Aus der Medizinischen Klinik für Kardiologie

CharitéCentrum für Herz-, Kreislauf- und Gefäßmedizin

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DISSERTATION

Systematic Use of Cardiac Magnetic Resonance Imaging in Myocardial Infarction with Nonobstructive Coronary Arteries increases the Incidence of Myocarditis

zur Erlangung des akademischen Grades

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ABSTRACT

Background: We recently have shown that systematic screening of patients presenting with myocardial infarction and non-obstructive coronary artery disease (MINOCA) using cardiac magnetic resonance imaging (CMR) led to a more than 6-fold increase of the incidence of myocarditis in our hospital. In this study, we expanded our analysis to preceding and subsequent years to rule out any potential temporary incidence peak in 2016.

Methods: We performed a retrospective chart review of patients presenting with angina-like symptoms and elevated high sensitivity troponin T (TnT-hs ≥14ng/l) and no significant coronary artery disease from 2011 to 2017. All patients underwent CMR to evaluate for myocarditis. During the years 2011 to 2015, only patients with elevated TnT-hs, no significant coronary artery disease, and moderate to high clinical likelihood of myocarditis underwent CMR. Starting 2016 and continued in 2017, CMR was obtained in patients with the same presentation, but independently of clinical likelihood of myocarditis.

Results: A total of 556 patients (70.5% male, 57±17 years, with an average left ventricular ejection fraction of 51±15%) qualified for analysis. A total of 240 CMR examinations were performed from 2011 to 2015 and 316 from 2016 to 2017. In total, myocarditis was diagnosed in 76 of the 556 patients (13.7%). Between 2011 and 2015, the measured incidence of myocarditis was 12.7 per 100,000 persons and increased 4.9-fold (P-value < 0.0001) between 2016 and 2017 to 62.5 per 100,000 persons.

Conclusion: A novel diagnostic screening algorithm led to an average 4.9-fold increase of the total incidence of myocarditis during the two subsequent years. This underscores the fact that myocarditis continues to be underdiagnosed if CMR is not systematically used in patients with MINOCA.

ABSTRACT IN DEUTSCH

Einleitung: Wir zeigten kürzlich in einer Pilotstudie, dass systematisches Screening von Patienten mit Myokardinfarkt und nicht stenosierender koronarer Gefässerkrankung (MINOCA) durch Magnetresonanztomografie (MRT) zu einem mehr als 6-fachen Anstieg der Inzidenz von Myokarditis im Jahr 2016 führte. In dieser Arbeit haben wir nun unsere Analyse erweitert und dem Jahr 2016 vorausgehende als auch nachgehende Jahre eingeschlossen, um eine mögliche temporäre Inzidenzerhöhung auszuschließen.

Methodik: Wir führten eine retrospektive Untersuchung der Krankenakten von Patienten durch, welche sich mit Angina Pectoris und erhöhtem high sensitivity troponin T (TnT-hs ≥14ng/l) ohne relevante Koronarstenosen von 2011 bis 2017 präsentiert haben. Alle Patienten erhielten MRT zur Evaluation auf Myokarditis. Während der Jahre 2011 bis 2015 erhielten nur Paitenten mit hohem klinischen Verdacht auf Myokarditis ein MRT. Im Jahr 2016 und 2017 erhielten alle Patienten mit Angina Pectoris, erhöhtem TnT-hsm und nicht stenosierten Koronarien ein MRT – unabhängig vom klinischen Verdacht.

Ergebnisse: Es wurden insgesamt 556 Patienten (70.5% Männer, 57±17 Jahre alt, mittlere linksventrikuläre Auswuffraktion: 51±15%) eingeschlossen. Von 2011 bis 2015 wurden 240 MRTs durchgeführt und von 2016 bis 2017 waren es 316. Insgesamt wurde Myokarditis bei 76 von 556 Patienten diagnostiziert (13.7%). Von 2011 bis 2015 war die Inzidenz von Myokarditis 12.7 pro 100,000 Personen. Die Inzidenz stieg im Jahr 2016 und 2017 auf 62.5 pro 100,000 Personen an.

