A CLINICAL STUDY OF IDIOPATHIC DILATED CARDIOMYOPATHY IN AN OMANI POPULATION

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By

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ABSTRACT

This is a clinical study of idiopathic dilated cardiomyopathy (IDC) in an Omani population. Clinical data in this condition has been lacking in Arabia. 1164 patients with heart failure referred to the only secondary care hospital in the Dhakliya region of Oman were evaluated. This region has an indigenous adult population of 225,000 over 12 years of age.

Over a three-year period, 1992 to 1994, 97 patients with idiopathic dilated cardiomyopathy were identified, with a median age of 50 years (range 15 to 69) giving an yearly prevalence of 14.4/100,000. There was a male predominance of 1.4/1. Parental consanguinity was high (30%) but among the 770 (87%) first-degree relatives screened, cases of IDC were found to be few (6.5%). Familial cases were younger at presentation and more often had consanguineous parents. Familial and sporadic forms did not differ in survival. There was no HLA-DR4 association and cardiac specific antibodies were not detected making an autoimmune pathophysiology unlikely in these patients. During a mean follow-up period of 6 years (1 to 8 years) survivals were 94% at 1 year, 76% at 5 years, and 68% at 8 years with a mean overall survival of 9.8 years. As a predictor of poor outcome, severe dyspnoea (NYHA classes III & IV) at presentation, ventricular tachycardia and severe mitral regurgitation were significant on univariate analysis but left ventricular ejection fraction was the only significant factor identified by multivariate analysis. Plasma noradrenaline levels were elevated but did not correlate with the severity of the disease. In children with short duration of illness, such a correlation however, was evident. Mild coronary artery disease was present in 6.3% of cases at angiography but had no correlation with mortality.

No aetiopathogenic mechanisms could be identified and alcohol consumption was not involved. 75% of the patients were from a low socio-economic background. This needs further evaluation. With the completion of this report further research is ongoing into the genetics and autoimmunity of IDC in the Omani population, with studies being extended to other regions of Oman to collect data at a national level.

STATEMENT

This project was initiated by the observation that heart failure due to IDC appeared to be more prevalent in Oman than in the UK, where I worked for 11 years. There was no clinical data available to support this observation. I discussed this with the late Prof. David de Bono, Head of Cardiology at the Glenfield General Hospital, University of Leicester, UK, who encouraged me to start this project. The collection of clinical data in this study has been personally supervised by me. The planning of investigations and liaison with the referral hospitals was a tedious task but with the support of colleagues it was successfully achieved. During the course of this project, I have become aware of many more aspects of this disease and other related clinical conditions in the Omani population. The data was fed into the SPSS "Files for statistical analysis". Multivariate analysis was performed to assess mortality variables. Statistical analysis was performed by Professor Anjali Saha of the Department of Epidemiology and Medical Statistics. I feel that the objectives which were initially set out have been achieved with the completion of this project. I am now looking forward to further research on some of the questions, which have remained unanswered or have arisen from this study.

ACKNOWLEDGMENTS

I am greatly indebted to the late Prof. David de Bono (University of Leicester, Division of Cardiology, Glenfield General Hospital, Leicester, U.K.) who was instrumental in his guidance and encouragement during the progress of this work. It would not be inappropriate to say that without his initial support this research project would never have taken off. Later, despite his ill health, he continued his support with patience, perseverance and enthusiasm. It is unfortunate that he is not with us to see the end result of this project. I deeply miss him for he was to be the mentor of some of the further research in this field, which we had planned together.

I wish to thank my colleagues in the Sultan Qaboos University Hospital, Dr. Mehar Ali and Dr. Poothirikovil Venugopalan who contributed to the clinical assessment of the patients inducted in the study and Dr. W. J. Johnston for critical review of the script.

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The department of Epidemiology and Medical Statistics gave full support in this work with Prof. Anjali Saha providing statistical help in analysing somewhat complex data. I wish to thank her for her active involvement in the study. Furthermore, Mr. Shabbir Ahmed Patel, the secretary of Medical Statistics worked tirelessly in compilation of this work.

Finally, I wish to extend my deep appreciation to Prof. N.J. Samani of Glenfield General Hospital and Prof. L.L. Ng, and Dr. I. Squire of Leicester Royal Infirmary, Leicester University, U.K. for guiding me on the final composure of this thesis.

ABBREVIATIONS

ACEI	=	angiotensin converting enzyme inhibitor
AF	=	atrial fibrillation
AIDA	=	anti-intercalated disk antibody
ANA	=	anti-nuclear antibody
ANP	=	atrial natriuretic peptide
AR	=	aortic regurgitation
ATA	=	atrial tachyarrhythmias
AV	=	atrio ventricular
BBB	=	bundle branch block
BNP	=	brain natriuretic peptide
BVH	=	biventricular hypertrophy
CAD	=	coronary artery disease
CAG	=	coronary angiography
CTR	=	cardiothoracic ratio
DCM	=	dilated cardiomyopathy
DVT	=	deep vein thrombosis
ECG	=	electrocardiogram/graphy
EDTA	=	ethylene diamine triacetate
FDC	=	familial dilated cardiomyopathy
G6PD	=	glucose 6 peroxidase dehydrogenase
HHIFL	=	human heart immunofluorescence
HLA	=	human leukocyte antigen
HSKIFL	=	human skeletal muscle immunofluorescence
IDC	=	idiopathic dilated cardiomyopathy
IFL	=	immuno-fluorescence
IHD	=	ischaemic heart disease
INR	=	international normalized ratio
IVCD	=	intraventricular conduction defect

LA	=	left atrium
LBBB	=	left bundle branch block
LV	=	left ventricle
LVD	=	left ventricular diastolic dimension
LVEF	=	left ventricular ejection fraction
LVH	=	left ventricular hypertrophy
MHC	=	major histocompatibility complex
MHR	=	maximal heart rate
MR	=	mitral regurgitation
MUGA	=	multiple gated isotope pool scan
NYHA	=	New York heart association
PPCM	=	peripartum cardiomyopathy
PR	=	pulmonary regurgitation
RHR	=	resting heart rate
RV	=	right ventricle
SD	=	standard deviation
SPSS	=	statistical package for social sciences
SQU	=	Sultan Qaboos University
SQUH	=	Sultan Qaboos University Hospital
TET	=	total exercise time
TOE	=	transoesophageal echocardiography
TR	=	tricuspid regurgitation
TTE	=	transthoracic echocardiography
VT	=	ventricular tachycardia
WHO	=	world health organisation
XLCM	=	x-linked cardiomyopathy

CHAPTER - 1

REVIEW OF LITERATURE OF DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is a chronic cardiac muscle disease leading to impairment of the contractile function of the ventricle(s). An aetiological factor is generally not known therefore strictly it should be called idiopathic dilated cardiomyopathy (IDC) but the term often in general use is simply "dilated cardiomyopathy" (DCM).
(For convenience the term IDC is used here, and while I believe the term is used accurately in respect of the data in this study, in some of the references the terms IDC and DCM may not be clearly distinguished).

IDC is essentially an exclusion diagnosis in patients with heart failure. In the 1970s a classification proposed by Goodwin [1] outlined its clinical features and helped in the diagnosis. The diagnosis of IDC is based on the demonstration of a dilated and poorly contracting left ventricle in the absence of a known aetiological factor for myocardial injury (WHO) [2]. An important criterion for diagnosis is a reduced left ventricular ejection fraction of <50%.

Main exclusions are:

1. Coronary artery disease.
2. Systemic hypertension.
3. Systemic or endocrine diseases known to cause left ventricular dysfunction.
4. Pregnancy.
5. Inflammatory myocarditis.
6. Excessive alcohol intake.
7. Pulmonary hypertension.
8. Congenital and valvular heart diseases.

EPIDEMIOLOGY

Despite many years of research, IDC continues to be a serious and challenging problem for physicians around the world. Its prevalence and incidence appears to vary in different parts of the world and depending upon the diagnostic criteria used, the reported annual incidence varies between 5-8 cases per 100,000 population. However, the true incidence is probably underestimated, since many asymptomatic patients remain unrecognised. Few true incidence studies of IDC are available since estimates are based on different diagnostic criteria including sometimes a referral bias and secular trends [3]. In the United States prevalence is estimated at around 36 cases per 100,000 population, the incidence being 8 new cases per 100,000 per year [4-6]. Similar figures are reported in other studies [7-14].

In China, in a population-based study, 275 new cases were reported between 1985 and 1989 among 2,098,175 residents [15] giving an incidence of 2.6/100,000. The incidence rate had increased from 1.7/100,000 in 1985 to 3.3/100,000 in 1989. Faez et al simply compared number of cases of IDC in Moscow and Dubai [10]. The ethnic distribution of the population was not defined. Although they did not report prevalence and incidence, this is the only study comparing IDC from two different geographical areas and therefore made interesting reading. It suggested that IDC in Dubai produced a greater degree of systolic dysfunction and arrhythmias, and that the peripartum cases were commoner, while alcohol and virus infection underlie IDC more frequently in Moscow.

The Finland Heart Failure Study [11] reported age adjusted incidence of heart failure at 4/1000 in men and 1.0/1000 in women in one year, but a breakdown of the aetiology was not reported. In the UK, a hospital based study in northwest London serving a population of 155,000 admitted 140 patients in heart failure but the diagnosis of DCM was proved in only one patient and in 36% patients the aetiology was unknown[12]. The study has several drawbacks. It was a short period study of six months which only considered acute hospital admissions and simply an evidence of fluid retention in the presence of heart failure was considered as inclusion criteria. The study contained patients both retrospectively and prospectively. Since only 58% of patients had echocardiography performed, the diagnostic workup in this study would be considered incomplete. In an another questionnaire based general practitioners study from two different regions of England overall point prevalence was 8.3/100,000 but there was a significant regional variation between East Anglia and Essex [13]. This survey lacks complete coverage of the regions, firstly because only 420/771 people replied to the questionnaire and secondly, the survey was not conducted by all practioners of the region but only by the members or the fellows of the Royal College of Practioners. Another survey attempting an assessment of incidence of IDC was undertaken in Sweden [9], which during an eight year period reported an incidence of only 3/100, 000, but this was not a population study and the patients were collected only from hospital attendance. A further inclusion of post-mortem cases during the same period however, increased the incidence to 5/100,000 patients per year.

A literature search of IDC in hot countries revealed one review from Saudi Arabia [16] reporting 55 cases in one year [1984-1985] with no other data analysed and an

editorial [17] on IDC in Africa. A further search revealed an abstract from an Italian study [18] showing an increasing annual incidence of IDC of 1.8/100,000 to 3.4/100,000 from 1970-79 to 1980-89.

In general the incidence of IDC among patients with heart failure is thought to be higher in less industrialised countries: {Uganda 19% [19] and Sri Lanka 26% [20]}. The studies however, do not report a detailed diagnostic work-up but simply included idiopathic cardiomegaly as inclusion criterion. In South Africa it constituted 14% of cardiac deaths at autopsy in blacks [21]. In the majority of these studies the condition was shown to be more prevalent in middle aged males [22] and from the United States there is evidence that the black community is at high risk [5, 14].

AETIOLOGY

Dilated cardiomyopathy (DCM) can be caused by a number of pathological processes, which affect cardiac muscle primarily or secondarily from a systemic illness. However, in a large number of patients no aetiological factor is demonstrated. Dilated cardiomyopathy due to a known cause is not the subject of this study.

It was long accepted that IDC might be the consequence of an episode of viral myocarditis in the past . This was supported by the finding of a similar syndrome in animals following some cases of viral myocarditis. But with the development of better diagnostic techniques it became clear that this is not always the case. Indeed the syndrome of IDC with dilated and depressed ventricles following viral myocarditis is an uncommon sequela as assessed pathologically [23]. The problem is that patients do not generally present early enough for the viral phase of myocarditis to be

identified by biopsy. However, evidence continues to accumulate on the relationship between viral myocarditis and dilated cardiomyopathy at experimental level and in man [24-26].

As the new information is emerging, although the pathogenesis remains uncertain, a better understanding is being established. It is more and more being thought that idiopathic dilated cardiomyopathy is a multifactorial disease with different factors operating singly or in combination in different cohorts. A proposed pathogenic mechanism presented by Mestroni et al [27] is given in figure 1. He suggested the following factors:

1. Chronic persistent viral infection of the myocardium with subsequent myocardial cell damage.
2. Autoimmune damage.
3. Genetic factors.

VIRAL INFECTION

Though the viral hypothesis continues to disappoint researchers the possibility of viral damage to myocardium as an initiating factor remains. Keeling and Tracy [28] recently reviewed the viral hypothesis in detail. In acute viral myocarditis Coxsackie B4 (CVB) has been isolated from the myocardium [29]. Such isolation is not demonstrated in IDC.

Several case studies [30-37] based on long term clinical follow up and in some cases on pathological grounds have supported the viral hypothesis. Clinical criteria have

their limitations and histopathology of the myocardium is unable to resolve the controversy [38-40].

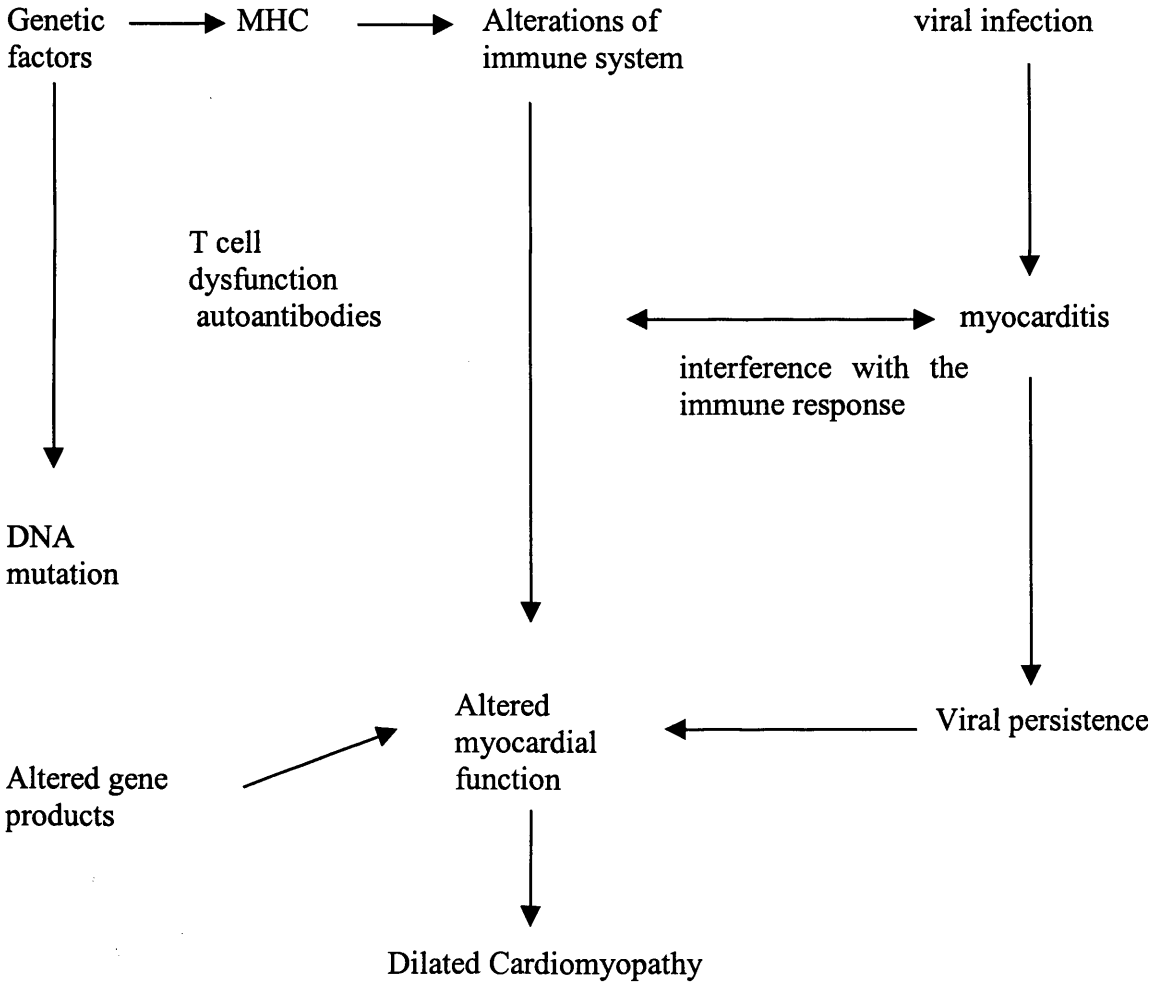


Figure 1. Hypothesis to explain the pathogenesis of dilated cardiomyopathy.

To show a viral presence serological studies were carried out demonstrating raised viral antibody titres in patients with DCM by Kawai [41] and Cambridge et al [42]. However other workers have not shown this association [43]. The demonstration of virus specific IgM by radioimmuno-assay [44] was a further step to chase the viral hypothesis. Keeling et al [45] found CVB IgM to be more common in patients with

IDC compared to unmatched controls but failed to show a significant difference when compared it with matched group and patients' household contacts.

The introduction of slot blot hybridisation of nucleic acid has provided molecular biological methods to demonstrate direct evidence of viral persistence. Initial results were very promising. Archard et al [46] found that over 40% of myocardial tissue samples from patients with IDC were positive for enterovirus RNA. Kendolf and Hofschneicler [47] detected up to 25% positivity of enterovirus RNA in IDC patients compared to none in control subjects using in situ hybridisation. In situ hybridisation has the added advantage of providing information about pathological changes in the myocardial biopsies [48,49] but has the disadvantage of being slow. In this respect RNA amplification by polymerase chain reaction (PCR) technique is faster, more sensitive and more specific. Studies using this technique have demonstrated enterovirus RNA in up to 45% of patients with myocarditis and IDC [50-55]. Contrary to these, other studies either showed positive results in cardiomyopathic and control hearts alike [55] or the results were totally negative [56, 57].

Sevirini and colleagues [58] developed a method of nested PCR which enables the detection of a single molecule of viral RNA from a broad range of enteroviral types present in as small as 1 mg of cardiac tissue. Despite the high sensitivity of this method Mestroni et al [27] could demonstrate positive results in only 7% cases of IDC. All this accumulated data suggest that the enteroviral aetiology is playing a significant role in some cases but in others viral persistence is not a major factor.

Although mechanisms responsible for virus-related myocardial damage are unknown, an autoimmune response triggered by aberrations in the induction of MHC–antigen expression could be responsible for both the initial insult and disease progression. Myocarditis is a histopathological diagnosis defined by the presence of inflammatory cellular infiltrate and myocardial necrosis or degeneration. There is considerable debate about the frequency of inflammatory changes in endomyocardial biopsy specimens and the proportion of patients with IDC who have "burnt out" myocarditis. The incidence of biopsy-proven myocarditis varies among series of patients with IDC ranging from 1% to 67%. The incidence is highest in cases with the shortest interval from the onset of symptoms to biopsy [59, 60]. More recently however, the need to biopsy acute myocarditis has been questioned with the findings of Mason et al, that at most only 10% of subjects with clinically suspected acute myocarditis will have a positive tissue confirmation and that immunosuppression is not helpful [61].

AUTOIMMUNE THEORY

While the viral theory is "not proven", certainly not in all patients, the focus has shifted to an autoimmune aetiology. This has been outlined in some detail by Caforio [62]. Generally when tolerance to 'self' antigens is lost autoimmune disease results with circulating autoantibodies. Despite that, it has to be stated in general that detecting autoantibodies in a particular disease does not prove that these antibodies contribute to the pathogenesis of the disorder but they do represent markers of continuing tissue damage.

Autoimmunity can be organ-specific or non organ-specific. Non organ-specific autoimmunity causes generalised tissue damage. Organ-specific autoantibodies have

specificity for target cells, which are primarily involved in the disease process offering a plausible explanation for the tissue damage. Abnormal findings in the immune system in IDC are both cellular and humoral, i.e. decreased natural killer cell activity and decreased function of suppressor T-cell activity [63-66] but these findings are not cardiac specific. Cell mediated immunity is less well investigated and results are controversial [67, 68].

Cardiac antibodies (organ specific cardiac, heart reactive, antimitochondrial M7, anti β receptor, anti ANT, α and β myosin heavy chain isoforms) have been demonstrated in IDC by many workers [69-74]. Caforio et al [72] reported organ and disease specific antibodies of the 1gG class in 26% patients of DCM. In addition their cardiac specificity was confirmed by absorption studies. In some of the previous studies the antibodies were shown to cross-react with skeletal muscle, and therefore were not cardiac specific. In Caforio's study [72] these did not stain the skeletal muscle using indirect immunofluorescence (IFL) and can be regarded as cardiac specific. The β chain is expressed in skeletal muscle and is therefore not cardiac specific but the α isoform is solely expressed in the myocardium [74-76].

The hypothesis that IDC is an immune disorder is further supported by its association with specific HLA class 2 (DR & DQ) antigens [77] but it is not known how the HLA system determines the predisposition to specific disease.

Most organ-specific autoimmune diseases are chronic and apparently idiopathic with genetic predisposition [27, 78, 79]. Antibodies are found in the affected patients and

are also detected in the family members, sometimes years before the disease develops identifying symptom free relatives who are at risk.

Features of organ-specific autoantibodies

- Middle aged women most frequently affected.
- Familial aggregation.
- Organ and disease specific circulating autoantibodies are found in patients and in unaffected family members.
- Cell mediated autoimmunity is impaired.
- There is associated autoimmune disease in the patient or in family members.
- An HLA association is found.
- There is mononuclear cell infiltration and abnormal HLA molecule expression in the target organ.
- Disease can be induced in animal models after immunisation with relevant auto-antigen.

GENETICS OF DILATED CARDIOMYOPATHY

Familial analyses have shown that cardiomyopathy may have a genetic or inherited basis. Descriptions of individual kindreds with IDC of unknown cause transmitted as autosomal dominant, autosomal recessive and X linked traits have appeared [80-85]. Michels et al [86] in 1985 in a retrospective study reported a 6% frequency of familial disease. The same group in 1992 reported a 20% frequency of familial IDC in a prospective study. Mestroni et al [81] however, found an incidence of only 7% in their 165 patients.

Recently Zachara et al [79] have analysed 14 families with IDC and discussed the clinical profile of their relatives. Kelly and Strauss [87] in a detailed review under the heading "mechanisms of disease" produced a good account of inherited cardiomyopathies but almost all description is related to hypertrophic cardiomyopathy. Nevertheless it does provide an understanding of familial heart muscle disease.

The genetic aspect which has largely been overlooked in the past started to gather pace and as the workers started to look for it, more reports appeared to show that the familial form of IDC is not as uncommon as earlier thought [88]. A review of studies carried out during the last 12 years reveals how the assessed frequency of familial IDC has risen :

Fuster et al 1981 [89]	2/104
Michels et al 1985 [86]	6/169
Fragola et al 1988 [90]	12/33
Griffin et al 1988 [91]	10/32
Valantine et al 1989 [92]	9/184
Karen et al 1990 [93]	10/56
Mestroni et al 1990 [81]	7/165
Michels et al 1992 [78]	20/59
Zachra et al 1993 [79]	13/105

Autoimmune disease may have a genetic basis and often runs in families. IDC has similarities with type I insulin dependent diabetes mellitus. Both have male predominance and have shown association with HLA-DR4 phenotype [77, 94, 95].

The regulation of the gene expression is related to a promoter - a specific DNA region. Muntoni et al [96] reported one X linked familial DCM due to deletion in the promoter region and the first exon of the X-chromosome gene that codes for the protein dystrophin. This deletion was thought to be the cause of IDC due to deficiency of cardiac dystrophin, which is a component of myofibrils. Normally dystrophin is present in similar levels in skeletal and cardiac muscle fibres. Male patients with skeletal muscular dystrophies, especially Becker's, are well recognised to show myocardial function impairment. Although the skeletal muscle weakness is the main feature, patients predominantly presenting with IDC have been reported. Females with Duchenne's muscular dystrophy on the other hand rarely show IDC [97]. Mitochondrial mutation causing IDC is associated with neuromuscular disorders.

It has been suggested that the renin – angiotensin system may be involved in the pathogenesis of IDC. Raynolds et al [98] reported 48% higher frequency of ACE DD genotype in individuals with IDC compared with the control population ($p = 0.008$). It was thought that the molecular variants in ACE, which possibly alter local cardiac angiotensin activity, could affect ventricular structure and function through the tropic effects of angiotensin II on cardiac myocytes. ACE variants may also directly contribute to the onset of the heart muscle disease or may trigger the progression of disease following an initial precipitating event. A commentary by Swales [99] further clarifies the role of ACE DD genotype in atheromatous ischaemic heart disease and hypertrophic cardiomyopathy and suggests further research into IDC.

Heavy alcohol intake [100] (40gms daily for 10 years or more) and pregnancy have also been reported to play a part in familial IDC. Generally alcoholic cardiomyopathy is not regarded as IDC and this is not the subject of the present work. However, work by Gardner et al [85] has shown familial aggregation of dilated cardiomyopathy within patient groups with high alcohol consumption. It is also to be considered that alcohol may modify the course of the disease by potentiating viral or autoimmune damage.

Peripartum dilated cardiomyopathy is often not considered as part of the spectrum of IDC but in the absence of an aetiological factor it seems reasonable to take it as a sub group of IDC. Genetic and autoimmune factors are thought to be responsible. Familial peripartum cardiomyopathy is reported by Voss et al [101].

With all the data accumulating in support of a genetic basis of DCM, there still remain a large number of patients with no evidence of familial disease where an alternative aetiology is to be perceived.

CLINICAL ASPECTS OF DILATED CARDIOMYOPATHY

PRESENTATION

The first diagnosis of dilated cardiomyopathy may be accidental as pre-symptomatic DCM may be present for several years without coming to notice until a routine electrocardiogram (ECG) or chest X-ray, performed for some other purpose, reveals cardiac enlargement. The abnormal ECG and/or chest X-ray will usually lead to an echocardiogram, which demonstrates a dilated left ventricle to raise further suspicion of IDC. These patients though usually asymptomatic may have subtle diminution of effort tolerance, but unless the subject concerned is a regular exerciser or an athlete, this usually goes unnoticed or is ascribed to normal ageing. The left ventricular systolic function at this stage is generally only mildly impaired (ejection fraction 40 - 50%).

Clinical features are that of cardiac failure. The majority of the patients present with symptoms of fatigue and dyspnoea on effort and in some patients palpitation due to the development of cardiac arrhythmias is an important presenting complaint [102]. In more advanced disease overt heart failure sets in with symptoms - mainly shortness of breath and fatigue appearing on minimal exertion (class III NYHA). Episodes of paroxysmal nocturnal dyspnoea and acute left ventricular failure are part of worsening heart failure and may be a presenting complaint in patients with deteriorating myocardial function.

Chest pain though uncommon is a recognised feature of IDC. It is reported to occur in approximately 10% of patients. [103]. Chest pain is generally atypical in nature but occasionally has the features suggesting myocardial ischaemia.

PHYSICAL SIGNS

In asymptomatic disease the physical signs are minimal and subtle but as the heart failure develops the signs of congestive heart failure without obvious cause appear. The peripheries are constricted and the peripheral pulse is small in volume. There is commonly tachycardia at rest. Jugular venous pressure is usually raised. When the patient is in sinus rhythm, there is a prominent "a wave" followed by a poorly marked "X descent" and a prominent "V wave" due to tricuspid regurgitation. When there is atrial fibrillation the "a wave" disappears with the presence of a single wave due to a combination of right atrial filling and tricuspid regurgitation. Cyanosis appears in severe cases.

The apex impulse is displaced laterally due to cardiac enlargement and is diffuse. Pulsations to the left of the sternum may also be present suggesting right ventricular dilatation. Auscultation often reveals murmurs of tricuspid and mitral regurgitation. A gallop rhythm is common. At this time pulmonary congestion, hepatomegaly due to vascular congestion and oedema (often with ascites) are commonly present. As the cardiac output becomes dangerously low a trace of icterus appears, due to hepatic congestion (or occasionally to pulmonary infarction) associated with signs of peripheral vasoconstriction.

INVESTIGATIONS :

BLOOD INVESTIGATIONS

Examination of the blood is usually unrewarding. The results of the full blood count and haemoglobin are commonly normal. Occasionally a low haemoglobin is seen due

to bone marrow depression or an increase due to chronic hypoxia or possibly the effect of diuretics. Biochemistry is generally unremarkable unless hepatic congestion is marked when liver function tests including the INR may be grossly deranged.

ELECTROCARDIOGRAPHY

Electrocardiography usually shows non-specific changes. The T waves are flat or gently inverted. There is often some atrial enlargement and left ventricular hypertrophy is commonly present which can be marked when disease is long standing. Frontal plane QRS axis is usually normal. Intraventricular conduction delays especially left bundle branch block are common [22, 89]. In a small number of patients q waves may be seen in the precordial leads which may suggest myocardial infarction [104-105] but usually there is no ST segment elevation. Patchy fibrosis leads to loss of positive vectors in the anterior chest leads. This state of the myocardium has been confirmed on necropsy [106,107].

24 HOUR AMBULATORY HOLTER ECG

Arrhythmias are of common occurrence in patients with IDC regardless of the duration of the disease [102]. Atrial fibrillation occurs in around 20% patients [108]. This may be initially paroxysmal but later becomes established. Ventricular arrhythmias vary from simple ectopic activity to complex tachyarrhythmias. The incidence of non-complex ventricular arrhythmias is reported at around 95% and complex arrhythmia at around 50%. Non-sustained ventricular tachycardia occurs in about 60% of patients [109,110]. In spite of the frequency of ventricular arrhythmias these are not commonly seen on the standard resting electrocardiogram and many

patients are asymptomatic during non-sustained ventricular tachycardia. However, 24 hour ambulatory ECG can help to recognise these arrhythmias. Other arrhythmias - atrial flutter, junctional rhythms, supraventricular tachycardia and heart blocks also occur but are infrequent.

