Reprogramming of the Human Atrial Transcriptome in Permanent Atrial Fibrillation
Expression of a Ventricular-Like Genomic Signature

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Abstract—Atrial fibrillation is associated with increased expression of ventricular myosin isoforms in atrial myocardium, regarded as part of a dedifferentiation process. Whether reexpression of ventricular isoforms in atrial fibrillation is restricted to transcripts encoding for contractile proteins is unknown. Therefore, this study compares atrial mRNA expression in patients with permanent atrial fibrillation to atrial mRNA expression in patients with sinus rhythm and to ventricular gene expression using Affymetrix U133 arrays. In atrial myocardium, we identified 1434 genes deregulated in atrial fibrillation, the majority of which, including key elements of calcium-dependent signaling pathways, displayed downregulation. Functional classification based on Gene Ontology provided the specific gene sets of the interdependent processes of structural, contractile, and electrophysiological remodeling. In addition, we demonstrate for the first time a prominent upregulation of transcripts involved in metabolic activities, suggesting an adaptive response to increased metabolic demand in fibrillating atrial myocardium. Ventricular-predominant genes were 5 times more likely to be upregulated in atrial fibrillation (174 genes upregulated, 35 genes downregulated), whereas atrial-specific transcripts were predominantly downregulated (56 genes upregulated, 564 genes downregulated). Overall, in fibrillating atrial myocardium, functional classes of genes characteristic of ventricular myocardium were found to be upregulated (eg, metabolic processes), whereas functional classes predominantly expressed in atrial myocardium were downregulated (eg, signal transduction and cell communication). Therefore, dedifferentiation with adoption of a ventricular-like signature is a general feature of the fibrillating atrium. (Circ Res. 2005;96:1022-1029.)

Key Words: atrial fibrillation ■ gene expression ■ atrial myocardium ■ functional genomics

Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with extensive structural, contractile, and electrophysiological remodeling,1 stabilizing AF in the long run. Because current pharmacological treatment of AF is limited by ventricular proarrrhythmia and inefficacy to prevent recurrences of AF, understanding the molecular events of these remodeling processes is essential for the development of new targeted therapeutic interventions. Even though knowledge of genes involved in remodeling processes exists on a gene-by-gene basis including transcripts of the extracellular matrix compartment,2 ion channels,1,3 and signal transduction molecules,4 microarray analysis offers a broader and unbiased approach to identify pathophysiologically relevant pathways. Therefore, we performed a systematic functional analysis of gene expression in permanent atrial fibrillation (pmAF) based on information from the Gene Ontology (GO) database to relate expression changes of single transcripts to known remodeling processes.

Moreover, atrial fibrillation has been shown to be associated with an atrial-to-ventricular switch by expressing ventricular myosin isoforms, which is regarded as part of a dedifferentiation process of fibrillating atrial myocardium.5

To explore the hypothesis that pmAF leads to upregulation of ventricular transcripts other than those encoding for contractile proteins, we used a genome-wide approach to compare atrial mRNA expression of patients with pmAF to atrial mRNA expression of patients with sinus rhythm (SR) as well as to ventricular (LV) gene expression. Our findings indicate

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that pmAF leads to repression of atrial transcriptional activity and induces a ventricular-like genomic signature in atrial myocardium.

Materials and Methods

Patients and Tissue Selection
Right atrial appendages were obtained from 30 patients undergoing open heart surgery for valve repair or coronary artery bypass grafting. Of these, 10 patients had pmAF defined as duration of AF longer than 3 months as documented by ECG, whereas 20 patients had no history of AF and were in SR when open heart surgery was performed. All patients gave written informed consent. Transtural LV transverse-section biopsial ventricular wall from subepicardium to subendocardium were obtained from 5 nonfailing donor hearts that were not transplanted because of palpable coronary calcifications. After excision, all tissue specimens were immediately frozen in liquid nitrogen and stored at −80°C. The investigation was approved by the Institutional Review Board. Detailed patient characteristics are listed in online Table I (available at http://circres.ahajournals.org).

mRNA Preparation and Hybridization to Affymetrix U133A+B Oligonucleotide Microarrays
Total RNA was purified from homogenized deep-frozen tissue samples following the TRIZOL standard protocol as described by the manufacturer (GibcoBRL) and quantified by photometry. Then, 150 ng total RNA was used for quality control using the RNA 6000 Nano LabChip kit and Agilent Bioanalyzer 2100 (Agilent Technologies).

