensive sections of the left ventricle become accessible for study. Most difficult to display are the apex and part of the anterior wall merely because they are outside the pericardial window. Regional akinesis, hypokinesis, or dyskinesis can be recognized when the behaviour of these areas is compared to the normal or exaggerated contraction of the rest of the left ventricle. Furthermore, quantitation of left ventricular volumes and calculation of ejection fractions is possible with the area-length method.

**Congenital heart disease** Since cardiac structures and their relations are visualized without distortion with the multiscan technique, cross-sectional anatomy can be assessed. This makes the diagnosis of congenital malformations a major potential application. Thus far, however, our experience has been limited. Mitral-aortic and septal-aortic continuity or discontinuity and the size and orientation of the great vessels relative to the position of the ventricles are visualized, providing important information in many forms of complex cyanotic congenital malformations. Septal overriding of an enlarged aorta has been observed in patients with tetralogy of Fallot.

In patients with small left-to-right shunts no specific abnormalities were seen. With larger shunts, however, enlargement of the right ventricular chamber because of the volume overload becomes apparent. The most specific changes are related to the interventricular septum. The interventricular septum commonly runs posteriorly instead of anteriorly from the aortic root in the presence of a significant shunt lesion (Fig. 8). Systolic anterior or paradoxical septal motion has been described as a reliable finding in right ventricular overload and can be seen clearly with the multiscan display. We have the impression that the paradoxical motion never involves the whole intraventricular septum. The upper part moves always anteriorly and the

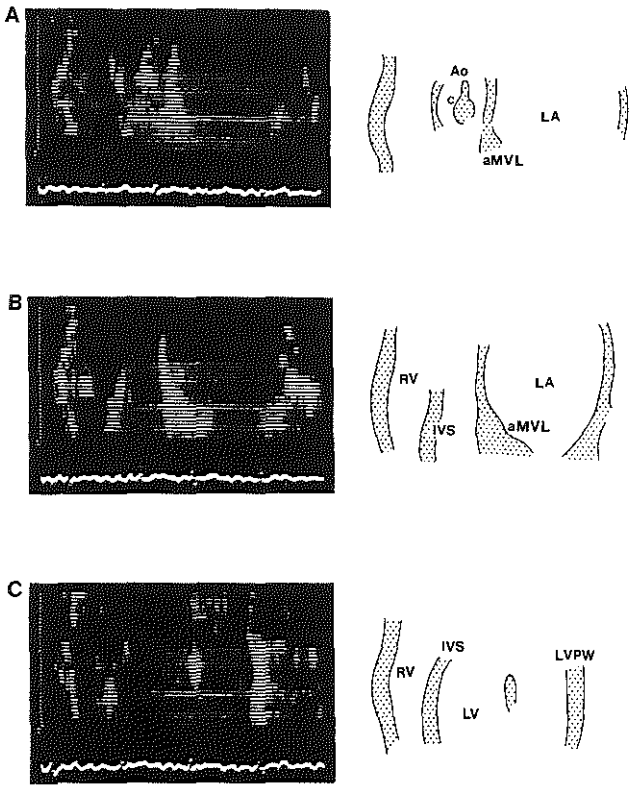
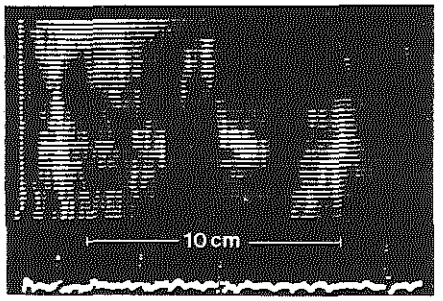



FIG. 6 *A transverse scan in the same patient as shown in Fig. 5. Panel A shows that cross-section where the root of the aorta (Ao) is visualized with a dense thickened echo of the calcified cusps (c). Part of the calcified anterior mitral valve (aMVL) is seen in continuity with the posterior aortic wall. The much enlarged left atrium (LA) is visualized posterior to the aorta. In an intermediate position (panel B), the interventricular septum (IVS) is seen at the same depth as the anterior aortic wall in panel A demonstrating septal-aortic continuity. There is a dense thickened anterior mitral valve echo (aMVL) and the left atrium is still visible at this level. Further tilting of the transducer (see position A in Fig. 1) shows a cross-section through both the right ventricle (RV) and left ventricle (LV). A dense echo, most probably of calcified chordae, is visible in the left ventricular cavity.*

lower part posteriorly. The point around which the interventricular septum pivots is lower in the septum when larger shunts are present but no systematic study has been undertaken yet. In all patients with right ventricular chamber enlargement, the tricuspid valve is visualized and has increased motion amplitude. In the record shown in Fig. 8 the pulmonary cusps were visualized also.

**Cardiomyopathies** In the hypertrophic types, recently unified and described as asymmetrical septal hypertrophy (Henry, Clark, and Epstein,



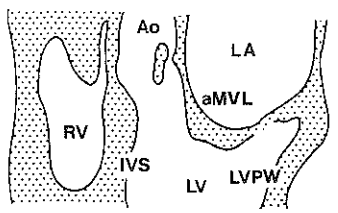
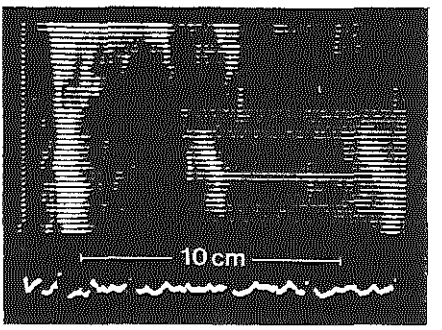




FIG. 7 *Long-axis cross-section in another patient with calcific aortic and mitral valve disease. A dense echo of the posterior coronary cusp of the aorta remains visible during systole. (RV = right ventricle; IVS = interventricular septum; Ao = aorta; LA = left atrium; aMVL = anterior mitral valve leaflet; LV = left ventricle; LVPW = left ventricular posterior wall.)*



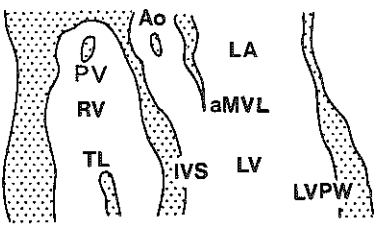




FIG. 8 *A long-axis cross-section in a patient with atrial septal defect (secundum type) and pulmonary hypertension. A greatly dilated right ventricle (RV) is apparent and the movements of both the tricuspid valve (TL = tricuspid leaflet) and pulmonary valve (high in the right ventricle) were seen on the oscilloscope display. The structures were identified by their typical motion pattern on the M-mode recordings made from the selected single elements passing through these structures. The interventricular septum (IVS) runs posteriorly instead of anteriorly as seen normally (see Fig. 3). This is a common finding with right ventricular dilatation. Note also the enlarged left atrium (LA). (Ao = aorta; aMVL = anterior mitral valve leaflet; LV = left ventricle; LVPW = left ventricular posterior wall.)*

1973), the most apparent features are increased thickness of the interventricular septum and a banana-like shape of the small-sized left ventricle. Motion of left ventricular walls is normal or even exaggerated. An enlarged left atrium points to coexistent mitral regurgitation. Where abnormal systolic motion of the anterior leaflet of the mitral valve was present, it resulted in a narrow left ventricular outflow tract in those patients in whom an outflow gradient was found during left ventricular heart catheterization. Fig. 9 shows the typical appearance of the multiscan echocardiogram in a patient with asymmetrial septal hypertrophy and a left ventricular outflow gradient. Asymmetrical septal hypertrophy is an instance which strikingly illustrates the unique qualities of the multiscan for instantaneous and complete diagnosis. In the dilated or congestive types of cardiomyopathies a large left ventricle of globular shape with generalized hypokinesis is so characteristic that the diagnosis is made immediately (Fig. 2 and 10). The increased distance between the anterior leaflet of the mitral valve and the interventricular septum in contrast to the decreased distance in the hypertrophic types is another characteristic finding. In all patients studied the left atrium was greatly enlarged (Fig. 2).

**Pericardial effusion** A few patients with pericardial effusion were studied. Small amounts of fluid, detected with the single element technique as

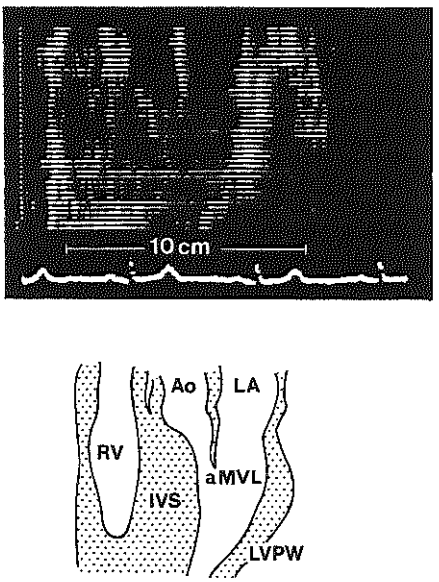



FIG. 9 *The typical features found in patients with asymmetrical septal hypertrophy are seen on this cross-section. The thickened septum (IVS) as compared to the left ventricular posterior wall (LVPW) is clearly shown and the banana-like shape of the left ventricle is striking. The frame shows a systolic cross-section and the anterior mitral valve leaflet (aMVL) is in an abnormal anterior position, close to the interventricular septum instead of in a posterior and superior position as seen normally. This causes narrowing of the left ventricular outflow, and in this patient an outflow gradient of 60 mmHg at rest was measured during cardiac catheterization.*

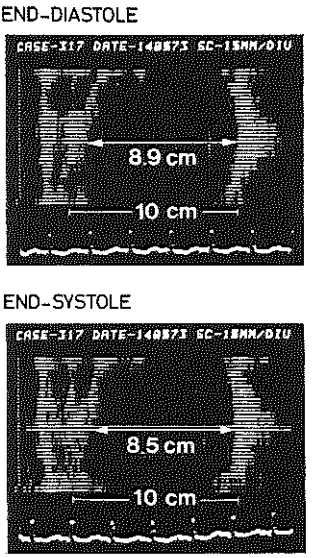



FIG. 10 *End-systolic and end-diastolic long-axis cross-sections obtained from a patient with a dilated congestive cardiomyopathy. An extremely large ventricle of a globular shape is seen. Generalized hypokinesis was immediately diagnosed from the oscilloscope display and is here shown by the small changes of a left ventricular dimension between end-diastole and end-systole (8·9 cm vs. 8·5 cm).*

an echo free space between posterior epicardium and pericardium during systole, were not visualized with the multiscan. Larger amounts, seen on the M-mode as an anterior and a posterior echo free space, were always detected with the multiscan. An example is given in Fig. 11. This patient had massive pericardial effusion and a large amount of fluid in the anterior pericardial space. In this case, an oscillating anterior-posterior movement of the whole heart in the pericardial fluid was seen. This total cardiac displacement has been described as a common finding when large pericardial effusions are present (Feigenbaum, Zaky, and Grabhorn, 1966).

### Applications for quantitation and dimensional measurements

In a first attempt to employ the system for quantitative analysis, a comparison was carried out in 23 patients of the aortic root diameter measured from calibrated angiograms and from videotape recordings of multiscan images. A significant correlation was found ($P < 0{\cdot}001$, $\chi^2$ test) with a small standard error (Kloster *et al.*, 1973a). When the interventricular septum and left ventricular posterior wall are visualized and recorded simultaneously, dimensional analysis of the left ventricle is possible. On records from the line scan recorder with a selected single line passing through the left ventricular cavity good definition of the left side of the interventricular septum and the posterior left ventricular endocardium is usually obtained (Fig. 12). By selection of the most representative diameter of the left ventricle, it should also be possible to calculate the

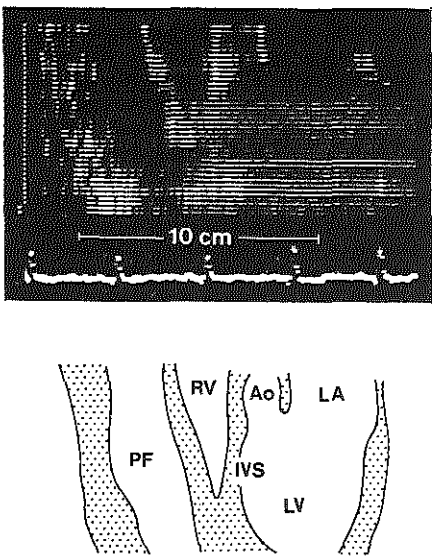



FIG. 11 *In this patient with massive pericardial effusion, a large echo-free space is recognized anterior to the heart. (PF=pericardial fluid.) The whole heart was displaced and the posterior heart wall was at a depth of about 16 cm. On the oscilloscope display, an oscillating movement of the entire heart was demonstrated.*

rate of midwall circumferential fibre shortening, as suggested by Paraskos *et al.* (1971) and Cooper *et al.* (1972). In addition, data on cardiac volumes with the echocardiographic formulae proposed by Popp and Harrison (1970), Pombo, Troy, and Russell (1971), and Feigenbaum *et al.* (1972) should be obtainable. As it is also possible to record both the endocardium and pericardium separately, by changing the depth gain compensation, measurements of left ventricular posterior wall and interventricular septal thickness come within reach (Fig. 12). However, since multiscan provides instantaneous left ventricular cross-sections suitable for the calculation of left ventricular volumes from generally accepted and anatomically correct angiographic formulae, this approach was first pursued (Greene *et al.*, 1967; Sandler and Dodge, 1968). When the whole left ventricle is visualized it proved possible to measure the long axis and to outline the left ventricular cavity. Fig. 13 shows an end-diastolic and end-systolic frame used for these measurements. To assess the possibilities and feasibility of this method, left ventricular volumes calculated from multiscan frames and quantitative left ventricular angiograms have been compared in 14 patients.

Multiscan end-diastolic volume showed a high degree of correlation with angiographic volumes (mean values 90·4 versus 95·9 ml/m$^2$; $r=0{\cdot}92$). However, end-systolic volumes determined by multiscan were consistently larger than those determined by angiography (56·2 versus 44·5 ml/m$^2$; $r=0{\cdot}89$), so that the stroke volume by multiscan was consistently smaller. As a result the left ventricular ejection fraction by multiscan as compared to that by angiography is lower. This was also found with other techniques of volume measurement which similarly indicate that assessment of end-systolic volume by angiography shows a systematic underestimation of volume (Bartle and Sanmarco, 1966; Hugenholtz, Wagner, and Sandler, 1968). The methods and results will be discussed elsewhere in greater detail (Kloster *et al.*, 1973b).

## Discussion

At present there are many echocardiographic techniques available to obtain two-dimensional information about the heart. All techniques based on B-scan (Ebina *et al.*, 1967; Kikuchi and Okuyama, 1970; King, 1973) produce 'frozen' images of the heart at a selected part of the cardiac cycle. As many cardiac cycles are required to construct the image, changes in cardiac position and difficulties caused by irregularities in rhythm render these systems suboptimal for clinical application. Åsberg (1967) obtained two-dimensional information with a mechanical mirror system rotated over an arc of about 30° at a rate of seven frames a second. Hertz and Lündström (1972) obtained 16 frames a second with a similar system. For these mechanical rocking systems limited scanning rates, bulky transducer size, difficult transducer aiming, and image distortion are some of the problems. Gramiak *et al.* (1972) developed a technique which produces ultrasonic cross-sectional images of the heart in motion. However, cine-ultrasound cardiography is time consuming and there is some image distortion as the wedge-shaped section of the heart obtained by the sound beam is represented in a rectangular format. None of these drawbacks pertains to the multiscan system presented here. Thus, the capabilities of diagnostic ultrasound are expanded by instantaneous two-dimensional moving cross-sections of the heart. Furthermore, when compared to the negative shadow images obtained with angiography, there is the advantage of a positive cross-section of the heart with all its structures visualized in a manner familiar

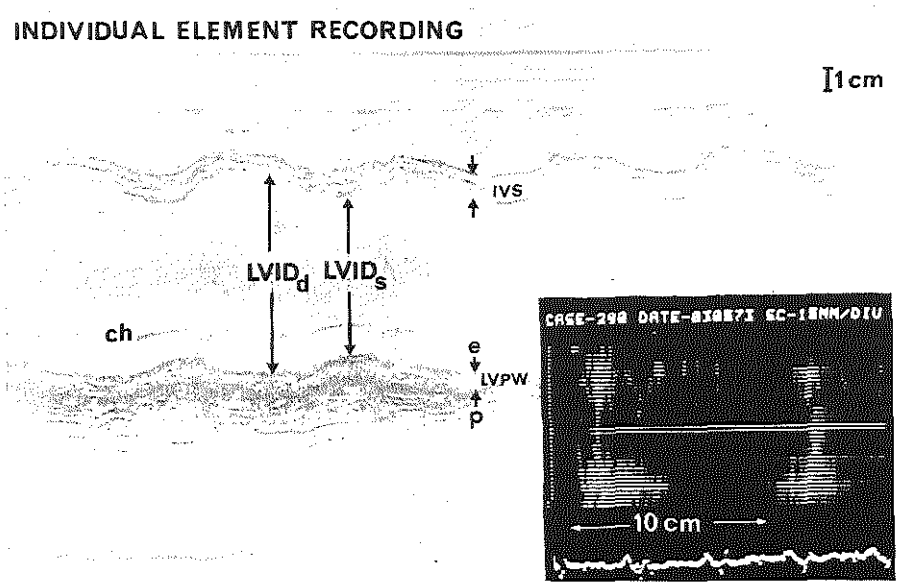



FIG. 12 *This M-mode tracing is recorded from a single element of the multiscan transducer. The selected signal is the bright line running through the left ventricular cavity, seen on the insert photograph. The patient has coronary artery disease with a hypokinetic posterior wall and an enlarged left ventricular cavity. Both the interventricular septum and left ventricular posterior wall are recorded with satisfactory resolution. Changing the time gain compensation allows measurements of interventricular septum and left ventricular posterior wall thickness. This record is most suitable for dimensional left ventricular measurements and calculation of derived volume data. ($LVID_s$ and $LVID_d$ = left ventricular internal dimension during systole and diastole; ch = chordae echo; e = endocardium; p = pericardium; IVS = interventricular septum, LVPW = left ventricular posterior wall.)*

to those who know cardiac anatomy. In addition, information on the relations of cardiac structures is provided without distortion.

Congenital malformations, especially in newborns and infants, offer a major potential application for the system particularly when the risk of unnecessary catheterization may be avoided by appropriate preselection of candidates by means of the echoscan. Qualitative valve motion analysis in valvular heart disease and evidence of thickening and/or calcification in cases with rheumatic mitral and aortic valve disease is immediately available. Furthermore, the size, shape, and contraction pattern of the left ventricle can be interpreted and a qualitative assessment of the left ventricular function made. Evaluation of left ventricular function and detection of localized disorders of wall motion in patients with coronary artery disease is a most promising area for investigation. When the long-axis cross-section and a transverse scan are performed, a large part of the left ventricle becomes accessible for study.

While the most unique application of the system is the study of the dynamics of cardiac contraction and valve motion, it allows also quantitative measurements of cardiac dimensions and left ventricular volumes. This is an area of major interest in clinical cardiology today. Despite the excellent correlations between echo and angio volumes found in some studies using the single element echocardiographic techniques, it is not known if the echo axis truly approximates the angiographic short diameter of minor axis of the left ventricle (Pombo *et al.*, 1971;

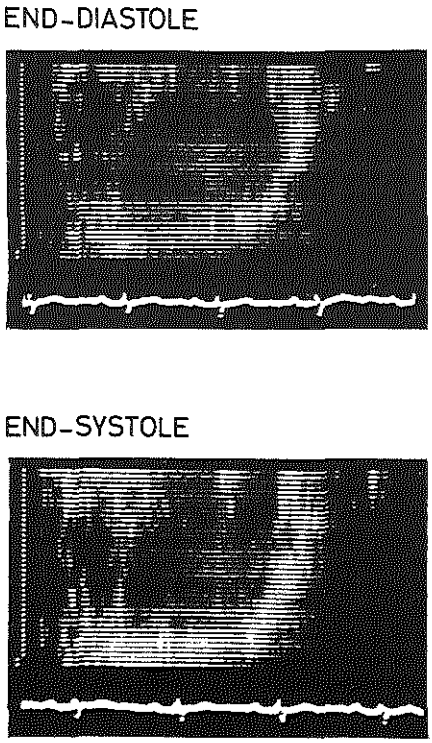



FIG. 13 *Examples of end-diastolic and end-systolic frames used for calculation of left ventricular volumes are shown. The cross-section resembles the left ventricular image obtained with angiocardiography in the right anterior oblique position but is a mirror image of it as the apex is to the left on the multiscan images. The aorta and mitral valves are clearly seen, and it is possible to outline the interventricular septum and the left ventricular posterior wall readily. Calculations of volumes are performed using the area-length method.*

Feigenbaum *et al.*, 1972). Indeed, to calculate the volume from echo-determined left ventricular dimensions, one has to assume that the measured dimensions have constant relations to the axes of the left ventricle both at end-systole and at end-diastole. This is not true for dilated ventricles and patients with segmental abnormalities of contraction due to coronary artery disease. The multiscan system appears to offer a ready solution, since the precise location of each echo axis through the left ventricle is known. As both the septal and posterior left ventricular endocardial echoes are displayed on M-mode recordings of a selected element from the transducer, this information is also present on the two-dimensional images (Fig. 12). Therefore a real cross-section of the left ventricle is obtained comparable to the shadow of the left ventricle during angiography in the right anterior oblique position. The area-length method proposed by Greene *et al.* (1967) can be applied and, since both length and area are measured, this method is applicable to ventricles of all sizes and shapes. The initial results of studies in 14 patients are encouraging. End-diastolic volumes calculated from multiscan frames agree well with angiographically calculated volumes. There is a consistent overestimation of the multiscan end-systolic volume compared to angio, resulting in a smaller stroke volume and an underestimation of left ventricular ejection fraction. However, a systematic underestimation of end-systolic volumes by cineangiography has been found with other indicator dilution methods (Hugenholtz *et al.*, 1968; Bartle and Sanmarco, 1966), and may simply reflect methodological differences. The fact that these qualitative analyses and quantitative measurements can be made in a non-invasive manner with an unlimited frequency opens new areas for clinical investigation as well as for teaching and training.

Some problems have still to be resolved in displaying and recording the multiscan information. Different display and recording methods are still under evaluation (Fig. 14). Considerable technical improvements in the instrument are also possible and will increase the capabilities of the system.

In general, the multiscan is subject to the same physical limitations of sound transmission and reflection as conventional single element systems (Bom, 1972; Bom *et al.*, 1973a). Significant distortion of images behind ribs because of higher ultrasound velocities in bone has not been observed. Insufficient lateral resolution, a problem of all echo systems, continues to be a limitation (Bom *et al.*, 1973a). Also echoes originating from side lobe beams can deform the display of specific structures. Though these side lobe effects were negligible in *in vitro* experiments, their overall effects in the clinical situation remain unpredictable (Bom, 1972), and practical experience will have to be collected before a definite statement as to their influence can be made. The commonest cause of failure is the presence of only a small pericardial window, for example, when pulmonary emphysema or an anterior chest wall deformation is present. Intervening dense tissue, such as heavily calcified ribs, may obscure

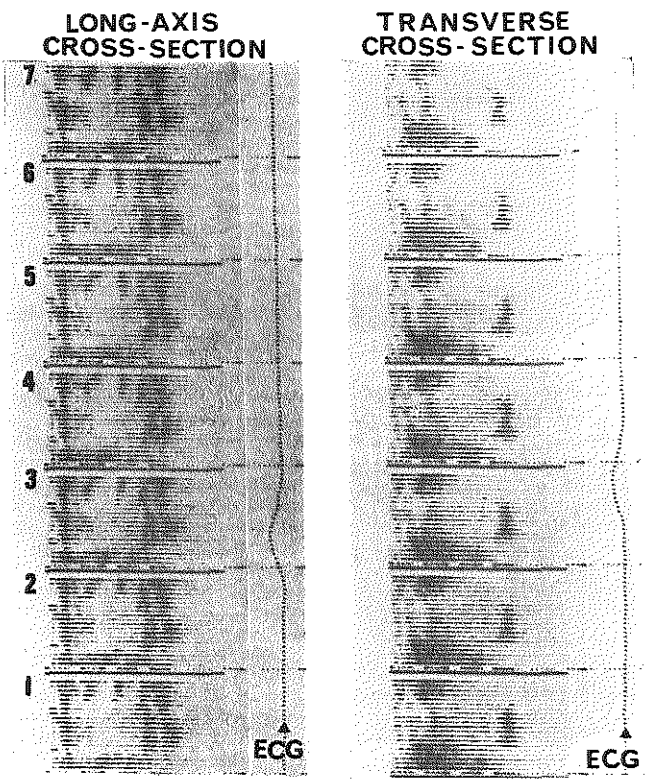



FIG. 14 *Seven cross-sections recorded on the Honeywell 1856 Visicorder with the transducer in the long-axis and transverse positions are shown together with the electrocardiogram. The format of the images is small but the definition of the echoes is quite good. These 'stampsize' pictures are recorded at 25 frames/sec.*

parts of the image. This factor is operative especially in elderly people. However, considerable detail remains visible between the obscured areas, and structures can be recognized by extrapolation. Difficult or unsatisfactory studies occur particularly with a large anteroposterior chest diameter resulting in greater distance of the structures from the probe.

From the results presented in this paper one may conclude that multiscan echocardiography is a valuable extension of the now widely accepted single element technique and will become a fundamental addition to non-invasive methods for the study of the normal and diseased heart.

## References

Åsberg, A. (1967). Ultrasonic cinematography of the living heart. *Ultrasonics*, **5**, 113.

Bartle, S. H., and Sanmarco, M. E. (1966). Comparison of angiocardiographic and thermal washout technics for left ventricular volume measurement. *American Journal of Cardiology*, **18**, 235.

Bom, N. (1972). *New Concepts in Echocardiography*. Stenfert Kroese, Leiden.

Bom, N., Lancée, C. T., Honkoop, J., and Hugenholtz, P. G. (1971). Ultrasonic viewer for cross-sectional analyses of moving cardiac structures. *Bio-Medical Engineering*, **6**, 500

Bom, N., Lancée, C. T., van Zweiten, G., Kloster, F. E., and Roelandt, J. (1973a). Multiscan echocardiography. Part I: Technical description. *Circulation*. In the press.

Bom, N., Roelandt, J., Kloster, F. E., ten Cate, F. J. Popp, R. L. Pridie, R., Sahn, D. J., and Hugenholtz, P. G. (1973b). Evaluation of structure recognition with the Multiscan echocardiograph: a cooperative study in 580 patients. In preparation.

Cooper, R. H., O'Rourke, R. A., Karliner, J. S., Peterson, K. L., and Leopold, G. R. (1972). Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. *Circulation*, **46**, 914.

Ebina, T., Oka, S., Tanaka, M., Kosaka, S., Terasawa, Y., Unno, K., Kikuchi, Y., and Uchida, R. (1967). The ultrasonotomography for the heart and great vessels in living human subjects by means of the ultrasonic reflection technique. *Japanese Heart Journal*, **8**, 331.

Feigenbaum, H. (1972). *Echocardiography*. Lea and Febiger, Philadelphia.

Feigenbaum, H., Popp, R. L., Wolfe, S. B., Troy, B. L., Pombo, J. F., Haine, C. L., and Dodge, H. T. (1972). Ultrasound measurements of the left ventricle; a correlative study with angiocardiography. *Archives of Internal Medicine*, **129**, 461.

Feigenbaum, H., Zaky, A., and Grabhorn, L. L. (1966). Cardiac motion in patients with pericardial effusion: a study using reflected ultrasound. *Circulation*, **34**, 611.

Gramiak, R., and Shah, P. H. (1971). Cardiac ultrasonography: a review of current applications. *Radiologic Clinics of North America*, **9**, 469.

Gramiak, R., Waag, R. C., and Simon, W. (1972). Cine ultrasound cardiography (abstract). *Circulation*, **45** and **46**, Suppl. 2, 159.

Greene, D. G., Carlisle, R., Grant, C., and Bunnel, I. L. (1967). Estimation of left ventricular volume by one-plane cineangiography. *Circulation*, **35**, 61.

Henry, W. L., Clark, C. E., and Epstein, S. E. (1973). Asymmetric septal hypertrophy (ASH): the unifying link in the IHSS disease spectrum. Observations regarding its pathogenesis, pathophysiology, and course. *Circulation*, **47**, 827.

Hertz, C. H., and Lündström, K. (1972). A fast ultrasonic scanning system for heart investigation. 3rd International Conference on Medical Physics, Göteburg, Sweden, August 1972, 35.6.