CHEST RADIOGRAPHY

Mild cardiomegaly noted on the plain chest X-ray is often the first indication of the disease process as patients may be entirely asymptomatic in the early stages. Later there is considerable cardiomegaly due to dilated ventricles but the atria may also be enlarged. The pulmonary vasculature shows evidence of high left atrial pressure with increased size of the upper lobe vessels. The main pulmonary arteries are slightly enlarged. In patients who are in overt heart failure, lung fields are congested with interstitial pulmonary oedema. When the right-sided heart failure is a prominent feature pleural effusion occurs. Occasionally pericardial effusion may be present causing a flask shaped cardiac shadow.

ECHOCARDIOGRAPHY

Two dimensional real time (2 D) echocardiography is a crucial investigation in all patients with suspected IDC. It is helpful in differentiating IDC from other forms of cardiomyopathies - restrictive cardiomyopathy, endomyocardial fibrosis and amyloid heart disease. Because of its non-invasive nature it is also useful for serial assessment of the progress of the disease.

The striking feature is a dilated left ventricle (normal dimension Diastole: 3.6-5.2cm,Systole: 2.3-3.9cm) with globally reduced systolic function. There is usually no evidence of a segmental wall motion defect but in some patients, in spite of the diffuse nature of the disease, regional wall motion abnormalities are seen [111-114].

Although the left ventricle is dilated and both the septal and posterior ventricular wall can be seen to move poorly, the wall thickness is within normal limits. Generally the septal motion is normal though excursion is reduced due to poor ventricular function but in the presence of intraventricular conduction defects septal motion becomes abnormal.

The apical four chamber images of the heart usually demonstrate enlargement of all cardiac chambers. The left ventricular cavity is particularly dilated and spherical because of the proportionately greater increase in the minor rather than in the major axis, with the ratio of short/long cavity axis approaching unity. This view also provides an assessment of papillary muscle function [115]. Another potential value of apical 2D studies is the detection of thrombus formation in the ventricular cavities which usually forms at the apex [116-119].

The mitral valve leaflets exhibit a characteristic motion denoting diminished left ventricular contractile function and often increased end-diastolic pressure. Mitral E point-septal separation of more than 1cm and a beta hump are seen [120, 121]. Functional atrioventricular valve regurgitation (mitral and tricuspid regurgitation) commonly accompanies ventricular dilatation due to geometrical distortion of the sub-

valvular apparatus and the stretched atrioventricular valve ring. The regurgitant jets are easily picked up on Doppler or colour flow imaging.

Until the advent of 2D echocardiography, M mode examination was mainly used to assess cavity size and valve motion patterns in DCM. While the 2D examination has taken over the prime role in the diagnosis of DCM, the M mode images still remain valuable especially in the assessment of septal motion and calculation of the ejection fraction which is an important objective assessment of the systolic myocardial function. Depending upon the severity of the disease the ejection fraction can be even < 20%. The advent of transoesophageal echocardiography has further enhanced our assessment of patients with IDC particularly in the detection of intracavity and mural thrombi, left atrial thrombi and a better evaluation of atrioventricular valve rings and sub-valvular apparatus.

A specific form of cardiomyopathy involving only the right ventricle also occurs. The echocardiographic findings are those of right ventricular (RV) volume overload. Uhl's disease is also a type of right ventricular dysplasia or myopathy. Massive RV dilatation is a striking feature [122-124].

RADIONUCLEOTIDE VENTRICULOGRAPHY

In patients with cardiac failure, information derived from radionucleotide ventriculography can have an impact on diagnosis and prognosis in the ways listed :

Differentiate

- Ischaemic versus non ischaemic aetiologies.
- Right versus left ventricular failure.

Assess

- Chamber size.
- Right and left ventricular global and regional function, systolic and diastolic.

Determine

- Prognosis.
- Serially monitor pharmacological treatment.

More recently radionucleotide techniques have been used to diagnose myocarditis, subsequently correlated with biopsy findings in patients with IDC [125]. Indium-111 labelled monoclonal antimyosin antibodies have been shown to be promising with a specificity of 58% and sensitivity of 100% [126, 127]. Monoclonal antimyosin antibodies in IDC and myocarditis suggest a continuing process of active myocyte damage. The correlation of these changes with myocardial histology and the detection of enteroviral RNA may in the future provide further insight into the pathogenesis of IDC. In clinical practice radionucleotide studies are generally used to assess the systolic myocardial function by calculation of the ejection fraction (EF). It gives a more accurate measurement of EF as it is capable of measuring EF in various sections of the cardiac chambers separately and then averaging this to give overall systolic cardiac function. It also allows (by using First Pass Study) the assessment of right ventricular function which is not accurately done by conventional echocardiography.

HAEMODYNAMICS

The haemodynamics are essentially those of failure of the heart as a pump. In the early stages of the disease the reduced stroke volume may be compensated for by

tachycardia which maintains the cardiac output. The minute volume however, does not rise normally on exercise, which produces an increase in end-diastolic pressure in the left ventricle and thus dyspnoea on exertion. In the late stages of the disease both minute volume and stroke volume are seriously compromised. However, it is quite possible that for a considerable period of time the mechanical advantage of dilatation may allow reasonable effort tolerance. Eventually however, the disadvantages of dilatation outweigh the advantages. According to Laplace's law dilatation is accompanied by greater wall tension for any given pressure / wall thickness, which results in higher metabolic needs and oxygen demand. There is in addition, a decreased rate of fibre shortening, diminished maximal rate of increase in pressure (dp/dt max) and diminished velocity of ejection. Over-dilatation is therefore essentially disadvantageous. It can be compensated by wall hypertrophy but this is characteristically lacking in IDC.

The reduced cardiac output and stroke volumes are accompanied by a permanent increase in left ventricular end-diastolic pressure. The ejection fraction, which is reduced, is inversely related to ventricular end diastolic pressure. Systolic and diastolic volumes are increased.

Reduced oxygen saturation of mixed venous blood is found in most patients and results in a high arteriovenous oxygen gradient. Pulmonary artery pressure and pulmonary vascular resistance are often moderately raised as a result of left ventricular failure but severe pulmonary hypertension does not occur.

CARDIAC CATHETERISATION

The primary role of cardiac catheterisation in patients with IDC is to assess the coronary arteries. Clinically IDC may resemble extensive myocardial damage due to severe coronary artery disease and may not be differentiated by non-invasive investigative techniques [128]. Coronary arteriography may be necessary to ascertain the diagnosis of IDC. It also allows full angiographic visualisation of cardiac anatomy and haemodynamic data important for patients who may be considered for cardiac transplantation.

ENDOMYOCARDIAL BIOPSY

Endomyocardial biopsy is not a routine procedure performed on patients with IDC but its role in recognising specific myocardial disease is useful. More commonly the histological changes in IDC are non-specific showing loss of myocytes and their replacement by fibrous tissue. One other morphological change, namely that due to myocarditis, can also be recognised. Myocarditis is characterised by an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes. Evidence had accumulated on the relationship between viral myocarditis and IDC at the experimental level and in man [24-26, 41-45, 129], but it was not until the development of hybridisation molecular biological methods that the evidence of viral presence was documented clearly in cardiac tissue obtained by biopsy [46, 52-54].

Since the complications of endomyocardial biopsy are not greater than those of cardiac catheterisation, in some centres endomyocardial biopsy is combined with

angiography to obtain maximum information, but its clinical application still remains limited.

PATHOLOGY

Macroscopically, heart weight is increased occasionally to twice the normal value. The heart muscle is pale and flabby with all heart chambers being dilated [130]. The endocardium is thickened and has a glossy white appearance. Whiteness in the ventricular chambers indicates abnormal thickening, which in IDC is haphazardly distributed. Not infrequently thrombus is present, usually at the apex [131]. Coronary arteries are usually of large calibre but the presence of coronary artery disease has been reported [104]. The naked eye appearance of the necropsy specimen gives no clue to the aetiology.

Light microscopy is usually equally disappointing. At times the myocardium may appear virtually normal though in some cases there is fibrosis, necrosis of muscle fibres and infiltration with round cells. Myocardial fibres show nuclear changes of hypertrophy in the form of vesicular changes or pyknosis. Despite these nuclear changes, the myocardial fibres are often normal in diameter (12μm). This is due to stretching of the fibres. Intramyocardial vessels are usually normal [132]. Focal accumulations of lymphocytes are a frequent finding. These are non-specific and do not necessarily represent myocarditis. The histological changes are therefore non-specific consisting of hypertrophied dilated myocardium, together with varying severity of a chronic inflammatory infiltrate indistinguishable from myocarditis.

COMPLICATIONS

The complications of IDC are mainly those of severe heart failure. Associated atrial fibrillation (AF) increases the risk of thrombo-embolism. Embolus from ventricular cavities may occur even in the absence of AF and is due to formation of a friable thrombus in the poorly contracting ventricular cavity. Both systemic and pulmonary embolism may occur. Pulmonary embolism may also occur secondary to deep venous thrombosis in patients with low cardiac outputs and extensive peripheral oedema who are immobilised by severe heart failure. Sudden death is usually due to ventricular tachyarrhythmias. Infective endocarditis is rare in dilated cardiomyopathy. Valve regurgitations (mitral and tricuspid) that accompany cavity dilatation are well-recognised complications.

NATURAL HISTORY AND PROGNOSIS

The course of the disease is usually steadily downhill but can be rapid and death commonly ensues within 6 months to 5 years after the onset of the symptoms. 5 year mortality is variable at around 40% [6, 89, 133-136]. However some patients especially those with early disease run a stable course with a variable natural history and a better prognosis, sometimes with significant recovery of myocardial systolic function [137]. With energetic treatment of heart failure patients improve but relapses are frequent. Recurring episodes of heart failure become increasingly difficult to control and finally the patient develops resistant heart failure from which recovery is unlikely. High degree NYHA functional class heart failure and the presence of advanced atrioventricular conduction delays are adverse factors. In recent years the mortality and morbidity of this condition seems to be changing with improved

survival [138]. A common cause of death is resistant severe heart failure or malignant ventricular arrhythmia [139-142].

Factors noted to be independently predictive of a poor prognosis are :

- age 55 years or greater.
- cardiothoracic ration of 0.55 or greater.
- cardiac index of less than $3L/min/m^2$.
- left ventricular end-diastolic pressure $\geq$ 20 mmHg.

Prognostic assessment by endomyocardial biopsies has been inconsistent [143] but work on quantitative microscopy suggest that there may be a correlation between myofibrillar volume or myocyte area and left ventricular systolic function and prognosis [144,145].

OBJECTIVES AND REASONS OF THE STUDY

1. How prevalent is heart failure in the Omani population selected for the study? At the initiation of this research the first objective was to collect all patients with heart failure irrespective of the aetiology. This was intended to produce concise data on the prevalence and aetiology of heart failure from a country of the Arabian Peninsula with a population different from the west in cultural and ethnic origin, and from this group to select patients with IDC for the purpose of the main study, thus ensuring complete coverage of the population studied.

2. What is the demography, clinical profile and natural history of IDC in this population? In certain developed countries (Europe, UK, USA) the prevalence of IDC is approximately 20/100,000 with an incidence of 6 new cases per year affecting mostly young men [4-6]. It was my observation from outpatient attendances and hospital admissions in the Sultan Qaboos University Hospital and other hospitals in Oman that IDC was a common diagnosis. Other physicians in the country shared this view. It must be admitted that the majority of these patients who had presented in heart failure were often not investigated fully in the past and therefore the diagnosis of IDC required validation. Due to a paucity of organised medical information collection systems, there was little data available related to IDC, not even regarding the basic demography. Its clinical characteristics, natural history and prognosis were not known in this population. This necessitated investigating the following aspects of IDC in the Omani population, namely prevalence, demography, clinical characteristics, natural history and survival.

3. Is there a role of autoimmunity in the pathogenesis of IDC in this population? The autoimmune pathogenesis of IDC is recognised but studies show variable results. A combined analysis of published data, based largely on Anglo-Scandinavian patients, showed positive association with HLA-DR4 and a possible negative association with DR6 [77]. The data in that analysis included results from Pittsburgh, in which no HLA-DR4 association could be demonstrated [146]. In 1989 Arbustini et al reported a positive association with HLA-DR4 and DR5 and a negative association with HLA-DR3 in IDC patients population from Northern Italy [147]. A recent study on 98 British patients with IDC did not show any association with HLA antigens [148]. A major hypothesis to explain chronic myocardial damage in human myocarditis and IDC invokes autoimmune mediated damage to myocytes. Conclusive evidence of organ specific cardiac autoantibodies would be consistent with the involvement of organ specific autoimmunity in the pathogenesis of DCM, but these antibodies have been found with similar frequency in other conditions [149-154]. In addition, such heart-reactive antibodies may cross-react with skeletal muscles [155, 156].

This disparity in the results and the possibility of racial influences in HLA association with a lack of any previous studies into an autoimmune pathogenesis of IDC in Omanis prompted the investigation of the frequency of HLA antigens and cardiac autoantibodies in Omanis with IDC.

4. What is the state of sympathetic over-activity? Enhanced sympathetic activity in heart failure although beneficial in early stages, persistent and excessive stimulation is harmful in long term leading to increased susceptibility to cardiac

arrhythmia and inappropriately elevated afterload [157, 158]. Consequent downregulation of beta 1 adrenoreceptors [159-161] and a direct cardiotoxicity of catecholamines [162] also contribute to progression to resistant heart failure. Raised catecholamine levels have been reported to be prognostic indicators in IDC [163, 164] and therapy by beta-blockade seems to improve outcome [165]. However studies have not yielded uniform results [166, 167] and routine beta blockade in all patients with IDC is not recommended [168]. The purpose of measuring plasma catecholamine levels was to see if these correlated well with the severity of heart failure.

5. Family screening of patients diagnosed as IDC. Idiopathic dilated cardiomyopathy is a disorder of a heterogeneous group of diseases where familial predisposition is well recognised [78-93]. Consanguineous marriages being common in Arab society it would be expected that familial disease would tend to be increased. There is no valid data on the prevalence of familial dilated cardiomyopathy (FDC) in the Arabian Peninsula. This prompted family screening as part of this study.

6. What is the role of pregnancy in the pathogenesis of IDC in this population? Peripartum Cardiomyopathy (PPCM) is now considered to be a subgroup of IDC in women without pre-existing heart disease [169, 170]. There is only one report on PPCM from the Arab Region, from Dubai, where PPCM was found to be a more common cause of DCM compared to Moscow. However, the population was not defined in that study. Dubai being inhabited by a large expatriate population from countries all around the world, the figure in the Dubai study may not reflect the true prevalence of PPCM in the region [10]. The study of the frequency of

PPCM in the indigenous Omani population thus constituted an important part of the research.

7. **What is the natural history of IDC in children?** Dilated cardiomyopathy in children needs special considerations because of difficulty in diagnosis and a possibility of finding a treatable aetiology. It is also thought to run a different clinical course than that seen in adults. Data on DCM in children is rather sketchy in the literature and is lacking from this part of the world. With the help of our paediatric cardiologist, I took the opportunity of including certain aspects of this, particularly the natural history, in this study.

Thus in summary the **objectives of this research** were to investigate the following features of IDC in an Omani population.

1. Prevalence.
2. Demographic pattern.
3. Clinical characteristics.
4. Natural history and Survival.
5. HLA association.
6. Cardiac autoantibodies detection.
7. Catecholamine levels.
8. Familial frequency.
9. Peripartum frequency.
10. Paediatric dilated cardiomyopathy : Clinical features & Survival.

It was intended that this work, together with the comprehensively compiled description of IDC, would benefit recently qualified Omani medical graduates by making them aware of the apparently high prevalence of this disease in Oman stimulating further research in this field.

SULTANATE OF OMAN

The Sultanate of Oman is the second largest country of the Arabian Peninsula with an area of approximately 300,000 square kilometres. It is bordered by the Kingdom of Saudi Arabia and the United Arab Emirates to the west, Yemen to the south, the Strait of Hormuz to the north and to the east by the Arabian Sea. It occupies the most south-eastern part of the peninsula with a long coastline of approximately 1700 kilometres.

Dominated by an interior of jagged mountains simply called Al-Hajr 'the rock; the country is a magic tapestry of different terrains. The mountains, including the soaring 3075 meters of the terraced "Jabal Al-Akhdar", "The Green Mountain", rise straight out of the coastal plains of the sea, or out of gravel plateaux and shifting sand dunes in the interior. The country ranges from the fjord - like barren majesty of the Musandam peninsula that plunges into the strait of Hormuz in the north, to the fertile Batinah plain that inclines south-east towards Muscat (the capital city), from the vast sandy edge of the "Rub Al Khali" (The Empty Quarter) through the mountains to the lush, monsoon based, near tropical Salalah plains in the south. Geographically Oman falls into a number of distinct areas.

AREA	MAIN TOWNS
Muscat	Old Muscat Capital City, Ruwi, Quriyat
Batinah Plains	Barka, Suwaik, Siham, Sohar
Western Hajr Mountains	Rustaq, Nakhl

The Interior (Dhakliya)	Nizwa, Bahla, Samail, Izki, Adam
Dhahira Area	Ibri
Shariqiya Area	Sur, Qabil, Sinaw, Ashkara
Barr Al-Hekam	Masirah Island
Southern Region (Dhofar)	Salalah, Marmul
The Musandam	Khasab, Bukha

INHABITATION AND PEOPLE

The most populous areas are Muscat, Batinah and Dhakliya. The total indigenous local population is estimated at around 1.8 million. In addition there is a substantial population of expatriates from other countries who are temporarily resident in Oman. The cross currents of history with its migrants and invasions have swept Oman since time immemorial but its people have remained of basically Arabian peninsular origin though with many tribes spread across the country.

Omani society consists of four basic categories: the people of the sea who live by fishing, the agriculturists of the south, those of mountains in the interior, and the Bedouin of the desert areas. Oman was largely an isolated country until the early 1970s, when His Majesty Sultan Qaboos came to power. His Majesty's reign was the

beginning of a new chapter of development which has transformed the Sultanate into a modern country with enormous social and economic progress in just 30 years, while maintaining its historical cultural values of a Muslim nation.

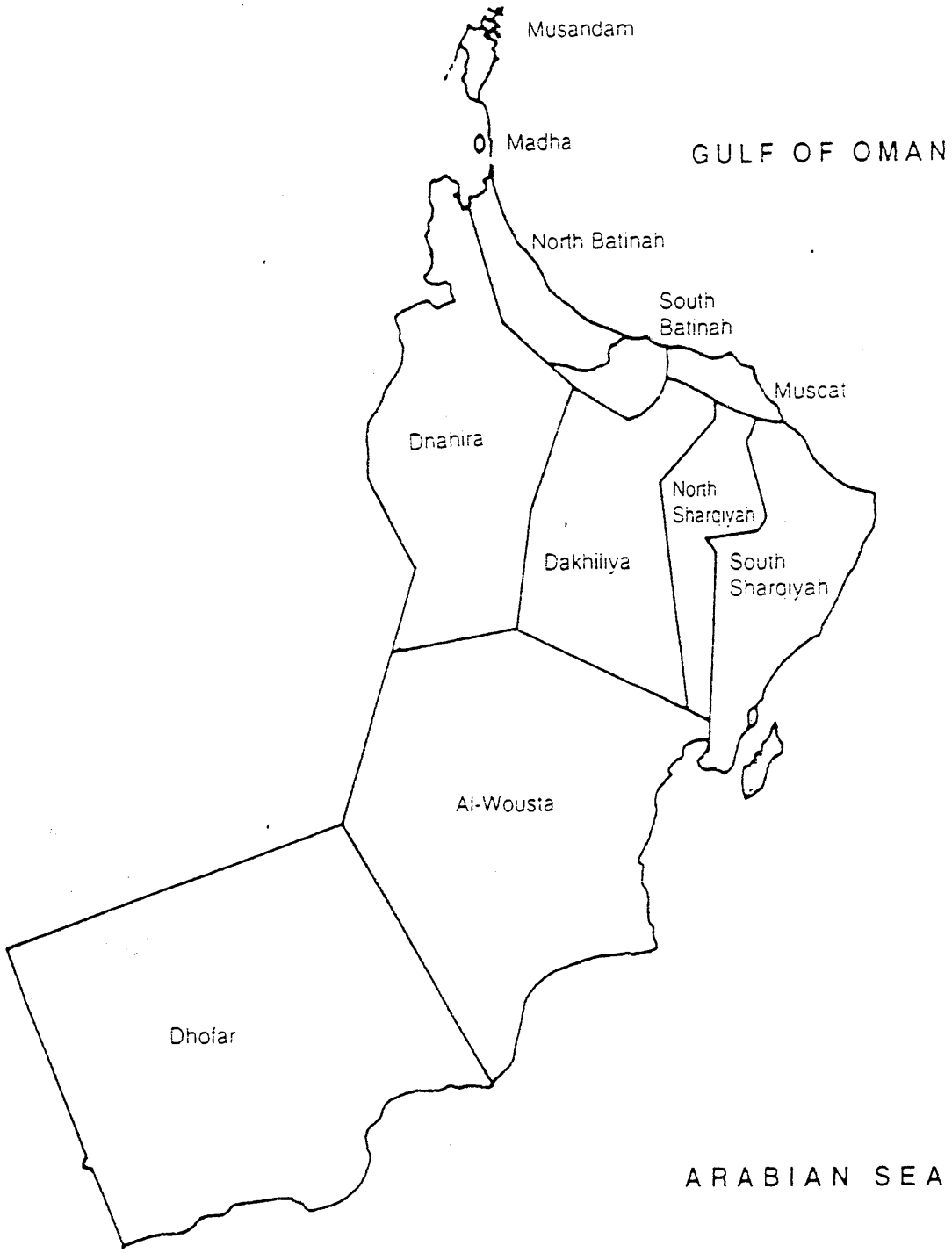
As a part of development drive higher education was high on the agenda. In 1970 there were only three boys' school in the country and koranic schools in towns and villages. There were no girls' schools. Today there are many primary and secondary in all cities providing free education to all Omani nationals. The crowning achievement was the opening of the Sultan Qaboos University at Al Khod (50 km. from the capital city Muscat) in September 1986.

The University

The Sultan Qaboos University comprises seven colleges or faculties: Education and Islamic Sciences, Agriculture, Science, Engineering, Arts, Business and Medicine. All colleges and faculties have full support facilities with computer centres and large well-stocked libraries.

The Faculty of Medicine, mostly staffed by academicians and doctors trained in the UK, USA and Europe, comprises all disciplines for the comprehensive teaching of medical students. A 300-bedded teaching hospital is affiliated to the medical school for the training of Omani doctors. This hospital is furnished with modern equipment for diagnostic and therapeutic purposes in most major specialities. Sultan Qaboos University Hospital provides free medical care to all Omani nationals and government employees.

SULTANATE OF OMAN



This Diagram is not an authority on international boundaries
Internal boundaries are Ministry of Health administration areas

CHAPTER – 2

ORGANISATION OF THE STUDY AND METHODS

HEALTH SERVICES IN OMAN

Health services in the Sultanate of Oman are largely run by the State. Until 1990 it was solely the jurisdiction of the Ministry of Health, structured as primary, secondary and tertiary health care. Since the opening of the Medical School and its' affiliated University Hospital, the health care is shared by the Ministry of Higher Education. Primary care is in the form of health centres situated close to the community in various areas of the country both in villages and cities. These are staffed by medical officers similar to general practitioners in the United Kingdom. There are however certain areas in the mountains where families live in small communities not readily accessible by road. These areas are served by flying doctors in helicopters visiting once a week. Secondary health care is provided by 200 bedded hospitals situated in the larger cities. Until a few years ago these hospitals were equipped to provide only essential basic health care in major disciplines (medicine, surgery, obstetrics, paediatrics, ophthalmology, accident and emergency services). Recently the facilities and the bed capacity of these hospitals have been vastly upgraded.

Tertiary health system comprises two major national referral hospitals in the capital city of Muscat, the Royal Hospital and Sultan Qaboos University Hospital. Although the University Hospital accepts emergencies, it only has restricted access by strict referral, from either a primary or secondary health centre. Both the Royal and the University hospitals are equipped with modern (state of the art) facilities in all disciplines of the health services. In addition to these there are other small satellite hospitals catering for armed forces and royal guard personnel and their families.

PATIENT COLLECTION

While planning the study I looked at what I ideally would like to do and what is actually possible.

To study the epidemiology of a disease, it is important that all patients of the disease are identified for accurate estimation of prevalence and incidence. In relation to this study following approaches would have been appropriate :

Population based survey – A door to door visit to all inhabitants of the Dhakliya region to identify the patients with both symptomatic and asymptomatic heart failure. This would require history taking, full clinical examination and ECG taken of all members of household supported by a preliminary blood test (natriuretic peptide) which can also identify asymptomatic patients of heart failure. Essentially the target would be to identify the patients with symptoms and signs of fluid detention and heart failure i.e. shortness of breath, oedema, paroxysmal nocturnal dyspnoea, orthopnoea, raised jugular venous pressure and crepetations in the lungs. Auscultatory signs of heart failure (S3, S4) associated with or without evidence of cardiomegaly on clinical examination would also need to be included in the preliminary screening. All such identified people would then need further investigations, particularly chest x-ray and an echocardiogram to establish the diagnosis of heart failure. This approach would ensure that all patients with cardiac dysfunction are identified for complete coverage.

A similar survey can also be organised if all general practioners in the region are requested to screen all the families registered with them.

Both these approaches were not possible due to problems associated with the local cultural regulations and limitations of the facilities available including a high demand for time and man-power to conduct such kinds of survey. Furthermore, the primary health care does not enjoy the set-up of general practioners in a structured system as established in the National Health Services of the United Kingdom.

Thus, perhaps the most difficult part of the study appeared to be the patient collection. It was impossible to organise referral of every suspected IDC patient from all primary and secondary hospitals across the country. Dhakliya region was chosen because it is one of the larger regions in Oman with a predominantly local population. Nizwa is the main city of this region, situated 160 Km. from Muscat. Nizwa Central Hospital with 100 medical beds is the only secondary health care facility of this region and serves a total population of 305,000 with 249,000 adults aged over 12 years (225,000 local Omanis and 24,000 expatriates). There are also three smaller cottage type local hospitals and many primary health care clinics. There are no private care hospitals in the region. I was able to develop a liaison with the administrative authority and physicians at the Nizwa hospital and the health centres in the area. The proposed project was mutually agreed. Thankfully they kindly co-operated to refer all patients with suspected heart failure to Nizwa hospital. It also needs to mentioned that since the cottage hospitals have limited facilities, patients attending these hospitals are almost always referred to the secondary care facility of the Nizwa hospital for further care. But to ensure that all patients suspected to have heart failure were seen, it was emphasised to medical officers of these hospitals and primary health centres to cooperate. A further attempt was also made to keep a close contact with them by visiting these facilities on a regular interval. Official permission was obtained for me

to run a cardiac clinic once a month in Nizwa hospital. In this clinic I saw all cardiac in-patients and in anticipation of my visit patients with interesting cardiac problems, heart failure and suspected IDC were given appointments to attend. Thus I was able to see nearly all patients with heart failure and suspected IDC from this region attending Nizwa hospital. It must be admitted that despite all these efforts some patients, particularly the asymptomatic ones may have been missed.

It was not possible to visit hospitals in other parts of the country and a personal request was made to the physicians in these hospitals to refer patients with suspected IDC to my cardiac clinic at the Sultan Qaboos University Hospital. This did not materialise and as I received very few patients through these channels they were not included in the analysis. I also attempted to organise a house to house survey but due to the cultural restrictions and resource limitations it was not possible to conduct a community-based study.

PATIENT SELECTION

Initial selection of patients was based on the presence of symptoms and signs of heart failure (dyspnoea, bilateral basal crackles, raised jugular venous pressure, pedal oedema, hepatomegaly, gallop rhythm). Any with evidence of fluid retention (ascitis, pleural effusion) were also screened and included only after liver or pulmonary disease and non-cardiac cause of fluid over-load had been excluded. The study population comprised of a mixture of diagnosed cases of heart failure and IDC already on the records of Nizwa hospital and new cases that presented during the study period of three years (1992 – 1994). All patients with heart failure were first booked to undergo preliminary screening including a search for any identifiable

cause. This was done by detailed history taking, physical examination, chest x-ray, an ECG and echocardiogram.

Preliminary selected patients attended the SQUH for a second screening by echocardiographic examination. If this showed global impairment of myocardial systolic function with morphologically normal valves, they were provisionally enrolled for the study. In some patients where the primary aetiology causing the symptoms and signs of heart failure may not have affected the myocardial systolic function, the ejection fraction may remain within normal values. In such patients, clinical diagnosis of heart failure was confirmed by a chest x-ray showing pulmonary congestion. Informed consent was obtained from every patient and the study had an approval from the Ethics Committee of the Sultan Qaboos University.

Inclusion Criteria

- Age ≥ 13 years . All patients in heart failure with no identifiable cause.
- Impaired left ventricular systolic function (LVEF < 50%).
- Asymptomatic unexplained cardiomegaly (CTR > 50%).

Exclusion Criteria

- Age ≤ 12.
- Ischaemic heart disease.
- Hypertension.
- Valvular heart disease.
- Diabetes mellitus.
- Thyroid disease.
- History of alcohol abuse.

- Any other disease process which can cause secondary heart failure.

