Differential Distribution of Inward Rectifier Potassium Channel Transcripts in Human Atrium Versus Ventricle

Zhiguo Wang, PhD; Lixia Yue, MSc; Michel White, MD, FRCP(C); Guy Pelletier, MD; Stanley Nattel, MD

Background—The inward rectifier K⁺ current (I_{K1}) plays an important role in governing cardiac electrical activity and is well known to have different properties in the atrium compared with the ventricle. Several inward rectifier K⁺ channel (IRK) subunits (hIRK, HH-IRK1, HIR, and TWIK-1) with different properties have been cloned from human tissues, but their relative expression in cardiac tissues has not been quantified. The present study was designed to define the relative levels of mRNA for various IRKs in human atrium and in failing and nonfailing ventricle.

Methods and Results—Competitive reverse transcription–polymerase chain reaction was used to quantify in human atrium and ventricle the mRNA levels of hIRK, HH-IRK1, HIR, and TWIK-1. The absence of important noncardiac contamination was confirmed by demonstrating a lack of detectable mRNA markers for neuronal (acetylcholine receptor) and vascular (maxi-K channel) tissue. mRNA of HIR was more abundant in normal atrium (7.1±1.3 amol/μg total RNA) than ventricle (0.6±0.1 amol/μg, P<0.05), whereas TWIK-1 mRNA was more concentrated in ventricle (18.1±4.3 amol/μg) than atrium (1.4±0.3 amol/μg, P<0.05). Concentrations of hIRK (42.7±6.7 amol/μg in atrium vs 57.1±9.2 amol/μg in ventricle) and HH-IRK1 (2.0±0.5 amol/μg in atrium vs 1.5±0.5 amol/μg in ventricle) were comparable. No significant differences in IRK subunit transcript concentrations were found between normal and failing ventricles.

Conclusions—mRNAs for all 4 IRKs are detected in human atrium and ventricle, but the mRNA copy number of a low-conductance subunit (HIR) is larger in atrium and the copy number of a weakly rectifying subunit (TWIK-1) is larger in ventricle. These differences in relative message levels may provide a potential molecular basis for different properties of I_{K1} in human atrium compared with ventricle. (Circulation. 1998;98:2422-2428.)

Key Words: atrium ■ ventricles ■ heart failure ■ potassium ■ RNA

The inward rectifier potassium current I_{K1} plays a critical role in determining membrane resting potential and contributing to the final phase of action potential repolarization in cardiac cells. Four different cDNA clones belonging to the IRK (inward rectifier K⁺ channel) family have been detected in the human heart: HH-IRK1, 1–3 hIRK, 4 HIR, 5–7 and TWIK-1 8 (Table 1). Expression of each in heterologous systems gives rise to currents qualitatively similar to native I_{K1}, 1–8 although functional differences exist. Evidence has accumulated that endogenous I_{K1} may actually be composed of a number of distinct channel populations. 9–14

Important differences of I_{K1} exist between atrium and ventricle. 14–18 Atrial I_{K1} has a smaller conductance, current density, and channel open times compared with ventricular I_{K1}. It is possible that differences between atrial and ventricular I_{K1} are due to differences in concentrations of various IRK clones. It is further conceivable that differences in I_{K1} between normal and failing ventricles 19,20 may be due to varying IRK subunit distribution.

The present study was designed to quantify mRNA levels of IRK clones in normal human atrium and in normal and failing human ventricle. We particularly sought to determine whether there are differences in IRK mRNA expression profiles between atrium and ventricle that could be related to some of the differences in their I_{K1} properties.

Methods
Tissue Handling
Normal atrial appendages (~0.3 g each) were obtained from 15 patients undergoing coronary bypass surgery. Diseased ventricular tissues (~1 g each) were dissected from the left ventricle of explanted hearts from 6 patients undergoing heart transplantation. Two had myocarditis, 2 idiopathic cardiomyopathy, 1 aortic valve disease, and 1 ischemic cardiomyopathy. Healthy ventricular preparations (~5 mg) were obtained by endocardial biopsy in follow-up after heart transplantation. Samples (2 per patient) were obtained from 14 patients free of rejection (disease before transplantation: ischemic cardiomyopathy [6], idiopathic cardiomyopathy [6], myocarditis [2]). Atrial samples were quickly frozen in liquid nitrogen and stored at −80°C. Ventricular tissues were immediately immersed into Trizol solution and processed for RNA isolation.
RNA samples were stored in DEPC-treated, double-distilled H₂O at 80°C.