Synthesis of double-stranded cDNA and of biotinylated cRNA probes as well as subsequent steps of hybridization, washing, and staining followed instructions provided by Affymetrix.

Data Extraction and Statistical Analysis
One set of U133A+B chips (together representing 44 928 probe sets) was used for each human heart sample. The original data files have been deposited in Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo) and are accessible through GEO Series accession number GSE2240. All U133 GeneChips passed quality control to eliminate scans with abnormal characteristics, ie, abnormal low or high dynamic range, high perfect match saturation, high pixel noise, grid misalignment problems, and low mean signal-to-noise ratio. Low level and statistical analysis was done using R 1.8.1. Microarray data of all atrial and ventricular samples was normalized simultaneously using robust multiarray average (RMA) implemed in Bioconductor’s “affy”-package. Probe sets with “absent” calls in more than 50% of tissue samples in either group (SR, pmAF, or LV) were filtered out and omitted from further analysis. To determine differentially expressed genes between the groups, Welch t test was applied. Considering multiple hypothesis testing, differences in expression were regarded as statistically significant if a false discovery rate (FDR) of q < 0.03 was achieved.7 Duplicate probe sets within the gene lists were eliminated by means of the “MatchMiner” software tool.8 Hierarchical clustering was performed by using average linkage algorithm with Euclidian distance measure comprised in the Genesis software.9 Functional classification was based on the “cellular component,” “biological process,” and “molecular function” of GO using “FatiGO.”10 After accounting for uncharacterized transcripts, up to 70% of all known genes were annotated across all GO levels. As many genes are not annotated at a particular level of ontology, three adjacent ontology levels are presented to increase the amount of information.

Validation by Semi-quantitative Real-Time Reverse Transcription PCR
Expression patterns of 13 genes, selected with respect to the central role in the proposed working model of AF (Figure 3) were validated by real-time SYBR-Green PCR. A detailed list of the genes examined by RT-PCR including the design of the primers and a descrip-
EDNRB; online Tables 3 and 5, “cellular component” and “molecular function,” level 5).

There is also evidence for contractile remodeling in pmAF, as troponin I1 (TNNI1) was downregulated. Moreover, deregulation of several genes linked to a cardiomyopathic phenotype was observed (downregulation of ErbB2, ErbB3, and ErbB4; downregulation of lamin A/C (LMNA) and several genes involved in the formation of the dystrophin glycoprotein complex, including dystrophin, dystroglycan 1, δ-sarcoglycan, and β2-syntrophin; online Table 3).

Regarding electrophysiological remodeling, 5 transcripts encoding for subunits of l-type calcium channels were found to exhibit downregulation (online Table 3). The repolarization process was also disturbed, reflected in deregulation of several potassium channel transcripts (KCNN2, KCNJ3, KCNJ5, KCNQ1, and KCNK3). In addition to changes of sarcolemmal ion channels, sarcoplasmic Ca²⁺ handling is expected to be altered by upregulation of RYR3 (a dominant-negative splice variant of the ryanodine receptor) and downregulation of ATP2A2 (sarcoplasmic Ca²⁺-ATPase). Changes in expression levels of KCNK3 and 12 additional transcripts were validated using real-time RT-PCR assays, confirming expression changes for 10 of 13 selected transcripts (Table 1).

Energy processes emerged as further area of pronounced changes, as 5 of 12 GO classes for biological processes found to be deregulated in pmAF serve metabolic functions (online Table 4, “biological process,” level 5). Except for fatty acid and glycoprotein metabolism, there was a trend toward upregulation for all metabolic classes, as identified by GO (Figure 1 and online Table 4, “biological process,” level 5).

Comparison of atrial- and ventricular-predominant transcripts with the genes deregulated in pmAF revealed that the ventricular-type transcription pattern of fibrillating atrial myocardium is mainly the result of downregulation of atrial-specific transcripts and only to a lesser degree of upregulation of ventricular-specific transcripts (Table 2).

Expression of a ventricular signature is also reflected in GO classes, as functional classes previously shown to be characteristic of atrial myocardium, such as those involved in signal transduction and cell communication, were downregulated in pmAF, whereas functional classes overrepresented in ventricular myocardium (eg, metabolic processes) were found to be upregulated in pmAF (Figure 1 and online Table 4, “biological process”).

