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The role of anti-myosin antibodies in perpetuating cardiac damage following myocardial infarction

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ABSTRACT

Recent improvements in the medical and surgical management of myocardial infarction mean that many patients are now surviving with greater impairment of cardiac function. Despite appropriate management, some of these patients subsequently develop pathological ventricular remodelling, which compounds their contractile dysfunction and can lead to congestive cardiac failure (CCF). The pathophysiological mechanism underpinning this process remains incompletely understood. One hypothesis suggests that a post-infarction autoimmune response, directed against constituents of cardiac myocytes, including cardiac myosin, may make an important contribution. Our review summarises the current literature related to the formation and clinical relevance of anti-myosin antibodies (AMAs) in patients with myocardial infarction. This discussion is supplemented with reference to a number of important animal studies, which provide evidence of the potential mechanisms underlying AMA formation and autoantibody mediated cardiac dysfunction.

1. Introduction

Over the past two decades, considerable advances in the acute management of myocardial infarction (MI) have reduced mortality and improved patient outcomes [1]. However, despite appropriate treatment, the hearts of many MI survivors undergo a process of pathological ventricular remodelling, which compounds their contractile dysfunction and can lead to congestive cardiac failure (CCF). Accordingly, an unwelcome side effect of improved MI survival is an increase in the incidence, morbidity, mortality and associated cost of post-infarction CCF. Heart failure now consumes approximately 1–2% of national health care budgets in the western world [2] and, when severe, its diagnosis carries a 5-year survival rate of approximately 25% [3].

Despite a significant amount of research into the process, the pathogenesis of ventricular remodelling is yet to be fully elucidated and we remain largely unable to arrest or reverse it. One hypothesis suggests that a post-infarction autoimmune response, directed against constituents of cardiac myocytes, may make an important contribution. This literature review summarises the role of anti-myosin antibodies (AMAs) in determining post-infarction outcomes.

2. Anti-myosin antibodies

Myosin is an intracellular protein that consists largely of repetitive amino-acid sequences, which arrange themselves into a coiled-coil alpha helical conformation [4,5]. In humans, there are two isoforms of this protein. The alpha isoform is exclusively located in atrial myocytes, while the beta isoform is expressed in both ventricular myocytes and skeletal muscle fibres [6].

Anti-myosin antibodies have been described in animal models of myocarditis [7–10], healthy individuals [6,11–17], and patients with cardiomyopathy [16–19], rheumatic heart disease [20,21], Kawasaki disease [22], post-pericardiotomy syndrome [23], myocarditis [11,24–26], dilated cardiomyopathy (DCM) [16,17,26–28] and myocardial infarction [13,14,23,29–31]. The most common pathogenic epitopes appear to be located in the S2 region of cardiac myosin, particularly in myocarditis and cardiomyopathy [9,21,32,33].

The reported prevalence of AMA in a healthy study population varies from 0–18% [6,11–17] (Table 1). However, the control group with the largest prevalence, reported by Dangas et al., had a relatively grave cardiovascular risk-factor profile, with 50% of patients having systemic hypertension and approximately 25% having a history of smoking or diabetes [13]. It is therefore conceivable that a proportion of these individuals may have experienced subclinical cardiac damage and subsequently developed AMA. If this study is excluded, along with other small studies (n < 20 patients), then the range is 0–3.4% (median

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Table 1
Anti-myosin antibodies in healthy individuals.

Patient numbers	% positive (n)	Age	M:F	Reference
203	2 (4)	45 ± 16	1:1.04	Goldman et al. [16]
78	3.85 (3)	NR	NR	Gottumukkala et al. [15]
59	3.4 (2)	40 ± 9.6	1.56:1	Warraich et al. [17]
39	2.5 (1)	NR	NR	Lauer et al. [11]
22	18 (4)	57 ± 2	6.14:1	Dangas et al. [13]
20	0 (0)	NR	NR	Pang et al. [14]
10	10 (1)	48 ± 12	9:1	Maixent et al. [12]

NR: not reported.

2.5%). In any case, reported AMA titres are much lower in healthy controls than in patients with cardiovascular disease.

The reported prevalence of AMA following MI ranges between 16–43% (Table 2) [13,29,30]. Given that these autoantibodies appear early and remain elevated beyond six months after MI, it is plausible that they contribute to long-term ventricular remodelling and subsequent cardiac failure.

3. Determinants of anti-myosin antibody formation following myocardial infarction

Many studies have investigated the correlation between various clinical and demographic parameters and AMA titres, with varying results. As they are associated with a greater degree of tissue necrosis, it seems plausible that patients with a larger myocardial infarction would mount a greater autoimmune response to cardiac myosin than those with a smaller area of infarction. This was demonstrated by Dangas and colleagues [13], who found that in-hospital troponin-I levels correlated closely with AMA titres at one and three months of follow-up ($p < 0.05$) in a cohort of 33 patients with acute coronary syndrome (ACS). Conversely, in a study of 80 MI patients, De Scheerder et al. did not find any association between creatine kinase release and AMA titres and concluded that the extent of cardiac injury is only of minor significance in triggering an autoimmune response [23]. In addition to differences in specificity and serum concentration profile, these conflicting conclusions may be explained by a number of important methodological differences between the two studies. Most significantly, there was substantial variation in patient follow-up patterns and antibody detection techniques between the studies. While Dangas et al. used an Enzyme-Linked Immunoassay (ELISA) to determine autoantibody positivity at three time-points between admission and three months, De Scheerder and colleagues utilized an Indirect Immunoflourescent Assay (IIFA) to detect antibodies over a two-month period. Further research is therefore required to clarify the relationship between infarct size and autoantibody development.