**TABLE 1. Cloned Human Inward Rectifier K⁺ Channels**

<table>
<thead>
<tr>
<th>IRK Clone</th>
<th>Standard Nomenclature</th>
<th>Tissue†</th>
<th>Inward Rectification</th>
<th>Conductance, pS‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH-IRK1⁺⁺</td>
<td>Kir2.2</td>
<td>Heart</td>
<td>Strong</td>
<td>30</td>
</tr>
<tr>
<td>(HHRIRK1, hIRK1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hIRK⁺⁺</td>
<td>Kir2.1</td>
<td>Heart</td>
<td>Strong</td>
<td>36</td>
</tr>
<tr>
<td>(HRK1, hIRK2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWIK-1⁺⁺</td>
<td>Heart</td>
<td>Weak</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

*Designation used in this study. Designations in parentheses are alternates suggested in references cited.
†Human tissues from which the clone was originally isolated.
‡Single-channel conductance under symmetrical K⁺ conditions.

**Patch-Clamp Recording**

The procedure for isolating human cardiac cells has been described previously in detail. When cell yield was optimal the cells were suspended in a storage solution (in mmol/L, KCl 20, KH₂PO₄ 10, K glutamate 70, EGTA 5, glucose 10, taurine 10, albumin 0.1%, pH 7.3, with KOH).

Ca²⁺-tolerant, quiescent rod-shaped cells with tight gigaseals were used for data analysis. Borosilicate glass micropipettes (1 mm optical density) had tip resistances of 1 to 2 MΩ when filled with (mmol/L): KCl 20, K aspartate 120, MgCl₂ 1, HEPES 5, Na₂-ATP 4, K-ATP 5, pH 7.3, with KOH. Cells were superfused with Tyrode solution at 37°C containing (mmol/L): NaCl 137, KCl 5.4, CaCl₂ 1, MgCl₂ 0.8, HEPES 10, glucose 10, CaCl₂ 0.2, 4-aminopyridine 1, glyburide 0.01, and atropine 0.001. The electrodes were connected to an Axopatch 1-D amplifier (Axon Instruments). Command pulses were generated with pCLAMP6 software.

After gigaseal formation (seal resistance ≥ 10 G), suction was applied to rupture the membrane for whole-cell recording. Series resistance and system capacitance were compensated.

**RNA Purification**

Tissue specimens were homogenized in Trizol reagent (Gibco BRL). Total RNA was extracted by the acidic guanidinium isothiocyanate method with chloroform and isopropanol precipitation and incubated with DNase I (0.1 U/µL) at 37°C for 15 minutes. Genomic DNA was removed by phenol/chloroform extraction. Isolated RNA was quantified (spectrophotometric absorbance at 260 nm) and purity was confirmed by the A₂₆₀/A₂₉₀ ratio. Integrity of total RNA was evaluated by ethidium bromide staining in denaturing agarose gels. RNA samples were stored in DEPC-treated, double-distilled H₂O at −80°C.

**Construction of RNA Mimics (Internal Standards)**

**Primers**

Primers were designed to avoid secondary and complementary structures. Gene-specific primer (GSP) pairs were designed on the basis of published cDNA sequences from regions with minimal homology among IRKs and specificity verified by comparison with the GenBank database with the use of BLAST and FASTA. The process for synthesis of the RNA mimic and reverse transcription–polymerase chain reaction (RT-PCR) is illustrated in Figure 1. Chimeric primer pairs (Table 2) were constructed with sequences homologous to human cardiac α-actin cDNA flanked at the 5’ end and an antisense sequence to the 3’ end. A second run of PCR was performed with the T7 promoter sequence as a forward primer and a reverse IRK GSP. The resulting products were cDNA fragments carrying a T7 promoter followed by a forward IRK GSP, an α-actin fragment and then a reverse IRK GSP. The products were then gel-purified with the Glassmax DNA Isolation Spin Cartridge System (Gibco BRL). RNA internal standards (mimics) were generated by in vitro transcription with purified cDNA mimics as templates (mMESSAGE mmACHINE kit, Ambion). To remove remaining cDNA templates, the reaction products were incubated with RNase-free DNase I (37°C, 30 minutes) followed by phenol/chloroform extraction and isopropanol precipitation. The uniqueness of RNA mimics was confirmed by the presence of single bands of expected size on a denaturing gel. The synthetic RNA mimics thus had GSPs for the target IRK mRNA at both ends and a 460-bp fragment of human cardiac α-actin in the middle.

