Perspective

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Beat shock proteins and atrial fibrillation

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Abstract In this mini-review, the role of heat shock proteins in susceptability to induction of atrial fibrillation (AF) or in the process of AF is discussed. AF is the most common arrhythmia in humans, is self-perpetuating in nature and hence tends to become more persistent in time. Some studies show a correlation between high Hsp70 (HspA1A) expression in cardiac tissue and a reduced susceptability to induction of postoperative AF. Expression of Hsp70, Hsc70 (HspA8), Hsp40 (DnaJB1), Hsp60 (HspD1), Hsp90 (HspC1) was not associated with progression of AF. However, both correlative studies in human and experimental studies suggest that Hsp27 (HspB1) may delay progression of AF to the more permanent forms and hence Hsp27 might be referred to as a ''Beat shock protein''.

In this issue, Yang et al (2007) report on the expression of heat shock proteins in atrial tissue from patients with atrial fibrillation (AF), the most common arrhythmia in humans and a main contributor to cardiovascular morbidity and mortality (Nattel 2002). AF frequently is seen in conjunction with other cardiovascular diseases, such as hypertension, ischemic heart disease, valve disease, or cardiac failure. However, in a substantial number (>20%) of the patients AF is not associated with any underlying disease (so-called lone AF; Murgatroyd and Camm 1993).

Based upon the temporal characteristic of the arrhythmia, AF can be roughly divided into 3 categories: paroxysmal, persistent, and permanent AF. Paroxysmal AF occurs in episodes that terminate spontaneously and generally last less than or equal to 7 days (most less than 24 hours); persistent AF does not terminate spontaneously but can be converted to sinus rhythm and usually lasts more than 7 days; and permanent AF is AF for which electrical cardioversion is unsuccessful or deemed unnecessary (Fuster et al 2006).

AF is self-perpetuating in nature and hence tends to become more persistent in time (Godtfredsen 1975; Van Gelder et al 1996). AF self-perpetuation is caused by atrial remodeling, involving complex changes in cardiomyocyte electrical and contractile function resulting from increases in beating frequency of the atrial cardiomyocyte activation-rate (Wijffels et al 1995; Nattel 2002). When AF persists, progressive changes at the structural level emerge, predominantly myolysis (disruption of the myofibril structure), which is associated with contractile dysfunction and the perpeptuation of AF (Ausma et al 1997, 2003; Thijssen et al 2000; Allessie et al 2002; Olgin and Verheule 2002; Todd et al 2004; Verheule et al 2004; Brundel et al 2006).

Given the roles of heat shock proteins (Hsp) in the protection of cells from a variety of stresses, various groups, including Yang et al (2007) have tested the hypothesis that Hsp is involved in AF initiation or progression. However, in dealing with publications, it must be noted that some reports deal with the susceptibility to develop AF following coronary artery bypass grafting (CABG) (St Rammos et al 2002; Mandal et al 2005), whereas most others deal with the comparison of Hsp expression in atrial appendages of AF patients and patients in sinus rhythm ([SR]; Schafler et al 2002; Kirmanoglou et al 2004; Brundel et al 2006).

Regarding Hsp expression and AF susceptibility, both St Rammos et al (2002) and Mandal et al (2005) exclusively studied Hsp70 (or HspA1A) expression. Both studies consistently show that patients with higher atrial HspA1A expression levels have a lower incidence of postoperative AF. However, to date no mechanistic studies have been reported to explain the elevated expression of Hsp70 in the subset of patient with reduced AF susceptibility: is it (epi)genetic or related to external factors such as drug treatment or different levels of cellular stress prior to surgery? Also, it is as yet unclear what could be the

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mechanism for Hsp70-related protection. Possibly, increased expression of Hsp70 protects against CABG-related ischemia/reperfusion injury, as observed in experimental studies (Trost 1998).

In addition, expression of Hsp has been studied in atrial tissue from AF patients in comparison with patients in SR. So far, these studies have yielded rather diverse results, likely due to several reasons including low patient numbers, diffuse patient characteristics (seldom sufficient lone AF patients), and noncomitant medication and inaccurate classification of AF. When comparing persistent/permanent AF to SR patients, some studies reported elevated expression of mitochondrial Hsp, being Hsp60 (Schafler et al 2002) or mortalin/mtHsp70 (Kirmanoglou et al 2004). Other Hsp were not investigated in these studies and it is thus unclear whether this upregulation specifically implies a mitochondrial stress response reflecting mitochondrial damage and/or a general cytoprotective response. In the study by Yang et al (2007) published in this issue of CS&C, elevated Hsp60 expression in permanent AF versus SR patients could not be confirmed. Furthermore, this study and our study (Brundel et al 2006) also show that the expression of several nonmitochondrial Hsp, including Hsp70 (HspA1A), Hsc70 (HspA8), Hsp40 (DnaJB1), and Hsp27 (HspB1), is not elevated in persistent/permanent AF patients compared to SR patients. Consequently, at this stage there is no consistent evidence that Hsp is upregulated in atrial tissue of persistent/permanent AF patients.

