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Research Paper

Application of magnetocardiography for myocarditis assessment in a testosterone-substituted female-to-male individual

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ABSTRACT

Background: The diagnosis of myocarditis remains challenging due to its diverse clinical manifestations. We recently demonstrated the ability of magnetocardiography (MCG) to screen for myocarditis and applied it successfully to detect myocarditis in this case study of a female-to-male (FtM) patient who had undergone sexual reassignment surgery. This case highlights two significant points: first, sex differences in myocarditis may be promoted by higher levels of testosterone, and second, the ability of MCG to diagnose myocarditis.

Case presentation: We report on a 38-year-old FtM patient who was hospitalized for chest pain following testosterone therapy. The patient received testosterone every 2 weeks for 6 months following his FtM surgery. Two days after the last administration of testosterone, he developed chest pain. Electrocardiography identified non-significant ST elevations in V3–6, II and aVF and echocardiography revealed reduced left ventricular ejection fraction and apical hypokinesia. High-sensitivity troponin-T (539 ng/L to 676 ng/L) and creatine kinase elevation (592 U/L) were elevated. Coronary CT angiography ruled out coronary artery disease. Cardiac magnetic resonance imaging confirmed suspected myocarditis.

Additionally, we used MCG to detect abnormalities in the electromagnetic field. A pathologic vector (0.179) supported the diagnosis of myocarditis in this patient. During therapy with ibuprofen the vector improved to 0.067 after 3 weeks accompanied by symptom improvement.

Conclusion: Testosterone treatment may have promoted myocarditis in a FtM individual. Additional MCG assessment was consistent with a diagnosis of myocarditis and highlights the promising potential of this method to facilitate diagnostic screening for cardiomyopathy in the future.

1. Background

Myocarditis is characterized by inflammation of the myocardium typically following viral infections such as coxsackievirus and SARS-CoV-2 [1,2]. Sex differences in myocarditis have been well described clinically and in animal models. The most recent Global Burden of Disease report provided data on sex differences in the prevalence of myocarditis worldwide separate from cardiomyopathy for patients aged 35 to 39 years at 6.1 per 100,000 (95 % UI: 4.2 to 8.7 per 100,000) in men and 4.4 per 100,000 (95 % UI: 3.0 to 6.3 per 100,000) in women [3]. Myocarditis not only occurs more often in men but they also tend to have a worse disease course compared to women [4,5]. We recently reported a sex ratio of around 3:1 male to female for patients with suspected or biopsy confirmed myocarditis [6].

Although a number of factors may contribute to the sex difference in myocarditis, studies in animal models of viral myocarditis have demonstrated a role for testosterone in promoting inflammation and estrogen in protecting against cardiac dysfunction [3,6–8]. Testosterone affects the cardiovascular system through genomic and non-genomic action [9]. Genomic effects of testosterone influence apoptosis and reactive oxygen species (ROS) generation. Non-genomic effects of testosterone are regulated via calcium channels and second messengers present on cardiac myocytes. This results in an increase in intracellular calcium concentration activating various signaling cascades and

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increasing myocardial contractility [9,10]. In rat studies, it was demonstrated that rats after gonadectomy developed cardiomyocyte hypocontractility and showed reversal by following administration of testosterone demonstrating the positive effect testosterone on Calcium channels and on cardiac function [11].

A challenging metabolic situation is supranormal supplementation of synthetic androgens, in the case of body builders or FtM transgender individuals [8]. The goal of testosterone supplementation in body builders is to increase the efficacy of physical exercise, muscle size and strength [12]. Adverse effects in body builders with unsupervised testosterone supplementation vary, ranging from ventricular hypertrophy [13,14], coronary artery disease (CAD) [14,15], increase in blood pressure [14], cardiovascular toxicity [16], heart failure [15] and myocarditis [17]. FtM experience masculinization such as a change in body fat location, increase in muscle mass and increased libido [18,19].

