



Study on Causes and Investigative Findings in Cardiomyopathy Patients in A Tertiary Care Hospital in Eastern India

Dr. Subhashis Chakraborty,

RMO cum Clinical Tutor, M.D. (Medicine), D.M. (Cardiology), Department of Cardiology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal 700014.

Dr. Hema Malathi Rath,

Assistant Professor, M.D. (Medicine), D.M. (Cardiology), Department of Cardiology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal 700014.

Dr. Soumendu Biswas,

Assistant Professor, M.D. (Medicine), D.M. (Cardiology), Department of Medicine, Calcutta National Medical College, Kolkata, West Bengal.

Dr. Biva Bhakat,

Senior Resident, M.D. (Medicine), Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal 700014.

Dr. Prantik Bhattacharya,

Resident, M.D. (Medicine), Department of Cardiology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal 700014.

Dr. Debarshi Jana,

PhD (Cal), Biostatistics and Epidemiology (IBRI), Consultant Biostatistician and Epidemiologist, Young Scientist (Associate Professor), Department of Science & Technology, Government of India, IPGMER and SSKM Hospital, Kolkata, West Bengal 700020.

Corresponding Author

Dr. Soumendu Biswas,

Assistant Professor, M.D. (Medicine), D.M. (Cardiology), Department of Medicine, Calcutta National Medical College, Kolkata, West Bengal.

Address: Flat 3 B, Sakharitola Street, Kolkata - 14.

(Received: 27 October 2023

Revised: 22 November

Accepted: 26 December)

KEYWORDS

Imaging, implantable cardioverter-defibrillator, remodelling

ABSTRACT

Introduction: For a long time, confusion about terminology and definitions has kept the public and medical organisations from fully understanding the wide range of conditions known as cardiomyopathies. In an effort to bring more clarity to these complex illnesses, numerous classification systems have been devised to help with their characterization and to help establish connections or distinctions between them.

Aims: To evaluate 100 cases of dilated cardiomyopathy and identify various etiological factors, the clinical profile of patients with dilated cardiomyopathy and to study the electrocardiographic and echocardiographic profile of these patients

Materials and methods: It was a Cross sectional study this study was conducted from May 2022 to December 2023 at Nil Ratan Sircar Medical College and Hospital

Result: Our study indicated that ischemic dilated cardiomyopathy, which accounts for 47% of all cardiomyopathies, is followed by alcoholic cardiomyopathy at 15% and diabetic cardiomyopathy at 11%. Twelve percent of patients had idiopathic DCM, and nine percent had peripartum cardiomyopathy. Three cases of valvular cardiomyopathy (mitral regurgitation and aortic regurgitation), two cases of HIV cardiomyopathy, and one case of post viral myocarditis made up the six cases (or 6% of the total) representing the miscellaneous category.

Conclusion: Sinus tachycardia, atrial fibrillation, and left bundle branch block are the most prevalent abnormalities found in electrocardiograms. Electrocardiogram (ECHO) results showed generalised



hypokinesia and reduced EF. Mitral regurgitation and pericardial effusion were conditions experienced by a significant number of persons. Patients with NYHA class 1V were more common.

INTRODUCTION

Cardiomyopathies are a diverse and significant class of disorders, but there has long been a lack of consensus on terminology and classifications, which has hindered public and medical understanding of these conditions. There have been numerous classification schemes, and they all serve to clarify these complicated disorders by identifying them and showing connections or differences between them.

Adults are expected to have a prevalence of 1 to 1.5% for heart failure. The median survival time for women is 3.2 years and for men it is 1.7 years, indicating that mortality and morbidity rates are still significant. Up to 25% of all cases of congestive heart failure are caused by dilated cardiomyopathy. Heart failure (CHF) due to cardiomyopathy seems to be on the rise. Approximately 5 to 8 out of every 100,000 individuals are impacted by DCM annually. Men are three times more likely to have DCM than women. Black people also have a higher rate of occurrence ¹.

There are a lot of poorly-designed categories in the literature, and none of the solutions offered are perfect. The wide variety of symptoms seen by this umbrella illness category is the root of the problem. A relatively short document published under the auspices of the World Health Organisation reflected a previous major classification of cardiomyopathies (1995). (WHO) ².

