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Cardiomyopathies: retrospective and perspective

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My personal retrospective and perspective message

In 1985 our interaction began with an Alexander von Humboldt Foundation Scholarship to Dr. Tohru Izumi to the cardioimmunology laboratory of Prof. Bernhard Maisch at the University Hospital of Internal Medicine in Wuerzburg. Dr. Izumi participated in the first International Symposium on Inflammatory Cardiomyopathies in Würzburg in 1986 with a presentation on "Experimental murine myocarditis after immunization with membranous cardiac proteins," which was published in the European Heart Journal in 1987,[1] demonstrating both in NMRI and Balb/c mice that infiltrates to the epi- and myocardium and circulating and bound antimyolemmal autoantibodies (AMLAs) could be induced in this animal model of autoreactive myocarditis.

Our personal relationship continued from Dr. Izumi's time at Niigata University Medical School until today, until Prof. Izumi became Director of the Department of Internal Medicine and Cardiology at Kitasato University. Dr. Shibasaburo Kitasato, himself, was a collaborator of Emil von Behring, Marburg's first Nobel laureate in Medicine. The continuous relationship was emphasized by the exchange of Japanese medical students to Marburg's Philipps-University and the Faculty and Department of Medicine over the last 8 years. This exchange in itself is a message to the next generation.

Abstract

This focused review deals with the different phenotypes and etiologies of cardiomyopathies in general and myocarditis and dilated inflammatory and noninflammatory cardiomyopathy in particular. It refers to the genetic background, the predisposition for heart failure and inflammation in different cohorts of patients. It examines the epidemiologic and pathogenetic shift from the enteroviruses to Parvo B19 virus, human Herpes virus B6, cytomegalo- and Ebstein Barr viruses and describes the different phases after a viral infection and their clinical phenotypes (faces). The review also outlines current options and perspectives on treatment in inflammatory heart diseases.

Key words: dilated cardiomyopathy, endomyocardial biopsy, genetics, myocarditis, immunology, treatment

Retrospective analysis on cardiomyopathies

Myocarditis was the term used for any form of heart disease until the beginning of the 20th century,[1,2] since coronary artery disease was a rare disease in the middle age with low life expectancy. The definition of inflammatory cardiomyopathy combines the presence of an inflamed myocardium with a poorly functioning heart.[3] The term cardiomyopathies was introduced by Hickie and Hall in 1960[4] and further developed by Goodwin et al.[5] The WHO/ISFC (World Health Organization/ International Society and Federation of Cardiology) Task Force defined it first as "heart muscle diseases of unknown cause,"[6] which was broadened by its classification of 1996 to all heart muscle diseases, which lead to functional disturbances of the heart.[7] In its essence it made dilated cardiomyopathy to an equivalent of heart failure.[3] It named five clinical and hemodynamic phenotypes as idiopathic and primary forms:

1. dilated cardiomyopathy (DCM),
2. hypertrophic cardiomyopathy (HCM),
3. restrictive cardiomyopathy (RCM),
4. right ventricular cardiomyopathy (ARVC)
5. unclassified, those cardiomyopathies that did not conform to the other four.

As secondary cardiomyopathies, the task force listed

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Table 1. Classification of cardiomyopathies according to the AHA 2006[13]

A. Primary cardiomyopathies (predominantly involving the heart)		
Genetic	Mixed	Acquired
HCM	DCM	Inflammatory (myocarditis)
ARVC/D	RCM (nonhypertrophied, nondilated	Tako-Tsubo (stress provoked)
LVNC		Peripartum
Glycogen storage		Tachycardia-induced
Conduction defects		Infants of insulin-dependent diabetic mothers
Mitochondrial myopathies		
Ion channel disorders (LQTS, Brugada, SQTS, CVPT, Asian SUNDS)		

