European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 25 – June 2010

Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

please find enclosed the 25th issue of our Newsletter.

In addition to the 'clinical case of the month' and the 'paper of the month' you will find within this issue the case resolution from the May case.

On the last page of the newsletter you will find some recommendations for further reading with a list a recently published papers in the field of our WG……

Best wishes for all of you.

S. Pankuweit

The paper of the month:

DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model. Wordsworth S, Leal J, Blair E, Legood R, Thomson K, Seller A, Taylor J, Watkins H. Eur Heart J. 2010 Apr;31(8):926-35.

Presented by Philippe Charron, Centre national de référence pour les maladies cardiaques héréditaires, Hôpital Pitié-Salpêtrière, Université Paris 6. Paris. France.

Introduction

Recent advances in the understanding of the molecular genetics of cardiomyopathies present new challenges for clinicians that manage patients with these heart muscle diseases. Cardiologists in particular have to learn how to integrate this new knowledge into diagnostic strategies in order to improve the management of families with inherited cardiomyopathies. However the translational of this technology to routine practice is low. One reason for is probably the lack of data and uncertainties about the economic efficiency of such a strategy.

Wordsworth et al. recently published a cost-effectiveness study in Hypertrophic cardiomyopathy (HCM). HCM is the most common monogenic cardiac disorder and most frequent cause of sudden cardiac death (SCD) in young people and trained competitive athletes. Disease prevalence amongst adults is around 0.2% (1:500) and in recent studies the annual SCD rate from HCM is about 1% on average. HCM is caused by mutations in at least ten sarcomeric protein encoding genes and the inheritance is autosomal dominant, with the child of an affected parent having a 50% chance of inheriting the disease causing allele. The HCM phenotype is dynamic and the onset of cardiac expression (left ventricular hypertrophy diagnosed by echocardiography or ECG) may be delayed until adulthood, and sometimes until 40 to 60 years of age, a phenomenon known as age-related penetrance. Clinically, this presents a problem when assessing families with HCM, and the currently recommended follow-up strategy of relatives involves repeat evaluations every 1 to 5 years (according to age) with echocardiography and ECG.

Summary of the paper

The authors explored the cost-effectiveness of alternative methods of screening family members for HCM. They used an economic decision model comparing cascade screening by genetics, as opposed to clinical methods, for identifying individuals at risk of sudden death due to HCM. The model was built to estimate the lifetime resource costs and health outcomes (life years gained) of alternative strategies for assessing first degree asymptomatic family members of an individual diagnosed with HCM (proband). According to detailed information from the literature, various information and simulations were entered into the model including the familial structure (1 to 3 children, the youngest aged 18 years old), the yield of genetic testing (63% in the proband, then 50% in each child), the sensitivity and specificity of screening tests (such as those of ECG and echocardiography according to age-groups), and the natural history of the disease (such as the prevalence of sudden death major risk factors and related mortality rates). Costs of alternative screening strategies were evaluated according to UK estimation, including the cost of molecular testing (552 euros for the proband, 225 euros for a relative), of regular cardiac examination (ECG and echocardiography every 5 years), of associated consultations (cardiologist, geneticist sessions) as well as cost of ICD implantation (16910 euros), ICD replacement and follow-up.

The incremental cost per life year saved was 14397 euros for the cascade genetic compared with the cascade clinical approach, which is well bellow the acceptable threshold of 35000 euros per life saved (according to NICE decision making guidance, National Institute of Health and Clinical Excellence, UK). Genetic diagnostic strategies were more likely to be cost-effective than clinical tests alone. The costs for cascade molecular genetic testing were slightly higher than clinical testing in the short run, but this was largely because the genetic approach is more effective and identifies more individuals at risk.

Comments and discussion

The authors concluded that the use of molecular genetic information in the diagnosis and management of HCM is a cost-effective approach to the primary prevention of SCD in these patients. One explanation is that genetic strategy is able to discharge more individuals (individuals who do not carry the mutation) when compared to the clinical investigation.