Cases of synthetic androgen misuse with cardiac symptoms in young athletic body builders have been reported. Fatigue, shortness of breath and chest pain that occur with androgen misuse fit the symptoms of myocarditis more than myocardial ischemia [20]. Supranormal testosterone levels, such as can occur in body builders and FtM transgender individuals, impair normal function of mitochondria resulting in an increase in ROS, decrease in mitochondrial oxygen consumption, membrane potential, sex-hormone binding globulin and high-density lipoprotein resulting in increased oxidative stress [13–16,21]. Furthermore, studies have linked activation of androgen receptor by testosterone to increased myocardial inflammation, fibrosis and dilated cardiomyopathy in males [2,6–8,10,22].

In summary, testosterone substitution has various effects on cardiac myocytes ranging from activating to depressing function and may pose cardiac risks for FtM patients as a consequence [23]. Currently, the diagnosis of myocarditis can only be achieved through resource- and cost-intensive diagnostic methods such as contrast-enhanced cardiac magnetic resonance imaging (CMR) or FDG positron emission tomography-computed tomography (PET-CT). Endomyocardial biopsy (EMB) is the invasive gold standard to diagnose myocarditis [24]. There is a clinical need for a relatively cheap and rapid diagnostic method that can be utilized as an initial screening tool, following the exclusion of CAD, to determine the necessity of further diagnostic workup for differential diagnoses such as myocarditis.

In this case report, we present the interesting case of myocarditis occurring in a FtM individual after testosterone treatment and application of magnetocardiography (MCG) as a method for initial diagnostic screening and therapeutic monitoring of myocarditis.

2. Method: magnetocardiography measurement

The movement of ions into and out of cardiomyocytes underlies the initiation of an action potential leading to the creation of voltages and, consequently, an electromagnetic field. The magnitude and direction of the magnetic field are influenced by intra- and extracellular ion flux. The electromagnetic field generated by the heart typically ranges in strength from 10^{-15} to 10^{-11} Tesla [25].

The MCG system comprises an array of 64 highly sensitive magnetic sensors known as superconducting quantum interference devices (SQUIDs). The measurement apparatus is housed within a shielded room to minimize interference from extraneous electromagnetic signals. SQUIDs detect alterations in the cardiac magnetic field during the cardiac cycle and represent these changes in accordance with the QRS complex. Several frequency filters are employed to eliminate electromagnetic interference. The magnetic field measurement provides three-dimensional resolution, enabling the derivation of a composite vector representing the primary electrical axis of the heart. In the evaluation of inflammatory cardiomyopathies, attention is given to the vector of the action potential T-wave and the T-wave maximum, characterized as the T-beg-Tmax interval. A T-wave/MCG vector T-beg-Tmax exceeding 0.051 is indicative of pathology, as we have shown in our previous work [25]. It is important to note that the MCG T-beg-Tmax vector lacks specificity for inflammatory cardiomyopathy, as other forms of cardiomyopathy, such as ischemic cardiomyopathy or amyloidosis, can also influence the electromagnetic field. However, it can be used as a sensitive screening tool for acute inflammatory cardiomyopathy.