Hugenholtz, P. G., Wagner, H. R., and Sandler, H. (1968). The in vitro determination of left ventricular volume: a comparison of the fiberopticindicator dilution and the angiocardiographic methods. *Circulation*, **37**, 489.

Kikuchi, Y., and Okuyama, D. (1970). Ultrasono-cardiotomography. *Japan Electronic Engineering*, 53, No. 47, pp. 53–60, October 1970.

King, D. L. (1973). Cardiac ultrasonography: cross-sectional ultrasonic imaging of the heart. *Circulation*, **47**, 843.

Kloster, F. E., Roelandt, J., ten Cate, F. J., Bom, N., and Hugenholtz, P. G. (1973a). Multiscan echocardiography, Part II: Technique and initial clinical results. *Circulation*. In the press.

Kloster, F. E., Roelandt, J., ten Cate, F. J., Bom, N., Meester, G. T., and Hugenholtz, P. G. (1973b). Comparison of left ventricular dimensions by multiple element echocardiography and angiography. In preparation.

Meyer, R. A., and Kaplan, S. (1973). Noninvasive techniques in pediatric cardiovascular disease. *Progress in Cardiovascular Diseases*, **15**, 341.

Paraskos, J. A., Grossman, W., Saltz, S., Dalen, J. E., and Dexter, L. (1971). A noninvasive technique for determination of velocity of circumferential fiber shortening in man. *Circulation Research*, **29**, 610.

Pombo, J. F., Troy, B. L., and Rusell, R. O., Jr. (1971). Left ventricular volumes and ejection fraction by echocardiography. *Circulation*, **43**, 480.

Popp, R. L., and Harrison, D. C. (1970). Ultrasonic cardiac echography for determining stroke volume and valvular regurgitation. *Circulation*, **41**, 493.

Popp, R. L., and Harrison, D. C. (1973). The use of ultrasound in cardiac diagnosis. In *Non-invasive Technics in Cardiac Evaluation*. Ed. by Weissler. Grune and Stratton, New York.

Roelandt, J., Kloster, F. E., ten Cate, F. J., Bom, N., and Hugenholtz, P. G. (1973). Multiscan echocardiography; description of the system and initial results in 100 patients. *Heart Bulletin*, **4**, 51.

Sandler, H., and Dodge, H. T. (1968). The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *American Heart Journal*, **75**, 325.

Ulrich, W. D. (1971). Ultrasound dosage for experimental use on human beings. Report No. 2, *Naval Medical Research Institute*, Bethesda, Maryland, U.S.A.

Woodward, B., Pond, J. B., and Warwick, R. (1970). How safe is diagnostic sonar? *British Journal of Radiology*, **43**, 719.

Requests for reprints to Dr. J. Roelandt, Department of Clinical Echocardiography, Thoraxcenter, Erasmus Universiteit, Postbus 1738, Rotterdam, The Netherlands.

CHAPTER 3

# ASYMMETRIC SEPTAL HYPERTROPHY (ASH)

## Diagnosis and treatment

### 3.1 Introduction

Obstruction to left ventricular outflow can be congenital or acquired, and the location of the stenosis can be valvular, subvalvular or supravalvular. Clinical assessment should not only endeavor to recognize the presence and degree of obstruction, but also requires the identification of its level and of the type of obstruction, whether fixed or variable.

Subvalvular aortic stenosis can be divided into two main categories, according to whether the obstruction is fixed (discrete subaortic stenosis) or variable.

Although the etiology of asymmetric septal hypertrophy (ASH) is yet not well established, there is now echocardiographic evidence that the disease is of familiar and genetic origin (see also chapter 5 and 6).

In the following paragraphs the clinical features of ASH will be discussed in its relation to functional anatomy and pathophysiologic abnormalities.

The focus of attention, however, will remain on the echocardiographic signs of these abnormalities.

## 3.2 Functional anatomy

The characteristic features of anatomy are:

1. Disproportionate thickening of the ventricular septum, when compared to the free wall of the left ventricle.
2. Often reduced size of the left and right ventricular cavities.
3. Endocardial mural thickening of the left ventricular outflow tract.
4. Thickened mitral valve with shortened chordae tendinae.
5. Severe abnormalities of the organozation of muscle cell bundles and of the arrangement and orientation of myofibrils and myofilaments of individual muscle cells particularly in the ventricular septum. The latter appears the only characteristic morphologic microscopic features while all other features are propably secondary.

Of nine patients known at the Thoraxcenter, who have been operated for their disease and in whom a myectomy of ventricular septal muscle was carried out, the microscopic features were as described. This was also true for the electron microscopic features, which were studied in one patient.

## 3.3 Pathophysiology and pathology

The septum thickens most midway between the base of the aortic root and the apex of the left ventricle (LV). In fact, it protrudes into the small LV outflow tract (LVOT), giving the LV a characteristic S-shaped configuration. The papillary muscles are malpositioned. Especially the posteromedial papillary muscle is maligned during contraction.

The endocardial thickening of ventricular septum, often with a mirror image lesion on the anterior mitral leaflet (AML), is probably caused by the approximation of these structures.

Angio- and echocardiographic studies clearly show this touching of these structures over extended time periods. The similarity to the jet lesion in a ventricular septal defect presents itself readily.
This abnormal systolic anterior motion (SAM) probably also serves to obstruct the left ventricular outflow tract during parts of the ejection phase. Several authors have described this abnormal motion of the AML[2-4], which they thought to be caused by either a foreshortened or malpositioned papillary muscle apparatus. However, recent echocardiographic studies have proposed this phenomenon to be due to a Venturi-effect[5], when the markedly increased ejection velocity caused by the strong muscle mass caused a negative pressure next to the jet. This hydraulic effect is thus thought to suck the AML towards and against the septum. Mitral regurgitation appears to be an inherent result of this anatomic distortion of the mitral valve apparatus leading to secondary enlargement of the left atrial cavity.

### 3.4 Hemodynamics and angiocardiography

Hemodynamic measurements are abnormal in the majority of patients with asymmetric septal hypertrophy wether or not obstruction coexists. It is likely that the massive hypertrophy and the small ventricular compliance which in turn is reflected in the elevated ventricular enddiastolic pressure. size account for the decreased left
All pressures distal may become elevated as a result of the increased filling pressure. In addition when mitral regurgitation is present, the characteristic elevation of the systolic wave ("V"-phase) in the left atrial pressure tracing can be recognized. In the patients with obstruction, the hallmark is the systolic pressure difference between the LVOT and the aorta.

This obstruction, caused by apposition of the AML and the hypertrophied ventricular septum, is usually demonstrable during mid- and late systole[4-6], by a marked difference in pressurecontours above and below the obstruction. When two catheters are positioned close to one another in the cavity of the left ventricle, withdrawal of one catheter towards the aorta under continuous fluoroscopy, will record a sudden decrease in systolic pressure to the level of that in the aorta at a site 2 - 4 cm below the aortic valve, whilst the pressure curve in diastole remains identical to that obtained from the other catheter.

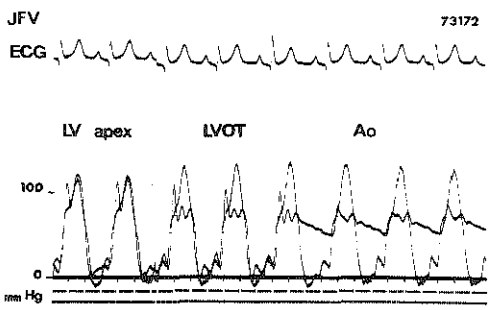



*Fig. 1 Pull back LV pressure tracing from the apex of the left ventricle (LV) to the ascending Aorta (Ao). Observe the sudden decrease of LV pressure at the level of the left ventricular outflow tract (LVOT). At this site therefore the obstruction is localized.*

This site corresponds to the anatomic localization of the obstruction by abnormal SAM of the AML as seen during angiocardiographic[2-3] and echocardiographic studies[4]. (fig. 1)

The aortic pressure pulse may also have characteristic features, since it shows a sharp rise at the onset of left ventricular ejection, much exceeding that of the usual aortic pressure pulse. This accelerated ejection rate is a result of the fact that the LV attempts to empty itself before the obstruction blocks further forward ejection. Particularly in mid-systole the aortic pressure may fall temporarily, whereas the left ventricular pressure still rises.

This pattern is reflected in the typical notch one can observe (and feel) in the carotid artery.
The sharp rise in initial arterial pressure contrasts with the characteristically slow rising arterial pressure seen in fixed obstruction to left ventricular outflow whether this is of valvular, supravalvular or fibrous subvalvular origin.
When extra systoles are present or evoked the so called Brockenbrough phenomenon can be elicited. In obstructed cases, the aortic pulse pressure in the post-extrasystolic beat, will be smaller than in normal sinus beats. This is in contrast to the findings in the fixed varieties of left ventricular outflow obstruction, where the aortic pulse pressure in the post-extrasystolic beat may be greater than in normal sinus beats[7].
The magnitude of the pressure difference across the left ventricular outflow tract will vary considerably, not only in repeated studies but also during the course of a single study. This is readily understandable since many physical, physiological and pharmacological stimuli, mediated via changes in ventricular preload, contractility and afterload, as well as heart rate, will influence these pressure differences. In fact, it is the use of these manoeuvres through factors that will increase contractility and cardiac rate that may bring out the obstruction in patients without apparent obstruction at rest.
The use of isoprenaline, digoxine and the onset of a supraventricular tachycardia will increase the obstruction, whereas the use of propranolol, which decreases contractility, or of methoxamine, which increases afterload, may decrease the obstruction. One should beware of factitious pressure differences which sometimes can occur from catheter entrapment, due to cavity obliteration.
The cineangiographic features of this disease are characteristic[2-3], the left ventricular walls are hypertrophied, especially the interventricular septum.

The LV cavity is reduced in size and may take the shape of a banana in the antero-posterior projection and in end-systole it becomes slitlike. The hypertrophied interventricular septum causes an convex indentation on the margin of the LV lumen so that again in the frontal view the lower half of the chamber may seem obliterated by the approximation of the anterior and inferior borders. A linear radiolucent area extending across the left ventricular outflow tract ± 2,5 cm beneath the aortic annulus corresponds to the mitral leaflet in the left oblique and lateral projection.

In such clear cut cases the components of the obstruction can be seen to consist anteriorly of the hypertrophied septum and posteriorly of the anterior mitral leaflet pressed upwards and anteriorly into the left ventricular outflow tract. As a consequence of the high LV pressure and the mitral valve abnormality, some mitral regurgitation is seen in almost all cases especially in midsystole.

In summary, the cineangiographic sequence of events in systole could be something like "eject-obstruct-leak", particularly in those individuals when the obstruction is so severe that a significant part of the ventricular volume must be regurgitated into the left atrium. (fig.2)

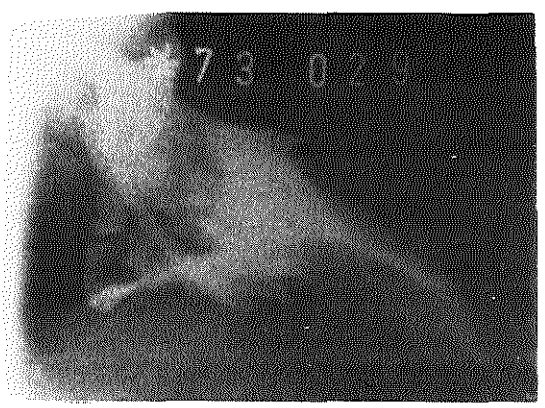


*Fig. 2 Left ventricular cineangiocardiogram in Right anterior oblique position at end systole of a patient with ASH and obstruction. Observe the characteristic slit like left ventricle. A radiolucent area ± 2.5 cm beneath the aortic valves representing the mitral valve apparatus is seen in an abnormal position during systole.*

Of 20 patients, known at the Thoraxcenter, having hemodynamic evaluation and angiocardiography, 14 of them had a gradient across the left ventricular outflow tract under basal conditions, whereas 4 developed a gradient using isoprel (5mg/min.). In 10 patients who had a gradient across the left ventricular outflow tract, all of them had mitral regurgitation of significant degree in addition. Only 2 patients who had no gradient using isoprel (5mg/min.) developed a gradient in the postextrasystolic beat.

### 3.5 Right heart involvement

Several authors have reported right ventricular cineangiocardiograms to show a narrowed right ventricular (RV) outflow tract which is pushed anteriorly and either to the right or left by the hypertrophied interventricular septum. When there is a right ventricular pressure gradient the obstruction occurs at the junction of the outflow tract and the body of the RV. Presumably the same underlying process is at state, however, the incidence of these findings varies greatly, particularly when pressure recordings are obtained at the apex of the right ventricle[8].

The nature of the obstruction in the right ventricular outflow tract suggest as its cause both muscular hypertrophy and a dynamic disorder of contraction[8].

The disease presents itself rarely as isolated right ventricular outflow obstruction[9].

To our experience, 3 patients with significant gradient across the left ventricular outflow tract had small gradients (range:5-13 mm Hg) across the right ventricular outflow tract. This gradient was not augmented during provocative manoeuvres, suggesting a nature of fixed obstruction. We have not seen any patient who presented as isolated obstruction to right ventricular outflow.

## 3.6 Clinical manifestations

### 3.6.1 Natural history

Asymmetric septal hypertrophy may occur at any time in life. It has been seen for the first time at infancy[10-11] or late in life[12-14]. However, clinical recognition is most common through the third to fifth decade. Sex distribution is even[12-13]. The disease is thought to be of familial cause in some cases[12-13], however recent echocardiographic studies have revealed that the familial prevalence of the disease is much more common[15-16]. Since the disease appears to be transmitted as an autosomal dominant trait with high degree of penetrance, (see also chapter 5 and 6) it may be underestimated because of silent or asymptomatic forms of the syndrome. The echocardiographic methods are not yet so well established and the true prevalence can not be estimated, while its prevalence is unknown and may vary with the diagnostic method employed. Furthermore it is of clinical interest that[15-16] routine autopsies of large numbers of elderly veterans have revealed no cases of ASH[17]. Braunwald's[12] classic study has shown that the clinical course in patients with obstruction is extremely variable although the disease process itself is usually progressive. Patients who present without or with minor symptoms tend to run a more favourable course than those with severe symptoms at the outset. Favourable features are said to be an early age of detection, absence of left atrial hypertrophy in the electrocardiogram and a relatively low enddiastolic pressure, presumably indicating the absence of compromised ventricular compliance. Deterioration and disability are usually associated with clinical and hemodynamic signs of left ventricular inflow resistance[13].

Particularly the appearence of atrial fibrillation with the consequent loss of the atrial contribution to ventricular filling is such a sign. The loss of the systolic murmur may herald a decrease of obstruction, often to be followed by congestive heart failure especially when atrial fibrillation is present also[13-14].
The major complications are sudden death, which may take place at any age, independent of clinical classification of the magnitude of the gradient[12-14,18], infectious endocarditis and intractable heart failure. These are discussed in section 3.7.
The knowledge of natural history of ASH is incomplete particularly since the natural history is interfered with medical or surgical treatment.

### 3.6.2 Symptoms

The average detection occurs after 15 years of age[12,21]. This is in contrary to the experience with patients with fixed congenital aortic stenosis where the murmur is usually detected in the newborn period.
Growth and development are seldom affected and symptoms may even be absent in the presence of severe outflow tract obstruction[12]. Yet the appearence of angina or effort syncope should arouse suspicion in a young individual, in whom a history of dyspnea and fatigue can be elicited and in whom a cardiac murmur is found. Recurrent syncopal episodes are particularly dangerous since they are said to herald sudden death in childhood or adolescence[20]. Rhythm disturbances are likely though not common[19]. Atrial fibrillation has been found to initiate significant clinical detoration[13], while occasionally there is a history suggestive of the Wolff-Parkinson White[12] syndrome with arrhythmias and syncope. The incidence of bacterial endocarditis is low, but it increases with age[12-13].

Most studies have shown a normal coronary artery tree, however, incidence of coronary artery disease seems to increase after age of 45[22].

### 3.6.3 Physical examination

Growth, development and general appearence are normal in the majority. However, ASH is seen in association with muscular dystrophies, Friedreichs ataxia, lentigines, phaeochromocytoma, tuberous sclerosis, Noonan's syndrome and cutaneous neurofibromatosis[23], all primary cellular disturbances. Their physical signs should prompt a search for those of ASH. The jugular venous pulse often has a prominent "a" wave, perhaps reflecting decreased right ventricular compliance in those cases where it occurs. The apex beat is double with a palpable left atrial gallop (fourth heart sound) and a sustained heave in far advanced cases[6,24]. Sometimes a triple impulse can be detected. The arterial pulse may have a fast upstroke. In some cases a systolic thrill is palpable, not over the carotids but, characteristically maximally at the apex. Ejection sounds are rare[25] in fact their absence may serve as a confirmation of ASH. The first heart sound is normal and the regurgitant systolic murmur which begins after the first sound, is heard best at or just medial to the left ventricular apex. This crescendo-decrescendo systolic murmur is caused both by the obstruction to the left ventricular outflow and the mitral regurgitation. The murmur is medium pitched. It rarely radiates to the left axilla and towards the left sternal border. Over the aortic area it is diminished in intensity and is seldom heard over the carotid vessels. At the apex a third sound and a diastolic inflow murmur may be heard. When also RV outflow obstruction exists, a separate systolic murmur can be heard in the second or third intercostal space to the left of the sternum.

Left ventricular ejection time is prolonged, resulting in delay of aortic closure and consequently a single or even paradoxically split second heart sound is present. Occasionally, an early diastolic sound, resembling an opening snap, can be detected, probably because of the apposition of the septum and the anterior mitral leaflet. The same mechanisms that increase or decrease the gradient across the left ventricular outflow tract may increase or decrease the loudness of the systolic murmur (see also 3.6.6.). In asymptomatic individuals, echocardiographic studies have demonstrated that only a limited percentage of such individuals with ASH have typical cardiac murmurs. A more detailed description of clinical findings in our series is described in chapter 6.

### 3.6.4. The electrocardiogram

Patients with asymmetric septal hypertrophy frequently have electrocardiograms and vectorcardiograms which meet criteria for left ventricular hypertrophy, ventricular conduction delay or for myocardial infarction[12-14,26]. (see fig. 3 and 4)

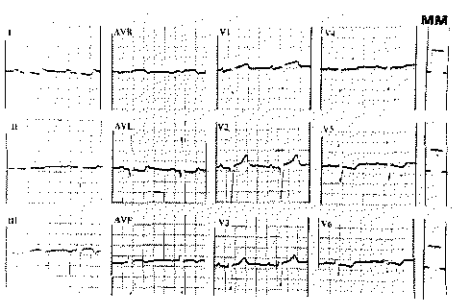



*Fig. 3 Twelve-lead electrocardiogram of a patient with ASH and obstruction. Features consistent with left axis deviation, left ventricular hypertrophy and secundary repolarization disturbances are observed.*

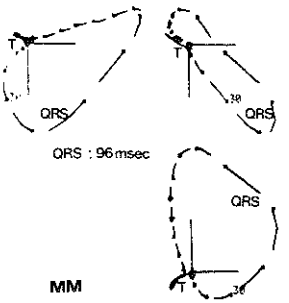



*Fig. 4 Vectorcardiogram of the same patient as described in figure 3. QRS duration is 96 msec.. Main T-vector and main QRS vector are pointing in oppisite direction, suggestive of left ventricular hypertrophy.*

In fact all types of initial activation abnormalities can be described as well as variations thereof.
Abnormal "q" waves may exist in all leads but especially in lead II, III and AVF and V4-V6, sometimes accompagnied with tall R-waves in the right precordial leads.
When left ventricular compliance decreases, left atrial hypertrophy may be evident. In rare cases the same applies to the right atrium. Features of the WPW-syndrome are seen in a few patients. Frequent atrial and ventricular arrythmias have now been demonstrated during long-term ambulatory ECG monitoring[19].

3.6.5. Chest X-ray

The most striking feature is the prominence of the left ventricle, with a bulge along the left heart border between the left atrial appendage and the left ventricular apex. Some authors consider this a reflection of the hypertrophied ventricular septum[12]. Usually there is no cardiac enlargement as such. Left and right atrial cavities are commonly enlarged as a result of decreased ventricular compliance. The aortic contour is normal and calcification of the mitral valve is rarely seen.

### 3.6.6 The echocardiogram

In this paragraph the pertinent echocardiographic findings in our series will be discussed and related to findings as described by others.
The anatomic marker of ASH is the disproportionately thickened septum, as already mentioned in other parts of this chapter. Henry and co-workers have shown that its morphology could be used as the common denominator of the disease spectrum provided it is diagnosed echocardiographically[27].
This is based on the experience that in all cases there is hypertrophy of the left ventricular septum with relatively much less hypertrophy of the left ventricular posterior wall, in contrast to concentric left ventricular hypertrophy, for example in valvular aortic stenosis, where both walls are equally thickened. Septal thickness usually exceeds 15 mm, the ratio of septal to posterior wall thickness is above 1.5 in characteristic cases[28-29]. This ratio may be higher, while sometimes a ratio of 1.3 is already considered suggestive of ASH when also a thickened septum is present[30].
In a recent study, ratio of septal to posterior wall of 1.3 was present in 10% of the overall cardiac population, in 20% of patients with pulmonary stenosis or primary pulmonary hypertension and in 15% of those with the Eisenmengers syndrome.
When there was no evidence of genetic transmission of ASH they suggested that these patients had just disproportionate septal thickening[31,11]. It would seem more prudent therefor to maintain a ratio of 1.5 or more.
The left ventricular outflow tract (LVOT) is narrow (less than 20 mm at endsystole) in all cases. In classic IHSS (fig. 5) the anterior mitral leaflet (AML) shows an abnormal systolic anterior motion (SAM)[32].

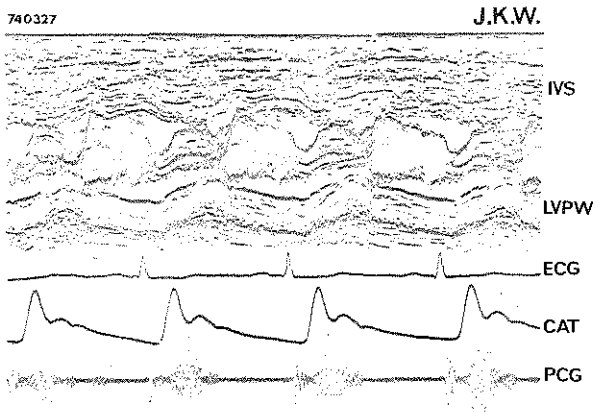



*Fig. 5 M-mode echocardiogram at the level of the mitral valve leaflets of a patient with ASH and obstruction. Septal hypertrophy is evident, whereas the left ventricular posterior wall is of normal thickness. An abnormal systolic anterior motion (SAM) of the mitral valve leaflets is observed, coincident with the appearance of mid- and late apical systolic murmur. Furthermore the carotid artery tracing (CAT) shows its characteristic bisferiens appearance. One can clearly see that the upstroke of CAT and SAM have different steepnesses and are appearing after each other.*

This SAM coincides with the characteristic murmur of this disease and is related to the gradient in the LVOT found during cardiac catheterization. Several factors can influence the magnitude of SAM and thus the severity of obstruction (fig. 6). It can be explained by hydrodynamic forces generated in the LV[5] or by malaligment of the papillary muscles and the mitral valve apparatus[2]. When only a labile gradient exists and no SAM is observed on the echocardiogram, provocative manoeuvres such as use of amylnitrite (fig. 7) can demonstrate SAM.

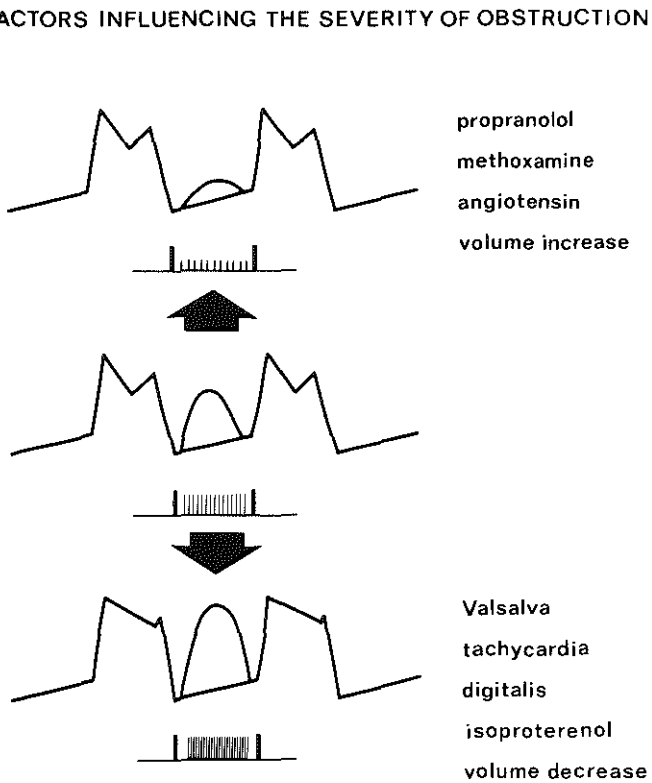



*Fig. 6 Diagram of echocardiogram and SAM and heart murmur, indicating which factors can contibute to the magnitude of SAM and the loudness of the heart murmur.*

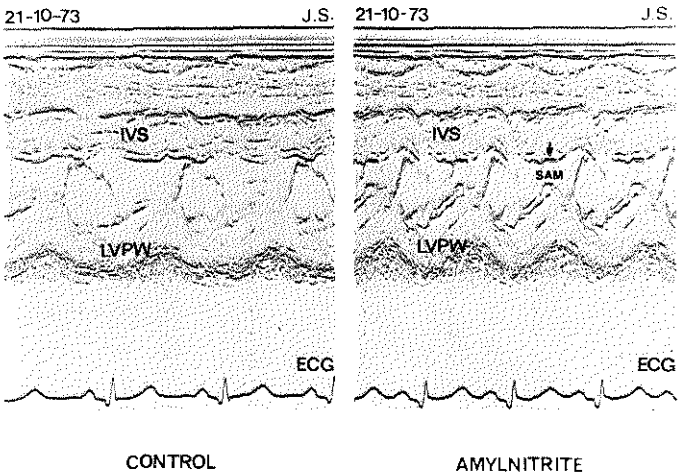



*Fig. 7 M-mode echocardiogram of a patient with ASH who showed no obstruction under basal conditions. After use of amylnitrite SAM appears.*
*For further explanation see text.*

Dual M-mode recordings show a mid-systolic closure of the aortic valve, as a consequence of the reduction of flow through the aorta by the obstruction in the LVOT (fig. 8). This closure coincides with SAM. An obstruction-index has been calculated as the ratio of the duration of narrowing (expressed in msec.), to the mean septal-mitral distance (in mm) (fig. 9)[30].
A linear relationship between the calculated obstruction-index and the gradient across the LVOT during cardiac catheterization has been found by several authors[33-34] (fig. 10).

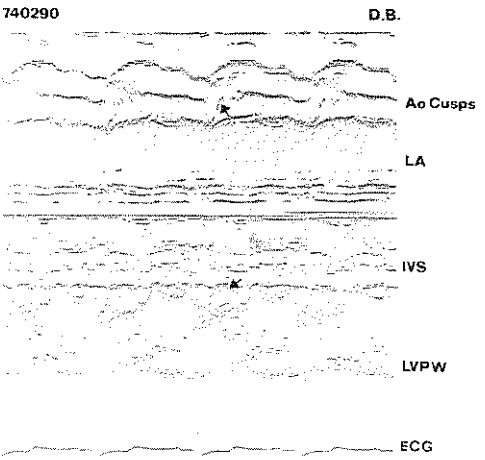
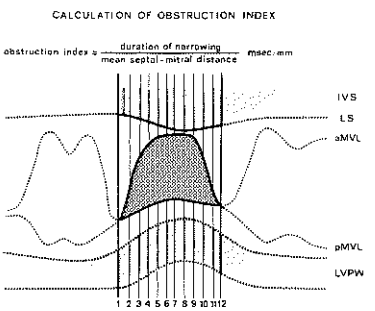



*Fig. 8 Dual M-mode recordings at the level of the aortic valve and mitral valve. One can clearly see that midsystolic closure of the aortic cusps (see arrow) coincides with peak of SAM (see arrow). For further explanation see text.*

*Fig. 9 Diagram of calculation of the obstruction - index. For detailed description see text.*



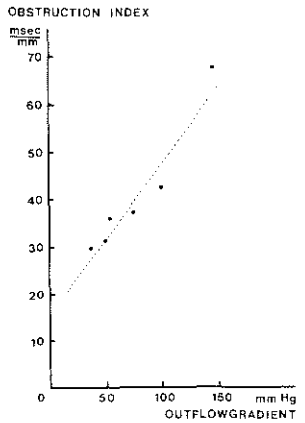



*Fig. 10 The relation between the calculated obstruction index and the gradient across the LVOT found during cardiac catheterization. Obstruction index can exist when no outflow gradient is present.*

It has also been clear that the interventricular septum does not contract normally, whereas the left ventricular posterior wall may demonstrate increased systolic thickening and velocity of contraction. This is in contrast with the findings in patients with coronary artery disease and septal akinesia[35]. (see also 4.4) The left ventricular chamber shape in ASH is very characteristic with its bananalike configuration. (see fig. 11)

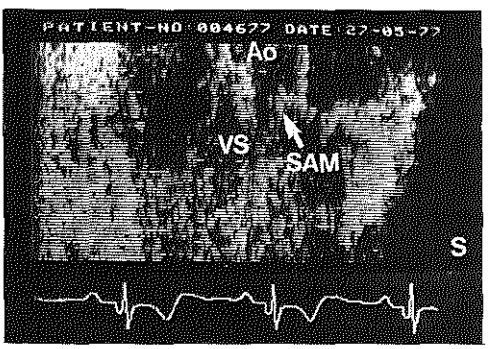



*Fig. 11 Realtime cardiac image at mid systole (S) of a patient with ASH and obstruction. The abnormal thickened IVS is evident, giving the LV a characteristic shape. SAM is shown (see arrow).*

In exceptional cases with ASH, the hypertrophied part of the septum is located near the apex. This can be confusing since on M-mode echorecordings this phenomenon and therefore the diagnosis can be easily missed (fig. 12).

