Troponin I Isoform Expression in Human and Experimental Atrial Fibrillation

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Background—Atrial fibrillation (AF) is accompanied by re-expression of fetal genes and activation of proteolytic enzymes. In this study both aspects were addressed with respect to troponin I (TnI) isoform expression.

Methods and Results—Western blotting and real-time reverse transcription–polymerase chain reaction were used to study TnI isoform expression in patients with paroxysmal or chronic AF and in goats after 1, 2, 4, 8, and 16 weeks of AF. In addition to cardiac TnI (cTnI), low expression of slow-twitch skeletal TnI (ssTnI) protein was found in 60% of patients in sinus rhythm or paroxysmal AF and in 8% of patients with chronic AF. In adult goat atrium, ssTnI protein expression was undetectable. Calcium-dependent degradation of cTnI protein was found in 1 or 2 of 6 animals after 1 to 4 weeks of AF. Although always low, ssTnI mRNA levels were significantly higher in patients who expressed ssTnI protein than in those who did not. Relative ssTnI mRNA expression was significantly lower in patients with paroxysmal AF and chronic AF than in those in sinus rhythm. In goats there was a tendency toward higher relative levels of ssTnI at the onset of AF followed by a normalization when AF had become sustained.

Conclusions—Atrial re-expression of ssTnI during paroxysmal AF in patients and during the first 2 weeks of pacing-induced AF in goats does not seem to be part of the process of AF-associated cardiomyocyte dedifferentiation but seems to result from transient cardiomyocyte stress at the onset of AF. (Circulation. 2004;110:770-775.)

Key Words: atrial fibrillation ■ troponin I ■ myocytes, cardiac ■ gene expression ■ atrium

Atrial fibrillation (AF) is accompanied by electric, structural, and contractile remodeling of the atrium that results in reduced atrial function. In both patients and animal models, it has been shown that the structural alterations are indicative of cardiomyocyte dedifferentiation.1–3 Atrial cardiomyocyte dedifferentiation is accompanied by protein expression and cellular organization patterns that are reminiscent of fetal cardiomyocytes, eg, titin, desmin, cardiotin, α-smooth muscle cell actin, and α- and β-myosin heavy chains.4–5 Using differential display, we also found down-regulation of cardiac troponin I (cTnI) mRNA expression in the goat model of AF.5 In the adult heart, this cTnI is the main troponin isoform, whereas the fetal human heart predominantly expresses the slow-twitch skeletal TnI (ssTnI) isoform.6–9 Until now, re-expression of the ssTnI isoform has not been detected during cardiac disease.6,10,11

Recently, it was shown that activation of calpains was responsible for elevated TnI degradation during increased preload or hypoxia.12,13 Activation of calpains has also been found during AF.14 As a consequence, AF might result in calpain-controlled degradation of cTnI, which could affect the contractile function of the atrium. To elucidate the involvement of changes in TnI isoform expression in cardiomyocyte dedifferentiation and contractile dysfunction during AF, we analyzed TnI isoform composition at the protein and mRNA levels in patients with AF and in a goat model.

Methods

Human Tissue

Human tissue from right atrial appendages was obtained from patients with the following: (1) sinus rhythm (n=5) undergoing coronary bypass surgery; (2) mitral valve disease and sinus rhythm (n=4); (3) mitral valve disease and chronic AF (n=4); (4) lone paroxysmal AF (n=6); and (5) lone chronic AF (n=8). Atrial tissue was obtained during surgery, snap-frozen in liquid nitrogen, and stored at −80°C. The patients with lone AF underwent MAZE surgery, and none of these patients suffered from any underlying cardiac disease. Patients’ characteristics have been described previously.15,16 All the patients gave their written consent, and the study was approved by the institutional review board. Infarcted human heart samples were kindly provided by Dr F. Dal Monte, Cardiovascular Research Center, Massachusetts General Hospital, Boston.

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Animal Tissue
The goal model of AF was essentially as described by Ausma et al.17 A total of 36 goats were used, and animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes. Right and left atrial appendages were obtained from animals that had remained in sinus rhythm or after 1, 2, 4, 8, and 16 weeks of AF (n=6 in each group). Hearts from fetuses (n=5) at different days of gestation (4 weeks before end term up to a few days before birth) were obtained from the abattoir. Tissues were immediately frozen in liquid nitrogen– precooled isopentane. From 1 adult animal, additional tissues were taken (skeletal muscle, diaphragm).