Zusammenfassung: Ein neuer diagnostischer Screening Algorithmus hatte zu einer 4.9-fachen Erhöhung der Inzidenz von Myokarditis während zwei aufeinanderfolgender Jahre geführt. Dieses Ergebnis bestärkt die Tatsache, dass Myokarditis weiterhin unterdiagnostiziert wird, wenn MRT nicht systematisch bei Patienten mit MINOCA eingesetzt wird.

ABBREVIATIONS

CAD	coronary artery disease
CMR	Cardiac magnetic resonance imaging
CT	computed tomography
DCM	Dilated cardiomyopathy
EMB	Endomyocardial biopsy
HCM	Hypertrophic cardiomyopathy
MINOCA	Myocardial infarction and non-obstructive coronary artery disease
LVEF	Left ventricular ejection fraction
SCD	Sudden cardiac death
TnT-hs	High-sensitivity Troponin
TTS	Takotsubo syndrome

INTRODUCTION

Myocarditis is a heterogeneous inflammatory heart disease presenting with a variety of symptoms[1,2] and potentially poor clinical trajectory resulting in dilated cardiomyopathy (DCM), impaired left ventricular ejection fraction (LVEF)[3], malignant arrhythmias, and sudden cardiac death (SCD).[2,4–6] While endomyocardial biopsy and cardiac magnetic resonance imaging (CMR) are increasingly used to diagnose myocarditis[2,7–9], the true incidence of myocarditis is unknown.[10] In that regard, post mortem studies have identified myocarditis in up to 42%[5,11] of cases of SCD suggesting its great epidemiological impact. Hence, a systematic change is necessary in the way patients with myocarditis can be identified.[12]

As symptoms of myocarditis can mimic myocardial infarction and lead to elevated troponin levels[2,13], inflammatory cardiomyopathy is commonly found amongst patients with angina-like symptoms, elevated high-sensitivity Troponin (TnT-hs), and unobstructed coronaries (i.e. myocardial infarction and non-obstructive coronary artery disease [MINOCA]).[14–16] This clinically challenging population often lacks specific treatment[17,18] and was found to have an increased mortality.[19] In patients with MINOCA, multiple underlying mechanisms have been suspected including coronary spasm, coronary microvascular dysfunction, myocarditis, Takotsubo syndrome (TTS), spontaneous coronary thrombosis and emboli.[19,20] Interestingly, myocarditis is one of the most common underlying causes within this patient population, ranging from 16% to 50%.[21–23]

While endomyocardial biopsy (EMB) remains the gold standard[24,25] for the diagnosis of myocarditis, CMR has been established as a non-invasive alternative for the diagnosis of myocarditis, when EMB is not indicated.[7,13,15,20,26] In a previous pilot study, we have shown that the introduction of a novel diagnostic algorithm whith a low threshold for CMR at a tertiary care center, led to a 6.3-fold increase of the incidence of myocarditis in patients presenting with MINOCA. Furthermore, the algorithm increased the percentage of CMRs that were positive for

myocarditis.[27] In order to confirm these first results, we expanded our analysis to preceding and subsequent years to evaluate for any potential temporary incidence peak in 2016. We hypothesized an increased incidence of myocarditis in the time period of 2016 and 2017 with systematic use of CMR as compared to the period of 2011 to 2015, when CMRs were performed only if there was a moderate to high clinical suspicion of myocarditis.

MATERIAL AND METHODS

Study design

This is a retrospective single-center study investigating a new screening algorithm for myocarditis amongst patients with MINOCA. The cohort includes patients who presented from January 2011 to December 2017 with angina-like symptoms, elevated levels of TnT-hs (normal range: 0-14ng/l), and nonobstructive coronary artery disease (CAD) (<50% stenosis), who underwent CMR for further diagnostic workup. CAD was excluded using coronary angiography by cardiac catheterization or computed tomography (CT) and CMR if pretest probability of CAD was very low.[27]

In the years 2011 to 2015, only patients with classical symptoms of myocarditis such as chest pain, dyspnoea and palpitations after viral prodrome underwent CMR. Starting in 2016, the threshold for CMR imaging was lowered to examine all unexplained cases of MINOCA within 30 days after first presentation to our hospital.

