Basic Science for the Clinical Electrophysiologist

Proteomics of Atrial Fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, affecting 1.5% to 2.0% of the population in the developed world. The lifetime risk for the development of AF is ≈1 in 4 men and women aged ≥40 years.1,2 A 2.5- to 3.0-fold increase in the incidence of AF has been projected during the next 50 years,3 and with the aging population, both the prevalence and economic impact of AF are increasing progressively.4 In addition, current therapeutic options are suboptimal, some even proarrhythmic. For these reasons, it is of clinical importance to identify and elucidate the underlying mechanisms of this arrhythmia for the identification of new therapeutic targets.

The notion that AF begets AF was first described by Wijffels et al5 in 1995. They demonstrated that electrically induced AF for different lengths of time resulted in prolongation of the duration of AF. This observation, taken together with the clinical experience of paroxysmal AF in humans often progressing with time to the persistent form and of AF becoming more difficult to reverse when present for a period of time, generated great interest in the underlying molecular mechanisms responsible for maintaining AF. Although extensive basic research has been performed and the role of electric, structural, and contractile remodeling identified, the underlying mechanisms still require further exploration. The development of numerous animal models of AF, with clinically relevant disease duration of AF, has been a major advance during the past 12 years,8,9 and with the aging population, both the prevalence and economic impact of AF are increasing progressively.4 In addition, current therapeutic options are suboptimal, some even proarrhythmic. For these reasons, it is of clinical importance to identify and elucidate the underlying mechanisms of this arrhythmia for the identification of new therapeutic targets.

Structural changes that have been identified in atrial myocytes, secondary to prolonged AF in the goat10 and in heart failure dogs,11 include redistribution of nuclear chromatin, loss of myofibrils, accumulation of glycogen, alterations in mitochondrial shape and size, fragmentation of the sarcoplasmic reticulum, Z-line disruptions, and complete interruptions of myofibrils. Reversal of these structural changes after prolonged AF in the goat was shown to be a slow process and was incomplete after 4 months post-AF,12 thus demonstrating a different time course to the reversibility of both electric and contractile remodeling.

Electric, contractile, and structural remodeling are all established contributors to AF in both animal and human studies.5,7,8,10,12–25 Metabolic remodeling has been suggested as another factor contributing to the mechanisms underlying AF initiation and persistence5,15 and requires further investigation.

Proteomics

The term proteome was first coined in 1995 by Wilkins et al26 as the protein complement of a genome. Since then, technological advances in proteomics have been greatly expanded along with the use of this technology, especially in cardiovascular research.27 Although important information can be obtained from gene expression profiling, it should be noted that mRNA may not always correlate with protein levels and no information can be obtained from mRNA regarding posttranslational modifications (PTMs). These PTMs may be key for protein function and activity and need to be examined. Proteomics is the large-scale study of gene expression at the protein level. It enables the investigator to identify protein alterations responsible for the development and pathological outcome of disease, thus potentially leading to the discovery of new protein markers, so-called biomarkers for diagnostic or prognostic purposes and of novel molecular targets for drug discovery. This article highlights the recent developments in AF research using proteomic technologies.

Atrial Remodeling

AF leads to several different forms of remodeling within the atria: electric, contractile, and structural. During electric remodeling, the most marked effect is a striking reduction in the L-type Ca2+ current, which explains the shortening of the action potential duration and the loss of physiological rate adaptation of the duration of the action potential.7 In addition to the reduction in L-type Ca2+ current, a reduction in the transient outward current has been observed. Atrial contractility is decreased in AF, largely because of electric remodeling associated with a downregulation of the L-type Ca2+ current, and this follows the same time course as electric remodeling.8,9 Both these parameters have been shown to be fully reversible within 2 to 5 days.8

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1036
expressed in a related sample subject to a specific variation. In addition, proteomic technologies allow the elucidation of PTMs and identification of proteolytic events that are known to be of functional importance. These could then be used for downstream hypothesis-driven experimental studies. The targeted analysis of PTMs has been previously well described.27

Proteomics: The Key for Therapeutic Identification in AF?