This study represents a turning point as it is the first economic evaluation of the impact of genetic testing in hereditary cardiac diseases and the conclusion is clearly in favour of the use of genetic testing in familial screening.

Potential limitations of this economic decision model are related to the precise scenarios that were addressed but the authors carefully examined the detailed issues related to the strategies they evaluated. The price of genetic testing used for the proband was quite cheap and may have overestimated the real benefit of the genetic strategy, although such low price will be diffused very soon in many laboratories thanks to the coming next generation sequencing (NGS) that will revolutionize genetic practice. On the other hands, some points may have underestimated the benefit of genetic strategy as only first degree relatives were taken into account whereas other relatives may benefit from the cascade strategy thus amplifying the cost savings.

The results of this paper fully support the increasing use of genetic testing and genetic counselling in families with a cardiomyopathy. They also suggest a need for better reimbursement of genetic testing by national health care systems.

References

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The clinical case of the month: *What is your diagnosis?*

Answers will be given in the next newsletter and on the web site

Presented by Arthur Pollak MD[1], Dan Admon MD[1], Dina Ben-Yehuda MD[2], Andre Keren MD[1] from the Division of Cardiology[1] and the Department of Hematology[2], Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Sudden Cardiac Death Ten Months After Delivery

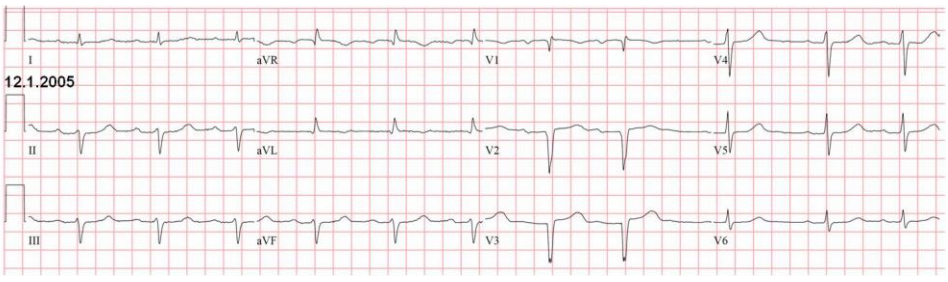
Case Presentation:

A 45 year old woman was admitted to the hospital after resuscitation from ventricular fibrillation (VF). Cardiac risk factors were hypertriglyceridemia and positive family history of coronary artery disease (father and brother). There was no history of sudden cardiac death (SCD) or known cardiomyopathy in the family. Her past medical history was significant only for bilateral carpal tunnel syndrome, for which she underwent right wrist operation several months prior to the present admission. She had always been an active person, working full time and enjoying a regular exercise schedule. She had three uneventful pregnancies and deliveries, the latest delivery being 10 months prior to the present event.

Two months before admission the patient started to experience exertional fatigue and mild shortness of breath while walking uphill. She attributed these complaints to the fact that she had resumed a full working schedule early after delivery and had to take care of her three children including a newborn. One night, while getting-up to her crying baby and walking to the baby's crib, she suddenly collapsed to the floor. Hearing the fall, her husband rushed to the other room and found his wife lying unconscious. He immediately called the emergency mobile services and initiated basic CPR, following instructions received over the phone from the dispatcher. On arrival of the ambulance team (within 6 minutes) the patient was found to be in ventricular fibrillation (VF). Two high-energy shocks were delivered, followed by asystole. Advanced CPR continued for 9 minutes, resulting in restoration of spontaneous circulation, stable sinus rhythm (80 bpm) and normal blood pressure (130/80 mmHg). In hospital, while ventilated and still comatose, a cooling therapy protocol was applied for 24 hours. Within 48 hours of admission the patient regained consciousness and underwent successful weaning from respiratory support, followed by full neurological recovery. While monitored in-hospital for arrhythmia, a single episode of non-sustained ventricular tachycardia (NSVT - 4 beats) was recorded. A procainamide challenge test failed to induce Brugada pattern on the electrocardiogram.