Although the effect of infarct size on AMA titre is equivocal, there is some evidence that underlying autoimmune conditions may affect AMA levels following MI. Gottumukkala and colleagues investigated AMA titres in patients with Type 1 Diabetes (T1D) following MI [15]. Of the 18 post-infarction T1D patients in their study, 15 (83%) were positive for AMA against the S1 epitope of the alpha myosin heavy chain (∝ — MyHC) and these autoantibodies were absent in both post-infarction Type-2 Diabetes (T2D) patients and healthy controls. A cardiac Magnetic Resonance Imaging (MRI) study of one of the antibody positive patients revealed diffuse myocardial inflammation [15]. It is therefore possible that AMAs are causally associated with ongoing inflammation and contribute to the poorer outcome experienced by patients with T1D following MI, although this proposition needs further investigation.

Consistent with usual antigenic responses, it seems likely that patients who experience re-infarction would mount a more robust response against myosin than those experiencing their first event. This hypothesis also requires verification in future studies, but could contribute to the poorer outcome seen in patients with multiple MIs [34].

Table 2
Anti-myosin antibodies in myocardial infarction, dilated cardiomyopathy and myocarditis patients.

Condition	Patient numbers	% positive Adm (F/U)	Age	M:F	Reference
Myocardial infarction	80	(16)	64 (42–86)	4.26:1	De Scheerder et al. [23]
	67	27 (20)	66 ± 11	2.70:1	Pang et al. [14]
	33	42 (34–38)[b]	57 ± 2	6.14:1	Dangas et al. [13]
	28	36 (43)	67 (39–82)	2.45:1	De Scheerder et al. [29,30]
Dilated cardiomyopathy	259	27	44 ± 12	2.03:1	Caforio [27][a]
	123	20	42 ± 14	3.17:1	Goldman [16]
	110	25	44 ± 13	3.35:1	Caforio [28][a]
	82	23	43 ± 12	5.25:1	Warraich [17]
Myocarditis	53	17	42 ± 15	1.94:1	Caforio [26]
	40	42	NR	NR	Lauer [11]
	33	52 (39)	47 ± 13	1.56:1	Lauer [25]

Adm: admission; **F/U:** follow-up; HT**:** hypertension; NR**:** not reported.
[a] All serum samples were analysed using ELISA techniques, aside from Caforio et al., who used immunoflourescence.
[b] Patients followed up at two timepoints.

4. Proposed mechanism of AMA formation following myocardial infarction

Following MI, cardiac myocytes release damage-associated molecular pattern molecules (DAMPs) that interact with the immune system [35–38]. This results in the formation of immunoglobulin M (IgM), which may contribute to acute inflammation [39,40], but is unlikely to have a persistent effect on myocardial dysfunction.

It is probable that any sustained pathogenic AMA effect must be mediated by the immunoglobulin G (IgG) isotype. Although these antibodies are ultimately released by autoreactive B-cells, their production is also dependent on co-stimulation by a specific T-cell, which is directed against the same antigen [41]. In most cases, this is prevented by the apoptosis of autoreactive T-cells in the thymus [42,43]. Occasionally however, thymic epithelial cells fail to express particular 'self' antigens and autoreactive T-cells escape thymic deletion, allowing them to move into the peripheral circulation. Given that cardiac myosin is not always expressed by thymic epithelial cells [44], this hypothesis may be operational in post-MI AMA formation.

Alternatively, it is possible for antibody production to occur independently of T-cell help. This process is considered operational in responses that are directed against large antigens with repetitive sequences [45,46]. Given myosin's size and structure, it is therefore plausible that AMA production occurs via this mechanism. However, it is usually described in responses against polysaccharide, rather than polypeptide, antigens [47].

Although the distribution of autoantibody subclass has not been investigated in MI patients, IgG_2 and IgG_3 have been demonstrated to be the dominant AMA isotypes in patients with cardiomyopathy [48]. This is consistent with a T-Helper 1 (Th1) cell mediated response, and is associated with higher levels of circulating interferon gamma, which may lead to an autoimmune inflammatory process.

Once formed, the precise mechanism by which autoreactive T-cells are able to access myosin, which is an exclusively intracellular protein, remains incompletely understood. It has been suggested that structural homologies between myosin, myocyte surface proteins and exogenous antigens (such as viruses) results in autoantibody production through a process of molecular mimicry [49]. Alternatively, it is also possible that myosin is presented to T-cells on the major histocompatibility complex type-II (MHC-II) of inflamed myocytes, or local antigen presenting cells (APCs) [49,50]. This may beget the activation of an autoreactive T-cell, which provides help to autoreactive B-cells that recognize epitopes of the myosin protein.