**Competitive RT-PCR**

**Reverse Transcription**

RNA mimic samples with serial 10-fold dilutions were prepared and added to 1 µg of sample RNA. RNAs were denatured at 65°C for 15 minutes. RT was conducted in a 20-µL reaction mixture containing an IRK GSP sense sequence at the 5’ end and an antisense sequence at the 3’ end. A second run of PCR was performed with the T7 promoter sequence as a forward primer and a reverse IRK GSP. The resulting products were cDNA fragments carrying a T7 promoter followed by a forward IRK GSP, an α-actin fragment and then a reverse IRK GSP. The products were then gel-purified with the Glassmax DNA Isolation Spin Cartridge System (Gibco BRL). RNA internal standards (mimics) were generated by in vitro transcription with purified cDNA mimics as templates (mMESSAGE mmACHINE kit, Ambion). To remove remaining cDNA templates, the reaction products were incubated with RNase-free DNase I (37°C, 30 minutes) followed by phenol/chloroform extraction and isopropanol precipitation. The uniqueness of RNA mimics was confirmed by the presence of single bands of expected size on a denaturing gel. The synthetic RNA mimics thus had GSPs for the target IRK mRNA at both ends and a 460-bp fragment of human cardiac α-actin in the middle.

**TABLE 2. Primer Pairs Used**

<table>
<thead>
<tr>
<th>Clone</th>
<th>Primer Pair</th>
<th>Position, bp</th>
<th>Size, bp</th>
<th>Tm, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH-IRK1</td>
<td>F: 5’TGAGATACGAGGACTGAC’</td>
<td>844–1233</td>
<td>389</td>
<td>56.7</td>
</tr>
<tr>
<td></td>
<td>R: 5’CTGTTGTAAGGAATTATGCC’</td>
<td></td>
<td></td>
<td>54.4</td>
</tr>
<tr>
<td>hIRK</td>
<td>F: 5’ACCTGGAGACAGGACGAC’</td>
<td>855–1248</td>
<td>393</td>
<td>61.8</td>
</tr>
<tr>
<td></td>
<td>R: 5’AGCCTGATTCGTTCCACATT’</td>
<td></td>
<td></td>
<td>62.5</td>
</tr>
<tr>
<td>hIR</td>
<td>F: 5’TATGGCAGTGGCGACAGGA’</td>
<td>813–1176</td>
<td>363</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>R: 5’AGCGTTCTCTCCAGTT’</td>
<td></td>
<td></td>
<td>65.5</td>
</tr>
<tr>
<td>TWIK-1</td>
<td>F: 5’CCTCTGCTCTCTTCTTCCCG’</td>
<td>577–960</td>
<td>383</td>
<td>63.4</td>
</tr>
<tr>
<td></td>
<td>R: 5’AGGCTTATITGGTGCTGTCG’</td>
<td></td>
<td></td>
<td>65.3</td>
</tr>
<tr>
<td>α-Actin</td>
<td>F: 5’ACGGGAGAAGATGACTGAC’</td>
<td>329–1583</td>
<td>460</td>
<td>63.0</td>
</tr>
<tr>
<td></td>
<td>R: 5’AAGTACCGGACTTGGAG’</td>
<td></td>
<td></td>
<td>63.2</td>
</tr>
</tbody>
</table>

Tm indicates annealing temperature calculated by nearest-neighbor method using Oligo software; F, forward; and R, reverse.
reaction buffer (10 mmol/L Tris-HCl [pH 8.3], 50 mmol/L KCl, 2.5 mmol/L MgCl₂, 1 mmol/L dNTPs (Boehringer Mannheim), 3.2 μg random primers p(dN)₆ (Boehringer Mannheim), 5 mmol/L DTT, 50 U RNase inhibitor (Gibco BRL), and 200 U M-MLV RT (Gibco BRL). First-strand cDNAs were synthesized at 42°C for 60 minutes and the remaining enzymes inactivated at 99°C for 5 minutes.