Only 2 studies have been published in which expression of a number of main Hsp in both paroxysmal AF and persistent/permanent AF were compared to SR (control). In the current study by Yang et al (2007), 8 PAF and 9 persistent/permanent AF patients were compared to 7 SR patients for cardiac expression of Hsp27, Hsp60, Hsp70, and Hsc70 levels. Although the study group was small and included AF patients with various underlying heart diseases, the authors found trends for higher expression of Hsc70 and especially Hsp27 (but not Hsp60 or Hsp70) in atrial tissue of PAF patients compared to persistent/permanent AF and SR patients. In a study on 17 PAF, 14 persistent/permanent AF and 13 SR patients, we recently found elevations of Hsp27 and to a lesser extent Hsp70 levels in PAF patients (Brundel et al 2006). Pooling of the patients from both studies (Fig 1) suggests that two Hsps, Hsp70 and Hsp27, are significantly elevated in PAF compared to persistent/permanent AF and SR, whereas the expression of Hsc70, Hsp40, Hsp60, and Hsp90 are not significantly changed in AF compared to SR. Certainly more studies and a proper meta-analysis thereof are required to substantiate these data. Yet, the finding that elevated Hsp27 (and maybe Hsp70) levels are specifically associated with PAF and not persistent/permanent AF may imply that some Hsp are involved in

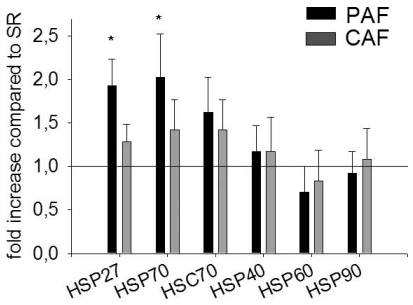

Fig 1. Expression of Hsp in cardiac tissue from patients with persistent/permanent AF (CAF) or paroxysmal AF (PAF) relative to the expression in cardiac tissue from patients in sinus rhythm (SR = 1.0). Data were pooled from Yang et al (2007) and Brundel et al (2006).

maintenance of SR under arrhythmogenic conditions and thus could be referred to as beat shock proteins.

Especially for Hsp27, evidence from additional studies support the hypothesis that it exerts a protective role against atrial remodeling and the progression of AF from PAF to more permanent forms of AF. As mentioned, we observed myolysis only in atrial tissue from persistent/permanent AF patients (Brundel et al 2002). The degree of myolysis inversely correlated with Hsp27 expression levels (but not Hsp70 levels) (Brundel et al 2006). In agreement with this, overexpression of Hsp27 (but not Hsp70) was found to result in protection against tachypacing-induced myolysis in an in vitro cell model for AF (Brundel et al 2006). In addition, we showed that Hsp27 localizes to myofibrils during in vitro tachypacing. Moreover, Hsp27 (but not Hsp70) overexpression also prevents AF-induced contractile dysfunction (Brundel et al 2006). A similar protection also could be obtained with the nontoxic Hsp (co)inducer geranylgeranylacetone (GGA). This drug-mediated protective effect was negated by siRNA-mediated knockdown of Hsp27 (Brundel et al 2006). Hsp27 therefore may represent the crucial Hsp to protect cardiac myocytes from AF-induced atrial remodeling and hence may delay or prevent progression from PAF to permanent AF. All of this would be consistent with the literature indicating that Hsp27 that protects against stress-induced disruption of F-actin and myofibril structures and/or accelerates recovery of cytoskeletal integrity after disruption (Lavoie et al 1995; Bryantsev et al 2002; Somara and Bitar 2004), an action that is strongly dependent on Hsp27 phosphorylation (Lavoie et al 1995). Our finding that a pseudophosphorylated Hsp27 mutant (Hsp27-DDD) was protective, but a nonphopshorylatable Hsp27 mutant (Hsp27-AAA) was not protective against AF-induced remodeling (Bryantsev et al 2002) further supports the idea that Hsp27 may protect against AF by stabilizing myofibrils through a direct interaction. However, direct evidence for such a mechanism is lacking so far.

The reason(s) for the differential expression of Hsp27

among patients still remains elusive. One option could be that (epi)genetic differences exist between individuals that differentiate patients such that some do and others do not progress from PAF to permanent AF. Alternatively, the differential expression may be a reflection of an exhaustion of the stress response with time. For intermittent periods of stress, such as during PAF in which arrhythmias are separated by nonstressful intervals of normal sinus rhythms, myocytes are capable of increasing Hsp amounts, as a result of which PAF patients overcome AF paroxysms without the induction of structural changes. The heat shock response, however, is known to attenuate with age or chronic stress (Demirel et al 2003) and when this happens PAF eventually may progress to permanent AF. Irrespective of the cause for the differential Hsp27 expression, in vivo experiments in dogs demonstrated that the pharmacological upregulation of the stress response is an effective therapeutic strategy to prevent electrical and structural remodeling and eventually the promotion of AF (Brundel et al 2006).

CONCLUSION

In summary, the stress response and in particular the induction of Hsp27 expression and phosphorylation may play a significant role in the attenuation of progression of AF. Certainly larger studies in patients would strengthen the observation that high Hsp27 expression consistently is associated with reduced progression of paroxysmal AF to permanent AF and establish Hsp27 as an actual beat shock protein. In this respect it is of pivotal importance that in these human studies patient groups are well defined. Molecular genetics and longitudinal follow-up of patients and/or in experimental models will be needed to reveal whether or not (epi)genetic factors or aging of the stress response underlie the higher Hsp27 levels in PAF versus persistent/permanent AF patients. In parallel, in vitro studies are needed to further establish the mechanism by which Hsp27 protects AF-mediated atrial remodeling and to screen for clinically applicable drugs that are able to selectively induce Hsp27 and/or its phosphorylation.

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