

Ministry of Defence

Synopsis of Causation

Cardiomyopathies

Author: Dr Tony Fisher, Medical Author, Medical Text, Edinburgh
Validator: Professor Richard Sutton, Chelsea and Westminster Hospitals, London

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1. The cardiomyopathies are a heterogeneous group of diseases in which the common feature is [myocardial](#) dysfunction. They are a complex group, currently the focus of much research, and present understanding is incomplete. They were reclassified by a WHO/ISFC Task Force in 1995.¹
- 1.2. The "true" cardiomyopathies are idiopathic or of unknown origin while the term "specific" cardiomyopathies encompasses heart muscle disease secondary to specific cardiac or systemic disorders. By definition, myocardial disorders occurring as part of [ischaemic](#), valvular, hypertensive or congenital heart disorders and [pericardial](#) abnormalities are excluded. The most commonly used clinical classification is based on pathophysiology rather than aetiology.
- 1.3. The three main groups are:
 - dilated cardiomyopathy
 - hypertrophic cardiomyopathy
 - restrictive cardiomyopathy
- 1.3.1. **Unclassified cardiomyopathies** Not all cases fit neatly into the above classification and may be regarded as belonging to a group of unclassified cardiomyopathies. Two important but rare conditions in this group are [arrhythmogenic](#) right [ventricular](#) cardiomyopathy and [peripartum](#) cardiomyopathy. In addition, certain inherited disturbances of the electrical excitation process of the heart are sometimes included in this group, such as long QT syndrome (LQTS) and Brugada syndrome.

2. Clinical features

2.1. **Cardiomyopathies of unknown origin (true or idiopathic cardiomyopathies)**

2.1.1. **Dilated cardiomyopathy** This is the most common form (90% of cases). It is characterised by dilatation and impaired contraction of the left ventricle, or both ventricles. Presentation is usually with heart failure which is often progressive. [Arrhythmias](#), [thromboembolism](#) and sudden death are common and may occur at any age.

2.1.2. **Hypertrophic cardiomyopathy** This condition is characterised by left and/or right [ventricular hypertrophy](#), which is usually asymmetrical and involves the interventricular septum. Contractile function is preserved or enhanced and typically, the left ventricular volume is normal or reduced. [Myocardial ischaemia](#) of multifactorial origin may occur but the condition is often asymptomatic and consistent with long life. However arrhythmias are not uncommon and there is a constant risk of sudden death.

2.1.3. **Restrictive cardiomyopathy** This is the least common variety. It is characterised by abnormal [diastolic](#) function; the ventricular walls are excessively rigid and impede ventricular filling. The ventricles have normal or near normal [systolic](#) function and wall thickness. There are therefore similarities with constrictive [pericarditis](#) and differentiation is essential because of the potential for successful surgical treatment of the latter. [Interstitial fibrosis](#) may be present.

2.2. The distinction between these three functional categories is not absolute and often there is overlap. In particular, patients with hypertrophic cardiomyopathy also have increased wall stiffness due to the myocardial hypertrophy and so exhibit some of the features of restrictive cardiomyopathy.²

2.3. **Unclassified cardiomyopathies**

2.3.1. **Arrhythmogenic right ventricular cardiomyopathy** The usual presentation is arrhythmia, particularly multiple ectopic beats or right ventricular tachycardia, and it is a cause of sudden death in previously symptom-free young people.^{3,4}

2.3.2. **Peripartum cardiomyopathy** Cardiac dilatation and unexplained heart failure may develop during the last trimester of pregnancy or within six months of delivery. The signs and symptoms are similar to those in patients with idiopathic dilated cardiomyopathy, and the mortality rate may be as high as 25 to 50%.