The World Health Organization's categorization system is now essentially useless due to the discovery of new diseases and significant advances in cardiovascular diagnostics and aetiology knowledge throughout the past decade. Indeed, cardiac molecular genetics has advanced at a breakneck pace in recent years. Ion-channelopathies are a new class of illnesses characterised by abnormalities in the channels that carry sodium, potassium, calcium, and other ions. These abnormalities can lead to ventricular tachyarrhythmias, which can be fatal if left untreated.

The American Heart Association has now released a new taxonomy of cardiomyopathies that is largely based on recent advances in the understanding of myocardial diseases. The new classification system makes this area of research easier to understand and fosters better collaboration between the scientific and clinical

communities to evaluate the treatment, prognosis, and diagnosis of these complex diseases.

We currently know very little about the natural history of DCM. This is because there is a great deal of variety in patient presentations and this diagnosis clearly covers a broad range of causes. Potential symptoms of left ventricular dysfunction include mild, moderate, or severe congestive heart failure, while some patients may have no symptoms at all. Death rates are estimated to range from 10% to 50% every year, according to different research. For a long time, people have thought that symptomatic heart failure invariably gets worse. But there are a number of pieces of evidence that suggest we should reevaluate this paradigm and that physiological factors may impact the long-term effects, for better or worse.

There may be substantially more variation in DCM prognosis than was previously believed. It is possible to utilise a number of clinical presentation characteristics to forecast a patient's prognosis. ³. Also, the natural history is heavily impacted by the underlying aetiology of cardiomyopathy, thus it's important to find out why. The prognosis is not good for certain cardiomyopathies, such as amyloidosis and HIV-related illnesses, however it is good for others.

The development of molecular genetics and the identification of underlying causes have led to a shift in the discussion of dilated cardiomyopathy from an exclusionary to a diagnostic framework. In Western countries, DCM is the leading cause of heart transplantation.^{4,5}

MATERIALS AND METHODS

Place Of Study : NRS medical college and Hospital

Study Design : Crosssectional study

Ethical Committee Clearance : Obtained **Period of Study**: May 2022 to Dec 2023

SELECTION CRITERIA

Inclusion Criteria

Clinical criteria:

Patients with symptoms and signs of heart failure.



ECHO criteria:

Left ventricular ejection fraction < 45% Global hypokinesia of LV
Dilatation of all the chambers of heart

Left ventricular end diastolic dimension > 3 cm / body surfacearea.

Exclusion criteria

1. Pericardial disease
2. Cor pulmonale with CHF.
3. Hypertrophic cardiomyopathy
4. Restrictive cardiomyopathy
5. Congenital heart disease

RESULTS

Table Distribution with all parameters

	Age groups	Number of case	Percentage
Gender	Male	57	57
	Female	43	43
Alcohol duration	< 10 Yrs	21	21
	10-20 Yrs	9	9
	>20 Yrs	6	6
Symptoms	Dyspnea	100	100
	Palpitation	60	60
	PND	60	60
	Orthopnea	53	53
	Chest pain	35	35
	Pedal edema	70	70
	Cough	60	60
	Abdominal pain	33	33
	Easy fatigability	83	83
	Syncope	17	17
	Asymptomatic	0	0
	Misc	23	23
Signs	Basal crackles	93	93
	Raised JVP	73	73
	Hepatomegaly	47	47
	Pedal edema	77	77
	LVS3	47	47
	RVS3	20	20
	PSM(MR)	47	47
	PSM(TR)	10	10
	SBP<100 mmHg	31	31
	Focal neurological	4	4



	deficit		
Pulse	Tachycardia	45	45
	Bradycardia	6	6
	AF	14	14
	Ectopic beats	23	23
	Pulses alternans	3	3
QRS Axis	Normal	74	74
	Left axis deviation	17	17
	Right axis deviation	9	9
Arrhythmias	Sinus tachycardia	45	45
	Atrial ectopics	11	11
	AF	14	14
	SVT	7	7
	Ventricular ectopics	46	46
	VT	4	4
	CHB	3	3
	LBBB	42	42
	RBBB	13	13
ST-T Changes		29	29
Atrial enlargement	LAE	16	16
	RAE	6	6
Ventricular hypertrophy	LVH	22	22
	RVH	9	9
	BOTH	6	6
EF	40-45%	17	17
	30-39%	37	37
	20-29%	40	40
	<20%	6	6
LVEDD	4.5-4.9cm	13	13
	5.0-5.9cm	33	33
	>6cm	54	54
	3.5-4cm	20	20
	4-4.9cm	33	33
	>5cm	47	47
MR		68	68