Outcome measurements

The primary goal of this study was to measure the incidence of myocarditis amongst patients suffering from MINOCA by systematic CMR screening and after implementation of a new diagnostic screening algorithm. To evaluate its impact, we compared the incidence of myocarditis after its introduction in 2016 and 2017 with the preceding 5 years from 2011 to 2015. Secondary measures included 1) baseline characteristics of patients with MINOCA without signs of myocarditis vs. patients suffering from myocarditis 2) Incidence of other types of cardiomyopathies identified by CMR amongst patients with MINOCA between 2011 and 2017.

Clinical database

The clinical data was generated with the help of the electronic medical records database from our institution. Before the analysis, all patients were anonymized and continuously numbered. IBM SPSS Statistics version 22 and MedCalc version 18.5 were used for calculation and analysis.

CMR examination

CMR images were generated using a 1.5 or 3.0 Tesla scanner (SiemensSkyra, Erlangen, Germany or Phillips Achieva Best, Netherlands) with electrocardiography-gated breath-hold protocol. Diagnosis of myocarditis was based on cine-CMR, T2-weighted imaging and T1-weighted LGE images.[28–30] The latter were acquired 10 minutes after an intravenous injection of a gadolinium-based contrast agent. The examination protocol did not change between 2011 and 2017. Values were indexed for age, gender and body surface area.[31]

Statistical analysis

Descriptive statistics were used to examine clinical data. Metric scaled parameters were described as averages with their standard deviation. Nominal scaled parameters were reported as total numbers and as percentages of the total number of patients per year. Rare diagnoses such as scleroderma, pericardial effusion and coronary anomalies were summarized as "others". Baseline characteristics of patients with myocarditis vs normal CMR findings were compared using student T-test and Chi^2 Test for equality of proportions. P-value < 0.05 was considered significant for all statistical tests.

In order to compare the detection rate for myocarditis by CMR in 2016 and 2017 vs 2011 to 2015, percentages of positive CMR findings for myocarditis for each time interval were

compared using Chi^{2}-test. Incidence rate was calculated within the total number of patients admitted to our institution. Incidence ratio compares the total incidence rate from 2011 to 2015 and 2016 to 2017.

RESULTS

Baseline Characteristics

A total of 556 patients, who presented from January 2011 to December 2017 with MINOCA underwent CMR. The mean age of this group was 57 years (range: 19-92 years) with 392 (70.5%) male patients and an average LVEF of 51±15% measured by CMR (Table 1). Patterns of myocarditis were present in 76 patients (13.7%), DCM in 34 (6.1%), ischemia during stress in 41 (7.4%), hypertrophic cardiomyopathy (HCM) in 15 (2.7%), pericarditis in 13 (2.3%), amyloidosis in 8 (1.4%), TTS in 7 (1.3%), sarcoidosis in 5 (0.9%), Fabry's disease in 3 (0.5%) and "other" diagnoses were present in 22 patients (4%). In total, 332 (59.7%) of the performed CMRs were unremarkable (Table 2).

Comparison of Incidence in 2011-2015 vs. 2016-2017

Amongst the total 556 patients initially idenfied as MINOCA, 35 (6.3%) cases presented in 2011, 27 (4.9%) in 2012, 28 (5%) in 2013, 62 (11.2%) in 2014, 88 (15.8%) in 2015, 199 (35.8%) in 2016 and 117 (21%) in 2017, leading to 240 (43.2%) patients enrolled during the time period from 2011 to 2015, while during the years 2017 to 2017 it was 316 (56.8%). There was no difference in baseline parameters such as age, gender or LVEF between these two time periods. The average number of CMRs performed annually was 49 from 2011 to 2015 and increased to 142 from 2016 to 2017. There were significantly less annual cases of DCM (P=0.0072) from 2015 to 2016, while the average annual proportions of CMR reports that were negative for any

pathology did not change (P= 0.25; Table 3). In total, 24 cases of myocarditis were identified in 2011 to 2015 vs. 52 cases between 2016 and 2017 resulting in 4.8 (10%) cases of myocarditis on average between 2011 and 2015 and 26 (16.7%) cases on average in 2016 to 2017.