Notes:
1. Patients come to the physician not with a genetic analysis of their cardiovascular disorder but with symptoms (e.g., dyspnea, arrhythmia, angina, cardiomegaly, hypertrophy)
2. A mixed form may relate to fact that dilatation and restriction can be observed in both the genetic and acquired forms. It refers to the dilemma describe in 1 above.
3. Many ion channel disorders show no hemodynamic dysfunction (cardiomyopathy). They should be listed as cardiopathies and not as cardiomyopathies.[3,16]

B. Secondary cardiomyopathies (systemic disorders involving the heart)	
Infiltrative (accumulation between the myocytes)	Amyloidosis (primary, familial autosomal dominant, senile, secondary forms), Gaucher,* Hurler's,* Hunter's* diseases
Storage (accumulation within the myocytes)	Hemochromatosis, Fabry's disease,* glycogen storage disease (Pompe),* Niemann-Pick disease*
Toxicity	Drugs, heavy metals, chemical agents
Endomyocardial	Endomyocardial fibrosis (EMF), hypereosinophilic syndrome (HES), e.g., Löfflers' endocarditis
Inflammatory granulomatous	Sarcoidosis
Endocrine	Diabetes mellitus,* hyperthyroidism, hypothyroidism, hyperparathyroidism, phaeochromocytoma, acromegaly
Cardiofacial	Noonan syndrome,* lentiginosis*
Neuromuscular/neurological	Friedreich's ataxia,* Duchenne-Becker muscular dystrophy,* Emery-Dreifuss muscular dystrophy,* myotonic dystrophy,* neurofibromatosis,* tuberous sclerosis*
Nutritional deficiencies	Beriberi (thiamine), pellagra, scurvy, selenium, carnitine, kwashiokor
Autoimmune/collagen	Systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, polyarteritis nodosa
Electrolyte imbalance	
Consequence of cancer therapy	Anthracyclines (doxorubicin, daunorubicin), cyclophosphamide, radiation

*genetic or familial origin
Notes: The distinction between primary and secondary cardiomyopathy in the AHA classification 2006 reminds to the differentiation in the 1996 classification of the WHO/ISFC classification, in which primary was labeled of "unknown cause" (idiopathic) and secondary as specific cardiomyopathies with an established pathogenetic origin. The dilemma lies in the use of primary and secondary for different meanings in cardiomyopathy classifications, which causes misunderstandings, which could have been otherwise avoided.[3,16,18]

heart muscle diseases of known causes, such as inflammatory heart muscle diseases (myocarditis, perimyocarditis), hypertensive cardiomyopathy, ischemic cardiomyopathy, valvular cardiomyopathy, and other forms of heart failure of known origin.

With the discovery of a genetic background in several forms of cardiomyopathies previously alluded to as "of unknown origin," a new genomic classification was proposed taking the underlying gene mutations into consideration.[3,8-12] So DCM or ARVC were attributed to cytoskeletal, HCM and RCM to sarcomeric mutations. Modified ion channels (channelopathies, e.g., long or short QT syndromes and the Brugada syndrome) were introduced into the classification of cardiomyopathies in 2006 by the American Heart Association (AHA), some even without overt hemodynamic dysfunction.[13] The European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases oriented their clinical classification still according to morphology and function. Only in a second step was familial from non-familial/acquired disease distinctly labeled.[14,15] In this ESC position statement of 2008 cardiomyopathies were defined as "myocardial disorder, in which the heart muscle is structurally and functionally abnormal, and coronary artery disease, hypertension, and valvular and congenital heart disease are absent or do not sufficiently explain the

Table 2. Classification of cardiomyopathies according to the ESC Scientific Statement 2008[14]

A. Functional classification and clinical phenotype precedes genetic and disease subtypes

Phenotypes	HCM	DCM	ARVC	RCM	unclassified
Genetics	a. Familial/Genetic	a. Familial/Genetic	a. Familial/Genetic	a. Familial/Genetic	a. Familial/Genetic
	b. Non-familial/ Non-genetic	b. Non-familial/ Non-genetic	b. Non-familial/ Non-genetic	b. Non-familial/ Non-genetic	b. Non-familial/ Non-genetic