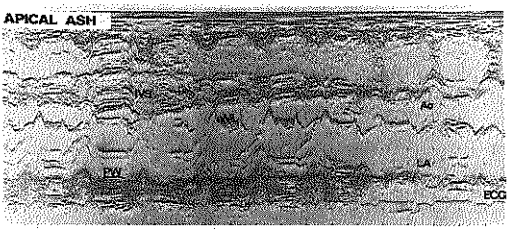



*Fig. 12 M-mode sector scan of a patient with Apical ASH. One can clearly see that the level of the aML, the IVS is of normal thickness, whereas at the level of the apex the IVS is hypertrophied and the PW is still of normal thickness.*

It is our opinion that real time cardiac imaging is obligatory in the proper assessment of patients with ASH. In fact, it is the experience in this laboratory that ASH can be present along the length of the entire septum.

### 3.6.7 Associated cardiac diseases

As indicated earlier, asymmetric septal hypertrophy may be associated with a large number of congenital heart diseases[22,37,38]. These consist of pulmonary valve stenosis, atrial septal defect, aortic valvular, subvalvular, supravalvular stenosis or coarctation of the aorta[39]. Despite early speculation that severe systemic hypertension could be another cause of functional subvalvular obstruction[40], a true association remains uncertain[41]. The occurrence of coronary artery disease seems to increase with age[21], but may reflect the general incidence of that disorder at these ages.

The association of asymmetric septal hypertrophy and the short PR- interval is wellknown[12] with an incidence of ± 5%. The association of ASH and complete heart block has also been reported[42].
In our series, 2 patients had significant coronary artery disease in addition to ASH, whereas no patient had other forms of associated cardiac disease. No patient in our series had signs of severe systemic hypertension.

### 3.7 Complications

The three major complications which may supervene in patients with asymmetric septal hypertrophy are sudden death, infectives endocarditis and progressive heart failure. The most feared complication is obviously the unexpected or sudden death. This can indeed occur during vigorous exercise but has also been seen under resting circumstances. Sometimes these catastrophies are foreshadowed by syncopal attacks[12,19], but between the incidence of sudden death and the degree of clinical disability or the magnitude of gradient across the left ventricular outflow tract no predictable relation has been found. Severe ventricular rhythm disturbances are the most likely cause of sudden death[12].
The incidence of bacterial endocarditis varies from five to nine percent[12-14]. Anatomic observations in necropsy studies show involvement of the aortic and/or mitral valve in all patients[43,44]. These studies show that the infectious process originates in the traumatically damaged ventricular side of the anterior mitral leaflet. This area is commonly thickened due to repeated trauma of the anterior mitral leaflet and the ventricular septum. The prognosis of bacterial endocarditis is not different from that of this complications in general.

When the clinical course is acute, cardiac failure and sepsis predominate; when the clinical course is chronic, immunologic manifestations such as nephropathy, anemia and vasculitis may become evident. Adequate prophylactic precautions are important[44].
The incidence of congestive heart failure is about 7%[12], and this progression of the disease may be surmised from increasing disability of patients, the development of dysrythmias (especially atrial fibrillation) and the progressive loss of cardiac murmurs. (chapter 6)

## 3.8 Treatment

Anginal complaints, dyspnea, arrhythmias and strong positive family history of sudden death all require intervention. Propranolol is the current drug of choice when medical treatment is chosen. Furthermore the as yet asymptomatic patient must be urged to avoid strenuous exercise and to follow endocarditis prophylaxis. When it was demonstrated that catecholamine[45] induced obstruction could be prevented by propranolol[46], the administration of this B-blocker found rapid acceptance[47]. Unfortunately in patients with significant clinical disability, propranolol therapy has been disappointing, so that at present a variety of other drugs is being considered, one of which is the group of calciumantagonists. Indeed, a therapeutic trial is indicated in every symptomatic patient. Most patients will respond favourably, while those severely symptomatic patients who do not improve and who have considerable pressure gradients, should be considered for surgery[47,48,48a]. It has been found that in particular patients with anginal complaints show symptomatic improvement[48]. However, little change in effort tolerance[49] or in frequency of ventricular rhythm disturbances was seen. Also the incidence of sudden death appears not influenced by medical therapy[47].

Our present approach is that maximal dosage in the individual, symptomatic patient should be high (maximal dosage 600 mg/day) before improvement can be expected. Gratifying symptomatic and hemodynamic improvement may follow left ventriculotomy and myectomy initially. In rare cases this may be sustained over an observation period of maximal 14 years[50]. Operative mortality with this technique is high (9%)[50,51]. Furthermore, the underlying primary myocardial disorder remains unaffected. Some have advocated mitral valve replacement[52]. However, because of the unaltered left ventricle, a high incidence of mechanical and thrombo-embolic problems may be anticipated, even with the low profile prosthetic mitral valve. The technique[51] has not been applied in our center.

## 3.9 References


1. Roberts W.C. and Ferrans V.J.: Morphologic observations in cardiomyopathies. In myocardial disease by Noble O. Fowler page 59.
   Editor Grune and Stratton, New York, 1973.
2. Simon A.L., Ross J. Jr. and Gault J.H.:
   Angiographic anatomy of the left ventricle and mitral valve in idiopathic hypertrophic subaortic stenosis. Circulation 36: 852, 1967.
3. Adelman A.G., Mc Loughlin M.J., Marquis J., Auger P. and Wigle E.D.: Left ventricular cineangiographic observations in muscular subaortic stenosis.
   Amer. J. Card. 24: 689, 1969.
4. Shah P.M., Gramiak R. and Kramer D.H.:
   Ultrasound localisation of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. Circulation 40: 3, 1969.
5. Henry W.L., Clark C.E., Griffith J.M., Epstein S.E.:
   Mechanism of left ventricular outflow obstruction in patients with obstructive asymmetric septal hypertrophy (Idiopathic hypertrophic subaortic stenosis). Amer. J. Card. 35: 337. 1975.
6. Braunwald E., Morrow A.G., Cornell W.P., Aygen M. and Hilbish T.: Idiopathic hypertrophic subaortic stenosis. Clinical, hemodynamic and angiographic manifestations. Amer. J. Med. 21: 924, 1960.
7. Brockenbrough E.C., Braunwald E. and Morrow A.G.:
   A hemodynamic technic for the detection of hypertrophic subaortic stenosis. Circulation 23: 189,1961.
8. Lockhart A., Charpentier A., Bourdanis J.P.,
   Ben Israil M., Outbak P. and Scebat L.: Right ventricular involvement in obstructive cardiomyopathics: hemodynamic study in 13 cases.
   Brit. Heart J.: 28, 122, 1966.

9. Barr P.A., Celermayer J.M., Bowder J.D. and Cartmill T.B.: Idiopathic hypertrophic obstructive cardiomyopathy causing severe right ventricular outflow tract obstruction. Brit. Heart J. 35: 1109, 1973.

10. Maron B.J., Edwards J.E., Henry W.L., Clark C.E., Bingle G.J. and Epstein S.E.: Asymmetric septal hypertrophy (ASH) in infancy. Circulation 50: 809, 1974.

11. Neufeld H.N., Ongly P.A. and Edwards J.E.: Combined congenital subaortic stenosis and infundibular pulmonary stenosis. Brit. Heart J. 22: 686, 1960.

12. Frank S. and Braunwald E.: Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the Natural History. Circulation 37: 759, 1968.

13. Swann D.A., Bell B., Oakley C.M. and Goodwin J.F.: Analysis of symptomatic course, prognosis and treatment of hypertrophic obstructive cardiomyopathy. Brit. Heart J. 33: 671, 1971.

14. Adelman A.G., Wigle E.D., Ramganathan N., Webb G.D., Kidd B.S.L., Bigelow N.G. and Silver M.S.: The clinical course in muscular subaortic stenosis. A retrospective and prospective study of 60 hemodynamically proved cases. Ann. of Int. Med. 77: 515, 1972.

15. Clark C.E., Henry W.L. and Epstein S.E.: Familiar prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis. New Engl. J. Med. 289, 709, 1973.

16. Ten Cate F.J., Roelandt J., Vletter W.B. and Hugenholtz P.G.: Asymmetric septal hypertrophy: entirely a familiar disease? Circulation (Suppl. III) 50: 17, 1974. (abstr.)

17. Robinson J.J.: Asymmetric septal hypertrophy in autopsies on men.
Arch. Path. Lab. Med. 100: 121, 1976.

18. Shah P.M., Adelman A.G., Wigle E.D., Gobel F.L., Burchell H.B., Hardarson T., Curiel R., De la Calzalda C., Oakly C.M. and Goodwin J.F.: The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy.
Circ. Research (Suppl. II) 34: 179, 1974.

19. Ingham R.E., Rossen R.M., Goodman D.J. and Harrison D.C.: Ambulatory electrocardiographic monitoring in idiopathic hypertrophic subaortic stenosis.
Circulation (Suppl. II) 52: 93, 1975 (abstr.).

20. Lambart E.C., Menon V.A., Wagner H.R. and Vlad P.: Sudden unexpected death from cardiovascular disease in children. A cooperative international study. Amer. J. Card. 34: 89, 1974.

21. Parker B.M.: The course in idiopathic hypertrophic muscular subaortic stenosis.
Ann. Int. Med. 70: 903, 1969.

22. Walston II A, Behar V.S.: Spectrum of coronary artery disease in idiopathic hypertrophic subaortic stenosis. Amer. J. Card. 38: 12, 1976.

23. Elliott C.M., Tajik A.J., Guilani E.R. and Gordon H.: Idiopathic hypertrophic subaortic stenosis associated with cutaneous neurofibromatosis: Report of a case.
Amer. Heart J. 92: 368, 1976.

24. Wigle E.D., Heimbecher R.O. and Gunton R.W.: Idiopathic ventricular septal hypertrophy causing muscular subaortic stenosis.
Circulation 26: 325, 1962.

25. Goodwin, J.F., Hollman A., Cleland W.P. and Teare D.: Obstructive cardiomyopathy simulating aortic stenosis. Brit. Heart J. 22: 403, 1960.

26. Walston A., Behar V.S., Wagner G.S. and Greenfield Jr. J.C.: Electrocardiographic and hemodynamic correlations in patients with idiopathic hypertrophic subaortic stenosis. Amer. Heart J. 91: 11, 1976.

27. Henry W.L., Clark C.E. and Epstein S.E.: Asymmetric septal hypertrophy (ASH). The unifying link in the IHSS disease spectrum. Observations regarding its pathogenesis, pathophysiology and course. Circulation 47: 225, 1973.

28. Abassi A.S., Mc Alpin R.N., Eber L.M. and Pearce M.L.: Echocardiographic diagnosis of idiopathic hypertrophic cardiomyopathy without outflow obstruction. Curculation 46: 897, 1972.

29. Criley J.M.,Blaufun A.H. and Abassi A.S.: Nonobstructive IHSS. Circulation 52: 963, 1975.

30. Epstein S.E., Henry W.L., Clark C.E., Roberys W.C., Maron B.J., Ferrans V.J., Redwood D.R. and Morrow A.G.: Asymmetric septal hypertrophy. Annals of Int. Med. 81: 650, 1974.

31. Maron B.J., Clark C.E., Henry W.L., Fitenda T., Edwards J.E., Mattheus E.C., Jr., Redwood D.R. and Epstein S.E.: Prevalence and characteristics of disproportionate ventricular septal thickening in patients with acquiered or congenital heart diseases. Echocardiographic and morphologic findings.
Circulation 55: 489, 1977.

32. Popp R.L. and Harrison D.C.: Ultrasound in diagnosis and evaluation of therapy of idiopathic hypertrophic subaortic stenosis.
Circulation 40: 905, 1969.

33. Henry W.L., Clark C.E., Glancey D.L., Epstein S.E.: Echocardiographic measurement of the left ventricular outflow gradient in idiopathic hypertrophic subaortic stenosis. New.Engl.J.Med.19: 989, 1973.

34. Ten Cate F.J. and Roelandt J.: Belang van echocardiografie voor de diagnose van Asymmetrische Septale Hypertrofie (ASH). Hart Bull. 5: 32, 1974.
35. Ten Cate F.J., Hugenholtz P.G. and Roelandt J.: Ultrasound study of dynamic behaviour of left ventricle in genetic asymmetric septal hypertrophy. Brit. Heart J. 39: 627, 1977.
36. Shah P.M.: ISHH-HOCM-MSS-ASH. Editorial. Circulation 51: 577, 1975.
37. Shem-Tov A., Deutsch V., Yalini J.H. and Neufeld H.: Cardiomyopathy associated with congenital heart disease. Brit. Heart J. 33: 782, 1971.
38. Sommerville J. and Mc Donald L.: Congenital anomalies in the heart with hypertrophic cardiomyopathy. Brit. Heart J. 30: 713, 1968.
39. Blom K.B., Hieyer R.A., Bove K.E. and Kaplan S.: The association of fixed and dynamic left ventricular outflow obstruction. Amer. Heart J. 89: 586, 1975.
40. Brock R.: Functional obstruction of the left ventricle. Acquired aortic subvalvular stenosis. Guy's Hosp. Report 28: 221, 1957.
41. Hamby R.I., Robert G.S. and Menon J.M.: Hypertension and hypertrophic subaortic stenosis. Amer. J. Med. 51: 474, 1971.
42. Tajik A.J., Giuliani E.R., Frye R.L., Mc Goon D.C. and Nunn S.L.: Muscular subaortic stenosis associated with complete heart block. Amer. J. Card. 31: 101, 1973.
43. Wang K., Gobel F.L. and Gleason D.F.: Bacterial endocarditis in idiopathic hypertrophic subaortic stenosis. Amer. J. Heart 89: 359, 1975.

44. Vecht J.R. and Oakly C.M.: Infective endocarditis in three patients with hypertrophic obstructive cardiomyopathy. Brit. Med. J. 2: 455, 1968.

45. Braunwald E. and Ebert P.A.: Hemodynamic alteration in idiopathic hypertrophic subaortic stenosis induced by sympathomimetric drugs. Amer. J. Card. 10: 489, 1962.

46. Flamm M.D., Harrison D.C. and Hancock E.W.: Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. Circulation 38: 846, 1968.

47. Goodwin J.F.: Treatment of the cardiomyopathies. Amer. J. Card. 32: 341, 1973.

48. Stenson R.E., Flamm M.D., Harrison D.C. and Hancock E.W.: Hypertrophic subaortic stenosis. Clinical and hemodynamic effects of long term propranolol therapy. Amer. J. Card 31: 763, 1973.

48a Verbiest E.: Hypertrophische obstructieve cardiomyopathie. Natuurlijk verloop vergeleken met late post-operatieve resultaten. Acad. Proefschrift, Leiden, 1975.

49. Edwards R.A., Kristinsson A., Wanell D.A. and Goodwin J.F.: Effects of propranolol in response to exercise in hypertrophic obstructive myocardiopathy. Brit. Heart J. 32: 219, 1970.

50. Morrow A.G., Reitz B.A., Epstein W.E., Henry W.L., Conkle D.M., Itscoitz S.B. and Redwood D.R.: Operative treatment in hypertrophic subaortic stenosis, techniques and the results of pre- and post operative assessments in 83 patients. Circulation 52: 88, 1975.

51. Epstein S.E., Morrow A.G., Henry W.L. and Clark C.E.: Editorial: The role of operative treatment in patients with hypertrophic subaortic stenosis. Circulation 48: 677, 1973.

52. Cooley D.A., Leachmann R.D. and Wukasch D.C.: Diffuse muscular subaortic stenosis: Surgical treatment. Amer. J. Card. 31: 1, 1973.

*British Heart Journal*, 1977, **39**, 627–633

# Ultrasound study of dynamic behaviour of left ventricle in genetic asymmetric septal hypertrophy

F. J. TEN CATE, P. G. HUGENHOLTZ, AND J. ROELANDT

*From the Department of Clinical Echocardiography, Thoraxcenter, University Hospital Dijkzigt and Erasmus University, Rotterdam, the Netherlands*

*Genetic asymmetric septal hypertrophy is a primary myocardial disease with characteristic echocardiographic features. Echocardiographic studies in patients have shown that the ventricular septum is a hypocontractile structure. Since overall cardiac systolic function in this disease is normal, the present study was undertaken to explain this phenomenon.*

*Nineteen patients with proven genetic asymmetric septal hypertrophy, and 15 patients with coronary artery disease and echocardiographic akinesis of the ventricular septum with an angiographically complete obstruction of the descending branch of the left coronary artery, were compared with 20 normal subjects.*

*Analysis includes calculation of systolic thickening of the septum and left ventricular posterior wall, calculation of systolic posterior wall velocity, and determination of left ventricular internal dimensions with ultrasound.*

*Results showed that the ventricular septum was a hypocontractile structure in asymmetric septal hypertrophy, whereas the left ventricular posterior wall seems to compensate for this as is seen by the augmented indices for systolic thickening and velocity of the posterior wall. Left ventricular size was small. This was in contrast to the findings in coronary artery disease with septal akinesia. Indices for thickening and velocity of the posterior wall were decreased, whereas left ventricular size was enlarged. We propose that systolic function of the left ventricle can be maintained by three different compensatory mechanisms; (1) increase of dimension (Starling mechanism); (2) increase in systolic thickening; and (3) increase in systolic velocity of contraction.*

Genetic asymmetric hypertrophy of the interventricular septum is a primary myocardial disease with distinct morphological abnormalities (Henry *et al.*, 1973).

Several studies using electron microscopy have identified ultrastructural changes consisting of abnormal architecture of the interventricular septum with bizarrely shaped muscle cells (Ferrans *et al.*, 1972; Maron *et al.*, 1974).

Although one would expect these changes to result in an impaired overall cardiac function, this does not occur. Indeed, the systolic cardiac function in these patients is often normal (Goodwin and Oakley, 1972). In an attempt to clarify this enigma, an echocardiographic study was undertaken. In this study we paid special attention to the posterior wall of the left ventricle and analysed its contraction pattern in an effort to explain the existence of a normal overall cardiac systolic function in this disease.

Received for publication 9 August 1976

## Patients and methods

Nineteen patients with genetic asymmetric septal hypertrophy, 11 women and 8 men, ages 14 to 53 years were studied.

The diagnosis was based on the echocardiogram (septal hypertrophy was defined as a thickness greater than 15 mm, and a ratio of septal to posterior wall thickness of greater than 2:1).

All patients underwent haemodynamic evaluation and left ventriculography. In 11 patients, a resting gradient across the left ventricular outflow tract was present and all patients had abnormalities consistent with asymmetric hypertrophy on their right anterior oblique left ventricular cine angiocardiogram. In addition, 15 patients with coronary artery disease, all having an angiographically complete obstruction of the descending branch of the left coronary artery and septal akinesia on their echocardiograms, were also studied.

As a control group 20 'normal' volunteers were

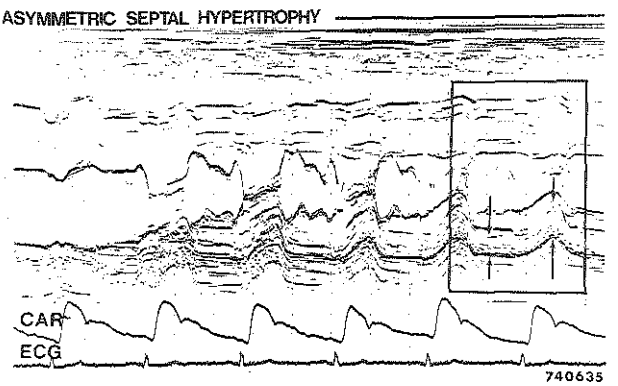



Fig. 1 *A standard M-mode sectorscan in a patient with haemodynamic proof of genetic asymmetric septal hypertrophy. The motion pattern of the anterior mitral leaflet is normal during systole, indicating no outflow obstruction. The area studied is that part of the left ventricle between the tips of the mitral valves and the papillary muscles. This is shown at the right of the picture. The two important features are that: (1) the motion of the interventricular septum is much reduced as is the systolic thickening and (2) the motion pattern of the left ventricular wall is increased and shows excessive thickening.*

used. ('Normal' was defined on the basis of the absence of complaints, clinical examination of the heart, electrocardiogram, and chest *x*-ray).

ECHOCARDIOGRAPHIC EXAMINATION

The ECHOcardioVISOR 01 (Organon Teknika, Oss, The Netherlands), which has both the conventional single and the recently developed two-dimensional imaging facilities was used (Kloster *et al.*, 1973; Roelandt *et al.*, 1974).

A 1·4 cm, 2·25 MHz transducer focused at 7·5 cm was employed and the M-mode echocardiograms recorded simultaneously with the electrocardiogram by a Honeywell Linescan-recorder (Visicorder 1856) on light-sensitive paper (Kodak Linagraph 1895). All patients were examined in the supine or slightly left lateral recumbent position, with the transducer placed as close as possible to the left side of the sternum and perpendicular on the chest wall until the characteristic pattern of motion of the anterior mitral valve leaflet was maximally recorded. The ultrasonic beam was then directed laterally and slightly inferiorly to define the 'standard area' of the left ventricle just distal to the tips of the mitral valve in which the motion of the interventricular septum and left ventricular posterior wall could be detected together. After the standard left ventricular echocardiograms, sector scans were made and recorded from the aortic root across the left ventricular cavity to the left ventricular apex. During the examination gain settings were continuously adjusted until the best available recordings could be made.

Fig. 1 shows a representative M-mode sector scan of a patient with genetic asymmetric septal hypertrophy without left ventricular outflow gradient under basal conditions during cardiac catheterisation. The disproportionate thickness of the interventricular septum compared with the left ventricular posterior wall thickness is striking. Furthermore, the motion of the interventricular septum is reduced compared with the increased motion of the left ventricular posterior wall.

In order to show the accuracy of the single element recordings another procedure was carried out. It is evident that a single beam recording does not show motion perpendicular to the sound beam axis

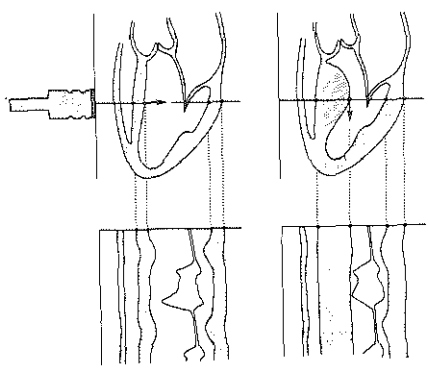


Fig. 2 *Motion of cardiac structures as recorded in M-mode (left side) is not seen when this motion is perpendicular to the sound beam (right side).*

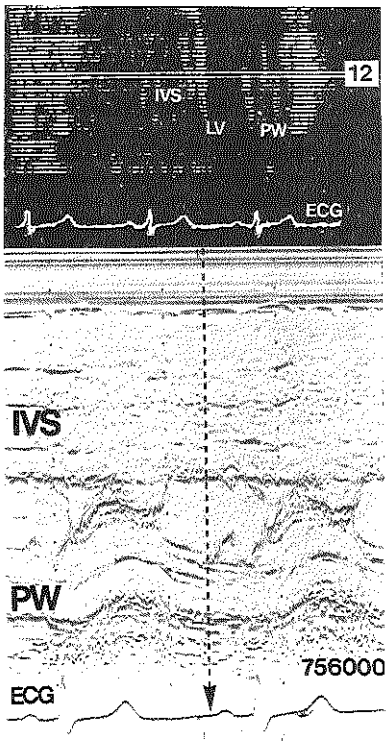



Fig. 3 *Stop-frame image in diastole obtained from a patient with outflow obstruction. A single crystal of the 20 crystal transducer at the level of the anterior mitral valve leaflet—labelled 12—is selected and its echo information is recorded in the M-mode and represented below. The dotted line shows the timing of the cross-sectional image within the cardiac cycle.*

(Fig. 2). Therefore, real time two-dimensional imaging was performed to observe this motion. This was done by selection of a single crystal out of the 20-crystal transducer at the level of the tip of the anterior mitral leaflet. A recording of this echo information in the M-mode is shown in Fig. 3.

This procedure was repeated using two elements —one above and one below the chosen one—in order to show that septal thickness is not changed by a vertical motion which could be seen from the two-dimensional real time images (Fig. 4). This procedure was included in the echocardiographic examination of all patients studied.

ANALYSIS OF ECHOCARDIOGRAPHIC DATA

The left ventricular internal diameter (D) was measured in mm from the left septal endocardium to the left ventricular posterior wall endocardium at end-diastole (Dd) and at end-systole (Ds) (end-diastole at the R-peak of the QRS complex and end-systole at the shortest dimension (ten Cate *et al.*, 1974)).

Septal and posterior wall thickness (T) was also measured at the same points of reference (Td = end-diastole and Ts = end-systole). Fractional or per cent systolic thickening of both interventricular septum and left ventricular posterior wall was determined as $\frac{Ts-Td}{Td} \times 100\%$ (in %) where Ts and Td are the systolic and diastolic thickness of either the interventricular septum or left ventricular posterior wall. Normalised posterior wall velocity was calculated as $\frac{Ts-Td}{Td \times ET}$, where ET is the ejection time measured from the onset to peak contraction (Cooper *et al.*, 1972) (see also Fig. 8).

Student's t test for independent observation was used to determine the statistical significance of these measurements (Fisher, 1970).

## Results

The results of our measurements are summarised in the Table. Systolic thickening of the interventricular septum in the 3 groups of patients studied is shown in Fig. 5. Differences between the normal group and the patients with genetic asymmetric septal hypertrophy, as well as those with coronary artery disease, were statistically significant ($P < 0.005$).

Table *Results of echocardiographic measurements ($m \pm SD$)*

| | *Heart rate (beats/min)* | *IVS thickening (%)* | *LVPW thickening (%)* | *Normalised PW velocity* | *Dd (mm)* | *Ds (mm)* |
|---|---|---|---|---|---|---|
| N | 72 ±6 | 42 ±8* | 52 ±9* | 1·2 ±0·2* | 53 ±5* | 38 ±4* |
| ASH | 77 ±7 | 10 ±6* | 70 ±30* | 1·7 ±0·5* | 41 ±10* | 26 ±7* |
| CAD | 70 ±8 | 15 ±12* | 33 ±8* | 1·3 ±0·4 | 63 ±11* | 50 ±13 |

N, normal subjects; ASH, asymmetric septal hypertrophy; CAD, coronary artery disease; IVS interventricular septum; LVPW, left ventricular posterior wall; PW, posterior wall.
*$P < 0.005$.