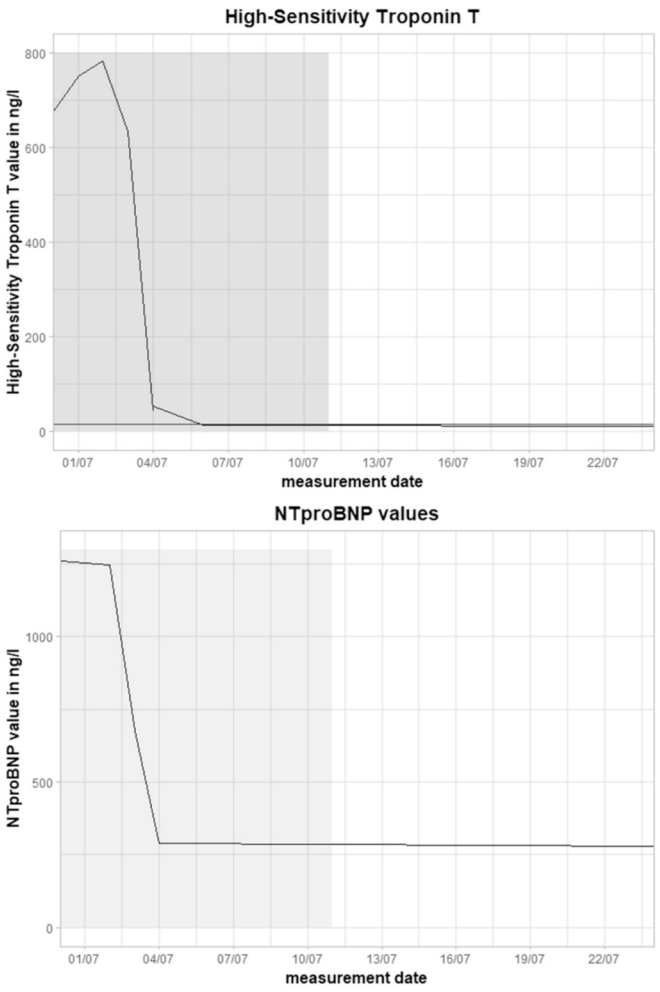

Fig. 1. Values of high-sensitivity troponin T (hsTnT) and NT pro brain natriuretic peptide (NTproBNP) during the clinical course. The red bottom line represents the pathological threshold of hsTnT (>14 ng/L). The grey box marks the time the patient was hospitalized. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Case description

We report on a 38-year-old FtM transgender patient, who presented with episodes of chest pain and exercise intolerance. His past medical history included two gender reassignment surgeries (female to male) at the genital organs and the mammae. The patient did not have any metabolic diseases, surgeries, or medical problems until his current presentation of chest pain. The patient was treated with 250 mg testosterone every two weeks for 6 months subcutaneously as part of his gender transformation. The most recent injection took place 2 days before the symptoms started. Family history was unremarkable.

Clinical examination was unremarkable. The patient was hemodynamically stable and euvolemic. There were no murmurs, rubs or gallops on cardiac auscultation. The ECG revealed sinus rhythm with ST-elevations in II, aVF and V3-V6. Holter monitoring ruled out any relevant arrhythmias. The echocardiographic examination identified a mildly reduced left ventricular ejection fraction (LVEF) of 55 % with left

