

## Tako-Tsubo Cardiomyopathy through Adalimumab

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### LEARNING OBJECTIVES

The new TNF-alpha antibody Adalimumab - given to treat rheumatoid Arthritis may causes Tako-Tsubo Cardiomyopathy.

### INTRODUCTION

Tako-Tsubo Cardiomyopathy is a cardiac distress syndrome triggered through sympathetic nervous stress like anger, anxiety, pain, dyspnoea<sup>[1]</sup> or others<sup>[2]</sup>. Due to the reversible manner of the disease, (1) all findings resolve without further specific treatment<sup>[2]</sup> and (2) there are only betablockers established to reduce the recurring occurrence of the disease<sup>[3]</sup>. In the literature, other mechanisms are described triggering Tako-Tsubo Cardiomyopathy. i.e. patients applied with Trastuzumab or with immunoglobulines<sup>[4]</sup>. Here, first and exclusively, we are demonstrating a new tumor necrosis factor-alpha antibody (TNF-alpha antibody: Adalimumab) as potential trigger for Tako-Tsubo Cardiomyopathy lacking any sympathetic nervous stress.

### CASE REPORT

A 66-year old woman was admitted to the hospital with typical pressure pain on the left chest as well as tenderness on palpitation since 3 days. Historically, she is suffering a chronic rheumatoid arthritis set on Adalimumab [40mg subcutaneously per 2 weeks, tumor necrosis factor-alpha (TNF- alpha)-antibody] given second time, 3 days prior to admission as well as on Methotrexat (10 mg per week) linked by Hydrocortisone (5 mg daily) in remission phase. Distress situations were declined: there is no history of personnel