Fig. 6 shows a typical example of a patient with asymmetric septal hypertrophy with a posterior wall systolic thickening of 100 per cent. In Fig. 7, the results of systolic thickening of the left ventri-

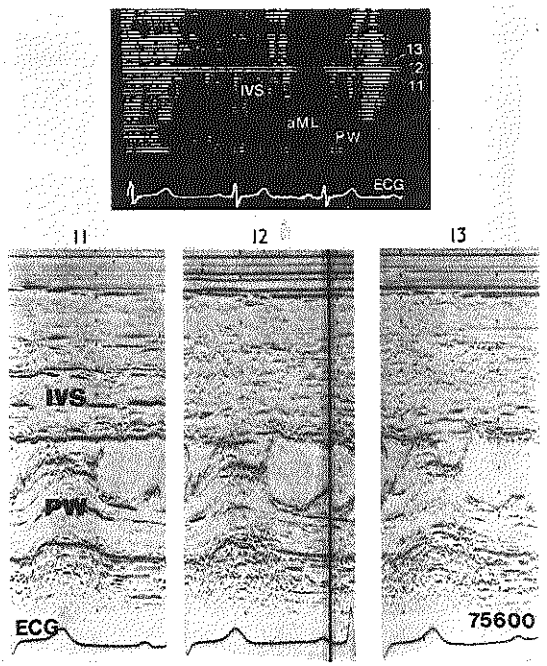



Fig. 4 *The procedure described for crystal 12 in Fig. 3 is repeated for crystal 11 and crystal 13. M-mode recording of these 3 consecutive elements shows no large difference in systolic thickening of the septum or the posterior ventricular wall, indicating that vertical motion seen on the real-time two-dimensional images does not influence quantitative measurements by single element echocardiography.*

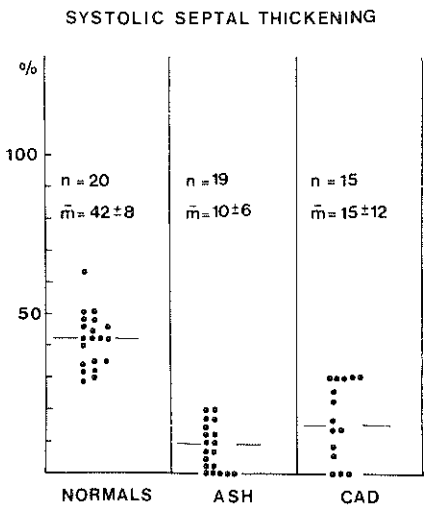



Fig. 5 *Systolic septal thickening in 20 normal subjects is 42 ± 8 per cent, 10 ± 6 per cent in 19 patients with genetic asymmetric septal hypertrophy, and 15 ± 12 per cent in 15 patients with coronary artery disease and septal akinesia. The difference between systolic septal thickening in normals and in patients with asymmetric septal hypertrophy or coronary artery disease is statistically significant ($P < 0.005$) (values expressed as mean ± 2 SD).*

cular posterior wall for the same groups of patients are summarised. Values of left ventricular posterior wall thickening were significantly higher ($P < 0{\cdot}005$) in asymmetric septal hypertrophy as compared with normals, whereas these values were significantly lower in patients with coronary artery disease and septal akinesia ($P < 0{\cdot}005$). Fig. 8 shows the normalised posterior wall velocity of $2{\cdot}6\ s^{-1}$ in a representative patient with genetic asymmetric septal hypertrophy. Fig. 9 shows the values for the normalised posterior wall velocity in the three patient groups studied.

Again values for left ventricular posterior wall normalised velocity were significantly higher in asymmetric septal hypertrophy ($P < 0{\cdot}005$), whereas no statistical significance has been found ($P < 0{\cdot}10$) between patients with coronary artery disease and normals.

The Table also shows that left ventricular internal dimensions in asymmetric septal hypertrophy both in diastole and systole were definitely smaller ($P < 0{\cdot}005$) than in the normal group, whereas in patients with coronary artery disease and septal akinesia these dimensions were higher than in normal individuals ($P < 0{\cdot}005$).

## Discussion

Most patients with genetic asymmetric septal hypertrophy display a clinically observable rapid arterial pulse pressure rise corresponding to a rapid systolic pressure rise in the left ventricle and an increased ejection fraction. These observations suggest an overall left ventricular systolic function which is better than normal. However, echocardiographic analysis of septal contraction (Rossen *et al.*, 1974; Cohen *et al.*, 1975) and the morphological findings of cardiac muscle in this disease (Ferrans *et al.*, 1972) suggest that at least this part of the left ventricle has a reduced function. In this study, the mechanical behaviour of the left ventricle in genetic asymmetric septal hypertrophy was studied by analysis of the contraction patterns of the interventricular septum and left ventricular posterior wall, including the calculation of systolic thickening and the 'normalised' wall velocity. The results indicate that in genetic asymmetric septal hypertrophy the interventricular septum is indeed a hypocontractile structure with decreased values for

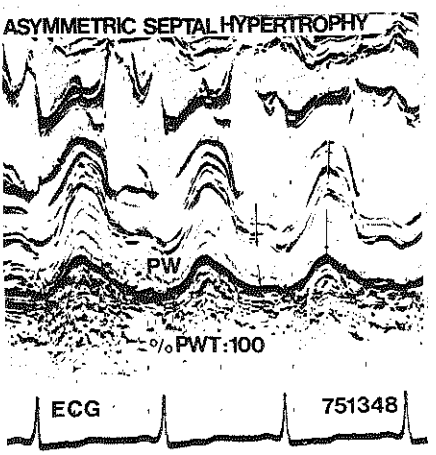



Fig. 6 *Representative example of the posterior wall dynamics in a patient with asymmetric septal hypertrophy. Systolic posterior wall thickening in this particular case is 100 per cent.*

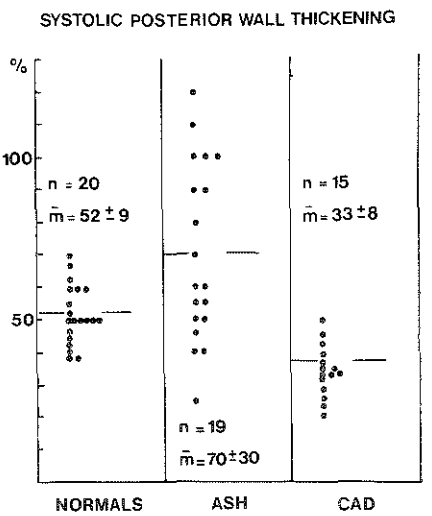



Fig. 7 *Systolic posterior wall thickening in 20 normal individuals is 52 ± 9 per cent, in 19 patients with asymmetric septal hypertrophy 70 ± 30 per cent, and in the 15 patients with coronary artery disease 33 ± 8 per cent. Systolic posterior wall thickening in normal individuals and in patients with coronary artery disease is significantly different from that seen in patients with asymmetric septal hypertrophy ($P < 0{\cdot}005$). Note that patients with asymmetric septal hypertrophy have a large range of systolic thickening (values expressed as mean ± 2SD).*

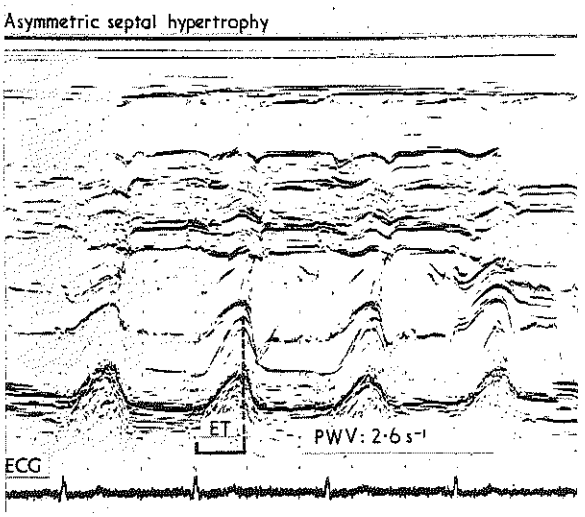



Fig. 8 *Representative example of normalised posterior wall velocity in a patient with asymmetric septal hypertrophy (ASH). Ejection time is calculated as the time from peak QRS to the point where the internal dimension of the left ventricle is smallest. 50 ms is subtracted from this value to account for the isovolumic phase (Cooper* et al., *1972). The value of normalised posterior wall velocity in this particular patient with asymmetric septal hypertrophy is 2·6 s⁻¹.*

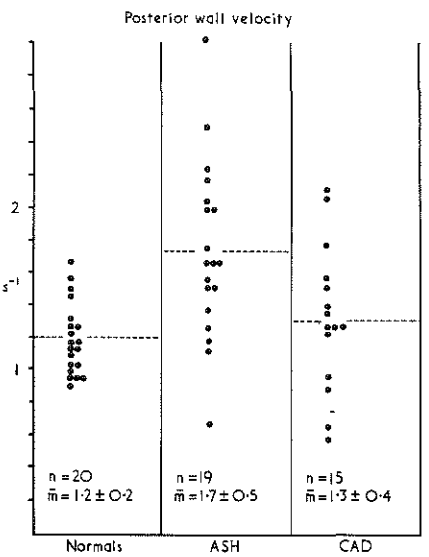



Fig. 9 *Normalised posterior wall velocity in 20 normal individuals was 1·2 ± 0·2 s⁻¹, for 19 patients with asymmetric septal hypertrophy (ASH) 1·7 ± 0·5 s⁻¹, and for 15 patients with coronary artery disease (CAD) 1·3 ± 0·4 s⁻¹. Normalised posterior wall velocity is statistically significantly different for patients with asymmetric septal hypertrophy compared with normals (P < 0·005), whereas this is not the case for patients with coronary artery disease (P < 0·10). Note that in the three groups studied there is a broad range of values for normalised posterior wall velocity (values are expressed as mean ± 2SD).*

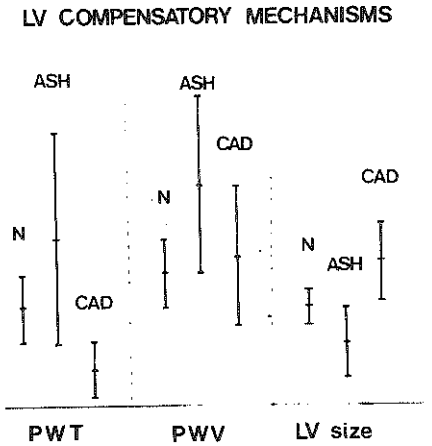



Fig. 10 *Left ventricular compensatory mechanisms in the three groups of individuals studied. Patients with asymmetric septal hypertrophy (ASH) compensate for the akinetic interventricular septum by a greater posterior wall thickening (PWT) and higher velocity of contraction of the posterior wall (PWV), whereas left ventricular size remains small, as compared with normal subjects. This is not true for patients who have coronary artery disease with septal akinesia. In these patients posterior wall thickening and velocity of contraction are not augmented, while left ventricular size is usually greater than normal.*

systolic thickening and that the left ventricular posterior wall tends to compensate for this effect. Indeed both systolic thickening and contraction velocity are higher than the corresponding indices measured from normal individuals. However, this is not the only mechanism that the left ventricle has available to maintain its overall systolic function, which becomes apparent when patients with coronary artery disease and septal akinesia are analysed. In those patients the left ventricular posterior wall percentage systolic thickening was uniformly decreased whereas the contraction velocity was normal. However, in these patients the left ventricular dimensions were larger than in the asymmetric septal hypertrophy group (Fig. 10). Thus it appears that the left ventricle has three different compensatory mechanisms in order to maintain its systolic function: (1) increase dimension (Starling mechanism); (2) increase systolic thickening, and (3) increase velocity of systolic contraction.

A review of the data reveals that the interventricular septum in genetic asymmetric septal hypertrophy is indeed a hypocontractile structure. Contractile function of left ventricular posterior wall as assessed from its systolic thickening and velocity is augmented or at least normal. Thus, the left ventricular mechanical behaviour in genetic asymmetric septal hypertrophy is mainly determined by normal or augmented left ventricular posterior wall contraction pattern while left ventricular size remains small. This is in contrast to findings in patients with coronary artery disease, where the left ventricular dimensions are increased while systolic thickening and normalised posterior wall velocity are usually decreased. These findings suggest that the left ventricle has at least three different compensatory mechanisms to maintain its systolic function as noted above.

**References**

Cohen, M. V., Cooperman, L. B., and Rosenblum, R. (1975). Regional myocardial function in idiopathic hypertrophic subaortic stenosis. An echocardiographic study. *Circulation,* **52,** 842–847.

Cooper, R. H., O'Rourke, R. A., Karliner, J. S., Peterson, K. L., and Leopold, G. R. (1972). Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. *Circulation,* **46,** 914–923.

Ferrans, V. J., Morrow, A. G., and Roberts, W. C. (1972). Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis. A study of operatively excised left ventricular outflow tract muscle in 14 patients. *Circulation,* **45,** 769–792.

Fisher, R. A. (1970). *Statistical Methods for Research Workers,* 14th ed. Oliver and Boyd, Edinburgh.

Goodwin, J. F., and Oakley, C. M. (1972). The cardiomyopathies. *British Heart Journal,* **34,** 545–552.

Henry, W. L., Clark, C. E., and Epstein, S. E. (1973). Asymmetric septal hypertrophy: echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation,* **47,** 225–233.

Kloster, F. E., Roelandt, J., ten Cate, F. J., Bom, N., and Hugenholtz, P. G. (1973). Multiscan echocardiography. II. Technique and initial clinical results. *Circulation,* **48,** 1075–1084.

Maron, B. J., Ferrans, V. J., Henry, W. L., Clark, C. E., Redwood, D. R., Roberts, W. C., Morrow, A. G., and Epstein, S. E. (1974). Differences in distribution of myocardial abnormalities in patienrs with obstructive and nonobstructive asymmetric septal hypertrophy (ASH). *Circulation,* **50,** 436–446.

Roelandt, J., Kloster, F. E., ten Cate, F. J., van Dorp, W. G., Honkoop, J., Bom, N., and Hugenholtz, P. G. (1974). Multidimensional echocardiography. An appraisal of its clinical usefulness. *British Heart Journal,* **36,** 29–43.

Rossen, R. M., Goodman, D. J., Ingham, R. E., and Popp, R. L. (1974). Ventricular systolic septal thickening and excursion in idiopathic hypertrophic subaortic stenosis. *New England Journal of Medicine,* **291,** 1317–1319.

ten Cate, F. J., Kloster, F. E., van Dorp, W. G., Meester, G. T., and Roelandt, J. (1974). Dimensions and volumes of left atrium and ventricle determined by single beam echocardiography. *British Heart Journal,* **36,** 737–746.

Requests for reprints to Dr. F. J. ten Cate, Department of Clinical Echocardiography, Thoraxcenter, P.O. Box 1738, Rotterdam, the Netherlands.

EUROPEAN JOURNAL OF CARDIOLOGY, 1976, 4/3, 349–357. EXCERPTA MEDICA

# Familial prevalence of asymmetric septal hypertrophy

**Wim G. van Dorp, Folkert J. ten Cate, Wim B. Vletter, Henk Dohmen and Jos Roelandt**

*Department of Clinical Echocardiography, Thoraxcenter, Academic Hospital Dijkzigt and Erasmus University, Rotterdam, and Department of Cardiology, University Hospital Wilhelmina Gasthuis, Amsterdam, The Netherlands*

Received 20 June 1975 Revised version accepted 29 March 1976

VAN DORP, W.G., TEN CATE, F.J., VLETTER, W.B., DOHMEN, H. and ROELANDT, J. (1976): Familial prevalence of asymmetric septal hypertrophy. *Europ. J. Cardiol., 4/3,* 349–357.

Echocardiography was used to detect the familial prevalence of asymmetric septal hypertrophy in relatives of patients with proven idiopathic hypertrophic subaortic stenosis. Idiopathic hypertrophic subaortic stenosis is only one clinical expression of a cardiomyopathic disease spectrum, including asymptomatic patients having asymmetric septal hypertrophy as a characteristic anatomic marker which can be detected by echo. The validity of previous proposed criteria to detect this marker was checked in our population. Therefore we examined normal subjects, patients with fixed left ventricular outflow obstruction (valvular aortic stenosis), and those with idiopathic hypertrophic subaortic stenosis who served as index cases. A septal thickness exceeding that of the free left ventricular posterior wall by 30% separates patients with a cardiomyopathy from those without this disease. 27 of 73 examined relatives of 14 index cases were found to have asymmetric septal hypertrophy. In those instances where information was available from the parents of the index cases, one parent was found to be affected. When the examined group is considered from a parent–child relationship (including the index case when appropriate), it included 78 children of affected single parents of which 20 males and 19 females had asymmetric septal hypertrophy. The history, clinical examination and electrocardiogram were not useful to detect the disease.

The results suggest an autosomal dominant mode of inheritance of asymmetric septal hypertrophy with a high penetrance.

echocardiography; genetics; hypertrophic obstructive cardiomyopathy; idiopathic hypertrophic subaortic stenosis

Asymmetric septal hypertrophy is the constant and characteristic abnormality of a cardiomyopathic disease spectrum ranging from asymptomatic individuals to patients with the full-blown clinical picture of idiopathic hypertrophic subaortic stenosis [1]. Echocardiography provides an accurate method to noninvasively measure the thickness of both the interventricular septum and the free left ventricular posterior wall, and thus to demonstrate asymmetric hypertrophy of the septum [2]. This method was used by Clark et al. [3] to study the familial prevalence of this cardiomyopathic disease. In contrast to the current belief that this disease was sporadic in about 75% of all cases and familial in only 25% [4,5], they found that this disease almost always was genetically transmitted as an autosomal dominant trait with a high degree of penetrance.

The present study was undertaken to confirm this familial prevalence of asymmetric septal hypertrophy in the relatives of patients with proven idiopathic hypertrophic subaortic stenosis in The Netherlands.

## Materials and methods

15 symptomatic patients, 5 males and 10 females, ages ranging from 15 to 58 years, all having idiopathic

hypertrophic subaortic stenosis (IHSS) proven by cardiac catheterization and angiography served as index cases. Their relatives including parents, brothers, sisters and first cousins were asked to cooperate with the study which consisted of history, physical examination, electrocardiography and echocardiography. The only selection criterion to include a given family in this study was having data of at least two first-degree relatives available. Of those who could not cooperate, the history was recorded from other family members. Autopsy findings, if available, were collected of those who were deceased. Complaints of dyspnea, fatigue, chest pain and palpitations were specifically asked for in the history. On physical examination systolic murmurs were noted. The ECHO$^{cardio}$VISOR 01 (Organon Teknika, Oss, The Netherlands) was used to obtain the echocardiograms, and electrocardiograms were recorded with the Hewlett Packard 1515A electrocardiograph. The echocardiogram was recorded in the M-mode, using a line scan recorder (Honeywell Visicorder 1856) and light-sensitive paper (Kodak type 1895).

During examination the position of the patient was changed from supine to lateral decubitus until the best resolution of the right side of the septum was obtained.

M-mode sector scans were performed from a standard position on the chest wall where the transducer

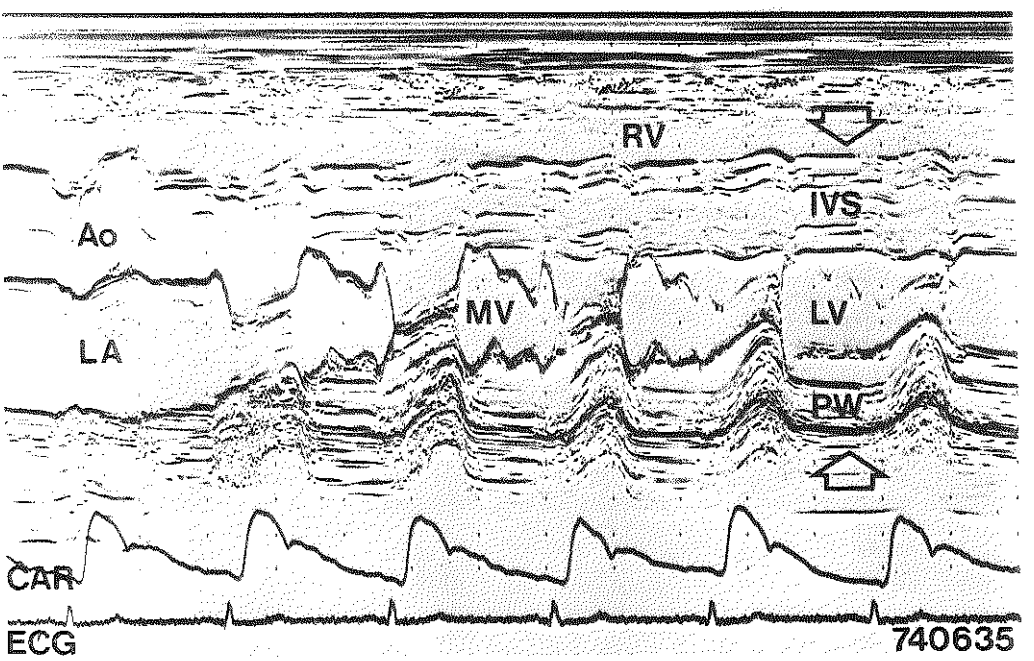



Fig. 1. M-mode sector scan obtained from a patient with asymmetric septal hypertrophy without left ventricular outflow obstruction. Arrows indicate the place where the thickness of both the interventricular septum (IVS) and the left ventricular posterior wall (PW) is measured. The IVS thickness is 23.5 mm whereas the PW thickness is only 11.0 mm. The septal to posterior wall thickness ratio (SPW ratio) is 2.1. Calibration dots are 1 cm apart on this and subsequent echocardiograms. (Ao = aorta; CAR = carotid artery tracing; ECG = electrocardiogram; LA = left atrium; LV = left ventricular cavity; MV = mitral valve; RV - right ventricle).

is held perpendicularly when recording the largest motion amplitude of the anterior mitral valve leaflet [6].

Recordings were then made with the transducer aimed at a point just below the tips of the mitral valve leaflets (Fig. 1), while adjusting the ultrasonic beam direction in order to obtain optimal resolution of the endocardial surfaces of both the IVS and the LVPW (transverse scan) [2]. The thickness of the interventricular septum (IVS) and the left ventricular posterior wall (LVPW) were measured at the same time in the cardiac cycle, at the onset of the P wave of the simultaneously recorded ECG (Fig. 1). All records were independently analyzed by 3 investiga-

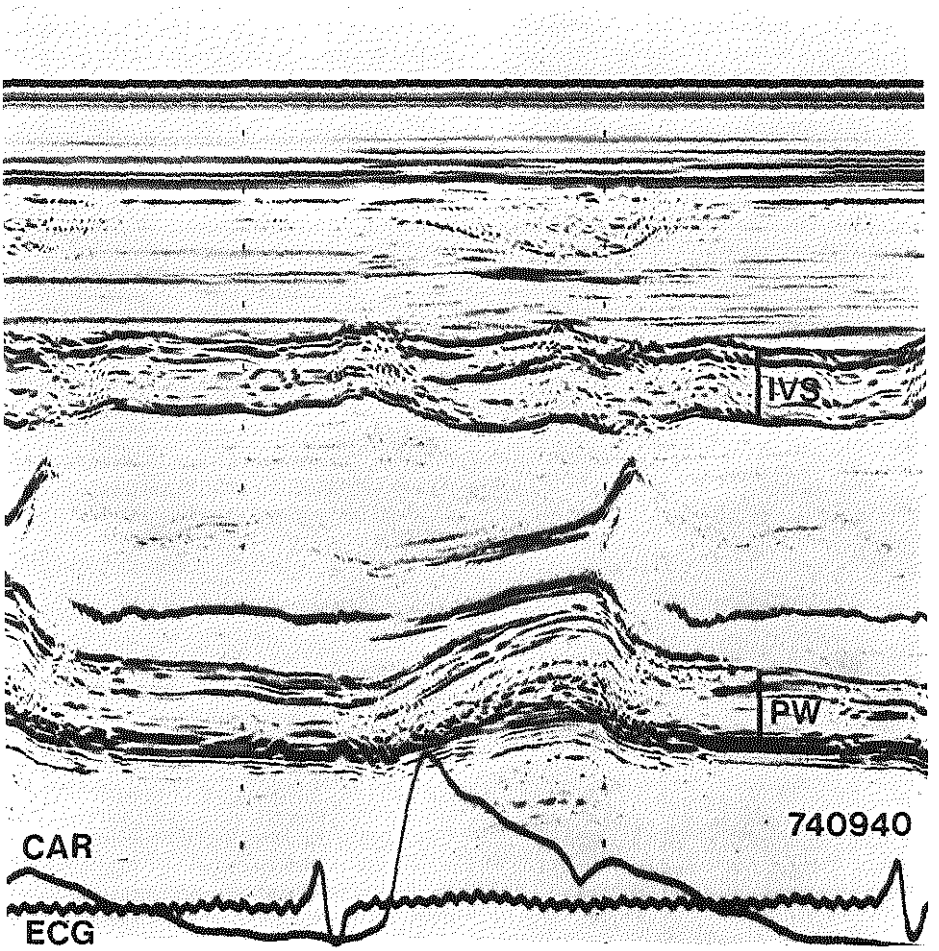



Fig. 2. Echocardiogram obtained from a normal subject. Thickness of both the interventricular septum (IVS) and left ventricular posterior wall (PW) is 9.5 mm, their ratio being 1.0.

tors. The examined individuals were classified by the echocardiographic data independently of history, physical findings and ECG. Following the criteria proposed by Henry et al. [2] based on large series of anatomico-pathological and clinical data a patient was considered to have asymmetric septal hypertrophy (ASH) when the IVS thickness exceeded that of the LVPW by 30%, i.e. a septal–posterior wall ratio (SPW ratio) >1.3. To validate this criterion in our patient population, the IVS and LVPW thicknesses were also measured in 25 normal subjects (based on negative history, physical examination, ECG and chest X-ray) and 20 patients with valvular aortic stenosis, proven by cardiac catheterization.

ASH can exist without and with outflow obstruction. Patients with outflow obstruction are those previously referred to as having IHSS with the characteristic abnormality being the prominent systolic anterior movement of the anterior mitral valve leaflet on the echocardiogram. This peculiar finding is by definition present in all index cases. When noted in some of the family members studied, they were considered as having ASH with obstruction (IHSS).

## Results

### *1. Normal subjects*

Figure 2 shows an echocardiogram typical of a normal subject. The thickness of the IVS in the 25 normals ranged from 8.5 to 12.0 mm and the LVPW thickness from 8.0 to 11.5 mm. The mean SPW ratio was 0.97 with a standard deviation of 0.06. The diagram of Figure 3 shows the distribution.

### *2. Patients with valvular aortic stenosis (AS)*

An echocardiogram obtained from a patient with AS is shown in Figure 4. The thickness of the IVS in the 20 patients with aortic stenosis ranged from 12.5 to 24.0 mm, and the LVPW thickness from 11.5 to 22.5 mm. The mean SPW ratio was 1.05 with a standard deviation of 0.07. This ratio is not significantly different with that of the normal subjects (Fig. 3).

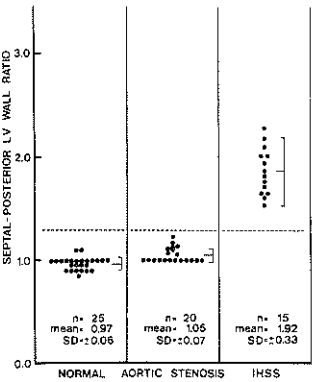



Fig. 3. The septal–posterior LV wall ratios found in three different groups of subjects: 25 normals (no relatives of the index cases), 20 patients with valvular aortic stenosis and 15 patients with IHSS (the index cases of this study).

### *3. Index cases*

The thickness of the IVS in patients with IHSS who served as index cases for this study ranged from 16.5 to 27.0 mm, the LVPW thickness from 9.0 to 14.0 mm. The mean SPW ratio for this group of patients was 1.92 with a standard deviation of 0.33 (Fig. 3). This is significantly higher when compared with the findings in normals and patients with aortic stenosis ($P < 0.05$), there is no overlap.