With the promise that proteomics holds in elucidating such underlying mechanisms for potential therapeutic target in AF, how samples are processed and used are fundamental, along with the question that is being addressed. In addition, the choice of tissue used is highly important. As will become evident below, the majority of studies has used right atrial tissue because of ease of accessibility. However, the left atrium may be more important to examine, because AF is usually initiated and maintained in the left atrium and because the cycle length is generally, but not always, shorter in the left than in the right atrium during AF. Despite this, removal of left atrial tissue is not routinely performed at the time of cardiac surgery, as is often the case with the right atrial appendage (RAA). The first step embarked on when undertaking such experiments is sample preparation. How the samples are prepared influences the downstream technologies used and also the quality of the results. This is something that needs significant consideration, with regard to cardiac tissue because of the high degree of complexity and abundant proteins present. The majority of studies using proteomic technologies in the setting of AF has examined crude tissue preparations rather than focusing on particular subproteomes. Agnetti et al28 highlighted the importance of such detailed mining, which may be invaluable in identifying potential pathways to target in AF.

There are predominantly 2 main branches for protein separation in proteomics: gel-based and gel-free. These have been previously described in detail27,29,30 and will only be briefly discussed here.

Gel-Based Protein Separation by 2-Dimensional Gel Electrophoresis

Two-dimensional gel electrophoresis (2-DE) was described in 1975 by O’Farrell11 and is a well-established method for intact protein separation. In the first dimension, proteins are separated by their isoelectric point, which is the pH at which the protein has no net charge in an electric field. This is performed using predetermined immobilized pH gradients, chosen via the experimenter, through a process known as isoelectric focusing. After this, proteins are separated in the second dimension by their molecular weight (MW) using SDS-PAGE. On completion of the second dimension, gels are stained for protein visualization, followed by the use of bioinformatics software to highlight differentially expressed proteins, which can be excised for protein identification via mass spectrometry (MS). Along with the ability to separate ≈1000 to 1500 per gel, 2-DE also allows the visualization of PTMs that may be crucial to the protein function and activity. These PTMs manifest themselves as shifts in either the protein’s isoelectric point or molecular weight.11

Advances in 2-DE have led to the development of a technology known as differential in-gel electrophoresis. This was first introduced in 1997 by Unlü et al32 and has several advantages over traditional 2-DE. Differential in-gel electrophoresis uses 3 spectrally resolvable fluorescent dyes: cyanine (Cy) 2, Cy3, and Cy5, with which the protein samples are labeled before separation. As a result, multiple samples can be run on a single gel, thus minimizing potential gel-to-gel variations. Furthermore, an internal standard is run on each gel, which substantially increases the accuracy of quantitative analyses. This internal standard is a pool of all the samples in the experiment and is labeled with Cy2. On completion of the second dimension, gels are scanned using an appropriate laser scanner, with images obtained for each of the fluorescent dyes. The images are imported into specialized software for analysis, where differentially expressed proteins are highlighted for identification using MS. The Figure shows representative differential in-gel electrophoresis technology and fluorescent images from Cy3 and Cy5 gels, along with the corresponding overlay from human left atrial samples (A. I. De Souza, unpublished data, 2011).

Gel-Free Shotgun Proteomics

Shotgun proteomics uses 2 main separation techniques, high-performance liquid chromatography and tandem MS. Protein samples are enzymatically digested, producing peptides for downstream separation and analysis. The 2 most widely used methods of quantification for gel-free proteomics are stable isotope labeling of amino acids in cell culture and isobaric tagging for relative and absolute quantification. Stable isotope labeling of amino acids in cell culture depends on the incorporation of amino acids with substituted stable isotopic nuclei (eg, 13C, 15N). The resulting peptides containing either the light or heavy isotopes can then be discriminated by their mass difference. With isobaric tagging for relative and absolute quantification, protein digests are first labeled with the isobaric mass tag, followed by sample fragmentation. Fragmentation of the tag attached to the peptide results in the release of a low-molecular-mass reporter ion, which is specific to the tag used to label the sample.33 Isobaric tagging for relative and absolute quantification can be used with any sample to determine relative protein levels, and 4- and 8-plex reagents are available for multiplex experiments.