IHD was considered as exclusion criterion if patient gave history of angina, previous myocardial infarct supported by ECG changes (presence of Q-waves) and/or a treadmill exercise test which was positive for myocardial ischaemia at low work load (≤ stage III of modified Bruce protocol). Blood pressure was measured non-invasively by an electronic sphygmomanometer (standardised by mercury sphygmomanometer) in both arms individually in supine position on three separate occasions. Multiple recordings of >150/90 were considered as hypertensive. Presence of fourth heart sound, hypertensive retinopathy, LVH on ECG and a review of patient's previous medical records helped to identify these patients. Since clinical and ECG findings in chronic hypertensives who have developed heart failure can be indistinguishable from IDC, left ventricular wall thickness was also evaluated by echocardiography to ensure appropriate patient selection. Absence of concentric LVH and the presence of left ventricular cavity dilatation as the predominant feature confirmed that the patients did not have "burnt-out" hypertension.

Diabetes was excluded if fasting blood glucose level did not exceed 6.0 mmols/l on multiple occasions. Exclusion of thyroid disease was done by estimation of thyroid function tests (free T4 and thyroid stimulating hormone). In the Omani society use of alcohol is prohibited culturally, therefore alcohol abuse was an automatic exclusion but it was further ensured by close questioning.

As follow-up was not always possible in the city of Nizwa due to factors such as commuting to work from villages to the capital city of Muscat a special

Cardiomyopathy Research Clinic was also started at the Sultan Qaboos University Hospital to ensure regular patient contact.

In anticipation of possibly unreliable attendance by some patients in the out patient clinic together with the fact that in many of these patients the diagnosis of IDC was not yet proven, I admitted these patients to SQUH for clinical work up which ascertained that the relevant diagnostic investigations, appropriate treatment and the correct selection of the patients for the purpose of the study was carried out. A detailed history was taken by an Arabic-speaking doctor and a full clinical examination performed. The clinical details were transferred to the data collection protocol sheets with a record of their NYHA functional class dyspnoea. If there was no evidence of any exclusion criteria the patient was finally enrolled in the study and underwent full evaluation and investigation according to the protocol prepared for this study (protocol sheet attached at the end of this dissertation).

INVESTIGATIONS

CHEST X-RAY: A plain chest x-ray in posterior - anterior view was taken in the standing position in full inspiration and was reported by a qualified radiologist. The following were noted :

- Cardio-thoracic ratio.
- Pulmonary vasculature.
- Lung fields.
- Any other abnormality.

A 12 LEAD ECG : was recorded on HP pagewriter machine (12 channels) after a 10 minutes rest in bed. The following parameters were noted :

- Heart rate.
- Rhythm.
- Chamber hypertrophy.
- QRS duration.
- Bundle branch block pattern.
- Atrio-ventricular blocks.
- Any other abnormality.

24 HOUR HOLTER ECG : 24 hour Holter ECG was recorded on a two channel solid state Oxford Medilog recorder. Tapes were analysed using Oxford analyser. The computerised analysis was then reviewed by an experienced technician and tracings of any suspected abnormal rhythms expanded. These were then reported by myself according to the format of the protocol. The following parameters were recorded :

- Dominant rhythm.
- Maximum and minimum heart rates.
- Presence of arrhythmias.

If ventricular ectopic activity was recorded, a further analysis was done to record the following :

- Total number of ectopics.
- Unifocal or multifocal.
- Right or left ventricular configuration .
- If ventricular tachycardia (runs of 4 or more ventricular ectopics) was recorded

following features were further noted :

Monomorphic or polymorphic.

< 10 beats or > 10 beats or Torsade de Pointes.

- The diurnal pattern of ventricular activity was also recorded to note the frequency of ectopics and the presence of VT in three periods of the 24 hours. (6am to 3.59pm, 4pm to 11.59 pm and 12 midnight to 6am). These times were particularly selected to relate to the working hours of people in this part of the world.

ECHOCARDIOGRAPHY : Transthoracic echocardiography (TTE) and Doppler studies were performed on HP 1600 Sonolayer machine by qualified experienced technicians. All standard (parasternal long axis and short axis, apical and subxiphoid) views were recorded using a 2.5 MHZ probe. Doppler studies were performed with a 5 MHZ pencil probe. Blood flow was recorded across all four valves. The following parameters were recorded :

- Left ventricular diastolic dimension.
- Left atrial dimension.
- Left ventricular ejection fraction.
- Left ventricular diastolic dysfunction.
- Valvular regurgitation.
- Thrombus formation.
- Visual assessment of right ventricular systolic function.

Left atrial and ventricular dimensions were recorded in M-mode using standard parasternal long axis view with the cursor passing through the mid LA for the left atrium measurement and through the LV cavity just below the tips of mitral leaflets in

diastole for LV diastolic dimension. LV systolic function was assessed by ejection fraction measured in M-mode at the mid cavity level calculated by the software programme built-in the echocardiography machine (normal range 50 – 70%). Any limitation of the measurement by this method was further overcome by the 2-D measurement in apical 4-chamber view. The software programme built in the echocardiography machine used the Simpson's rule for the calculation of ejection fraction [171, 172]. Valvular regurgitation was assessed by the area of regurgitant jet into the atrium during colour flow map examination and by the density of the signal during continuous wave Doppler examination, in comparison to forward flow. Regurgitant area of ≥ 8 cm^2 and/or the presence of dense signal on CW Doppler were classified as severe [173]. Right ventricular systolic function was assessed visually ("eye-balling") by two observers. The limitation of this assessment was recognised. LV diastolic dysfunction was assessed by mitral inflow Doppler pattern (E/A ratio) . The Doppler echocardiographic recording of diastolic mitral flow was done by positioning a sample volume in the apical 4 chamber view between the tips of the mitral leaflets approximately 5 to 10 mm from the mitral annular plane towards the left ventricle. When a consistent wave form was obtained, it was "frozen", and the outlined traced to obtain the peak early diastolic inflow velocity coincident with the E-wave, the peak rate diastolic inflow velocity coincident with the A-wave (measured from the base line). Respiratory variation of the mitral flow was nullified by asking patients to hold their breath after expiration. In the normal person, the early velocity (E-wave) is higher than the velocity during atrial systole (A-wave) and the E decent is quick. Two distinct abnormal mitral flow patterns were taken as indicative of diastolic dysfunction [174]: one in which the early filling phase is reduced and compensated for by an increased atrial filling phase (reduced E-wave and tall E-wave,

Type 1) and the other where early filling is pronounced followed by a reduced atrial filling (tall E-wave and a reduced A-wave, Type 2).

Transoesophageal echocardiography (TOE) examination was undertaken following written consent. Patients were fasting overnight. 1% lignocaine was sprayed on the soft palate and midazolam was used for sedation by a venous access. Blood oxygen saturation was monitored by a finger sensor throughout the procedure. Both vertical and horizontal sections were recorded at various levels including gastric views. Parameters recorded were :

- Presence of swirling spontaneous echo contrast (SEC) in cardiac chambers.
- Thrombus formation in cardiac cavities including left atrial appendage.

All recorded echocardiographic tapes were reported by myself and one of my experienced cardiological colleagues independently. Any discrepancy was resolved by a third joint review. All patients had the echocardiography repeated at 3-6 months interval after entering the study once full appropriate pharmacological therapy had been introduced and , again during their follow-up at 12-24 months interval.

MUGA SCAN : First pass multiple gated pool isotope scan (MUGA) was organised through the nuclear radiology department at the SQUH. The reporting was done by a consultant in nuclear radiology. The following parameters were recorded :

- Left ventricular ejection fraction.
- Right ventricular ejection fraction.

While using the ejection fraction value determined by the MUGA scan a consideration of vascular background is important, since the values can vary. It is in essence tissue cross talk, and it reflects the activity of isotope in the vascular compartment in front of and behind the heart as well as contribution from scatter into camera field. Some programme assume that the background is constant during the cycle; this is incorrect but a reasonable first approximation [175]. Other programmes assume a cycle-dependent background. The package used in this study was cycle-dependent with a normal ejection fraction estimation set at 50-75%[176]. This has been shown to correlate well with that derived from contrast ventriculography [177-179]. Intra and inter-observer variation in the calculation of ejection fraction is < 5%. Calculation of right ventricular ejection fraction by MUGA scan is less reliable.

TREADMILL EXERCISE TEST : All patients underwent a computerised graded treadmill exercise testing by Modified Bruce Protocol (each stage of 3 minutes duration) soon after entry into the study. Those who were in class IV heart failure or were admitted in acute heart failure waited until they improved their functional class. If patients were taking digoxin it was discontinued for 3 days before the exercise test. The test was performed under the supervision of a qualified medical doctor who had already been supervised by myself on a number of occasions. The principal aim of this test was the initial screening to rule out significant ischaemic heart disease. The test was considered positive for myocardial ischaemia if any of the following developed during the exercise : ST segment elevation or depression of >1mm at 0.08 seconds after the J point, hypotension or malignant ventricular arrhythmia. ST segment change was visually analysed to ensure that no computer artefacts were misinterpreted and that it was measured at the point of steady baseline recording. If

the exercise test was positive for reversible myocardial ischaemia in the early stages of the exercise (stage III and below) the patient was not included in the study, since this was taken as suggestive of significantly severe coronary artery disease. These patients eventually had coronary angiography as part of their further management to confirm the diagnosis of IHD. Patients who had mildly positive exercise test (stage V and beyond) were provisionally included in the study but also had coronary arteriography to rule-out significant coronary artery disease. Thus it can be clarified that all patients who were provisionally enrolled for the study progressed to have coronary arteriography. The following parameters were recorded :

- Rhythm at the start of the test.
- Resting heart rate.
- Peak heart rate.
- Total exercise time.
- ST changes of myocardial ischaemia.
- Any arrhythmia precipitated.
- Blood pressure response.
- Limiting symptoms.

CORONARY ANGIOGRAPHY : The most important differential diagnosis of IDC is ischaemic cardiomyopathy. A meticulous effort was made to ensure that coronary artery disease was ruled out, as the aetiological factor of impaired myocardial systolic function, by coronary angiography in all patients entering the study. It was performed using Judkins technique. Multiple views of the left and right coronary arteries were taken. A left ventriculogram was also performed in right anterior oblique view. In a selected group of patients where right ventricular dysfunction was suspected, right

heart cardiac catheterisation to measure pulmonary artery pressure was performed via the femoral vein approach. Angiographic pictures recorded on a 35-mm cine film were reported by myself and another consultant cardiologist in the format of the protocol. The following parameters were recorded :

- Atheroma in main vessels (left main stem, left anterior descending, circumflex, right coronary and posterior descending).
- Atheroma in major branches (diagonals, marginals, first septal and right ventricular branch).

It was considered that a small number of post-myocardial infarct patients can have a normal coronary angiogram. Presence of global hypokinesia on echocardiography in such patients would suggest IDC as the cause of heart failure. Other methods such as stress thallium and stress echocardiography are also helpful in this respect.

BLOOD INVESTIGATIONS: Blood samples were collected in the mornings around 8.00AM after 12-hour over-night fasting. All blood samples were immediately transported to relevant laboratories of the SQUH for analysis. A further 20 ml of blood was drawn and transferred into 10 ml each in EDTA and plain tubes. These were stored in -80^0 celsius freezer for later transportation to the St. George's Hospital London, UK for analysis of organ specific cardiac antibodies. The samples were transported to UK by hand packed in dry ice and delivered to the courier waiting at the Heathrow Airport who took it straight to the immunology laboratory of the St.

George's hospital for proper storing and analysis. The following investigations were performed :

Routine Blood Investigations

- Complete blood counts including haemoglobin level and haematocrit and red cell indices.
- Sickle cell disease status.
- G6 PD levels.
- Blood glucose.
- Liver function tests.
- Renal function tests.
- Creatine kinase level.
- Erythrocyte sedimentation rate.
- Hepatitis screen.
- Human immune deficiency virus status.
- Lipid profile.
- Viral titres. (Coxsackie B, Echo).

Since Coxsackie B and Echoviruses are commonly known to be involved in the development of myocarditis leading to dilated cardiomyopathy, these are included in the "group package" to be tested in the virology laboratory of our hospital.

Special Blood Investigations

- Human leukocyte antigen profile.

- Antiheart antibodies.
- Catecholamine levels.

The details of methods and results on these special investigations are mentioned and discussed separately in chapter 4.

ON COMPLETION OF THE EVALUATION OF THE PATIENTS: Once all the investigations were completed, the selected patients with a confirmed diagnosis of IDC were followed up in the cardiomyopathy clinic at regular intervals depending upon their clinical state. IDC was considered to be the working diagnosis according to the WHO criteria [2]. At follow up, their clinical progress was recorded in their hospital files and relevant information transferred to the data protocol sheet. During this period the emphasis was to record new developments or complications of IDC which may have not been present when the patient first entered the study.

Having gone through this thorough screening process and evaluation, **97 patients** finally entered the study as having IDC for full analysis. Patient recruitment occurred between 1992 to 1994. **End points** of the study were death or completion of follow-up in December 1998.

NATURAL HISTORY : Patients were regularly followed-up at three monthly intervals in the cardiomyopathy clinic at SQUH or Nizwa hospital. They underwent ECG and echocardiogram at yearly interval or earlier if their symptoms changed. Holter ECG was repeated if arrhythmias were suspected. Acute deterioration in heart failure was treated appropriately and a repeat evaluation by echocardiography was performed. Their treatment regimen was modified as indicated. If the patients failed to

attend the scheduled appointment in the clinic, a contact was made to enquire about their progress and a new appointment was issued to ensure follow up.

FAMILY SCREENING: All patients were requested to bring their first-degree relatives (father, mothers, sisters, brothers, sons and daughters) for family screening. The general response was good although a small a number of patients failed to co-operate. Relatives undergoing family screening had an ECG and echocardiographic study in addition to history taking and physical examination. If there was evidence of IDC they were formally entered in the study as any other patient and underwent full protocol work up. If there was no evidence of IDC no further action was taken. Since familial dilated cardiomyopathy (FDC) can be identified early in life and frequently in children, I approached the local paediatrician of the Nizwa hospital to identify children with IDC during the same period. They underwent family screening by history, physical examination, ECG and echocardiography. 11 children were found suitable and these together with 97 adult patients (total 108) were included in the study of FDC.

To investigate this aspect, in addition to the evaluation of frequency of FDC by screening family members, all index patients and affected family members had relevant biochemical investigations (Table 35, page 156) to exclude any metabolic cause for the familial disease. Index patients with the affected family members were categorised as Group I and patients without affected family members as Group II. The characteristics of these two groups related to outcome were compared.

PERIPARTUM DILATED CARDIOMYOPATHY : This was diagnosed by evidence of the development of heart failure during the peripartum period with no other aetiology identified. The frequency of PPCM was calculated in the background of the number of live births in the Dhakliya region during the study period. Information of the number of live births was gathered from the local regional office of the public health.

DILATED CARDIOMYOPATHY IN CHILDREN : During the course of the research I approached my paediatric cardiologist colleague Dr. P. Venugopalan to initiate collection of similar data in children with IDC. Together we were able to record information on the clinical profile and outcome of all children with IDC between June 1992 and June 1997 who presented at SQUH. Therefore this is not a study from the Dhakliya region but constitutes essentially the natural history of paediatric IDC in general.

Entry criteria for the study included (1) Unexplained cardiac failure in the age group of 0 to 12 years, (2) echocardiographic left ventricular diastolic dimension of more than the 95th percentile for the body surface area and (3) left ventricular ejection fraction of less than 50% on echocardiography. Electrocardiogram, echo-Doppler study and blood investigations (to rule out biochemical/enzymatic defects) were used to exclude known causes of dilated cardiomyopathy in children. The blood investigations are shown in the flow diagram for diagnosis on page 156, table 35. Duration of the disease was taken from the date of the confirmation of the IDC by echocardiography. For calculation of the actuarial survival, the patients who had been lost to follow up were included until they were withdrawn alive at the time of their last known evaluation. The patients were divided into two groups for evaluating the

variables related to the outcome. Group I were those patients who became asymptomatic on treatment and group II those who died or remained symptomatic.

STATISTICAL METHODS

The data recorded in the data collection sheets of each patient was saved in a file prepared on Statistical Package for Social Sciences (SPSS) for Windows 97 and analysed with the help of the Department of Epidemiology and Medical Statistics of SQU, Muscat, Sultanate of Oman. The outcome was categorised as alive or dead at the time of last contact in December 1998. The statistical significance of the differences in the variables related to the outcome was tested using the unpaired t test in case of continuous variables and the Chi square test in case of discrete variables, accepting a $p < 0.05$ as significant. For the purpose of survival analysis the duration of illness was taken from the onset of first symptom of heart failure. It was assumed that all patients entered the study at the same point and patients were taken off the analysis as they died or completed the follow up period. Survival curves were constructed by the Kaplan-Meier method and the log rank method was used to compare the survival data on patient subgroups defined with reference to possible risk factors.

CHAPTER - 3

RESULTS AND DISCUSSIONS

RESULTS

Prevalence and Aetiology of Heart Failure

The total native population of Dhakliya region was 305,000 (males 159,000 and females 146,000). Non-Omani expatriates and children aged < 13 years living in the region were not included in the study. Thus 225,000 people (males 118,000 and females 107,000) in the age group of ≥13 years were considered as the study population. Age and sex distribution of the Omani population given in table 1 shows a high proportion of young people. During the three-year study period 1164 patients were identified as having symptomatic heart failure, giving a prevalence of 5.17/1000 population. This is based on the assurance that almost all patients who had presented to primary health centres with suspected heart failure were referred to the secondary care facility of Nizwa Hospital for further investigations. Table 2 shows the age and sex distribution of these patients. There were 713 males and 451 females, giving a higher prevalence in males [males 6.04/1000, females 4.21/1000, $p < .001$]. The prevalence increased with age from 1.05/1000 in the age < 45 years to 15.7/1000 in 45-64 years ($p < .001$) and 25.2/1000 in ≥ 65 years ($p < .001$). Age related analysis of aetiologies in table 3 shows that ischaemic heart disease was the commonest (51.7%) cause of heart failure followed by hypertensive heart disease (24.9%) and IDC (8.3%). 183 (15.75%) patients (males 103 and females 80) had signs, symptoms and radiological evidence of heart failure but exhibited a normal left ventricular ejection fraction (LVEF) of ≥ 50% (table 4). Diastolic dysfunction was present in 232/1164 (19.9%) patients.

Table 1. Age and sex distribution of the native Omani population of Dhakliya region*

Age	Male	Female	Total
≤ 12 yr.	41,000	39,000	80,000
13-24 yr.	64,000	46,000	110,000
25-34 yr.	14,000	22,000	36,000
35-44 yr.	12,000	13,000	25,000
45-54 yr.	10,000	12,000	22,000
55-64 yr.	10,000	8,000	18,000
≥ 65 yr.	8,000	6,000	14,000
Total	159,000	146,000	305,000

*figures are rounded to the nearest thousand

Table 2. Age and sex distribution of patients with heart failure (n=1164)

Age	Male	Female	Total
13-24 yr.	11	7	18 (1.5%)
25-34 yr.	31	12	43 (3.7%)
35-44 yr.	76	44	120 (10.3%)
45-54 yr.	100	95	195 (16.7%)
55-64 yr.	255	180	435 (37.3%)
≥ 65 yr.	240	113	353 (30.3%)
Total	713	451	1164 (100%)

Table 3. Distribution of the aetiology of heart failure by age (n=1164)

Age	IHD	HTN	IDC	ARR	LD	VHD	PE	CHD	MYO	PER	TOTAL
15-24 yr.	0	0	5	0	0	6	0	4	3	0	18
25-34 yr.	4	7	10	0	0	16	0	2	3	1	43
35-44 yr.	52	22	21	0	0	17	6	2	0	0	120
45-54 yr.	80	50	24	16	12	8	4	0	0	1	195
55-64 yr.	242	131	26	14	20	0	2	0	0	0	435
≥ 65 yr.	224	80	11	20	18	0	0	0	0	0	353
Total (n)	602	290	97	50	50	47	12	8	6	2	1164
Total (%)	51.7	24.9	8.3	4.3	4.3	4.0	1.1	0.7	0.5	0.2	100

IHD = ischaemic heart disease; HTN = hypertension; IDC = idiopathic dilated cardiomyopathy; ARR = cardiac arrhythmia; LD = lung disease; VHD = valvular heart disease; PE = pulmonary embolism; CHD = congenital heart disease; MYO = myocarditis; PER = pericardial disease

Table 4. Aetiologies of heart failure in patients with LVEF ≥ 50%

IHD	HTN	IDC	ARR	LD	VHD	PE	CHD	MYO	PER
40 (21.8%)	56 (30.6%)	0	20 (10.9%)	25 (13.7%)	20 (10.9%)	12 (6.6%)	8 (4.4%)	0	2 (1.1%)

Abbreviations as in table 3

Idiopathic Dilated Cardiomyopathy

Prevalence

A total of 111 patients were initially entered into the study with a provisional diagnosis of heart failure due to IDC. Of these 111 patients 14 (12.7%) were excluded as they were found on investigation to have coronary artery disease leaving 97 patients for analysis. The prevalence of IDC in Dhakliya region was thus 43.1/100,000 population over 3 years, i.e. 14.4/100,000 population/year.

Demography

(Table 5)

Patients were aged 15-69 years (median age 50 years) and included 56 males and 41 females (M: F=1.4:1). Social make up of patients recorded nearly all females being housewives and 34 of 56 males (60%) were either unemployed or only performed odd jobs mainly living on social benefits. Some of these were retired. No correlation could be found between IDC and their previous work pattern. Nearly all patients were married. Majority of married females had 5 or more children to care for. Parental consanguinity, a common occurrence in Arab culture, was apparent (31.9%). However only 3 patients could be identified as having another affected member in the family, and none of these had consanguineous parents. Since these patients were regarded as having familial IDC they were combined with the children with familial disease in the paediatric group for analysis and are further discussed in the sub-sections of chapter – 5 under familial dilated cardiomyopathy.

Out of 97 only 2 were smokers and all patients gave a satisfactory dietetic history with regular consumption of milk, meat, fish, green vegetables and fruits. All used iodised salt. The cooking habits of these people usually consists of roasting the meat

and boiling the vegetables. They used corn oil or sun flower oil as a cooking medium. Arabic coffee and dates were consumed daily.

None of these patients had any travel history out of the country except for occasional travel to visit relatives in close by towns. Their ethnic origin was local Omani. None of the patients reported any organised physical training program and only performed little regular exercise other than walks to the work.

Table 5. Demographic profile (n=97)

Characteristics	Groups	Numbers (%)
Age	15-24 years	5 (5.2%)
	25-34 years	10 (10.3%)
	35-44 years	21 (21.6%)
	45-54 years	24 (24.7%)
	55-64 years	26 (26.8%)
	≥ 65 years	11 (11.4%)
Sex	Male	56 (57.7%)
	Female	41 (42.3%)
Occupation	Civil servants	18 (18.5%)
	Business	3 (3.1%)
	Farmer	1 (1.1%)
	Student	1 (1.1%)
	Housewife	40 (41.2%)
	Unemployed	34 (35%)
Marital status	Single	3 (3.1%)
	Married	91 (93.8%)
	Divorced	1 (1.1%)
	Widow	2 (2.2%)
Consanguineous parents	Yes	31 (31.9%)
	No	66 (68.1%)
Affected family member	Yes	3 (3.1%)
	No	94 (96.9%)

Clinical Features

(Table 6)

Duration of symptoms at entry ranged from 1 month to 7 years [median 1 year, mean (SD) 1.3 (1.4) years], with majority (69/97) 12 months or less. Shortness of breath of varying severity was reported by all (100%) as the presenting complaint, with general fatigability being a common association. Other less frequently reported symptoms were palpitation, and syncope. Chest pain when reported (36%) was mostly atypical.

Table 6. Symptoms on presentation (n=97)

Symptoms	Number (%)
Shortness of breath	97 (100 %)
NYHA Class I	8 (8.2 %)
Class II	51 (52.6%)
Class III	36 (37.1 %)
Class IV	2 (2 %)
Fatigue	92 (94.8 %)
Paroxysmal nocturnal dyspnoea	54 (55.7 %)
Palpitations	28 (28.8 %)
Angina typical	7 (7.3 %)
atypical	35 (36 %)
Syncope	4 (4.1 %)
Peripartum onset	4 (4.1 %)
History of acute myocarditis	2 (2 %)

Investigations

Chest x-ray

(Table 7)

Chest X-ray revealed cardiomegaly (CTR of >50%) in all patients but only 72 (74%) had congested lung fields at presentation. There was no radiological evidence of pulmonary hypertension in any patient. 2 patients had acute LVF with pulmonary oedema at first presentation.

Resting / 24 hour Holter Electrocardiography

(Table 7 and 8)

Cardiac rhythm at entry was sinus in 87 (89.6%) patients, atrial fibrillation in 8 and, atrial flutter and junctional rhythm in 1 each. Frontal plane QRS axis was either normal (45.3%) or leftward (49.5%). The major conduction abnormality as assessed by QRS configuration and duration was of left bundle branch block and intraventricular conduction delay type. ECG evidence of left or biventricular hypertrophy was the predominant feature (78.4%) and isolated right ventricular hypertrophy was seen only in 1 patient.

ECG features of 14 patients, who were initially included but later excluded from the study due to the detection of CAD, were analysed to see if there were any special features which would help differentiate them from other 97 who finally entered the study as IDC patients. No distinctive features were noted. All 14 were in sinus rhythm. From the morphological point of view left ventricular hypertrophy pattern of deep S-wave in lead V1 or V2 and a tall R-wave in lead V5 or V6 was evident in all 14 patients (sum of S and R waves > 35mm). However, T-wave inversion noted in

Table 7. Chest X-ray, ECG and Echocardiographic findings (n=97)

Finding	Number (%)	
Chest X-ray		
CTR 50-69%	93 (95.9%)	
CTR >70%	4 (4.1%)	
Congested lung fields	72 (74%)	
ECG		
Sinus rhythm	87 (89.6%)	
Atrial fibrillation	8 (8.2%)	
Atrial flutter	1 (1.1%)	
Junctional rhythm	1 (1.1%)	
LAD	48 (49.5%)	
RAD	5 (5.2%)	
RBBB	1 (1.1%)	
LBBB	16 (16.5%)	
IVCD	25 (25.8%)	
LVH	67 (69.1%)	
RVH	1 (1.1%)	
BVH	9 (9.3%)	
24 Hour Holter ECG		
Atrial tachycardia	4 (4.1%)	
Atrial fibrillation	8 (8.2%)	
Ventricular ectopics	95 (97.9%)	
Unifocal	10 (10.3%)	
Bi or multifocal	85 (87.6%)	
Salvos (3 beats)	30 (30.9%)	
Ventricular tachycardia		
≤10 beats	60 (61.8%)	
>10 beats	9 (9.3%)	
Torsade de Pointes	3 (3.1%)	
CHB	1 (1.1%)	
Echo-Doppler studies		
	Initial (n=97)	Final (n=74)
LVEF < 30%	33 (34%)	27 (36.5%)
30 - 49%	64 (66%)	47 (63.5%)
MR Mild	61 (62.8%)	60 (81%)
Severe	27 (27.8%)	10 (13.5%)
TR Mild	38 (39.2%)	20 (27%)
Severe	12 (12.3%)	6 (8%)
AR Mild	27 (27.7%)	20 (27%)
PR Mild	21 (21.6%)	15 (20%)
Diastolic dysfunction	39 (40.2%)	20 (27%)

CTR = Cardio-thoracic ratio; ECG = electrocardiogram; LAD = left axis deviation; RAD = right axis deviation; RBBB = right bundle branch block; LBBB = left bundle branch block; IVCD = intraventricular conduction delay; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; BVH = biventricular hypertrophy; CHB = complete heart block, LVEF = left ventricular ejection fraction; MR = mitral regurgitation; TR = tricuspid regurgitation; AR = aortic regurgitation; PR = pulmonary regurgitation.

V5 or V6 of seven patients was rather symmetrical and more prominent compared to similar changes noted in IDC patients representing so called "strain pattern" of LVH. But, similar symmetrical T-wave inversion was also noted at least in some patients of IDC group. Most patients (65/97) in IDC group had non-symmetrical T-wave inversion.

24-hour Holter ECG recorded both atrial and ventricular arrhythmias. Previously unsuspected arrhythmias seen included atrial fibrillation in 4 patients and ventricular tachycardia in 15. The frequency of ventricular ectopic activity reduced considerably during sleeping hours (Table 8).

Table 8. Ventricular ectopic activity (n = 97)

Ventricular Ectopic Activity	Min	Max.	Mean	St. Dev.
Total No. of VE	4	52844	9910	13827
VE 6 AM – 3.59 PM	0	18338	2847	4125
VE 4 PM – 11.59 PM	1	18874	2712	4022
VE 12 Midnight – 5.59 AM	1	3050	1516	820
VT 6 AM – 3.59 PM	0	840	34	145
VT 4 PM – 11.59 PM	0	285	15	51
VT 12 Midnight – 5.59 AM	2	56	8	2.5

VE = ventricular ectopics; VT = ventricular tachycardia

Echocardiography

(Table 7 and 9)

Echo-Doppler studies revealed global hypokinesia of the left ventricle with ejection fractions < 50% in all and severe left ventricular dysfunction (LVEF ≤ 30%) was seen in 33 (34%) patients, of whom only 18 had class III or IV symptoms. Lowest LVEF recorded was 18%. Mitral regurgitation was present in most (88/97) but was severe only in 27 (27.8%) with no MR detected in 9/97. About one half of patients also had tricuspid regurgitation and a few had mild aortic and pulmonary regurgitation. There was no evidence of floppy/myxomatous mitral valve prolapse or evidence of papillary muscle/chordae dysfunction which could have caused mitral regurgitation. But all 27 with severe MR had dilated LV cavity (≥ 6.1 cms) and a significantly reduced LVEF (18-40%) (table 10). Within its diagnostic limitations diastolic dysfunction as assessed by mitral diastolic Doppler flow pattern was found in 40.2% patients. Although global systolic hypokinesia was the major contractile abnormality disproportionately impaired septal motion was seen in 50% (51/97) of patients. Right ventricular ejection fraction was reduced in only 12 patients (< 30% in 8 and 30-49% in 4). LV Thrombus formation was detected in 10 patients.