Western Blotting
Monoclonal antibodies that react specifically with the cTnI isoform (TI-1) or with both cTnI and ssTnI (TI-4) were used.18 Equal protein amounts were separated on polyacrylamide gels, transferred onto nitrocellulose filters, and incubated with primary antibody (TI-4, 1:3000; TI-1, 1:1000). After a second incubation with peroxidase-conjugated secondary antibody (1:5000), the peroxidase activity was determined by enhanced chemiluminescence. As control for TnI degradation, the homogenization of goat atrial sections was preceded by incubation in propionate buffer for 30 minutes at 37°C in the presence or absence of 10 mmol/L CaCl₂, as previously described.19 Additional experiments were performed in the presence of the calpain inhibitor calpeptin (Z-Leu-Nle-CHO, Novabiochem).

Isolation of Goat cTnI and ssTnI cDNA
To obtain the goat-specific sequence for cTnI, a goat atrial cDNA library was screened according to standard procedures, with human cTnI used as a probe. The goat-specific sequence of ssTnI was obtained by rapid amplification of cDNA ends (5’RACE-kit, Life Technologies) from 1 µg of RNA isolated from goat diaphragm tissue. Gene-specific primer (GSP) sequences (GSP-1: CCCGCA-GATCCATGGACACCTTGTG; GSP-2: CGCTTGAACTTC-TCTTCAGCAGGAG, probe FAM-CCCAAGATCACTGCCTGCCACCTCAAGCAGGTG, reverse CATGCCGGAAGTCGAGAGAAA, reverse TTGCGCCAGTCTCCTACCTC, probe TAMRA-AGAA-GGAGGACACGGAGAAGGAAAACCG-DABCYL; goat ssTnI: forward GCCCACCTCAAGCAGGTG, reverse TTGCGCCAGTCTCCTACCTC, probe TAMRA-AGAAGGAGGACACGGAGAAGGAAAACCG-DABCYL; human ssTnI: forward GCCCACCTCAAGCAGGTG, reverse CATCAGGCTCTTCAGCAGGAGAAGGAAAACCG-DABCYL; goat cTnI: forward GCCCACCTCAAGCAGGTG, reverse TTGCGCCAGTCTCCTACCTC, probe TAMRA-AGAAGGAGGACACGGAGAAGGAAAACCG-DABCYL; human cTnI: forward GCCCACCTCAAGCAGGTG, reverse TTGCGCCAGTCTCCTACCTC, probe TAMRA-AGAAGGAGGACACGGAGAAGGAAAACCG-DABCYL) were based on homologies between ssTnI of human, rat, and mouse.

Quantitative Real-Time Reverse Transcription–Polymerase Chain Reaction
Total RNA was isolated from a 30-mg atrial appendage with the use of the RNeasy mini kit (Qiagen). Genomic DNA contamination was removed by on-column DNase treatment with the RNase-free DNase set (Qiagen). After reverse transcription, quantitative real-time reverse transcription–polymerase chain reaction (RT-PCR) was performed with the Real-Time PCR Taqman Kit (Eurogentec) with the ABI PRISM 7700 Sequence Detection System apparatus and software (PE Applied Biosystems). Primer Express software (PE Applied Biosystems) was used to design the specific primers and probes, and all primers/probes were synthesized by Eurogentec (human cTnI: forward GCCCACCTCAAGCAGGTG, reverse TTGCGCCAGTCTCCTACCTC, probe TAMRA-AGAAGGAGGACACGGAGAAGGAAAACCG-DABCYL; goat ssTnI: forward GCCCACCTCAAGCAGGTG, reverse CATCAGGCTCTTCAGCAGGAGAAGGAAAACCG-DABCYL; goat cTnI: forward GCCCACCTCAAGCAGGTG, reverse CATCAGGCTCTTCAGCAGGAGAAGGAAAACCG-DABCYL; human ssTnI: forward GCCCACCTCAAGCAGGTG, reverse CATCAGGCTCTTCAGCAGGAGAAGGAAAACCG-DABCYL; human cTnI: forward GCCCACCTCAAGCAGGTG, reverse CATCAGGCTCTTCAGCAGGAGAAGGAAAACCG-DABCYL). Absolute mRNA amounts were calculated with the use of standard curves generated by quantitative RT-PCR on dilution series of cloned cTnI and ssTnI.