Notes: For the familial/genetic forms of each phenotype either an already specified disease subtype or an unidentified gene defect is assumed.
For the non-familial/non-genetic forms of each phenotype either an already specified disease subtype or an idiopathic form is assumed. ARVC has been shown to affect also left ventricle in up to 70% of cases. The histology may also show features of myocarditis in the left and the right ventricle, although the histological hallmark is fibrous fatty tissue degeneration.[3,16]

B. Examples of specified subtypes (known genes) of familial/genetic forms of cardiomyopathies[3,16]

Phenotype	HCM (hypertrophic cardiomyopathy)
a) Familial/Genetic	Sarcomeric protein disease: β-myosin heavy chain, cardiac myosin binding protein C, cardiac troponin I, troponin I, a-tropomyosin, essential myosin light chain, regulatory myosin light chain, cardiac actin, a-myosin heavy chain, titin, troponin c, muscle LIM protein. Glycogen storage disease: e.g., GSDII (Pompe's disease), GSD III (Forbe's disease), AMP kinase (WPW, HCM, conduction disease, Danon disease). Lysosomal storage diseases: e.g., Anderson-Fabry disease, Hurler's syndrome. Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies: e.g., MELAS, MERFF, LHON Syndromic HCM: Noonan's & LEOPARD syndromes, Friedreich's ataxia, Beckwith-Wiedermann & Sawyer's syndromes (pure gonadal dysgenesis) Other: Familial amyloid, phospolamban promoter
b) Non-familial/Non-genetic	Obesity, infants of diabetic mothers, athletic training, Amyloid (AL/pre-albumin)

Notes: HCM was originally thought to be a sarcomeric protein disease, which it still is, but note the overlap with DCM for sarcomeric protein mutations and with RCM for storage diseases with an HCM phenotype. Clinically important are amyloidosis and Anderson-Fabry disease.
Some patients with the clinical phenotype of HCM also demonstrate sporadic infiltrates. In such patients, infection with inflammation has to be considered.[3,16]

observed myocardial abnormality."[14] In addition, we proposed a clinical pathway for the diagnosis and treatment of dilated cardiomyopathy with or without inflammation.[16] One year later, a scientific statement on the role of endomyocardial biopsy in the management of cardiovascular disease also made useful recommendations for the use of endomyocardial biopsy in an individual patient by different clinical scenarios.[17] With these recommendations[3,16,17] the clinician can now identify genetic, autoimmune, and viral etiological factors in patients with familial and non-familial forms of the underlying structural heart muscle diseases and even propose them a perspective and treatment options (Tables 1A, B and 2A, B).[3,16,18]

Dilated cardiomyopathy

In accordance with the ESC classification[14] the prevalence of DCM is 1/2500 individuals, the mortality at 5 years: 30%-50%, depending on treatment. Echocardiographic criteria are a reduced ejection fraction <55%, in some studies <45% and a left ventricular end diastolic diameter (LVEDD) >117% of the normal value predicted from age and body surface area by Henry's criteria.

Myocarditis and inflammatory cardiomyopathy

Inflammatory cardiomyopathy was a new and distinct entity in the 1996 classification[7] and was defined as inflamed myocardium assessed histologically (myocarditis) in association with cardiac dysfunction. The pathohistological criteria at that time were the Dallas criteria,[19] which distinguished active, recurrent, healing, and borderline myocarditis. Infectious and autoimmune forms of inflammatory cardiomyopathy were recognized, viral cardiomyopathy was defined as "viral persistence in a dilated heart without ongoing inflammation." If the condition was accompanied by myocardial inflammation, it was termed "inflammatory viral cardiomyopathy" (or viral myocarditis with cardiomegaly). This entity was specified in a World Heart Federation consensus meeting in 1999 by quantitative immunohistological criteria for inflammation (≥14 infiltrating cells/mm^2)[20,21] and applied consecutively.[22] We selected the upper limit of a borderline situation to overt inflammation by the double standard deviation of infiltrating cells observed in a cohort of normal individuals, who died from noncardiac reasons and a panel of 50 biopsied patients with hypertension from the Marburg Registry. The infiltrating cells could be T- and B lymphocytes, their activated forms and up to 4 monocytes or macrophages per mm^2. A causative microbial agent in the myocardial tissue had to be looked for by molecular biological methods.[9,15,16,19,21-23] The current classifications are the following:[3,16,20]