**PCR Amplification**

First-strand cDNA (10 μL) was used as an amplification template in a 50-μL reaction mixture. Reagents in each reaction included 10 mmol/L Tris-HCl (pH 8.3), 50 mmol/L KCl, 1.5 mmol/L MgCl₂, 1 mmol/L dNTPs, 0.5 μmol/L of each GSP pair, and 2.5 U of Taq polymerase (Gibco BRL). Reactions were hot-started at 94°C and continued for 3 minutes of initial melting. The cycling profiles were 30 seconds of denaturing (94°C), 30 seconds of annealing (54°C), and 40 seconds of extension (72°C) for 30 cycles, followed by a final extension step (5 minutes at 72°C).

**Quantification of PCR Products**

Densitometry was used for quantification of PCR products. PCR products were visualized under UV light with ethidium bromide staining in 1.5% agarose gel. Ethidium bromide fluorescence images were captured by a Nighthawk camera under UV light and band density determined with Quantity One software. A DNA mass marker (100 ng) was used to analyze the size and quantity of PCR products. The density of the DNA mass ladder was used to generate a standard curve by linear regression with extrapolation to zero for each experiment. The density of each sample band was then converted to an absolute quantity by calibrating to the standard curve.

**Control Experiments**

To ensure the equality of RNA input, additional experiments were performed to PCR-amplify human cardiac α-actin from each sample. Equal amplification from different RNA samples makes it unlikely that observed differences are due to biased input of initial amount of total RNA (Figure 2). Equal efficiency of PCR amplification for sample RNA and RNA mimic was verified by quantitative analyses of PCR products for each construct coamplified in a single reaction tube, as illustrated in Figure 3.

**Data Analysis**

Data are expressed as mean±SEM. Each determination for a given mRNA concentration was performed on a sample from an individual heart, for example, numbers of determinations given are for separate hearts. Statistical comparisons were performed with unpaired Student’s t tests. A 2-tailed probability <0.05 was taken to indicate statistical significance.

**Results**

**Comparisons of Iᵦ in Human Atrial and Ventricular Cells**

Figure 4 shows examples of Iᵦ recorded from human atrial (Figure 4A) and ventricular (Figure 4B) cells. Iᵦ is smaller in atrium than in ventricle. Atrial cells showed very little outward current at voltages positive to the reversal potential, whereas ventricular myocytes carried significant outward currents between −80 and 0 mV. Figure 4C shows mean current density-voltage relations for 5 atrial and 6 ventricular myocytes. Iᵦ currents are shown relative to maximum current (at −100 mV) in Figure 4D. Despite this control for differences in maximum density between atrial and ventricular Iᵦ, atrial cells carry much less outward current.
Comparisons of IRK Transcriptional Profiles in Human Atrium and Ventricle

Figure 5 shows representative gels of competitive RT-PCR products. The upper bands represent products from RNA internal standards, and the lower bands are target gene sequences coamplified in the same RT-PCR reactions. As the RNA internal standard concentration in the initial reaction mixture decreased, the target gene signals became stronger. The TWIK-1 internal standard bands are comparable for atrium and ventricle, but the target gene bands are more intense in ventricular tissue. The point of equivalence (where the density of bands are comparable) for TWIK-1 occurs at the fourth lane in atrium but at approximately the third lane in ventricle, indicating a '10-fold greater concentration in ventricle.