2.3.3. **Other inherited disturbances of the electrical excitation process of the heart**
LQTS includes the Romano-Ward syndrome characterised by [QT prolongation](#) and ventricular [tachyarrhythmias](#), or the Jervell and Lange-Nielsen syndrome characterised by congenital deafness, QT prolongation, and ventricular arrhythmias. There is also a sporadic form. Sudden death may occur in these syndromes. The **Brugada syndrome** may also cause sudden cardiac death in apparently healthy individuals with a structurally normal heart. Patients with the condition show

characteristic changes in their electrocardiogram with [elevation of the ST segment](#). Variants do occur with minimal electrocardiographic changes and even concealed forms that are only unmasked when [class I antiarrhythmic drugs](#) are administered. ⁵

2.4. **Specific cardiomyopathies**

2.4.1. In general most specific cardiomyopathies are of the dilated variety, the exception being the group attributed to infiltrative disorders such as amyloidosis, haemochromatosis, neoplasia, sarcoidosis, Fabry disease and the fibroplastic disorders. These tend to have mainly restrictive effects.

3. Aetiology

CARDIOMYOPATHIES OF UNKNOWN ORIGIN -TRUE CARDIOMYOPATHIES

- 3.1. By definition, the true cardiomyopathies are idiopathic. However with greater understanding of genetic and immunological mechanisms the size of this group is diminishing⁶ and it is now thought that at least 30 to 40% of cases are inherited. However it has become clear that these diseases are genetically highly heterogeneous, with multiple genes identified for each of the major forms of cardiomyopathy.⁷ This suggests that the genetic diagnosis of most patients with cardiomyopathy will be impractical with current technology. Nevertheless there are a few exceptions, such as patients with X-linked cardiomyopathies, or those with cardiomyopathy linked to conduction disease. These conditions appear to be associated with mutations in a small subset of genes, and are now being actively investigated.
- 3.2. **Dilated cardiomyopathy** may be idiopathic, familial/genetic or associated with recognised cardiovascular disease where the degree of [myocardial](#) dysfunction is disproportionate to the abnormal loading conditions or the extent of [ischaemic](#) damage. Single gene mutations in the structural proteins of the [myocyte](#) or mitochondrial DNA are recognised causes of dilated cardiomyopathy. The role of familial factors is increasingly recognised and as many as 30% of cases will have other family members with evidence of left [ventricular](#) dysfunction or enlargement.⁸ Recent research suggests that autoimmune responses against heart tissue may play a significant role in the pathogenesis of dilated cardiomyopathy.⁹
- 3.3. **Hypertrophic cardiomyopathy** is now recognised in many cases as being caused by mutations in genes coding for [myofibrillary](#) proteins. The characteristic finding is inappropriate myocardial [hypertrophy](#) occurring in the absence of any obvious cause (such as aortic stenosis or systemic hypertension). Affected individuals are [heterozygous](#). There is variation in the distribution of myocardial involvement, which may be localised or affect the whole of the left (and sometimes right) ventricles.¹⁰
- 3.4. **Restrictive cardiomyopathy** This entity may be caused by a diffuse fibrosis of unknown origin. One form of the condition may have a familial basis.

UNCLASSIFIED CARDIOMYOPATHIES

- 3.5. **[Arrhythmogenic right ventricular](#) cardiomyopathy** This condition is familial with a predominance in young males, [autosomal dominant inheritance](#) and [incomplete penetrance](#). A recessive form is described.
- 3.6. **[Peripartum](#) cardiomyopathy** The cause of this disorder is unknown, although the current view is that it is multifactorial in origin. It is rare, and so far little research has focused on the condition. The prognosis for future pregnancies depends largely upon whether the heart size returns to normal after delivery.
- 3.7. **Other inherited disturbances of the electrical excitation process of the heart** The **Romano-Ward syndrome** is characterised by a familial occurrence with autosomal dominant inheritance. In the **Jervell and Lang-Nielsen (JLN)** syndrome there is also

familial occurrence with autosomal recessive inheritance. The **Brugada syndrome** is also hereditary and is caused by mutations in the cardiac sodium channel gene SCN5A. Arrhythmia in these patients can be precipitated by a variety of stimuli, including exercise, emotion, loud noise, and swimming, but it may also occur without any precipitating events.