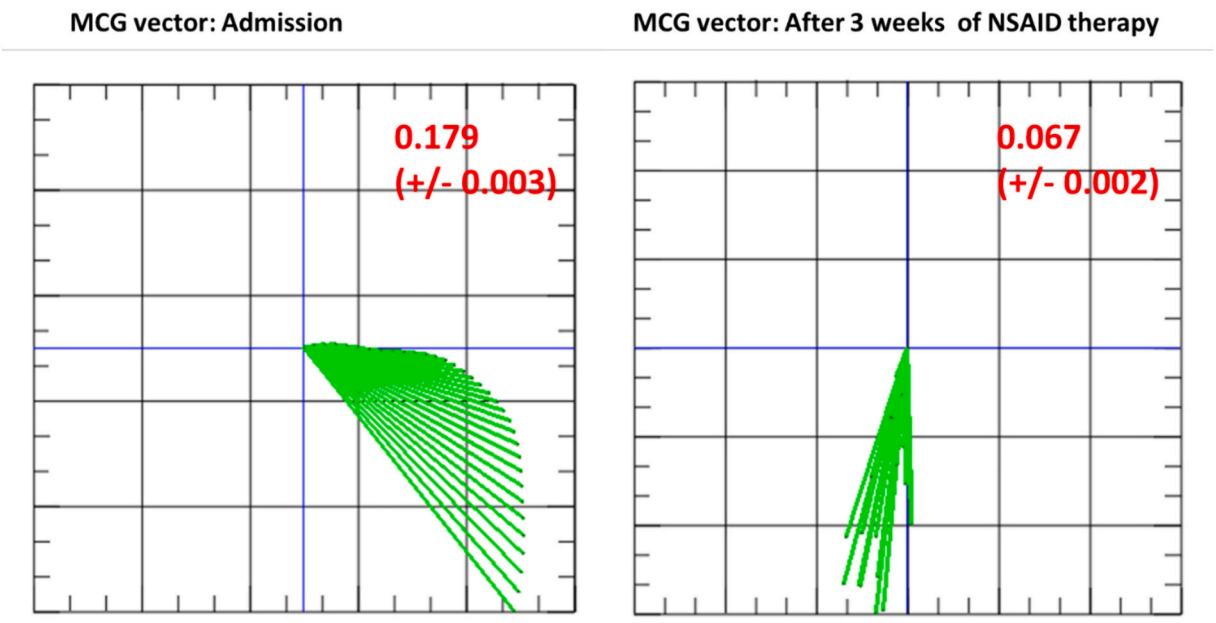

Fig. 2. Initial magnetocardiography (MCG) vector and MCG vector after 3 weeks of anti-inflammatory therapy with non-steroidal anti-inflammatory drugs (NSAID). The MCG vector (green plane on web version) decreases, moving towards a score that is considered normal (<0.052) based on our previous findings [9] and suggestive of a response to therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ventricular apical hypokinesis.

Laboratory testing was suggestive for an inflammatory state. Leukocytes were increased to 13.20 /nL (reference range < 10.50/nL), C-reactive protein (CRP) to 164 mg/L (reference range < 5 mg/L), high sensitivity troponin T (hsTnT) to 539 ng/L (reference range < 14 ng/L), NT pro-brain natriuretic peptide (NTproBNP) to 1248 ng/L, creatine kinase 592 U/L (reference range < 190 U/L) and creatine kinase-myoglobin 37 U/L (reference range < 24 U/L). Furthermore, the D-dimer was positive (>0,5 mg/L). HsTnT increased from 539 ng/L (reference range < 15 ng/L) to 676 ng/L within 1 h. The course of hsTnT and NTproBNP is visualized in Fig. 1.

In the emergency department the dynamical change in hsTnT and the positive D-dimers led to a chest computed tomography (CT) scan to rule out pulmonary embolism and a coronary CT scan to rule out acute coronary syndrome (ACS). After that the patient was transferred to the intensive care unit (ICU) for monitoring and further diagnostics with the suspected diagnosis of myocarditis.

At this time, the patient was examined using MCG. A pathological MCG vector of 0.179 was observed (Fig. 2, left panel). We previously established a cut-off value of >0.051 for the detection of cardiomyopathy [25], suggesting that this patient's MCG vector was highly pathologic. Three sequential measurements suggest a statistical uncertainty of 1.7 % (MCG vector +/− 0.003).

Anti-inflammatory therapy was initiated with Ibuprofen 800 mg three times daily. Additionally, thromboprophylaxis was administered using fractionated heparin, and pain management was provided with metamizole 1 g four times daily.

The next day, a CMR with contrast agent was performed. Here in native and T2 weighted maps local, patchy and subendocardial lesions in the apical and inferolateral region were detected. These findings were consistent with the diagnosis of acute myocarditis (Fig. 3).

In consideration of all findings from medical history, clinical examination, cardiac CT and CMR imaging, the diagnosis of myocarditis was confirmed. The anti-inflammatory therapy Ibuprofen was continued.

Due to the known risk of myocarditis associated with testosterone therapy [10], and in consultation with the endocrinologist we recommended a pause of the testosterone treatment. After careful consideration and workup of an individualized supplementation approach, the interval of testosterone injections (250 mg subcutaneously every 2 weeks) was increased to 250 mg every 3 weeks. The patient reported subsequent symptom improvement.

Regular echocardiographic follow-up exams and laboratory testing for cardiac enzymes and testosterone levels were conducted. Just 10 days after admission, a significant improvement in LVEF was observed, from 55 % to 63 %. Before discharge, another MCG measurement was performed, showing an improved MCG vector from 0.179 at baseline to 0.067 (Fig. 2 right panel). Three sequential measurements suggest a statistical uncertainty of 2.9 % (MCG vector +/− 0.002). Cardiac enzymes also normalized, NTproBNP from 1260 ng/L to 280 ng/L and hsTnT from 676 ng/L to 10 ng/L.