TR		8	8
AR		4	4
Pericardial effusion		9	9
Heart failure	LVF	19	19
	RVF	4	4
	Biventricular	77	77
Cause	Ischemic	47	47
	Alcoholic	15	15
	Idiopathic	12	12
	Diabetic	11	11
	Peripartum	9	9
	Miscellaneous	6	6

Table Distribution of mean parameter with group

Parameter	Group			P value
	All Cases	IschemicDCM	Non IschemicDCM	
Mean EF	31.26 ±7.59	31.10±8.44	31.40±6.83	0.85
Mean LVEDD	6.044±0.75	6.07±0.79	6.02±0.71	0.72

Of the men in our study, 36 had a history of alcoholism. Fifteen of them drank more than 100 grammes of alcohol daily and had a history of alcohol abuse dating back more than a decade. The other twenty-one used to drink alcohol less than twice a week, for less than ten years, and less than forty grammes a day.

SYMPTOMATOLOGY

In this study, exertional dyspnea was a symptom that all patients experienced. The second most prevalent symptom was pedal edoema, which was experienced by 70% of patients, and easy fatigability by 83% of participants. Sixty percent of patients had a history of intermittent nighttime dyspnea, coughing, and palpitations; next on the list were orthopnea (53%), chest

discomfort (35%), abdominal pain (33%), and syncope (17%). The symptoms are illustrated in the table.

PHYSICAL FINDINGS

Nearly all of the individuals (93%) showed signs of basal crackles. Among the subjects surveyed, 77% showed signs of pedal edoema. Hepatomegaly, an apical pansystolic murmur, and LVS3 were all observed in 47% of patients, whereas 73.3% had elevated JVP. Thirteen percent of our patients had RVS3, and ten percent had a pansystolic murmur in the tricuspid area (TR). Stroke occurred in four patients, and 31% of those patients had systolic blood pressure below 100 mmHg.



PERIPHERAL PULSE

Atrial fibrillation, bradycardia, tachycardia, ectopic beats, and pulseus alternans were among the abnormalities of peripheral pulse. Atrial fibrillation was detected in 14% of patients, tachycardia in 57%, and ectopic beats in 23%. Six percent of patients had bradycardia, while three percent had pulsus alternans.

RADIOLOGICAL FEATURES

Chest X-rays revealed cardiomegaly in nearly all patients. In 12% of individuals, the cardio thoracic ratio was greater than 0.7; in 46%, it was moderate, falling between 0.6 and 0.7; and in 42%, the cardiomegaly was mild, falling between 0.5 and 0.6. While 27% of patients showed signs of pleural effusion, 51% of participants showed signs of pulmonary plethora.

ELECTROCARDIOGRAM

Abnormalities of rhythm, size of the chambers, axis, and rate are all part of the electrocardiogram profile. Ventricular ectopics were the most prevalent anomaly, detected in 46% of individuals. A third of the people surveyed experienced sinus tachycardia. In 42% of cases, there was a left bundle branch block. Only 13% of patients had a right bundle branch block. In 29% of cases, nonspecific ST-T alterations were observed, while in 14% of cases, AF was evident. Half of the patients had left ventricular hypertrophy and one-fifth had left atrial enlargement. Only 3% of patients had complete heart block. The majority of patients had nearly normal axis. Fifteen percent had a left axis deviation and six percent a right axis variation.

ECHOCARDIOGRAPHY

Research showed that the average left ventricular ejection fraction was 30.87 percent. Less than 20% of patients had a left ventricular ejection fraction. Forty percent fell within the 20-29% range, 37% within the 30-39% range, and 17% between the 40-45% range. The majority of individuals (54%), with an average LVEDD of 6.04 ± 0.74 cm, had an LV end diastolic diameter greater than 6 cm. With 47% of patients having an end systolic diameter more than 5 cm, the average left ventricular end-systolic diameter (LVESD) was 4.92 ± 0.62 cm. Almost every patient exhibited global hypokinesia and dilated all four chambers. Pericardial effusion affected 9% of patients, mitral regurgitation affected 68%, and tricuspid regurgitation affected 8% of patients in our study.