### *4. Relatives of index cases*

In one family we could not find any relative having ASH. We considered this patient as a sporadic case and excluded this family from the study. In the remaining 14 families, 80 relatives were examined; 73 had an echocardiogram of diagnostic quality (success rate 91%). In this group 27 had ASH. Figure 1 shows an echocardiogram of a patient with ASH. The distribution of the SPW ratios of all persons included in this study is shown in Figure 5. The index cases as well as the relatives with ASH with obstruction (IHSS) are indicated. Maintaining an SPW ratio of 1.3 as the separation between normals and abnormals there is a significant difference ($P < 0.05$) between the mean SPW ratio of the normal relatives (i.e. those

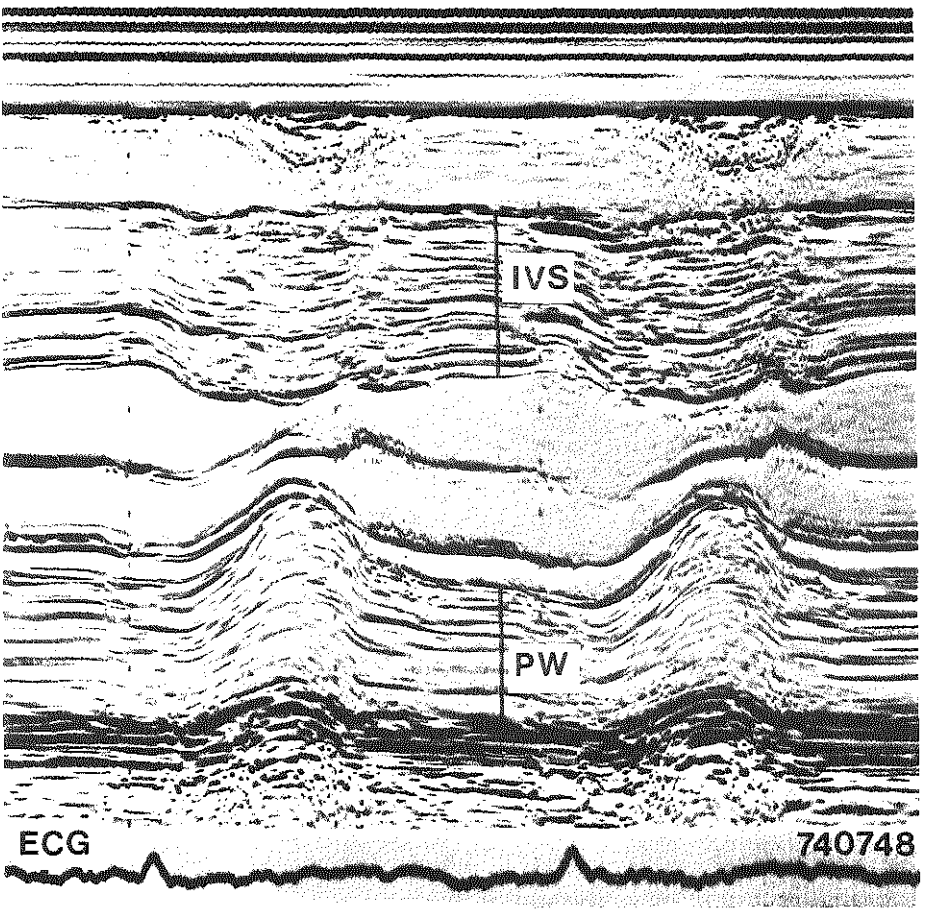



Fig. 4. Echocardiogram of a patient with severe left ventricular hypertrophy resulting from valvular aortic stenosis. It shows proportional thickening of the septum (30.0 mm) and the posterior wall (27.0 mm). The SPW ratio is 1.1 (IVS = interventricular septum; PW = left ventricular posterior wall).

without ASH) and the relatives with ASH. There is, however, no difference in SPW ratio in the 3 subgroups with ASH (index cases, relatives with ASH without obstruction and relatives with ASH and obstruction (IHSS)). The results of the other methods to detect ASH are shown in Figure 6.

Only 8% of the 27 relatives with ASH had one or more of the previously mentioned complaints, 56% a systolic murmur and 72% an abnormal ECG. No abnormality at all was found in 17%, all of them were in the group without outflow obstruction.

We were able to examine both parents of 3 index

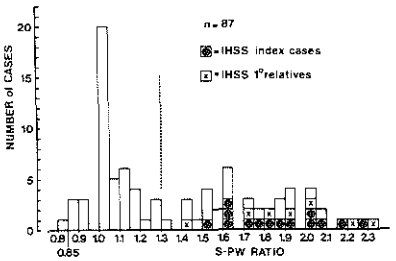



Fig. 5. Histogram of the septal–posterior wall ratios of all subjects examined, including the index cases. Ratios are separated in groups of 0.05. The index cases and their relatives with IHSS (outflow obstruction at rest) are indicated. Separation by the SPW ratio of 1.3 is indicated by a vertical broken line.

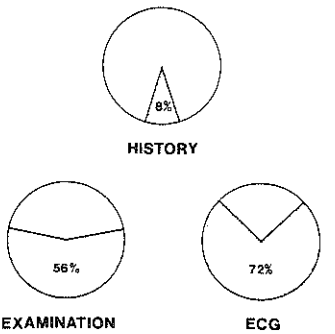



Fig. 6. The prevalence of complaints in the history, abnormal findings at physical examination and abnormalities in the ECG are indicated in percentages (shaded area) for the affected relatives. No abnormality at all was found in 17%.

cases. In all 3, one of the parents was affected. In 7 other index cases, we found one parent with an indicative history of a cardiomyopathic disease (sudden death at early age, cardiomegaly and systolic murmur). In the remaining 4 no data concerning the parents could be obtained.

To determine the percentage of affected children of parents with ASH, we looked for parent–child relations in the 14 families. Three groups were distinguished.

*Group I* consists of parents with ASH (confirmed by catheterization, echo or autopsy).

*Group II* includes the parent–child relations where one parent had an indicative history of IHSS and at least one child had proven ASH.

*Group III* includes the parents without data available, but having at least two children with ASH.

The findings in these three groups are presented in Table I. We found 25 different single-parents with 78 children (41 males and 37 females); 20 males (49%) and 19 females (51%) showed to have ASH.

## Discussion

### *Validity of criteria*

Our study showed that an SPW ratio of 1.3 separates normal subjects and patients with aortic stenosis on the one hand and patients with IHSS on the other

TABLE I The number of single parents with their total number of children, divided in three different groups (see text)

| | Single parents | All children | Mean age ± SD | Children with ASH | Same in % |
|---|---|---|---|---|---|
| Group I | 14 | 37 | 24 ± 9 | 14 | 38 |
| Group II | 7 | 26 | 37 ± 16 | 15 | 58 |
| Group III | 4 | 15 | 55 ± 6 | 10 | 66 |
| Total | 25 | 78 | | 39 | 50 |
| Sex ratio | | 41 37<br>m f | | 20 19<br>m f | |

The mean age of the children, the absolute number and the percentage of the children who have asymmetric septal hypertrophy are indicated. Total numbers are broken down in sex (m = male; f = female).

(Fig. 3). This is in agreement with the results of Henry et al. [2]. Abbasi et al. [7], in a series of 8 selected patients with nonobstructive hypertrophic cardiomyopathy, found an SPW ratio always greater than 2.00. In his control group of 15 normals the ratio exceptionally exceeded 1.3 (mean 1.17; SD 0.14). However, in this study polaroid photographs were used limiting the accuracy of the measurements. In the family investigation to detect ASH, the separation seems less clear, as is shown in Figure 5. A bimodal

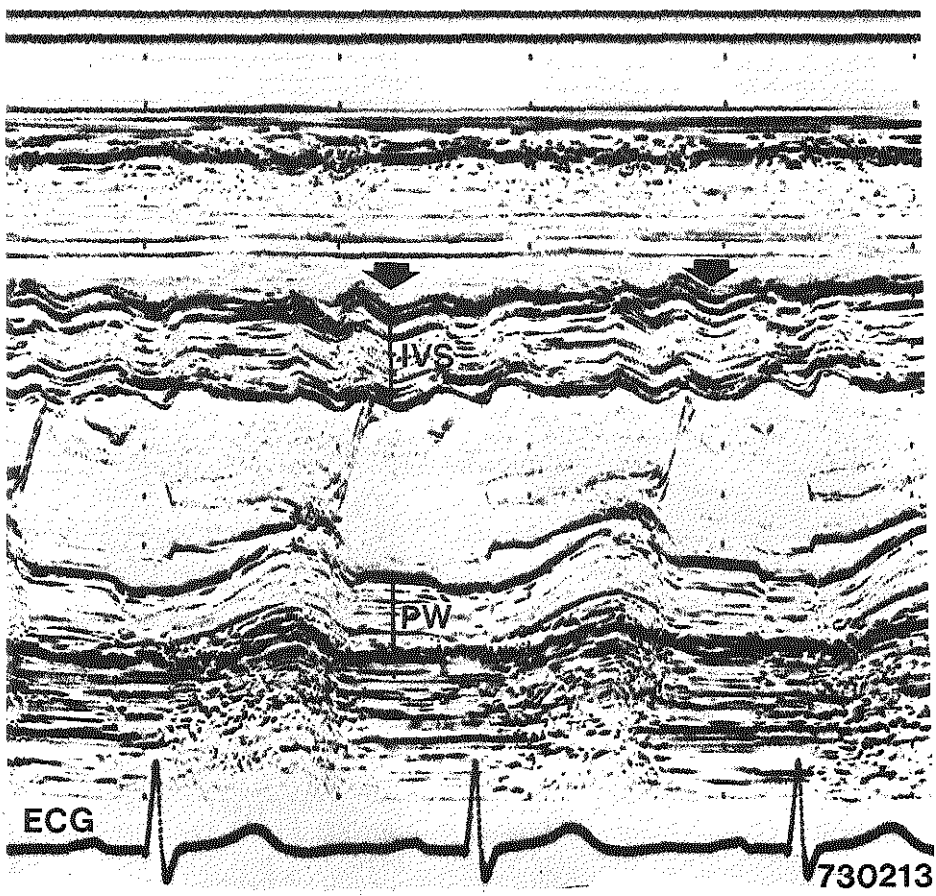



Fig. 7. This echocardiogram demonstrates the problem to diagnose asymmetric septal hypertrophy in borderline cases. The transducer is kept stationary during the registration. At the place of the left arrow the calculated ratio 1.25 whereas one cardiac cycle later it is 1.35. Correct classification when a ratio of 1.3 alone is applied, becomes difficult. Other criteria may eventually be used such as the reduction or absence of systolic thickening of the septum and the excursion or motion of the mitral valve, indicative for a decreased LV compliance, as demonstrated by this example.

curve results with a slight overlap around 1.3. Presence of such an overlap implies that false positive and false negative diagnoses may occur. Although this will not influence the conclusions concerning the prevalence of the disease in large series, correct classification may pose serious problems in some individuals. Recently, a slightly different technique has been proposed to determine the SPW ratio [8], which probably can reduce this overlap. Using this technique septal thickness is measured below the level of the distal margins of the mitral valve, but then posterior wall thickness is measured behind the posterior mitral valve leaflet. A source of false positive diagnoses may be the presence of right ventricular pressure overload with concomitant septal hypertrophy. However, this situation is unlikely or rarely to occur in a population as studied here and other signs should point to this condition. False negative diagnoses can occur in patients with IHSS, who develop secondary hypertrophy of the LVPW. This may result in an SPW ratio being less than 1.3. It seems, however, that such cases are unusual [8].

More important, however, is the fact that even with high quality recordings, obtained with a correct transducer position, measurements are not always constant, which is especially troublesome in the borderline cases. This is illustrated in Figure 7. The SPW ratio calculated from measurements at two different places ranges from 1.25 to 1.35, respectively. The problem is whether one should classify this person as ASH or not, relying only on the SPW ratio. When this situation was present, the patient was classified on account of the smallest SPW ratio.

*Familial prevalence*

This study demonstrates a high familial prevalence of ASH. In all parents of the index cases of whom information could be obtained, we found some indication for ASH (proven diagnosis or indicative history). Furthermore, in a series of 78 children where one of the parents was considered to be affected, 50% has ASH, with an almost equal distribution between males and females. Furthermore, it was demonstrated that ASH can be transmitted through either males or females. These data suggest an autosomal dominant mode of inheritance and the 50% incidence in the children of the index case indicates an almost complete penetrance. The results shown in Table I suggest an increase in penetrance of the disease with increasing age in the three different groups. However, in none of the three groups do the numbers differ significantly from the expected values in the case of complete penetrance (50% of the children affected). The genealogical tree of a representative family included in this study is shown in Figure 8. Aside from the female index case we found her son, brother and his son affected. One sister of the proband had no ASH and none of her children were affected. The parents of the index case were deceased.

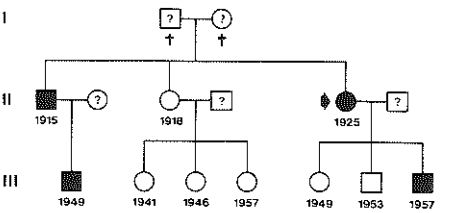



Fig. 8. Genetic tree of a representative family included in the study. The index case is indicated with an arrow. Three other subjects showed to have asymmetric septal hypertrophy, the son, brother and cousin of the index case.

*Symbols:* □ = men; ○ = women; black symbols mean ASH; ? = not examined; † = dead.

The year of birth is indicated for each family member.

*Sporadic case*

One male index case had no other family members with ASH. We examined both parents, 3 sibs, and 2 children. Most striking is that both parents were free of detectable ASH. This may indicate that the index case had a sporadic form of ASH, or that one parent was affected after all, but had incomplete expression of the disease and could not be detected echocardiographically.

*Criticism of the study*

Some biases and sources of errors which may influence the results of this study are present:

a. The index cases were selected, all had severe IHSS.

b. It is not known whether the index cases were homo- or heterozygote for the disease, this may influence the number of affected children.

c. Spouses of the index cases were not examined consistently, so it is unknown to what extent children from parents both having the disease are present in this study. However, this must be considered exceptional as the estimated occurrence of ASH in the population is low.

d. By considering the total number of affected children, some index cases were included in the affected group. It follows, that in this situation always one affected person is present in each family, the index case. Such truncate selection introduces a bias with respect to the expected 50% ratio increasing the apparent prevalence of affected children.

e. We have no information concerning the number of stillbirths and miscarriages of the index cases.

f. To estimate the number of affected children, families were included in which no echo information of the parents was available. Although it is rather likely that these individuals had familial ASH, no absolute certainty exists.

## Conclusion

We conclude that echocardiography is a sensitive method to detect septal hypertrophy, the characteristic anatomic marker of the IHSS disease spectrum.

It is demonstrated that conventional examination techniques are not sufficient to detect ASH. The results strongly suggest that, with possible exception of rare sporadic cases, ASH is transmitted as an autosomal dominant trait with a variable expressivity and a high degree of penetrance.

## References

[1] Henry, W.L., Clark, C.E. and Epstein, S.E. (1973): Asymmetric septal hypertrophy (ASH). The unifying link in the IHSS disease spectrum. *Circulation, 47,* 827.

[2] Henry, W.L., Clark, C.E. and Epstein, S.E. (1973): Asymmetric septal hypertrophy. Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation, 47,* 225.

[3] Clark, C.E., Henry, W.L. and Epstein, S.E. (1973): Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis. *N. Engl. J. Med., 289,* 709.

[4] Frank, S. and Braunwald, E. (1968): Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. *Circulation, 37,* 759.

[5] Emanuel, R. (1971): The familial incidence of idiopathic cardiomyopathy. In: *Hypertrophic Obstructive Cardiomyopathy,* p. 50. Editors: G.E.W. Wolstenholme and M. O'Connor, J & A Churchill, London. (Ciba Foundation Study Group No. 37)

[6] Feigenbaum, H. (1972): *Echocardiography.* Lea & Febiger, Philadelphia, Pa.

[7] Abbasi, A.S., MacAlpin, R.N., Eber, L.M. and Pearce, M.L. (1972): Echocardiographic diagnosis of idiopathic hypertrophic cardiomyopathy without outflow obstruction. *Circulation, 46,* 897.

[8] Henry, W.L., Clark, C.E., Roberts, W.C., Morrow, A. and Epstein, S.E. (1974): Differences in distribution of myocardial abnormalities in patients with obstructive and nonobstructive asymmetric septal hypertrophy (ASH). Echocardiographic and gross anatomic findings. *Circulation, 50,* 447.

*Address for reprints:* W.G. van Dorp, Thoraxcenter, P.O. Box 1738, Rotterdam, The Netherlands

CHAPTER 6

# PREVALENCE OF DIAGNOSTIC ABNORMALITIES IN PATIENTS WITH GENETICALLY TRANSMITTED ASYMMETRIC SEPTAL HYPERTROPHY.

Folkert J. ten Cate, Paul G. Hugenholtz,
Wim G. van Dorp and Jos Roelandt.
(Submitted for British Heart Journal, 1978)

## 6.1 Abstract

Echocardiographic studies were performed in 100 patients out of the general cardiac population, 33 patients with classic hypertrophic obstructive cardiomyopathy and their 116 available first degree relatives. The findings were compared to findings out of 35 normal individuals.
Prevalence of asymmetric septal hypertrophy (ASH) (ventricular septal to posterior wall ratio $\geq$ 1.3) was 8% in the general cardiac population, whereas no clinical or echocardiographic evidence was found for a familial disease.
The ventricular septal to posterior wall ratios for this group and the normal individuals show an unimodal distribution curve. All patients with hypertrophic obstructive cardiomyopathy show ASH, decreased systolic septal thickening less than 25% and a characteristic left ventricular shape.

The ventricular septal to posterior wall ratios in the 116 family members show a bimodal distribution curve of 35 individuals with ASH and 81 individuals with normal ratios.
All 35 individuals with echocardiographic evidence for ASH show in addition decreased systolic septal thickening (less than 25%) and 17 of them had an LV-shape characteristic for hypertrophic cardiomyopathy. These findings are in contrast to these in the other 81 indivuduals who show no ASH nor decreased systolic septal thickening and had a normal LV-shape and thus appear to be normal.
Clinical examination, electrocardiogram and chest film were less sensitive to detect diagnostic abnormalities in the 35 relatives with ASH. It is concluded that echocardiographic determined ASH can only be considered as the anatomic marker for hypertrophic cardiomyopathy when in addition decreased systolic septal thickening and into lesser degree characteristic left ventricular shape exist. Furthermore the data confirm that ASH probably represents the anatomic expression of a genetic defect that has an autosomal dominant pattern of inheritance.

## 6.2 Introduction

Echocardiographic studies in first degree relatives of patients with proven symptomatic hypertrophic obstructive cardiomyopathy (HOCM) (Goodwin et al, 1960) or Idiopathic hypertrophic subaortic stenosis (IHSS) (Braunwald et al, 1960) have shown that both in Europe and in the USA the disease is genetically transmitted. (Clark, Henry and Epstein, 1973; van Dorp et al, 1976). In these important studies asymmetric septal hypertrophy (ASH) was used as the anatomic marker, establishing the presence of this primarily muscular disorder.

However echocardiographically determined septal hypertrophy can also exist in congenital heart disease infants (Larter et al, 1976), and even in valvular heart disease in adults (Maron et al, 1977).
Following earlier reports from this laboratory that ASH is a familial disease, genetically transmitted by an autosomal dominant trait, the present study was undertaken to show if echocardiographically determined ASH is indeed a specific disease entity, which can be separated from other cardiac diseases in the general cardiac or apparently normal population.

## 6.3 Patient selection and methods

Four groups of patients were compared to a group of ostensibly healthy individuals, who served as controls. The five groups were constitued as follows:

### Group 1:

As a control group served 35 individuals with a negative cardiac history, a normal physical examination, a normal electrocardiogram (ECG) and a normal postero-anterior chest X-ray. (X-ray)

### Group 2:

One hundred individuals underwent complete hemodynamic evaluation for cardiac diagnosis. Right and left heart catheterization was followed by single plane left ventriculography. They consisted of 29 patients (pts) with severe coronary artery disease (CAD), 18 pts with aortic valvular disease (AVD), 30 pts with mitral valve disease (MVD), 16 pts with congenital heart disease (CHD), and 7 pts with minimal heartdisease (MHD). Fiftynine were male and 41 female (mean age 41 $\pm$ 15 years (yrs)).

Group 3:

Thirtythree individuals (13 male and 20 female with a mean age of 42 ± 14 yrs) had hemodynamic (21 pts) and echocardiographic (33 pts) proof of HOCM. Diagnosis in the 12 pts who had no cardiac catheterization was based on characteristic clinical findings, family history, ECG and phono- and mechanocardiographic findings.
These patients are further referred to as Index cases.

Group 4:

Thirtyfive first degree relatives of pts with proven HOCM (19 male, 16 female with a mean age of 36 ± 4 yrs) were found to have echocardiographic evidence of ASH.
These patients were identified when 116 available first degree relatives were screened by means of history taking, physical examination, ECG and chest röntgenogram, as well as examinations with single and multi channel echo equipment, for the presence of the disease.

Group 5:

Eighty-one first degree relatives of patients with proven HOCM (36 male, 45 female with a mean age of 28 ± 12 yrs) underwent the same screening procedure as the individuals of group 4, but showed no evidence of ASH.

## 6.4 Echocardiographic method

The echocardiograms were made with a commercially available apparatus which included single element and multi array equipment with two-dimensional (2D) display facilities. The echocardiograms were recorded in M-mode, with a Honeywell linescanrecorder (Visicorder 1856) on light sensitive paper (Kodak linagraph 1856).

The 2D images were registered on videotape through a videorecorder (Sony V-12). During examination the position of the patients was changed until the best resolution of the right side of the septum was obtained.
The continuous sectorscans were recorded in M-mode, starting with the transducer perpendicular to the chestwall until the septum and posterior wall could be identified clearly. Gain settings were continuously adjusted to obtain best visualization of both interventricular septum (LVPW) at a level just beneath the tips of the mitral leaflets. (fig. 1)

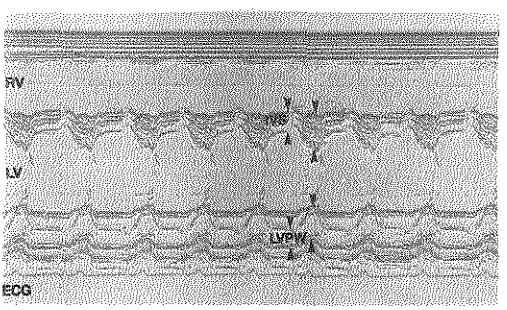



*fig. 1 M-mode echocardiogram of interventricular septum (IVS) and left ventricular posterior wall (LVPW). Measurements for enddiastole and endsystole are shown. (see arrows) For further explanation see text.*

The thickness of IVS and LVPW were measured, just after the P-wave of the simultaneously recorded ECG for enddiastole (Td).
The largest dimension of IVS and LVPW were taken to represent endsystole (Ts).
Fractional thickening of both IVS and LVPW were calculated as Ts-Td/Td x 100% (ten Cate, Hugenholtz and Roelandt, 1977).
The 2D images were performed in the long-axis corss-section (Roelandt, 1977).

From these images a qualitative description was given of left ventricular (LV) shape and of the contraction pattern of IVS and LVPW (akinetic, normal or hyperkinetic). Derived measurements consisted of IVS/LVPW ratio, percent systolic septal thickening and the LV shape and contraction pattern. ASH was considered to be present, when on the echocardiogram IVS thickness exceeded LVPW thickness by 30% (Henry, Clark and Epstein, 1973), regardless whether history physical examination, ECG or X-ray provided supportive evidence.

## 6.5 Analysis of data

Student's t-test for independent observation was used to determine the statistical significance of the measurements involved. (Fisher, 1970) Validity of septal measurements has been described for our laboratory earlier (van Dorp et al, 1976). In borderline cases "echo"-contrast has been ejected into a peripheral vein for better definition of right septal side. (Seward et al, 1977)
All measurements were carried out in duplicate by two independent observers.

## 6.6 Results:

### Distribution of study populations on basis of IVS/LVPW ratio.

### Group 1:

The IVS/LVPW ratio varied from 0.8-1.2 (mean 0.9 $\pm$ 0.1) in the 35 individuals who served as a control group. The IVS/LVPW ratios in this group are identical to those obtained from the "general" cardiac population and represent a unimodal distribution curve. (fig. 2)

It is apparent that, when IVS/LVPW ratios are considered, group 2 ("general" cardiac population), group 5 (unaffected family members) as well as group 1 (normal individuals) present the same distribution, which can readily be separated from group 3 (Index cases) and group 4 (affected family members).

Group 2:

IVS/LVPW ratio in this group was 1.0±0.1 (range 0.8-1.8). (fig. 2)
Eight pts (8%) had a ratio which exceeded 1.3, 3 of these had CAD, 2 AVD and 3 CHD. Of these 8, one patient with CAD and true posterior wall infarction had a ratio of 1.6, while another with a ventricular septal defect and infundibular pulmonic stenosis had a ratio of 1.8. In none of them there was evidence of a primary cardiomyopathy by family history or otherwise.
The remaining six had ratios between 1.3 and 1.6.

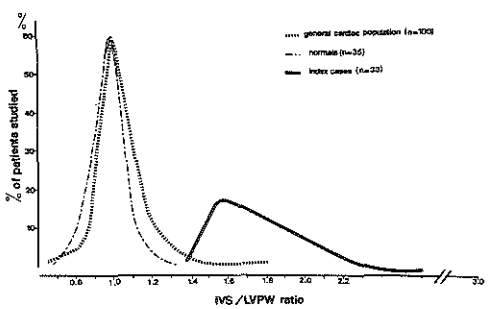



*Fig. 2 The distribution if IVS/LVPW ratios given in 100 patients out of the general cardiac population, 35 normal individuals and 33 patients with hypertrophic cardiomyopathy. (Index cases)*
*One can observe that slight overlap exists between the general cardiac population and the Index cases, but that separation between those groups is evident, when IVS/LVPW ratios are considered. The normal individuals have the same IVS/LVPW distribution as the general cardiac population.*

Group 3:

The ratio IVS/LVPW in these 33 pts ranged from 1.4-2.6 with a mean of 2.2±0.4 while the obsolute septal and LVPW thickness were 24±6 mm and 12±3 mm respectively.
(fig. 3 and table I-IV)
It is evident that these patients represent a specific group of individuals.

Group 4:

The ratio IVS/LVPW in the 35 relatives who had echocardiographic evidence of ASH was 1.7±0.2(range 1.3-2.3).
The average septal and LVPW thickness in these individuals were 19±2 mm and 11±2 mm respectively.
Distribution of IVS/LVPW ratios was virtually identical to group 3. (fig. 3)

Group 5:
The IVS/LVPW ratio in these 81 individuals ranged from 0.9-1.2. (mean: 1.0±0.1) The average septal and posterior wall thickness were 11±2 mm (see table IV). This group of individuals did not differ from the control group (group 1) nor from the pts out of group 2, insofar as distribution of this ratio is concerned. (fig. 2 and 3)

Analysis of clinical data

Since the purpose of this study was to describe the clinical and echocardiographic evidence in pts with ASH and their family members, the clinical analysis of the data is restricted to groups 3, 4 and 5.
Detailed data for history, symptoms and signs, ECG and chest X-ray are given in table I-III.

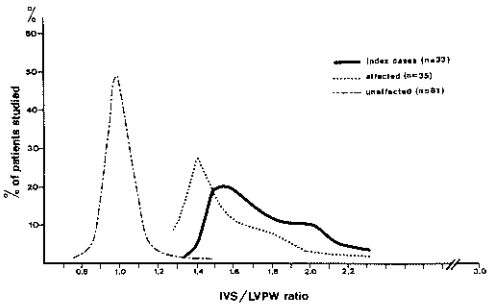



*Fig. 3 Distribution of IVS/LVPW ratios from 33 Index cases, 35 first degree relatives with ASH and 81 first degree relatives without echocardiographic evidence for ASH. The socalled unaffected individuals can clearly be separated from the Index cases and "affected" first degree relatives.*
*Therefore the first degree relatives of patients with hypertrophic cardiomyopathy represent a bimodal distribution curve of IVS/LVPW ratios.*

Echocardiographic findings:

In table IV results of pertinent echocardiographic data are shown for group 3, 4 and 5 and compared to normal values.
These groups had the following echocardiographic characteristics:

In group 3:

1. increase in absolute septal thickness
2. IVS/LVPW ratio exceeds 1.3
3. septal akinesia and
4. abnormal LV-shape.

In group 4:

1. increase in septal thickness
2. IVS/LVPW ratio exceeds 1.3
3. septal akinesia and
4. abnormal LV-shape in 17 of the 35.

Most individuals of group 4 present the same echocardiographic characteristics as the individuals of group 3, while unaffected first degree relatives in group 5, at least at the time of the study, were classofied as normal individuals.

Analysis of genetic transmission

Of the 33 pts (33 families) out of group 3, 116 first degree relatives were available. In 14 families no other case of ASH (echocardiographically) was found apart from the Index case. However in 2, documented ASH could be established by necropsy data of deceased family members. Of the 21 families with evidence of genetic transmitted ASH, pedigree charts were made (fig. 4). The results show a horizontal distribution (relation between sibs) present in 58%, a vertical distribution (parentsib relation) in 42% and both kinds of distribution in 38%.
These findings are in agreement with an autosomal dominant trait. (Emery, 1974)

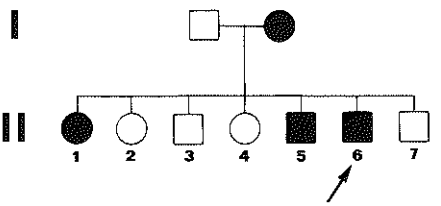



*Fig. 4 Pedigree chart of a representative family of a proband with hypertrophic cardiomyopathy (see arrow).*
*Echocardiographic study in this particular family show two other sibs with ASH and one parent with ASH.*
*This pedigree chart is in agreement with an autosomal dominant mode of transmission.*

## 6.7 Discussion

### Asymmetric septal hypertrophy as a separate disease entity:

The results of this study indicate that an abnormal IVS/LVPW ratio (septum to posterior wall ratio> 1.3) can occur in patients with a variety of acquired or congenital heart diseases.
The question arises as to whether this abnormality is secundary to the underlying cardiac disorder or a manifestation of a coexistent and etiologically separate disease, i.e.g. genetically transmitted ASH. (Clark, Henry and Epstein, 1973).
Our findings in patients with acquired or congenital cardiac diseases suggest that when an abnormal IVS/LVPW ratio exists, it is usually not a manifestation of genetically transmitted ASH.