An important observation is that none of the patient had septal or posterior wall hypertrophy suggesting that there is a poor correlation of LVH pattern seen on ECG with the echocardiographic evidence of concentric left ventricular hypertrophy.

Table 9. Echocardiographic measurements of patients with IDC (n=97)

Measurements	Initial	Final
LVDD (cms)	5.6 – 7.2 (6.1)	5.4 – 7.9 (6.4)
LAD (cms)	3.9 – 5.3 (4.4)	4.0 – 5.6 (4.3)
IVST (cms)	0.8 – 1.1 (1.0)	0.8 – 1.1 (1.0)
LVPWT (cms)	0.9 – 1.2 (1.0)	0.9 – 1.2 (1.0)
LVEF (%)	18 – 45 (38)	20 –54 (42)

LVDD = left ventricular diastolic dimension; LAD = left atrial dimension IVST = intra-ventricular septal thickness; LVPWT = left ventricular posterior wall thickness; LVEF = left ventricular ejection fraction

Table 10. Echocardiographic values in patients with mitral Regurgitation (n=88)

Measurements	Mild MR (n=61)	Severe MR (n=27)
LVDD (cms)	5.7 – 6.4 (6.2)	6.1 – 7.9 (6.7)
LAD (cms)	3.9 – 4.4 (4.1)	4.2 – 5.6 (4.4)
LVEF (%)	28 – 48 (45)	18 – 40 (32)

Abbreviation as in table 9

Transoesophageal echocardiography could be performed in only 95 patients since 2 patients died on initial presentation and were too sick to undergo this procedure. It showed a LV cavity thrombus in ten patients, LA appendage clot in 3 and presence of spontaneous echo contrast in 13 patients.

Multiple Gated Pool Scan (MUGA)

(Table 11)

MUGA scan could be performed in only 71 patients. All exhibited global hypokinesia but the severity varied in various segments. Septal motion impairment was evident as seen also on echocardiography. LVEF was < 50% in all 71 patients but RVEF was reduced in only 14. In all 71 patients who underwent both MUGA scan and echocardiography, a comparison of LVEF measurement revealed that the one measured by MUGA scan was consistently lower than as measured by echocardiography (12-44% and 18-45% respectively). There was a strong correlation in the values of EF between the two methods of measurement (Pearson's $r = 0.881$, $p < 0.001$ and Spearman's $r = 0.849$, $p < 0.001$).

Table 11. Ejection fraction as assessed by MUGA Scan (n = 71)

LVEF	No. (%)	RVEF	No. (%)
< 30%	21 (29.6%)	< 30%	2 (2.8%)
30 – 49%	50 (70.4%)	30 – 49%	12 (16.9%)
≥ 50%	0 (0%)	≥ 50%	57 (80.3%)

Exercise Testing and Coronary Arteriography

These could be performed in only 95 patients since two patients died on initial presentations. Fatigability and dyspnoea were the major limiting symptoms on exercise testing but palpitation also occurred in a significant number of patients. Significant ventricular arrhythmias (salvos of 4 or more, multifocal ectopics, brief episodes of VT) necessitated termination of the test in 37.8%. But ventricular tachy-arrhythmia was not the sole reason for terminating the test in all these 37.8% patients. These arrhythmias were noted in association with other limiting factors, mainly dyspnoea and fatigue. Exercise induced chest pain was reported by 18 patients but ST segment changes suggesting myocardial ischaemia were seen only in 13 (table 12). There was no correlation between chest pain and ST segment changes. 13 patients who developed ST segment changes were further analysed for the type of the change. 3 had horizontal, 3 down-sloping and 7 had up-sloping ST segment depression. None had ST segment elevation. Reduction in exercise capacity was evident in most patients with a highest total exercise time of only 14.3 minutes (± 3.61) by modified Bruce protocol (table 13).

Coronary arteriography revealed no demonstrable narrowing in 89/95 patients. Minor atheroma of major epicardial vessels and their branches was seen in 6 patients but in all patients it was causing < 40% luminal narrowing (table 14).

Treadmill Exercise Testing (n = 95)

Table 12. Reasons for the termination of the exercise test

Fatigue	68 (70.1%)
Chest Pain	18 (18.9%)
Dyspnoea	86 (90.5%)
Ventricular Arrhythmia	36 (37.8%)
Palpitation (Excessive Heart Rate Response)	34 (35.0%)
Excessive Blood Pressure Response	0 (0%)
ST Segment Changes	13 (13.6%)

Table 13. Heart rate response on exercise testing

	Min	Max.	Mean	St. Dev.
At Rest	45	115	82.63	15.33
At Peak Exercise	94	190	141.13	23.17
Total Exercise Time (Min)	1.5	14.3	11.1	3.61

Table 14. Coronary arteriography (n = 95)

Normal Coronaries	89 (93.7%)
Short Left Main Stem	70 (73.6%)
Left Main Stem Disease	0 (0%)
Left Anterior Descending Disease	3 (3.1%)
Left Circumflex Disease	3 (3.1%)
Right Coronary Artery Disease	1 (1%)
Multiple Vessel Disease	2 (2.1%)
Major Branches Involvement	3 (3.1%)

Natural History

Clinical Course (Figure 2)

Two patients died from acute heart failure at presentation. Their echocardiographic parameters are given in table 15. The remaining 95 patients were followed up for periods ranging from 1 to 8 years (median 6 years). Among them, 40 (41.2%) remained stable in the same functional class of heart failure throughout the study period. Another 28 (28.8%) experienced acute exacerbation of heart failure requiring hospitalisation, but remained stable thereafter. These 68 patients (aged 18-62 years, males 34 and females 34) together were placed in Group A for analysis. Of the remaining 27 patients (aged 20-66 years, males 20 and females 7) 13 (13.4%) had repeated exacerbations of heart failure and deteriorated in spite of initial improvement and along with another 14 patients (14.4%) who experienced gradual deterioration were placed in Group B for analysis. This grouping was done to separate two groups of patients, one which runs a stable course and the other with a down-hill course. Mean echocardiographic values did not change significantly in group A but LVDD and LVEF deteriorated in group B (table 16). Patients in group A did not exhibit any deterioration in LVEF or require modification of anti-heart failure medication. In fact few patients (6/68) in this groups actually showed mild improvement in their LVEF. Group B patients exhibited deterioration in LVEF by 5-11%. Among the 41 patients with exacerbations of heart failure (28 of Group A and 13 of Group B), the recurrence of symptoms could be attributed to non-compliance to medication in 12, development of new arrhythmias in 8, and no specific factor could be identified in the remaining 21. Other notable events were hemiplegia (thromboembolic) in 2/97 (2.1%) and pulmonary embolism in 4 (4.2%).

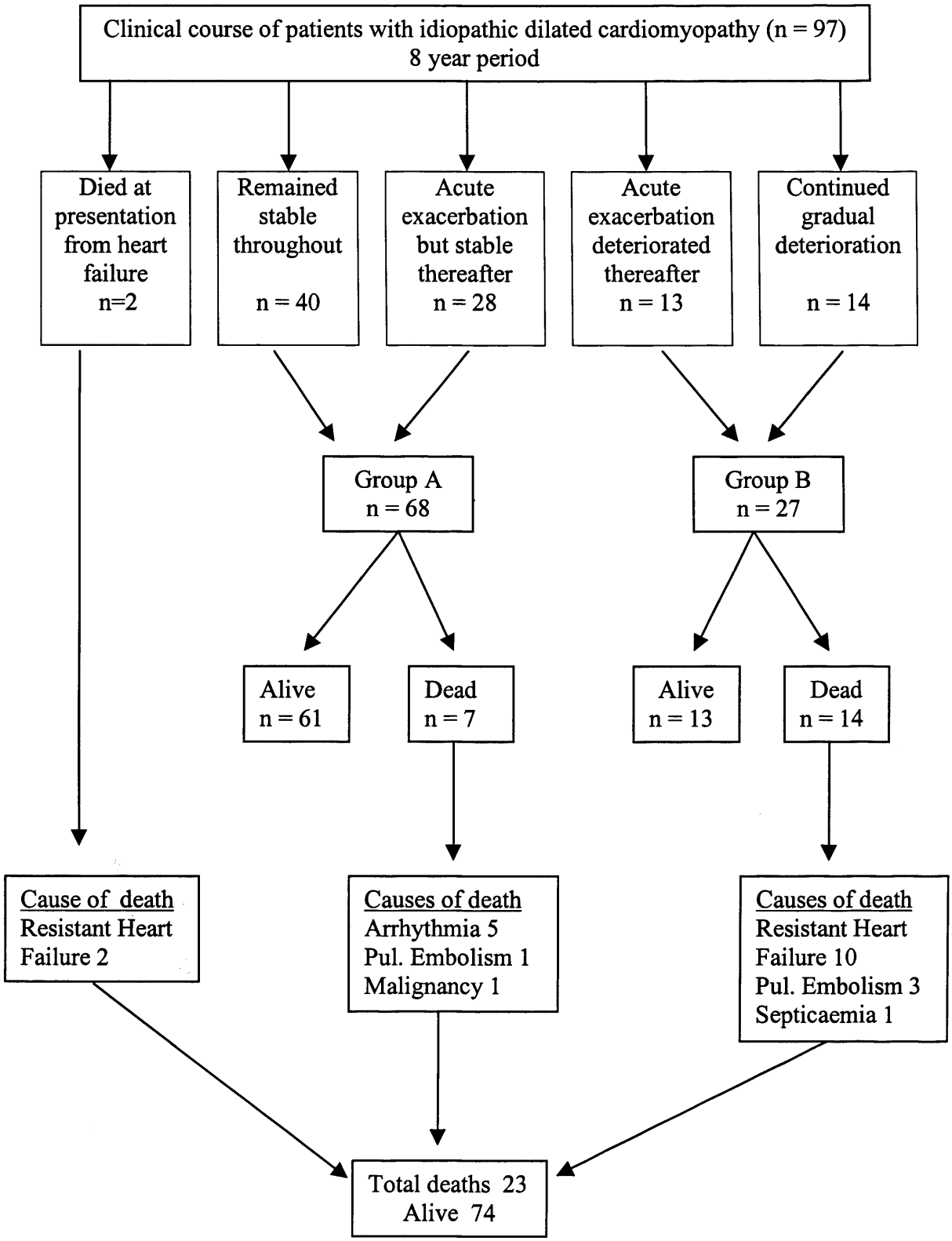

Clinical course of patients with idiopathic dilated cardiomyopathy (n = 97)
8 year period
Died at presentation from heart failure n=2
Remained stable throughout n = 40
Acute exacerbation but stable thereafter n = 28
Acute exacerbation deteriorated thereafter n = 13
Continued gradual deterioration n = 14
Group A n = 68
Group B n = 27
Alive n = 61
Dead n = 7
Alive n = 13
Dead n = 14
Cause of death
Resistant Heart Failure 2
Causes of death
Arrhythmia 5
Pul. Embolism 1
Malignancy 1
Causes of death
Resistant Heart Failure 10
Pul. Embolism 3
Septicaemia 1
Total deaths 23
Alive 74

Figure 2.

Table 15. Echocardiographic parameters of 2 patients who died on admission

Measurement	Patient -1	Patient -2
LVDD (cms)	7.6	7.3
LAD (cms)	5.0	5.0
LVEF (%)	18	20
MR	Severe	Severe
TR	Severe	Severe

LVDD = left ventricular diastolic dimension; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; TR = tricuspid regurgitation

Table 16. Echocardiographic measurements in Group A and Group B

Mean values (Range)	Group A		Group B	
	Initial	Final	Initial	Final
LVDD (cms)	6.1 (5.6-6.7)	5.9 (5.1-6.6)	6.5 (5.9-7.9)	6.9 (5.9-7.9)
LAD (cms)	4.1 (3.9-4.6)	4.1 (3.8-4.6)	4.3 (4.2-5.6)	4.3 4.2-5.4)
LVEF (%)	42 (26-45)	44 (28-54)	32 (18-36)	24 (18-30)

Abbreviations as in table 15

Death occurred in 23 of the 97 (23.7%) patients during the study period, 2 at initial presentation, 7 in group A and 14 in group B. Deaths in group A occurred in patients whose heart failure was well under control and could be attributed to fatal ventricular arrhythmias in 5 (3 of which were at home), pulmonary embolism in 1 and disseminated malignancy (non cardiac) in 1. All the remaining 14 deaths occurring in

group B can be attributed to resistant heart failure. Terminal events in these patients were mainly unresponsive hypotension despite aggressive inotropic and other supportive measures but eventually cardio-respiratory arrest followed. Additional contributing factors in this group included pulmonary embolism in 3 and Pseudomonas septicaemia in 1.

Survival *(Figure 3)*

The survival rates from the onset of first symptoms were 94% at one year [95% CI 88% to 99%], 86% at 3 years [95% CI 79% to 93%], 76% at 5 years [95% CI 67% to 86%], and 68% at 8 years [95% CI 54% to 82%]. Mean survival was 9.8 years [95% CI 8.8 to 10.9 years,]. Median survival i.e. time at which 50% of the patients died could not be computed as more than 50% of patients were alive at the conclusion of the study.

Analysis of outcome variables

Live and dead patients were compared with regard to age, sex, duration and severity of symptoms and LVEF on presentation, and presence of ventricular tachycardia during follow-up. NYHA Functional Class III or IV, low LVEF (< 30%) and presence of significant ventricular tachycardia (>10 beats or Torsade de Pointes) on 24 hour Holter ECG were identified as significant predictors of poor outcome on univariate analysis (Table 17). A multivariate regression analysis was performed with the above variables, and low LVEF was the only factor that predicted death ($p = .01$). Severe mitral regurgitation was also a significant predictor ($p = < .001$) (Table 18). Survival curves were plotted for the different values of the LVEF. Patients with LVEF < 30% (Figure 4) had mean survival of 6 years (95% CI 4.5 yr. to 7.4 yr.) while for those

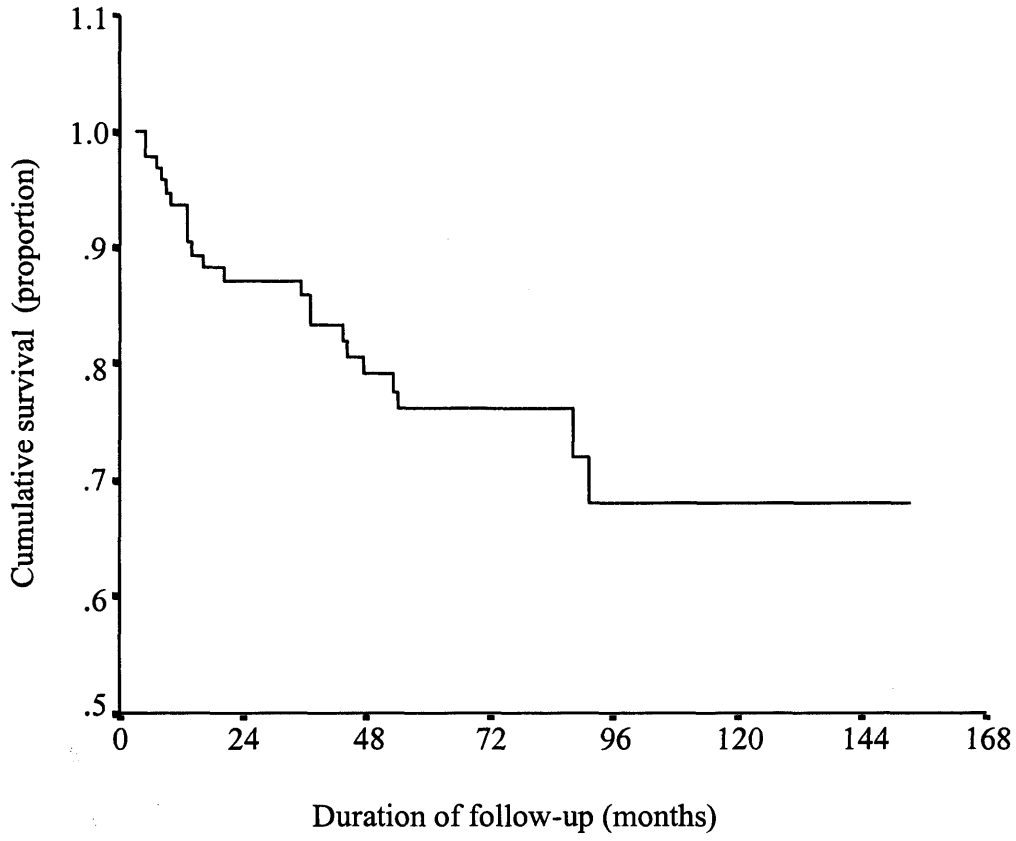


Figure 3. Cumulative survival in idiopathic dilated cardiomyopathy (n = 97)

with LVEF >30% it was 10.8 years (95% CI 9.5yr to 11.9 yr.). The difference was highly significant (Log Rank 7.22, p = < .01). Similarly NYHA class 3 and 4 (Figure 5) were associated with decreased survival (8.3 yrs. Vs 10.5 yrs.; Log Rank 3.9, p = < .05).

Table 17. Analysis of variables related to outcome in Idiopathic dilated cardiomyopathy (n = 97)

Outcome variable	Live Mean (SD)	Dead Mean (SD)	Live (Number)	Dead (Number)	Univariate p value	Multivariate p value
Age*	48 yr. (13 yr.)	46 yr. (12 yr.)			0.52	0.49
Sex			M/F 44/30	M/F 12/11	0.53	0.73
Duration of symptoms*	1.5 yr. (1.3 yr.)	1 yr. (1.2 yr.)			0.20	0.09
LVEF*† ≠	36% (8.6%)	31% (7.5%)			0.037	0.07
Severity of symptoms* ≠			A/B 50/24	A/B 10/13	0.008	0.02
Significant VT** ≠			6/74	6/23	0.012	0.32

*At entry into study; ** during follow up; † significant on multivariate analysis; ≠ significant on univariate analysis; M = male; F = female; LVEF = left ventricular ejection fraction; VT = ventricular tachycardia; A = NYHA functional class I & II; B = NYHA functional class III & IV

Table 18. Analysis of severity of MR in dead and alive patients

Patients	No MR and mild MR	Severe MR	Total
Alive	64	10	74
Dead	6	17	23
Total	70	27	97

MR = mitral regurgitation; (p = < .001)

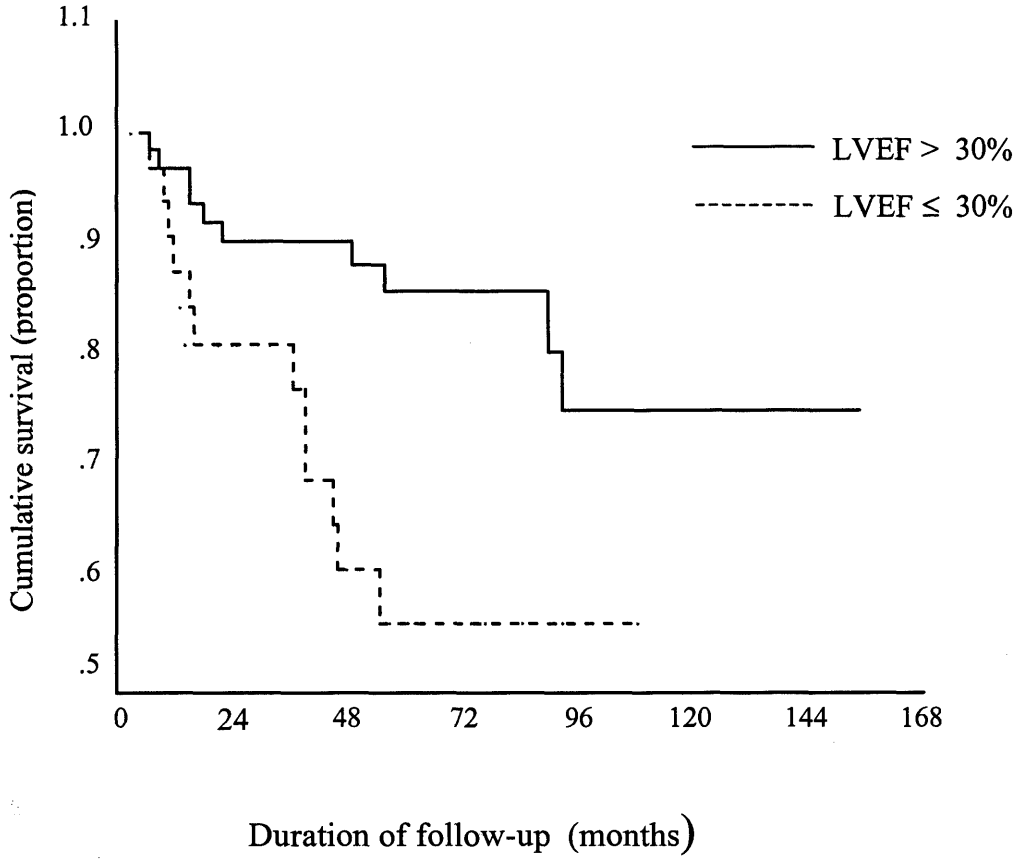


Figure 4. Comparison of survival in IDC based on initial left ventricular ejection fraction (LVEF)

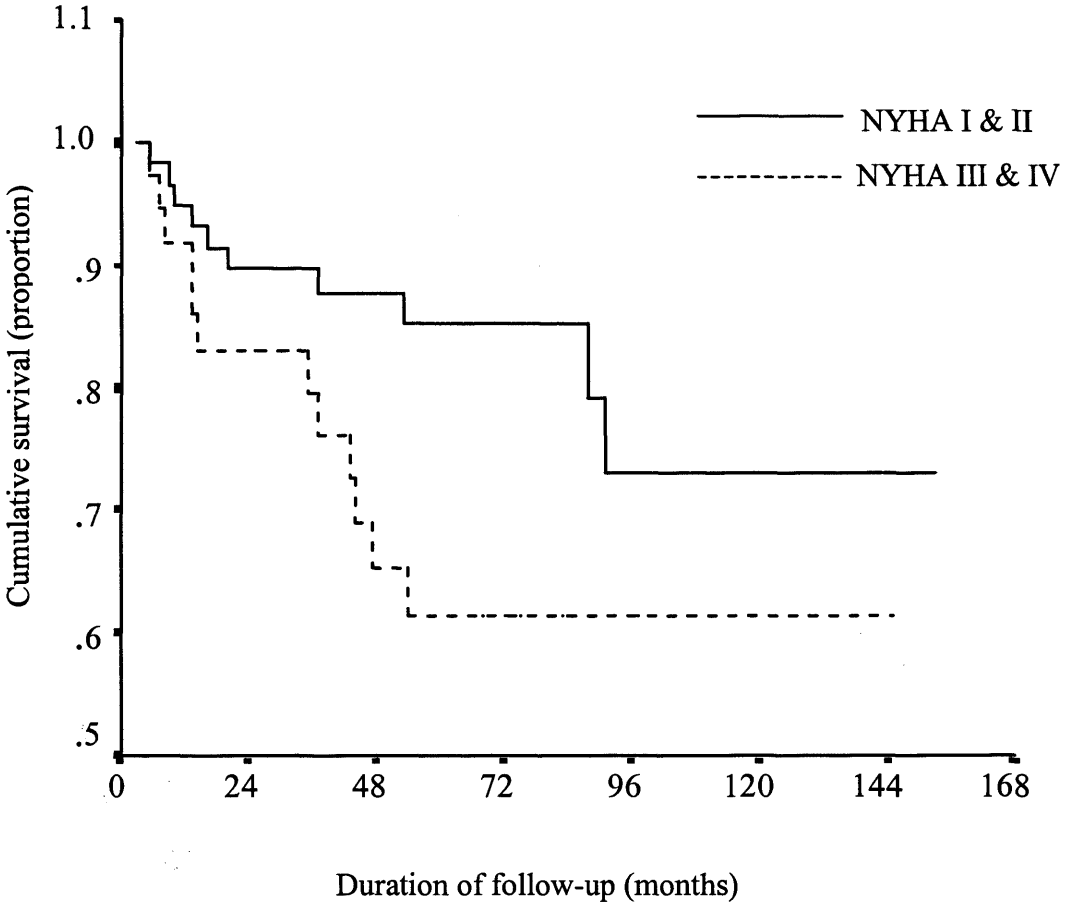


Figure 5. Comparison of survival in IDC based on NYHA functional class

This present chapter 3 was dedicated to prevalence, demography, clinical features, diagnostic investigations and natural history of IDC. Since the results related to other aspects investigated in this study were considered under special groups of patients, these are presented in separate chapters as follows : **Blood Investigations** - Chapter 4; **Family Screening, Peripartum IDC, IDC in children** – Chapter 5.

DISCUSSIONS

PREVALENCE AND AETIOLOGY OF HEART FAILURE

This study represents the first systematic compilation of data on the prevalence and aetiology of symptomatic heart failure in the Arabian Peninsula. Health services in the Dhakliya region of Oman chosen for the study are entirely run by the State and Nizwa Central Hospital is the only secondary care hospital in this region. It receives patients from all state run primary health centres and other small hospitals in the region, with a direct access outpatient clinic. With a close liaison and by my regular visits to the centres it was ensured that all patients with heart failure were referred to Nizwa hospital. Thus I believe that I have been able to include in this study almost all patients with symptomatic heart failure who had come to medical attention from this region of Oman.

It is necessary that the epidemiology of this condition ascertained to meet the future challenges of increasing numbers of patients with heart failure posing additional health care burden on the hospital system. Published studies on heart failure have reported the extent of the problem both in terms of the incidence and the prevalence. Some studies have also used the term yearly prevalence to indicate the total prevalence divided by the duration of study in years.

Heart failure is an increasing cause of morbidity and mortality, especially in people aged above 65 years [180-182], but its epidemiological data remains scarce [183,184]. This increased prevalence of heart failure can largely be attributed to the ageing population and an improved survival of affected patients [185-187]. There are hospital and population based studies but the result are variables mainly due to

differences in the study design particularly with the method of the survey used [188-192]. In this study the objective evidence of heart failure was established by the demonstration of impaired systolic and /or diastolic dysfunction by echocardiography. Furthermore where the primary aetiology causing the symptoms and signs of heart failure may not have affected the myocardial systolic function, the clinical diagnosis of heart failure was confirmed by a chest x-ray showing pulmonary congestion. This represents a sub-group of patients of heart failure with preserved systolic function. This is discussed later.

The reported prevalence of heart failure ranges between 3-20 cases/1000 population, while the incidence ranges from 1-5/1000 population and increases to 40/1000 per annum for those over 75 years of age [180-182, 193]. The Framingham Study [194] had placed the annual incidence at 3.7/1000, while another study from USA showed the prevalence of self-referred cardiac failure in the adult population as 1.1% [195]. Cowie et al [192], through a surveillance of acute hospital admissions over a 20 month period showed a crude incidence of 1.3/1000 per year for newly diagnosed heart failure among those aged $\geq$ 25 years which increased sharply to 11.6 in those aged $\geq$ 85 years. In this Omani project, the documentation of a prevalence of 5.17/1000 population over a three-year period is not strictly comparable due to a large population of young people and low population of old people over 65 years of age in the Omani population of the study sample. In future, with the increase in the number of elderly people in the community this is likely to change. The Rotterdam study [196] is however, closer to this survey in its design of assessment by clinical signs. It reported an overall prevalence of 3.9% but stated that asymptomatic LV dysfunction can be present in up to 60% of patients. In a similar study using echocardiography as

the screening method, McDonagh et al [197] from a sub-study of "Third Glasgow MONICA Coronary Risk Factor Survey" (response rate 83%), in a sample of 1640 patients reported that 2.9% of the population had definite LV dysfunction (LVEF < 30%) of which 50% were asymptomatic. Symptomatic LV dysfunction was present in only 1.5%, but increased in older age group. Therefore, it is important to appreciate that the data in the published studies are significantly influenced by the methodology. In this clinically designed Omani study only symptomatic heart failure was covered. Thus the differences in the prevalence data as seen in Omani population can also be partly due to variation in the study design.

Although population-based information in heart failure is limited [198], there is evidence of a 60% increase in hospital admissions for heart failure in Scotland from 1980 to 1990 [185]. A similar trend has been seen in the USA in the last two decades [186, 199]. There is gathering evidence that the incidence of heart failure is increasing with a progressively ageing population and increased survival of patients with ischaemic heart disease (IHD) and hypertension [181, 182, 200]. Rodriguez et al from Spain [187] reported a 71% increase in hospital admissions due to heart failure from 1980 to 1993. Hospitalisation rates for heart failure also rose by 47% during the same period predominantly in persons aged > 65 years and proved greater among women, accounting for 5% of all hospital admissions in this age group. The findings of the Spanish study were, in general, similar to the Scottish [185] and the American [186, 199] studies. In Scotland however, the increase in hospitalisation was also reported for young adults, and in addition the percentage of heart failure admissions over total admissions grew in the period 1980-1990. In the USA, on the other hand, the rise in hospitalisation in the period 1971-1990 basically affected above 65-year age group.

A comparison of this study from Oman to the trends published from Europe or USA is not feasible due to the non-availability of any previous Omani data.