Admission blood tests included CBC (Hemoglobin 12.5 gr/dl, WBC 12,500 /µL, Platelets 413,000 /µL), Glucose 148-98 mg/dl, Na 137 mEq/L, K 4.0 mEq/L, Chloride 104 mEq/L, Magnesium 1.9 mEq/L, Creatinine 0.7 mg/dl, AST 118-54 IU/L, LDH 627 IU/L, CPK 981-474-29 IU/L, CRP < 0.5 mg/dl, Total Protein 6.4 gr/dl, Albumin 4.2 gr/dl; TSH 3.3 mIU/L, Calcium 10.8 mg/dl, Phosphor 3.8 mg/dl.

Figure 1: Initial electrocardiogram



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Chest X-ray showed a normal cardiac silhouette, mild pulmonary venous congestion and a small right-sided pleural effusion.
First echocardiogram was reported as "normal size ventricles with normal function and no significant valvular disease".
Left heart catheterization showed normal left ventricular (LV) segmental contraction and systolic function, normal coronary arteries, the aortic pressure was 104/63 (mean 82) mmHg and LVEDP measured 18 and 20 mmHg (pre- and post-LV injection, respectively).
Based on these findings, the diagnosis of idiopathic VF was made. The patient underwent an uneventful ICD implantation and was discharged, being prescribed aspirin and a statin. However, within a month after discharge, her functional capacity deteriorated. She experienced general weakness, worsening shortness of breath with minimal effort, orthopnea and aggravating peripheral edema. Diuretic therapy was initiated. A repeat echocardiogram was performed (figure 2) and the patient was referred to our service for further evaluation and treatment.

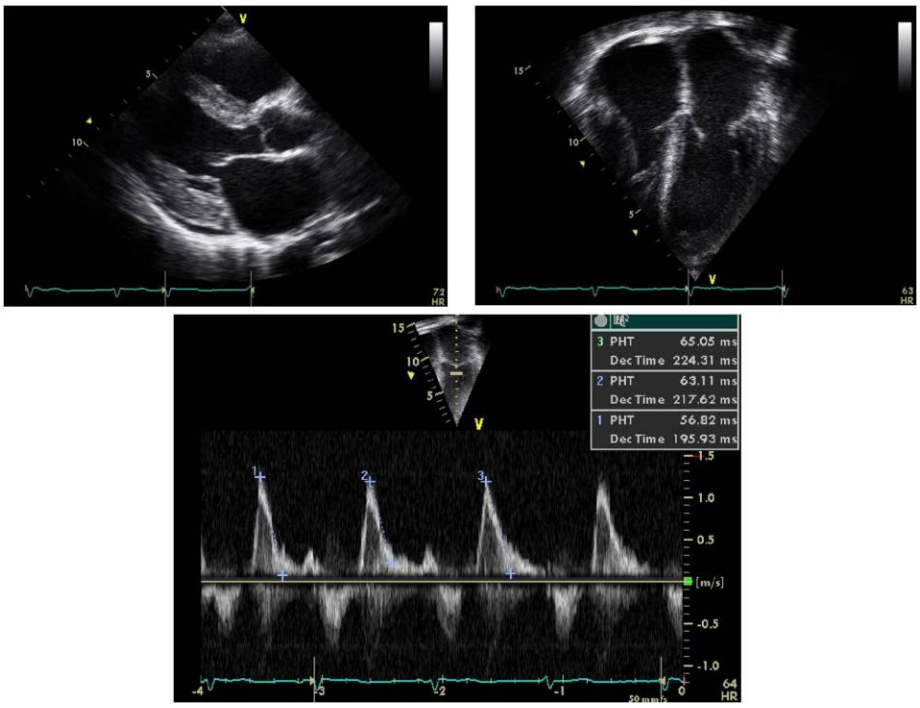


Figure 2:
Echocardiogram showing normal biventricular internal dimensions, dilatation of both atria, concentric wall thickening (septal and posterior LV wall thickness 13-14 mm) and a small pericardial effusion. Biventricular systolic function was normal (estimated LVEF 60%) and there were no segmental wall motion abnormalities. LV inflow Doppler tracing, 2-D parasternal and four-chamber views are presented.