SPECIFIC CARDIOMYOPATHIES

3.8. The specific cardiomyopathies originate from specific cardiac disorders or from systemic disorders. The many causes may be grouped as follows:

- **Inflammatory causes (infective)** including viral, rickettsial, bacterial and fungal agents
- **Inflammatory causes (non-infective)** including collagen diseases, Kawasaki's disease
- **Metabolic conditions (nutritional)** including thiamine deficiency, selenium deficiency, obesity, scurvy etc.
- **Metabolic conditions (endocrine)** including acromegaly, thyrotoxicosis, myxoedema, diabetes
- **Metabolic conditions (altered metabolism)** including gout, porphyria
- **Toxic causes** including alcohol, phenothiazines, lead, chloroquine, phosphorus, mercury, corticosteroids, cocaine and certain [chemotherapeutic agents](#), e.g. doxorubicin
- **Infiltrative diseases**, including amyloidosis, haemochromatosis, neoplasia, sarcoidosis, Fabry disease
- **Fibroplastic disorders**, including endomyocardial fibrosis, endocardial fibroelastosis, carcinoid
- **Haematological disorders**, including sickle cell anaemia, polycythaemia vera, leukaemia
- **Hypersensitivities** to various agents, including certain antibiotics, phenylbutazone
- **Genetic disorders**, including Duchenne muscular dystrophy, Friedrich's ataxia
- **Miscellaneous acquired conditions** including obesity
- **Physical agents**, including therapeutic radiation
- **The congenital myopathies**

3.9. Some of the commoner specific cardiomyopathies are discussed below.

ALCOHOLIC CARDIOMYOPATHY

- 3.10. Chronic excessive consumption of alcohol is the major cause of dilated cardiomyopathy in the Western world and accounts for upwards of one-third of all cases.
- 3.11. Alcohol may result in [myocardial](#) damage by two basic mechanisms: (1) a direct toxic effect of alcohol or its metabolites; and (2) nutritional effects, most commonly in association with thiamine deficiency. The distinguishing features include reduced contractility with typically left-sided low-output failure in the former and peripheral vasodilatation and high output heart failure, often right-sided, in the latter.
- 3.12. Alcohol results in acute as well as chronic depression of myocardial contractility and may produce reversible cardiac dysfunction even when ingested by normal non alcohol-dependent individuals. The reason for the transition from the reversible acute effects to permanent myocardial damage is unclear.

AMYLOIDOSIS

- 3.13. Amyloidosis results from the deposition of a material consisting of unique twisted B-pleated sheet fibrils formed from various proteins and may affect almost any organ. It may be senile, hereditary, or due to immunocyte dyscrasia (malfunctioning of cells normally involved in the response to infection) and it may be associated with chronic inflammatory disorders or malignant neoplasms. Involvement of the heart may occur in any variety of the condition although clinically significant amyloidosis is most common in patients with immunocyte dyscrasia.
- 3.14. Cardiac amyloidosis is commoner in men and is rare before the age of 30 years. The most common presentation is that of restrictive cardiomyopathy with right [ventricular](#) failure and [arrhythmia](#).

DIABETES MELLITUS

- 3.15. Diabetes mellitus increases the risk of congestive cardiac failure from all causes and it appears that this is attributable to factors other than atheroma and coronary heart disease. The correlation between diabetes and cardiomyopathy is substantial¹¹ and [interstitial fibrosis](#) and arteriolar hyalinisation are the most frequent abnormalities found. The severity of dysfunction is inversely related to the degree of diabetes control.