Statistical Analysis
Data are displayed as mean±SEM values of 3 independent experiments. Mean values were used for statistical analysis. Significant differences between the groups were analyzed by means of the Wilcoxon-Mann-Whitney rank sum test. All probability values are 2

Results
TnI Protein Expression During AF
To establish whether AF can affect TnI isoform expression, we performed Western blotting on atrial tissue from patients with AF. The patients could be divided into 3 groups when atrial rhythmic activity was used as the sole selection criterion (Table 1): sinus rhythm (n=9), paroxysmal AF (n=6), and chronic AF (n=12). When the underlying disease was taken into account, 5 different groups could be distinguished: normal sinus rhythm (n=5), mitral valve disease and sinus rhythm (n=4), mitral valve disease and chronic AF (n=4), lone paroxysmal AF (n=6), and lone chronic AF (n=8). Western blot of human skeletal muscle with an antibody that recognizes both cardiac and skeletal TnI (TI-4) revealed 2 bands, representing ssTnI and fast-twitch skeletal TnI (sTnI) (Figure 1A, top). In human cardiac tissue, a prominent band of lower mobility was detected, representing cTnI (Figure 1A, top). Several patients displayed a faint band with the same electrophoretic mobility as the ssTnI band in skeletal muscle. To distinguish between cTnI degradation and ssTnI expression, Western blotting was also performed with a cTnI-specific antibody (TI-1). No bands were detected with human skeletal muscle, proving TI-1 specificity. None of the atrial samples displayed reactivity with TI-1 on the minor band, at variance with infarcted myocardium (Figure 1A, bottom). The latter shows that cTnI degradation does not result in loss of the TI-1 epitope. Additionally, multiple degradation products reacted with TI-4 (lane M1 Figure 1A, top). These results indicate that the additional band decorated by TI-4 in atrial samples corresponds to ssTnI.

To determine whether ssTnI re-expression could result from ongoing dedifferentiation, the TnI isoform expression was analyzed in the goat model, in which AF-induced dedifferentiation of atrial cardiomyocytes has been studied extensively. Western blotting with TI-4 on adult goat heart revealed a single cTnI band. In fetal heart, both cTnI and ssTnI isoforms were present, and skeletal muscle contained the ssTnI as well as the ssTnI isoforms (Figure 1B). TI-1 reacted only with the slower TnI isoform in fetal heart sample and with the isoform present in the adult heart, corresponding to cTnI (not shown). To determine whether TI-1 was able to detect cTnI degradation, atrial tissue from goats in sinus rhythm was treated with high levels of calcium. As observed for human infarcted myocardium, a cTnI degradation product retaining the TI-1 epitope could be observed (Figure 1C). This band was less intense in the presence of the calpain inhibitor calpeptin. On Western blot analysis with the TI-4 antibody, an additional band was detected in only a few atrial samples (not shown). The band was also detected by TI-1, indicative of cTnI degradation (Figure 1D). Western blot results indicate that the additional band decorated by TI-4 in atrial samples corresponds to ssTnI.

TnI mRNA Expression During AF
Next, quantitative RT-PCR was performed to analyze changes at the TnI mRNA expression levels in atrial tissue samples from patients and goats with AF. During normal sinus rhythm, the cTnI mRNA amount in human atrial tissue was approximately 600-fold higher than that of ssTnI mRNA (Table 3). Either
mitral valve disease or AF increased this value to approximately 2200-fold ($P < 0.05$), and the combination increased this value to 3500-fold ($P < 0.05$). The amount of cTnI mRNA over ssTnI mRNA was lower in patients displaying an ssTnI band in Western blotting compared with those who did not (1200-fold versus 2600-fold; $P < 0.05$).