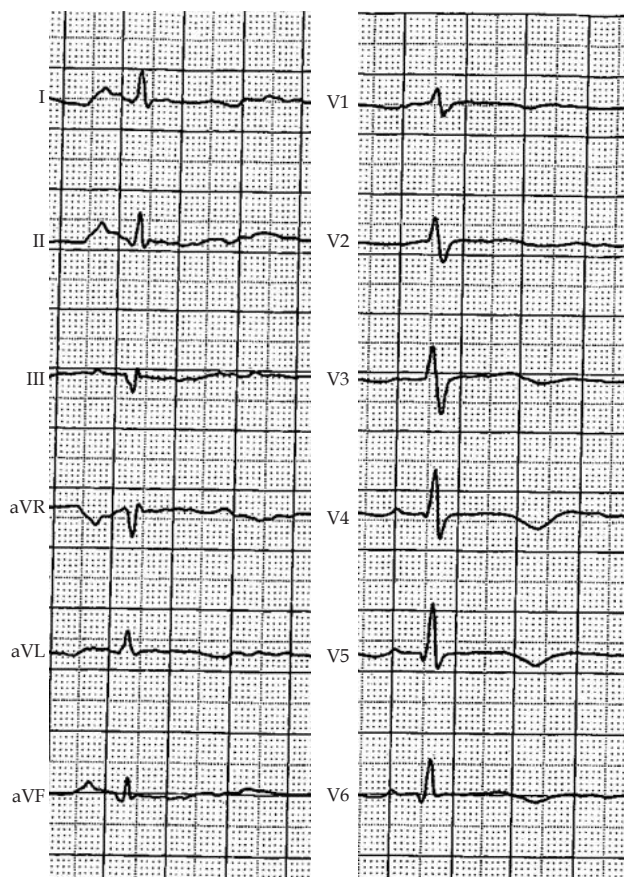
### ABSTRACT

A 66-year old woman was admitted with typical clinical signs of angina pectoris. In her history only a chronic rheumatoid arthritis, treated through Adalimumab was reported. The electrocardiograph (ECG) showed sinus rhythm with terminal negative T-waves in V1-V6 without any ST-elevations. Laboratory tests revealed a positive Troponin-I level and the transthoracic echo showed a reduced left ventricular (LV) function by apical akinesia. We immediately performed cardiac catheterization to rule out the suspected coronary artery disease and documented surprisingly a Tako-Tsubo Cardiomyopathy with severe reduced LV function and signs of apical ballooning. Personnel distress, feeling of severe pain, any kind of anger, or anxiety could not be stated in the case history. A further invasive electrophysiological testing ruled out arrhythmias as trigger mechanisms for the Tako-Tsubo Cardiomyopathy. We stopped the Adalimumab therapy and could directly illustrate improved LV function to the normal status under resolved healthy conditions. This is the first time to report Adalimumab as cause for Tako-Tsubo Cardiomyopathy while there is to date literally no direct effect of TNF-alpha antibodies on the myocardium published - lacking any sympathetic nervous stress.

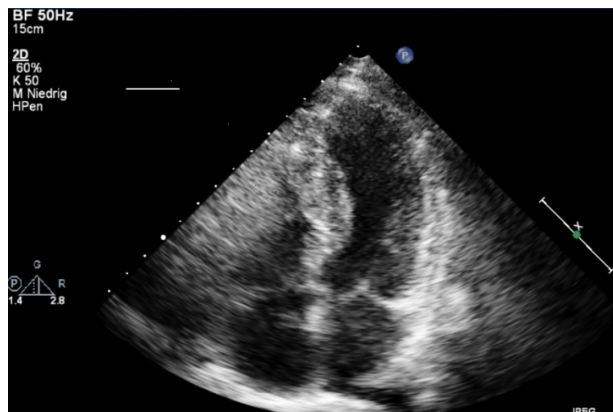
stress, anger, pain, dyspnoea, or anxiety. Further, no tachycardia could be reminded.

Clinically we found a woman in a good general condition and normal nutritional status, awake, oriented, her blood pressure 120/70mmHg, her pulse 62/min., her respiratory rate was normal, 14/min., oxygen saturation of 97%, no pathologic murmurs, auscultation of the lungs reveals no bilateral wheezes and rales, unobtrusive physical examination. Auscultation of the heart revealed normal findings.

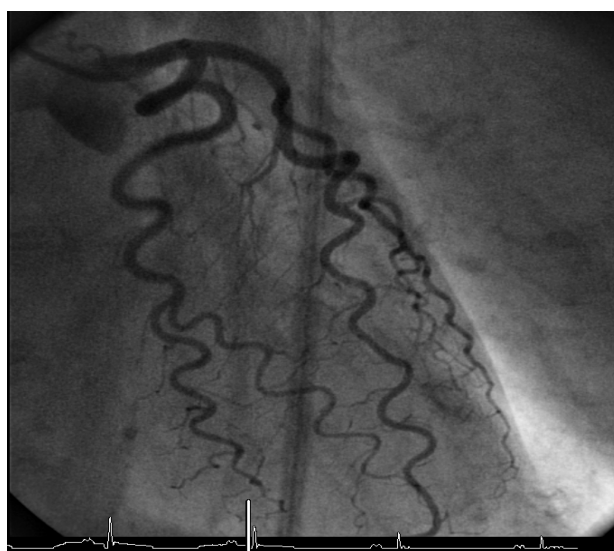
Laboratory tests resulted positive for troponin I (0.78ng/m), other laboratory values (particularly inflammation parameters) were within normal range. The electrocardiographic (ECG) showed a sinus rhythm at the rate of 62/min., terminal negative T waves in V1-V6 as well as remarkable (non Pardee-Q) Q-waves in III, aVF (Figure 1). X-ray of chest revealed complete normal. The transthoracic echocardiography showed reduced left ventricular function, ejection fraction was determined to 40% using Simpson's equation with akinetic apical walls of all regions (Figure 2). In respect to the supposed non-ST-elevation myocardium infarction (NSTEMI), we immediately performed an invasive cardiac catheterization to rule out the suspected coronary artery disease. All coronary arteries were inconspicuous, clean and smoothly perfused (Figure 3). Further, we illustrated severe reduced left ventricular function with signs of typical ballooning in respect to Tako-Tsubo Cardiomyopathy (Figure 4). Clinically, the tenderness on palpitation as well as the signs of "cardiac memory" in the ECG resisted both, so that we were forced to rule out further arrhythmias as trigger mechanisms for the identified



**Figure 1** ECG of the Patient during admission. Shown here is the regular sinus rhythm at the rate of 62/min., terminal negative T-waves in V1-6 and Q-waves in III, aVF as demonstrated in respective ECG's.