ENDOMYOCARDIAL DISORDERS

- 3.16. Endomyocardial fibrosis is a form of secondary restrictive cardiomyopathy, occurring most commonly in certain ethnic groups in tropical countries, where it accounts for 10 to 20% of deaths attributable to heart disease. Loeffler's [endocarditis](#) (hypereosinophilic syndrome) with which it shares many similarities, is associated with a hypereosinophilia of unknown cause. The end-stage intense endocardial fibrotic thickening in both diseases produces restrictive features. The aetiology is unknown.

HAEMOCHROMATOSIS

- 3.17. Haemochromatosis is characterised by the excessive deposition of iron in a variety of

parenchymal tissues, including the heart, pancreas, and liver. Causes include chronic liver disease, a defect in haemoglobin synthesis, chronic excessive intake of iron over a number of years, or as a familial or idiopathic disorder. The severity of cardiac involvement varies widely and only roughly parallels that in other organs. It manifests itself as a mixed dilated/restrictive cardiomyopathy with both [systolic](#) and [diastolic](#) dysfunction and is thought to be due to toxicity of the free iron moiety.

HIV

- 3.18. The heart is involved in up to 50% of people with AIDS but symptoms arise in only 10% and death attributable to heart disease occurs in only 5%. The cause is complex and probably multifactorial. It may arise secondary to myocarditis due to a wide variety of opportunistic cardiotoxic organisms or may be attributable to human immunodeficiency virus itself by means of an immunocyte mediated reaction. Antiviral drugs have also been implicated in the process, including zidovudine and interferon. The changes are those of dilated cardiomyopathy.¹²

NEUROMUSCULAR DISORDERS

- 3.19. The inherited neuromuscular disorders are associated with varying degrees of heart muscle involvement. In Duchenne's progressive muscular dystrophy cardiac involvement is uncommon, but if it occurs the resulting congestive cardiac failure is often refractory to treatment. In myotonic dystrophy a variety of conductive abnormalities may occur and syncope and sudden death are major hazards. In limb-girdle dystrophy and fascioscapulohumeral dystrophy cardiac involvement is uncommon and seldom severe. Cardiac involvement is common in Friedreich's ataxia where a hypertrophic pattern may occur.

SARCOIDOSIS

- 3.20. Sarcoidosis is a granulomatous disorder of unknown cause. Almost any tissue may be involved although the skin, reticulo-endothelial system and lungs are most commonly affected. Diffuse pulmonary fibrosis may result in fatal right heart failure. Clinical manifestations of sarcoid heart disease are present in less than 5% of patients and may cause heart block, congestive cardiac failure, [ventricular arrhythmias](#) and sudden death. Features of restrictive and dilated cardiomyopathy may coexist because both increased stiffness of the ventricular wall and diminished contractile function may be present.

THERAPEUTIC CHEST IRRADIATION

- 3.21. The prevalence of radiation-induced cardiomyopathy is increasing, associated with the increased survival of many malignancies. The majority of affected individuals are Hodgkin's disease survivors, followed by cases of non-Hodgkin's lymphoma, oesophageal, lung and breast cancer and metastatic seminoma. Radiation dosage (total) is likely to be in the region of 60Gy or even higher. Pericardial disease is the commonest expression of radiation damage but restrictive cardiomyopathy may occur, with congestive heart failure.¹³

THE CONGENITAL MYOPATHIES

- 3.22. Cardiomyopathy may be a feature of the congenital myopathies. These are hereditary

conditions which usually (but not invariably) present in early life or infancy with hypotonia and weakness. Most are relatively non-progressive. Muscle biopsy reveals unique morphological features on histochemical or ultrastructural examination, and in the common congenital myopathies, mutations have been identified in genes that encode for muscle proteins. The loss or dysfunction of these proteins is thought to lead to the specific morphological features seen on muscle biopsy and to the clinical disease.