Heart failure in general is more common in elderly males mainly due to a preponderance of IHD. In the Framingham Study the incidence in males was 2.3/1000 while that in females was 1.4/1000 [194]. A similar ratio is seen in other studies [183, 185, 186, 192, 197] excepting the Spanish study [(187], which reported increased hospitalisation due to heart failure in women over 65 years of age, and no sex difference was found in the Rotterdam study [196]. In this Omani study the large number of patients between 45-64 and ≥ 65 years of age groups indicate a higher prevalence of this condition in the older population. The male/female ratio showed male predominance but the ratio narrowed with advancing age due to the increasing number of females with hypertension and IHD in the older age group.

Patients presenting with symptoms of heart failure but preserved myocardial systolic function need attention. Diastolic dysfunction can be responsible for symptoms in some of these patients. A Study by Caruana et al [201] showed that for most such patients (102/109) there is an alternative explanation for their symptoms – for example, obesity, lung disease and myocardial ischaemia – and the diagnosis of diastolic heart failure is rarely needed. Finding of preserved LV systolic function in 109/159 (68%) of the patients referred as heart failure in this study appears high. This could be due to referral bias to a specialised centre.

It is also interesting to note that in a latest study by Petrie et al [202], a new measure of LV systolic function is described – Left ventricular systolic atrio-ventricular plane

displacement. It was suggested that approximately 25% of the patients of suspected heart failure but preserved systolic function by conventional echocardiography may in fact have heart failure caused by subtle systolic dysfunction, measured by this method, rather than isolated "diastolic heart failure". This new method would need further validation by other workers. 15.7% of the patients with normal LV systolic function in this Omani population had mixed aetiologies. These patients either had conditions where the clinical picture of heart failure may not necessarily be due to LV dysfunction, e.g. mitral stenosis, arrhythmias and pericardial diseases or had diastolic dysfunction without systolic impairment as is sometimes seen in systemic hypertension. A significant number of patients in this cohort had IHD. This could reflect a patchy regional dysfunction with a satisfactory over all systolic function. Only 9 patients in this study can be regarded as significantly obese (BMI 32-38 kg/m^2) but in the rest BMI ranged between 26–30 kg/m^2. The presence of acute heart failure which could have been precipitated by a variety of factors justified the inclusion of these patients in the study.

A report by Kasper et al [203] puts IHD as the cause of heart failure in only 11% with IDC as the most common at 47% and Felker et al [204] report IDC at 51%, but both these studies were referring to the patients who were initially classified as dilated cardiomyopathy. The most frequent causes of heart failure in Omani patients were IHD and hypertension, consistent with the data published earlier [198]. IDC at 8.3% however, is higher than as reported from USA and Europe considering that these are not selected patients and represent heart failure in general [200, 205]. A comparatively lower number of patients with lung disease can be attributed to the low prevalence of smokers in the community. A significant number of patients with

arrhythmias without structural heart disease can be explained by the presence of all cases of this aetiology in our study being in the older age group when cardiac arrhythmias are more frequent. Atrial fibrillation was the commonest arrhythmia present in 145 (12.6%) of the patients. In the majority (70%) it was of long duration, present for months or years and was idiopathic in 30%, with other aetiologies (VHD, IDC, IHD, LD, HTN, PE & CHD: abbreviations as in table 3, page 66) in the rest. The low percentage of patients with valvular heart disease was interesting. With the falling incidence of rheumatic fever [206] and widespread use of surgical and interventional valvular procedures, chronic rheumatic valvular heart disease as the cause of heart failure is less common. Nevertheless, it is an important morbidity factor due to heart failure in the younger age group. Finding congenital heart diseases to be even lower in frequency is hardly surprising since almost all defects are surgically corrected in childhood.

A challenging aspect of heart failure is to establish an early diagnosis at primary care level, particularly when patients are asymptomatic or have minimal symptoms. It is often mis-diagnosed or under-diagnosed at this level, particularly in those with symptomless or borderline left ventricular dysfunction. Echocardiographic assessment of LV function with suspected heart failure leads to more effective diagnosis [207], but is not available readily to general practioners. A survey of a random sample of primary care physicians in six European countries reported that only a maximum of 37% of general practioners had direct access to echocardiography [208, 209]. Measurement of plasma concentration of BNP is emerging as a potential tool for easy and early diagnosis [210, 211], but reports that it was not helpful and did not add significantly to early diagnosis have also appeared [212, 213]. It is suggested

however, that the BNP assay holds an exciting potential for diagnosis of heart failure with the possibility that it can aid in the treatment and predicting prognosis [208]. An inclusion of this test in this Omani study would have been useful but this could not be done due to non-availability of the test.

Thus this survey of **symptomatic** heart failure in a native adult Omani population revealed a prevalence of 5.17/1000 population over a three year period with a preponderance of males and older age group. This prevalence could be an under-estimate since asymptomatic patients were not included. IHD was the most common cause of heart failure. Hypertension and IDC were other significant aetiologies. 15.7% of symptomatic heart failure patients had normal LVEF.

In addition to providing data on the aetiology of heart failure this exercise, as part of the protocol for preliminary screening was of enormous help in selecting the patients with IDC for the purpose of the main project.

IDIOPATHIC DILATED CARDIOMYOMATHY

Prevalence

Again it needs to be mentioned that Nizwa Central Hospital is the only general hospital in the Dhakliya region of Oman. It has direct access out-patient and emergency services. It also receives referred patients from primary health centres and other small hospitals in the region. The system of free medical services and the good health infrastructure in Oman facilitated referral and investigation of these patients. I have in this study followed WHO criteria for diagnosis of IDC [2] and excluded

patients with alcoholism, diabetes, hypertension, ischaemic heart disease and thyrotoxicosis. In fact all patients initially screened denied any history of alcohol intake. This is not surprising since alcohol consumption is not common in Omani society. Thus I believe that I have included all patients with only a specific diagnosis of IDC who came to medical attention from the Dhakliya region. It was also ensured that patients with other causes of dilated cardiomyopathy were excluded.

Physicians and general practitioners in Oman for some time had observed a higher prevalence of IDC in this country compared to other parts of the world particularly Europe, UK and USA (personal communication). Depending on the diagnostic criteria used incidences reported from Caucasian population range from 5-8/100,000 population. Williams and Olsen [13] in their study covering a population of about 913,000 over two distinct areas in United Kingdom reported a yearly prevalence rate of 8.3/100,000. A similar figure of 9.9/100,000 was reported in a Scottish study over a five-year period and it was thought that this rate was higher than earlier reported [214]. However, Codd et al [4] in a study in Olmsted County in USA found a much higher prevalence of 36.5/100,000 population in a cross-sectional study. The latter 2 studies were retrospective in nature and included in addition to IDC, all patients with heart failure such as ischaemic, hypertensive and alcoholic heart diseases. In a postmortem study of 5252 necropsies over a period of 2 years, Rakar et al [205] from Italy reported 4.5/100,000/yr incidence of IDC but only 2.45/100,000/yr of clinical incidence during the same period - combined together giving a total incidence of 6.95/100,000 new cases a year. A large case registry based study in China [15] during a 5-year period (1985-89) reported 2.6/100,00 person years, increasing from 1.7 in 1985 to 3.3 in 1989. A relatively limited comparative report of dilated

cardiomyopathy in Dubai (United Arab Emirates) and Moscow showed that incidence of IDC and peripartum cardiomyopathy was higher in Dubai [10], however this study did not report the racial origin of their sample and Dubai being a cosmopolitan state with a large expatriate population, the validity of the data in relation to the local Arab population is not verified.

This prospective study of IDC in the native population in a circumscribed region of the Sultanate of Oman ensured exclusion of patients with other causes of dilated cardiomyopathy and concluded a relatively high yearly prevalence (14.4/100,000/year) of IDC in the study population. This higher prevalence is likely to be due to the use of a generous LVEF of < 50% as the diagnostic criterion compared to < 45% or even < 40% in many studies [215]. In the Omani study, a selection of LVEF of < 50% was taken to ensure that patients with even the mildest systolic dysfunction are not missed out. Another contributing factor could be referral bias to a specialised cardiac unit. Since this was not a population-based study and some patients may have escaped attention, particularly the asymptomatic ones, the true prevalence of this disease is likely to be even higher.

Demography

Sex and Race

Idiopathic dilated cardiomyopathy (IDC) can develop at any age and affects both sexes. In our study population maximum number of patients (84.5%) were in the age group 35-64 years and males outnumbered females (M:F=1.4:1). Findings in this study are similar to those of Coughlin et al who reported an incidence of 3.5/100,000 in males compared to 2.5 in females [7,8]. Pan et al [15] have also reported a slight male preponderance of 3.0:2.2/100,000 population. Heart failure in general was also shown to be commoner in males compared to females in a Finnish Study [11]. Regarding racial predisposition IDC is reported to be more prevalent in black race [216] with an increased risk of death [217]. Coughlin et al [218] suggested a strong association with black race with an estimated relative risk of mortality of 5.41 ($P < or = .02$). This was thought to be caused by a greater severity of disease at the time of diagnosis or by racial differences in cardiac care accounted for by socio-economic factors [219]. Sanderson et al however, from Kenya found nearly 50% of their patients with IDC to have biopsy proven myocarditis in the local black race population [59]. A recognised 2.5 fold increase in the risk of developing IDC [5, 14] in black males as compared to white, which is unexplained by other variables may provide an explanation to the finding of a high prevalence in Omani male population due to its East African background. Although the local Omani population cannot be described as black race there are ancestral East African connections. Since the family tree dating back several generations was not available, a clear explanation for this high prevalence on the basis of race cannot be defined but a higher prevalence of IDC in the local population of other Arab countries (personal communication by

observation) does point to the role of local factors and cultural practices in this region – genetic, environmental and infection.

Some interesting data have been reported by De Maria et al [220] showing that females presented with more severe symptoms and signs of heart failure, higher cardiothoracic ratio (CTR) and higher frequency of left bundle branch block. They also exhibited significantly greater left ventricular (LV) end diastolic dimensions. Exercise duration was shorter in women than in men but did not show different prognosis. Coughlin et al [8] in their report have examined the risk factors for IDC in women showing asthma, diabetes mellitus, hypertension and black race among women below 50 years of age. This study is not entirely specific by the strict criteria for diagnosis of IDC and actually reflects patients only with non-ischaemic cardiomyopathy and therefore is not comparable to our study. They however, interestingly wondered about the protective effect of the oral contraceptives. Since oral contraception is not common among Omani women a comparison of our female patients with controls cannot be studied.

Smoking

While smoking is an established major risk factor for cardiovascular disease, any causal relationship with non-ischaemic dilated cardiomyopathy is unknown. Interestingly, Juilliere et al [221] reported a favourable predictive effect of smoking on survival of patients with IDC. Metayer et al [222] showed that life-long nonsmokers and former smokers were about twice as likely to die as compared with smokers but this association was not statistically significant. In the same study multivariate analysis failed to show cigarette smoking as an independent predictor of

survival. In contrast Coughlin et al [217] claimed statistically significant independent association of increased risk with cigarettes smoked per day. Cigarette smoking is not prevalent in the Omani community particularly in people of middle age and since none of our patients were smokers this aspect cannot be commented on.

Socio-economics

There is some evidence that dilated cardiomyopathy is associated with low socio economic status [216-219]. No aetiological correlation has been established but a lack of high quality health care among low socio-economic groups will have direct effect on the morbidity and mortality due to DCM. Psychological stress in this subgroup may also have some correlation but this is difficult to prove. In our cohort of patients this factor is worth considering. Nearly 75% (41.2% housewives and 35% unemployed) of patients came in the category where psychological stress is expected to be high (large families & low income). 35% who were unemployed on social benefits (RO 50 equivalent to USD 125 per month) were males running their families with the help of additional income from part time work and limited farming. Although the level of income cannot be compared with Europe and USA, these patients fall into a low socio-economic group by local standards. Furthermore, the psychological stress of chronic disease plays a role in the eventual health related quality of life and satisfactory profile of the patients [223]. Overcrowded living conditions would further contribute to viral infections that might be implicated in the pathogenesis of IDC in the Omani population. The impact of socio-economics on IDC in Oman may become clearer with the rising living standards in recent years, and the widening role of women in society.

Clinical features

Dyspnoea on exertion of varying severity, the major presenting symptom, was present in all our patients. Other studies [224, 225] have reported 75-85% patients presenting with this complaint, while Sugrue [226] in a population based study of IDC found that 90% of patients were in III or IV functional class NYHA (New York Heart Association). In our study only 38% patients were in these classes. This is due to an early detection of disease in less severe heart failure.

Chest pain, a less common symptom was present in 36% of Omani patients as has been reported in other studies [225-227]. Sometimes when typical, this pain can be indistinguishable from ischaemic anginal pain necessitating need for coronary angiography to rule out coronary artery disease. Chest pain could also be secondary to the mechanical effect of an enlarged heart, a reduction in the coronary flow reserve [228, 229] or a rise in pulmonary artery pressures. Investigating chest pain by exercise testing and/ coronary angiography is an important consideration in such patients since the clinical picture and echocardiography may not be able to differentiate between IHD and IDC.

Syncope, an uncommon complaint, may be due to transient ventricular arrhythmias. The presence of this symptom in 4% of our group does not correlate well with the recording of ventricular arrhythmias on 24-hour ambulatory Holter ECG. In one patient it was due to complete heart block. Since this particular patient was aged 62 years, conduction tissue degeneration of old age could be the cause of CHB. Another explanation of syncope or pre-syncope in patients with IDC could be a low cardiac output state.

INVESTIGATIONS

X-Ray

Generally the first suspicion of diagnosis of dilated cardiomyopathy arises when cardiomegaly is found on the routine chest film, with or without pulmonary congestion. Interstitial and alveolar oedema is uncommon unless the patient presents in acute heart failure. Asymptomatic cardiomegaly found accidentally triggers further evaluation. In this study 2 patients were detected to be initially asymptomatic but later on objective questioning conceded to NYHA class I symptoms. Also, during the family screening one asymptomatic cardiomegaly subsequently proved to be dilated cardiomyopathy. Symptomless left ventricular dysfunction can now be diagnosed by detecting increased levels of plasma ANP and BNP [230-232]. The severity of cardiomegaly does not always relate to the symptoms. 5 of our patients with cardio-thoracic ratio of over 60% had minimal symptoms. A plain chest film is also less accurate in detecting specific chamber enlargement, particularly in children. Nevertheless, the chest x-ray remains the most important primary investigation in the evaluation of patients of IDC.

Resting / 24 hour Holter Electrocardiography

Resting ECG

The resting ECG is almost always abnormal in IDC [107]. A variety of abnormalities may be present, the most consistent being left ventricular hypertrophy (LVH) pattern and occasionally biventricular hypertrophy (BVH) pattern. In the initial stages only non-specific depolarisation abnormalities may be seen.

Although all 97 patients but one had echocardiographic evidence of left and /or bi-ventricular enlargement, this was reflected in only 76 patients as hypertrophy pattern on surface ECG (LVH 69, BVH 9) suggesting that the surface ECG is not entirely sensitive to detect ventricular enlargement, particularly in milder cases.

Conduction defects were noted in 42/97 (43%) cases. This is in contrast to earlier reports of conduction defects found in 80% of cases [106, 107]. Intraventricular conduction delay (IVCD) was the most common conduction defect (26%) with LBBB in 16% and RBBB the least common at 1%. Xiao et al [233] have reported similar data on their 77 patients (37.6% IVCD, 25.9% LBBB, 7.9% RBBB & 19.9% no conduction defect). The presence of bundle branch block or IVCD has been related to adverse outcome and sudden deaths. In this study, out of the 23 deaths 12 had evidence of conduction defects, LBBB or IVCD and all deaths in these patients were due to resistant cardiac failure rather than sudden. Analysis of the 12 deaths with conduction defects revealed that 3 occurred in the first 12 months and 9 within 5 years from the onset of the symptoms. 30 patients with conduction defect were still alive at 8 years of follow-up. The survival analysis of conduction defects as an adverse prognostic factor appears to be clinically relevant but failed to reach statistical significance when compared to deaths with no conduction defects ($p = 0.24$). Other conduction defects such as AV blocks are also seen but these were not present in any of our patients on initial presentation.

Roberts et al [107] in their necropsy study of 152 IDC patients found conduction defects in 51 patients in their last 6 months of life. However, in Omani cohorts of patients conduction defects had been present since the beginning of the study and a

change was observed in only one of these, who showed degenerative complete heart block during follow-up.

At the first presentation the cardiac rhythm in IDC is usually sinus. This was evident with nearly 90% of patients being in sinus rhythm (SR). Atrial fibrillation (AF) is reported in 20% of the patients in the course of their natural history, particularly in the older age group, in many studies [136, 225-227, 234-238]. Atrial fibrillation on its own is also more prevalent with increasing age. In addition to the 8 patients in AF at initial presentation 4 more developed new atrial tachyarrhythmias (ATA) over the period of study. All these 12 patients with ATA were aged >40 years signifying the greater prevalence of these arrhythmias in the older age groups. Analysis for survival for ATA in our patients did not reach statistical significance ($p = 0.85$).

24 Hour Holter ECG

Holter ECG is essential in the routine assessment of patients with DCM to detect transient and new arrhythmias that might develop during the course of its natural history, particularly in patients who report episodic palpitation, dizziness or syncope. Although all types of arrhythmias are recorded [216, 239-243], emphasis has been on ventricular arrhythmias due to their role as markers of sudden death. Sustained ventricular tachycardia (VT) is the most important of these as it can lead to ventricular fibrillation [239]. Ventricular ectopics and non-sustained VT are common. Haung et al reported ventricular ectopics to be present in all their patients and non-sustained VT in 25.7% [244]. Similarly Chetty et al and De Maria et al [216, 240] reported ventricular arrhythmias in over 90% with high ectopic activity (pairs or tachycardia) in over 55-60% of their patients. In this study the results were in line with the

previous reports showing ventricular ectopics activity of various degree in 98% (95/97) of patients in a bi or multi-focal pattern with couplets and salvos of 3 ectopics beats but VT, as defined in methods, was present in only 74% of patients (61.8% VT of < 10 beats, 9.3% VT of > 10 beats and Torsade de Pointes 3.1%). A further discussion on ventricular ectopic activity will be presented later in survival analysis on page 116. A reduction in the number of ventricular ectopics during sleeping hours suggests the role of enhanced parasympathetic activity in IDC and an added mechanism of benefit of beta blockers in this disease. This would however, need to be further investigated before the effect of sleep on ventricular ectopic activity can be firmly established. It must be clarified here that an afternoon nap is widely practised in this part of the world. This explains the reduced ectopic activity between 12 PM to 3.59 PM and 12 midnight to 6 am.

Echocardiography

Echocardiography is perhaps the most important diagnostic aid in IDC patients. Although the presence of global hypokinesia is traditionally thought to be a core diagnostic feature [245], segmental wall motion abnormalities are reported to be evident in 60% of cases of proven IDC. When present as demonstrated by various methods it is thought be a favourable prognostic factor [113, 246, 247]. This was evident in this study. With careful review of echocardiograms in M mode it was found that septal motion was usually more severely affected than left ventricular posterior wall motion (disproportionate septal motion impairment). This leads to a suspicion of IHD as the cause of heart failure in these patients necessitating coronary angiography and undermining the strength of echocardiography in the evaluation of IDC, as the sole diagnostic tool. This limitation of echocardiography was evident in a sizeable

proportion of patients. Poor septal motion seen in M mode found in 50% of patients in this study could be explained by altered regional wall stress. An additional explanation for such observation could just be an echocardiographic view related abnormality. To exclude this artefact septal motion impairment was confirmed in other sections before a final decision was made.

This disproportionately reduced septal motion in patients with IDC points towards septal contractility as perhaps a major contributor to stroke volume. It must be clarified that when referring to septal motion impairment I do not mean the abnormal septal motion seen in bundle branch block (BBB). However, of the 17 patients with BBB in this study, 11 had disproportionate impairment of septal motion. 10 of these 11 fell in the cohort with an ejection fraction < 40%, which suggests that BBB has a further contribution in reducing the stroke volume. Patients with disproportionate septal motion impairment (51 patients) were compared with the other 46 patients having no disproportionate septal motion impairment regarding the reduction of ejection fraction. This analysis failed to reach statistical significance ($p = 0.22$).

In terms of cavity enlargement, LV dilatation was the most consistent feature, seen in various degrees in all patients. LA dilatation was a less common finding. When present it could either be part of the IDC or be the long-term effect of deteriorating LV function and associated mitral regurgitation. LA dilatation was not related to LV dilatation or LV ejection fraction. Since increased LV wall thickness can persist even after the development of the heart failure in patients with hypertension, absence of concentric left ventricular hypertrophy in all patients in this study, as evident from

septal and posterior wall thickness measurements suggested that these patients are not likely to have hypertensive heart failure.

Right ventricular (RV) dilatation and dysfunction when present is generally an accompaniment of LV dysfunction. Latham et al found 20 of their 52 patients (37%) with IDC had RV dysfunction [248]. RV dilatation and dysfunction was present in only 12% of my patients as initially assessed by echocardiography. Such selective dilatation and dysfunction of the left ventricle in 90% patients is in contrast with the findings of William and Fuster [249] who reported left ventricle dysfunction without concomitant RV involvement in only 10 to15% of their patients. Since RV function assessment is always difficult it is possible that RV dysfunction in some patients could have been missed on echocardiography. This was evident when 20% (14/71)of our patients who were thought to have normal RV function on echocardiography were later shown to have RV dysfunction by MUGA scan. Such a pattern of sparing of right or left ventricle may raise a suspicion of IHD rather than a primary myocardial process but it is well established that selective right or left-sided cardiomyopathy is a clinical entity [250, 251]. It also needs to be clarified that these 14 patients do not include 5 patients who were clearly shown to have reduced RVEF initially. They either failed to have MUGA scan due to early death or it is also possible that some of them could have improved their RV systolic function with the treatment. Therefore it can be stated that if all 97 patients would have undergone MUGA Scan, the number of patients showing reduced RVEF could have been larger.

Diastolic dysfunction is now part of the recognised clinical spectrum of the myocardial disease process even with normal systolic function [252, 253] and has

been postulated as a contributor to the pathophysiology of systolic heart failure [254]. Diastolic mitral flow pattern analysis used for diastolic function assessment of the left ventricle has also been shown to correlate well with indices derived from radionucleotide and contrast angiography [255-257]. VE/VA ratio, as assessed by mitral inflow Doppler pattern, thus determined has been shown to be of value in monitoring the long term follow up of patients with IDC and is closely related to concomitant changes of symptoms of heart failure. Werner et al showed that an increase in VE/VA during follow up indicated a deterioration in clinical status and conversely a decrease of the ratio related to improvement of symptoms [258].

In Omani cohort of 97 patients, diastolic dysfunction (abnormal mitral flow pattern) was present in 39 patients. Pattern Type 1 was more frequently observed (26/39) with pattern Type 2 seen in 13/39. There was a significant relationship of pattern Type 1 with the functional class of heart failure with 20/26 patients falling in milder heart failure group (NYHA I and II) ($p = < 0.01$). Similarly patients in Type 2 pattern showed a significant relationship to functional class with 10/13 falling in more the severe heart failure groups (NYHA III and IV) ($P = < 0.01$). This method of diastolic dysfunction evaluation, while did help to recognise the abnormality of blood flow during diastole, has certain drawbacks. In particular, it is significantly affected by age, heart rate and variations of PR intervals [174, 259]. A significant number of patients (60/97) in this study, as a whole, were < 54 years of age and furthermore, of the 39 patients who were thought to have diastolic dysfunction 18 were in this age group of younger patients. To see the prevalence of such an abnormal mitral flow pattern related to age, 40 healthy individuals, attending echocardiography laboratory, were randomly selected, matched for age between 13-54 years. None had

hypertension. They had echocardiography performed as part of the cardiac check-up or were referred for evaluation of innocent murmurs. Type-1 altered E/A ratio was found in only 7/40 (1 aged ≤ 30 years and 6 aged > 30 years). When a further 25 patients were gathered from the echo room aged > 55 years (referred for evaluation of aortic sclerosis murmur), the abnormal mitral flow pattern was detected in 14/25 patients. This finding does clarify some of the doubts related to abnormal flow in the younger patients with IDC that this was probably not age related. However, it must be admitted that in rest of the patients the altered E/A ratio could well be due to their greater age. Variations due to heart rate and PR interval were not studied.

A significant limitation in this study is the choice of a single echocardiographic variable: only the E/A ratio and omission of others, such as isovolumic relaxation time, deceleration time, deceleration rate [260]. This is justified by the fact that E/A ratio is one of the easiest, quickest and most reproducible to perform and therefore suitable for rapid use in large number of patients, as done in this study. Furthermore, it is one of the most frequently quoted indicators of diastolic dysfunction often without critical appraisal and therefore worthy of further careful study.

The **left ventricle filling pattern** is the result of various haemodynamic influences, namely left ventricular relaxation, compliance, filling pressure, heart rate and mitral valve area [261, 262]. In patients with left ventricular hypertrophy the filling pattern is typically of Type 1, whereas in a poorly contracting left ventricle a wide range of filling patterns are observed. A major determinant of the filling pattern in IDC is the LV filling pressure, which indirectly reflects the degree of severity of LV systolic dysfunction. In accordance with the previous reports, finding of Type 1 in milder

heart failure and Type 2 in severe heart failure reflects the contractile state of the myocardium in these patients. These patterns of mitral flow can change with therapy as the clinical condition improves. In this Omani cohort diastolic dysfunction was thought to be present in fewer patients on follow-up after the optimisation of their therapy, compared to the initial findings (39 vs 20). But these 20 patients do not include 8 other patients with diastolic dysfunction who had died during the follow-up. Therefore the total number of patients with diastolic dysfunction during follow-up could have been a little larger.

Valvular Regurgitation: Atrio-ventricular valve regurgitation of various degrees due to cavity dilatation is common in IDC. However, valve morphology is usually unaffected. MR is the most frequent finding and TR is also present when the right side of the heart is involved. AR and PR are less common. In Omani cohort MR was present in 89% (mild 62%, severe 27%) and TR in 51% (mild 39%, severe 12%) with mild AR and PR being present in 27% and 21% respectively. One may argue that in 27% of patients who had severe MR, the valve lesion might have been the primary cause of heart failure. But clearly a significantly reduced ejection fraction with no morphological abnormality of the mitral valve in these patients suggests that, the mitral regurgitation in these patients is likely to be secondary to IDC. Junker et al [263] in their study of the prognostic significance of echo Doppler proven MR in heart failure reported MR in 60% but their patients were a mix of both IHD and IDC. They failed to demonstrate an effect of MR on survival, but Blonheim et al [264] showed that IDC patients with MR have a decreased survival. The effect of TR on morbidity and mortality is less extensively studied. Ge and Pu [265] reported that the presence of TR predicted mortality due to sudden death. This is not reported by other

workers [239, 263]. Indirect evidence of a favourable effect on mortality and morbidity by reduction of severity of TR by aggressive treatment of heart failure, particularly right sided, with spironolactone may reflect the role of TR in survival of patients with IDC. In Omani patients, TR failed to correlate with ejection fraction or survival ($p = > 0.05$.) but severe MR stood out significant on univariate analysis as factor related to out-come ($p = 0.001$).

Another usefulness of echocardiography in DCM patients is its ability to detect **thrombus formation** in the cardiac chambers. It has been estimated that in 15% of all ischaemic strokes the thromboembolic material originates from the heart [243]. It has also been estimated that about 40% of such strokes occurred in patients with DCM of all causes [243, 266]. Indeed, high thromboembolic rates in DCM or IDC have been noted during long term follow up regardless of the presence of a thrombus in LV at the time of baseline echocardiography [116]. This could be explained by undetected small LV thrombi at initial evaluation, formation of thrombus later in the course of the disease or by an atrial source of thrombus. The sensitivity to detect the thrombus formation can be increased by use of transoesophageal echocardiography (TOE) by better scanning of the atria, the appendages and by detection of spontaneous contrast echoes (SCE) which are recognised to predispose to thrombus formation [267]. This fact was highlighted in our finding of thrombus in 10/97 in the LV cavity by TTE but TOE later detected LA appendage thrombus also in 3, previously unseen by TTE. In addition 13 patients had SCE by TOE, indicative of high risk of thrombus formation.

***Multiple Gated Pool Scan* (MUGA)**

Since echocardiography may not give reliable parameters to assess right ventricular (RV) function, MUGA scan was performed primarily to assess RV ejection fraction. Left ventricular ejection fraction measurements matched with the assessment done by echocardiography but MUGA scan consistently showed lower EF. "Eyeball" assessment of RV function by echocardiography however, correlated poorly with the MUGA scan. RV dysfunction has been reported to be an important predictor of survival and is present in nearly 40% of patients [248]. In our cohort of patients MUGA scan could be performed only in 71 patients in this study due to non-compliance and logical problems. However, within this number of patients studied, reduced RV ejection fraction was documented in 14 with 8 of these thought to have no RV dysfunction on echocardiography. Discrepancy in ejection fraction values between echocardiography and MUGA scan, particularly that the RVEF was found to be low in only a small number (20%) of the patients needs clarification. It has been mentioned earlier that RV function assessment is difficult both by echocardiography and by MUGA scan, and can be erroneous. More significantly, since MUGA scan examination had a long waiting list in our hospital, every patient could not had it performed at the start of the study. They had it done at different times during the course of the study. Therefore in a number of patients, myocardial systolic function could have improved with the optimisation of their treatment by the time they had the MUGA scan performed. Why there were less number of patients with LVEF < 30% on echocardiographic examination compared to MUGA scan also needs to be explained. Firstly the number of patients undergoing MUGA scan were smaller compared to echocardiography (71 vs 97) and, secondly few with low LVEF had died before they could have their MUGA scan performed or did not comply with their

appointment for this investigation. When LVEF calculation by MUGA scan was compared to LVEF recorded by echocardiography, MUGA scan consistently revealed lower LVEF by 5–7%. This is likely to be due to a multiplane calculation of EF by MUGA scan while echocardiographic calculation generally is based on one plane. Furthermore, there is also a possibility of operator error during echocardiographic measurement of ejection fraction, while during MUGA scan measurement whole process is computerised. Since the number of patients was not complete, correlation with other parameters was not performed.