**Figure 2** Transthoracic Echocardiography. Shown here is the typical apical four-chamber view frozen in systole with reduced left ventricular function, ejection fraction measured to 40% (Simpson) and apical akinesia.



**Figure 3** Coronarangiography of the left coronary arteries. Invasive cardiac catheterization was performed. The contrast enhanced angiography (10ml Imeron 350, applied manually) of the left coronary artery systems reveals inconspicuous, clean and smoothly perfused arteries. The right coronary artery looked the same (data not shown). The coronary artery disease could be rule out completely. Here frozen in diastole.



**Figure 4** Left Ventriculography. Invasive cardiac catheterization was performed as mentioned above (see figure 3). The contrast enhanced left ventriculography (pressure guided application: 10ml/sec; volume of Imeron 350: 25ml) revealed the typical apical ballooning for Tako-Tsubo Cardiomyopathy. Here frozen in systole.

Tako-Tsubo Cardiomyopathy. We performed an electrophysiological examination with normal, inconspicuous findings.

Further examinations (holter ECG to rule out unidentified arrhythmias, the sonography of the complete abdomen; the gastroscopy and the coloscopy) were completely without any pathological findings.

We suggested Adalimumab as trigger for the Tako-Tsubo Cardiomyopathy and stopped immediately the treatment. Therefore, we increased Methotrexat to 20 mg per week resolving the symptoms and improved left ventricular function to the normal status without any further regional wall motion irregularities. Finally, the patient was under healthy and stable condition at discharge.

## DISCUSSION

Tako-Tsubo Cardiomyopathy is a cardiac distress syndrome triggered through sympathetic nervous stress like anger, anxiety, pain, dyspnoea<sup>[1]</sup> or others<sup>[2]</sup>. Clinically, patients with Tako-Tsubo Cardiomyopathy suffer acute chest pain, dyspnoea, or cardiac syncope leading to specific disease related alterations in ECG (ST elevations or terminal negative T-waves), in transthoracic echocardiography (apical hypo- to akinesia), or in invasive cardiac catheterization (left ventricular dysfunction with apical ballooning, and no signs of coronary artery disease). Cardiac myocardial markers as Creatininkinase or Troponin I show increased levels typical for the pathological mechanism behind the Cardiomyopathy: reversible myocardial sympathetic nervous stress with additional catecholamine overload of the left ventricular<sup>[5,6]</sup>.

Due to the reversible manner of the disease, (1) all findings resolve without further specific treatment<sup>[2]</sup> and (2) there are only betablockers established to reduce the recurring occurrence of the disease<sup>[3]</sup>. A general treatment suggestion is the reduction of psychic stress for the patient<sup>[1]</sup>. Further, (3) in cardiac shock, only intra-aortic pulsation treatment is established to secure the left ventricular function while catecholamines have to get discontinued<sup>[7]</sup>.

In the literature, other mechanisms are described triggering Tako-Tsubo Cardiomyopathy, i.e. patients applied with Trastuzumab or with immunoglobulines<sup>[4]</sup>. Here, first and exclusively, we are demonstrating a new tumor necrosis factor-alpha antibody (TNF-alpha antibody: Adalimumab) as potential trigger for Tako-Tsubo Cardiomyopathy lacking any sympathetic nervous stress.

This is a new human monoclonal antibody<sup>[8]</sup> binding to the TNF- $\alpha$  antigen and is established in chronic rheumatoid arthritis<sup>[9]</sup>. Side effects are opportunistic infectious diseases. In respect, contra indications are active tuberculosis, or sarcoidosis, as well as heart failure NYHA III-IV<sup>[10,11]</sup>.