**Discussion**

The present study is the first analysis of gene expression changes on a whole-genome level in human atrial fibrillation, providing specific gene sets underlying distinct remodeling processes and uncovering, for the first time, a prominent adaptation to long-term metabolic stress. Upregulation of ventricular-predominant metabolic genes as well as repression of atrial-specific transcriptional activity both contributed

<table>
<thead>
<tr>
<th>TABLE 1. Validation of Expression Changes Observed in Microarray Experiments With RT-PCR</th>
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<tr>
<td>Affymetrix ID</td>
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<tr>
<td>214316_s_at</td>
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<td>204312_s_at</td>
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Mean values of fold-changes were compared between all SR and pmAF tissue samples (same samples as for array experiments).
to the ventricular-like genomic signature in fibrillating atrial myocardium.

**Transcriptional Basis of Distinct but Interconnected Remodeling Pathways in Fibrillating Atrium**

Remodeling in AF has been recognized to consist of 3 major processes, affecting structural, contractile, and electrophysiological properties. Analysis based on GO identified major changes in several genes connecting these seemingly distinct areas of remodeling. For instance, downregulation of TIMP3 represents a possible link between extracellular matrix remodeling and depressed contractile function, as TIMP3-deficient mice have recently been shown to develop a cardiomyopathic phenotype with chamber dilatation and contractile dysfunction. Likewise, conditional mutations of the ErbB2 receptor in myocardium lead to dilated cardiomyopathy, and prolonged exposure of cultured human and rat cardiomyocytes with anti-ErbB2 antibody causes loss of contractile function. Thus, downregulation of the ErbB2 receptor might not only provide an explanation for extracellular matrix remodeling with dilatation in pmAF, but may also be linked to the contractile dysfunction that persists for some time after cardioversion of AF. Similarly, downregulation of several genes involved in the formation of the dystrophin glycoprotein complex, which is essential in providing the mechanical link from the intracellular cytoskeleton to the extracellular matrix, would also promote a cardiomyopathic phenotype.

Other mechanisms, like endothelin activation, initiated to compensate for the contractile insufficiency in pmAF, may also be maladaptive in the long run by promoting cardiac fibrosis through activation of TGF-β. Alterations of TGF-β signaling have been connected to a number of cardiovascular and fibrotic diseases. Loss-of-function mutations in TGF-β receptor 2 and fibrillin 1 have recently been linked to Marfan syndrome, an extracellular matrix disorder associated with atrial dilatation and atrial fibrillation. This suggests that the observed downregulation of both TGF-β receptor 2 (TGFBR2) and fibrillin 1 (FBN1) in pmAF might provide the link to extracellular matrix remodeling. Interestingly, one of our AF patients had been diagnosed with Marfan syndrome based on the clinical phenotype. Figure 2 demonstrates individual measurements for FBN1 and TGFBR2 in all tissue specimens, illustrating that downregulation of these genes was not restricted to the patient with Marfan syndrome but common to all AF patients. Considering further genes for which mutations are associated with hereditary atrial fibrillation, it is important to note that Sébillon et al identified a lamin A/C missense mutation with early-onset AF as presenting symptom, preceding the development of dilated cardiomyopathy. Based on the observation that the same genes that have been shown to lead to hereditary forms of dilated atrial chambers and contractile dysfunction are also downregulated in our patients with acquired, valvular AF (eg, LMNA, TGFBR2, FBN1, TIMP3, and members of the dystrophin complex), it is tempting to speculate that these genes also contribute significantly to atrial dilatation and contractile dysfunction in acquired AF. Although transcriptional changes observed in the present study are the consequence rather than the cause of pmAF, it appears that some of the changes that occur initially to provide a substrate for pmAF are similar to alterations in the course of AF supporting the concept that AF promotes its own substrate (“AF begets AF”).

**TABLE 2. Comparison of Atrial- and Ventricular-Specific Gene Expression in Myocardium to Genes Differentially Expressed in pmAF (Atrium Only)**

<table>
<thead>
<tr>
<th>Atrial-Specific Transcripts</th>
<th>Ventricular-Specific Transcripts</th>
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<tr>
<td>Transcripts upregulated in AF</td>
<td>56</td>
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<tr>
<td>Transcripts downregulated in AF</td>
<td>564</td>
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</tbody>
</table>

