Conflict of interest

- Principal Investigator: HEROICS trial
  - HVHF after complicated heart surgery
  - NCT01077349
  - Sponsored by GAMBRO
- Principal Investigator: EOLIA trial
  - VV ECMO in ARDS
  - NCT01470703
  - Sponsored by MAQUET, Getinge Group
- Received honoraria from MAQUET, Getinge Group
Definition - Etiologies

- «Myocarditis» is defined as inflammation of the heart muscle
- Histology: cellular infiltrate and myocyte necrosis
- Etiologies:
  - Infectious diseases
    - Viruses: Coxsackie, Adenovirus, HIV, CMV, Hep B Parvovirus B19, HHV6, (H1N1)
    - Bacteria
    - Parasites (Toxoplasma, Chagas)
    - Fungi
  - Hypersensitivity (Drugs)
  - Autoimmune and systemic diseases
    - Lupus, Wegener, Eosinophilic, Sarcoidosis, Giant cell
  - Myocardial toxins (Cocaine, chemotherapy)
  - Peripartum
Sudden Death in Young Adults: A 25-Year Review of Autopsies in Military Recruits

Robert E. Eckart, DO; Stephanie L. Scoville, DrPH; Charles L. Campbell, MD; Eric A. Shriv. MD; Karl C. Stauduhar, MD; Robert N. Potter, DVM, MPH; Lisa A. Pearse, MD, MPH; and Renu Virmani, MD

- 6.3 millions military recruits over 25 yrs
  - 126 non-traumatic sudden deaths, autopsy performed
  - 10% of myocarditis-related deaths

<table>
<thead>
<tr>
<th>Cardiac Abnormality</th>
<th>Sudden Deaths, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>23 (36)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Right ventricular dysplasia</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Coronary artery pathology</strong></td>
<td>39 (61)</td>
</tr>
<tr>
<td>Anomalous coronary artery</td>
<td>21 (33)</td>
</tr>
<tr>
<td>Atherosclerotic coronary artery disease</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Coronary artery hypoplasia</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Coronary aneurysm</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Intramyocardial coronary bridge</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Coronary dissection</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Miscellaneous cardiac findings</strong></td>
<td>2 (3)</td>
</tr>
<tr>
<td>Bicuspid aortic valvular stenosis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Embolic myocardial infarction</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Clinical manifestations

- From asymptomatic EKG abnormalities to overt cardiac failure...
- Clinical features:
  - Preceding viral illness, flu-like syndrome
  - Fever
  - Chest pain, mimicking acute coronary syndromes
  - Tachycardia
  - Arrhythmia
  - Sudden death:
    - 10% of cases (Eckart, AnnIntMed, 04)
  - Clinical signs of heart failure
    - Minimal, slow evolution
    - Fulminant, leading to refractory cardiogenic shock in a few days
EKG findings
- Sinus tachycardia
- Diffuse ST-T wave abnormalities
- Prolonged QT interval
- Bundle branch block (LBBB++)
- **Myocardial infarction pattern**
- Complete heart block
- Supraventricular tachyarrhythmias
- Ventricular tachyarrhythmias

- May be normal...
EKG mimicking AMI
EKG: LBBB
Laboratory Findings
Biology: Troponin (Smith, Circ, 97)
Many patients with acute/fulminant myocarditis will undergo coronary artery angiography...
Other laboratory findings

- Non specific tests
  - Leucocytosis/leucopenia, Eosinophilia+++ 
  - Mononucleosic syndrome 
  - Sedimentation rate, CRP, PCT...

- Specialized tests 
  - Virological diagnosis 
    - Serology (limited value) 
    - Cultures: throat and stools 
    - PCR (blood, CSF, tissues) 
  - Inflammation: 
    - Antinuclear Ab, ANCA, Angiotensin Conversion Enzyme

- Research tests 
  - Autoantibodies (mitochondria, myosin, β-receptor) 
  - Immunohistochemical myocardial studies (research)
Doppler Echocardiography
- Fulminant myocarditis
  - Markedly decreased LV EF
  - *Near normal LV dimension*
  - *Increased septal thickness*

- Acute myocarditis
  - Markedly decreased LV EF
  - *Dilated LV*
  - *Normal septal thickness*
Other findings

- Regional wall motion abnormalities
- Diastolic dysfunction
- Change in echocardiographic image texture:
  - Increased brightness
  - Heterogeneity
- Thrombi
- Pericardial effusion
Cardiac MRI…