On examination she had a regular heart rate of 65 bpm and blood pressure of 110/65 mmHg, without postural hypotension. There was mild speech dyspnea, orthopnea, elevated jugular venous pressure and moderate (+2) peripheral edema. Heart sounds were somewhat distant, without diastolic gallop. A soft systolic murmur was heard at the left sternal border and apex. Chest auscultation was notable for bilateral basal rales and a small right pleural effusion. The liver was enlarged and palpable 3 cms below the right costal margin. There was no evidence of ascites.

Questions:

What are the possible differential diagnoses in this case?
What are the recommended diagnostic procedures?
What treatment regimens should be considered?

Answer for the previous" Clinical case of the month" presented in May

"A case of DCM in a young person"

by Dr. Giuseppe Limongelli[1] and Dr. Perry M. Elliott[2]. [1]Department of Cardiology, Monaldi Hospital, Second University of Naples, Naples, Italy. [2]Inherited Cardiovascular Disease Unit, Department of Cardiology, The Heart Hospital, University College of London, London, UK.

Diagnosis, case resolution and treatment

Polymerase chain reaction (PCR) analysis on the nasopharyngeal swab failed to detect rickettsial DNA. Doxycyclin therapy was then stopped. The patient complained of migraine and increasing dyspepsia and nausea, with sweating and vomiting, associated with palpitations and elevated BP (max 170/100mmHg). A 24 hour BP Holter monitoring (on top of therapy with bisoprolol 10mg; ramipril 10mg; furosemide 25mg; spironolactone 37mg), showed elevated mean systolic and diastolic blood pressure (150/90mmHg), with marked circadian rhythm alteration. Increased 24 hours urine catecholamines (>2 fold) were found. She underwent a CT scan revealing an inhomogeneous right adrenal mass (6.5x 5.cm), with central necrosis, suggesting a malignant pheocromocytoma (Figure 2A and B).

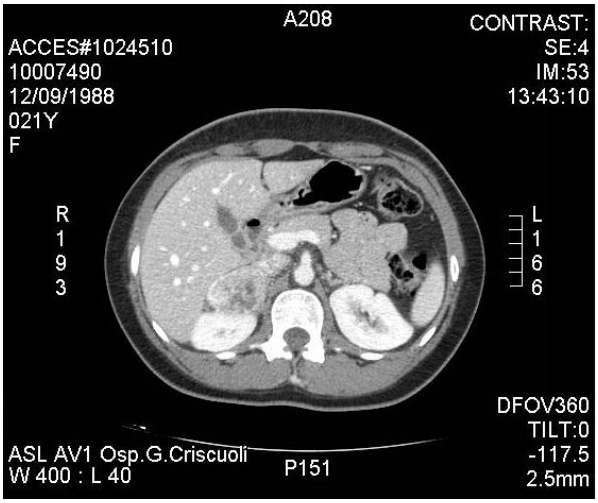
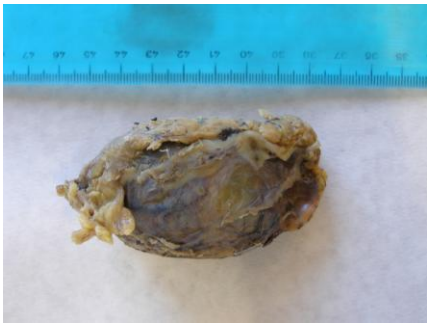


Figure 2 (A and B). Abdominal CT scan revealed a right adrenal tumor with internal mild heterogeneous density (red arrow).