To perform quantitative RT-PCR in the goat model, cDNAs of the different goat TnI isoforms were isolated. A partial cDNA encoding 330 nucleotides of the 3' end of cTnI (GenBank accession number: AY033589) was picked up from a goat atrium cDNA library. Overall homology with human cTnI was approximately 90% at the nucleotide level and 97% at the protein level (Figure 2A). A partial cDNA of ssTnI (GenBank accession number: AY033587) containing 330 nucleotides of the 5' end was isolated with the use of 5'RACE. Homologies at the nucleotide and the protein level were 88% and 93%, respectively (Figure 2B). Goat specific primers/probe combinations were designed for quantitative RT-PCR (Figure 2C). A control PCR with cTnI primers on a dilution series of the partial cTnI cDNA from the goat generated an amplicon of the expected size (Figure 2D, top right inset). Figure 2D shows the amplification plots obtained during quantitative RT-PCR on the same dilution series that was used to generate a standard curve (Figure 2D, top left inset). The standard curve had a linear detection range down to 10 pg DNA. Similar results were obtained for ssTnI (data not shown).

In fetal goats, atrial expression of cTnI mRNA was only 30-fold higher than that of ssTnI, whereas in adult goats, the cTnI mRNA expression level was approximately 11 000-fold higher. In animals that had been in AF, there were no significant changes in the atrial expression levels of cTnI and ssTnI mRNA. However, there appeared to be a tendency toward a lower cTnI over ssTnI expression at the onset of AF, followed by a normalization after longer periods of AF. This was confirmed by a significant difference in the level of expression after 2 weeks of AF compared with 16 weeks of AF (3200-fold versus 12 000-fold, respectively; $P < 0.05$).

### Discussion

Throughout cardiac development, 2 TnI isoforms are expressed in the heart.6,7 Expression of the slow-twitch skeletal isoform decreases around birth, together with an increase in expression of the cardiac isoform. Consequently, the TnI isoform expression pattern reflects the differentiation state of the cardiomyocyte, which might be used to monitor AF-induced cardiomyocyte dedifferentiation. In addition to cardiomyocyte dedifferentiation, a relation has been found between AF and the activity of calpain I,14 a protease involved in cTnI degradation.12,13 In this study the effect of AF on the atrial TnI composition in patients with AF and mitral valve disease was evaluated. The goat model of AF was included to study the alterations in TnI composition at the onset of AF.

Western blot analysis revealed ssTnI expression in most patient groups, except for patients with chronic AF in the absence of any underlying heart disease (lone chronic AF).

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SR</th>
<th>PAF</th>
<th>CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>6/3</td>
<td>6/0</td>
<td>7/5</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>48±8*</td>
<td>61±12</td>
</tr>
<tr>
<td>Median duration (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAF, h</td>
<td>...</td>
<td>9 (0.2–14.4)</td>
<td>...</td>
</tr>
<tr>
<td>CAF, mo</td>
<td>...</td>
<td>8.6 (0.5–20)</td>
<td>...</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

$*$Values are mean±SD, except where indicated otherwise. SR indicates sinus rhythm; PAF, paroxysmal AF; CAF, chronic AF; NSR, normal sinus rhythm; MVDSR, mitral valve disease combined with SR; lone PAF, lone paroxysmal AF; MVDFAF, mitral valve disease combined with AF; lone CAF, lone chronic AF; and NYHA class, New York Heart Association class for exercise tolerance.

$P < 0.05$, PAF vs CAF; $P < 0.05$, lone PAF vs SR.
Zhu et al, who detected ssTnI mRNA in cells of the AF, results in cardiomyocyte dedifferentiation.3 re-expression of ssTnI appeared to support the hypothesis that specialized in conduction within the atrial appendages that evidence for the existence of significant numbers of cells conductive tissue throughout adulthood. Because there is no patients with chronic AF, normalization of expression occurs.

In patients with chronic AF, only 1 displayed atrial ssTnI expression. This discrepancy might be a consequence of the persistence character of the atrial arrhythmic activity during chronic AF. In patients with lone paroxysmal AF, the repetitive cycles of AF followed by sinus rhythm might result in the repeated activation of ssTnI expression, whereas in patients with chronic AF, normalization of expression occurs.

This is supported by the absence of ssTnI expression in the goat model, which is a model for chronic AF.

The fact that ssTnI expression was also observed in patients with sinus rhythm suggests that in these patients the underlying cardiac disease (coronary ischemia) also triggered ssTnI expression. This is supported by the absence of ssTnI expression in the goat model, which is a model for chronic AF.