- Viral myocarditis, if the inflammation in the endomyocardial biopsy was associated with a positive test for viral RNA or DNA. The hemodynamic profile could be normal or abnormal.
- Viral inflammatory cardiomyopathy, if a positive PCR on microbial agents in the biopsy was associated with a dilated and inflamed heart.
- Viral heart disease, if dilated cardiomyopathy was associated with viral persistence without inflammation.
- Autoreactive myocarditis or autoreactive inflammatory cardiomyopathy was defined as an inflamed heart with ≥14 infiltrating cells but with no detectable microbial agent.
- Rare but important entities are bacterial myocarditis in borreliosis and rickettsiosis in Europe and America, tuberculosis with pericardial effusion primarily in Africa. In borreliosis, at our institution, we treat with 3-week-long i.v. ceftriaxon therapy; in rickettsiosis, 9 to 12 months of oral tetracycline treatment will most likely prevent a fatal outcome. Tuberculous perimyocarditis needs long-term, multidrug, tuberculostatic treatment. If accompanied by human immunodeficiency virus (HIV) infection, which is often the case in Africa, adjuvant antiretroviral treatment is mandatory.
- A combination of acute parasitic and later chronic autoimmune myocarditis in South America is Chagas disease.
- Distinct by their clinical and pathogenetic phenotype are eosinophilic myocarditis, giant cell myocarditis, and cardiac sarcoidosis. All three etiologies respond to cortisone and immunosuppression, which should be planned for the long term, even lifelong.[16]

If histologically proven inflammation in a heart with normal systolic function and ejection fraction but signs of diastolic dysfunction in a symptomatic patient is present, we suggested to use the term "myocarditis with normal ejection fraction" (MNEF). Viral (V) or autoimmune (A) etiology can be used as attributes, so the abbreviations could be, VMNEF and AMNEF, respectively.[16] The assessment of diastolic heart failure under these conditions would conform with the consensus document of the heart failure and the echocardiography associations of the ESC.[24] If systolic function is compromised in a symptomatic patient myocarditis with reduced ejection fraction (MREF) could be employed and the prefixes viral (VMREF) or autoimmune (AMREF) used to classify the etiology in a systolic heart

failure situation associated with inflammation.

The spectrum of viral pathologies in inflammatory cardiomyopathy assorted to different hemodynamic profiles can be appreciated from Table 3.[3] Since the late 1980's, we observed a gradual epidemiologic and pathogenetic shift from enteroviruses, which were prevalent at that time, to Parvovirus B19, human herpes virus B6, cytomegalo- and Ebstein Barr viruses. Our pathogenetic understanding of myocarditis still very much depends on the pathogenetic phases from enteroviral disease (viral infection [phase 1], inflammation [phase 2], followed by either reparation and healing or chronic autoreactive disease leading to heart failure/ cardiomyopathy [phase 2]). Enteroviral infection, which is systemic, affects the entire cardiac tissue. Therefore, the different phases after a viral infection have different clinical phenotypes (faces). Parvo B19 docks to the P-receptor, which is found on small vessels but so far not on myocytes. So the clinical phenotype can resemble coronary artery disease or small vessel disease in addition to heart failure symptoms.