This conclusion is first based on the unimodal distribution curve found in the patients of group 1 and 2, and second on the negative family history for the presence of genetically transmitted heart disease in the 8 patients of group 2, who had an IVS/LVPW ratio of > 1.3.
This finding is in contrast with the apparent bimodal distribution curve found in the population of first degree relatives of patients with symptomatic ASH (see fig. 2), and the positive family history in most of them (table I).
However, since we have not separately examined the prevalence of abnormal septal to posterior wall ratio in coronary artery disease, until now we cannot definitely exclude on echocardiographic criteria alone the occurence of ASH and coronary artery disease together.

Is ASH a familial cardiomyopathy?

Since symptomatic patients with HOCM or IHSS have a cardiomyopathic disease, with characteristic signs for this disorder as evaluated in our laboratory i.e. abnormal decreased systolic thickening of the interventricular septum (ten Cate, Hugenholtz and Roelandt, 1977) and an abnormal LV shape, as observed from cross sectional imaging, the question had to be answered as to whether these abnormalities are also present in first degree relatives that have an abnormal IVS/LVPW ratio (ASH).
The results of this study have indicated that 35 out of 116 first degree relatives of patients out of group 3 had decreased systolic thickening of the interventricular septum, whereas 17 of them had also an abnormal LV shape, in addition to the IVS/LVPW ratio of > 1.3 (ASH) (Henry, Clark and Epstein, 1973).
Therefore we conclude that patients of group 3 and their family members of group 4 have the same echocardiographic characteristics whereas clinical signs and symptoms are different (see table I, II and III).

Characteristic echocardiographic signs are present which provide the firm diagnosis of a genetic transmitted cardiomyopathy with a wide variety of clinical signs and symptoms.

Clinical implications:

On the basis of these findings, the question also arises as to how genetically transmitted ASH can be excluded as a cause of an abnormal IVS/LVPW ratio in the occasional otherwise individual with a IVS/LVPW ratio of $\geq$ 1.3 and in the patient with a congenital or acquired heart disease with an abnormal IVS/LVPW ratio.

Our experience indicates that the only practical and reliable way to make such a distinction is to examine first degree relatives for ASH by echocardiography. This examination should include a detailed echocardiographic analysis of the criteria for ASH described in this study. Although histologic examination of cardiac septal muscle for the presence of disorganized cardiac muscle cells or by biopsy or extensive hemodynamic and angiocardiographic studies would provide the absolute evidence, these techniques are not readily applicable or indicated in most clinical situations (Maron et al, 1977).
Currently the echocardiographic technique remain the only realistic approach.

Echocardiographic limitations:

It should be emphasized that accuracy in detecting ASH is critically dependent on carefully executed echocardiographic technique. In this regard it must be recognized, that it is sometimes difficult to define the anterior, right, side of the ventricular septum accurately.

Patient position and gain settings should be adjusted for best visualization of the interventricular septum. Errors in measurement can be reduced by better definition of right septal side, with "echo"-contrast (5% dextrose or saline) injected into a peripheral vein. (Seward et al, 1977) Furthermore all septal measurements should be carried out at the level just beneath the tips of the mitralvalve leaflets.

In conclusion, this study has shown that a clinical spectrum exists that ranges from asymptomatic persons to patients with typical HOCM or IHSS. All affected individuals have the same characteristic echocardiographic features, finally asymmetric septal hypertrophy (ASH) can be considered as the anatomic expression of a genetic defect, which is transmitted as an autosomal dominant trait.

Table I

History, symptoms and signs in Asymmetric Septal Hypertrophy

| | |
|---|---|
| A. Group 3 (13 male, 20 female, ages: 42 ± 14 yrs) | N=33 |
| Family history positive of cardiomyopathy | 21 |
| No clinical abnormality | 0 |
| Systolic murmur | 32 |
| Congestive heart failure | 5 |
| Syncope | 2 |
| Arrhythmias | 10 |
| Palpitation and dyspnea | 22 |
| Anginal complaints | 14 |
| On medication | 33 |
| B. Group 4 (19 male, 16 female, ages: 36 ± 4 yrs) | N=35 |
| Family history positive of cardiomyopathy | 35 |
| No clinical abnormality | 15 |
| Systolic murmur | 10 |
| Congestive heart failure | 0 |
| Arrhythmias | 3 |
| Palpitations and dyspnea | 6 |
| Anginal complaints | 10 |
| On medication | 2 |
| C. Group 5 (36 male, 45 female, ages: 28 ± 12 yrs) | N=81 |
| No clinical abnormality | 81 |
| Family history positive of cardiomyopathy | 41 |

Table II

Electrocardiographic abnormalities in Asymmetric Septal Hypertrophy

A. Group 3

| | |
|---|---|
| Abnormal "Q" waves | 16 |
| Left ventricular hypertrophy | 5 |
| Right ventricular hypertrophy | 3 |
| T-wave abnormalities | 20 |
| Intraventricular conduction abnormalities | 3 |
| Preexcitation syndrome | 1 |
| Supraventricular tachycardias | 3 |
| Ventricular rhythm disturbances | 10 |

B. Group 4

| | |
|---|---|
| Abnormal "Q" waves | 9 |
| Left ventricular hypertrophy | 8 |
| Right ventricular hypertrophy | - |
| T-wave abnormalities | 10 |
| Supraventricular rhythm disturbances | 1 |
| No electrocardiographic abnormalities | 6 |

C. Group 5

| | |
|---|---|
| No significant electrocardiographic abnormalities | 81 |

Table III

Chest film findings in Asymmetric Septal Hypertrophy

A. Group 3

| | |
|---|---|
| Cardiothoracic ratio $>$ 50% | 31 |
| Lung changes due to left heart failure | 8 |
| Normal chest film | 2 |

B. Group 4

| | |
|---|---|
| Cardiomegaly (cardiothoracic ratio 50%) | 14 |
| Lung changes due to left heart failure | - |
| Normal chest film | 21 |

C. Group 5

| | |
|---|---|
| Normal chest film | 40 |

In children younger than 15 yrs of age of group 5, no chest X-ray was made routinely.

Table IV

Pertinent echocardiographic findings in family members of 33 patients with hypertrophic obstructive cardiomyopathy

| | Group 3 (Index cases) | Group 4 | Group 5 |
|---|---|---|---|
| N | 33 | 35 | 50 |
| IVS thickness (mm) | 24 ± 6 | 19 ± 2 | 11 ± 2 |
| LVPW thickness (mm) | 12 ± 3 | 11 ± 2 | 11 ± 2 |
| Ratio IVS/LVPW | 2.2 (1.4 - 2.8) | 1.7 (1.3 - 2.3) | 1.0 (0.9-1.2) |
| Systolic thickening of IVS (%) | 9 ± 6 | 12 ± 12 | 50 ± 11 |
| Systolic thickening of LVPW (%) | 66 ± 30 | 60 ± 15 | 70 ± 12 |
| LV shape | banana shape | banana shape in 17 | ellipsoid |

($p < 0.005$)

Normal values for IVS (interventricular septum): 8 - 14 mm.;
for LVPW (left ventricular posterior wall): 8 - 14 mm.;
for systolic thickening of IVS: 42 ± 8(%) and for systolic thickening of LVPW: 52 ± 9(%).
Normal shape of left ventricle (LV): ellipsoid.

## 6.8 References


1. Braunwald E., Morrow A.G., Cornell W.P., Aygen M. and Hilbish T. (1960).
Idiopathic hypertrophic subaortic stenosis:
Clinical hemodynamic and angiographic manifestations.
American Journal of Medicine, 21: 924-931.

2. Clark C.E., Henry W.L. and Epstein S.E. (1973).
Familial prevalence and genetic transmission of idiopathic hypertrophic subaortic stenosis.
New England Journal of Medicine, 289, 709-712.

3. Emery A.E. (1974).
Elements of Medical Genetics.
3rd Ed. Churchill and Livingstone, Edinburgh and London.

4. Fisher R.A. (1970).
Statistical Methods for Research workers.
14th ed. Oliver and Boyd, Edinburgh.

5. Goodwin J., Gordon H., Hollman A. and Bishop M.B. (1961).
Clinical aspects of Cardiomyopathies.
British Medical Journal, 70: 5219-5224.

6. Henry W.L., Clark C.E. and Epstein S.E. (1973).
Asymmetric septal hypertrophy (ASH): The unifying link in the IHSS disease spectrum.
Observations regarding its pathogenesis, pathophysiology and course.
Circulation, 47, 225-233.

7. Larter W.E., Allen H.D., Sahn D.J. and Goldberg S.J. (1976).
The asymmetrically hypertrophied septum.
Furhter differentiation of its causes.
Circulation, 53: 19-27.

8. Maron B.J., Clark C.E., Henry W.L., Fitenda T., Edwards J.E., Mattheus E.C., Redwood D.R. and Epstein S.E. (1977).
Prevalence and characteristics of disproportionate ventricular septal thickening in patients with acquired or congenital heart diseases.
Echocardiographic and morphologic findings.
Circulation 55: 489-499.

9. Roelandt J. (1977).
Practical Echocardiology.
Research Studies Press Inc., Forest Grove, Ore.

10. Seward J.B., Tajik A.J., Hagler D.J. and Ritter D.G. (1977).
Peripheral venous contrast echocardiography.
The American Journal of Cardiology, 39, 202-212.

11. Ten Cate F.J., Hugenholtz P.G. and Roelandt J. (1977).
Ultrasound study of dynamic behaviour of left ventricle in genetic asymmetric septal hypertrophy.
British Heart Journal, 6, 627-633.

12. Van Dorp W.G., ten Cate F.J., Vletter W.B., Dohman H. and Roelandt J. (1976).
Familial prevalence of asymmetric septal hypertrophy.
European Journal of Cardiology 4/3, 349-357.

CHAPTER 7

# PROGRESSION TO LEFT VENTRICULAR DILATATION IN PATIENTS WITH HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

F.J. ten Cate, M.D. and J. Roelandt, M.D.

(Accepted American Heart Journal, 1978)

## 7.1 Abstract

Congestive heart failure with dilated left ventricle developed in two patients with symptomatic hypertrophic obstructive cardiomyopathy. Both patients previously underwent cardiac surgery for relief of their outflow obstruction.
Alterations in structure and function of the left ventricle during their episode of cardiac failure and thereafter were documented by echocardiography.
The findings suggest that progression to left ventricular dilatation is a potential complication in patients with hypertrophic obstructive cardiomyopathy.

## 7.2 Introduction

Left ventricular dilatation has been found during postmortem examination in one patient who was known to have hypertrophic obstructive cardiomyopathy during life.[1]

The progression to left ventricular dilatation, however, has not been documented with clinical methods in patients with symptomatic hypertrophic obstructive cardiomyopathy developing congestive heart failure.

This paper reports on two patients with symptomatic hypertrophic obstructive cardiomyopathy, who presented with congestive heart failure and a dilated left ventricle.

## 7.3 Case histories.

### 7.3 Case 1

A 59 year-old woman underwent a myotomy-myectomy in 1973 for symptomatic hypertrophic obstructive cardiomyopathy. The histologic examination of the surgical specimen demonstrated characteristic abnormalities as found in hypertrophic cardiomyopathy.

Despite improvement of her symptoms, beta-blocking medication was continued.

Echocardiographic examination in 1974 showed asymmetric septal hypertrophy (ASH) with a ratio between interventricular septal thickness (IVS) to that of the left ventricular posterior wall (LVPW) of 2.0 Left ventricular (LV) size was normal and no signs of outflow obstruction were present. The left atrial (LA) cavity was slightly enlarged (figure 1).

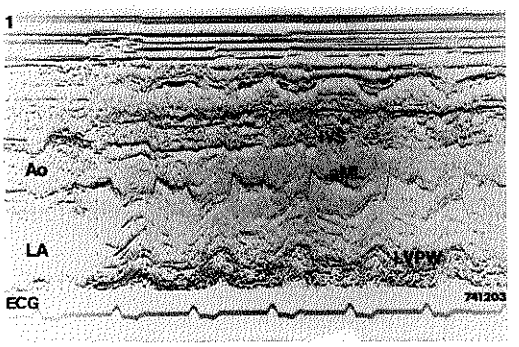



*Figure 1.*
*Echocardiogram of case 1 in 1974. The interventricular septum (IVS) is thickened compared to the left ventricular posterior wall (LVPW). The left atrium (LA) is enlarged. (Ratio of LA to Aortic Root (Ao) is 1.4; normal value $\leq$ 1.2). Left ventricular (LV) size is normal (52 mm).*

In december 1975, she was hospitalized because of severe congestive heart failure. The echocardiogram showed dramatic changes. Disproportionate thickening was now only seen in the upper part of the septum close to the aorta. In its midportion, the LV was extremely dilated (90 mm, upper limit of normal 56 mm). LA size had increased and there was pericardial effusion. (see figure 2 and table 1). At cardiac catheterization, no pressure gradient across the LV outflow tract was measured and the dilated LV was confirmed by angiocardiography. The coronary arteries were found to be normal. Beta-blocking therapy was discontinued and digitalis and diuretics prescribed resulting in clinical improvement. Follow-up echocardiographic studies over a period of 14 months showed a decrease of the LV dimension up to 60 mm (figure 3).

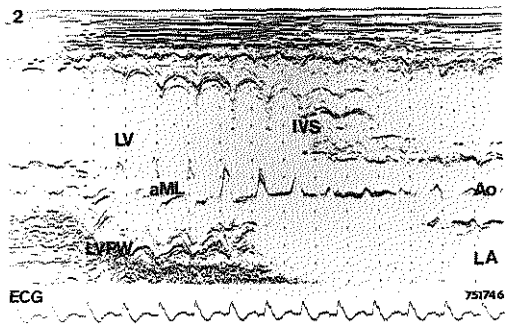



*Figure 2.*
*Echocardiogram of case 1 during a period of congestive heart failure in 1975. The interventricular septum (IVS) is thickened at the level, just beneath the aortic valves, but thereafter significant thinning of IVS is observed. Left ventricular sizes are enlarged to 90 mm and 75 mm in end-diastole and end-systole respectively. Left atrial posterior wall is not registered on this tracing. Pericardial effusion is noted.*

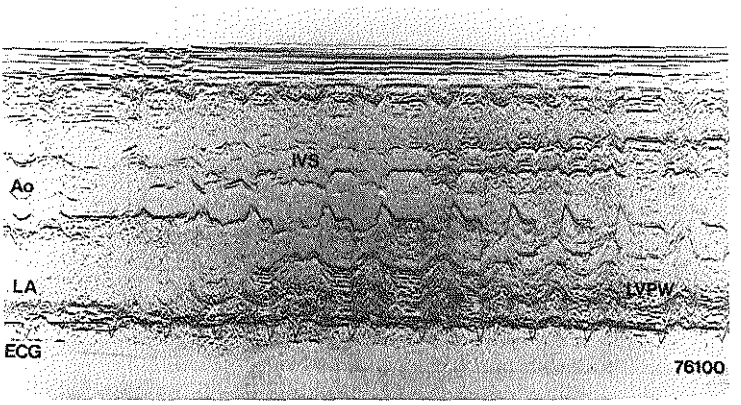



*Figure 3.*
*Echocardiogram of case 1 in 1976. Significant changes occured compared to figure 2. Left ventricular (LV) size has changed to 60 mm and 45 mm at end-diastole and end-systole respectively. Left atrial size has significantly changed. (Ratio of LA to Aortic Root is 1.4; normal value $\leq$ 1.2).*

7.3.2 Case 2

A 59-year-old man was operated upon for symptomatic hypertrophic obstructive cardiomyopathy in 1973. His preoperative hemodynamic study has revealed a resting LV outflow gradient of 60 mm Hg. The histologic examination of the excised septal muscle showed abnormalities typical for hypertrophic cardiomyopathy. His symptoms improved subsequently and no medical treatment was felt necessary. His follow-up controls during three years occurred at another hospital. In January 1976 he was referred to our unit because of severe congestive heart failure. His echocardiogram made at admission showed LV dilatation (end-diastolic dimension: 70 mm). The LA was also dilated (ratio LA/Ao: 1.9; normal value $\leq$ 1.2).
Remnants of septal hypertrophy were seen on the echocardiogram and confined to the region just beneath the aortic valve (figure 4).

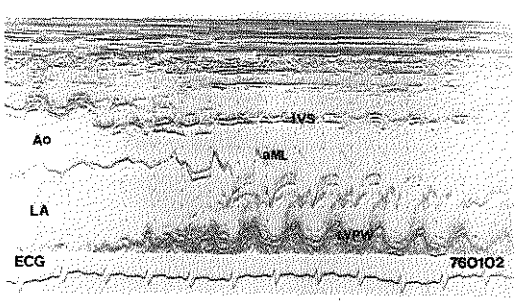



*Figure 4.*
*Echocardiogram of case 2 druing a period of congestive heart failure in 1976. Septal hypertrophy could only be seen just beneath the aortic valve, below that level the interventricular septum (IVS) is thin and akinetic. Left ventricular posterior wall (LVPW) has a normal thickness and shows increased amplitude of motion. Left ventricular (LV) size is enlarged to 68 mm at end-diastole. The left atrial (LA) cavity is enlarged.*
*(LA) toAortic Root (Ao) ratio: 1.4; normal value $\leq$ 1.2).*

Below that level, the septum was thin, possibly as a result of previous surgery, and akinetic.
Despite left ventricular failure, the left ventricular posterior wall had still an increased amplitude of motion. The patient was treated with digoxine and diuretics and the symptoms improved. The echocardiogram made 3 months later showed an LV end-diastolic diameter of 64 mm, while there was no apparent change in LA size (table 1).

## 7.4 Discussion

Left ventricular dilatation has been documented in one of 32 heart's from patients with previously known hypertrophic obstructive cardiomyopathy during necropsy examinations.[1] Frank and Braunwald[2] concluded from their analysis of 126 patients with hypertrophic cardiomyopathy that in this progressive disease with a variable clinical course, congestive heart failure was a rare complication. Only twenty patients in their series had cardiac enlargement on their routine chest film and only one was found with clinical signs of congestive heart failure. Adelman[3] in a series of 60 patients, reported 7% incidence of congestive heart failure. No data on their cardiac size was included. Shah and Sylvester[4], during an echocardiographic follow-up study of 42 months in a small series of patients with hypertrophic obstructive cardiomyopathy, could not demonstrate significant changes in left ventricular size. Thus, it appears that the development of congestive heart failure with dilated ventricle is a rare complication indeed.
Over a 4 year period, we have echocardiographically documented hypertrophic cardiomyopathy in 50 patients. Of these, 25 had systolic anterior motion of the anterior mitral valve leaflet in a narrow outflow tract typical for dynamic outflow obstruction. Ten were operated upon and are now being followed regularly. Five developed

clinical signs of congestive heart failure, of which two had a dilated left ventricle and are described here. It is difficult to infer to an etiological factor for progression to LV dilation in hypertrophic obstructive cardiomyopathy. It is true that both patients underwent myotomy - myectomy but surgery has now been performed in many patients and follow-up data over periods of up to 14 years have been reported.[5]
No patient with progression to LV dilatation has been documented sofar. Beta-blocking treatment could have been a causative factor in case 1. However, this seems unlikely since more cases should have been found over the last decade as beta-blockade is a common treatment. Nonetheless, it appears that progression to congestive heart failure with left ventricular dilatation does occur as a rare complication in the course of hypertrophic obstructive cardiomyopathy.

Table 1.

Pertinent echocardiographic data of the two patients with hypertrophic cardiomyopathy during congestive heart failure (A) and after medical treatment (B).

| | Case 1. | | Case 2. | |
|---|---|---|---|---|
| | A | B | A | B |
| LV dimension | | | | |
| ED | 90 | 60 | 70 | 64 |
| ES | 75 | 45 | 43 | 44 |
| LA/Ao ratio | > 1.5 | 1.4 | 1.9 | 1.7 |

Ao: aortic root; ED and ES: end-diastolic and end-systolic left ventricular internal dimensions in millimeters; LA: left atrium; LV: left ventricle.

## 7.5 References


1. Roberts, W.C. and Ferrans, V.J.:
Morphologic observations in cardiomyopaties. In:
Myocardial diseases: Editor, Noble O. Fowler.
Grune and Stratton, New York and London, 1973.

2. Frank, S. and Braunwald, E. :
Idiopathic hypertrophic subaortic stenosis: clinical analysis of 126 patients with emphasis on the natural history. Circulation 35: 759, 1968.

3. Adelman, A.G., Wigle, E.D., Ranganathan, N., Webb, G.D., Kidd, B.S.L., Bigelow, W.G., Silver, M.D.:
The clinical course in muscular subaortic stenosis.
Ann. Intern. Med. 77: 515, 1972.

4. Shah, P.M. and Sylvester, L.J.:
Echocardiography in the diagnosis of hypertrophic obstructive cardiomyopathy.
Amer. J. Med. 62: 830, 1977.

5. Morrow, A.G., Reitz, B.A., Epstein, S.E., Henry, W.L., Conkle, D.M., Itscoitz, S.B., Redwood, D.R.:
Operative treatment in hypertrophic subaortic stenosis. Techniques and the results of pre- and post- operative assessment in 83 patients.
Circulation 52: 88, 1975.

CHAPTER 8

# FIXED SUBAORTIC STENOSIS:

## The value of echocardiology for its diagnosis and differentiation between the various types.

F.J. ten Cate, W.G. van Dorp,
P.G. Hugenholtz and J. Roelandt.
(Submitted British Heart Journal, 1978)

## 8.1 Abstract

The M-mode echocardiographic and cross-sectional findings in 19 patients with proven fixed subaortic stenosis are described. Based on their hemodynamic, angiocardiographic and surgical analysis, two main groups of patients were identified.
Group I consisted of 13 patients with the membranous form of the disease which was further subdivided in patients having a thin membrane with a normal outflow tract (group Ia; 3 patients) and those with a thicker fibrous ring or collar associated with some degree of outflow tract narrowing (group Ib; 10 patients).
Group II comprised 6 patients with the typical long-segment or tunnel form of the disease.

The outflow tract was of a normal size in all three patients of group Ia and an abnormal echo, most likely representing the subaortic membrane, was seen in only one patient on M-mode and cross-sectional images.
The narrowed left ventricular outflow tract was diagnosed with both methods in all patients of group Ib and II.
The area of narrowing extended over a longer segment in the patients of group II which was more easily appreciated from the cross-sectional images.
Premature closure of the aortic valve cusps was recorded in 2 patients of group Ia, 5 of group Ib and 2 of group II.
It seems from these findings that fixed subvalvular aortic syenosis with isolated discrete subaortic membrane cannot reliably be diagnosed by echo. Patients with narrowed outflow tract, however, are reliably detected by echo.
The differentiation between a short and a long-segment of narrowing is made with more confidence from cross-sectional images.

## 8.2 Introduction

Fixed subaortic stenosis, a condition causing obstruction to left ventricular outflow, can be produced by an isolated discrete fibrous membrane, located just beneath the aortic valve, a thicker fibrous ring of collar which is always associated with some degree of left ventricular outflow tract (LVOT) narrowing, or by diffuse long-segment fibro-muscular narrowing.
The correct differentiation between these different anatomic forms is important since they involve a different natural history. Furthermore each type has its specific problems and a different prognosis when surgery is considered in symptomatic patients. (Maron et al, 1976, Katz, Buckley and Liberthson, 1977)

A few studies have indicated that echocardiography could be a helpful and noninvasive means for the diagnosis and the differentiation between the types of fixed subaortic stenosis. (Popp et al, 1974; Davis et al, 1974; Roelandt, 1977)
In addition, cross-sectional imaging has been proposed as an important method for the evaluation of the left ventricular outflow tract. (Weyman et al, 1976)
The purpose of this study was to test both M-mode echocardiography and cross-sectional imaging for their role in diagnosing and differentiating the different types in 19 patients with proven fixed subaortic stenosis.

## 8.3 Patient material and methods

### - Patient population

Nineteen patients with fixed subaortic stenosis (FSAS) were included in this study. There were 8 male and 11 female (ages: 16 - 60 years: median 20). Major complaints were inappropriate exterional dyspnoe in 18, chest discomfort during exercise in 12, and dizziness, faintness and/or syncopal attacks in 3.
None had signs of heart failure at the time of their examination. Based on the hemodynamic, angiocardiographic and surgical findings, patients were divided into 2 main groups (table I).
Group I: 13 patients had the membranous form of the disease. 3 had a normal LVOT (group Ia) whereas the other 10 had different degrees of LVOT narrowing over a short segment (group Ib).
Group II: 6 patients with the long-segment or tunnel type of subaortic stenosis.

- Hemodynamic, angiocardiographic and surgical data (table I):

Group I: The diagnosis of FSAS in the 13 patients of this group was mainly based on the demonstration of a significant pressure gradient between the left ventricular cavity and LVOT. A distinct membrane with a subvalvular chamber beneath the aortic valve was demonstrated in only 7 patients on the left ventricular cine-angiocardiogram, made in the right anterior oblique projection. In 11 patients, aortic regurgitation was seen during supra-aortic valve angiography.
Nine patients underwent surgery. In 3, a thin subsaortic membrane attached to the anterior mitral valve leaflet was found and could be excised. In the other 6 patients, the abnormality consisted of a thicker membranous collar having a 2-5 cm circumference, located just beneath the aortic valve. This anbormality was excised as much as possible. A bicuspid aortic valve was described in one patient and no further information on the aortic valve was available in the surgical reports. Severe concentric hypertrophy of the left ventricle was mentioned in one and a thickened interventricular septum in 2 patients.

Group II: All 6 patients had a severe systolic pressure gradient across the LVOT. In 4 patients, the long-segment narrowing of the LVOT was diagnosed from the LV cine-angiocardiogram. Aortic regurgitation was present in four. Five patients were operated upon. Myectomy was performed in three, myotomy in one and a LVOT reconstruction in the fifth one.
The latter patient died postoperatively.

- Ultrasonic examination

The apparatus used was a commercially available instrument (EchocardioVisor 03), having both M-mode and cross-sectional imaging facilities (Roelandt, 1977).
From the standard transducer position on the chest (Roelandt, 1977), several M-mode scans were made with a transducer scanning speed as constant as possible.
Patients were examined in the supine or slightly left-lateral recumbent position. During the examination, gain settings were continuously adjusted for best visualization of cardiac structures. Registrations were recorded with a Honeywell linescanrecorder (Visicorder 1856) on light sensitive paper (Kodak Linagraph, 1892).
The following parameters were studied on the M-mode recordings: width of the outflow tract at end-systole, motion of the aortic valve cusps, the presence of a high frequency vibration on the anterior mitral valve leaflet during diastole and the systolic motion pattern and contraction pa-tern of the LV walls (obliteration of LV cavity during systole in the area beyond the posterior papillary muscles). Cross-sectional studies were performed in the long-axis sagittal plane following the LVOT and recorded on Videotape.
During the analysis, special attention was paid to the width and the length of narrowing of the LVOT, the presence of left ventricular hypertrophy (LVH) and apical LV cavity obliteration during systole.

## 8.4 Echocardiographic results

Group Ia: Only in one of the 3 patients, an abnormal echo within the LVOT, which most likely represented a membrane, was visualized (fig. 1). This size of the LVOT was larger than 20 mm in all three patients.

Premature closure of the aortic cusps was seen in two patients. No specific abnormalities could be detected on cross-sectional images.