**TABLE 2. TnI Isoform Composition in Patients With AF**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>ssTnI Expression</th>
<th>cTnI Degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSR (n=5)</td>
<td>3</td>
<td>Absent</td>
</tr>
<tr>
<td>MVDSR (n=4)</td>
<td>2</td>
<td>Absent</td>
</tr>
<tr>
<td>Lone PAF (n=6)</td>
<td>4</td>
<td>Absent</td>
</tr>
<tr>
<td>MVDAF (n=4)</td>
<td>1</td>
<td>Absent</td>
</tr>
<tr>
<td>Lone CAF (n=8)</td>
<td>Absent/Absent</td>
<td>Absent/Absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Animal group (RA/LA)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SR (n=6)</td>
<td>Absent/Absent</td>
<td>Absent/Absent</td>
</tr>
<tr>
<td>1-wk AF (n=6)</td>
<td>Absent/Absent</td>
<td>1/1</td>
</tr>
<tr>
<td>2-wk AF (n=6)</td>
<td>Absent/Absent</td>
<td>1/1</td>
</tr>
<tr>
<td>4-wk AF (n=6)</td>
<td>Absent/Absent</td>
<td>2/2</td>
</tr>
<tr>
<td>8-wk AF (n=6)</td>
<td>Absent/Absent</td>
<td>Absent/Absent</td>
</tr>
<tr>
<td>16-wk AF (n=6)</td>
<td>Absent/Absent</td>
<td>Absent/Absent</td>
</tr>
<tr>
<td>Fetal (n=5)</td>
<td>5/5</td>
<td>Absent/Absent</td>
</tr>
</tbody>
</table>

NSR indicates normal sinus rhythm; MVDSR, mitral valve disease combined with sinus rhythm (SR); lone PAF, lone paroxysmal AF; MVDAF, mitral valve disease combined with AF; lone CAF, lone chronic AF; RA, right atrium; and LA, left atrium.

**TABLE 3. mRNA Expression Levels of cTnI and ssTnI**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Ctss Ctc</th>
<th>Absolute Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR (n=9)</td>
<td>27.64±0.38</td>
<td>21.42±0.33</td>
</tr>
<tr>
<td>PAF (n=6)</td>
<td>28.27±0.61</td>
<td>20.62±0.49</td>
</tr>
<tr>
<td>CAF (n=12)</td>
<td>28.19±0.59</td>
<td>20.39±0.47</td>
</tr>
<tr>
<td>NSR (n=5)</td>
<td>27.00±0.46</td>
<td>21.67±0.34</td>
</tr>
<tr>
<td>MVDSR (n=4)</td>
<td>28.44±0.35</td>
<td>21.11±0.63</td>
</tr>
<tr>
<td>MVDAF (n=4)</td>
<td>28.48±0.39</td>
<td>20.57±0.15</td>
</tr>
<tr>
<td>Lone PAF (n=6)</td>
<td>28.27±0.61</td>
<td>20.62±0.49</td>
</tr>
<tr>
<td>Lone CAF (n=8)</td>
<td>28.04±0.88</td>
<td>20.29±0.72</td>
</tr>
<tr>
<td>No ssTnI (n=17)</td>
<td>28.17±0.45</td>
<td>20.56±0.38</td>
</tr>
<tr>
<td>ssTnI (n=10)</td>
<td>27.77±0.39</td>
<td>21.16±0.33</td>
</tr>
</tbody>
</table>

Ctss indicates cycle threshold of ssTnI; Ctc, cycle threshold of cTnI. Other abbreviations are as defined in Tables 1 and 2.

