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Myocarditis or "true" infarction by cardiac magnetic resonance in patients with a clinical diagnosis of myocardial infarction without obstructive coronary disease: A meta-analysis of individual patient data

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ABSTRACT

Objective: Myocardial Infarction with Non-Obstructed Coronary Arteries (MINOCA) is common, but the causes are to a large extent unknown. Thus, we aimed to study the prevalence of myocarditis and "true" myocardial infarction determined by cardiac magnetic resonance (CMR) imaging in MINOCA patients, and risk markers for these two conditions in this population.
Methods: A search was made in the PubMed and Cochrane databases using the search terms "Myocardial infarction", "Coronary angiography", "Normal coronary arteries" and "MRI". All relevant abstracts were read and seven of the studies fulfilled the inclusion criteria; studies describing case series of patients fulfilling the diagnosis of acute myocardial infarction with normal or non-obstructive coronary arteries on coronary angiography that were investigated with CMR imaging. Data from five of these studies are presented.
Results: A total of 556 patients from 5 different sites were included. Fifty-one percent were men with a mean age of 52 ± 16 years. Thirty-three per cent of the patients had myocarditis (n = 183), whereas 21% of the patients had infarction on CMR (n = 115). Young age and a high CRP were associated with myocarditis whereas male sex, treated hyperlipidemia, high troponin ratio and low CRP were associated with "true" myocardial infarction.
Conclusion and relevance: The results of this meta-analysis of individual data showed that myocarditis and "true" myocardial infarction are common in MINOCA when determined by CMR imaging. This information emphasizes the importance of performing CMR imaging in MINOCA patients and can be used clinically to guide diagnostics and treatment of MINOCA patients.

1. Introduction

Myocardial Infarction with normal or Non-Obstructive Coronary Arteries (MINOCA) is common with a prevalence of 1–12% of all patients with a clinical diagnosis of myocardial infarction [1]. Recently, Collste et al. [2] suggested a prevalence of 7–8 %. MINOCA is a heterogeneous condition with patients fulfilling the diagnostic

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criteria of acute myocardial infarction. There are several different sub-groups of MINOCA, including myocarditis, “true” myocardial infarction and Takotsubo stress cardiomyopathy (TSC). Taking into account the heterogeneity of the condition, the mechanisms behind MINOCA are to a large extent unknown [3]. Cardiac magnetic resonance (CMR) imaging has been shown by several investigators to be of value in the investigation of MINOCA patients [2,4–9]. CMR imaging makes it possible to differentiate between myocarditis, “true” myocardial infarction and TSC although the latter is dependent on a short delay from symptom to investigation and clinical findings. The prevalence of myocarditis has varied from 7 to 63 % [2,6] whereas the prevalence of “true” myocardial infarction has varied from 12 to 30 % [4,5]. The studies have been small and heterogeneous regarding patient characteristics, in particular age and sex have varied between studies. The size and heterogeneity of the studies makes it difficult to find out the true prevalence and risk markers of myocarditis and “true” myocardial infarction among MINOCA patients investigated with CMR imaging. Thus, a large sample size is needed to study CMR imaging results in MINOCA.

The presents study, including consecutive individual data from five studies [2,6–9], aimed at establishing the prevalence and risk markers for myocarditis and “true” myocardial infarction among MINOCA patients investigated with CMR imaging. Our hypothesis was that it was possible to find clinical markers to predict the occurrence of myocarditis and “true” myocardial infarction.

2. Material and methods

A search was made by two of the authors (SA, PT), who independently of each other performed the search in PubMed using the MeSH search terms “Myocardial infarction”, “Coronary angiography” and “MRI” with the addition of the free search term “Normal coronary arteries”. An additional search was made in the Cochrane Library. All relevant abstracts were read and five of the studies described case series with all patients fulfilling the diagnosis of acute myocardial infarction with normal or non-obstructive coronary arteries that were investigated with CMR imaging [2,6–9]. Two more publications were found by reading references from the relevant publications [4,5]. In total, seven relevant studies with similar methodology were found, and the corresponding authors were invited to collaborate within the present study. The final study was able to combine data from five of those studies in the present analysis. Informed consent was obtained from corresponding and senior authors. Original data was transferred between researchers after agreement by e-mail. All included studies were approved by the local ethics committees.