*The new diagnostic gold standard?*
Cardiac MRI

- Combination of
  - T1-weighted and T2-weighted
  - Gadolinium contrast-enhanced MRI +++

- Visualize localization, activity and extent of inflammation
  - One or several foci in the myocardium
  - Foci most frequently located in lateral free wall
  - Frequent subepicardial lesions
  - Can guide myocardial biopsies+++
Cardiovascular Magnetic Resonance Assessment of Human Myocarditis
A Comparison to Histology and Molecular Pathology

Circulation March 16, 2004
Still indication for myocardial biopsies?
3 histological grades \cite{Aretz1987}:

- **Active Myocarditis**: Cellular infiltrate +, myocyte necrosis +
- **Borderline Myocarditis**: Cellular infiltrate +, myocyte necrosis -
- **Negative Biopsy**: Cellular infiltrate -, myocyte necrosis -

- Distribution and diffusion of the cellular infiltrate:
  - Focal, confluent or diffuse
  - Mild, moderate, severe

- However, low to moderate sensitivity/specificity
Histology: Dallas Criteria

Borderline

Active
Predictors of Outcome in Patients With Suspected Myocarditis

Ingrid Kindermann, MD; Michael Kindermann, MD; Reinhard Kandolf, MD; Karin Klingel, MD; Burkhard Büttmann, MD; Thomas Müller; Angelika Lindinger, MD; Michael Böhm, MD

# The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease

A Scientific Statement From the American Heart Association, the American College of Cardiology, and the European Society of Cardiology

*Circulation* 2007;116;2216-2233

## Table 2. The Role of Endomyocardial Biopsy in 14 Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario Number</th>
<th>Clinical Scenario</th>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New-onset heart failure of &lt;2 weeks’ duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure of &gt;3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Heart failure associated with suspected anthracocytic cardiomyopathy</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>Heart failure associated with unexplained restrictive cardiomyopathy</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>Suspected cardiac tumors</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>Unexplained cardiomyopathy in children</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>9</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>Heart failure of &gt;3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>Heart failure associated with unexplained HCM</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>12</td>
<td>Suspected ARVD/C</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>13</td>
<td>Unexplained ventricular arrhythmias</td>
<td>Iib</td>
<td>C</td>
</tr>
<tr>
<td>14</td>
<td>Unexplained atrial fibrillation</td>
<td>Ii</td>
<td>C</td>
</tr>
</tbody>
</table>
Grade 1, Level B:

New-onset heart failure of <2 weeks’ duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise

New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks

11 Heart failure associated with unexplained HCM  
12 Suspected ARVD/C  
13 Unexplained ventricular arrhythmias  
14 Unexplained atrial fibrillation
Prognosis

Survival without transplantation

McCarthy, NEJM, 2000

Fulminant myocarditis (15 patients)

Acute myocarditis (132 patients)

P=0.05
Predictors of Outcome in Patients With Suspected Myocarditis

Ingrid Kindermann, MD; Michael Kindermann, MD; Reinhard Kandolf, MD; Karin Klingel, MD; Burkhard Büttmann, MD; Thomas Müller; Angelika Lindinger, MD; Michael Böhm, MD

2003 - 2009

- 41 patients refractory cardiogenic shock due to fulminant myocarditis
  - Mean age 38±12 years
  - 66%, women

- Mechanical assistance
  - Thoratec BiVAD (n=6) or
  - ECMO (n=35)
Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support

Mariana Mirabel, MD; Charles-Edouard Luyt, MD, PhD; Pascal Leprince, MD, PhD; Jean-Louis Trouillet, MD; Philippe Léger, MD; Alain Pavie, MD; Jean Chastre, MD; Alain Combes, MD, PhD

41 Myocarditis patients

BiVAD
n=6

- 2 died in ICU
- 0 Heart transplant
- Long-term survival n=4

Peripheral ECMO
n=33

- 10 died in ICU
- 4 Heart transplants
- Long-term survival n=23

Central ECMO
n=2

- 1 died in ICU
- 0 Heart transplant
- Long-term survival n=1

Crit Care Med 2011 Vol. 39, No. 5
Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support

Mariana Mirabel, MD; Charles-Edouard Luyt, MD, PhD; Pascal Leprince, MD, PhD;
Jean-Louis Trouillet, MD; Philippe Léger, MD; Alain Pavie, MD; Jean Chastre, MD; Alain Combes, MD, PhD