ΔP<0.05 vs SR (n=9); †P<0.05 vs SR (n=5); ‡P<0.05 vs ssTnI band; §P<0.05 vs 2-wk AF; ‖P<0.01 vs all other groups.
ischemia, stretch). The rationale behind re-expression of ssTnI is not known, but it has been suggested that myofilaments with ssTnI are more resistant to acidosis and have increased calcium sensitivity. 21,22 AF is also accompanied by activation of calpain I, 14 a calcium-dependent proteolytic enzyme for which cTnI has been shown to be a substrate. 12,13,23 In the present study no sign of cTnI degradation was seen in any of the patients. It is possible that, although our cTnI-specific antibody can detect a cTnI degradation product in human infarct hearts, other proteolytic modifications, as described by McDonough et al, 24 were not detected. However, cTnI degradation may also depend on the duration and severity of cardiac stress. Thomas et al 25 did not find increased cTnI degradation in a swine model of stunned myocardium, representing mild cardiac stress. In most studies that find cTnI degradation, it was observed in the time frame immediately after an acute and severe cardiac stress. 13,23,26 This would explain why some level of cTnI degradation was detected during the first 1 to 4 weeks of AF in the goats. The patients described in this study all suffered for prolonged periods of time from heart disease and/or AF. During such long periods of cardiac stress, cTnI might be protected from degradation through an increased expression of heat shock proteins 27,28 or an increased cTnI phosphorylation. 29

Further analysis of TnI isoform expression was performed by quantitative RT-PCR. During sinus rhythm, low levels of atrial ssTnI expression were detectable. Previous studies, in which in situ hybridization or Northern blotting was used, did not find any evidence for the presence of ssTnI mRNA in normal adult cardiac tissue or re-expression of ssTnI during cardiac disease. 5,8,9 However, quantitative RT-PCR is more sensitive than these techniques. Calculation of the absolute TnI mRNA content in atrial tissue during sinus rhythm showed that cTnI was expressed at a 600-fold higher level than ssTnI. In patients with an ssTnI band on the Western blot, the relative expression of ssTnI was significantly higher than that in patients with no detectable ssTnI band. Mitral valve disease, paroxysmal AF, or chronic AF increased the level of cTnI mRNA, which could have several causes. First, cTnI mRNA turn-over might be increased. Second, it might reflect cardiomyocyte hypertrophy, which has been shown to occur during AF. 1,2 Third, cTnI expression upregulation could be a response to an altered calcium sensitivity of cTnI as a result of increased cTnI phosphorylation. 30,31 Finally, the increased expression of cTnI might represent the response of the cardiomyocyte to counterbalance alterations in calcium homeostasis to maintain optimal contractile activity. The latter is supported by observations in patients with chronic AF, in whom the reduced contractile force could be completely restored by high calcium levels. 32

On the basis of our observations, we propose the following model for TnI expression regulation (Figure 3). At the onset of AF, increased atrial activity and ischemia result in calcium overload, leading to decreased calcium sensitivity and to the activation of calpain I, causing cTnI degradation. Re-expression of ssTnI, which protects the cardiomyocyte from acidic stress and improves the calcium sensitivity, is a response to this unstable early phase. After a longer duration of AF, calcium homeostasis normalizes, ssTnI expression decreases, and protection against excessive cTnI degradation may be achieved by cTnI phosphorylation. In addition, the cTnI expression is up-regulated, either as compensation for the decreased calcium sensitivity of phosphorylated cTnI or because of a hypertrophic response. During paroxysmal AF, the recurring AF episodes compromise the stabilization, which results in repeated activation of ssTnI expression and cTnI phosphorylation. Thus, rather than cardiomyocyte dedifferentiation, the expression of TnI isoforms appears to be involved in protection of the contractile apparatus against the cellular stress induced by AF. The mechanisms of this protective response, ie, cTnI degradation, ssTnI expression, cTnI re-expression, and cTnI phosphorylation, are likely to contribute to the contractile dysfunction.
Figure 3. Schematic display of expression regulation of TnI during AF. The early stage of AF is characterized by unstable conditions, caused by calcium overload and acidosis, which result in degradation of cTnI, re-expression of ssTnI, and downregulation of cTnI expression. To protect cTnI from degradation, the protein may be phosphorylated, and the expression is upregulated. After a longer duration of AF, a more stable condition arises in which ssTnI expression is downregulated and cTnI degradation is no longer detectable. In vivo, the unstable condition is represented by patients with paroxysmal AF (PAF) and goats at the onset of AF, although in patients cTnI degradation is no longer detectable because of repetitive activation and subsequent cTnI phosphorylation. Patients and goats with chronic AF (CAF) represent the stable condition (no ssTnI expression, presence of cTnI phosphorylation). Patients and goats with chronic AF (CAF) represent the stable condition (no ssTnI expression, absence of cTnI degradation). SR indicates sinus rhythm.

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References

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