3. Study designs

All studies included consecutive cases of the respective time periods of inclusion from the respective catchment area of the involved centers [2,6–9]. The inclusion criteria were similar although there were differences regarding the angiographic definitions. Exclusion criteria were similar although one study excluded patients with a high coronary heart disease (CHD) Framingham risk score whereas another study included only patients 35–70 years old (Table 1).

4. Risk markers

An Excel sheet was prepared and sent to the interested authors of the included studies. The requested background information included age, sex, history of present smoking and diabetes mellitus, treatment for hypertension and dyslipidemia, and the ratio of maximal troponin (I or T) increase to the upper limit of normal and C-reactive protein (CRP) level in plasma. In cases where the CRP level was given as < 5 mg/l, the value was set to 3. Information about smoking, diabetes mellitus and treated dyslipidemia was missing in four patients. Information about treated hypertension was missing in five patients. Information about troponin ratio was missing in five patients whereas data were lacking in 87 (42 with myocarditis, respectively 16 with infarction) patients regarding CRP.

5. CMR imaging

The CMR imaging protocols were similar in all studies and included cine images, T2-weighted oedema sequences and delayed enhancement after gadolinium contrast injection. Left ventricular ejection fraction was determined by the respective software of the CMR equipment (data from 11 patients were missing). The evaluation of CMR images varied between the studies. However, the final CMR imaging diagnosis was based mainly on the myocardial distribution of delayed enhancement of gadolinium in order to differentiate between myocarditis (subepicardial) and infarction (subendocardial). TSC was diagnosed clinically by Zaldumbide el al [6]. and Collste and al [2]. and by a combination of CMR imaging and clinical data in the remaining studies [7–9]. Hence, a CMR imaging diagnosis was only possible for myocarditis and infarction. In all studies, the final CMR imaging diagnosis was made by two experts blinded to clinical data. For information regarding detailed protocols see references [2,6–9] and for en overview of the included studies, see Table 1.

6. Statistics

Values are presented as percentage, mean ± standard deviation or median (interquartile range). Uni- and multivariable odds ratios (OR) with 95% confidence intervals (CI) of risk markers for myocarditis and infarction were calculated using logistic regression. For this analysis, the material was divided into clinically relevant categories: troponin ratio ≤10 or >10 and CRP ≤10 or >10 mg/l. Uni- and multivariable analyses of the OR of cardiac risk factors for myocarditis and infarction determined by CMR imaging were performed. In model 1 age, sex, smoking, diabetes mellitus, hypertension, dyslipidemia, troponin ratio and CRP were included and model 2 included all variables in model 1 with the addition of

Table 1
Characteristics of studies included in the meta-analysis.

	Number of patients	Age, years	Male sex %	CA findings	Restrictions	Time from AMI to MRI	MRI equipment
Ref. [6]	80	48	64	Non-obstructive	No major	3 days	Philips® or Siemens® 1.5 T
Ref. [7]	107	44	63	Non-obstructive	No major	5 days	Philips® 3 T
Ref. [9]	87	53	40	Normal	Low risk score*	10 days	GE® 3 T
Ref. [8]	130	54	52	Non-obstructive	No major	6 days	Siemens® 1.5 T
Ref. [2]	152	58	36	Normal	Age 35–70	12 days	GE®, Philips® or Siemens® 1.5 T

* Framingham risk score > 10% in 10 years. No = Number, CA = Coronary angiography, AMI = Acute Myocardial Infarction, MRI = Magnetic Resonance imaging, GE = General Electric, T = Tesla.