There was a total of 272,688 hospitalized patients at our institution from 2011 to 2017 (37,520 in 2011, 36,484 in 2012, 36,941 in 2013, 38,896 in 2014, 39,694 in 2015, 41,121 in 2016, 42,032 in 2017). As a result, the annual incidence was 12.7 per 100,000 (CI: 0.00008-0.00019) persons in the years 2011 to 2015 with an increase to 62.5 per 100,000 persons (CI: 0.00047-0.00083) in the time period of 2016 to 2017, which results in an incidence ratio of 4.9 (P-value= <0.0001). Incidence for each year is shown in Figure 1.

Myocarditis vs. MINOCA

We identified 76 cases of myocarditis in 2011 - 2017. Patients suffering from myocarditis were significantly younger (47±17 years vs. 58±17; P-value= 0.00000075) and more likely to be male (81.6% vs. 68.8%; P-value= 0.023) as compared to MINOCA patients, in whom no CMR signs of myocarditis could be detected. Average LVEF on CMR was 51±14% and did not vary between the two groups (P-value=0.84).

DISCUSSION

In the present study, we found a remarkable increase in the incidence of myocarditis at our institution in two subsequent years after the implementation of a systematic CMR screening algorithm for patients suffering from MINOCA.

Recently, we reported the detection rate of myocarditis in 2015 vs 2016 after the implementation of a novel diagnostic screening algorithm in January 2016 in a smaller study, in which systematic screening of patients with MINOCA through CMR was performed.[27] We were able to detect a 6.3-fold increase in the incidence of myocarditis. Given the success of this algorithm, it was continued during the year 2017. With the current study we could verify our

previous results over a longer time period by comparing the number of cases of myocarditis in 2016 - 2017 diagnosed by CMR in patients suffering from MINOCA with the number of identified cases of myocarditis in the previous years 2011 - 2015, in which the threshold for CMR in patients with MINOCA was higher. The measured sharp 4.9-fold increase of the total incidence of myocarditis in 2016-2017 in our hospital demonstrates the still persisting room for improvement regarding the diagnostics of myocarditis and its potential underestimation, which was already discussed in literature.[1,5,15,16,22,23,27,32,33] Nonetheless, the real incidence of myocarditis remains unknown. A previous study by Karjalainen and Heikkilä et al. from 1999 evaluating the incidence of myocarditis in young military recruits in Finland from 1977 - 1996 based on clinical criteria found myocarditis to have an incidence of 17 per 100000 person years.[1]

In comparison to our previous study in which we only compared the years 2015 and 2016, the percentage of positive cases of myocarditis of all CMRs performed in 2016 - 2017 did not increase significantly (P=0.28). One possible explanation is that 2015 had the lowest percentage of positive cases of myocarditis in CMR in our hospital resulting in an increased contrast in comparison to 2016. All things considered, CMR screening of MINOCA patients regardless of clinical suspicion apparently does not change the proportions of CMR findings but the greater number of CMR scans leads to an overall higher number of pathological findings also resulting in a higher incidence of myocarditis among the MINOCA population after 2016. Hence, it seems that the indication for CMR based on clinical decision (as it was practiced before 2016) has no advantage over our new algorithm, where all MINOCA patients underwent a CMR scan. Interestingly, Pathik et al. demonstrated that the clinically suspected diagnosis by cardiologists in patients with MINOCA changed in approximately 50% after CMR scanning, thereby demonstrating the difficulties of correctly predicting the underlying diagnosis in patients suffering from MINOCA.[34]

Similar to previous studies, we found myocarditis to be the most common underlying diagnosis in patients suffering from MINOCA undergoing CMR.[15,16,19,35] Interestingly, the percentage of CMR scans positive for myocarditis (which reached 22.2% in 2017) was lower than previously described in literature. For instance, Pasupathy et al. found myocarditis to present in around 33% of CMR in MINOCA patients based on 26 CMR publications.[19] Moreover, studies on the diagnostic yield of CMR in MINOCA showed myocarditis to be present in 41.6 - 59.9%[15,16,36]. In addition, they revealed a considerably lower rate of unremarkable CMR scans with only 8-10.3%[15,16,36] in comparison to our study (in total 59.7%). However, we did include all CMR scans with a clinical suspicion of myocarditis, while the before mentioned studies excluded patients suffering from known cardiac diseases which could have led to higher concentrations of relevant findings in their publications.