Downregulation in pmAF involved mainly atrial-specific transcripts, whereas transcripts predominantly found in ventricular myocardium were 5 times more likely to be up than down-regulated in atrial fibrillation.
In addition to the well-established remodeling processes affecting contractile, electrophysiological, and structural properties, we identified prominent deregulation of genes belonging to metabolic classes, suggesting changes in atrial bioenergetics with an increased energy demand in pmAF. In line with this finding, cellular hypertrophy is among the most consistent histological findings in fibrillating atrial tissue, suggested to reflect an adaptation to altered environmental conditions. Induction of AF has been shown to increase atrial oxygen consumption and coronary flow almost 3-fold, possibly the result of high wall stress and the dramatic increase in atrial depolarization frequency with enhanced energy demand for ion transport processes including calcium-handling to maintain physiological cytosolic ion levels. In a goat model of AF, phosphocreatine decreased by 60% in atrial myocytes after 1 week of AF, indicating enhanced demand for high-energy phosphates. As phosphocreatine levels increased thereafter and returned to baseline levels after 16 weeks of AF, compensatory mechanisms are assumed to be activated to restore the metabolic balance between energy demand and supply in pmAF. Our finding of prominent upregulation of metabolic processes as identified by GO strongly supports this concept (Figure 1). The well-established atrial-to-ventricular switch of myosin isoforms might also be related to the increase in metabolic demand in pmAF: contraction has been shown to be 5-fold more economical in ventricular than atrial myocardium, mainly because of the greater relative contribution of the slow ventricular β-myosin heavy chain (MHC) isoform compared with the fast atrial α-MHC transcript in ventricular muscle. Thus, increased expression of the ventricular-predominant slow β-MHC isoform in fibrillating atrial myocardium may represent an attempt to improve economy of contraction.

**Generalized Transcriptional Downregulation in Permanent AF, Likely Mediated by Altered Calcium Homeostasis**

In pmAF, we observed prominent downregulation of transcriptional processes with more than twice as many genes being downregulated than upregulated. The predominant pattern of transcriptional repression is reflected in downregulation of functional classes linked to transcriptional processes as identified by GO. In addition, our data are in agreement with the first microarray study in an animal model of AF and a recent study in human myocardium, also suggesting predominant downregulation of transcription in AF.

Even if transcript levels of several myocyte-specific markers were unchanged between SR and pmAF samples (cardiac myosin heavy polypeptide 7, cardiac troponin T2, and calsequestrin 2; data not shown), suggesting that the cardiomyocyte compartment has not been diminished in pmAF, a reduction in cardiomyocyte number might still have occurred, as myolysis and cellular hypertrophy are well-established features of pmAF. Therefore, because of simultaneous reduction of myocyte number and increase in the expression of cardiac-specific genes per single cell no change in overall cardiac-specific gene expression might be apparent in pmAF samples. As laser microdissection has not been performed, we cannot determine transcription on a myocyte level. However, the degree of AF-induced myolysis is expected to be modest and cannot fully account for the pronounced reduction of transcriptional processes.

As to the mechanisms regulating gene transcription in myocardial cells, calcium homeostasis, contractile function, and stretch have been shown to play key roles. Because all these factors are altered after prolonged AF, they must be considered potential initiators of altered gene transcription. Specifically, calcium is a potent activator of cardiac gene transcription. Although Ca\(^{2+}\) overload has clearly been established as an early event after initiation of AF, there is no direct experimental evidence to support the notion of a chronic calcium overload state in persistent and pmAF. In fact, after an initial increase, steady-state calcium levels begin to decrease as early as 30 minutes after initiation of AF and normalize within the first 48 hours. Moreover, Ausma and coworkers demonstrated decreased steady-state calcium levels after 16 weeks of AF in goats. Likewise, isolated
canine atrial myocytes displayed decreased resting intracellular calcium levels and blunted calcium transients after a 4-week period of rapid atrial pacing. The idea that high intracellular calcium levels may no longer be present after prolonged AF is strongly supported by the experimental and clinical observation that calcium-channel blockers like verapamil are useful in preventing calcium-overload and electrical remodeling only when given very early or during paroxysms of AF but fail to have beneficial effects in persistent and permanent AF. Given our observation of transcriptional repression of several calcium-dependent pathways including calcineurin-NFATc3, MAPK, and CaMK in pmAF and the central, well-established role of calcium as a regulator of gene expression, we propose that the decrease in transcription during prolonged episodes of AF results from alterations in calcium homeostasis with alterations in the spatiotemporal properties of the calcium transients (Figure 3).

Permanent AF Leads to a Ventricular- and Fetal-Like Genomic Signature in Atrial Myocardium

Atrial and ventricular myocardium exhibit fundamental differences on a morphological, ultrastructural, and functional basis, because ventricular myocardium, above all, functions as contractile pump, thereby contrasting to the prominent neuroendocrine and regulatory functions of atrial myocardium.