Autoimmune reactivity in myocarditis

Both cellular and humoral immune reactions can contribute to the clinical and pathogenetic phenotype of myocarditis. We have described autoreactivity to the cardiac myocyte by T- and NK-cells as well as antibody-mediated cardiocytolysis *in vitro* and *in vivo*.[25] Our main focus was on cardio-specific membrane antibodies (ab) such as AMLAs (antimyolemmal ab), ASAs (antisarcolemmal ab) and anti-intercalated disc ab (AIDA). Meanwhile more than 50 distinct antibodies were identified, interestingly also antibodies to cardiac receptors such as the β-receptor.

Monitoring the clinical course

The clinical course of myocarditis should be monitored by "imaging biomarkers" such as echocardiography or cardiac magnetic resonance, and serological biomarkers of heart failure such as BNP and NT-proBNP, biomarkers of necrosis such as troponin I, and biomarkers of inflammation.[27] Hereby CRP (carbon-reactive protein) or hCRP (human C-reactive protein) may be insufficient and selected interleukins such as IL-10 as a prognostic marker[28] could be of particular interest as a diagnostic or prognostic marker. The activity of cardiac fibrosis can also be monitored by markers such as Gal-3, which has recently been introduced. This may be of importance in

Table 3. PCR based microbial etiology in the Marburg registry in patients with suspected myocarditis or inflammatory dilated cardiomyopathy[3,9,16]

	Inflammation (n = 1,098)		No inflammation (n = 2,247)	
Group	1	2	3	4
Ejection fraction	>45%	<45%	>45%	<45%
No. patients	816	282	1,663	584
LVEDD (mm)	54 ± 10	65 ± 7	51 ± 9	66 ± 11
Autoreactive (no microbial agent)	70,2	55,9	69,5	77,8
Parvo B 19 virus[a]	20,4*	33,3*/**	23,9*	17,6*
Cytomegalovirus	3,1	3,9	2,0	0,8
Enterovirus	1,5	2,8	1,1	0,5
Adenovirus	1,5	2,1	1,4	1,2
Ebstein Barr virus	1,2	0,9	1,1	0,8
Herpes humanus virus 6[a]	5,3	4,8	3,7	4,1
Borrelia burgdorferi	0	0	0,1	0
Hepatitis C	0	0,1	0	0
HIV	0	0	0,1	0
Chlamydia pneumoniae	0,1	0	0,1	0
Rickettsia burnetii	0,1	0	0,1	0

[a]Double infection of Parvo B19 and HHV 6 were found in 2,4 to 3,1%, for Parvo B19 and EBV in 0,6 to 0,8% across the hemodynamic groups. Data are given for each virus as positive independent from double infection. Therefore, positivity for microbial agents add up higher than the difference between 100% − no microbial agent (autoreactive group).

*P < 0.05 group 1 vs. group 2 or group 3 vs. group 4; **P < 0.05 group 2 vs. group 4

Table 4. Antibodies to cardiac antigen and their possible cross-reactivity and pathomechanism[16,27]