Exercise Testing and the Role of Coronary Arteriography

Treadmill stress testing was undertaken in this study primarily to rule out evidence of obstructive coronary disease. This attempt proved somewhat unhelpful. There were 13 positive stress tests out of the 95 patients but none of these positive test patients had obstructive coronary disease on coronary arteriography (CAG) giving a false positive exercise test frequency of 13.6%. Its limitation to diagnose CAD was well understood and therefore all patients irrespective of the result of the treadmill test underwent CAG. Stress tests however provided useful information about the heart rate response to exercise and limiting factors to exercise.

Coronary arteriography was performed in all patients except 2 who died on initial presentation, to exclude any form of CAD. This exercise was very informative since the initial entry criteria for selection of patients as IDC, based on echocardiographic demonstration of global hypokinesia in 111 patients proved inadequate. 14 of these 111 were found to have significant CAD and were subsequently treated by myocardial revascularisation. 2 of these 14 patients were aged under 35, further stressing the role

of IHD even in younger patients. Thus in patients presenting with LVF, irrespective of age, atheromatous CAD remains a possibility until ruled out by CAG. Serious complications and sudden deaths have been well documented in such subgroups. In a recent report by Basso et al [268] 23% of sudden deaths were due to obstructive CAD among 200 young individuals under 35 years of age.

One may argue that exercise ECG, stress thallium or dobutamine stress echocardiography can be substantially relied for the purpose of ruling out CAD. The sensitivity and specificity of exercise ECG and stress thallium are similar, ranging from 70 to 80% in different groups of patients with varying severity of CAD. These tests are also of limited feasibility in patient with IDC as fatigue and dyspnoea may render exercise testing inadequate and inconclusive. Dobutamine stress echocardiography provides a better option in this respect, but reaches only 71% in specificity to detect CAD. Its sensitivity for detection of triple, double and single vessel disease has been reported to be 100%, 83% and 69% respectively [269]. This still falls short of the objective for which CAG is recommended in patients with IDC.

Furthermore, with decreased coronary flow reserve [229] in patients with IDC without obstructive CAD, a positive stress test will be of only limited diagnostic value. Of our 95 patients who underwent a stress test 13 had positive test but none of those had angiographically demonstrated CAD. 8 patients in our cohort with angiographic disease however, had only minor atheroma (< 40% luminal reduction), involving a single vessel and / or one branch, which could not account for impaired myocardial function. Therefore from this data it can be commented that the frequency of CAD in IDC is 6.3%. It must also be noted that none of these 8 patients with angiographically

demonstrated CAD had a positive stress test. During follow up none of the deaths occurred in the patients shown to have CAD. Thus in IDC there does not appear to be a correlation between positive stress test, mortality and obstructive CAD at least in the early stages of the disease.

A further interesting observation was made during our initial analysis of coronary angiograms that the left main stem artery appeared to be of short length (<1.5 cms) in 70% of patients with IDC. To verify this observation we later blinded ourselves for the LV systolic function and the left main stem length and compared this to the equally matched groups of IHD for sex and age. This has not been reported before and the clinical implications of this finding remain unknown. But when coronary intervention is undertaken in patients with IDC it would be important for the operator to be alert to this to avoid selective cannulation of a coronary artery branch.

Natural History

Symptoms

Severe symptoms at the time of presentation were an important factor in the subsequent progression of heart failure. More than half (53.6%) of our patients were in NYHA functional class II at entry into the study. Patients in class I maintained a steady haemodynamic state with only 10% progressing into lower functional capacity. Similarly patients who came in severe heart failure (class III and IV) deteriorated faster and accounted for most of the deaths from resistant heart failure. Therefore special emphasis should be given to initiation of aggressive therapy for patients with severe symptoms. Treatment of asymptomatic unexplained cardiomegaly also needs to be reviewed. The substrate of myocardial impairment is laid much before

symptoms appear. Research in this field has revealed significantly increased circulating N-terminal atrial natriuretic peptide as a marker of symptomless left ventricular (LV) dysfunction [230]. The benefit of treating such patients has been highlighted in studies of ACEI vs. placebo in such patients showing significant reduction in mortality in the active treatment group [232, 270, 271].

Survival, death and outcome (mortality) variables

In 1960s and 70s Mayo clinic reported nearly 75% mortality in 2 years [234] and a 5-year mortality of 57% was assessed by Shirey et al in 1980 [103], while Koide from Japan claimed overall survival of 8 years after diagnosis [272]. In more recent data survival has improved considerably [165, 270-273]. Di Lenarda from Italy for the Heart Muscle Study Group reported 4 year survival of around 90% [138]. This improvement in survival has largely been due to early diagnosis, introduction of ACEI and beta-blockers in the therapy, and prevention of complications such as embolic events and arrhythmias. In this study of the 97 patients, all cause mortality of only 24% over 8 years follow-up could be achieved even without using beta-blockers initially but carvedilol, a vasodilating beta blocker was added later in the course of follow-up. Maximum number of deaths occurred in the 1st year of follow up and subsequent deaths were distributed over the 1-8 years. Published studies have shown both a progressively increasing mortality with the years [136, 138, 225] as well as a high mortality in the first years followed by a steep descent of the curve [226, 227, 274]. In general the crude death rate in Omani population is estimated at 3.65/1000/year with a life expectancy at birth of 73.38 years in both males and females. Oldest patient dying from IDC in this study was 58 years old and the youngest was 36 years. While it is clear that heart failure due to IDC is responsible

for early deaths in Omani population, an improved survival in these patients is almost certainly due to an optimised treatment of heart failure and care by a specialist trained in the management of patient with heart failure. Another plausible explanation for the difference in survival from other studies could be the differences in the patient selection : lower LVEF, inclusion of patient with alcohol abuse and smoking habit, all which will affect the survival adversely.

Surge et al [226] also showed that survival at one year differed dramatically between population based cohort and referral cases (95% compared with 69% respectively) and at five years (80% compared with 36% respectively) ($p < 0.001$). A better survival in Omani population can also be due to the fact that nearly all the patients were referred cases for specialist care.

As high as 30% of deaths among patients with IDC are reported to be sudden [93]. Fruhwald et al [275] however, found only 13.8% cases of sudden deaths in their long term follow-up of 167 patients. Similarly Romeo et al [276] had reported sudden death in 13% and resistant heart failure in 20%. In Hoffman et al study 36% died of heart failure but there was a high percentage (64%) of sudden deaths [277]. Depressed LV systolic function and presence of frequent complex ventricular arrhythmias identified patients who were at high risk of sudden deaths. Interestingly in this study, presence of atrial fibrillation significantly increased the risk of sudden deaths and death from heart failure.

Cause of death in this Omani study was mainly heart failure at 52% (12/23) but sudden deaths occurred in nearly 21.7% (5/23). Non-cardiac deaths occurred in the

rest. Findings as to the cause of deaths in this study are comparable with previous reports. Hoffman et al's report [277] of high rate of sudden death is likely to be due to their definition of sudden death where an arrhythmia as a terminal event was also considered as responsible for sudden death.

Fatal arrhythmias attributed to five sudden deaths in this study is somewhat presumptive. Since these patient's heart failure was under good control with stable haemodynamics, ventricular arrhythmia was considered as prime suspect. It is further relevant that all these five patients were taking amiodarone as part of their antiarrhythmic therapy. Pro-arrhythmia would also need to be suspected. Post-mortem examination would have helped to elucidate the cause of death but this could not be performed due to cultural restrictions. Strictly speaking at least 3 deaths at home thus can be argued to be of unknown cause.

Five patients who died in group A reflect the other important factor relevant to death in IDC - malignant ventricular arrhythmias. These patients had a stable haemodynamic state in NYHA II / III and LV ejection fraction of > 30%, but documented ventricular tachycardia had previously worsened their heart failure acutely before they joined group A. The correlation between ventricular arrhythmia and sudden death in IDC has never been fully established [282-284]. In univariate analysis the development of new sustained VT was associated in our study with poor outcome ($p = .02$) and in our 3 patients who died suddenly at home malignant ventricular arrhythmia could be a contributing factor. The role of arrhythmia is also interestingly more relevant in stable patients since none of the deaths in group B was primarily due to arrhythmia. Therefore the role of arrhythmia can be said to be

independent of severity of myocardial impairment. In group B with resistant heart failure, the mortality was nearly 50% (14/27) while it was only 10% (7/68) in stable patients of group A, favouring worsening myocardial function as the most important factor in the mortality.

The severity of heart failure at the time of initiating therapy is considered to be a significant factor affecting mortality due to resistant heart failure [226]. A number of studies have investigated the predictors of death in IDC [225, 275, 278-281]. The following parameters were independent predictors of mortality: first symptom, pulmonary oedema, peripheral oedema, syncope, duration of symptoms at the time of inclusion, end systolic LV volume, end diastolic LV diameter, pulmonary artery systolic pressure; and their combination had the most accurate predictive value for death. Romeo et al [276] found similar factors but added lower ejection fraction ($p = 0.0001$) and severe mitral regurgitation ($p = 0.0095$) in their patients. 14 out of 23 deaths (61%) in this Omani study occurred in patients who were in severe heart failure and had LVEF $\leq$ 30%. There was a positive correlation between the LVEF at presentation and mortality ($p = .01$), and this was the only predictive variable identified by multivariate analysis.

Arrhythmia on 24-hour Holter ECG in survival analysis

The occurrence of cardiac arrhythmias both tachycardias and bradycardias in IDC is well-established [216, 239-241, 244]. Ventricular arrhythmias in particular are important with their potential to cause sudden death [242]. Ventricular ectopics and non-sustained ventricular tachycardia, although more common, have not been associated with increased morbidity or mortality. Besides precipitating heart failure

all types of arrhythmias cause additional myocardial insult worsening the functional class of heart failure even after the acute episode is controlled. In addition, atrial fibrillation (a common arrhythmia in IDC) leads to a loss of the atrial support resulting in further reduction in cardiac output. Analysis of VT in Omani patients revealed that non-sustained VT was more common with equal distribution of mono and polymorphic patterns (48.7% and 51.3% respectively). 12 patients who developed prolonged ventricular tachycardia or Torsade de Pointes were in higher functional class of heart failure (NYHA classes III and IV) and had lower ejection fractions. Arrhythmias also occurred in otherwise stable patients in controlled heart failure in group A. The development of sustained VT or Torsade de Pointes was related to a poor outcome ($p = .02$) however, multivariate analysis failed to identify it as an independent factor of significance.

Embolic phenomena

Systemic and pulmonary embolism are known complications of IDC. Atrial fibrillation in particular is an independent risk factor for embolic events. A dilated poorly contracting ventricle in sinus rhythm itself predisposes to thrombus formation due to low blood flow rates. Two strokes and four pulmonary embolisms that occurred in our series were all in patients with atrial fibrillation even though they had been appropriately anticoagulated, reflecting the compounded thrombotic potential in this condition.

As discussed earlier, in approximately 15% of all ischaemic strokes the source of thromboembolism is the heart [234, 243] and around 40% of such strokes occur in dilated cardiomyopathy (regardless of the cause). A 15% rate of thromboembolism in

DCM by Bloudheim [264] and similar rate by Gottdiener [116] are higher than observation in this study. Finding of just fewer than 6% in the Omani cohort is more in line with the work of Komajda [225] and Fuster [234]. In view of the risk of thromboembolism routine anticoagulation has been recommended by certain authors [135, 224, 234]. Such a recommendation appears overkill and a more logical approach would be a periodic assessment by echocardiography to detect thrombus and to anticoagulate selected patients who show presence of thrombi in cardiac chambers or spontaneous echo contrast (SEC) which is an independent risk factor for thromboembolism [267]. With an estimated 5% risk of major bleeding and 1% risk of death associated with anticoagulant therapy [285, 286] it will be appropriate to identify high risk group for anticoagulation. Presence of atrial fibrillation would obviously be a strong indication for anticoagulation, which was the case in 6 patients in this study with embolic events.

DRUG PROFILE OF PATIENTS

97 patients who entered in the study were a highly selected group of patients with heart failure of no identified aetiology, and without concurrent disease. Their drug profile therefore almost entirely consisted of cardiac medication to treat their heart failure or its complications. However, their medication was modified during the course of their follow up as indicated.

	At first presentation	At the beginning of the study	At the end of the study
Frusemide	97/97	97/97	74/74
Amiloride	0/97	3/97	0/74
Bendrofluazide	0/97	2/97	3/74
Metolazone	0/97	3/97	1/74
Spironolactone	3/97	60/97	60/74
Digoxin	10/97	30/97	36/74
Beta-blocker	0/97	0/97	38/74
Amiodarone	2/97	14/97	6/74
Warfarin	8/97	20/97	18/74
ACE Inhibitor	72/97	90/97	68/74
Angiotensin receptor blocker	0/97	7/97	6/74

The drug regimen of the patients at the entry revealed certain degree of inadequate treatment. Although before this allegation can be made one has to clarify the clinical status of the patients and related treatment. Also it has to be accepted that a large number of these patients were being initially treated by primary care physicians who may not have been well conversant with the specialised approach to treat heart failure. Furthermore analysing the drug regimen was not the objective of the study.

Nevertheless this aspect of the patient profile was an essential information to be recorded since inadequate treatment has bearing on clinical course of the disease and eventual survival. A preliminary analysis of the treatment at entry revealed that 25/97 (25%) patients were not receiving ACE inhibitor and at least a further 20% were not taking optimal doses. Those who did not receive ACE inhibitor were thought to have ACE inhibitor induced cough but none were replaced by angiotensin receptor blockers due to non-availability of this agent in certain primary care facilities. Vasodilator treatment of these patients was facilitated by introducing or optimising the dose of ACE inhibitor (maximum tolerated dose) and where indicated an angiotensin receptor blocker was used. Further upgrading of treatment was done by addition of spironolactone and digoxin to comply with the standard treatment recommendation. The optimisation of the treatment regimen tailored for each patient ensured that the clinical follow up and survival analysis was as accurate as possible.

Use of beta-blockade, now firmly recommended [287-291] in functional class II and III heart failure was totally missing from the treatment at entry. This is not surprising since during the period these patients were recruited into the study, the use of beta-blockers in heart failure around the world was still sketchy and not well established. Towards the later stages of the study a significant number 34/74 (46%) were taking beta-blockers with beneficial effects.

CHAPTER – 4

BLOOD INVESTIGATIONS

ROUTINE BLOOD INVESTIGATIONS

Routine blood investigations failed to reveal any interesting abnormalities of significance. In some patients abnormal renal and liver function parameters were well explainable by impaired renal and liver functions due to cardiac failure. The results are summarised in tables 19 & 20. Thyroid function tests (T3, Free T4, and TSH) were within normal limits in all patients including those in atrial fibrillation.

G6PD deficiency and sickle cell disease (SCD) are common in Omani population. In a national genetic blood disorder survey based on screening of 6000 Omani children under 5 years of age sickle cell trait was found in 6% with SCD (homozygous) in 0.2%. G6PD deficiency was noted in 18% (data on file of Ministry of Health, Oman). In another survey of 3000 blood donors the presence of G6PD deficiency was 13-37% being higher in males. Sickle cell trait was seen in 6.3% and SCD in 0.5% (data on file of blood bank, SQUH). In this cohort of 97 IDC patients 4 (4.1%) were G6PD deficient while sickle cell disease/trait was present in 10.3%. However there was no correlation to the clinical features and outcome variables.

Cardiomyopathy has been associated with human immune deficiency virus (HIV). Only 1 patient was tested HIV positive but dilated cardiomyopathy in this patient was not thought to be due to HIV infection. His CD4 count was normal and he had no features of AIDS. Titres for viral screen otherwise were unremarkable for any evidence of recent viral illness in all 97 patients. However, in two patients a history of febrile illness before the appearance of their symptoms suggests a possibility of viral myocarditis as the initiating pathogenesis.

RESULTS

Table 19. Routine Blood Tests (n = 97)

Test	Min	Max	Mean	Std. Dev.
Hb	11.0	16.5	13.4	2.05
ESR	1	25	10.65	14.32
Na	116	146	138.2	16.12
K	3.2	6.2	44.4	0.48
Mg	0.6	1.4	0.83	0.12
ALT	6.0	900	70.36	148.93
Bilirubin	8.0	322	29.38	50.37
Proteins	47	60	50	6.50
ALK Phos.	28	419	86.43	63.05
Albumin	15	22	19	3.7
CK	20	65	41	6.1
Urea	2.2	36.1	7.12	4.64
Creatinine	98	266	96.27	30.18
Cholesterol	1.20	6.90	4.77	1.18
Triglyceride	0.40	3.2	1.83	3.40

Table 20. Other Blood Tests (n = 97)

G6PD Deficient	4 (4.1%)
Sickle Cell Disease	10 (10.3%)
HIV Positive	1 (1%)
Hepatitis Positive	2 (2.1%)

HUMAN LEUCOCYTE ANTIGEN (HLA)

INTRODUCTION

Autoimmune disease occurs as a result of the loss of tolerance to self-antigens [292-294]. In patients with autoimmune disease the immune system attacks one or several self components, through the same mechanism which operates in the normal immune response to foreign antigens. A major role, both in the normal immune response and autoimmunity, is played by CD4+ helper T lymphocytes. The activation of the cells occurs when their specific T cell receptor (TCR) recognises antigenic peptide fragments linked to human leukocyte antigens (HLA) molecules.

HLA molecules are polymorphic cell surface glycoproteins, which are encoded by a number of closely linked genes for the major histocompatibility complex (MHC). The MHC in man is known as the HLA region, which is located on the short arm of chromosome 6. The HLA region contains genes encoded for: 1. HLA-A, B, C molecules, also known as HLA class I antigens; 2. HLA -DP, -DQ and -DR molecules which represent the so-called HLA class II antigens; 3. Certain proteins of the complement cascade, factor B (B1), C2 and C4 (C4A and C4B), which are referred to as HLA class III antigens [294].

The HLA region is uniquely polymorphic; all individuals possess their own combination of HLA antigens expressed on the surface of their cells, where they play a major role in the regulation of physiological immune responses.

Autoimmune disease is characterised by the presence of circulating autoantibodies in the affected patients. These autoantibodies are not necessarily pathogenic but are

reliable serological markers of ongoing tissue damage due to the autoimmune process [292, 294]. In non-organ specific autoimmune disease the autoantibodies are against ubiquitous auto-antigens (e.g. nuclear antigens in SLE) and tissue damage is generalised. In organ specific autoimmune disease, the destruction process is largely restricted to one organ within the body and autoimmune antibodies react with auto-antigens that are unique to the target organ [295].

METHODS

As the initial part of the study, the first 50 patients entering the study were investigated and the results were compared with the data already available from the laboratory records of the 247 healthy Omanis who were blood donors or potential kidney or bone marrow donors. None of these patients or controls were related to each other. For HLA – A, B, C and DR typing 15-20 ml of blood in EDTA was used. Lymphocytes were separated by density gradient centrifugation and then the B lymphocytes further separated using magnetic beads (Class 11 Dynabeads; Dynal, Skoyen, Norway). The supernatant containing T cells was used for HLA-A,B,C typing and the purified B cells for HLA–DR typing. HLA typing was performed using a modified microcytotoxicity technique [296] with ethidium bromide/acridine orange staining and observation with a semi-automated fluorescent microscope. Although Class II DNA typing was not performed on this group of patients our current experience shows greater than 95% concordance with class II serology. HLA typing sera were obtained from Bhringwerke (Marburg Germany), Pelfreez (Brown Deer Wisconsin, USA) and Biotest (Dreieich, Germany).

The following specificities could be determined:

A locus : 1, 2, 3, 9, 10, 11, 19, 23, 24, 25, 26, 28, 29, 30, 31, 32, 33,

B locus : 5, 7, 8, 12, 13, 14, 15, 16, 17, 18, 21, 22, 27, 35, 37, 40, 41, 42, 47, 49, 53, 55, 57, Bw4, Bw6,

C locus : w1, w2, w3, w4, w5, w6.

DR locus : 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14, 15, 16, DRw52

DQ locus : 1, 2, 3, 7.

Statistical analysis was carried using the chi-square or Fisher Exact Test (with the Bonferroni correction obtained by multiplying the P value by the number of antigens tested to correct the P value for any chance association (Pc)). If the antigen association has been reported previously this correction is not necessary [297].

RESULTS

There was no association of HLA antigens with IDC that remained significant after correction for the number of antigens tested. The results are summarised in tables 21 to 24. Of the 50 patients 28 were males (aged 15-61 years, median 48) and 22 females (aged 24-46 years, median 40). 247 controls contained 165 males (aged 20-45 years, median 38) and 82 females (aged 22-40 years, median 34) Statxact 5 was used to compute the power. For the given sample size the power of the study was 66%.

DISCUSSION

HLA-DR4 association has been reported in several studies [77, 147]. The evidence presented in favour of a link between IDC and HLA-DR4 has however, been inconclusive. A meta-analysis of 8 studies [146, 147, 292-302] seemed to confirm

this association with HLA-DR4 [77], but at least two of these studies [299,301] failed to show the link. It is also suggested that much data must be available from several thousands heart transplants performed world-wide. Most of these would have been HLA typed. Approximately 50% of heart transplants are performed for IDC, thus there must be a lot of unpublished data on this subject. It may be, therefore, possible that many researches who have failed to show this association did not consider it worth reporting or have encountered publication bias against negative results.

Table 21. HLA-A antigens frequencies in Omanis with idiopathic dilated cardiomyopathy

HLA-A antigens	IDC n = 50		Controls n = 247		Rel. risk	Prob.	Prob. Corr.
	n	%	n	%	[rr]	[P]	[P_c]
A1	11	22	36	15	1.68	0.137	--
A2	22	44	94	38	1.28	0.264	--
A3	6	12	23	9	1.39	0.358	--
A9	7	14	33	13	1.10	0.527	--
A10	4	8	42	17	0.46	0.076	--
A11	6	12	48	19	0.60	0.148	--
A19	21	42	93	38	1.20	0.336	--
A23	2	4	11	4	1.06	0.621	--
A24	6	12	22	9	1.46	0.324	--
A25	0	0	0	0	--	---	--
A26	4	8	29	12	0.71	0.313	--
A28	5	10	27	11	0.96	0.540	--
A29	2	4	6	2	1.91	0.402	--
A30	7	14	52	21	0.64	0.173	--
A31	1	2	9	4	0.76	0.476	--
A32	17	34	47	19	2.20	0.018	ns
A33	6	12	7	7	1.81	0.198	--

ns, not significant

Table 22. HLA-B antigens frequencies in Omanis with idiopathic dilated cardiomyopathy

HLA-B antigens	IDC n = 50		Controls n = 247		Rel. risk [rr]	Prob. [P]	Prob. Corr. [P_c]
	n	%	n	%			
B5	22	44	89	36	1.39	0.183	--
B7	1	2	9	4	0.76	0.476	--
B8	4	8	42	17	0.46	0.076	--
B12	3	6	13	5	1.27	0.524	--
B13	2	4	8	3	1.45	0.524	--
B14	0	0	11	4	0.20	0.127	--
B15	2	4	16	6	0.72	0.389	--
B16	3	6	10	4	1.66	0.379	--
B17	17	34	53	21	1.89	0.046	--
B18	5	10	14	6	1.94	0.199	--
B21	4	8	24	10	0.88	0.474	--
B22	1	2	14	6	0.48	0.247	--
B27	0	0	1	0	1.62	0.832	--
B35	12	24	73	30	0.77	0.271	--
B37	0	0	6	2	0.36	0.327	--
B40	11	22	38	15	1.47	0.172	--
B41	0	0	1	0	1.62	0.832	--
B42	1	2	2	1	2.97	0.426	--
B47	0	0	1	0	1.62	0.832	--
B55	0	0	9	4	0.24	0.186	--
B57	1	2	2	1	2.97	0.426	--
BW4	42	84	170	69	2.27	0.020	ns
BW6	34	68	172	70	0.91	0.470	--

ns, not significant

Table 23. HLA-C antigens frequencies in Omanis with idiopathic dilated cardiomyopathy

HLA-C antigens	IDC n = 50		Controls n = 247		Rel. risk [rr]	Prob. [P]	Prob. Corr. [P_c]
	n	%	n	%			
Cw1	1	2	8	3	0.85	0.535	--
Cw2	1	2	13	5	0.52	0.283	--
Cw3	14	28	34	14	2.45	0.014	ns
Cw4	16	32	83	34	0.94	0.483	--
Cw5	5	10	7	3	3.87	0.035	ns
Cw6	7	14	35	14	1.03	0.589	--

ns, not significant

Table 24. HLA-DR and DQ antigens frequencies in Omanis with idiopathic dilated cardiomyopathy

HLA-C antigens	IDC n = 50		Controls n = 247		Rel. risk [rr]	Prob. [P]	Prob. Corr. [P_c]
	n	%	n	%			
DR1	3	6	19	9	0.71	0.353	--
DR2	39	78	131	63	2.05	0.027	ns
DR3	18	36	63	30	1.31	0.261	--
DR4	7	14	32	15	0.94	0.508	--
DR5	8	16	40	19	0.83	0.388	--
DR7	4	8	25	12	0.70	0.302	--
DR8	1	2	2	1	2.51	0.476	--
DR9	0	0	1	0	1.37	0.807	--
DR10	1	2	6	3	0.94	0.595	--
DR11	7	14	28	13	1.09	0.533	--
DR12	0	0	3	1	0.58	0.524	--
DQ1	44	88	156	75	2.34	0.029	ns
DQ2	20	40	79	38	1.10	0.447	--
DQ3	13	26	60	29	0.88	0.424	--

ns, not significant

The finding of no association of HLA with IDC in several studies is in agreement with those reported so far in the majority of autoimmune diseases. A possible explanation of this lack of association would be that the HLA-DR antigens do not influence antibody production. However, circulating autoantibodies to different cardiac antigens have been reported in DCM using IFL (cytoplasmic and sarcolemmal antigens), ELISA (M7 mitochondrial antigens, adenine nucleotide translocator) and ligand binding inhibition and immune blotting (beta1 adreno - receptor) techniques [70, 155, 303-305]. It has also been suggested that antibodies to the beta 1 adreno - receptor are associated with HLA-DR4 [306]. An alternative explanation for the lack of association between these antibodies and the HLA-DR markers would be that the cardiac antibody levels become undetectable with disease progression similarly to the Islet cell antibodies in IDDM [307].

This lack of association of HLA in DCM is probably reflective of this condition being a heterogeneous disease with different clinical and immunological features and that a strong immunological component is not a feature of all sub-groups.

Results in this study are similar to the finding of the Pittsburgh study [146] in which 91 white patients with dilated cardiomyopathy were studied and the British study of 98 patients [148]. Neither in the Pittsburgh study, the British study or in the Omani patients could an association with HLA-DR4 be demonstrated. The Pittsburgh study did find a significant increase in HLA-B7 which we did not (Table 22). Interestingly however, the Pittsburgh study only found 1 patient with HLA-B14 (uncorrected $P < 0.05$) and in Oman not one of the 50 patient had HLA-B14, giving a relative risk of

0.2 although this was statistically not significant. The incidence of HLA-B14 in healthy Omanis is only 4%.

It is important to keep the reported HLA-DR4 association in perspective. In the population summarised by Carlquist et al [77] for statistical meta-analysis, the control population frequency of HLA-DR4 was 27% compared to 51% in IDC patients (rr = 2.8 and P <0.001). Thus, almost half the patients studied (49%) for meta-analysis were HLA-DR4 negative indicating a significant role of other factors in the aetiology of IDC. This data would indicate ethnic/racial origin as being a significant factor in the reported HLA association with this disease. This is further supported by the absence of significant DR4 association in Chinese [308] and Japanese patients [309]. Lack of evidence of association of HLA-DR4 in other ethnic groups questions the reported HLA linked autoimmune pathology in all patients with this disease. Antibodies to the beta receptor have been strongly linked to the HLA-DR4 phenotype in Caucasian patients – 72% of DR4 positive patients having antibodies compared to 22% of the DR4 negative patients [73]. Thus in Omani patients, although antibodies studies were not carried out there is no evidence for an HLA-DR4 linked autoimmune response being involved. A study of North Italian Caucasian patients supports this, where although a significant association of HLA-DR4 and IDC was reported, no association could be found between HLA-DR4 and organ-specific cardiac antibodies [307].

Since no HLA association was found in the first 50 patients, further analysis was abandoned to minimise financial and workload costs. In summary, although immunological basis for IDC remains likely, findings of negative HLA association

demonstrates a lack of such association in this population. It is possible that racial and ethnic factors may be operating. Further studies using a larger number of patients from this population is needed before a firm answer can be established.

ORGAN SPECIFIC CARDIAC AUTOANTIBODIES

Caforio et al first reported organ specific antibodies in a sizeable proportion (26%) of patients with DCM [72]. The role of cardiac autoantibodies in Omani DCM patients has not been studied before. To complement my previous HLA investigation, I aimed to determine whether organ specific circulating cardiac autoantibodies could be found in these patients.

With the help of Professor W. J. Mckenna of the department of Cardiological Sciences of the St. George's Medical School London, sera of 28 patients with DCM and 8 with IHD (controls) were analysed for autoantibodies-HH IFL, HSK IFL, AIDA and ANA. HHIFL and HSKIFL can determine whether the antibodies being measured are organ specific or cross-reactive. The methodology of the assay was designed and performed by Dr. Alida Caforio. The details of the methodology can be found in reference 310. Due to financial constraints we could not send sera of all 97 patients of the study.