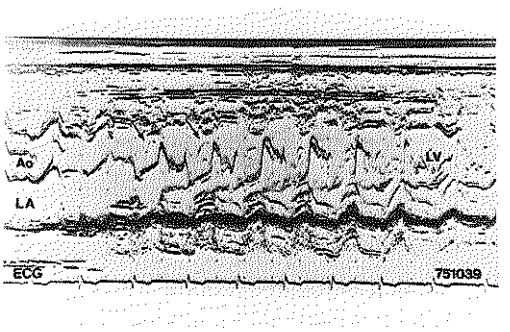



*Fig. 1 Echocardiogram of a patients with FSAS out of group Ia. A membrane was found and excised at surgery. Note the normal size of the left ventricular outflow tract (LVOT) and the discrete echoes of membrane in the LVOT. (see arrows) Because the membrane is attached to the mitral valve, the systolic motion pattern of that valve is abnormal. The aortic valve (Ao) cusps move normal.*

Group Ib: All 10 patients of this group had an end-systolic LVOT width of less than 20 mm (range 10 - 18 mm; normal value> 20 mm) (figure 2). Five patients had an initial rapid opening of at least one cusp of the aortic (Ao) valve followed by an abrupt closure shortly after the onset of ventricular ejection. In 4 of these, a distinct systolic fluttering of the Ao cusps was also recorded. A high frequency diastolic fluttering on the anterior mitral valve leaflet, suggestive of aortic regurgitation (Winsberg, Gabor and Hernberg, 1970) was seen in 5 patients.

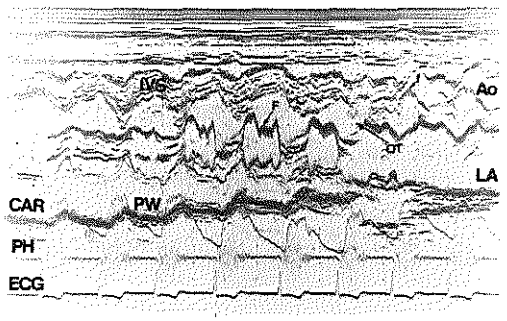



*Fig. 2 M-mode scan from the aorta (Ao) to the apex of the left ventricle (LV) in patient out of group Ib. The endsystolic width of the LVOT is narrowed over a rather short segment.*
*A high frequency diastolic flutter (F) on the anterior mitral valve leaflet, suggestive of Aortic regurgitation is seen. The aortic valve cusps show premature closure in midsystole, also a systolic flutter (f) on the aortic cusps is noted. The interventricular septum (IVS) and LV posterior wall (LVPW) are both symmetrically hypertrophied.*
*CAR= carotid artery tracing; PH= phonocardiogram.*

Concentric left ventricular hypertrophy (LVH) was present in 8, and one of them had an abnormal systolic anterior motion (SAM) of the anterior mitral valve leaflet. (fig. 3).
Asymmetric septal hypertrophy (ASH) was present in 2 patients; enddiastolic septal thickness of 18 and 20 mm respectively.
Systolic apical obliteration was seen in 5 patients.

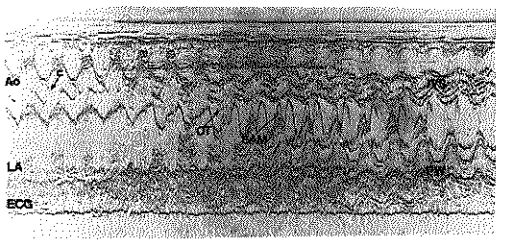



*Fig. 3 M-mode scan in patient out of group Ib.*
*All features suggestive for FSAS are seen on this echocardiogram. In addition the anterior mitral leaflet shows an abnormal systolic anterior motion (SAM), (see arrow), indicative of a dynamic obstruction to left ventricular outflow.*

On cross-sectional images, a short-segment narrowing of the LVOT which appeared as a "ridge" just below the aortic valve was diagnosed in all (figure 4A). Severe concentric LVH was present in 8 patients of which 5 demonstrated a systolic obliteration. In these patients, the papillary muscles were displaced more anteriorly in the LV cavity. The LV had an abnormal shape in 2 patients, similar to the LV shape seen in patients with genetic asymmetric septal hypertrophy.

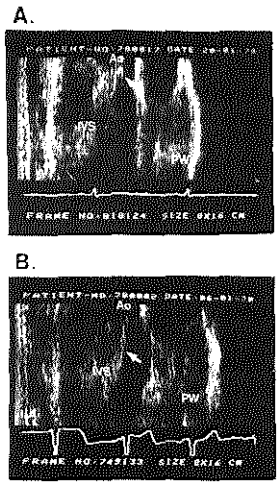



*Fig. 4A Ultrasonic cross-sectional image of patient whose M-mode sectorscan is described in figure 2. A narrow LVOT is observed, over a rather short segment (see arrow), appearing as a "ridge" just beneath the aortic valve cusps.*

*Fig. 4B Ultrasonic cross-sectional image of patient whose M-mode sectorscan is described in figure 5. A narrow LVOT is observed over a rather long segment from a level just beneath the Aortic cusps to the level of the mitral valve leaflets at LV mid-cavity. For abbreviations see text.*

Group II: All 6 patients showed a long, narrow LVOT on their M-mode recordings, which was quite distinctive from the echographic pattern seen in patients of group Ib (figure 5).
Two patients showed an early Ao cusp closure and three a systolic flutter. A diastolic mitral valve pattern consistent with aortic regurgitation was seen 1 patient and 2 had severe concentric LVH (end-diastolic septal and posterior LV wall thickness 18 mm and 18 mm respectively) of which one had SAM. Two patients showed in addition to concentric LVH an apical obliteration.

Two patients had disproportionate septal thickening (septal to free posterior wall ratio 1.3 and 6 respectively).

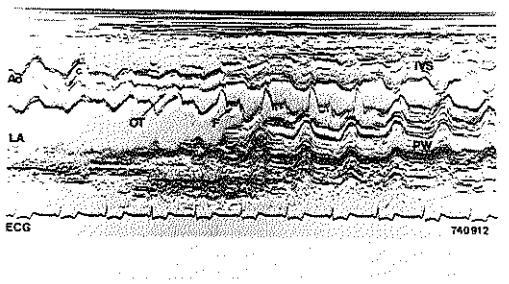



*Fig. 5 M-mode scan from the aorta (AO) to the apex of the left ventricle (LV) performed with a uniform transducer speed in patient of group II. Note the length of the narrowed LVOT (see arrow). For abbreviations see text.*

On their cross-sectional images, all 6 had narrowed LVOT over a considerable length which extended almost to the mid-cavity level of the LV (figure 4B).The severe concentric LVH present in two patients, resulted in a small cavity and systolic obliteration (figure 6).

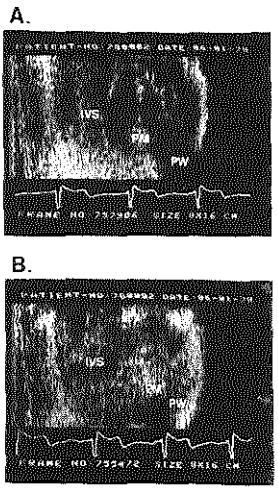



*Fig. 6A Ultrasonic transverse cross-sectional image at the level, just beneath the mitral leaflets at enddiastole.*
*The cavity of the left ventricle is well seen.*
*The IVS and LVPW are symmetrically hypertrophied.*

*Fig. 6B Same cross-section as described in figure 6A at endsystole.*
*Observe the systolic obliteration of the LV cavity.*
*PM= papillary muscle.*

## 8.5 Discussion

Two major types of subvalvular aortic stenosis are described: the type with fixed obstruction and the type with functional obstruction to left ventricular outflow. Distinct echocardiographic abnormalities are present in the latter form (Henry, Clark and Epstein, 1973).
The fixed form of subaortic stenosis can be divided into membranous type, either isolated or associated with LVOT narrowing, and the tunnel type of subaortic stenosis. Special attention has been given in recent studies to the different prognosis and clinical management for the different types of FSAS. A high incidence of sudden death has been observed and surgery should not be recommended to patients having the tunnel type of the disease because of a high risk and lack of symptomatic improvement (Maron et al, 1976; Katz, Buckley and Liberthson, 1977).

Contrary to this, surgical management of the membranous form is relatively safe and effective, although not always totally corrective (Kelly, Wulfsberg and Rowe, 1972). Therefore an accurate diagnosis of the type of FSAS seems important. The diagnosis of FSAS is often based on pressure recordings demonstrating a subvalvular gradient since angiocardiography may fail to demonstrate the membrane or to visualize the narrowed LVOT. This was the case in 6 patients of our group I and 2 patients of group II.

It should be recognized, however, that the quality of the angiocardiograms and especially the incidence of the X-ray beams are of major importance. It seems that this was not always carefully done in our series. It must be emphasized that a positive and uniquivocal visualization with ultrasound of an isolated subvalvular membrane is also exceptional since in only one patient of group Ia, the subaortic diaphragm was diagnosed. This has also been the experience of others. In a study of 11 patients, Lündstrom (1977) was not able to demonstrate the membrane in any of them. This is probably because the ultrasound beam is not easily aimed in a direction to hit this structure perpendicularly. With the exception of this uncommon type of the disease our findings do suggest that a narrow LVOT can reliably be diagnosed from echo. Therefore, echocardiography may play a major role for the diagnosis and differentiation between the different types of the disease and should be performed in all patients with LV outflow disease, before hemodynamic and angiographic analysis is considered. The combination of a narrow LVOT, early closure of the aortic cusps, the presence of aortic insufficiency and concentric ventricular hypertrophy with small cavity is suggestive if not diagnostic for the membranous form associated with narrow LVOT (see figure 2).

The tunnel form of FSAS can also be missed on the cine-angiocardiogram (pts.no. 14 and 19) but was always detected by echocardiographic examination, and is best appreciated from cross-sectional images. This is because the LVOT can be thought of as a flattened space in these cases. The echocardiographic beam most likely passes through the small dimension of the tunnel, whereas the X-ray beams in the antero-posterior projection are perpendicular to the tunnel, resulting in visualization of the large dimension of the tunnel on the angiogram. (Roelandt and van Dorp, 1977)

Early systolic closure and fluttering of one of the Ao valve cusps, earlier described as characteristic for FSAS (Davis et al, 1974) has not been found to be sensitive for detecting FSAS in our series. This finding is now recognized to be a nonspecific echographic abnormality (Weyman et al, 1977).

There was a striking descrepancy between echographic abnormalities of the mitral valve findings suggesting aortic insufficiency on echo and the angiocardiographic findings.

Only 6 patients were diagnosed from echo while 15 of the 19 patients had minor degrees of aortic incompetence on their cineangiocardiograms. This discrepancy could be explained by differences in direction of the regurgitant jet. ASH and an abnormal systolic anterior motion of the anterior mitral leaflet, features typically associated with IHSS, also occur in FSAS. This is important when surgery is considered, and in addition to excision of the fixed obstruction, a septal myotomy - myectomy should be performed. Otherwise, the patient may succumb in the immediate postoperative period.

The coexistence of ASH, SAM and FSAS suggest an interrelationship between FSAS and more diffuse functional types of LV outflow obstruction.

In fact, the history and echocardiographic study of family members of 2 patients (pat. 8 and pat. 17), showed first degree relatives with typical features of IHSS, confirmed at cardiac catheterization. A relationship between the membranous form of FSAS and tunnel subaortic stenosis has also been suggested (Kelly, Wulfsberg and Rowe, 1972). This is further substantiated by the observation in one of our patients (pat. nr. 14) who developed the typical form of tunnel subaortic stenosis after excision of a subaortic collar 10 years ago. Some authors believe in an age related incidence of this disease (Katz, Buckley and Liberthson, 1977). Many patients die in their adolescence as a result of sudden death or intractable heart failure. However, four of our patients were older than 50 years, an age rarely encountered for this disease in litterature.

In conclusion, it appears that echocardiography is a useful noninvasive means in the diagnosis of FSAS, except for the form where an isolated membrane in a LVOT of normal size exists. The echodiagnosis of FSAS is not always specific and may involve several findings to be searched for on M-mode recordings and cross-sectional images. The method certainly allows a better preoperative evaluation and hence surgical management. Echocardiography will also enlarge our knowledge of the natural history of FSAS.

Table I — Clinical features of 19 cases with FSAS

| Case No. | Age(yr) sex | Cath.findings+Angio | Surgical findings | Assoc. lesions |
|---|---|---|---|---|
| Group Ia(membr.) | | | | |
| 1 | 17 M | LV-Ao:115 mmHG; AI:++ | membrane | |
| 2 | 19 M | LV-Ao:106 " ; AI:++ | " | |
| 3 | 11 M | LV-Ao: 90 " ; AI:++ | " | bicuspid Ao |
| Group Ib | | | | |
| 4 | 57 F | LV-Ao:100 " ; AI:- | ----- | ----- |
| 5 | 58 F | LV-Ao: 41 " ; AI:++ | ----- | ----- |
| 6 | 38 F | LV-Ao: 80 " ; AI:- | thickened septum | small membrane |
| 7 | 20 M | LV-Ao: 23 " ; AI:+ | ----- | ----- |
| 8 | 20 M | LV-Ao: 80 " ; AI:+ | ----- | ----- |
| 9 | 20 M | LV-Ao: 60 " ; AI:+ | membrane | ----- |
| 10 | 50 F | LV-Ao: 60 " ; AI:+ | membrane | ----- |
| 11 | 14 F | LV-Ao:105 " ; AI:++ | membrane | ----- |
| 12 | 20 F | LV-Ao:110 " ; AI:++ | membrane | LVH |
| 13 | 18 M | LV-Ao: 90 " ; AI:+++ | membrane | thick IVS + thick Ao valve |
| Group II | | | | |
| 14 | 19 M | LV-Ao: 60 " ; AI:+ | membrane LVOT? | |
| 15 | 60 F | LV-Ao: 80 " ; AI:+ | tunnel SAS | |
| 16 | 20 F | LV-Ao:100 " ; | ----- | |
| 17 | 42 F | LV-Ao: 60 " ; AI:- | tunnel | thick septum |
| 18 | 20 F | LV-Ao: 80 " ; AI:++ | tunnel+thick sept. | |
| 19 | 30 F | LV-Ao:130 " ; AI:++ | abn. mitr. valve | |

Table II

Echocardiographic findings in 19 patients with FSAS

| Group | Ia | Ib | II |
|---|---|---|---|
| No of pts. | 3 | 10 | 6 |
| Narrow LVOT M-mode | - | 10 | 6 |
| 2D | - | "ridge"like | long segment |
| Thin "extra" echo | 1 | - | - |
| Early closure Ao cusps | 2 | 5 | 2 |
| Flutter Ao cusps | - | 4 | 3 |
| AI | - | 5 | 1 |
| Concentric LVH | - | 8 | 2 |
| ASH | - | 2 | 2 |
| SAM | - | 1 | 1 |
| Apical obliteration | - | 5 | 2 |

Table III LVOT width, septal and posterior wall thickness in 19 cases with FSAS

| Case No. | LVOT(mm) | IVS(mm) | LVPW(mm) | Ratio IVS/LVPW |
|---|---|---|---|---|
| 1 | 20 | 13 | 13 | 1.0 |
| 2 | 21 | 12 | 12 | 1.0 |
| 3 | 20 | 13 | 13 | 1.0 |
| 4 | 17 | 18 | 12 | 1.54 |
| 5 | 9 | 18 | 18 | 1.0 |
| 6 | 10 | 20 | 10 | 2.0 |
| 7 | 18 | 18 | 18 | 1.0 |
| 8 | 4 | 16 | 16 | 1.0 |
| 9 | 10 | 15 | 15 | 1.0 |
| 10 | 17 | 15 | 15 | 1.0 |
| 11 | 11 | 16 | 16 | 1.0 |
| 12 | 10 | 18 | 18 | 1.0 |
| 13 | 11 | 15 | 15 | 1.0 |
| 14 | 10 | 18 | 18 | 1.0 |
| 15 | 8 | 18 | 18 | 1.0 |
| 16 | 10 | 14 | 14 | 1.0 |
| 17 | 12 | 22 | 13 | 1.6 |
| 18 | 8 | 20 | 15 | 1.3 |
| 19 | 10 | 16 | 16 | 1.0 |

LVOT= width in mm of left ventricular outflow tract at endsystole
IVS = interventricular septal thickness (mm) at enddiastole
LVPW= left ventricular posterior wall thickness (mm) at end
mm = millimeters

## 8.6 References


1. Davis R.H., Feigenbaum H., Chang S., Konecke, L.L. and Dillon, J.C. (1974).
   Echocardiographic manifestations of discrete subaortic stenosis.
   The American Journal of Cardiology, 33, 277-280.
2. Henry W.L., Clark C.E. and Epstein S.E. (1973).
   Asymmetric septal hypertrophy: echocardiographic identification of the pathognomonic abnormality of IHSS.
   Circulation, 48, 1075-1084.
3. Katz N.M., Buckley M.J. and Liberthson R.R. (1977).
   Discrete membranous subaortic stenosis.
   Report of 31 patients, review of litterature, and delineation of management.
   Circulation, 56, 1034-1038.
4. Kelly D.T., Wulfsberg E. and Rowe R.D. (1972).
   Discrete subaortic stenosis.
   Circulation, 46, 309-322.
5. Lundström N.R. (1977).
   Echocardiography in the diagnosis of subaortic stenosis.
   In: Ultrasound echocardiography, Symposium, Lund, 1977.
6. Maron B.J., Redwood D.R., Roberts W.C., Henry W.L., Morrow A.G. and Epstein S.E. (1976).
   Tunnel subaortic stenosis. Left ventricular outflow tract obstruction produced by fibromuscular tubular narrowing.
   Circulation, 54, 404-416.
7. Popp R.L., Silverman J.F., French J.W. Stinson E.B. and Harrison D.C. (1974).
   Echocardiographic findings in discrete subvalvular aortic stenosis.
   Circulation, 49, 226-231.

8. Roelandt J. (1977): Practical Echocardiology. Research Studies Press, Forest Grove, Ore, USA.
9. Roelandt J. and van Dorp W.G. (1977). Long-segment (tunnel) subaortic stenosis. Chest, 72, 222-224.
10. Weyman A.E., Feigenbaum H., Hurnitz R.A., Girod D.A., Dillon J.C. and Chary S. (1976). Cross-sectional echocardiography in evaluation of patients with discrete subaortic stenosis. The American Journal of Cardiology, 37, 358-365.
11. Winsberg F., Gabor G.E. and Hernberg J.G. (1970). Fluttering of the mitral valve in aortic insufficiency. Circulation, 41, 225-236.

# CHAPTER 9

# CRITIQUE OF THE STUDY DESIGN, ITS TECHNIQUES AND RESULTS WITH SOME PERSPECTIVES FOR THE FUTURE

## 9.1 Introduction

In today's practice of cardiology, the echocardiographic examination has become an essential component. Many decisions concerning clinical management and therapy are influenced by it. It is clear therefore that the echocardiographic laboratory is obliged to maintain a high standard of quality in order to serve the cardiologist with assurance and reliability. This in turn requires a critical look at the limitations which affect this technique. These limitations are due to restrictions in the physical properties of ultrasound itself, in the examination technique and in the daily level of performence in the echocardiographic laboratory, all of which simultaneously or separately may have influenced the reliability of the data described in this study.

## 9.2 Limitations related to physical properties of ultrasound

Limitations due to physical properties of ultrasound are influenced by the angular dependence of reflections and of interface characteristics to restricted axial resolution, to beam divergence and to the wide range of amplitude of returning echosignals. Since ultrasound waves are reflected at boundaries between media of different acoustical impedance, optimal echoes will be only received from those boundaries which are perpendicular to the sound beam. However angles of incidence of the ultrasonic beam will vary greatly in the heart so that large variations in amplitude of reflecting ultrasound must result.
As a consequence continuous adjustment is necessary in the gain settings to achieve an echocardiographic examination which is optimal in clarity. This adjustment can be done in part automatically[1] , but does require some human "override". This latter factor, when erroneously or overzealously applied, may result in diagnostic errors.
Also the nature of the reflecting surface is of importance, since reflections from a rough surface will be of a diffuse or scattered character in contrast to the reflections of a smooth surface. Furthermore there is always some laterally reflected ultrasonic energy which will return to the transducer and may confuse the ultimate interpretation.
These experiences have led to the formulation of the concept of axial resolution, which is the minimal axial distance at which two separate structures can be recognized. Axial resolution is also dependent of the duration of the pulse of the ultrasound wave. It has been found in adult cardiology that 2.25 MHz is necessary since penetration up to 20 cm in the thorax is required; here the axial resolution is about 1.5 mm.

This resolution problem constitutes the limiting factor when wall thickness is measured by echo. Then, too, the ideal ultrasonic beam produced by the transducer should be "pencil" like over its entire distance. Unfortunately, this is not the case as the beam width remains the same only over a short distance in the near field end then diverges in the far field. This beam divergence is in turn dependent on the radius and the frequency of the transducer used. Since higher frequencies have less penetration of energy, a compromise has to be reached. Presently, most single transducers have a diameter of 1,5 cm and are focused at 7.5 or 10 cm. For the two-dimensional system a 3.5 MHz transducer is employed with 51 elements with capacities to vary the focus at different levels.
As indicated above the wide range of echo-signals has to be controlled by a time-gain compensation system. Since differences between the smallest and largest signals can vary up to 10.000 times, the need exists for earlier signals to be turned down and for the distant signals to be amplified. In the apparatus employed in this study the time-gain control system is divided into 5 segments. Here each segment can be controlled for the depth range of ultrasonic energy, so that at that level the best resolution is obtained by the examiner. In single beam studies aimed at the assesment of posterior cardiac structures, deep penetration should be combined with small beam divergence and high axial resolution. This compromise is best achieved by the use of a 2,25 MHz transducer of 1.5 cm radius focused at 7.5 or 10 cm. Obviously for near field studies a different compromise would apply.

## 9.3 Limitations to due to examination techniques

From the description of the details of the single beam examination technique given in Chapter 2 it is evident that every echocardiographic study should begin with several sectorscans from the base of the heart to the apex of the left ventricle. In this general orientation the examiner will most often surmise that ASH is present. Thereafter all different cardiac structures should be reached with the best combination of patient and transducer position, while simultaneously adjusting different time-gain control settings.
This can be tricky and requires patience, experience and dexterity as well as a thorough knowledge of normal anatomy as well as pathologic conditions. A normal strong sense of stereometric orientation is also needed, since the mental visualization of cardiac structures is essential in the proper recognition of echo-signals observed on the oscilloscope or recording paper. It is here that real time cardiac imaging have their greatest virtue. Measurements of septal and posterior wall thickness are made just below the level of the mitral leaflets and after the P-wave of the simultaneously registered ECG. This provides the end-diastolic dimensions. End-systolic dimensions are measured when maximal thickness of septum and posterior wall is seen. It is at this time that the cavity dimensions are smallest. Adherence to these factors is of utmost importance for the comparison between different patients. Furthermore the two-dimensional real time imaging apparatus is here again very helpful to relate various cardiac structures to one another so that the analysis of their function and motion pattern can be carried out with precision.

The results reported from this laboratory are not entirely comparable to the data of others since as yet no standardization has been arrived at for examination technique or of the origin and timing of different quantative measurements. This problem has generally been recognized and several echocardiographers in Europe and the U.S.A. are now trying to arrive at mutually acceptable standards. Even with these limitations most reported results show a very high degree of correspondence.

### 9.3.1 Daily level of performance

It is obvious that every laboratory should maintain a satisfactory level of performance. This can only be achieved by daily supervision of technicians and physicans, by regular inspection and analysis of all tracings produced on a given day and by regular teaching sessions. In order to test the average level of performance the records of 23 unselected patients referred over a 3-month period to the echocardiographic laboratory for various diagnoses were studied. Since this coincided with a research project on the use of echo-contrast 10 cc of glucose or saline was injected into a peripheral vein to study whether this improved the recognition of the right septal surface and thus the accuracy of measured septal thickness. Standard sector scans were made prior and after echocontrast injections. Duplicate measurements of septal thickness were made by two experienced echocardiographers. The results show no statistically significant difference between septal thickness measured with or without echocontrast, nor between the results from the two observers. It appears that while the use of echocontrast often clarifies the issue it does not increase the accuracy of septal measurements while it satisfying to note that interobserver variability proved negligible.

## 9.4 Critique of the study design and its results

The data described in this study are not only dependent of the physical qualities of ultrasound or on the examination technique and daily level of performance, but also on the nature of the origin of the signal obtained.
Is what one recognizes as the wall of the ventricle really that structure? Is the sensitivity of the method as high as expected? In order to solve this problem a series of experiments were carried out. Two sets of transducers were employed, one an experimental crystal sown on the epicardium and one a conventional clinical echo-transducer. In the open chested pig, recordings were made from both transducers at adjacent positions on the anterior wall of the left ventricle. The epicardial transducer was sutured tightly to the left ventricular muscle, whereas the other transducer was kept into hand contact with the heart just like it would be held on the chest wall in the clinical situation. (see figure 1)
To mark the endocardium two cc of saline was injected into the left ventricle. From the illustration it is evident that both signals are identical; therefore it can be concluded that the transducer delineates the endocardium and that muscle-thickness between epi- and endocardium can be measured accurately.
Epstein et al[2] have described the comparison of septal wall thickness from biventricular angiocardiograms with values found from echocardiograms and necropsy. Angiocardiographic values proved to be consistently lower than those obtained by echo or necropsy, where good agreement was found. It is unlikely from their data that methodologic differences will influence the results described in the present study in a significant manner. Furthermore the angiocardiographic methods are also fraught with difficulties[3].

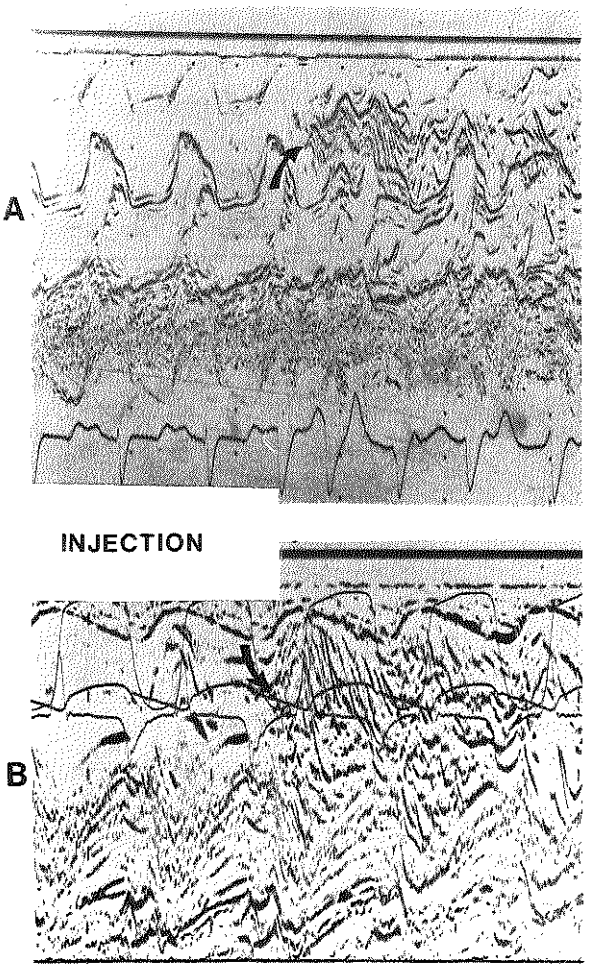



*Fig. 1:*
*A. M-mode echocardiogram made with a conventional transducer kept into direct contact to the anterior wall of the left ventricle.*
*Two cc of saline is injected into the LV to visualize the endocardium (see arrow). The epicardium is indicated by the thick line at the top of the figure, whereas the endocardium is followed by the contrast.*

*B. M-mode echocardiogram made with an epicardial transducer sutured to the anterior wall of the left ventricle.*
*Two cc of saline is injected into the LV to visualize the endocardium (see arrow). The epicardium is indicated by the thick line at the top of the picture, whereas the endocardium is followed by the contrast.*

Since catheterization studies in ASH patients from this study were only done when operation seemed indicated, only limited data are available.
A validation study could be done in only one patient at necropsy. Here again good agreement was seen.
In Chapter 4 the compensatory mechanisms of the left ventricle were discussed. These can exist of increased wall thickening or velocity of contraction or in augmented LV internal dimensions. To elucidate these mechanisms some further experimental studies were done. From an epicardial transducer, changes in myocardial wall thickness were continuously recorded in the M-mode. After control measurements, the coronary artery was temporarily occluded. Analysis of recordings with a computer assisted digitizing tablet of the time course of wall thickness changes, showed that the end-diastolic wall thickness decreases after a period of 30 sec. occlusion but increases again after timely reperfision.
Systolic wall thickness increases to an even greater extent during reperfusion. (figure 2 - 4)
From this it appeared too, that the muscle of the left ventricle can increase its maximal wall thickness without a change in its end-diastolic dimension. Whether this mechanism to the relates phenomena described in Chapter 4 remains to be proven, but it is evident that compensatory changes in wall thickness of experimental origin are reflected accurately in the echo signals.
Another critique may be directed at the specificity of the method. Echocardiographically it can be difficult to distinguish between genetic transmitted ASH and an abnormal septal to posterior wall ratio after, for instance, a true posterior wall infarction. The prevalence of abnormal septal to posterior wall ratios was given in Chapter 6. However no data could be given for these ratios in patients with coronary artery disease.