Long term survival: 68%
4 (10%) patients had heart transplantation

Independent predictors of ICU death determined at admission:
SAPS II >56 (OR, 10.23) and troponin Ic >12 microg/L (OR, 7.49)
Complete follow-up for 26 survivors
- Median follow-up was 525 [92–2400] days
- Mean LVEF was 57±9%
  - ≥60% for 12 non-transplant and all 4 transplanted
  - 40–60% for 10 nontransplanted survivors
- 21 patients had percutaneous femoral ECMO
  - 10 still complained of paresthesia/peripheral neurological defect
  - 2 had persistent leg ischemia requiring surgical repair for 1 and amputation for the other
Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support

Mariana Mirabel, MD; Charles-Edouard Luyt, MD, PhD; Pascal Leprince, MD, PhD; Jean-Louis Trouillet, MD; Philippe Léger, MD; Alain Pavie, MD; Jean Chastre, MD; Alain Combes, MD, PhD

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Crit Care Med 2011 Vol. 39, No. 5
Development of diastolic heart failure in a 6-year follow-up study in patients after acute myocarditis

Felicitas Escher,1 Dirk Westermann,1 Regina Gaub,1 Johannes Pronk,1 Thomas Bock,2 Nidal Al-Saadi,3 Uwe Kühl,1 Heinz-Peter Schultheiss,1 Carsten Tschöpe1,4

ABSTRACT

Background The aim of this study was to analyse the long-term prognosis of patients with acute myocarditis (AMC) who had been discharged from hospital while having normal left ventricular (LV) function.

Methods and results 50 patients with acute myocarditis who underwent endomyocardial biopsies (EMBs) were prospectively studied. Their clinical condition was examined during a mean follow-up period of 72 (54–78) months, including tissue Doppler imaging (TDI). 4% (2/50) died, and 6% (3/50) developed dilated cardiomyopathy. 45/50 (90%) showed a normal or improvement in LV function over time. In the course of the follow-up, 49% (22/45) suffered from heart failure symptoms despite a normal ejection fraction (HFNEF).

This was associated with an abnormal E/A ratio, an impaired deceleration time of early mitral flow velocity and isovolumic relaxation time, and a pathological increase in the LV filling index E/E∗ (9.3–13.8) vs 6.8 (6.4–9.1); p=0.001. Plasma N-terminal proB-type natriuretic peptide levels were increased threefold in patients with HFNEF (19.9 (10.6–24.1) vs 7.3 (4.2–11.9) pmol/l; p=0.006).

Conclusions It is assumed that the evidence for AMC is associated not only with the risk of developing LV dilatation but also with an increased risk of symptomatic diastolic dysfunction after several years.

Heart 2011;97:709–714

recover fully over time or whether their morbidity is still compromised after years has not yet been clarified. Thus, definitive data of patients with AMC are lacking concerning the prediction of the long-term clinical prognosis and the identification of distinct aetiopathogenetic subsets based on endomyocardial biopsies (EMBs).

Therefore, we investigated the long-term follow-up and prognosis of patients after AMC.

METHODS

Patients

The study subjects consisted of 50 consecutive patients (37 males, 13 females) admitted to our institute from January 1995 to November 2004. In detail, the tentative, clinically suspected diagnosis of AMC was ascertained in patients who had presented with a very recent onset of congestive heart failure symptoms, with an abrupt onset of complaints such as angina or dyspnoea, and any infarct-like presentation such as elevated serum markers of myocardial injury (troponin T and creatine kinase/creatine kinase-MB) and/or newly developed ECG changes (ST-segment elevation or T wave inversion).

No patient was included with previously known cardiomyopathy or a family history of cardiomyopathy. Exclusion criteria were antiviral, immunomodulatory or immunosuppressive therapy within the last 6 months, clinical or biochemical evidence...
Methods and results 50 patients with acute myocarditis who underwent endomyocardial biopsies (EMBs) were prospectively studied. Their clinical condition was examined during a mean follow-up period of 72 (54–78) months, including tissue Doppler imaging (TDI). 4% (2/50) died, and 6% (3/50) developed dilated cardiomyopathy. 45/50 (90%) showed a normal or improvement in LV function over time. In the course of the follow-up, 49% (22/45) suffered from heart failure symptoms despite a normal ejection fraction (HFNEF). This was associated with an abnormal E/A ratio, an impaired deceleration time of early mitral flow velocity and isovolumic relaxation time, and a pathological increase in the LV filling index E/E′, in contrast to patients without heart failure symptoms (E/E′ septal 10.9 (9.3–13.8) vs 6.8 (6.4–9.1); p = 0.001). Plasma N-terminal proB-type natriuretic peptide levels were increased threefold in patients with HFNEF (19.9 (10.6–24.1) vs 7.3 (4.2–11.9) pmol/l; p = 0.006).