NYHA CLASS

Majority of the patients in our study were in NYHA class III (33%) and class IV (47%) group.

HEART FAILURE

Biventricular failure was present in 77 % of patients and isolated LV failure was seen in 19 %. 4 % of patients in our study had RV failure.

CAUSES OF DILATED CARDIOMYOPATHY

Our study indicated that ischemic dilated cardiomyopathy, which accounts for 47% of all cardiomyopathies, is followed by alcoholic cardiomyopathy at 15% and diabetic cardiomyopathy at 11%. Twelve percent of patients had idiopathic DCM, and nine percent had peripartum cardiomyopathy. One instance of post viral myocarditis, two cases of HIV cardiomyopathy, and three cases of valvular cardiomyopathy (mitral regurgitation and aortic regurgitation) made up the six cases that made up the miscellaneous category, accounting for 6% of the total.

DISCUSSION

We observed that out of 100 patients, 57% were men and 53% were females. Males with advanced age (mean age 56.6 ± 12.5 years) exhibited the highest prevalence of dilated cardiomyopathy. Typically, DCM manifests in middle-aged women. Different age groups had different underlying causes. Males in that research had an average age of 52.9 ± 15.1 years and females 51.3 ± 17.7 years. The average age of men was 64.4 years and that of females was 55.5 years, according to another survey. A study conducted in 2004 discovered that the average age of presentation was 42.6 ± 9.1 years, with men making up 73.6% of the sample and females 26.4%.

Symptomatology

Our research revealed that biventricular failure was the most common symptom, making about 77% of cases. The majority of individuals with isolated left ventricular failure (19%) had ischemic DCM. Predominate right ventricular failure was observed in two patients with alcohol cardiomyopathy. While 17% of patients were in NYHA class II, 47% were in class IV, and 33% were in class III. For almost every patient, dyspnea was the most common symptom. In 60 cases, orthopnea was observed in 53% of patients, and in 53 cases, paroxysmal nocturnal dyspnea was noted in 60%.

Taliercio CP et al (1985) were found to have 11 cases of congestive heart failure as the cause of death, 3 cases



of complications following cardiac transplantation, and 1 case of sudden cardiac death. After an average of 65 months of follow-up (ranging from 26 to 149 months), 5 patients have shown no symptoms and 9 are still living. All survivors had access to serial measurements of left ventricular systolic function, which showed improvement in six patients and no change in three. Only patients who succumbed to their conditions exhibited severe mitral insufficiency.

Cough

Lung congestion was presumably the cause of coughing in 60% of our patients. Six people, or 6% of the total, in our study had respiratory infections such as bronchitis or pneumonia.

Easy fatigability

Easy fatigability was the second most common symptom mentioned by 83% of our participants. Patients with biventricular failure were more likely to have it, but those with isolated left ventricular failure were less likely to. The majority of cases showed a correlation between chronic heart failure and easy fatigability. There are a number of factors that contribute to fatigability, including anaemia and cardiac cachexia.

Pedal edema

Pedal edema affected three-quarters of our patients. In cases of idiopathic DCM and alcoholic cardiomyopathy, pedal edema was the most prevalent symptom. Anasarca was noted in one patient with idiopathic DCM, five patients with ischemic DCM, and eleven patients (or 11% of the total) with alcoholic DCM.

Rangabashyam SR et al ⁷(2021) discovered that all fifty-nine individuals undergoing the research had shortness of breath. After hepatomegaly, which was detected in 17 individuals (34.69% of the total), the majority of patients (59.18%) exhibited pedal edema.

Abdominal pain

In our study, 33% of participants had stomach discomfort. Hepatic congestion was blamed for abdominal discomfort. Gastritis is another probable cause of stomach discomfort in these people.

Palpitation

Sixty people (or 60%) in our study reported palpitations. A majority of those suffering from chronic heart failure

(57%) experienced sinus tachycardia. A number of medical conditions have been associated with palpitations, including atrial fibrillation, supraventricular tachycardia, and atrial/ventricular ectopic.