Antigen	Antibody	Cross-reactivity	Pathomechanism	Reference
Actin	Anti-actin	Unknown	Unknown	Maisch et al. 1989
Ach receptor	Anti-Ach	Unknown	Bradycardia	Goin et al. 1999
Aconitate hydratase	Anti-AH	Unknown	Impaired metabolism	Pankuweit et al. 1995, 1997
ANT	Anti-ANT	Enterovirus	Impaired metabolism	Schultheiss et al. 1996
Beta1-receptor(a)	Anti-beta 1	Enterovirus	Positively inotropic	Wallukat et al. 1996
Beta1-receptor(b)	Anti-beta 1	Enterovirus	Negatively inotropic	Limas et al. 1990, Jahns et al. 2004
Ca^{2+}-channel	Anti-Ca^{2+}	ANT, Enterovirus	Impaired metabolism	Schulze et al. 1999
Carnitin	Anti-Carnitin	Unknown	Unknown	Otto et al. 1999
Conduction system	Anti-sinus node Anti-AV node Anti-Purkinje	Unknown Unknown Unknown	Bradycardia AV-Block Conduction defect	Maisch & Lotze 1986 Maisch & Lotze 1986 Maisch & Lotze 1986
Creatine kinase	Anti-CK	Unknown	Impaired metabolism	Pankuweit et al. 1995, 1997
Desmin	Anti-Desmin	Unknown	Structure, compliance	Obermayer et al. 1987
Dihydrolipoamide dehydrogenase (DLD)	Anti-DLD	Unknown	Impaired metabolism	Pankuweit et al. 1995, 1997
Extracted nuclear antigen	ENA	Unknown	Unknown	Naparstek et al. 1993
Hsp60, hsp70	Anti-hsp60; -70	Multiple	Unknown	Portig et al. 1997
Intercalated disk	Anti-intercalated disk (AIDA)	Unknown	Conduction, structure?	Maisch et al. 1993, Caforio et al. 2009
Laminin	Anti-laminin	Unknown	Structure	Obermayer et al. 1987
Mitochondria	AMA	Multiple	Inhibition of sarcosine dehydrogenase	Klein et al. 1984, Pankuweit et al. 1995, 1997
Myolemma	AMLA	Enterovirus	Cytolytic	Maisch et al. 1993
Myosin	Anti-myosin	Enterovirus	Negatively inotropic	Wittner et al. 1983, Caforio et al. 1996
NADD	Anti-NADD	Unknown	Impaired metabolism	Pankuweit et al. 1995, 1997
Nuclear antigen	ANA	Unknown	Immune complexes	Naparstek et al. 1993
Pyruvate kinase	Anti-PK	Unknown	Impaired metabolism	Pankuweit et al. 1995, 1997
Sarcolemma	Anti-sarcolemmal (ASA)	Enterovirus	Cytolytic	Maisch et al. 1993
SR-Ca^{2+}ATPase	Anti-SR-Ca^{2+}ATPase	Unknown	Metabolism	Khaw et al. 1995
SS-A	Anti-SS-A	Unknown	Degranulates Neutrophils	Naparstek et al. 1993
SS-B	Anti-SS-B	Unknown	Degranulates Neutrophils	Naparstek et al. 1993
Troponin I and T	Anti-Trop I	Unknown	Negatively inotropic	Göser et al. 2006
UCR	Anti-UCR	Unknown	Impaired metabolism	Pankuweit et al. 1995, 1997
Vimentin	Anti-Vimentin	Unknown	Structure	Obermayer et al. 1987

Ach, acetylcholin; AH, aconitate hydratase; AMA, antimitochondrial antibody; AMLA, antimyolemmal antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ANT, adenine nucleotide translocator; ASA, antisarcolemmal antibody; AV, atrioventricular; CK, creatine kinase; DLD, dihydrolipoamide dehydrogenase; ENA, extractable nuclear antigens; hsp, heat shock protein; NADD, nicotinamide adenine dinucleotide dehydrogenase; PK, pyruvate kinase; SR-Ca^{2+}ATPase, sarcoplasmic reticulum calcium ATPase; SS-A, single strand A; SS-B, single strand B; UCR, ubiquinol-cytochrome-c reductase