Conclusions It is assumed that the evidence for AMC is associated not only with the risk of developing LV dilatation but also with an increased risk of symptomatic diastolic dysfunction after several years.
Treatment
Treatment

- Supportive care always indicated
  - Bed rest, Diuretics, vasodilators
  - ACE inhibitors, angiotensin-receptor blocker
  - Aldosterone antagonists
  - β-blockers, (with caution in the acute phase)
  - Immunosuppressors if specific disease
  - Vasopressors/inotropic agents in case of shock

- Mechanical assistance +++
  - May be urgently needed if fulminant form or rapid deterioration of hemodynamic status
  - Patients should rapidly be transferred to experienced centers
  - Bridge to recovery:
    - ECMO++, First line assistance
    - (Heart transplantation)
Long term survival: 68%, 4 (10%) patients had heart transplantation
Independent predictors of ICU death determined at admission:
SAPS II >56 (OR, 10.23) and troponin Ic >12 g/L (OR, 7.49)
Myocarditis Treatment Trial

- 111 randomized patients, LVEF<45%
- Histologically proven myocarditis
- Immunosuppression protocol
- Placebo vs prednisone + Cyclosporine or azathioprine

Mason, NEJM, 1995
IV immune globulin

McNamara, Circ, 2001

- 62 patients with DCM, randomized, LVEF < 40%
- Placebo vs IVIg
- P = NS
Specific/Novel treatments

- **Immunosuppression**
  - First line therapy if
    - Giant cell
    - Systemic autoimmune diseases
  - Corticosteroids
  - Cyclosporine, Tacrolimus
  - Azathioprine

- **Immunomodulation/Stimulation**
  - IV Immune globulins
  - Interferon

- **Antiviral agents, vaccination**
Tailored immune-modulating strategies

Liu, Circ, 2001

Phase I
Viral Replication

Phase II
Autoimmune Injury

Phase III
Dilated Cardiomyopathy

Diagnosis:
Virus detection

Treatment:
Antiviral Immune support

Diagnosis:
Biopsy Immune markers

Treatment:
Immune suppression

Diagnosis:
Imaging Rule out

Treatment:
ACEI β-blocker
Immunomodulation vs Immunosuppression

- β-Interferon for patients with entero-adenovirus myocardial persistence
  - *Kuhl, Circ, 2003*
  - 22 patients, LV Dysfunction, viral genome +
  - Interferon: virus clearance, improved LVEF

- Immunosuppressants: prednisone+imurel
  - *Frustaci, Circ, 03*
    - 41 patients, active myocarditis, LV Dysfunction
    - 21 responders, 20 non responders
    - Responders: AutoAb +, viral genome -
  - *Wojnicz, Circ 01*
    - 84 patients DCM, HLA overexpressed on myocytes
    - Treatment 3 months
    - EF improvement in treated patients: 71% vs 31%
Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy
A Proof-of-Concept Pilot Study

Karen Sliwa, MD, PhD; Lori Blauwet, MD; Kemi Tibazarwa, MD; Elena Libhaber, PhD; Jan-Peter Smedema, MD, MMed(Int); Anthony Becker, MD; John McMurray, MD, FESC; Hatice Yamac, MD; Saida Labidi, MSc; Ingrid Struhaman, PhD; Denise Hilfiker-Kleiner, PhD

Background—Peripartum cardiomyopathy (PPCM) is a potentially life-threatening heart disease that occurs in previously healthy women. We identified prolactin, mainly its 16-kDa angiostatic and proapoptotic form, as a key factor in PPCM pathophysiology. Previous reports suggest that bromocriptine may have beneficial effects in women with acute onset of PPCM.