Chest pain

Among our participants, 35% reported frequent chest pain. Ischemic DCM developed in most of these people. Prolonged myocardial ischemia was found to be the cause of these patients' chest pain.

Syncope

17% of our patients had syncope. In most situations, syncope is caused by a decrease in cardiac output. Physical manifestations Pulse at the periphery Tachycardia was found in 45% of the individuals. Bradycardia was seen in six individuals as a result of total heart block. In 14% of individuals, atrial fibrillation was detected. Ectopic beats were found in 23% of the individuals in our investigation. Three patients had pulsus alternans.

Signs of left heart failure

In our investigation, 93% of the subjects showed signs of basal crackles. The most common cause of basal crackles was pulmonary edema or congestion caused by left ventricular failure.

During a cardiac test, 47% of our study participants had LVS3 identified. In nearly half of our patients (47%), a pan-systolic murmur was produced by mitral regurgitation. Twenty percent of patients had RVS3, and ten percent had PSM in the left parasternal region as a result of TR.

Signs of right heart failure

Raised JVP

Raised JVP was seen in 73 patients (i.e. 73 %) in our study secondary to RV failure.

Hepatomegaly

Hepatomegaly was present in 47 % of patients in our study secondary to congestive heart failure.

Pedal edema was seen in 77 % of our patient in our study.

Others

Brain embolisms killed four people who had ischemic dilated cardiomyopathy and atrial fibrillation.



Biventricular failure was present in most of the cases.

All of our patients had exertional dyspnea, the most common symptom in our study. Other symptoms included pedal edoema, coughing, palpitations, and stomach discomfort. Several other investigations have also shown a similar clinical profile.

Our study found that chest pain affected up to 35% of participants. In comparison to studies like S. Ahmad et al., where 29% of participants reported experiencing chest pain, this number is quite high. This might be because this study included people with ischemic cardiomyopathy, whereas the last one didn't.

Also, while previous studies have shown syncope in as few as 1.8% of patients (S. Ahmed et al., 2008), we found it in as many as 17% of our patients. Ischemic cardiomyopathy was included in our analysis, which could explain this high frequency. In ischemic cardiomyopathy, syncope is more common due to arrhythmias and severe left ventricular failure.

Radiological features

Almost every instance had an abnormal chest radiograph, revealing cardiomegaly of varied degrees with CT ratios ranging from 0.5 to 0.75. This was similar to the study done by Massumi et al,⁹ in that cardiomegaly was found in all cases with CT ratio between 0.51 to 0.80. 27 % of patients in our study had pleural effusion compared to 46% in the Massumi et al⁹ study and 10% in Ahmad et al study.

Pulmonary plethora was found in 51% as compared to 72% in Massumiet al study and 76.3% in the Ahmad et al study.

Electrocardiographic profile

That 74% of our subjects had normal QRS axes, with 17% showing left axis variation and 9% showing right axis deviation, is in line with all the prior studies. S. Ahmad et al. found sinus tachycardia in as many as 69% of patients, making it the most prevalent finding. A total of 45 participants in our study exhibited sinus tachycardia.

Other electrocardiogram features, including ventricular ectopics, left bundle branch block, atrial fibrillation, and atrial ectopics, were consistent throughout all studies. Nevertheless, compared to previous studies, our group had a higher prevalence of RBBB, complete heart block, and SVT. Ischemic cardiomyopathy was a part of our investigation, which could explain this.

Our study identified LVH in 22% of participants, which is lower than previous studies that found it around 30% to 40%. This study confirms previous studies showing that nonspecific ST-T changes were present in 29% of incidents.

Echocardiographic profile

Left ventricular EF averaged 30.34 percent in our study group. All prior studies on dilated cardiomyopathy have reached the same conclusion. The mean value of LVEDD was 5.78 cm. On average, the LVESD was 4.62 cm.

Our investigation found mitral regurgitation in 68% of individuals, which is similar to other study groups. The incidence of mitral regurgitation was 68% higher than that of tricuspid regurgitation, which was just 8%. The majority of this was caused by the fact that more people with ischemia DCM and severe LV dysfunction than nonischemic DCM were involved.