Bisoprolol was stopped, and she was commenced on carvedilol (up to 25mg 2 times a day: 50mg) and doxazosin 2mg (progressively increased to 4mg). A new 24 hour BP Holter revealed an improved BP profile, with persistent circadian rhythm alteration (particularly, diastolic BP values). After three weeks, she underwent laparoscopic resection of the right adrenal mass. Pathology examination confirmed the diagnosis of pheochromocytoma (Figure 3A and 3B).



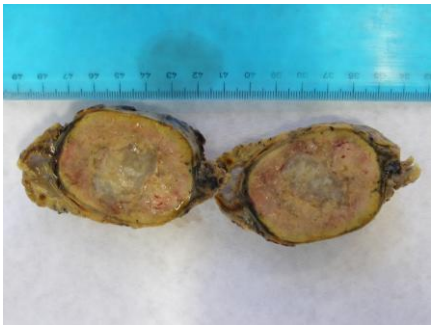
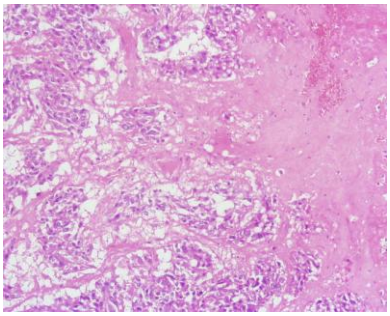


Figure 3 A + B. The figures show an ovoid, yellowish adrenal tumor, with a maximum diameter of 62X45 mm, and a large necrotic central core.

Histology confirmed confluent tissue necrosis and cellular atypia (Figure 3C and 3D).



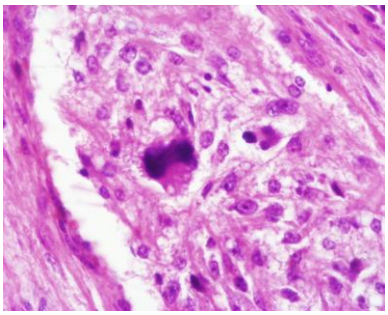


Fig. 3C: Histological evidence of tissue necrosis.
Fig. 3D: Extreme cytological atypia.

Immunoreactivity for chromogranin A (CgA), a major constituent of the matrix of catecholamine-containing secretory granules, representing the most specific and reliable generic neuroendocrine marker currently used in pathology practice, was evidenced (Figure 3 E).

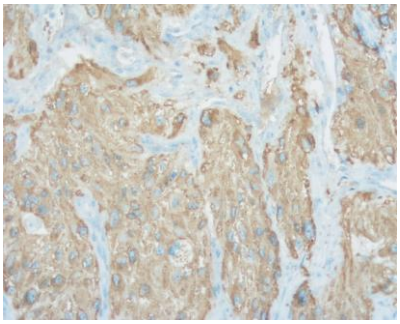


Fig. E: Intense immunoreactivity for CgA, one of many markers localized to the matrix of membrane-bound secretory granules, is helpful to discriminate pheochromocytoma from normal or neoplastic adrenal cortex.

Also, Ki-67 immunoreactivity, a marker of tumour malignancy, was positive (Figure 3 F).

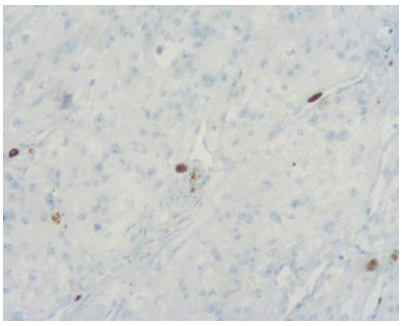


Fig. F: Immunohistochemical staining of Ki67 (marker of tumor malignancy).

The blood pressure became stable after the resection. She remained asymptomatic for dyspnoea and palpitations. Nevertheless, repeated echocardiographic examinations (1,3,6 months) showed persistent left ventricular systolic dysfunction (EF 35%).