Methods and Results—A prospective, single-center, randomized, open-label, proof-of-concept pilot study of women with newly diagnosed PPCM receiving standard care (PPCM-Std; n=10) versus standard care plus bromocriptine for 8 weeks (PPCM-Br, n=10) was conducted. Because mothers receiving bromocriptine could not breast-feed, the 6-month outcome of their children (n=21) was studied as a secondary end point. Blinded clinical, hemodynamic, and echocardiographic assessments were performed at baseline and 6 months after diagnosis. Cardiac magnetic resonance imaging was performed 4 to 6 weeks after diagnosis in PPCM-Br patients. There were no significant differences in baseline characteristics, including serum 16-kDa prolactin levels and cathepsin D activity, between the 2 study groups. PPCM-Br patients displayed greater recovery of left ventricular ejection fraction (27% to 58%; P=0.012) compared with PPCM-Std patients (27% to 36%) at 6 months. One patient in the PPCM-Br group died compared with 4 patients in the PPCM-Std group. Significantly fewer PPCM-Br patients (n=1, 10%) experienced the composite end point of poor outcome defined as death, New York Heart Association functional class III/IV, or left ventricular ejection fraction <35% at 6 months compared with the PPCM-Std patients (n=8, 80%; P=0.006). Cardiac magnetic resonance imaging revealed no intracavitary thrombi. Infants of mothers in both groups showed normal growth and survival.

Conclusions—In this trial, the addition of bromocriptine to standard heart failure therapy appeared to improve left ventricular ejection fraction and a composite clinical outcome in women with acute severe PPCM, although the number of patients studied was small and the results cannot be considered definitive. Larger-scale multicenter and blinded studies are in progress to test this strategy more robustly. (Circulation. 2010;121:1465-1473.)
Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy
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Early treatment with clarithromycin attenuates rat autoimmune myocarditis via inhibition of matrix metalloproteinase activity

Keiichi Hishikari, Ryo Watanabe, Masahito Ogawa, Jun-ichi Suzuki, Mayumi Masumura, Tomoko Shimizu, Kiyoshi Takayama, Yasunobu Hirata, Ryozo Nagai, Mitsuaki Isobe

ABSTRACT

Background Matrix metalloproteinase (MMP) activity is upregulated in the hearts with myocarditis, and its activation contributes to the changes in left ventricular function. A major macrolide antibiotic, clarithromycin (CAM), has many biological functions including MMP regulation. However, little is known about the effect of CAM in myocarditis via MMPs.

Objective To clarify the role of MMPs regulated by CAM in the progression of myocarditis.

Design CAM was given to experimental rats with autoimmune myocarditis (EAM) from day −7 to day 21 (early treated group, n=6) or from day 1 to day 21 (late treated group, n=6) twice a day.

Results Although the non-treated rats showed blood pressure decline and impaired cardiac function, early CAM treatment prevented this progression. Pathologically, severe myocardial cell infiltration (30.5±2.8%) and fibrosis (32.2±1.1%) were detected in the non-treated group, while early CAM treatment significantly suppressed these changes (infiltration 6.5±0.02%, fibrosis 5.9±3.9%). Zymography showed that non-treated EAM resulted in enhanced ventricular activities of MMP-9, while early CAM treatment reduced the alteration. However, late CAM treatment was less effective than the early treatment.

Conclusions Early CAM treatment is effective to attenuate myocarditis by suppressing MMP-9.

is an important event in the process of inflammation and tissue remodelling. A member of the MMPs, MMP-9 (gelatinase B), has an important role in tissue remodelling and the migration of smooth muscle cells, macrophages and other cells.8

Clarithromycin (CAM) is a 14-member ring macrolide and a potent antibiotic for the treatment of various microbial infections. CAM has been reported to have multiple biological effects, such as alteration of inflammatory factors and MMPs.9 10 Although we have shown that CAM suppresses cardiac rejection using murine heart transplant models,11 little is known about the effects of CAM in myocarditis.

This study, for the first time, demonstrates that CAM suppresses acute myocarditis through the inhibition of MMP-9 expression and activity.

MATERIALS AND METHODS

Reagents and animals
CAM was kindly provided by Taisho Toyama Pharmaceutical (Tokyo, Japan). Male Lewis rats (6 weeks old, 200–250 g) were purchased from Sankyo Laboratories (Tokyo, Japan). Rats were given CAM (100 mg/kg/day) orally twice a day. We selected the dose for rats based on our previous paper.11 Rats with EAM were divided into three groups: (a) early treated group (from day −7 to day 21, n=6); (b) late treated group (from day 1 to day 21, n=6) or (c) vehicle (untreated group, n=6) for 21 days. All experiments were performed in accordance with the guidelines of the European Economic Community guidelines for the care and use of laboratory animals.