Limitations of Proteomic Technologies

There are no perfect separation methods, and limitations of these technologies should be considered. Although 2-DE has excellent resolving power, it is technically demanding and labor-intensive. Furthermore, hydrophobic and basic proteins are poorly solubilized in the buffers used for 2-DE, whereas high- and low-molecular-weight proteins can be poorly resolved. In addition, membrane proteins are considerably underrepresented because of solubility problems. On the other hand, although isobaric tagging for relative and absolute quantification may address some of these, it
Proteomics of Animal Models of AF

The use of animal models of AF has been crucial in uncovering basic mechanisms that underlie this resilient arrhythmia. Animal models, in general, are extremely useful tools when trying to decipher the underlying pathophysiology associated with a particular disease. They allow the investigator the opportunity to control and establish clearly matched groups, drug regimen, along with full access to tissue/cell samples, which is not feasible with clinical samples. However, all findings need to be further validated and may not always translate to findings in the human setting. The translation from bench to bedside may not be straightforward. In addition, there is no such thing as a perfect animal model of any disease, let alone AF.

To date, only 2 articles have been published using proteomic technologies to investigate protein changes in animal models of this arrhythmia. In 2004, Lai et al.35 used both genomic and proteomic approaches to investigate a porcine model of rapid RAA pacing (4 weeks). Although they emphasized the ability of 2-DE as a global approach examining many proteins, they only highlighted 3 protein spots that were elevated in left atrial tissue from AF versus sinus rhythm (SR) animals. The proteins identified were the ventricular isoform of myosin regulatory light chain (MLC2V), and the authors suggested that varying degrees of phosphorylation may account for the 3 spots observed and that these changes may be important for contractile force and cross-bridge cycling properties. No significant change was found with the atrial isoform of this regulatory light chain. We have performed proteomic studies of atrial profibrillatory remodeling in a canine model of congestive heart failure induced by ventricular tachypacing.31 Using 2-DE differential in-gel electrophoresis technology, we examined protein changes in isolated left atrial cardiomyocytes at 2 time points of remodeling: early after the onset of tachypacing (24 hours) and at near steady-state remodeling (2 weeks). Our findings also identified an increase in protein expression of MLC2V, with a parallel decrease in the corresponding atrial isoform. Furthermore, our study revealed potential mechanisms underlying atrial dysfunction and arrhythmias in this canine model of congestive heart failure, which included the identification of modulators of oxidative stress, changes in heat shock proteins (HSPs), contractile and structural proteins, and severe perturbations in proteins associated with metabolism. Examining time-dependent alterations highlighted failure of the initial adaptive response and the appearance of maladaptive changes in the development of a molecular, metabolic, and functional environment favorable for AF maintenance. It has been proposed that enhancing the HSP reaction, an adaptive response in this setting, may allow for the development of novel AF-preventing therapies.36

Proteomic Findings Obtained From Clinical (Human) Samples of AF

Proteomic analyses of human tissue have been more widely investigated than animal models of AF, but are still in its infancy, with only 6 articles being published in the same number of years. Table 1 summarizes the main details of these studies.

In 2006, Eiras et al.20 used 2-DE to examine contractile protein composition in atrial dilatation and AF compared with SR. As is evident, 2-DE allows a global overview of a large number of proteins rather than individually investigating known proteins one-by-one. Whether in this study there were other proteins that may be involved in the underlying pathophysiology of AF that were differentially expressed between the groups is unknown. This study used RAA samples from patients undergoing coronary artery bypass surgery and mitral or aortic valve surgery. The main findings from the proteomic aspect of this work were an increase in desmin and monophosphorylated troponin T in the AF group compared with either SR and SR with dilation or SR only, respectively. It is worth noting that no differences were noted between SR and SR.
with atrial dilation with the proteins that were presented in this study. Atrial dilation can either contribute to or be a result of AF, so more in-depth studies examining this may be of potential interest.