The patient was discharged with a starting dose of Ibuprofen 2400 mg daily (divided in 3 doses) followed by a taper reducing the daily dose by 800 mg every two weeks. In addition, the patient received pantoprazole 20 mg daily. Follow-up appointments were scheduled every 2 weeks in the cardiology outpatient clinic.

During the last follow-up 2 months after discharge, the patient was symptom-free. Cardiac enzymes were without pathological changes.

4. Discussion

This case report describes the diagnosis and treatment of myocarditis in a transgender patient, highlighting the potential effect of testosterone to promote myocarditis and the low-threshold applicability of magnetocardiography to quickly screen for disease diagnosis and resolution. Importantly, this study represents the first documented case of myocarditis in a transgender patient following testosterone treatment.

The case raises the important question of the role of testosterone in the development of myocarditis and heart failure [10]. Testosterone is known to increase myocardial inflammation and fibrosis in mouse models of viral myocarditis. Individuals treated with high levels of testosterone such as body builders have been reported to develop cardiac mitochondrial dysfunction [21]. In particular, the increase in ROS formation in supranormal supplementation levels, mitochondrial dysfunction, cardiomyocyte apoptosis and heart failure are critical points to remember when applying hormone replacement therapy [11,21]. Transgender patients are in a unique situation, as they require sex hormone replacement therapy after sexual reassignment surgery [18]. This case study shows that a relatively short time of testosterone