RESULTS

Sera of all 28 but 1, and all 8 controls were negative for cardiac autoantibodies. All 28 were negative for AIDA and ANA. HHIFL and HSKIFL were negative in all but 1

patient. In one patient who was HHIFL and HSKIFL positive, the intensity of staining was weak and the pattern was striational.

DISCUSSION

When cardiac autoantibodies are detected disease may be claimed to be autoimmune. The other cohort of patient who have negative autoantibody pattern must have a different aetiopathological explanation. **Firstly** IDC may be an aetiologically heterogeneous condition. The absence of cardiac autoantibodies could indicate that the cell mediated autoimmune mechanism is predominant or that the autoimmunity is not involved in the antibody negative patients or both. **Secondly**, because cardiac antibodies are early markers of disease that become undetectable as the disease progresses (as seen in IDDM), they may not be detectable in some patients of DCM particularly with advanced disease and are more commonly (53%) reported in patients with less severe symptoms and with more recent onset of disease (< 2 years) [311].

Some workers have reported cardiac autoantibodies in patients with DCM with better exercise tolerance and in asymptomatic DCM relatives with early cardiac dysfunction [312, 313]. This data supports the possibility that the absence of cardiac antibodies at least in some patients is related to disease progression. Clinical and serological follow up studies can resolve this issue, and furthermore different DCM patients can have antibodies with different antigenic specificities. Collaborative work with exchange of sera by different laboratories and assessment of more than one antibody specificity in standard positive and negative sample is likely to clarify this. The analysis of Omani sera at St. George's Medical School was collaborated with this in

view. In the Omani DCM patients with negative findings thus points towards the lack of role of autoimmunity in this group.

All patients in our cohort analysed at St. George's medical School, London were in NYHA class II and above, with ejection fractions ranging from a 25% to 38% (mean 32%). A low detection rate of the autoantibodies in our cohort could be due to relatively more advanced disease.

Further support that the autoimmunity is minimally involved in our group of patients comes from the findings of our earlier report of lack of association of HLA in IDC in Omani population [314]. The point is that there may be different pathogenesis involved for IDC and the relative proportion of these in different population can vary. At least in Caucasian populations there is evidence of autoimmune mechanism in a proportion of cases.

In short, although autoimmunity is suggested to play a role in a group of patients with IDC, observations in this study failed to show such an association in Omani patients. This observation however, needs more extensive investigation, since only a small number patients were tested. With the limited data available it can only be stated that the absence of autoimmunity in these patients represents either a lack of autoimmune pathology in this population or can also be partly due to the fact that nearly all patients presenting in heart failure had symptoms for many months or years. It is likely that such patients are presenting at a later stage of disease when autoimmune damage has already occurred.

CATECHOLAMINE LEVELS

Although estimation of plasma catecholamine levels has its limitations, it is a recognised method of assessing sympathetic over-activity in heart failure. With increasing interest in controlling this high sympathetic activity it becomes imperative to make further investigations in the understanding of its relationship to the severity of the heart failure.

METHODS

Although a total of 97 patients had entered the IDC study, since the assessment of catecholamines in patients was done in the early morning after a period of rest I opted to admit patients temporarily in the hospital for this assessment. To this request all 97 patients did not agree and therefore only 55 patients, who agreed to be admitted could be assessed for catecholamine assay. All were on treatment for chronic heart failure with diuretics and angiotensin converting enzyme inhibitors.

After securing informed consent, blood samples were drawn for estimation of noradrenaline, adrenaline and dopamine levels. Blood collection was carefully monitored to avoid anxiety and posture related rise in catecholamines. Samples were collected after an over-night period of rest with patients in the supine position. 10ml of blood was drawn in ethylene diamine triacetate (EDTA) tubes and transported to the biochemistry laboratory protected from sunlight. Analysis was performed using High Performance Liquid Chromatography with electrochemical detection [315]. The catecholamines were separated on reverse phase columns and component retention and peak shape were enhanced by adding ion-pairing reagents to the mobile phase. The reference range for normotensive healthy Omani population was used as controls

(Noradrenaline 164-2360 pmol/L, adrenaline 152-542 pmol/L and dopamine 181-653 pmol/L). Inter-assay coefficient n=36, noradrenaline 4.8% (361 pmol/L), adrenaline 7.8% (53pmol/L), dopamine 10.9% (200pmol/L). Patients were divided based on severity of symptoms into Group A (NYHA class I and II) and Group B (NYHA class III and IV).

RESULTS

Patients were aged 18 to 65 years (median 50 years) and included 34 males and 21 females (M: F=1.6:1). There were 39 patients in Group A and 16 patients in Group B Treatment profile of patients in 2 groups is given in table 25. Only 38 patients were found to be on treatment with ACE inhibitor at the beginning of the study but their treatment was optimised soon during follow up. 15 patients were taking lisinopril (10 group A and 5 group B) and 23 patients were on cilazapril (10 group A and 13 group B). The dosage of ACE inhibitor was significantly higher in group B compared to group A (lisinopril 5-20 mg. mean 12.86 and 2.5-10 mg. mean 5.96 respectively, $t = 3.4$, $p = .032$; and cilazapril 2.5-7.5 mg. mean 5.0 and 1.25–5 mg. mean 2.69 respectively $t = 3.63$, $p = 0.009$). None of the patients in either group received beta-blocker therapy. Mean and median levels of noradrenaline, adrenaline and dopamine along with minimum and maximum values are shown in Table 26. Noradrenaline levels were elevated in 46/55 (83.6%) patients and adrenaline and dopamine in 32/55 (58%). Comparison of group A and B revealed that the levels of noradrenaline were elevated in 32/39 (80%) patients in group A and in 14/16 (82%) in group B. Similarly adrenaline levels were elevated in 21/39 and 11/16 patients and those of dopamine in 22/39 and 10/16 patients in group A and B respectively. Thus there were more patients in group A with elevated levels, however the differences did

Table 25. Treatment profile of patients with idiopathic dilated cardiomyopathy

Medication	Group A (n = 39)	Group B (n = 16)
Frusemide	39	16
ACE inhibitor	22	16
Digoxin	05	16

Group A = NYHA I and II; Group B = NYHA III and IV; ACE = angiotensin converting enzyme

Table 26. Plasma catecholamine levels in idiopathic dilated cardiomyopathy (n=55)

Catecholamine assayed	Mean levels (SD)*	Median Levels*	Minimum Levels*	Maximum Levels*	Normal Levels**
Noradrenaline	4,753 (3,343)	3,616	381	13,659	164-2,360
Adrenaline	1,218 (1,573)	638	152	6,046	152-542
Dopamine	4,926 (6,312)	1,449	170	21,092	181-653

*pmol/L; **for normotensive Omani population (pmol/L).

Table 27. Comparison of plasma catecholamine levels in group A (NYHA class I & II) and group B (NYHA class III & IV)

Catecholamine (pmol/L)	Group A Range (median) n = 39	Group B Range (median) n = 16	Significance (Wilcoxon test)
Noradrenaline	2392 – 13693 (4036)	2391-8204 (3760)	ns
Adrenaline	539-6046 (958)	567-5225 (749)	ns
Dopamine	727-21092 (8425)	710-20000 (3177)	ns

ns = not significant

not reach statistical significance. The levels of catecholamines in the two groups were also compared using the Wilcoxon test. Again the mean levels of noradrenaline appeared higher in group A but the difference was not significant (Table 27). The levels of noradrenaline in the two groups were again compared eliminating patients with normal values, revealing that the mean level in group A was higher, approaching near statistical significance ($p = 0.06$). A similar analysis with adrenaline and dopamine levels in the two groups did not show any significant difference.

DISCUSSION

Plasma catecholamine estimation helps to quantify the cardiac sympathetic response [158, 160, 316]. Though well established that catecholamine levels are elevated in chronic heart failure, their reduction by pharmacological or non-pharmacological means to effect patient survival is disputed. In a sub-study of VHEFT-2 [317], survival benefit of enalapril was confined to patients who on entry had elevated levels of plasma noradrenaline. Subsequent studies [162, 318, 319] have also shown the prognostic significance of plasma noradrenaline levels. However, Anker in his review [320] opined against such benefit and stated that spot catecholamine estimation was of limited value. Two recently published studies (CIBIS II and MERIT-HF) have recorded significant survival benefits of beta-blocker therapy [291, 321]. But these did not investigate the effect of therapy on catecholamine levels.

Raised catecholamine levels in heart failure were reaffirmed in this study. Nearly 84% of patients had elevated plasma noradrenaline levels but the levels of adrenaline and dopamine were raised only in a lower percentage of patients (59%). Thus despite symptomatic heart failure 16% of patients had normal levels of plasma noradrenaline.

This is consistent with an earlier study that had reported normal levels in 14% of patients with untreated heart failure [316]. In our patients with treated heart failure an interesting observation however, is that comparatively higher levels of noradrenaline were recorded in patients with mild heart failure. Although the difference was not statistically significant when the whole group was taken into account, it reached near significance ($p = .06$) when those with elevated levels alone were compared. Possible explanations for the lower levels in severe heart failure include decompensation and/or resetting of adrenergic reflexes, adrenergic depletion, inter-individual differences in sympathetic response, varying degrees of activation of counter-regulatory mechanisms such as release of atrial natriuretic peptide, and negating effect of ACE inhibitors [160-162]. The difference in the treatment received by the 2 groups could also be an important contributing factor. Although beta-blockers were not used in any of the patients, a more aggressive use of ACE inhibitor in severe heart failure could have lowered the catecholamine levels in group B.

Haemodynamic improvement associated with reduction in noradrenaline levels has been reported in both animal experiments [322] and human studies [323] but the use of beta-adrenoreceptor agents aimed at lowering the catecholamine levels is generally recommended only in class II and III patients. There is a concern that class IV patients may worsen [324] and a feeling that class I patients do not require it. It is also worth noting that patients with the same degree of symptomatology do not respond uniformly.

Despite the fact that neuroendocrine activation is an important component of chronic heart failure, neither does its assessment form part of the routine work up of patients

with heart failure nor is there such a recommendation in the guidelines set by recognised scientific authorities [324-326]. A survey conducted in Italian Hospital Cardiology Units [327] showed that less than 4% of patients undergo any kind of neuroendocrine assessment. This aspect merits review. The observation of high noradrenaline levels in the present study in mild heart failure, although not statistically significant, opens up the possibility that introduction of optimal beta-blockade early in the course of disease may help to minimise catecholamine induced myocardial damage. Whether this might reduce possible benefits of sympathetic stimulation is not at present known. In particular beta-blockers with a vasodilating effect may be more appropriate [287, 328, 329].

Spot catecholamine estimation however, has inherent limitations [158, 160]. Prominent among them are non-reproducibility and physiological variations in the measurements. All attempts were made to minimise these by collecting blood samples when the patients were in a stable state and by having the analyses performed by a single technician. 24-hour monitoring of levels may be more informative although less practical. Some workers have suggested that urinary metabolites of noradrenaline are more reliable indicators of enhanced sympathetic activity. However these are influenced by renal function, often impaired in chronic heart failure. Nevertheless observations in the study put forth a case to review the present stance towards the routine assessment of noradrenaline levels in heart failure and also show that beta-blockers remain under-utilised in spite of gathering evidence of their benefits. Further proof of advantages of sympathetic suppression aimed at lowering plasma noradrenaline in heart failure will require larger placebo controlled studies, where plasma noradrenaline levels are measured in patients prior to initiation of therapy,

followed by serial measurements to monitor the effect of treatment and relate these to prevention, progression and survival.

A **similar** study was done in **children** with the help of my paediatric cardiologist colleague. 20 children with chronic heart failure due to IDC attending the paediatric cardiology outpatient clinic were studied. The same number of matched healthy children with innocent cardiac murmurs were used as controls. Study patients were on anti-failure therapy for at least 1 year and were in stable haemodynamic state. Since the NYHA class symptoms can be difficult to access in children they were categorised in two groups based on the LVEF assessed by echocardiography (group I LVEF > 30% and group II $\leq$ 30%). The collection and analysis of blood samples was done exactly in the similar fashion as in adults.

Children were aged 1–12 years (Mean 5 years) and included 6 males and 14 females. 11 patients had clinically controlled heart failure with LVEF ranging from 32 – 38% (median 35%) they were classified as group I. The remaining 9, classified as group II had uncontrolled symptoms with LVEF ranging from 15 – 28% (median 22%). All children were on frusemide, captopril and digoxin. None received beta-blocker. The controls were healthy, asymptomatic, normotensive children and had normal chest x-ray, ECG and echo Doppler studies.

Levels of plasma noradrenaline and adrenaline were significantly higher in study patients compared to controls. (Table 28) Plasma noradrenaline levels in the study patients also exhibited a negative correlation with the LVEF (Table 29). Similar relationship was demonstrated with regard to plasma adrenaline levels with LVEF.

Table 28: Comparison of results in study patients and controls.

Feature	Study patients	Controls
Age (years)	1-12 (5)	1-12 (5.5)
Sex (M/F)	6 / 14	9 / 11
LVEF (%)	15-38 (32)	58-70 (65)**
NA (pmol/L)	690-12172 (2896)	784-3239 (2104)*
AD (pmol/L)	156-4009 (447)	102-980 (341)*

*p=< .05, **p = .001, NA = noradrenaline, AD = adrenaline

Table **29** : Comparison of Group I and Group II with controls.

Feature	Control (n= 20)	Group I (n = 11)	Group 2 (n = 9)
Age	1 – 12 yrs.	2 – 9 yrs.	2 -12 yrs.
LVEF %	58 – 70 (65)	33 – 38 (35)	15 – 28 (22)
NA (pmol/L)	784 – 3239 (2104)	690 – 4564 (1563)	1427-12172 (4019)*
AD (pmol/L)	102-980 (341)	156-1862 (341)	291- 4009 (1583)*

*p = < .001, NA = noradrenaline, AD = adrenaline

This study in children again confirmed raised adrenaline and noradrenaline levels in heart failure. Levels were higher in severe heart failure than mild heart failure. These results are in contrast to the findings in the adult cohort. A possible explanation of this could be that heart failure in children is more likely to be of shorter duration and the decompensation/resetting of adrenergic receptors responsible for loss of continuing increase in sympathetic drive may not have set in, contrary to the adult population where the heart failure is likely to be of longer duration before seeking the medical help. This aspect would need further investigation.

CHAPTER – 5

SPECIAL GROUPS OF PATIENTS

OF IDIOPATHIC DILATED CARDIOMYOPATHY

FAMILIAL DILATED CARDIOMYOPATHY

Recent data [27] show that familial dilated cardiomyopathy is not such a rare disease as was earlier believed. However, our knowledge about the age of onset and natural history of this form of disease is limited. It was expected that high parental consanguinity in the cohort of patients in this study could reveal a higher prevalence of this form of disease in the Omani population.

RESULTS

In addition to 97 adult patients, 11 children formed the index patients for family screening (total of 108 patients). 30% had consanguineous parents. A total of 890 first-degree relatives of these patients were identified but only 770 (87%) presented for family screening. Among the unevaluated family members 102 were reported to be asymptomatic, leading a healthy life and 18 had died from non-cardiac causes (road traffic accidents, cerebro-vascular accidents, malignancy, pneumonia). 7 of the 108 index patients (Table 30) on investigation were discovered to have affected first degree relatives, giving a familial frequency of 6.5%. 6 of the 7 patients had one affected relative and the remaining one had two affected relatives, thus the total number of patients with FDC (including the index patients) was 15 and their clinical data is summarised in table 31 (Group I). None of these patients had any metabolic abnormality to explain the familial tendency. The remaining 101 patients did not have any affected family member and formed the non-familial group (Group II). Characteristics of the familial group and non-familial group were compared with regard to age, sex, parental consanguinity, NYHA functional class, initial left ventricular ejection fraction and outcome (Table 32). Factors identified as more

common in FDC were a younger age at diagnosis (p=.001) and parental consanguinity (p=.04). There was no significant difference in the outcome between familial and sporadic groups.

DISCUSSION

Recognition of familial tendency was an important step towards identification of an aetiology for idiopathic dilated cardiomyopathy. Reported frequency of FDC has increased from 2% in 1981[234] to 20-25% in recent publications [78, 81, 330, 331]. Although several modes of transmission have been described, the most common variety is the autosomal dominant [332]. HLA association have also been reported [77, 333, 334] however, a previous report on patients with IDC from our unit did not identify any such association [314]. In the present study, among the 770 first degree relatives (87%) evaluated, applying strict diagnostic criteria, a relatively low frequency of FDC (6.5%) was found on preliminary screening.

Table 30. Details of first-degree relatives of patients with FDC

Index patient	First degree relatives (parents, siblings, children)		
	Total	Studied	Affected
1	10	10	1
2	6	6	1
3	9	9	2
4	3	3	1
5	2	2	1
6	13	13	1
7	14	12	1
Total	57	55	8

Table 31. Characteristics of patients with familial dilated cardiomyopathy

Index patients	Affected members	Age	Sex	Symp	PC	ECG	LVEF	Doppler	Outcome
1		2	M	Yes	Yes	LVH	31%	MR,TR	Live
	i - sibling	4	M	Yes	Yes	LVH	25%	MR	Live
2		1	F	Yes	No	BVH	40%	MR	Live
	ii - sibling	2	M	No	No	Normal	45%	N	Live
3		6	F	Yes	Yes	BVH	36%	MR, TR	Live
	iii - sibling	8	M	Yes	Yes	LVH	35%	MR	Died
	iv - sibling	10	F	Yes	Yes	BVH	30%	MR,TR	Died
4		2	M	Yes	Yes	LVH	24%	MR	Live
	v - sibling	1	M	Yes	Yes	LVH	28%	MR	Live
5		6	M	Yes	Yes	LVH	36%	MR	Live
	vi - sibling	8	M	Yes	Yes	BVH	30%	MR,TR	Died
6		55	F	Yes	No	RBBB, AF	28%	MR, TR	Died
	vii - sibling	48	F	Yes	No	RBBB	49	MR	Live
7		50	F	Yes	No	RBBB, LVH	25%	MR	Died
	viii - child	31	F	Yes	No	BVH	18	MR, TR	Live

Symp = symptomatic; PC = parental consanguinity

Table 32. Comparison of patients with familial (Group I) and non-familial (Group II) dilated cardiomyopathy

Parameter		Group I (n = 15)	Group II (n = 101)
Age (years)*	Mean	16	39
	SD	19	20
Sex	M	8	54
	F	7	48
Parental consanguinity*	Yes	9	34
	No	6	67
NYHA functional class	I&II	9	66
	III&IV	6	35
LVEF (%)	Mean	31	34
	SD	8	8
Outcome	Live	10	79
	Dead	5	22

*significant

A similar screening of 812/966 (84%) relatives by Michels et al [78] reported a 20.3% frequency of FDC. Keeling et al [330], who placed the frequency at 25%, did not mention the total number of relatives from whom the study patients were selected. A 7% frequency similar to this Omani study has also been reported from Italy [81], but this study offered screening only to families with suspected familial diseases and thus could have excluded the asymptomatic patients. In the present study families irrespective of the presence or absence of another known affected member were screened.

Referral bias is significant when studies are conducted in highly specialised centres where familial patients are more likely to be referred. SQU hospital has the advantage of being the only referral hospital catering to the population served and there are no other hospitals performing cardiac investigations in the catchment area. Furthermore there is a good system of liaison with primary and district hospitals in the region with a direct access echocardiography services for primary physicians. This would mean that a representative sample of the affected patients with IDC has been received. A low frequency of FDC in this study despite the high prevalence of IDC and consanguinity is interesting and may suggest a geographical variation with different aetiologies for this disease in a sub-group of patients. However, significantly higher frequency of FDC was found in offspring of related parents compared to those of unrelated ones, supporting a genetic role in the aetiopathogenesis.

Patients with FDC in this study were younger than those with sporadic disease ($p = 0.001$). Michels [78] and Keeling et al [330] did not find such a difference but Omani

data cannot be compared with their findings due to differences in study design. Particularly, in the Keeling's study the youngest patient was only 12 years old. Mestroni [335] however, reported younger age and high ejection fraction in their FDC patients of 281 relatives from 60 families with IDC. The younger age at diagnosis in Omani patients with FDC reflects the severity of familial disease and, furthermore some of the affected relatives of adult patients may have died undiagnosed in their infancy or childhood accounting for the low frequency. Early diagnosis has led to more cases in children and on account of the severity of the familial disease few would have survived into adult life. However, statistical difference in either outcome or survival between patients with FDC and the sporadic form was not seen. A larger study carried over a longer duration might bring out the relationship, if any.

The identification of asymptomatic patients is an important aspect of family screening. Only one such patient was found among the 770 relatives screened. It must be admitted that 13% of relatives who did not present for screening in this study may contain some of the asymptomatic individuals with IDC. Published studies report a much higher frequency of asymptomatic disease ranging from 9.2% to 16.5 % [78, 336].

An accepted limitation of the study is that the suggested strategy of screening of 3 generations and more distant relatives was not done. Some cases, particularly the asymptomatic ones and affected patients among the dead family members, may have missed our attention. Atrial natriuretic peptide levels and molecular mitochondrial studies which could have identified latent disease at the point of the evaluation was not performed. Genetic analysis was not included in our protocol.

Clinical implications

Screening and identification of the inherited nature of the disease leads to a series of investigations that help to identify treatable underlying metabolic disorders - for example systemic carnitine deficiency. The type of inheritance helps to prognosticate particularly in the case of X-linked cardiomyopathy. FDC has been suggested to have a poorer prognosis than the non-familial type [337]. Such a correlation was not documented in this study but the number of the familial patients was small. Screening family members helps to diagnose disease early during the asymptomatic phase. Since a molecular diagnosis of XLDC and of the carrier status is now possible, linkage analysis could be used to detect family members at risk. Genetic counselling could be offered to patients with IDC to inform them about the characteristics of the disease, the risk in the relatives, the scope of early treatment, and the likelihood of future developments. Mestroni et al [335] have published guidelines for the study of FDC and Towbin [338] has summarised the current state of knowledge of the associated genetic abnormalities (table 33).

Experience in family studies also brings up a need to redefine some of these disorders. Often relatives show minor signs of myocardial disease, such as wall motion abnormalities, dilatation without ventricular dysfunction [339], unexplained arrhythmias, and conduction defects that do not satisfy the traditionally accepted diagnostic criteria of dilated cardiomyopathy. These signs, in the context of a hereditary disease suggest early manifestations of the disorder. Follow up studies and, eventually a molecular diagnosis will resolve these questions with the possibility of disease prevention and development of genotype-based treatments. Genetic abnormalities predispose to the development of IDC, however the phenotypic

expression of the disease may require a precipitating factor such as infection or toxin and /or a perpetuating factor such as autoimmunity, which by itself could have a genetic basis. The recognition of abnormalities of endothelin will strengthen the interest of clinical studies with endothelin receptor antagonists and might help in defining subgroups of responders to such treatment [304].

Family screening thus is an important part of the clinical evaluation of patients with IDC. Despite the high rate of consanguinity, preliminary screening revealed only 6.5% cases of FDC. It was more common in the younger age group at first diagnosis and parental consanguinity was significantly higher but the outcome was not different from the sporadic form. Further studies in FDC in Omani patients are being set up including the genetics analysis.

Table 33. Genetic loci and disease genes
Identified for familial dilated cardiomyopathy*

Clinical pattern	Genetic loci identified	Diseases gene identified
Autosomal dominant (AD)	10q21-1023, 9q13-q22, 1q32, 15q14, 2q31, 1q11-21	Actin, Desmin Lamin A/C
AD with conduction defect	1p1-1q1, 3p22-3p25	
X-linked (XL)	Xp21	Dystrophin
XL cardio-skeletal (Barth syndrome)	Xq28 (gene G4.5)	Tafazzin

*summarised from Towbin [338]

PERIPARTUM CARDIOMYOPATHY

A relationship between pregnancy and dilated cardiomyopathy was first noticed in 1870 when Virchow and Porak first reported autopsy evidence of myocardial degeneration in patients who died in the puerperium [341]. Gouley et al [342] in 1937 later described the clinical and pathological features of 7 pregnant patients who had severe and often fatal heart failure. These women had a dilated, non-ischaemic cardiomyopathy in the later months of their pregnancies, which persisted after delivery. The aetiology of peripartum cardiomyopathy is currently unknown and its prevalence is thought to be one in five thousands live births. Currently more and more evidence suggests that peripartum cardiomyopathy is actually a type of myocarditis arising from an infective, auto-immune or idiopathic process. [343-345]. Early evidence of malnutrition associated with PPCM were not proved in recent studies [346-348]. Recently, an association with tocolytic therapy has been reported [349].

RESULTS

(Table 34)

Four patients were identified over a 3-year period among 15,000 live births (1:3750). All women were multiparous and their age ranged between 26-35 years. None had twin pregnancies. Their puerperal period had been uneventful. They presented complaining of dyspnoea between 6 to 10 weeks after delivery of the child. None had any febrile illness prior to presentation with no previous history of hypertension. ECG showed border-line LVH and shallow non-specific T-wave inversion. LV ejection fraction at presentation ranged from 38-43% with LV diastolic dimension of 5.7-6.2 cms. They received diuretics and an ACE inhibitor and all four showed

improved in symptoms with quick reduction in LV dimension and LV ejection fraction returning to normal values (≥ 50%) during the initial follow up period of six months. The LV indices then stabilised and did not change on subsequent follow up.

Table 34. Echocardiographic parameters of patients with peripartum cardiomyopathy

Patient No.	Age (Years)	LVDD (cms)		LVEF (%)	
		Initial	Follow-up	Initial	Follow-up
1	26	5.7	5.3	43	54
2	34	6.1	5.0	38	51
3	32	6.2	5.1	41	50
4	35	6.2	5.1	42	53

LVDD = left ventricular diastolic dimension; LVEF = left ventricular ejection fraction; Initial = at entry into the study; Follow-up = at 6 months interval

DISCUSSION

Due to relative rarity of this condition the data on PPCM is somewhat limited, reported to occur in one of every 1485 to 15,000 pregnancies with a higher incidence in Africa [341, 342, 346-348, 350,351]. This wide range is believed to be the result of geographical differences and variations in the manner in which authors define the condition. The criteria varied from just clinical evidence of fluid over-load to an objective demonstration of depressed myocardial function by echocardiography. Some even using the pathological features in their diagnosis. Currently accepted estimates of incidence are approximately 1/3000 to 1/4000 live births. This would translate into 1000 to 1300 women affected each year [352]. With four cases in

15,000 pregnancies in Omani population, the frequency of PPCM noted in this study is in line with the reported literature. With increased incidence recorded in Africa one may expect a higher incidence in the Omani population in view the fact that a significant proportion of people living in Oman have an East African ancestral background. But this cannot be truly translated to specific race in this study because all pregnancies occurred in ladies who were truly of Arabic descent. Of the 4 cases of PPCM in this study one patient however, agreed to have East African connections.

Multiparity and advanced maternal age, multifoetal pregnancy, pre-eclampsia and gestational hypertension are described as risk factors for PPCM. All four of my patients were multiparous but aged ≤ 35 years and none had multifoetal pregnancy, pre-eclampsia or gestational hypertension. Classically PPCM is described to occur during last trimester or within 5 months of the delivery [353]. All 4 patients in this study presented in acute left heart failure within 10 weeks of the delivery after going through the pregnancy uneventfully with no other risk factors except for being multiparous. They were treated conventionally with diuretics, digoxin and vasodilators. None received beta-blockers. There is some evidence that PPCM may be the result of myocarditis and immune-suppressive therapy has been used by some workers [343, 354] but this is not of proven value. There was no evidence to suggest myocarditis in this Omani cohort. There have been few reports of familial PPCM [355-357] but none of the patients in this study had any family history of heart failure in the puerperium.

The prognosis of women with PPCM has improved in line with the improved survival of patient with heart failure in dilated cardiomyopathy in general. In the 1970s a 5

year mortality of 85% was reported in those patients with PPCM where heart size did not return to normal and in 50% of patients spontaneous resolution of symptoms and heart size has been recognised [170, 358]. Most patients who recover show improvement in six months. If the congestive cardiomyopathy persist after six months it is likely to be irreversible and carries adverse prognosis [359]. Medei et al [343] reported a mortality rate of only 7% in their 1980 report. It has been reported that women with a history of peripartum cardiomyopathy who have regained a normal LV size and performance have decreased contractile reserve, and that these women may respond sub-optimally to haemodynamic stress in spite of evidence of recovery by routine echocardiographic evaluation [360]. In the present study in 1990s although I had only 4 patients who had only mild dilation of LV with mildly reduced LVEF, during their 5 to 7 year follow up all were still alive and haemodynamically stable with reduction in their LV dimension and improved LVEF confirmed by echocardiography. This improved morbidity and mortality of PPCM is almost certainly due to advanced medical treatment of heart failure and perhaps better control of certain modifiable risk factors during pregnancy. e.g. pre-eclampsia and gestational hypertension.

DILATED CARDIOMYOPATHY IN CHILDREN

Heart failure due to DCM in infants and young children presents special diagnostic difficulties. A high index of suspicion is essential for early diagnosis, as symptoms are non-specific and mimic chest infection. In older children features of heart failure as described in adults are generally evident. Echo-Doppler studies form the cornerstone of diagnosis and demonstrate dilated poorly contracting ventricle(s), predominantly the left (diastolic dimension >95th centile for body surface area and ejection fraction <50%). Preliminary tests are directed to identify the metabolic pathway that is affected. Results will then direct further specific analyses. Cardiac catheter studies and angiography are now performed only in selected patients. Idiopathic DCM is diagnosed after all triggering factors for the development of DCM have been excluded. The chart shown in Tables 35 can assist the physician in the correct diagnosis of children suspected to have DCM.