Consistent with previous studies, patients with myocarditis were significantly younger and more frequently male than those without a diagnosis of myocarditis[11,15] LVEF did not vary between cases of myocarditis and non-myocarditis with a globally just mildly impaired LVEF (51±15). Other underlying diagnoses in CMR, with the exception of DCM, did not differ between 2011 to 2015 and 2016 to 2017. The fact that DCM was less frequent in 2016 to 2017 shows that its detection rate is not positively influenced by a systematic screening of this patient group.

Finally, the increased rate of diagnosis of myocarditis through systematic screening of patients with MINOCA implemented in 2016 was reproduced in the consecutive year and therefore likely approached the true incidence of myocarditis. Moreover, the proportion of differential diagnoses and negative scans for any pathology was not influenced through systematic CMR screening independent of clinical suspicion. This demonstrates the difficulty of evaluating patients with MINOCA based on clinical suspecion and emphasizes the importance of

systematic screening with CMR in this patient population. Importantly, the increased detection rate of the underlying causes of MINOCA leads to a higher number of patients receiving adequate treatment, follow-ups and cessation of strenuous exercise for 3-6 months, which is essential in patients with myocarditis, as physical activity is suspected of triggering life threatening arrhythmias in patients suffering from myocarditis.[32,38]

SUMMARY

Though clinical judgment plays an important role in the diagnostics of myocarditis, patients suffering from MINOCA seem to be difficult to evaluate only based on clinical grounds. Although systematic CMR screening of all cases of MINOCA regardless of their clinical pretest probability for myocarditis reveals no change in the proportion of myocarditis in this patient population, the absolute number of patients receiving a proper diagnosis and management increases substantially. Therefore, we suggest a systematic use of CMR in patients with angina-like symptoms, elevated troponin T and no significant coronary artery disease.

Limitations

This study is subject to several limitation. First, histopathological confirmation myocarditis of was not performed, as endomyocardial biopsies are performed according to guidelines only in cases of suspected giant cell myocarditis or fulminant heart failure and severe clinical course.[38] Secondly, no prospective data of our population was collected in order to identify the true incidence rates and outcomes. In addition, the total number of patients suffering from MINOCA and the proportion of performed CMR investigations in this group was not evaluated in this study.

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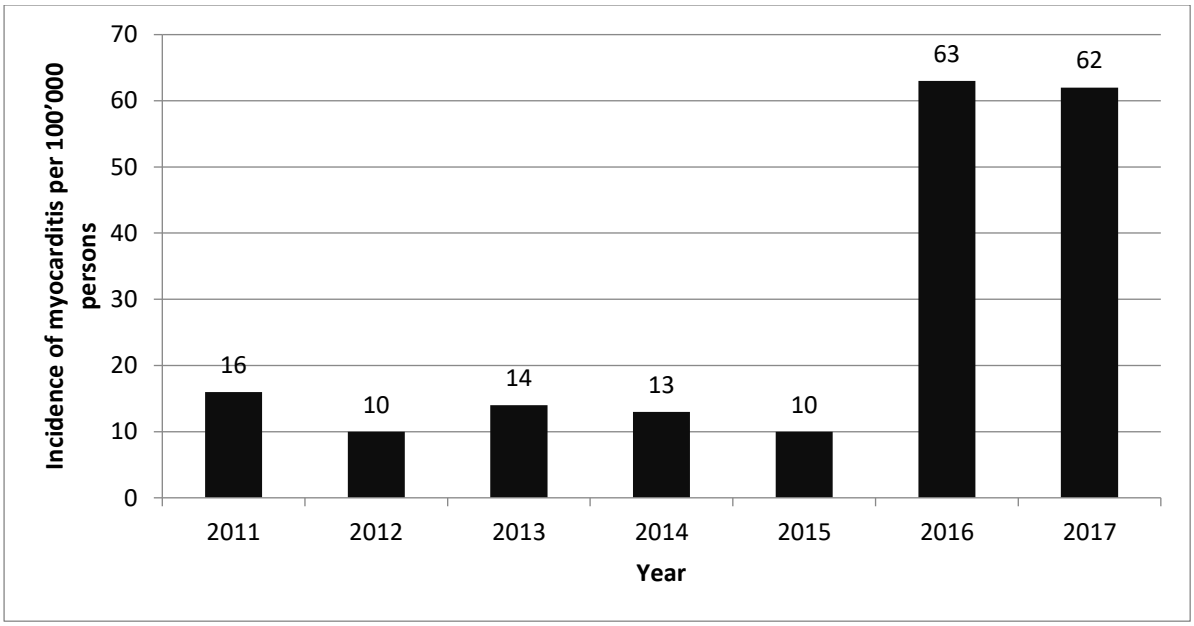
FIGURES