In AF, an atrial-to-ventricular switch has been shown for some individual genes in atrial samples of hypertrophied and cardiomyopathic hearts, eg, contractile protein isoforms like myosin heavy chains. It has been hypothesized that the atrial-to-ventricular switch of MHCs observed in these pathophysiological conditions is the result of the rise in intra-atrial pressure, similar to hemodynamic changes observed during postnatal development. Our approach of microarray analysis with simultaneous examination of thousands of genes extends these observations in single genes to a general pattern of regulation toward a ventricular gene program in AF. Central in the changes are genes related to energy metabolism, also reflected in ultrastructural changes occurring during long-term AF that resemble those seen in fetal cardiomyocytes and in hibernating myocardium. This led Ausma et al to put forward the concept of “cellular adaptation through dedifferentiation” in AF, where a fetal phenotype is thought to facilitate cardiomyocyte survival during stress conditions including stretch and ischemia. The coordinated transcriptional downregulation of enzymes controlling fatty acid oxidation and concomitant upregulation of enzymes involved in glucose utilization reported in our study is consistent with reinduction of a fetal energy metabolic program (Figure 1 and online Table 4). Equally, ultrastructural characteristics in AF like the perinuclear accumulation of glycogen are seen in fetal cardiomyocytes and are suggestive of a metabolic shift, as the glycogen storage is thought to act as supply for

![Figure 3. Working model for transcriptional changes in pmAF. The high rate of atrial activation in AF increases cellular calcium loading, mainly by calcium influx through sarcolemmal calcium channels. To compensate for the effect of increased rate on cellular calcium load, L-type calcium channel subunits are transcriptionally down-regulated. Likewise, reduced calcium transients are the result of deregulation of SR-calcium-handling proteins, including upregulation of RyR3 (inhibits RyR2). Alterations in calcium homeostasis with smaller calcium transients and reduced steady-state calcium levels may lead to downregulation of calcium-dependent signaling, including calcineurin-NFAT, MAPKs, and CaMK pathways. As a consequence, a widespread repression of transcriptional processes ensues, exemplified by downregulation of key transcription factors like NFAT, CREB, STAT3, STAT5, and NFκB. Diminished calcium transients and rapid electrical activation lead to contractile dysfunction. Likewise, structural remodeling contributes to contractile dysfunction and increased wall stress. Increased hemodynamic load imposed on the atria activates a metabolic gene program. Given the high metabolic demand of fibrillating atrial myocardium, suppression of transcriptional processes may be an attempt to save energy by limiting protein synthesis to a smaller number of selected proteins, possibly similar to the changes in chronic hibernation.](image-url)
high-energy–demanding processes and to enhance mechani-
cal cell stability. Thus, the observed expression of a
ventricular and fetal gene program with upregulation of
metabolic genes and downregulation of atrial-specific genes
appears to be an integral part of this adaptive response to
pmAF. Given the high metabolic demand of fibrillating atrial
myocardium, one might also speculate that the extensive
suppression of transcriptional processes and hence protein
synthesis is an attempt to save energy by restricting synthesis
to a smaller number of proteins, possibly similar to chronic
hibernation.

Limitation of the Present Study
Analysis of human myocardial tissue is complicated by
biological variability, which is expected to be greater than in
well-controlled animal models of AF. Different etiologies and
duration of AF, differences in age, gender, and medications,
as well as individual course of the disease of patients from
which tissue specimens were obtained contribute to variabil-
ity in gene expression when examining human tissue samples.
In the present study, however, we were able to detect robust
functional patterns extending beyond this biological variabil-
ity. The validity of our data-set is corroborated by expression
patterns of a wide variety of genes known to be regulated in
this is partly because of the incomplete annotational status of
the human genome at the time the Affymetrix U133A+B
arrays were designed. Even if we seek to present a compre-
hensive portrait of the transcriptional changes in pmAF, this
picture can by no means be complete. Moreover, it has to be
kept in mind that mRNA levels do not always directly
translate into changes in protein or functional levels, as
additional regulatory mechanisms on a posttranslational level
exist.

AF is usually initiated and maintained in the left atrium,
because the cycle length is shorter in left than in right atrium
during AF. Accordingly, a recent microarray study of a pig
model of AF suggested that the genomic changes are more
pronounced in left than right atrium with considerable over-
lap in the genomic response. As only right atrial tissue was
available for the present study, future studies will be needed
to account for regional heterogeneity in AF at the atrial level.

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