Following on from this study, Mayr et al. combined metabolomics and proteomics to examine underlying mechanisms associated with AF. Once again, 2-DE was used with RAA samples from patients undergoing surgery for valvular disease, which were either in SR or had persistent AF. For the purpose of this review, only the proteomic findings will be presented. From 1500 proteins that were resolved, 17 proteins were found to be differentially expressed and identified by MS. These included myofilament-associated proteins, enzymes involved with glucose and lipid metabolism, along with key respiratory chain proteins, antioxidants, and HSPs. Structural damage was highlighted in the AF group by fragmentation of the proteins actin, desmin, and tubulin.

García et al. used 2-DE to identify differentially expressed proteins that they hoped could be related to the development of AF. They also used RAA biopsies from patients undergoing either valve surgery or coronary artery bypass surgery. From 2300 protein spots that were resolved, they found 22 proteins that were differentially expressed between the groups. They revealed downregulation of the structural protein fibulin-1, a handful of enzymes, and alterations in small HSPs in AF. Interestingly, only 1 enzyme associated with metabolism (glycogen phosphorylase) was observed in this proteomic screen. The authors proposed that the decrease in fibulin-1 may explain the increase in spontaneous calcium release from the sarcoplasmic reticulum in AF, which may contribute to an increase in the number of afterdepolarizations, because fibulin-1 has been shown to reduce intracellular calcium levels. This protein has not been identified in any other proteomic studies.

As mentioned above, whether the use of left atrial over right atrial tissue would be preferable, and perhaps more valuable in terms of results, in such proteomic studies in AF was something that warranted further investigation. Modrego et al. compared protein expression in both left atrial appendage and RAA taken from patients with mitral valve disease in the presence and absence of AF. The authors focused on proteins associated with 3 main biological functions: cytoskeleton, energetic metabolism, and cardiac cytoprotection. Within these categories analyzed, few proteins were found to be differentially expressed between the atria from either SR or AF samples. For example, HSP27, GRP78, Ser/Thr phosphatase isotype 1, and glutathione-S-transferase were all downregulated in the left atrial appendage compared with RAA in AF samples, but no difference was observed in the SR group. Furthermore, ubiquinol cytochrome C reductase was upregulated in left atrial appendage versus RAA in SR patients, but this difference was abolished in the AF group. A similar pattern was seen for desmin isoforms 3/5 and α-actin isotype 1. This perhaps suggests that because of the small differences observed between the atria, with the particular proteins focused on for this study, your choice of atria to study makes little difference. Whether this is the case for proteins out of the realm of this study would need further investigation. Proteins in all classifications studied were found to be differentially expressed between AF and SR groups, with the majority of changes present in both atria. Cytoskeletal proteins, desmin and actin, were found to be increased, and this corresponded to findings in other studies. In addition, the metabolic enzyme, 3-oxoacid transferase, was upregulated in AF (left atrial appendage only), consistent with other groups. This enzyme plays an important role in ketone body metabolism, suggesting a potential increased role of ketone bodies as a substrate for ATP production in AF.