3.23. While skeletal muscle is primarily affected in this group of diseases, cardiac muscle may be involved in a number of the congenital myopathies, such as:

- Nemaline rod myopathy
- Multicore (minicore) disease
- Myopathy with tubular aggregates
- Desmin storage myopathy
- Congenital myopathy with excess of thin filaments

4. Prognosis

- 4.1. Patients with **hypertrophic cardiomyopathy** are at increased risk of sudden death due to ventricular tachycardia or fibrillation, especially if there is a family history of such events or if the onset of symptoms was in childhood. Although there is an annual mortality rate of about 1%, in most patients the condition is compatible with little or no disability and normal life expectancy. Subsets with higher mortality or morbidity are linked to the complications of progressive heart failure, and atrial fibrillation with thromboembolic stroke.¹⁴
- 4.2. The prognosis in patients with **dilated cardiomyopathy** – even those who are not critically ill and do not require urgent intervention – is less good, and some 20% of such patients will die within 1 year of diagnosis.¹⁵ In general, survival with restrictive disease is slightly better than for patients with a similar severity of symptoms from dilated cardiomyopathy.
- 4.3. Unlike other specific cardiomyopathies which are often marked by progressive clinical deterioration, stopping alcohol consumption early in the course of alcoholic cardiomyopathy may halt its progression or even reverse the condition.⁵
- 4.4. LQTS may lead to sudden cardiac death, which usually occurs in otherwise healthy young individuals, and the cumulative mortality rate reaches approximately 6% by age 40. The Brugada syndrome may also cause sudden cardiac death in apparently healthy individuals with a structurally normal heart. Patients with this syndrome have a high mortality (approximately 10% per year) but the use of an implantable defibrillator is effective.

5. Summary

- 5.1. The cardiomyopathies are a complex and diverse group of conditions in which the common feature is [myocardial](#) dysfunction. The true or idiopathic cardiomyopathies are of unknown origin while the specific cardiomyopathies signify heart muscle disease secondary to specific cardiac or systemic disorders.
- 5.2. As research gradually reveals the mechanisms of idiopathic cardiomyopathy it appears increasingly likely that genetic factors will be shown to play a significant part in their origin.
- 5.3. A large number of constitutional diseases, infections and toxic agents may be responsible for the specific cardiomyopathies, but alcohol abuse is the commonest cause.

6. Related Synopses

Atherosclerosis

7. Glossary

arrhythmia	An abnormal rhythm (of the heart), hence arrhythmogenic, producing an abnormal rhythm.
autosomal dominant inheritance	Requiring that only one affected parent need have a trait to pass it to offspring.
chemotherapeutic agents	Drugs used in the treatment of cancer.
class I antiarrhythmic drugs	A group of drugs used in the treatment of abnormal heart rhythms. They act by slowing conduction.
diastolic	Relating to the resting phase of the heart's action.
endocarditis	Inflammation of the inner lining of the heart (cf pericarditis).
heterozygous	Having two versions of the same gene, one version on one chromosome and the second version on the other.
hypertrophy	Abnormal over-growth, e.g. of a muscle.
interstitial fibrosis	In an organ, transformation of the normal connective tissue to scar tissue.
ischaemic	A low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow. Hence ischaemic.
myocardial	Relating to the heart muscle.
myocyte	Muscle cell.
myofibrillary	Relating to the contractile apparatus of a muscle cell.
incomplete penetrance	Denotes that only a proportion of individuals with a specific genetic character express that genetic character under a particular set of environmental factors.
pericarditis	Inflammation of the pericardium, the outer layer of tissue covering the heart (cf endocarditis).
peripartum	Relating to the process of giving birth.
QT prolongation	Abnormal prolongation of part of the electrocardiographic tracing.

ST elevation	Abnormal elevation of part of the electrocardiographic tracing.
systolic	Relating to the actively contracting phase of the heart's action (cf diastolic).
tachyarrhythmia	An abnormal, rapid and irregular action of the heart.
thromboembolism	Blood clot which is carried along the blood vessels and may lodge e.g. in the lungs or brain, causing damage.
ventricular	Relating to the largest chambers of the heart, the ventricles.

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