Pheocromocytoma and catecholamine-related myocardial diseases

Acute cardiac failure due to highly elevated catecholamines is a rare entity. In vitro and in vivo animal experiments have confirmed that chronic exposure to catecholamines is toxic to cardiac myocytes [1]. Catecholamine over-production ("catecholamine toxicity") can occur in different conditions, including:

-central nervous system trauma (*catecholamine dump);* [2]

-neuroendocrine tumors in the **adrenal medulla (pheochromocytoma)**;[3]

-genetic disorders, such as **monoamine oxidase A** deficiency (one of the enzymes responsible for degradation of cathecolamines); [4]

-**cocaine abuse**. [5]

Catecholamine toxicity has been also advocated as possible mechanism of myocardial damage in scorpion envenomation ("adrenergic myocarditis") [6] and transient basal left ventricular ballooning syndrome ("Takotsubo cardiomyopathy") [7].

Pheochromocytomas are rare neuroectodermal catecholamine-secreting tumors commonly found in the adrenal medulla. [8] Adrenal pheochromocytomas secrete both epinephrine and norepinephrine, unlike the extra-adrenal tumors (functional paragangliomas), which lack phenylethanolamine-N-methyl transferase and secrete only norepinephrine. They are often referred to as the "10% tumour" (10% bilateral, 10% malignant, 10% familial, 10% paediatric, 10% extra adrenal, and 10% inherited). They show no gender partiality and can occur at any age, although they are most common in the fourth and fifth decades of life. Although approximately 10% of all pheochromocytomas are inherited, they are relatively rare in the general population with a prevalence of 0.3% to 1.9%.[9] Pheochromocytomas are more frequent in patients with a history of von Recklinghausen disease, Von Hippel-Lindau disease, multiple endocrine neoplasia type IIA and IIB, and neuroectodermal disorders including Sturge-Weber syndrome and tuberous sclerosis. Up to 25% of pheochromocytomas may be familial. Mutations of the genes VHL, RET, NF1, SDHB and SDHD are all known to cause familial pheochromocytomas/extra-adrenal paragangliomas.

The clinical diagnosis is difficult, especially when few or none of the other classic signs or symptoms are present (i.e., the classic triad of palpitations, diaphoresis, and headache; hypertension; chest pain; shortness of breath; flushing; anxiety). They can be found in about 0.1% to 0.2% of hypertensive patients, and although hypertension is the most commonly noted clinical sign among other possible symptomatology, it may be paroxysmal in nature and not always evident. [9] Although it is rare, myocardial involvement, from a pheochromocytoma can include angina pectoris, acute heart failure and cardiogenic shock, acute myocarditis/dilated cardiomyopathy, myocardial infarction, and arrhythmias.[10]

The acute onset of severe congestive heart failure secondary to catecholamine overproduction from a pheochromocytoma is a rare entity, and the diagnosis is difficult in absence of a classic clinical picture. Nevertheless, a misdiagnosis may often lead to inappropriate treatment with a very poor outcome.

Diagnosis and screening for a suspected pheochromocytoma consists of obtaining 24-hour urinary catecholamine levels (epinephrine, norepinephrine, and dopamine), including their metabolites (metanephrine, normetanephrine, and vanillyl mandelic acid), or measurement of plasma fractionated metanephrine and normetanephrine levels. [11] Urinary metanephrines (metanephrine and normetanephrine) are highly sensitive and specific for diagnosing pheochromocytomas, although new research is showing plasma metanephrines to be the most consistent with nearly 100% sensitivity.[12]

Preoperative localisation of pheochromocytomas can be carried out by a variety of radiologic studies, such as CT, magnetic resonance imaging (MRI), and radiolabelled iodine-131 or 123-

metaiodobenzylguanidine scintigraphy.[13] CT has a reported sensitivity and specificity of greater than 90% in localising primary adrenal pheochromocytomas; however, it is less accurate in detecting extra-adrenal tumors. A T2-weighted MRI, with 91% to 100% sensitivity and 50% to 97% specificity, provides excellent anatomic detail and is more accurate than CT in localizing paragangliomas. Radiolabelled meta-iodobenzylguanidine (MIBG), which is structurally comparable with norepinephrine, is selectively taken up and concentrated in chromaffin tissue. With a sensitivity of 77% to 91% and specificity of 96% to 100%, it is the test of choice for localizing extra-adrenal neoplasms not appreciated on CT or MRI.