Until recently, IDC in adults generally carried a poor prognosis with up to 40% dying within two years of diagnosis but this has improved [291, 361-363]. A better outcome has been reported for children suffering from the disease [91], especially in those who present below the age of two years [364].

RESULTS

Eighteen children, 4 males and 14 females (M: F=1:3.5) who satisfied the entry criteria were studied. They were aged between 4 months and 8 years (median 1 year),

Table 35. Flow chart to approach to the differential diagnosis of DCM in children.

Approach	Findings	Possible diagnosis
Clinical features	Positive family history	Genetic cause for DCM
	Acute or chronic encephalopathy, muscle weakness, hypotonia, growth retardation, recurrent vomiting, lethargy	Inborn error of metabolism involving energy production
	Coarse or dysmorphic features, organomegaly, skeletal abnormalities, short stature, chronic encephalopathy, cherry red spot in eyes	Storage diseases
	Skeletal muscle weakness without encephalopathy	Neuro-muscular disorders
Blood investigations	High blood urea nitrogen & creatinine Low calcium, magnesium Electrolytes disturbances	Help in the initial management Occasionally points to a cause of DCM especially in neonate
	Elevated acute phase reactants and cardiac enzymes	Myocarditis
	Positive viral titres	Viral myocarditis
	Low serum carnitine	Systemic carnitine deficiency
	Hypoglycaemia - Low/no acidosis (ketosis) High insulin, low free fatty acid	Infant of diabetic mother, Nesidioblastosis
	Low insulin, high free fatty acid	Defect in fatty acid oxidation or carnitine metabolism
	Hypoglycaemia - Moderate/high acidosis (ketosis) Low / normal lactate and abnormal urine and serum organic acids	Organic (Propionic, methyl-malonic) acidaemias, or β-ketothiolase deficiency
	High lactate	Glycogen storage disease Bath and Sengers syndromes, Pyruvate dehydrogenase deficiency, Mitochondrial enzyme deficiency
	Hyperammonaemia with acidosis	Organic acidaemias (as above)
	Specific enzyme assay	Confirms enzymatic defect
	Absence of above physical and biochemical abnormalities	Post myocarditis or idiopathic DCM
Cardiac catheterisation	Evaluate haemodynamics	Useful to predict prognosis and evaluate for transplant
Coronary angiography	Abnormal origin of left coronary artery from pulmonary artery	Anomalous left coronary artery from pulmonary artery
Myocardial biopsy	Myocyte hypertrophy and fibrosis without lymphocytic infiltrate	Dilated cardiomyopathy
	Inflammatory cell infiltration, cell necrosis	Myocarditis
	Special stains	Mitochondrial or infiltrative diseases
Molecular studies (on blood, fibroblasts, or myocardial cells)	Nucleic acid hybridisation studies Polymerase chain reaction studies	Myocarditis
	DNA mutation analysis	Identifies specific genetic defect

15 (83%) being below 2 years. 14(78%) had symptoms of less than 2 months duration. Cough, dyspnoea and fever were the main symptoms. The major physical signs were tachycardia, quiet precordium, cardiomegaly, gallop rhythm and a systolic murmur of mitral regurgitation.

Chest X-rays revealed a mean cardiothoracic ratio of 67% ± 7.6% (range 58% to 87%). Pulmonary congestion was evident in 15 children, frank pulmonary oedema in one and pleural effusion in 2. Four also had pneumonia. The ECG revealed left ventricular hypertrophy in 9(50%), biventricular hypertrophy in 6(33%) with T wave inversion in left chest leads in 13(72%). 24-hour ambulatory ECGs was performed in 14 children and were abnormal in 4. The abnormalities included atrial and/or ventricular ectopic activity with abolition of the diurnal variation in heart rate, but ventricular tachycardia was seen in only one patient. Echo-Doppler studies showed significantly dilated left ventricles with low ejection fractions, ranging from 19% to 47%. Eight patients (44%) had LVEF less than 30%, eleven (61%) between 30% - 40% and two (1.1%) had a value of over 40%. Mild mitral regurgitation was demonstrable in all patients. The mean mitral valve E to A wave ratio was significantly lower than normal ($p<0.01$). Blood investigations revealed hypochromic anaemia in 7 patients, leucocytosis and raised erythrocyte sedimentation rate in 3. The serum creatine kinase (cardiac isoenzyme) was elevated in only one patient. Serum carnitine (total and free) levels were normal.

All children received diuretics and an ACE inhibitor. Five with recurrent resistant heart failure required monthly to once in three months intermittent dobutamine

infusion. Anticoagulants were given to two with thrombotic episodes and one received amiodarone for frequent ill sustained ventricular tachycardia.

Eighteen children were followed up for 1 to 7 years (mean 3.5 years) from the point of diagnosis for outcome. 10 children became asymptomatic (Group I) and 8 continued to be symptomatic or died (Group II). Seven (43%) in group I recovered completely with normal echocardiogram and 3 (19%) although becoming asymptomatic, continued to have abnormal echocardiograms. Among group II children 3 remained symptomatic, 3 died and 2 lost to follow up. Two deaths were sudden and unexpected in otherwise stable children with satisfactorily controlled cardiac failure. These two had shown ventricular ectopics on 24-hour ambulatory ECG. The other death was due to pneumonia and cardiac failure. 2 were lost to follow up after 1 year and 3.5 years respectively. Statistical analysis was done to look for any difference between groups I and II in their age of onset, sex, presence of arrhythmias, cardiothoracic ratio, initial left ventricular dimension and initial left ventricular ejection fraction. There was no significant difference between the two groups in the variables analysed ($p>0.05$). Among group I definite improvement was noted within a mean period of 11 months (range 4-22 months).

The survival curve revealed a probability of survival of 94% at 1 year and 87% at 3 years (Figure 6). There was no significant difference in the survival for sub-groups based on age, sex, left ventricular size and left ventricular ejection fraction during the period of follow up.

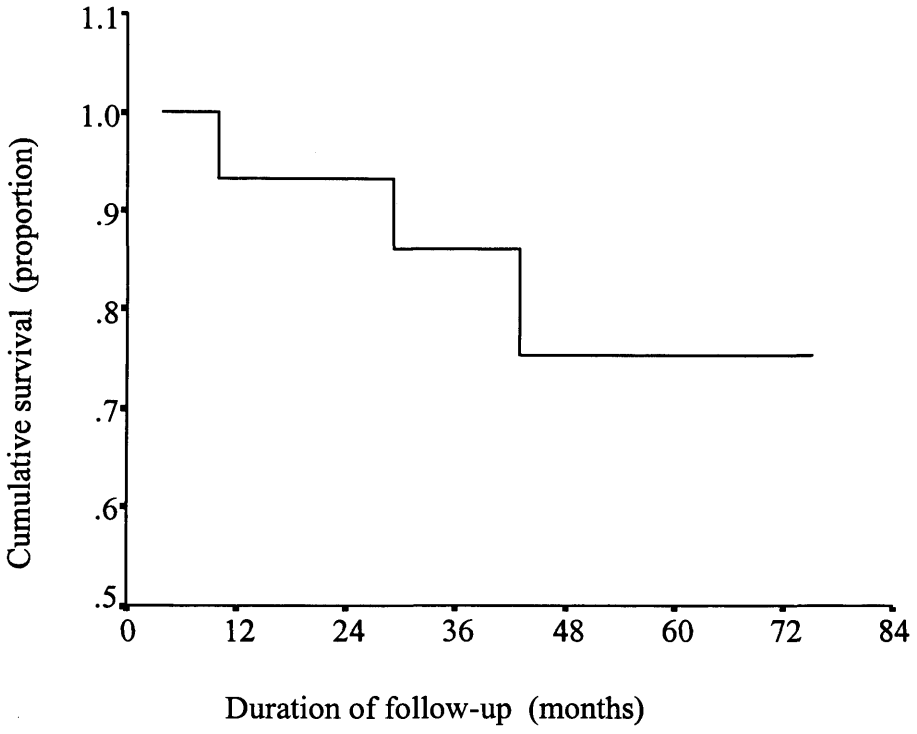


Figure 6. Cumulative survival in IDC in children (n = 18)

DISCUSSION

Dilated cardiomyopathy in children warrants careful investigation to look for an identifiable cause. The consensus of opinion suggests that these cases are due to a combination of factors namely - viral infections especially Coxsackie B virus, altered immune reactivity of the host and a genetic predisposition to altered myocardial response to injury [27, 28, 62, 365]. All children in this study presented with symptoms and signs of cardiac failure with dilated and globally depressed myocardial systolic function for which no specific cause could be identified. A substantial number of cases in the study were very young with a predominance of females. This is at variance with previously published series [366, 367]. Five children presented with primary chest problems. Chest X-ray and echocardiography led to their correct diagnosis. Serious arrhythmias have been reported to predispose to sudden death in patients with IDC [283]. Two sudden deaths are likely to be arrhythmic. Ambulatory electrocardiography could be helpful in detecting such arrhythmias early in the course of dilated cardiomyopathy, including those who are asymptomatic but continue to have dilated left ventricles.

It is well known that the beneficial effects of diuretics and vasodilators wane with time as the abnormal neuro-endocrine profile of chronic cardiac failure is re-established [368]. Periodic infusions of inotropes such as dobutamine may help to reverse this process and possibly re-establish the actions of diuretics and vasodilators [369, 370]. This mode of therapy helped 5 of our children who did not respond to conventional therapy and required frequent admissions for exacerbations of cardiac failure. In the absence of facilities for cardiac transplant or other surgical alternatives,

this was the only available therapeutic option. Survival figures were similar or slightly better than those published in the literature [91, 283, 364].

In brief, this study is featuring the clinical profile and follow up of children presenting in heart failure due to idiopathic dilated cardiomyopathy in Arab population and it suggests a younger age of onset and female preponderance of the disease in this country. Survival of children with IDC was better than those reported earlier. Improved total care of the patients and the use of elective dobutamine infusions were useful in improving the quality of life.

CHAPTER – 6

SUMMARY OF AETIOLOGICAL CONSIDERATIONS

In general patients who present with a poorly functioning dilated ventricle(s) without evidence of coronary artery or valvular disease are labelled as dilated cardiomyopathy. However, since a number of pathogenic factors are implicated in the development of dilated cardiomyopathy, in the true sense the term idiopathic dilated cardiomyopathy can be used only when all identifiable factors have been eliminated. Broadly, investigations into the pathogenesis of IDC have focused on 4 basic mechanisms. These mechanisms are not mutually exclusive, and several may combine to produce clinical disease in susceptible patients.

1. Familial and genetic factors.
2. Viral myocarditis and cytotoxic insult.
3. Immune abnormalities.
4. Metabolic and contractile abnormalities.

The present study was not truly designed to investigate the aetiological issues in IDC. It was intended that the knowledge of the clinical profile would help to pave the way for setting up pathogenic investigations for future studies. Nevertheless useful data has been gathered to discuss possible aetiological mechanisms involved in IDC in Oman.

FAMILIAL AND GENETICS

A low frequency of familial pattern in the population studied in this work is somewhat unexpected considering the high prevalence of consanguinity in Omani society. Within the limitations of the study design this aspect of pathogenesis needs further

investigations supported by genetic studies. This is being planned and a genetic laboratory is now being set up to investigate familial dilated cardiomyopathy.

VIRAL MYOCARDITIS

Investigations looking for markers of virus related myocardial damage are generally unrewarding at least in the assessment of past insult. Although molecular hybridisation studies have documented the presence of enterovirus in the myocardium in the patients with IDC [54] they can also be detected in control subjects. PCR techniques have also been unrewarding [52, 56, 371]. These findings have called into question the relation of viral myocarditis to IDC or certainly the frequency with which viral myocarditis results in the disease. A very recent report by Li et al [372] has revived interest for viral theory in IDC. Elevated levels of Coxsackie virus B3 titres reported in myocarditis and IDC were not found in any of our patients. This along with negative histories of viral illness in almost all patients prior to the development of symptoms was against recent viral myocarditis but does not rule out previous virus infection in our cohort. In fact it will remain an important suspect in the aetiopathogenesis of IDC in Oman at least in the present population which may be reflecting virus infections which occurred many years ago.

IMMUNE ABNORMALITIES

Abnormalities of both cellular and humoral immuno-modulation are well recognised; however, whether they are the cause or the effect or whether they have a pathogenic role remains unclear. A lack of HLA association and absence of antiheart antibodies in most patients is not supportive of this as a significant factor in IDC in Omanis. This however, requires further validation in a larger number of patients.

METABOLIC AND CONTRACTILE ABNORMALITIES

The pointers of these mechanisms are metabolic down regulation and uncoupling of beta-receptors, as well as abnormalities of cardiac high-energy phosphate substrate, actin-myosin interaction, and sarcoplasmic reticulum. Although norepinephrine secretion is enhanced in most patients with low output cardiac failure, adrenergic stimulation appears greater in IDC than in IHD [373]. The sympathetic over-stimulation was well documented in Omani patients. The pathogenic role of these mechanisms in IDC however remains unidentified.

ALCOHOL INTAKE

Epidemiological and clinical evidence exist to link alcohol to dilated cardiomyopathy, probably through a direct toxic effect on the myocytes. This has not been discussed in this work firstly, because alcohol intake was one of the exclusion criteria of the patient selection, it being assumed that cases with a history of alcohol intake would mean that the cause is identified and these cases are not truly idiopathic and, secondly, alcohol intake is very uncommon in this area. None of the patients screened reported any alcohol intake. This is perhaps an over simplification, because many patients hide their drinking habits, the level of drinking that is normal or safe is uncertain, and alcohol may potentiate viral or autoimmune damage. Patients were also interviewed for any substance abuse, which was found lacking in all cases.

OTHER CONSIDERATIONS

Dietary Factors

Gross dietary habits of this population in general and the patients with DCM were compared but no difference was found. Dates and local Omani coffee are not known

for any cardiotoxic substances and their consumption did not differ in patients and population. Therefore, there is nothing to suggest that any nutritional factors are involved. However, the genetic disposition to such or other environmental factors are not ruled out. Selenium deficiency implicated in some reports could not be investigated due to lack of availability to measure toenail selenium levels [374]. Thiamine deficiency implicated in IDC [375] was not assessed by serum thiamine levels but no other feature of vitamin B6 deficiency and zero alcohol consumption makes this factor unlikely.

Socio-economic Factors

In African Americans, who are a high risk group in the United States, in addition to genetic and environmental factors a low socio-economic status has been linked to IDC possibly because of reduced access to high quality health care. But there is no evidence of a direct aetiopathogenic correlation. A lack of available data on total socio-economic make up of the population in the region does not allow to make a conclusion that IDC was more prevalent in low socio-economic group. Any association to low socio-economic status is purely observational, but this aspect cannot be totally ignored since over 75% of our patients were in a low-income group. With improving socio-economic status of Omani society this aspect may further clarify itself in coming years.

In summary pathogenic mechanisms in dilated cardiomyopathy are as heterogeneous as its pathological features. Regrettably there is no direct match between pathology and pathogenesis. For example, the pathologist cannot distinguish between alcoholic cardiomyopathy and cardiomyopathy from other causes. The issue becomes even

more complex when dealing with the idiopathic group. In the coming years we, in Oman, will be concentrating our efforts to look in more detail into genetic and immune mechanisms of the pathogenesis of IDC in the Omani population with further clarification on socio-economic aspects. Data from other parts of the country will also help ascertain if local regional factors are operating.

LIMITATIONS OF THE STUDY

It was not a population-based study and incorporates only patients presenting with symptomatic heart failure. Although 2 asymptomatic patients were picked up during the family screening, there are likely to be patients, either totally asymptomatic or minimally symptomatic, who have not come to the medical attention. Thus the prevalence of heart failure and IDC reported in this study is related to only symptomatic cases and the true prevalence is likely to be higher.

In this study a valiant effort was made to ensure that the patient selection was strictly limited to idiopathic dilated cardiomyopathy. Despite this doubts may still persist : 1. were some patients actually previously may have had "chronic hypertension"? 2. Intrinsic mitral regurgitation may be responsible for heart failure in patients with severe MR. Both these issues have been discussed in the relevant sections. A poor correlation of LVH on ECG with echocardiography in this population and evidence of significantly reduced LVEF in the apparent absence of intrinsic mitral valve abnormality would help to clarify doubts to some extent. Indeed it would be therefore, appropriate to say that the coronary disease has been effectively excluded and the population described in this thesis may represent a cohort of patients with "non-ischaemic cardiomyopathy".

The interpretation of diastolic dysfunction is limited because of use of only E/A ratio as a diagnostic criterion.

In Family screening only the siblings and parents were screened. It is recommended that 3 generation should be studied as part of family screening. Further more, since

patients with early symptoms may have normal echocardiographic study, a measurement of natriuretic peptide could have been helpful in identifying such cases.

Sub-studies of cardiac autoantibodies, HLA typing and catecholamine level incorporated small number of patients with a possibility of sample bias. Despite a low power of the study, HLA and catecholamine assessment had enough number of patients to make a reasonable initial interpretation of the results but cardiac autoantibodies results are debatable. A larger number of patients in these studies would have put more power to the study

Explanations for these and some other minor limitations have been discussed in the relevant sections.

FINAL CONCLUSIONS

This effort is the first collection of organised data on heart failure particularly idiopathic dilated cardiomyopathy in Oman. A large region of Oman predominantly populated by indigenous Omanis was selected for the study over a three-year period with 8-year follow up. From this hospital based research the following final conclusions can be summarised:

1 The prevalence of symptomatic heart failure is 5.17/1000 population. This is higher than some of the studies reported from the other parts of the world.

2. Prevalence of symptomatic IDC at 14.4/100,000 population is also higher compared to that reported from USA and Europe.

3. There was significant male predominance (M: F = 1.4:1).

4. Clinical features (symptoms and signs), chest x-ray, ECG, MUGA Scan and 24 hour Holter ECG findings were as expected. 24 hour Holter ECG revealed considerable reduction in arrhythmias during sleeping hours .

5. Disproportionately impaired septal motion on echocardiography was common, present in 50% of cases suggesting a major role of septal contractile cardiac function.

6. Global hypokinesia on echocardiography although helpful is not diagnostic. Coronary arteriography is mandatory to exclude obstructive CAD in patients suspected of having IDC.

7. Mild coronary artery disease of < 40% maximal luminal narrowing was found to be co-existing in 6.3% of patients with IDC in this study but had no effect on mortality.

8. Survival figures of 94% at 1 year, 76% at 5 years and 68% at 8 years with a mean survival of 65% were recorded. They are representative of a different outcome in a population which is different from those previously reported.

9. The commonest cause of death was chronic resistant heart failure. This is somewhat different from some of the other studies where sudden deaths were thought to be more common.

10. Univariate analysis revealed LVD, VT, LBBB and severe MR as significant mortality variables but on multivariate analysis left ventricular ejection fraction was the only significant independent factor effecting the mortality.

11. ACE inhibitors and beta blockers were significantly underused at the beginning of the study. This research exercise helped to improve the treatment regimen of IDC patients in Oman.

12. No HLA association was found but the power of this study was low.

13. In the limited number of patients studied, organ specific cardiac autoantibodies were not detected. This aspect needs further evaluation.

14. Increased noradrenaline levels were in line with the established data but a linear relationship to the severity of the heart failure was lacking. In children with early symptoms this relationship was evident.

15. 770 first-degree relatives were screened for familial disease. Despite a high prevalence of parental consanguinity a frequency of FDC of only 6.5% was found. This is considerably lower than reported in the literature.

16. In familial cases symptoms at early age predicted poor outcome.

17. The frequency of peripartum dilated cardiomyopathy was 1/5000 live births. This is similar to that reported by other workers.

18. A large number of patients were of low socio-economic status. It's atio-pathogenic value needs further investigation.

OBJECTIVES ACHIEVED IN THIS STUDY

1. This is the first and only study to date on any aspect of heart failure and idiopathic dilated cardiomyopathy in Oman.

2. A circumscribed but large population of Oman (Dhakliya region) has been studied which is almost representative of the Omani population in general.

3. The demographic profile of IDC in this region of Oman is now known.

4. Clinical characteristics were extensively recorded.

5. Extensive investigational data has been collected.

6. The natural history of IDC was studied with a follow up of up to 8 years.

7. Mortality variables were analysed.

8. Differences in various aspects of clinical, investigative and natural history outcomes were compared with studies already published using data from Europe, USA and some countries in Africa.

9. Autoimmunity was studied by HLA phenotyping and antiheart antibody detection.

10. Sympathetic stimulation in IDC was assessed by studying catecholamine levels and relating them with the severity of heart failure.

11. The frequency of peripartum cardiomyopathy is now known.

12. Preliminary family screening was achieved by studying 87% of relatives.

13. During the course of the study initiative was taken to include some of the aspects of IDC in children.

Thus the **main objectives** which were initially set out have been **achieved**. Certain aspects that would have been helpful to fill the gaps were not included in the original protocol because these goals would not have been possible due to cultural restrictions and lack of facilities or funds. These are mentioned under the limitations of the study and referred to in appropriate sections. With the recognition of the high prevalence of IDC in Oman, this report has prompted to propose and initiate the following measures for further research in this condition.

1. Similar study of demographic and clinical profile of IDC with natural history from other areas of Oman.

2. Population based study to identify undiagnosed individuals is being suggested.

3. National Heart Failure Registry is in the process of being set up.

4. Recently, genetic laboratory is being set up at the SQUH to study genetic diseases. IDC has been included as one of the disease to be studied. Collaboration with genetic units outside Oman is also being sought.

5. Organ specific cardiac antibodies are being tested against human myocytes.

PUBLICATIONS ORIGINATING FROM THIS RESEARCH

Published in Peer Reviewed Journals:

1. Agarwal AK, Venugopalan P, Mehar Ali AK, de Bono D. Idiopathic dilated cardiomyopathy in an Omani population of Arab Peninsula: Prevalence, Clinical profile and natural history. A prospective study. Int. J. Cardiol 2000; 75 (2) : 147-158. – addressed by an editorial – prevalence and natural history dilated cardiomyopathy – Mohan NG, Hamid S, McKenna WJ in the same issue.

2. Agarwal AK, Venugopalan P, Woodhouse C, de Bono D. Catecholamine levels in heart failure due to dilated cardiomyopathy and their relationship to the severity of heart failure. Eur J Heart Failure 2000 Sep 1; 2 (3) : 261-263.

3. Agarwal AK, White AG, Ali M, Lehney A, Daar AS. HLA antigens in an Omani population with dilated cardiomyopathy. Int J Cardiol 1996; 55 : 29-32.

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6. Venugopalan P, Agarwal AK, et al. Improved prognosis of heart failure due to idiopathic dilated cardiomyopathy in children. Int. J Cardiol 1998; 65 : 125-128.

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8. Agarwal AK, Venugopalan P, de Bono D. Prevalence and aetiology of heart failure in an Arab population. Eur J Heart Failure 2001; 3 : 301-305.

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APPENDIX

Deep upper limb and jugular venous thrombosis in dilated cardiomyopathy : Two Case reports

INTRODUCTION

Deep venous thrombosis is a known complication of thrombotic states and disorders associated with sluggish systemic circulation such as dilated cardiomyopathy (DCM), common sites being pelvic or lower limb veins. Involvement of the upper limb veins is rare [1]. Anecdotal reports of cases of DCM exhibiting superior vena caval and jugular vein thrombosis have appeared in the literature [2]. During the clinical follow-up two patients developed spontaneous venous thrombosis of the upper limb and jugular veins.

Case 1.

KM, a 27-year-old Omani male was admitted with exacerbation of cardiac failure. He improved by treatment with frusemide, captopril and digoxin. Two weeks later he developed pain and swelling of the right upper arm and the right side of the neck. The arm was tender with bluish discoloration along with distended veins at the root of neck and over the right shoulder. He was well hydrated and lower limbs were normal. He did not have any central venous cannulation and there was no evidence of superficial thrombophlebitis. He was in sinus rhythm and echocardiogram excluded intracardiac thrombus. Compression ultrasonography, Colour flow Doppler evaluation and radioisotope scan using technetium-99m confirmed extensive thrombosis of the right brachial vein, extending to the right axillary, subclavian and internal jugular veins. Blood investigations revealed normal values for prothrombin time, activated partial thromboplastin time, protein C and protein S (functional assay), antithrombin III, plasminogen and plasminogen activator. Alpha 2 antiplasmin and plasminogen activator inhibitor were also normal and lupus anticoagulant was negative. Modified

activated Protein C resistance ratio was normal. Following anticoagulation, during last 6 years since the first episode of DVT he has remained well but has had mild exacerbations of DVT when the anticoagulant control had been unsatisfactory due to his poor compliance.

Case 2.

AJ, an eight-year-old Omani girl with dilated cardiomyopathy was admitted in heart failure. She made slow but steady progress on anti-failure measures. She also required brief dobutamine infusion through a peripheral venous cannula to improve her circulatory state. Three weeks after admission she developed swelling over the neck, extending to the upper chest. With the clinical suspicion of venous thrombosis an ultrasound examination was done which revealed complete thrombotic occlusion of right and left internal jugular veins, extending into the brachiocephalic vein. The findings were confirmed by a compression ultrasonography and colour flow Doppler evaluation. There was no evidence of DVT in the lower limbs. She was in sinus rhythm and cardiac chambers were free of thrombus as assessed by echocardiography. Blood tests for a hypercoagulable state (as in case 1) did not reveal any abnormality. Clinical improvement occurred with treatment by anticoagulant.

DISCUSSION

Deep vein thrombosis of the upper extremity is uncommon [1] and milder forms are often asymptomatic, usually occurring in association with indwelling central venous catheters, intravenous drug abuse and thoracic tumours. Coagulopathies both inherited and acquired can be associated with the syndrome. An idiopathic group of patients with no demonstrable cause has also been described [1]. Due to potentially fatal complication, early recognition of DVT is extremely important, and compression

ultrasonography supported by colour flow Doppler studies play a helpful role in the diagnosis [3]. Dilated cardiomyopathy is a well-recognised low flow state with high incidence of intracardiac thrombus formation. Such sluggish circulatory state also predisposes to DVT in legs [4] but thrombosis of the deep veins of the upper extremity and head and neck has been reported only rarely in this condition [2]. Both patients in this report had dilated cardiomyopathy with poor myocardial function and developed deep vein thrombosis at unusual sites during exacerbation of heart failure. They did not have any indwelling devices or thrombophilic states, neither was there a family history of such a disorder.

Factor V (Leiden) has now been identified as an important cause of hypercoagulability state and is present in 18% of Caucasian patients with venous thrombosis [5]. Both of our patients had screening for Factor V (Leiden) using the modified activated Protein C resistance (APC-R) ratio and were found to have normal values. 75 Omani patients with various thrombotic disorders and 150 normal Omani controls have been screened for Factor V Leiden using the APC-R ratio and no Omani with low APC-R ratio has been detected to date (unpublished data, personal communication from Haematology Department, Sultan Qaboos University Hospital). The incidence of Factor V Leiden in the Omani population may thus be considered very low.

The prothrombin gene variant 20210A has recently been implicated in thrombotic states. DNA analysis for this variant was not available and hence could not be performed. However this gene mutation has been shown to be extremely rare in non-Caucasians [6, 7]. Both patients have remained well on long term anticoagulation.

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BRIEF OUTLINE OF
STUDY PROTOCOL DATA COLLECTION SHEET

Name
Hospital No.
Sex
Weight
Height
Address At birth
At 25 years
At 50 years
Occupation

Socio-economic Income

Marital Status
Consanguinity
Dietetic history
Parity in females
Blood pressures Lying
Standing
Drug history
Travel history
Smoking
Alcohol intake
Physical activity
No. of family members
No of rooms in the house

Clinical assessment

Symptoms
Duration
Age of onset
Chest pain (angina) typical/atypical
Dyspnoea (NYHA class)
Orthopnoea present / not present
PND Present / not present
Palpitation Present / not present
Syncope present / not present
Presyncope present / not present

Family history of DCM
History of peripartum Heart Failure
History of previous myocarditis
Associated conditions
Past medical history
Physical examination

Investigations

Haemoglobin	ESR	Urea
Creatinine	Na	K
Bilirubin	Mg	ALK
ALT	Protein	Albumin
Cholesterol	Triglyceride	CK
T3	T4	TSH

Sickle cell status
G6PD status
HIV status
Hepatitis screen
Catecholamine levels
Antiheart antibodies
Viral titres

ECG	Heart rate Rhythm QRS axis P wave Amplitude/configuration QRS duration QRS configuration LBBB/RBBB/IVCD R wave amplitude V1/V2 R wave amplitude V5/V6 S wave amplitude V1/V2 S wave amplitude V5/V6 T wave P R interval Q T interval Q Tc interval Atrioventricular blocks
Chest X-ray	CTR Chamber enlargement Lung fields Pulmonary vessels Pulmonary conus
Echocardiography	LA LVED LVSD LVEF MR mild / severe TR mild / severe AR mild / severe PR mild / severe Septal motion Posterior wall motion Diastolic dysfunction RV dysfunction Thrombus present / not present Transoesophageal Echo – Thrombus SEC
MUGA Scan	LVEF RVEF
Holter ECG	Dominant rhythm Arrhythmia Diurnal pattern

Treadmill Exercise Testing	Rhythm	
	Heart rate at start	
	Maximum heart rate	
	Total exercise time	
	Limiting symptoms	
	ST segment changes	
	Any precipitated arrhythmia	
Coronary angiography	Left main stem	
	Left anterior descending	proximal / distal
	Circumflex	proximal / distal
	Right coronary	proximal / distal
	Major branches	
	LV angiography	
Follow up		