Figure 1: Incidence of myocarditis diagnosed by cardiac magnetic resonance imaging from 2011 to 2017



TABLES:

Table 1: Baseline parameters of patients undergoing CMR in years 2011-2017

Year	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Total number of patients	**n=35**	**n=27**	**n=28**	**n=62**	**n=88**	**n=199**	**n=117**	**n=556**
Male gender, n(%)	26(74.3)	18 (66.7)	22 (78.6)	36 (58.1)	71 (80.7)	139 (69.8)	80 (68.4)	392 (70.5)
Mean age, % (±δ)	54±16	56±17	55±15	52±17	66±15	60±16	49±18	57±17
Mean LVEF, % (±δ)	45±19	52±18	56±15	52±15	48±15	51±13	54±14	51±15

Abbreviations: LVEF=Left ventricular ejection fraction

Table 2: Diagnoses based on cardiac magnetic resonance imaging in years 2011 to 2017

Year	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Total CMRs performed	**n=35**	**n=27**	**n=28**	**n=62**	**n=88**	**n=199**	**n=117**	**n=556**
Normal heart,n (%)	18 (51.4)	13(48.1)	14(50)	43(69.4)	68(77.3)	110(55.3)	66(56.4)	332(59.7)
Myocarditis,n (%)	6(17.1)	4(14.8)	5(17.8)	5(8.1)	4(4.5)	26(13.1)	26(22.2)	76(13.7)
Ischaemia, n (%)	1(2.9)	1(3.7)	1(3.6)	1(1.6)	8(9.1)	26(13.1)	3(2.6)	41(7.4)
Pericarditis, n (%)	0(0)	0(0)	1(3.6)	2(3.2)	0(0)	4(2)	6(5.1)	13(2.3)
Amyloidosis, n (%)	1(2.9)	0 (0)	0(0)	1(1.6)	1(1.1)	2(1)	3(2.6)	8(1.4)
Sarcoidosis, n (%)	1(2.9)	0(0)	0(0)	0(0)	1(1.1)	1(0.5)	2(1.7)	5(0.9)
Fabry's disease, n (%)	0(0)	1(3.7)	0(0)	0(0)	1(1.1)	1(0.5)	0(0)	3(0.5)
TTS, n (%)	0(0)	0(0)	1(3.6)	0(0)	0(0)	4(2)	2(1.7)	7(1.3)
DCM, n (%)	6(17.1)	6(22.3)	6(21.4)	9(14.5)	0(0)	1(0.5)	6(5.1)	34(6.1)
HCM, n (%)	2(5.7)	2(7.4)	0(0)	0(0)	2(2.3)	9(4.5)	0(0)	15(2.7)
Others, n (%)	0(0)	0(0)	0 (0)	1(1.6)	3(3.4)	15(7.5)	3 (2.6)	22(4)

Abbreviations: TTS= Takotsubo syndrome, DCM=dilated cardiomyopathy, HCM= hypertrophic cardiomyopathy

Table 3: Diagnoses based on cardiac magnetic resonance imaging in 2011 to 2015 vs. 2016 to 2017