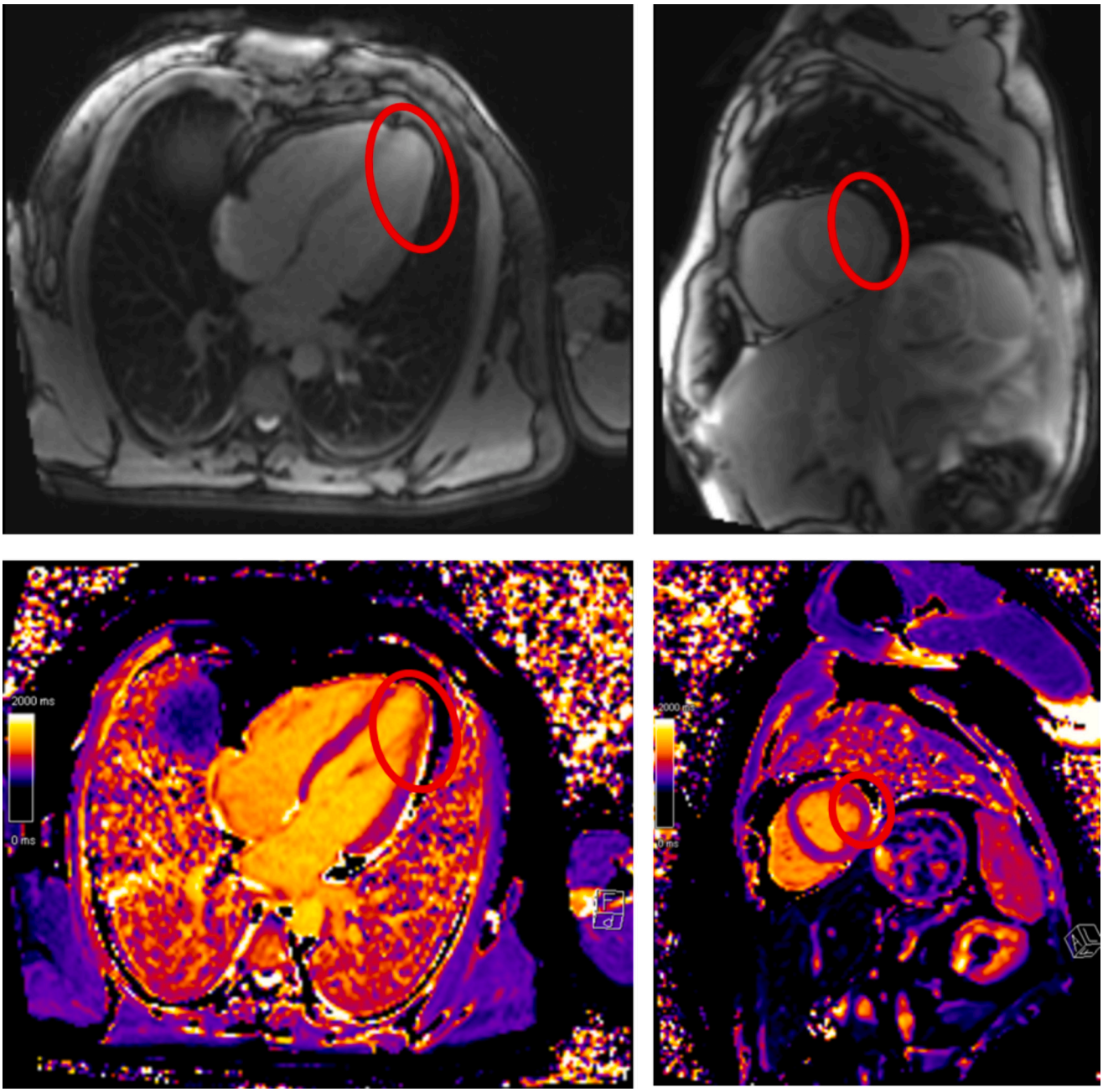

Fig. 3. Cardiac MRI with late gadolinium enhancement (LGE) and T2 map with increased SI times in 4 chamber and short axis view, especially apical and inferolateral indicating a myocardial oedema (red circle). This finding is consistent with the diagnosis of an acute myocardial process. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

supplementation on a background of a lifetime as a female was sufficient to increase the risk of developing myocarditis.

In addition to hormone substitution, individual predispositions such as pre-existing diseases and genetic variants can play a crucial role in determining the phenotype of myocarditis. Previous studies identified correlation between myocarditis and genetic risk profiles [26] [27,28].

More reports such as these are needed to ascertain how often myocarditis occurs in patients with FtM transition. Optimization of testosterone supplementation and active surveillance will be crucial for better outcomes.

The use of magnetocardiography to verify a diagnosis of myocarditis indicates the potential usefulness of this tool in surveillance of cardiac function and signs of inflammatory processes in patients with cardiomyopathy. Magnetocardiography screening for cardiac complications in transgender patients or patients undergoing hormone replacement therapy may facilitate earlier detection of cardiovascular complications.

5. Conclusion

In conclusion, this case report provides further evidence that testosterone promotes the development of myocarditis. It highlights the challenges faced by transgender patients, who rely on lifelong hormone replacement therapy, indicating the need for optimized supplementation, active surveillance and screening to enable early detection of cardiac complications. We suggest magnetocardiography as a potential screening tool for high-risk individuals with inflammatory cardiomyopathy.

Ethics statement and data availability

The ethics committee of the Deutsches Herzzentrum der Charité (DHZC) Universitätsmedizin Berlin approved the study (EA4/193/17). The presented patient provided written informed consent to participate in the study. Data from the study can be made available upon request from the principal investigator PD Dr. med. Bettina Heidecker in a de-identified form. A data use agreement must be signed before access to data. Access is only granted to academic staff.

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CRediT authorship contribution statement

Phillip Suwalski: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Finn Wilke:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **DeLisa Fairweather:** Writing – review & editing, Visualization, Validation. **Ulf Landmesser:** Writing – review & editing. **Bettina Heidecker:** Writing – review & editing, Writing – original draft, Supervision, Methodology.

Declaration of competing interest

PD Dr. med. Heidecker is an inventor on patents that use RNA for diagnosis of myocarditis. Patent protection is in process for MCG for diagnosis and measurement of therapy response in inflammatory cardiomyopathy. The remaining authors have no disclosures to report.

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Ethical statement

The local IRB approved this study. Informed consent was obtained from the human subject.

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