Recent work by Goudarzi et al. zoomed in on the mitochondrial proteome in preference to whole tissue homogenates in human RAA. The authors focused on mitochondrial proteomics, predominantly as a result of an earlier study by Mayr et al. This is of particular importance because a role for metabolic remodeling has been suggested in the pathophysiology of AF, along with mitochondrial dysfunction. An MS approach was used in this study, and from >700 proteins identified, 32 differentially expressed between the AF versus non-AF tissues. Increased expression of metabolic enzymes, structural proteins, antioxidants, and HSPs was observed in AF versus non-AF samples. Increased expression of CRAB and desmin has been demonstrated previously, whereas expression of

Table 1. Details of Published Proteomic AF Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Type</th>
<th>Underlying Pathology</th>
<th>AF Classification</th>
<th>Protein Extraction</th>
<th>Proteomic Technology/ Separation Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eiras et al.</td>
<td>RAA</td>
<td>CAD and valve disease</td>
<td>Persistent AF</td>
<td>Whole tissue extract</td>
<td>2-DE (pH 4–7 L), Coomassie blue</td>
</tr>
<tr>
<td>Mayr et al.</td>
<td>RAA</td>
<td>CAD and valve disease</td>
<td>Permanent AF</td>
<td>Whole tissue extract</td>
<td>2-DE (pH 3–10 NL), silver</td>
</tr>
<tr>
<td>García et al.</td>
<td>RAA</td>
<td>CAD and valve disease</td>
<td>Mix of paroxysmal, persistent and permanent AF</td>
<td>Whole tissue extract</td>
<td>2-DE (pH 4–7 L), SYPRO ruby</td>
</tr>
<tr>
<td>Modrego et al.</td>
<td>RAA and LAA</td>
<td>Mitral valve disease</td>
<td>Permanent AF</td>
<td>Whole tissue extract</td>
<td>2-DE (pH 4–7 L), silver</td>
</tr>
<tr>
<td>Goudarzi et al.</td>
<td>RAA</td>
<td>CAD and valve disease</td>
<td>Mix of paroxysmal, persistent and long standing AF</td>
<td>Mitochondrial extract</td>
<td>LC-MS-MS</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>RAA</td>
<td>RHD</td>
<td>AF for at least 6 months</td>
<td>Whole tissue extract</td>
<td>2-DE (pH 3–10 NL), Coomassie blue</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; RAA, right atrial appendage; CAD, coronary artery disease; 2-DE, 2-dimensional gel electrophoresis; LAA, left atrial appendage; LC-MS, liquid chromatography mass spectrometry; L, linear; NL, nonlinear; RHD, rheumatic heart disease.

Coomassie blue, silver, and SYPRO ruby are different postelectrophoretic staining methods for protein visualization after 2-DE.
the metabolic enzyme, glyceraldehyde 3-phosphate dehydrogenase, differed between this and the Mayr study. The authors suggest that this difference could be because of the different sample preparations used—total versus mitochondrial protein preparations. Unfortunately, with this study, no details are given regarding PTMs of proteins, which is one of the advantages of examining proteins using 2-DE, as such modifications can be easily observed. As previously mentioned, PTMs are crucial to the protein function, and thus it is important to know the status of the protein when hypothesizing about potential mechanistic changes. The authors conclude that the zooming on mitochondrial proteins specifically may be important in the hunt for AF-associated biomarkers because it has been shown that mitochondrial and mitochondrial-associated proteins are involved and affected during the onset of AF. This study included 3 different classifications of AF: paroxysmal, persistent, and long-standing. Whether this blend of differing AF status masked any differences requires further investigation.

Finally, Huang et al used 2-DE to examine protein changes in RAA samples from patients with rheumatic heart disease with or without AF. Those in the AF group had a significantly larger left atrial size compared with those in SR. From ≈800 proteins resolved, they found 30 to be differentially expressed, with 19 identified by MS-MS. They grouped these into 3 classifications: cytoskeletal and myofilament-associated proteins, proteins involved with energy metabolism, and those linked to oxidative stress. Although proteins associated with energy metabolism have been demonstrated by other proteomic studies, only 1 protein, pyruvate kinase, overlapped between this study and that of Goudarzi et al. Furthermore, this and previous work by Mayr et al highlighted differential expression of the antioxidant peroxiredoxin 1, being up- and downregulated, respectively. These differing findings may be because of several reasons, which will be discussed later.