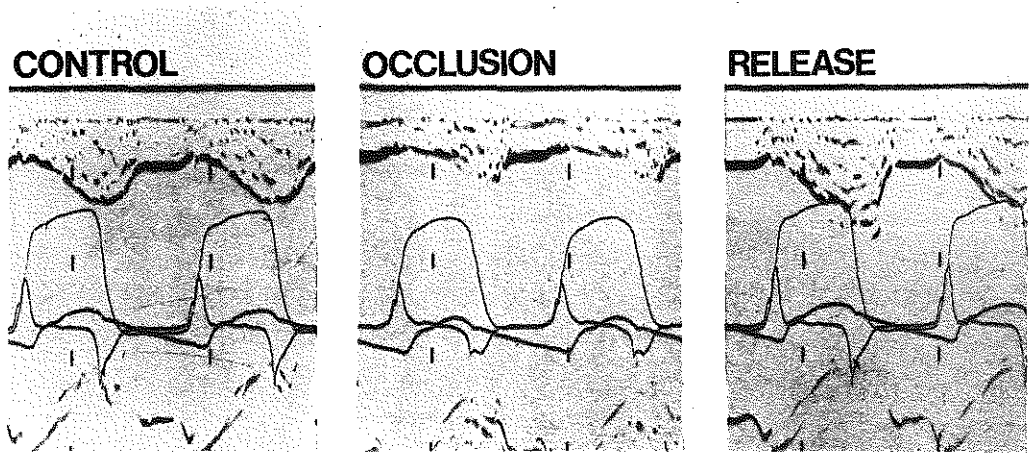



*Fig. 2 M-mode echocardiograms made with an epicardial transducer directly sutured to the anterior wall of the left ventricle during a control period, a period of 30 sec occlusion of the descending hanch of the left coronary artery and after 30 sec of reperfussion.*
*Also the LV pressure curve, Aortic pressure curve and LV dp/dt are registrated. One can observe that maximal wall thickness decreases during occlusion and is shifted towards diastole, whereas maximal wall thickness is increased and shifted backwards again towards systole during reperfussion.*

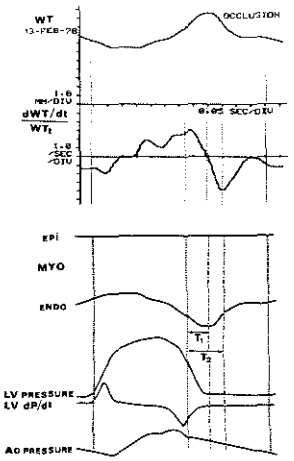



*Fig. 3 A diagrammatic representation of the wall thickness changes and its instant velocities during a period of occlusion shown at the top of the figure. The bottom part of the figure indicates the ultrasonic signal (epi- and endocardium) and the LV pressure, LV dp/dt and Ao pressure. End-systole is defined just before the closure of the Aortic valve, whereas the beginning of systole is indicated by the start of the upstroke of the dp/dt curve.*

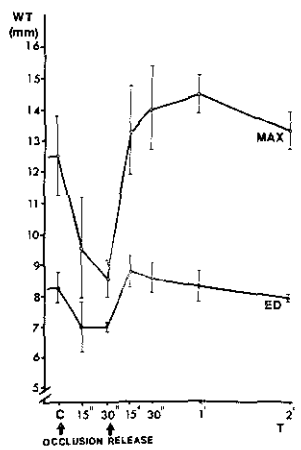



*Fig. 4 Results of maximal wall thickness (MAX) and its end-diastolic (ED) value during control, 30 sec occlusion and after 2 min release. It is shown that at 30 sec occlusion both ED and MAX decline by a value of about 10% for ED and 30% for MAX compared to control values, whereas maximal ED increases by 10% and MAX by 17% during release.*

This is perhaps an important omission, because coronary artery disease is such a frequent disease, that both diseases must occasionally coexist in the same individual. Here further studies seem indicated.
Another element not adequately described is the origin of the abnormal systolic anterior motion (SAM) of the anterior mitral leaflet, formerly considered, and described, to be a specific sign for ASH with obstruction. Since SAM has now been recognized in hypercontractile states, such as severe anemia, hyperthyreoidism, and after sudden decreases of afterload, for instance after aortic valve replacement for severe aortic stenosis, it is doubtful whether SAM is specific for ASH.
The possible interrelationship between the fixed and dynamic variety of subaortic stenosis was discussed extensively in Chapter 8. The tentative conclusion that there are some indications that ASH is developed during life, rather than of congenital origin, must be analyzed further before definite conclusions can be reached. The same applies to the description of the two patients, who developed LV dilatation and congestive heart failure. (Chapter 7).The cause of these observations remains unclear, since there is no evidence to explain the loss of contractile properties of LV muscle or the changes in compliance that may have led to the dilatation. Again, it is likely that longitudinal studies in the future will show more unexpected sequelae to the obstructed phases of ASH.
ASH is described as a marker that can be employed to detect so-called affected but asymptomatic family members with the disease. Since 1975 all individuals with ASH are followed in a systematic fashion. The results of this follow-upare partly described in Chapter 6.

The follow-up study itself can be faulted, because it is possible that not all early forms of ASH were recognized in the families studied. Microscopic changes must precede the echocardiographic "visible" changes.
Furthermore since most families are of small size and consisted less than five persons the prevalence of this genetic disorder must be low. Also some patients may have been missed whose echocardiograms were not of diagnostic quality. The data from Chapter 6 indicate further that clinical signs and the electrocardiogram in young persons with a family history of cardiomyopathy have a high sensitivity to detect the abnormalities.
(table I-II; Chapter 6)
In these instances the echocardiogram was of use only to confirm the clinically suspected diagnosis.
Finally from the history taking into possible causes of the disease no evidence has been found to suggest environmental factors. Therefore a genetic origin, remains a most attractive postulate.

## 9.5 Future perspectives

The purpose of this last section is to consider those aspects of Asymmetric Septal Hypertrophy in which inportant information is evolving, but about which conclusions remain elusive[4]. Current fashionable thinking is that the basic pathologic abnormality of the disease is a myofibrillar disalignment[2]. A recent study of congenital malformations in embryos and fetuses has indicated that marked myocardial disarray may occur in certain congenital lesions where abnormal systolic contraction such as in aortic or pulmonic atresia and tetralogy of Fallot, prevail[5]. Furthermore, these authors conclude that asymmetric septal hypertrophy and myocardial disarray may not be pathognomonic of ASH.

Yet further detailed studies on muscle fiber disorders by light- and electronmicroscopy must be related to other genetically transmitted diseases which involve voluntary muscle. Cardiac muscle studies should also be performed in patients with tunnel subaortic stenosis and hypertrophic cardiomyopathy in order to determine whether such abnormalities are indeed of acquired or of developmental nature. Perhaps experimental studies in tissue cultures may prove of help.

Others consider the evidence of a neural crest origin with catecholamine abnormality in this disease[4]. The association of systemic hypertension with pheochromocytoma and circumstential evidence that ventricular hypertrophy can be induced by excess catecholamines, leads to a hypothesis that any increase in afterload or preload may result in increased protein synthesis via the release of norepinephrine in the myocardium and via excess 3'-5'-cyclic-AMP. In the present study abnormal catecholamine secretion could not be detected but a direct relationship between systemic hypertension and ASH was not seen. Furthermore with the known prevalence of hypertension, ASH should have been much more often observed.

What other paths of investigation appear the most fruitful for the direct future?

First of all a systematic follow-up of patients and their relatives to determine the incidence of the disease and its pattern of progression. Since this study has demonstrated that echocardiography is a useful diagnostic tool, such a study should be extended. Next its value should continue to be compared to other methods, while the need for standardization of examination techniques and of the measurement of quantitative information is obvious.

Thirdly, serial examinations of patients by non-invasive means to determine the long-term effect of therapy essential.

Since myotomy and myectomy have been shown to give good results in patients with obstruction, it is recommended for selected patients, while in others long-term treatment with β-blockade or calciumantagonists may be in order. Such studies most likely will show unexpected results in the near future. In fact in the present study the findings in the affected families came as unexpected. Finally, one wonders whether further studies are required to determine the incidence of ASH in the general cardiac population. Surely, its prevalence in congenital malformations and in coronary artery disease needs to be investigated and criteria to classify this cardiomyopathy should be expanded. A case in point is systolic anterior motion (SAM) of the anterior mitral leaflet, previously described as pathognomonic and now considered as non-specific as this finding has now been reported in patients who have no other evidence of cardiomyopathy. Further combined ultrasonic and hemodynamic studies in patients with ASH with obstruction should elucidate the mechanism of SAM as a secondary phenomenon. Such a study may perhaps be done with ultrasonic contrast material injected into the left atrium to follow the blood stream across the mitral valve. Real time cardiac imaging seems essential to perform these studies.
Other features, such as abnormal thickening and increased velocity of contraction may well be studied in the experimental animal laboratory situation.

## 9.6 References


1. Vogel J.A., van Zwieten G. and Bom N.:
   Data processing of time - motion information in Echocardiography.
   In: Echocardiology, Ed. N. Bom, Martinus Nijhoff, The Hague, 1977.
2. Epstein S.E., Henry W.L., Clark C.E. et al:
   Asymmetric Septal Hypertrophy.
   An Int. Med. 81: 650, 1974.
3. Hugenholtz P.G., Kaplan E. and Hull E.:
   Determination of left ventricular wall thickness by angiocardiography.
   Am. Heart Journal 78: 513, 1969.
4. Goodwin J.: Prospects and predictions for the cardiomyopathies.
   Circulation 50: 210, 1974.
5. Buckley B.W., Westerfeldt M.L. and Hutckins G.M.:
   Asymmetric septal hypertrophy and myocardial fiber disarray. Features of normal, developing and malformed hearts.
   Circulation 56: 292, 1977.

# CHAPTER 10

## SUMMARY

In this thesis the results are presented of a study over several years, performed at the Thoraxcenter of the Erasmus University Rotterdam on the echocardiographic manifestations of Asymmetric Septal Hypertrophy (ASH) by single and multielement ultrasound systems.
After the goals of the study are introduced in Chapter 1 an extensive description of the echocardiographic examination both by single element and real time cardiac imaging is given in Chapter 2. In Chapter 3 an overview of the litterature on the subject is given with special emphasis on the characteristic echocardiographic signs of ASH. These remain first of all a disproportionate ventricular septal thickening compared to the free wall of the left ventricle with a septal to posterior wall ratio $\geq$ 1.3, second in obstuctive cases, an abnormal anterior motion of the anterior mitral leaflet during systole (SAM) and third a narrowed left ventricular outflow tract. Data given in Chapter 4 indicate that septal thickening during systole is decreased, whereas posterior wall dynamics are normal increased
The percent systolic thickening of the septum and posterior wall was determined, and defined as the increase of wall thickness during systole compared to the initial end-diastolic value, for 19 patients with ASH, 20 normal individuals, and 15 patients with coronary artery disease and a significant obstruction of the anterior

descending branch of the left coronary artery. Furthermore the posterior wall velocity, determined from systolic thickening during ejection time and left ventricular internal dimensions were calculated. The results show that patients with ASH have decreased systolic septal thickening (9±7 %) compared to controls (42±8 %), a smaller left ventricular size at end-diastole (41±10mm) versus normal (53±5mm) and increased posterior wall thickening (70±30 %) versus normal (52±9 %) and velocity (1.7±0.5 $sec^{-1}$; normal:1.2±0.2 $sec^{-1}$). These results are in contrast to the findings in patients with coronary artery disease who show also decreased systolic septal thickening (15±12 %), but normal or low values for posterior wall thickening (33±8 %) and an increased Left ventricular internal dimension (63±11 mm) at end-diastole.

Systolic function of the LV appears maintained through any or all of three different compensatory mechanisms: 1. increase of wall thickening of the posterior wall 2. increase of velocity of contraction of the posterior wall and 3. increase of LV internal dimension.

In Chapter 5 the familial prevalence of ASH is described. ASH was used as an anatomic marker of IHSS and studied in 73 first degree relatives of 14 proven cases. Twenty-seven of them showed echocardiographic signs of ASH. Other clinical signs were absent to detect ASH in 4 asymptomatic family members. The results suggest an autosomal dominant mode of transmission of ASH. These data were extended further in Chapter 6 and compared to the prevalence of ASH in the general cardiac population and normals. In 33 families of 33 so-called Index cases, 35 relatives with ASH were found out of 116 first degree relatives. Characteristic echocardiographic features in the Indexcases and 35 relatives with ASH were: a septal to posterior wall ratio $\geq$1.3 (by definition), decreased systolic septal thickening and abnormal LV shape as

observed from two-dimensional cardiac imaging. Prevalence of abnormal septal to posterior wall ratio $\geq$ 1.3 in the general cardiac population was 8 %, whereas family history for the presence of cardiomyopathy was negative in all of them. Chest X-ray, Electrocardiogram and physical examination when separately used were less sensitive to diagnose ASH. Evidence of genetic transmission by echocardiography was found in 19 of 33 families studied. Analysis of pedigree charts of these families showed transmission of ASH by an autosomal dominant trait. It is concluded that the diagnosis of ASH can be made by echocardiography when decreased systolic septal thickening and an abnormal LV shape coexist. In borderline cases an echocardiographic screening of the family members should be carried out.

In Chapter7 unexpected findings of LV dilatation in two patients with obstructive cardiomyopathy and severe congestive heart failure were described 4 years after myectomy. These findings were not reported earlier by clinical methods. LV dilatation proved reversible in both patients after conservative treatment for congestive heart failure.

In Chapter 8 the echocardiographic signs of fixed subaortic stenosis (FSAS) are given, a disease which is difficult to differentiate by clinical methods and even by hemodynamic and angiocardiographic techniques. Nineteen patients with FSAS of which 3 with discrete membranous FSAS, 10 with collar or ridge like FSAS and 6 with the tunnel form of the disease were studied. The results show that no single echocardiographic feature was diagnostic for FSAS, but that a narrow left ventricular outflow tract (less than 20 mm at end-systole), premature closure of the aortic valve cusps, the presence of aortic regurgitation and concentric LV hypertrophy with apical obliteration are all features that can separately or simultaneously be present in

FSAS. However echocardiography allows to distinguish between the short and long segment form of the disease, especially when real time cardiac images are analyzed. This differentiation is important for the hemodynamic evaluation and surgical therapy. It is concluded that diagnosis of FSAS can only be made when the described features for FSAS are searched for.
In Chapter 9 the limitations due to physical properties of ultrasound ,examination technique, daily level of performance and quality of the echocardiographic examiner, all of which can influence the interpretation of the data, are described. In the discussion it is shown that in this laboratory these limitations have not influenced the data significantly. Furthermore some evidence is provided of the reliability of the echocardiographic signal during an experimental study in the open chest pig, together with preliminary results of wall thickness changes during and after occlusion of a coronary artery. The last paragraph indicates what paths of investigations the author considers to be carried out in the future to solve some problems still existing in the understanding of this puzzling disease.
The final Chapter summarizes the data described in this thesis.

## HOOFDSTUK 10

## SAMENVATTING

In dit proefschrift worden de resultaten besproken van een echocardiografische studie uitgevoerd op het Thorax-centrum van de Erasmus Universiteit Rotterdam over asymmetrische septum hypertrofie (ASH) met behulp van enkele - en multi-element technieken, waarbij de studie zich over enkele jaren heeft uitgestrekt.
Na de beschrijving van het doel van de studie in Hoofdstuk 1, wordt de onderzoekstechniek m.b.v. enkel-element en twee-dimensionele echocardiografie uitvoerig beschreven in Hoofdstuk 2.
In Hoofdstuk 3 is een litteratuur-beschrijving, waarbij speciale aandacht wordt gevestigd op de typische echo-cardiografische tekenen van ASH.
Deze tekenen zijn:

1. een abnormale verdikking van het interventriculaire septum t.o.v. de vrije wand van de linker ventrikel met een verhouding tussen septum en achterwand $\geqslant 1.3$,
2. in gevallen met obstructie een abnormale beweging van de voorste mitralisslip naar voren toe gedurende systole (SAM) en
3. een nauw uitstroomgebied van de linker kamer.

De gegevens uit Hoofdstuk 4 tonen aan dat de systolische septum verdikking is afgenomen, terwijl de systolische verdikking van de achterwand normaal is of zelfs toegenomen.

De procentuele verdikking van septum en achterwand, gedefinieerd als de toename van de dimensie tijdens systole t.o.v. de initiele einddiastolische waarde, werd bepaald in 19 patienten met ASH, 20 normalen en 15 patienten met coronairsclerose en een significante obstructie van de arteria coronaria sinistra anterior.
Verder werden de contractie-snelheid (verdikking gedurende ejectie-tijd) en de linker ventrikel dimensies uitgerekend. De resultaten tonen aan dat patienten met ASH een afname hebben van de systolische septum verdikking (9 $\pm$ 7%; N: 42 $\pm$ 8%), een kleine linker ventrikel (LV) diameter (41 $\pm$ 10 mm; N: 53 $\pm$ 5 mm) in einddiastole en een toename van de verdikking van de achterwand (70 $\pm$ 30%; N: 52 $\pm$ 9%) en contractie-snelheid (1,7 $\pm$ 0.5 $sec.^{-1}$; N: 1.2 $\pm$ 0.2 $sec.^{-1}$). De resultaten zijn in tegenstelling met de bevindingen in patienten met coronaire hartziekte die ook een verminderde septum verdikking hebben (15 $\pm$ 12%), maar normale of zelfs lage waarden voor de achterwand verdikking (33 $\pm$ 8%) en een toename van de LV-dimensie (63 $\pm$ 11 mm) in einddiastole.
De systolische functie van de LV wordt gehandhaafd door elk of alledrie de verschillende compensatie mechanismen:

1. toename van de systolische verdikking van de achterwand,
2. toename van de contractie-snelheid van de achterwand en
3. toename van de LV binnen diameter.

In Hoofdstuk 5 wordt het familiair voorkomen van ASH beschreven. ASH werd gebruikt als een typisch anatomisch teken van IHSS en bestudeerd in 73 eerste graads familieleden van 14 bewezen gevallen met IHSS (idiopathic hypertrophic subaortic stenosis). Zeven en twintig toonden echocardiografische tekenen van ASH. Andere klinische tekenen waren afwezig om ASH te diagnostiseren in 4 asymptomatische familie-leden.

Deze resultaten werden verder uitgebreid in Hoofdstuk 6 en vergeleken met het voorkomen van ASH in de algemene populatie met hartziekten en normalen. In 33 families van 33 zogenaamde Index gevallen werden 35 familie-leden met ASH gevonden uit 116 eerste graads familie-leden. Karakteristieke echocardiografische bevindingen waren: een abnormale verhouding tussen septum en achterwand $\geq$ 1.3 (per definitie), verminderde systolische septum-verdikking en een abnormale vorm van de LV, aangetoond met twee-dimensionele apparatuur.
Voorkomen van een abnormale verhouding tussen septum en achterwand van $\geq$ 1.3 in de populatie met hartziekten was 8%, terwijl de familie-anamnese voor het voorkomen van hartspierziekten in allen niet afwijkend was.
De Thoraxfoto, het ECG en het fysisch onderzoek waren, afzonderlijk gebruikt, minder gevoelig om ASH te diagnostiseren.
Aanwijzingen voor erfelijke transmissie van ASH werd gevonden in 19 van de 33 families.
Analyse van de stambomen van deze families toonden een erfelijkheidspatroon dat overeenkwam met een autosomaal dominant overgebrachte eigenschap.
De conclusie luidt dat ASH echocardiografisch kan worden gediagnostiseerd als er ook een afname van de systolische septum verdikking en abnormale LV-vorm bestaan.
In grensgevallen wordt geadviseerd een echocardiografische screening van de familie te doen.
In Hoofdstuk 7 worden onverwachte bevindingen beschreven van LV-dilatatie in 2 patienten met obstructieve cardiomyopathie en decompensatio cordis, 4 jaar na een operatie voor deze ziekte (myectomie).
Deze bevindingen zijn tot nu toe niet beschreven gedurende het leven.
De LV-dilatatie bleek reversibel na conservatieve therapie.

In Hoofdstuk 8 staan de echocardiografische tekenen van gefixeerde subaorta stenose (FSAS), een afwijking die differentiaal diagnostisch moeilijk is te maken m.b.v. klinisch onderzoek en zelfs nog gemist kan worden met hemodynamisch en angiocardiografisch onderzoek. Negentien patienten met FSAS: 3 met de membraneuze (LVOT) vorm, 10 met een kraag in het LV uitstroomgebied en 6 met het tunneltype werden bestudeerd. De resultaten tonen aan dat er geen solitair echocardiografisch teken is dat typisch is voor ASH, maar dat een nauwe LVOT (minder dan 20 mm in eindsystole), premature sluiting van de aorta-klep, aorta-insufficiëntie en concentrische LV-hypertrofie met obliteratie van de apex allemaal tekenen zijn die afzonderlijk of tezamen aanwezig kunnen zijn in FSAS. Bovendien kan echocardiografie differentieren tussen de vorm van FSAS met een korte vernauwing van de LVOT en de tunnel vorm; vooral is dit duidelijk op het twee-dimensionele beeld.
Deze differentiatie is van belang voor de hemodynamische evaluatie en eventuele chirurgische therapie.
De conclusie is dat FSAS diagnose mogelijk is als naar alle tekenen voor de ziekte die beschreven werden gezocht wordt.
In Hoofdstuk 9 worden de beperkingen beschreven t.g.v. de fysische eigenschappen van ultrageluid, de dagelijkse kwaliteit van onderzoek en het vakmanschap van de echocardiografist; al deze factoren kunnen de interpretatie van de resultaten hebben beïnvloed.
Verder wordt er bewijs aangevoerd voor de betrouwbaarheid van het ultrageluidssignaal tijdens een studie in het dierenexperiment, tezamen met nog niet geplubiceerde resultaten over wanddikte-veranderingen tijdens coronair-occlusie in varkens.

De laatste paragraaf geeft de mening van de auteur aan over welk onderzoek in de toekomst nog moet gebeuren om enkele problemen die nog bestaan omtrent deze interessante ziekte, op te lossen.
Tenslotte volgt een laatste hoofdstuk waarin de resultaten van dit proefschrift worden samengevat.

ACKNOWLEDGEMENTS

It is hardly possible to acknowledge adequately the patients, their family-members and the referring physicians who so kindly collaborated in this study.
I am grateful to Professor P.G. Hugenholtz, who as Head of the Department of Cardiology and my promotor created such a stimulating atmosphere for young investigators to grow to valuable scientists. To Dr. J. Roelandt my deepest thanks for long hours, invaluable criticism and much assistance in preparing the study protocols and different manuscripts described in the chapters of this thesis. I must give particular recognition for continuous support during much of the time that the data were accumulated: Mister Willem Vletter, who is Chief laboratory technician of the clinical echocardiographic laboratory. Also my thanks to Els Leuftink, who later took part in the many examinations needed. Dr. Ir. N. Bom and his Department of Experimental Echocardiography my personal thanks for the opportunity to use directly all the new ultrasonic equipment developed by his engineers. Special appreciation goes to the Audiovisual Department who took such care with the preparation of the figures. To Wilma van Hassel a special recognition: it was upon her shoulders that the amount of secretarial help in preparing the completion of this manuscript fell. Wim van Dorp and Ton Bom were most useful students. I shall always be grate ful to my two coreferents: Prof. Dr. A.C. Arntzenius, Head of the Department of Cardiology at Leiden University and Celia Oakley M.D. F.R.C.P., consultant at the Royal Postgraduate Medical School at Hammersmith Hospital,London.
In many ways my wife Marion was my most important collaborator, whose confidence in the outcome of my efforts was my strongest motivation to continue.
The Dutch Heart Foundation financially supported the publication of this thesis.

Curriculum vitae

Folkert Jan ten Cate was born at 17th of August 1948 in Pontianak (Indonesia). In that country he spend his youth. In 1966 he graduated at the Stevinlyceum at The Hague (HBS-B). The same year he started his medical study at the new Medical Faculty in Rotterdam. During his medical study he was appointed as a student-assistent at the Department of Experimental Echocardiography of the Thoraxcenter, at which place Dr. Ir. N. Bom started the creation of the Multiscan two-dimensional echocardiographic apparatus. In 1972 he finished his medical study and joined the Erasmus University as a Cardiac Fellow and was involved in the clinical application of ultrasound. The thesis has been performed at the Department of Clinical Echocardiography under supervision of Dr. J. Roelandt and Prof P.G. Hugenholtz. His main interest is in clinical cardiology, echocardiography and in the search for clinically useful parameters to determine left ventricular function of the heart.

PUBLICATIONS OF THE AUTHOR


1. Roelandt J. Kloster F.,ten Cate F.J., et al: Multiscan echocardiography; description of the system and initial results in 100 patients.
   Hart Bulletin, 4:51, 1973.

2. Kloster F.E.,Roelandt J.,ten Cate F.J., et al. : Multiscan echocardiography; part II: Technique and initial clinical results.
   Circulation, 48:1066, 1973.

3. Roelandt J.,Kloster F.E., ten Cate F.J., et al. : Multiscan echocardiography.
   Cardiovascular application of ultrasound. North Holland publishing company. 1974. Chapter 32:402.

4. Bom N., Roelandt J., Kloster F.E., ten Cate F.J.,et al. Multi-element and its application to cardiology.
   Proceedings 2nd World Congress on Ultrasonics in Medicine. International Congress Series No 309. Rotterdam, 4-8 June p.297.

5. Roelandt j.,Kloster F.E.,ten Cate F.J.,van Dorp W.G., Honkoop J., Bom N, Hugenholtz P.G. : Multi dimensional echocardiography, an appraisal of its clinical usefulness.
   British Heart Journal 36:29, 1974.

6. ten Cate F.J., van Dorp W.G., Roelandt J.,Hugenholtz P, Asymmetrische septale hypertrofie; belang van de echocardiografie voor de diagnose en follow-up.
   Hart Bulletin 5:32, 1974.

7. Roelandt J., ten Cate F.J., van Dorp W.G., Bom N., Hugenholtz P.G. : Left ventricular function by multiple-element echocardiography.
Proceedings: Performance ventriculaire gauche chez l'homme. Ed. P.Besse Bordeaux. 1975, 227-237.

8. ten Cate F.J.,Kloster F.E., van Dorp W.G.,Meester G.T. and Roelandt J. : Dimensions and volumes of the left atrium and ventricle determined by single beam echo-cardiography.
British Heart Journal 36:737, 1974.

9. Roelandt J.,Hagemeijer F., ten Cate F.J., van Dorp W. Hugenholtz P.G. : Echocardiographie pour l'evaluation de la fonction ventriculaire gauche.
Compte-rendu du Symposion d'Echocardiographie (17-5-1974) Paris.

10. van Dorp W.G.,ten Cate F;J;,Vletter W.B.,Dohmen H. and Roelandt J. : Familial prevalence of asymmetric septal hypertrophy.
European Journal of Cardiology 4/3: 349, 1976.

11. Roelandt J., ten Cate F.J., van Dorp W.G.,Ligtvoet C.M., and Lancée C.T.: Ultrasonic two-dimensional analysis of the mitral valve.
In: The mitral valve, a pluridisciplinary approach. Ed. D.Kalmanson, Publ.Sciences Group, Acton,Mass. 1976

12. Roelandt J.,Vletter W.B.,Leuftink E.W., van Dorp W.G., ten Cate F.J., and Nauta J. Ultrasonic demonstration of right ventricular myxoma.
Journal of Clinical Ultrasound 5:191,1977

13. ten Cate F.J., Hugenholtz P.G. and Roelandt J. : Ultrasound study of dynamic behaviour of left ventricle in genetic asymmetric septal hypertrophy. British Heart Journal 39: 627, 1977.

14. ten Cate F.J.,:Echocardiologic assessement in asymmetric septal hypertrophy (ASH). In: Echocardiology Ed. N.Bom,Martinus Nijhof,The Hague 1977.

15. ten Cate F.J., van Dorp W.G., Hugenholtz P.G. and Roelandt J. : Fixed subaortic stenosis. The value of echocardiology for its diagnosis and differentiation between the various types. British Heart Journal (submitted)

16. ten Cate F.J., Vletter W.B., vanden Brand M.,Roelandt, The plain chest film as an unreliable index to determine left ventricular size. Japanese Heart Journal 18: 878, 1977

17. ten Cate F.J.,Roelandt J.,: Progression to left ventricular dilatation in patients with hypertrophic obstructive cardiomyopathy. Accepted American Heart Journal 1978.