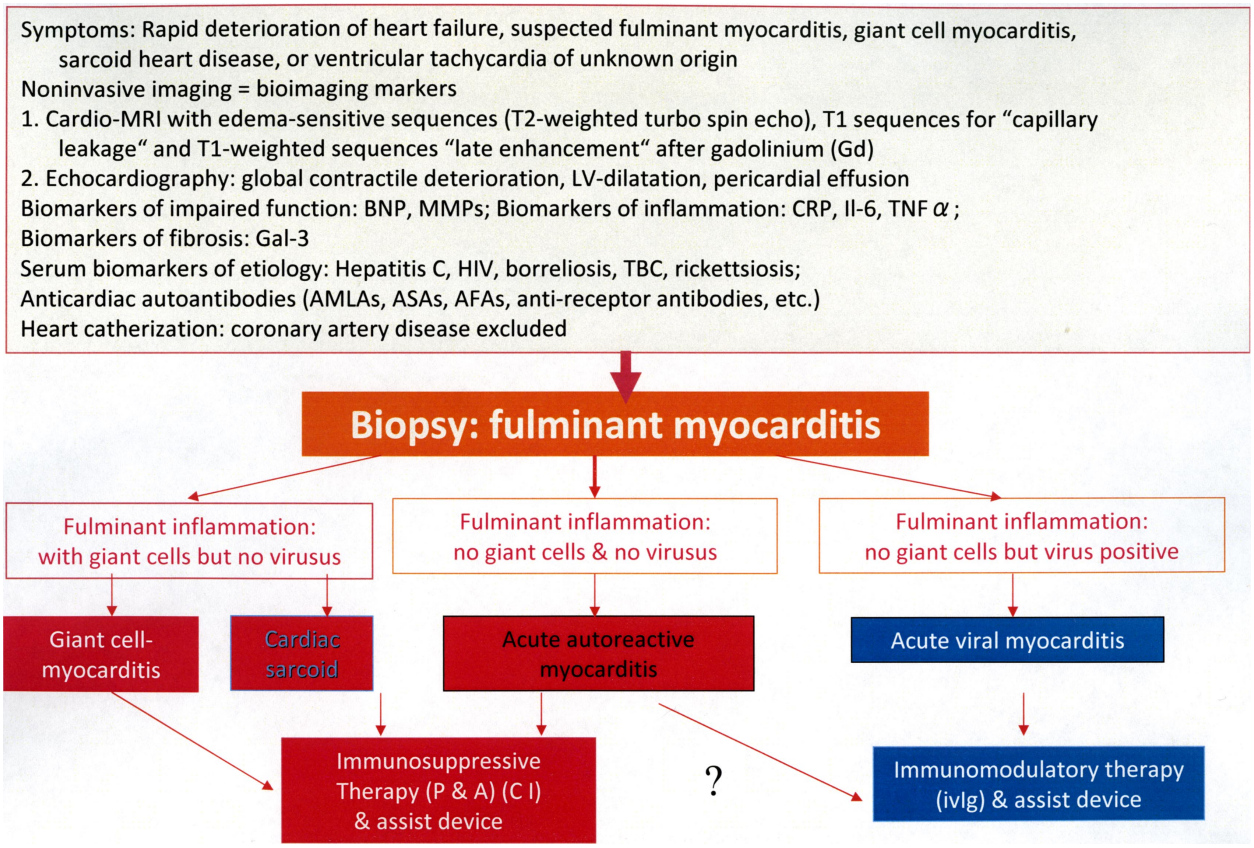

Figure 1. Fulminant myocarditis[16,17]