The chronic inflammatory disease rheumatoid arthritis (RA) assesses primarily articulations and secondarily extra-articular systems like i.e. the cardiovascular system<sup>[12]</sup>. The grade of inflammatory activity of the rheumatoid arthritis is known as established risk factor for coronary atherosclerosis. This increased risk may be attributable to RA-specific risk factors such as hyperhomocysteinemia, disease-related dyslipidemia or vascular inflammation, or to morbidity related to medications and high levels of TNF-alpha. The possible roles of TNF-alpha in the development of atherosclerosis include the recruitment of inflammatory cells to the site of injury or the promotion of adverse vascular smooth muscle cell remodelling. TNF-alpha may also act as a proinflammatory factor in plaque rupture<sup>[13]</sup>.

In contrast, Anticytokine therapy could prove beneficial in the treatment of patients with heart failure<sup>[13]</sup>. While early studies

supported this hypothesis, anti-TNF strategies have not demonstrated salutary benefits in large multicenter randomized and placebo-controlled clinical trials in patients with symptomatic heart failure<sup>[13]</sup>. There is a variety of possible explanations for the failure of anti-TNF therapy: (1) TNF antagonism has untoward effects in the setting of heart failure; (2) the biological agents used in the trials were intrinsically toxic; (3) sex and race may have important implications in the outcome after anticytokine therapy; (4) the TNF-alpha protein contains a polymorphism, and, in fact, genome plays a role in modifying the pharmacologic response to anticytokines; (5) anti-TNF-alpha approaches could have had pharmacodynamic interactions with other heart failure medications; and (6) the patients in these trials may have been inappropriately selected. These disappointing results may determine controversial attitude in the long-term treatment with anti-TNF agents in RA<sup>[14]</sup>.

The effects of TNF-alpha blockers on incident cases of congestive heart failure (CHF) in RA are controversial. Here, in this case, the disease was steady-state in remission under immune suppressed therapy [chemically in the blood test no signs of active inflammation]. In the transthoracic echo we ruled out pericardial or myocardial involvement while left ventricular function got resolved to a normal status by discontinuation of TNF-alpha antibody treatment. Direct TNF-alpha effects on the left ventricular function are to disclose<sup>[13]</sup>. Further, the ventricular function was primarily normal and got completely resolved (improved) after the acute/ active phase of the disease (Tako-Tsubo Cardiomyopathy). In general, the following suggestions were established through the guidelines for the treatment of RA: (1) RA patients with history of CHF and a concomitant indication for the use of TNF-alpha blockers do not need a baseline cardiac evaluation to screen for heart failure; (2) patients with well-compensated mild CHF New York Heart Association (NYHA) classes I and II and a concomitant indication for the use of TNF-alpha blockers should be evaluated at baseline and then be closely monitored for any clinical signs of worsening heart failure; and (3) patients with (NYHA) class III or IV heart failure should not be treated with TNF-alpha blockers in any case<sup>[14]</sup>.

## CONCLUSION

Adalimumab, a new TNF- $\alpha$  antibody, applied in chronic rheumatoid arthritis may directly trigger Tako-Tsubo Cardiomyopathy without any sympathetic nervous stress. Hence, monitoring of either clinical symptoms (palpitations) or the left ventricular function [through transthoracic echocardiography] is indicated while Adalimumab is applied. When Tako-Tsubo Cardiomyopathy occurs, the immediately discontinuation of the treatment with Adalimumab resolves left ventricular function and clinical symptoms.

However, it would be ambitious to conclude from a single case observation that Adalimumab causes Tako-Tsubo Cardiomyopathy. The authors hereby recommend a clinical trial to test this hypothesis in a multi-center fashion.

Sympathetic nervous stress is widely known as trigger for Tako-Tsubo Cardiomyopathy. However, the increasing number of other findings (like i.e. Adalimumab) as pathological mechanism triggering Tako-Tsubo Cardiomyopathy suggests the need for further studies of this specific disease.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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