References
Early treatment with clarithromycin attenuates rat autoimmune myocarditis via inhibition of matrix metalloproteinase activity

Keiichi Hishikari,1 Ryo Watanabe,2 Masahito Ogawa,2 Jun-ichi Suzuki,2 Mayumi Masumura,1 Tomoko Shimizu,3 Kiyoshi Takayama,3 Yasunobu Hirata,2 Ryozo Nagai,4 Mitsuaki Isobe1

* p<0.05 vs. vehicle

**Conclusions** Early CAM treatment is effective to attenuate myocarditis by suppressing MMP-9.

Paper.11 Rats with EAM were divided into three groups: (a) early treated group (from day -7 to day 21, n=6); (b) late treated group (from day 1 to day 21, n=6) or (c) vehicle (untreated group, n=6) for
Regulatory T Cells Protect Mice Against Coxackievirus-Induced Myocarditis Through the Transforming Growth Factor β–Coxsackie-Adenovirus Receptor Pathway

Yu Shi, PhD; Masahiro Fukuoka, PhD; Guohua Li, PhD; Youan Liu, MD; Manyin Chen, MD; Michael Konviser, MSc; Xin Chen, MD; Mary Anne Opavsky, MD, PhD; Peter P. Liu, MD

Background—Coxsackievirus B3 infection is an excellent model of human myocarditis and dilated cardiomyopathy. Cardiac injury is caused either by a direct cytopathic effect of the virus or through immune-mediated mechanisms. Regulatory T cells (Tregs) play an important role in the negative modulation of host immune responses and set the threshold of autoimmune activation. This study was designed to test the protective effects of Tregs and to determine the underlying mechanisms.

Methods and Results—Carboxyfluorescein diacetate succinimidyl ester–labeled Tregs or naïve CD4+ T cells were injected intravenously once every 2 weeks 3 times into mice. The mice were then challenged with intraperitoneal coxsackievirus B3 immediately after the last cell transfer. Transfer of Tregs showed higher survival rates than transfer of CD4+ T cells (P=0.0136) but not compared with the PBS injection group (P=0.0589). Interestingly, Tregs also significantly decreased virus titers and inflammatory scores in the heart. Transforming growth factor-β and phosphorylated AKT were upregulated in Tregs-transferred mice and coxsackie-adenovirus receptor expression was decreased in the heart compared with control groups. Transforming growth factor-β decreased coxsackie-adenovirus receptor expression and inhibited coxsackievirus B3 infection in HL-1 cells and neonatal cardiac myocytes. Splenocytes collected from Treg-, CD4+ T-cell−, and PBS-treated mice proliferated equally when stimulated with heat-inactivated virus, whereas in the Treg group, the proliferation rate was reduced significantly when stimulated with noninfected heart tissue homogenate.

Conclusions—Adoptive transfer of Tregs protected mice from coxsackievirus B3–induced myocarditis through the transforming growth factor β–coxsackie-adenovirus receptor pathway and thus suppresses the immune response to cardiac tissue, maintaining the antiviral immune response. (Circulation. 2010;121:2624-2634.)
Regulatory T Cells Protect Mice Against Coxsackievirus-Induced Myocarditis Through the Transforming Growth Factor β–Coxsackie-Adenovirus Receptor Pathway

N=25

$P=0.0136$ Treg vs CD4

$P=0.0589$ Treg vs PBS
Red Wine May be Used in the Therapy of Myocarditis

Chun-Juan Chen, Wei Yu, and Wei Wang

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ABSTRACT
Myocarditis is one of the most commonly cardiovascular diseases in clinical practice, but the treatment is always limited at present. Considering the multifactorial etiology of myocarditis, a novel therapeutic agent with multi-bioactivities should be presented. Red wine has been recognized as a favorable natural medicine against a large number of pathologic conditions. Recent results indicate that red wine could effectively decrease inflammatory factors secretion, reduce the migration of neutrophils, antagonize oxidation, and regulate immunity. By these bioactivities of anti-inflammation, anti-oxidation, and immunomodulation, red wine may be an effective therapeutic candidate to manage the symptoms and prevent the recurrence of myocarditis. J. Cell. Biochem. 111: 808–810, 2010. © 2010 Wiley-Liss, Inc.
Conclusion

- Myocarditis is a rare and severe condition
  - Especially the fulminant form
- Diagnosis based on clinical features, EKG, Echo, Troponin, MRI
  - Myocarditis can mimic acute coronary syndromes
- Mechanical circulatory assistance may be urgently needed if rapid hemodynamic deterioration
- Immunosuppression during the acute phase
  - Giant cell
  - Systemic autoimmune diseases
- Significant progresses in the understanding of the pathophysiology of the disease in recent years
  - Help design tailored immune-modulating strategies
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