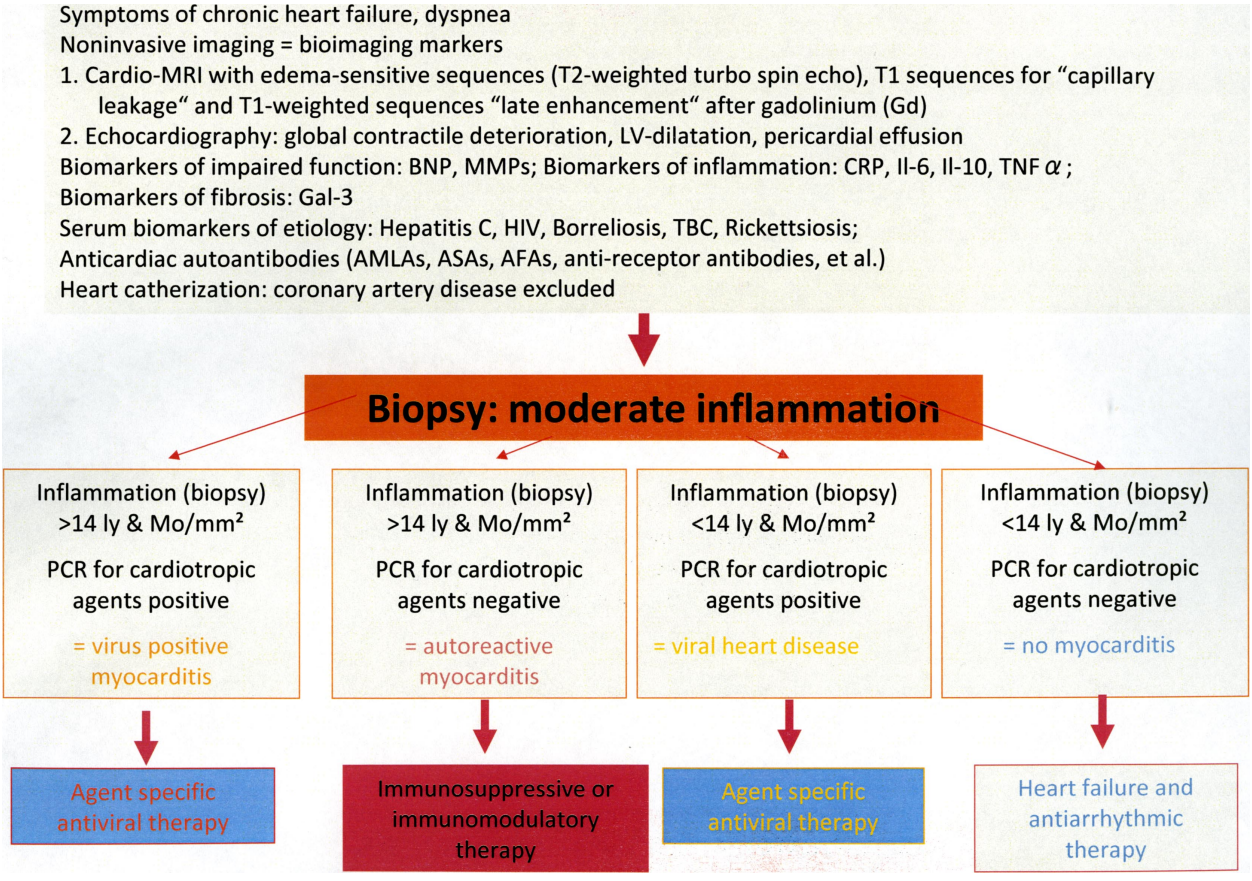

Figure 2. Inflammatory dilated cardiomyopathy and myocarditis[16,17]

early heart failure with normal ejection fraction or in the late stage of heart failure, when a restrictive pattern is dominating the hemodynamic profile with a reduced ejection fraction.

Current treatment modalities

We have recently reviewed the therapeutic options in different clinical situations of inflammatory heart disease such as rare fulminant myocarditis and chronic forms of myocarditis. From both of these extensive reviews,[3,16] further details on the different viral and non-viral forms of myocarditis, their diagnostic work-up and the treatment algorithm can be derived as well as the respective review of literature.

We could confirm the diagnostic and therapeutic measures suggested already 6 years ago[17] as demonstrated in Figures 1 and 2. In giant cell myocarditis, eosinophilic heart disease, cardiac sarcoid and non-viral acute lymphocytic or chronic autoreactive myocarditis the treatment is immunosuppression according to the algorithms outlined in the ESETCID (European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease)[29] and TIMIC (Tailored Immosuppression in Inflammatory Cardiomyopathy)[30] trials. For viral myocarditis we recommend i.v. Ig treatment either with a pure IgG (Intratect 20-30 g on days 1 and 3 as separate infusions over 7 hours) or an IgM enriched infusion (Pentaglobin), which improve symptomatology and can reduce the viral load or even eradicate viral RNA or DNA in the follow-up biopsy.[17]

Future treatment options

In addition to conventional therapy future treatment options may incorporate cyclopeptides, immunoadsorption in receptor specific disease, genetic engineering, stem cell therapy, or cytokine cocktails.

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