Optimisation of the patient before operative intervention is paramount and includes volume resuscitation and alpha-adrenergic blockade (particularly, phenoxybenzamine) for almost 2 weeks before surgery. [14] Beta blockade with propranolol has also been shown to be beneficial in patients who experience persistent tachycardia from alpha-adrenergic blockade or in those who have a predominately epinephrine secreting tumor. Patients who present with no underlying suspicion of pheochromocytoma and who undergo operative intervention without appropriate preoperative pharmacologic management can experience a potentially lethal hypertensive crisis with induction of anesthesia and biopsy, or intraoperative manipulation of the tumour, which can result in cerebrovascular accidents and death. [15]

Laparoscopic adrenalectomy is safe when employed by experienced laparoscopic surgeons, providing better operative visualisation, less postoperative pain, a shorter hospital stay, and improved cosmetic results. [16] Nevertheless, with preoperative or intraoperative evidence of local tumour involvement of venous structures or surrounding tissues, as well as with large adrenal tumours (greater than 6-7 cm) other approaches should be considered.

It has been shown that the cardiomyopathy is potentially reversible after surgical removal of a pheochromocytoma.[17] The improvement in left ventricular EF after surgical removal of the tumour is reported as gradual over many months [18]. However, patients who present with acute heart failure have the possibility of experiencing a poor prognosis secondary to extensive focal myocardial damage. [19] It has been postulated that catecholamine-induced dilated cardiomyopathy with functionally mediated impairment is more reversible than cardiomyopathy with structurally mediated damage, but significant literature on this subject is still lacking.[19]

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List of recently published papers in the field of our WG recommended for further reading:

Marchant DJ, McManus BM. Regulating viral myocarditis: allografted regulatory T cells decrease immune infiltration and viral load. Circulation. 2010 Jun 22;121(24):2609-11. Epub 2010 Jun 7

Lotze U, Egerer R, Glück B, Zell R, Sigusch H, Erhardt C, Heim A, Kandolf R, Bock T, Wutzler P, Figulla HR. Low level myocardial parvovirus B19 persistence is a frequent finding in patients with heart disease but unrelated to ongoing myocardial injury. J Med Virol. 2010 Jun 22;82(8):1449-1457.

Deubner N, Berliner D, Schlipp A, Gelbrich G, Caforio AL, Felix SB, Fu M, Katus H, Angermann CE, Lohse MJ, Ertl G, Störk S, Jahns R; on behalf of the ETiCS-Study Group. Cardiac {beta}1-adrenoceptor autoantibodies in human heart disease: rationale and design of the Etiology, Titre-Course, and Survival (ETiCS) Study. Eur J Heart Fail. 2010 Jul;12(7):753-762.

Sen-Chowdhry S, Syrris P, Pantazis A, Quarta G, McKenna WJ, Chambers JC. Mutational Heterogeneity, Modifier Genes, and Environmental Influences Contribute to Phenotypic Diversity of Arrhythmogenic Cardiomyopathy. Circ Cardiovasc Genet. 2010 Jun 22.

Parvatiyar MS, Pinto JR, Liang J, Potter JD.Predicting cardiomyopathic phenotypes by altering the Ca2+ affinity of cardiac troponin C. J Biol Chem. 2010 Jun 21.

Naga Prasad SV, Karnik SS. MicroRNAs--regulators of signaling networks in dilated cardiomyopathy. J Cardiovasc Transl Res. 2010 Jun;3(3):225-34.