Year **Average CMRs Performed per year**	**2011-2015** **Total:240** **μ = 48**	**2016-2017** **Total:317** **μ = 158**	**P-value for Chi^2 equality of proportions**
Normal heart, μ(%)	31.2(65)	88(55.7)	0.25
Myocarditis, μ(%)	4.8(10)	26(16.4)	0.28
Ischaemia, μ(%)	2.4(5)	14.5(9.2)	0.35
Pericarditis, μ(%)	0.6(1.3)	5(3.2)	0.48
Amyloidosis, μ(%)	0.6(1.3)	2.5(1.6)	0.88
Sarcoidosis, μ(%)	0.4(0.8)	1.5(0.9)	0.95
Fabry's disease, μ(%)	0.4(0.8)	0.5(0.3)	0.64
TTS, μ(%)	0.2(0.4)	3(1.9)	0.46
DCM, μ(%)	5.4(11.2)	3.5(2.2)	0.0072
HCM, μ(%)	1.2(2.5)	4.5(2.9)	0.97
Others, μ (%)	0.8(1.7)	9(5.7)	0.26

Abbreviations: TTS=Takotsubo syndrome, DCM=dilated cardiomyopathy, HCM= hypertrophic cardiomyopathy

Eidesstattliche Versicherung

„Ich, Bettina Heidecker, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Systematic Use of Cardiac Magnetic Resonance Imaging in Myocardial Infarction with Nonobstructive Coronary Arteries increases the Incidence of Myocarditis“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Datum Unterschrift

Mein Lebenslauf ist in der elektronischen Version der Dissertation aus datenschutzrechtlichen Gründen nicht enthalten.

LIST OF PEER-REVIEWED PUBLICATIONS
*=shared first/senior authorship

Original Research Articles

1. Berg J., Kottwitz J., Baltensperger N., Kissel C., Lovrinovic M., Scherff F., Schmied C., Templin C., Lüscher T., **Heidecker B.***, and Manka R.* Cardiac Magnetic Resonance Imaging in Myocarditis Reveals Persistent Disease Activity Despite Normalization of Cardiac Enzymes and Inflammatory Parameters at 3 Months Follow-up, *published online in Circulation Heart Failure November 2017* **With editorial:** The Changing Face of Cardiac Inflammation, New Opportunities in the Management of Myocarditis by Cooper L.T.; impact factor: 6.4
2. Patriki D., Gresser E., Manka R., Emmert M.Y., Lüscher T.F., and **Heidecker B.** Approximation of the Incidence of Myocarditis by Systematic Screening with Cardiac Magnetic Resonance Imaging, *published online in JACC Heart Failure in June 2018*; impact factor: 8.5
   With editorial: A light at the end of the myocarditis tunnel by Mariell Jessup; impact factor: 7.2
3. **Heidecker B.*,** Spencer R.*, Hayes V., Parikh N., Oestreicher Stock E., Redberg R., The High Prevalence and Clinical/Sociodemographic Correlates of Miscarriages Among Flight Attendants, in press at the *American Journal of Medicine;* impact factor: 5
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patients with new-onset heart failure reveals important gender-specific differences. *European Heart Journal* 10:*1188-1196*

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1. **Heidecker B.** and Cooper L.T., Acute Fulminant Myocarditis, i*n print for Brown: Cardiac Intensive Care, 3/e*
2. Kittleson M.M., Irizarry R., **Heidecker B**., and Hare J.M. (2008) Transcriptomics: Translation of Global Expression Analysis to Genomic Medicine, *Handbook of Genomic Medicine, Ch.12:143-156, eds.: Willard and Ginsburg, Elsevier*

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1. Walker R., Poggioli T., Katsimpardi L., Buchanan S., Oh J., Wattrus S., **Heidecker B.**, Fong Y., Rubin L., Ganz P., Thompson T., Wagers A., Lee R. (2016). Biochemistry and Biology of GDF11 and Myostatin: Similarities, Differences, and Questions for Future Investigation. *Circulation Research 118:1125-42*; impact factor: 11
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4. **Heidecker B.,** Moore P., Bergsland E.K., Merrick S.H., and Rao R.K. (2015) Transcatheter pulmonic valve replacement in carcinoid heart disease. *European Heart Journal – Cardiovascular Imaging 16:1046*; impact factor: 4.1
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Letter to the Editor

1. **Heidecker B.**, and Hare J., European Heart Journal, Jul 2010 http://eurheartj.oxfordjournals.org/content/31/10/1188/reply

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