**Limited Overlap of Differentially Expressed Proteins**

It is clear that although several studies have been performed using clinical samples, with patient populations with similar underlying cardiac disease, there has been little overlap between the findings. In reality, whether all the publications to date have presented all the potential differentially expressed proteins they found or just a particular subset is unknown, so direct comparisons are difficult to interpret. Table 2 highlights proteins that have been found to be differentially expressed in the human proteomic analyses published to date, focusing on those that can be grouped by function only. As is evident, from the 48 proteins tabulated, only 9 are present across >1 group, and not all these are in agreement with regard to being up- or downregulated. There are many factors that could contribute to this, and each study should be evaluated on an individual basis. First, the underlying pathology varies between the groups, along with the type of AF. Some studies used samples from patients with persistent AF, others with permanent AF, and others with a mix of both these and paroxysmal AF. Determining specific mechanistic changes with such mixed pathologies would be extremely difficult and may even mask potential differences. Five of the 6 studies used 2-DE, but using differing pH gradients for the protein separation in the first dimension (3 used pH 4–7 linear and 2 used pH 3–10 nonlinear) and 3 different post-electrophoretic stains (Coomassie blue, silver, and SYPRO ruby), all with differing sensitivities. Both these parameters would have downstream effects on the protein changes determined. Furthermore, although 5 of the 6 also used crude tissue preparations, all were with different isolation buffers, and thus direct comparisons are difficult to digest. Finally, different PTMs, which are important to the protein function, may differ between the studies and thus warrants further investigation.

It is clear that although these studies provide a platform for developing our understanding of the mechanisms underlying AF; proteins of interest require further validation in larger patient cohorts to confirm initial findings. Even if these markers could be identified, it would be questionable whether there is any causal relation to AF or whether they are rather because of the underlying structural heart disease. Ideally, protein markers related to AF but unrelated to left atrial dimensions would be sought, and this will be the next challenge. Furthermore, if diagnostic markers are to be clinically beneficial, they need to be found in easily accessible tissue, such as blood. Whether the proteins found in these studies are released into the systemic system and could be potential biomarkers of AF requires further investigation.

**Conclusions**

Global protein expression studies enable us to identify multiple changes and thus generate potential targets for further downstream investigations. Significant developments in proteomic technologies during the past decade have advanced the field and proteome coverage that can be achieved, thus enabling the generation of larger data sets. Such data sets may aid our understanding of the pathophysiological mechanisms associated with AF. Differentially expressed proteins identified from such proteomic experiments may highlight novel biomarkers for diagnostic/prognostic purposes or potential therapeutic targets for downstream AF drug discovery.

However, it is evident from the limited studies and the patchy nature of the findings that have been published so far that proteomics is clearly underdeveloped in the electrophysiology arena. Proteomics, similar to metabolomics, is generally not hypothesis driven but used to generate hypotheses. To date, however, there seems to be a lack of hypotheses generated by proteomic studies regarding pathophysiological mechanisms in AF, which clearly needs to be addressed. Future studies need to be performed at a cellular level to elucidate whether these changes have a functional impact on the underlying mechanisms responsible for the disease being studied. Complementary studies (eg, transgenic animals and gene transfer) to extrapolate the proteomic findings to either a cellular or animal model of AF with the specific intervention could be used to first see whether the targeted proteomic changes can be modified and second, whether this leads to AF suppression. In addition, the integration of descriptive proteomic findings with functional changes may provide important insights into pathophysiological mechanisms.