Our study found that 9% of patients had pericardial effusion, and four patients developed left ventricular clots and cerebral embolisms as a result of atrial fibrillation.

Etiological profile

In our study, ischemic dilated cardiomyopathy was found in 47% of patients, while alcoholic cardiomyopathy was the second most common at 15%. Out of the three types of cardiomyopathy, 12% of patients had idiopathic cardiomyopathy, 9% had peripartum cardiomyopathy, and 11% had diabetic cardiomyopathy. One patient had postviral myocarditis, two had HIV cardiomyopathy, and three had valvular cardiomyopathy; these six patients made up the mixed group. The term "ischemic cardiomyopathy" is controversial, hence most studies on dilated cardiomyopathy did not include it.

Coronary angiography was performed on all individuals with ischemic cardiomyopathy in our study. A previous myocardial infarction was found in 29 out of the 47 people that were studied. In all 47 patients included in our study, the epicardial coronaries were considerably constricted, meaning they were more than 70% of lumen. Two individuals had single vessel illness, six had triple vessel disease, and twenty-one had double vascular disease. Echocardiograms showed reduced ejection fraction and widespread hypokinesia in every single subject.



Cirrhosis of the liver was present in three of the patients diagnosed with alcoholic cardiomyopathy. Bilirubin levels were somewhat higher than normal (1.5 mg%), according to liver function tests, although liver enzymes were within normal ranges. Previous studies on alcoholic cardiomyopathy have shown the same thing.

While 37% of patients experienced anaemia, the majority of those individuals had mild anaemia, defined as haemoglobin levels between 8.5 and 11%. Among alcoholics, alcohol plays a significant etiological role (p value 0.0001). The mean EF in our research was 31.27.5. We found a mean LVEDD of 6.040.74 in our analysis. The average LVESD that we found was 4.920.62. Both ischemia and non-ischemic DCM do not significantly alter EF or LVEDD (p = 0.85 and p = 0.72, respectively).

CONCLUSION

Our findings indicate that ischemic cardiomyopathy, alcoholic cardiomyopathy, and idiopathic cardiomyopathy are the leading causes of dilated cardiomyopathy. The majority of patients will get biventricular failure. Cardiomegaly was revealed on chest radiographs in most individuals. Sinus tachycardia, atrial fibrillation, and left bundle branch block are the most prevalent abnormalities encountered in electrocardiograms. Electrocardiogram (ECHO) results showed generalised hypokinesia and reduced EF. Mitral regurgitation and pericardial effusion were conditions experienced by a significant number of persons. As a whole, the patients' NYHA classes were 1V.

REFERENCES

1. Anderson KM, Kannel WB. Prevalence of congestive heart failure in Framingham Heart study subjects. *Circulation* 1994;13: S107-S112.
2. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation*. 2004;93:841.
3. Vijayraghavan G. API Text book of medicine. Disorders of myocardium. 8th ed Chap 1X.27: 572-577.
4. Kothari S, Aajesh A, Saxena A, Juneja R. Dilated cardiomyopathy in Indian children. *Indian Heart J* 2003; 55 : 147.
5. WHO / ISFC. Task force on cardiomyopathies. Report of the WHO / ISFC. Taskforce on the definition and classification of cardiomyopathies. *Br. Heart journal* 1980 ; 44 : 672-673.
6. Taliercio CP, Seward JB, Driscoll DJ, Fisher LD, Gersh BJ, Tajik AJ. Idiopathic dilated cardiomyopathy in the young: clinical profile and natural history. *Journal of the American College of Cardiology*. 1985 Nov 1;6(5):1126-31
7. Rangabashyam SR, Kirubhakaran K, Moogaambiga S, Pandi SA, Anoosh G, Amrutbhai PV, Parajiya L. Clinical Profile of Patients with Dilated Cardiomyopathy-A Prospective Observational Study. *International Archives of Integrated Medicine*. 2021 Nov 1;8(11).
8. Ahmad S, Rabbani M, Zaheer M, Shirazi N. Clinical ECG and Echocardiographic profile of patients with dilated cardiomyopathy. *Indian J Cardiol* 2005 ; 8 : 25-29
9. Massumi RA, Jorge CR. Primary myocardial disease. Report of 50 cases and review of the subject. *Circulation* 1965 ; 31 : 19-40