Undoubtedly, there is need for much further study and investment into this area of research because it offers a
Table 2. Selected Differentially Expressed Protein Changes (of Known Function) Associated With AF in Published Studies From 2006 to 2011 Using Proteomic Technologies

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Protein Name</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat shock proteins</td>
<td>Heat shock protein β-7</td>
<td>Eiras et al&lt;sup&gt;20&lt;/sup&gt; Mayr et al&lt;sup&gt;15&lt;/sup&gt; Garcia et al&lt;sup&gt;37&lt;/sup&gt; Modrego et al&lt;sup&gt;38&lt;/sup&gt; Goudarzi et al&lt;sup&gt;39&lt;/sup&gt; Huang et al&lt;sup&gt;40&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Crystallin αβ</td>
<td>↔</td>
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<td></td>
<td>HSP60</td>
<td>↔</td>
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<tr>
<td></td>
<td>HSP27</td>
<td>↔</td>
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<tr>
<td></td>
<td>GRP78</td>
<td>↑ (RAA only)</td>
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<tr>
<td></td>
<td>Heat shock protein β-6</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Heat shock protein β-3</td>
<td>↑</td>
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<tr>
<td></td>
<td>HSP 75kDa, mitochondrial</td>
<td>↑</td>
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<tr>
<td>Antioxidative proteins</td>
<td>Peroxiredoxin 1</td>
<td>↓</td>
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<tr>
<td></td>
<td>Peroxiredoxin 3</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>Peroxiredoxin 6</td>
<td>→</td>
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<tr>
<td></td>
<td>Superoxide dismutase</td>
<td>→</td>
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<tr>
<td></td>
<td>Glutathione S-transferase</td>
<td>↑</td>
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<tr>
<td>Cytoskeletal proteins</td>
<td>Desmin</td>
<td>↑ (Desmin / actin)</td>
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<tr>
<td></td>
<td>Tubulin</td>
<td>↑ (fragments)</td>
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<tr>
<td></td>
<td>Actin</td>
<td>↑ (fragments)</td>
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<tr>
<td></td>
<td>Destrin</td>
<td>↑</td>
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<tr>
<td></td>
<td>Cofilin-1</td>
<td>↓</td>
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<tr>
<td></td>
<td>Fibulin-1</td>
<td>↑</td>
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<tr>
<td>Contractile proteins</td>
<td>Troponin T</td>
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<td></td>
<td>Troponin I</td>
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<td>Myosin light chain 1, ventricular</td>
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<td></td>
<td>Tropomyosin α-chain</td>
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<td></td>
<td>Tropomyosin β-chain</td>
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<tr>
<td></td>
<td>Myosin light chain 1, atrial</td>
<td>↑</td>
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<tr>
<td>Metabolic enzymes</td>
<td>Triosephosphate isomerase</td>
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<td></td>
<td>Glyceraldehyde-3-phosphate dehydrogenase</td>
<td>↑</td>
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<tr>
<td></td>
<td>3-oxoacid transferase</td>
<td>↑ (LAA only)</td>
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<tr>
<td></td>
<td>NADH dehydrogenase (ubiquinone) flavoprotein 1</td>
<td>↑</td>
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<tr>
<td></td>
<td>Ubiquinol cytochrome C reductase core protein 1</td>
<td>↑</td>
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<td></td>
<td>Very long-chain–specific metabolism acyl-CoA dehydrogenase, mitochondrial</td>
<td>↑</td>
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<tr>
<td></td>
<td>Δ(3,5)-b(2,4)-dieneoyl-CoA isomerase, mitochondrial</td>
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<tr>
<td></td>
<td>Pyruvate kinase isozymes M1/M2</td>
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<td></td>
<td>NADH dehydrogenase (ubiquinone) 1 α subcomplex subunit 10</td>
<td>↑</td>
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<tr>
<td></td>
<td>NADH dehydrogenase (ubiquinone) 1 α subcomplex subunit 13</td>
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<tr>
<td></td>
<td>Pyruvate dehydrogenase E1 β subunit</td>
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<td></td>
<td>ATPase β chain</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Creatine kinase M chain</td>
<td>↑ (RAA only)</td>
</tr>
<tr>
<td></td>
<td>Glycogen phosphorylase</td>
<td>↓</td>
</tr>
</tbody>
</table>
potential wealth of knowledge, uncovering biochemical and metabolic pathways and downstream pharmacological targets.

Disclosures

None.

References


Proteomics of Atrial Fibrillation
Ayesha I. De Souza and A. John Camm

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