For HIR, the target gene bands are stronger in atrium than in ventricle. The point of equivalence is in the third lane for atrium and the fourth lane for ventricle. Thus the HIR mRNA concentration is an order of magnitude higher in atrium. In contrast to TWIK-1 and HIR, the gels for hIRK and HH-IRK1 are quite similar in both tissues. Gels of the type shown in Figure 5 were used to quantify target gene mRNA concentrations as illustrated in Figure 6. The relation between log (target over mimic intensity ratio) and log (mimic concentration) was well fitted by linear regression. The

Figure 5. Representative ethidium bromide–stained gels of cDNA products from competitive RT-PCR of human atrium (left) and ventricle (right). Lane 0: DNA mass marker (200, 120, 80, 60, 40, 20 ng from top to bottom). Lanes 1 to 6: Upper bands represent RNA mimic signals and lower bands target mRNA products from reaction mixtures containing serial dilutions of RNA mimic (lane 1 = 200 ng, lane 2 = 20 ng, lane 3 = 2 ng, lane 4 = 0.2 ng, lane 5 = 0.02 ng, lane 6 = 0.002 ng) along with 1-μg sample RNA in 20 μL. Lane 7 is a RT-negative control containing 200 ng of RNA mimic to exclude genomic contamination. TWIK-1: mimic size 501 bp, target size 383 bp; HIR: mimic size 497 bp, target size 363 bp; hIRK: mimic size 499 bp, target size 393 bp; HH-IRK1: mimic size 500 bp, target size 389 bp.

Figure 6. Quantification of IRK mRNA in human atrium and ventricle. Left, Log-amplified target IRK/internal standard ratio versus known amount of RNA mimics. x-intercepts of linear regression to mean data in which log (target/mimic) equals zero indicate initial amount of target mRNA. Right, Amount of IRK transcript (amol/μg total RNA) calculated by dividing initial amount of target mRNA by molecular weight of respective PCR products (number of nucleotides×average molecular weight of single nucleotide, 310).
horizontal axis intercept (corresponding to a concentration ratio of 1) indicates the point at which target gene mRNA concentration equals that of the internal standard. The mean mRNA expression level of TWIK-1 was approximately 13 times higher in ventricle (18.1±4.3 amol/μg RNA, n=11) than in atrium (1.4±0.3 amol/μg RNA, n=8, P<0.05). HIR transcripts were 12-fold more abundant in atrium (7.1±1.3 amol/μg RNA, n=9) compared with ventricle (0.6±0.1 amol/μg RNA, n=7, P<0.05). Atrial and ventricular concentrations of hIRK and HH-IRK1 were similar.

The highest mRNA concentrations in both atrium and ventricle were for hIRK. TWIK-1 mRNA was abundant in ventricle, but its concentration was lower than that of any other clone in atrium. HIR concentrations were relatively high in atrium and very low in ventricle. Expression of HH-IRK1 mRNA was relatively weak in both atrium and ventricle.

Comparisons of IRK Transcription Profiles in Healthy and Diseased Human Ventricles
Comparisons of mRNA levels in ventricular tissues from non-failing and failing hearts are illustrated in Figure 7. There were no statistically-significant differences in mRNA concentrations between normal and failing ventricle for any of the clones.

Evaluation of Possible Contamination of Sample RNA by Noncardiac Tissue
Previous investigators have assayed mRNA for the neuronal acetylcholine β4 subunit to exclude neural contamination of cardiac mRNA measurements. We used published sequences of the human nicotinic receptor β4 subunit to design primer pairs for RT-PCR. Figure 8A shows representative ethidium bromide-stained PCR products in an agarose gel. β4 subunit mRNA was consistently detected in 3 samples from rat brain but was absent in all 9 atrial and 17 ventricular samples.

Contamination by vascular tissue was excluded by RT-PCR amplification of the maxi-K channel. Total RNA isolated from rat vascular smooth muscle, in which maxi-K channels carry a substantial current, was used as a positive control. PCR primer pairs were designed on the basis of published sequences. Figure 8B shows the strong maxi-K channel signal typical of vascular preparations (lane 1) and the absence of a corresponding band in heart tissue (lanes 2 to 4).

Discussion
In this article, we report the results of an analysis of the relative abundance of mRNAs of 4 IRK clones in human atrium and ventricle. We found measurable concentrations of all clones and significant expression profile differences between normal atrium and ventricle.

Biophysical Differences Among Cloned IRK Channels
The 4 different IRK cDNA clones isolated from the human heart have distinct biophysical characteristics. A distinguishing feature of TWIK-1 is its weak inward rectification. Unlike other IRKs, which begin to rectify at potentials positive to −50 mV ([K+]o=5 mmol/L), TWIK-1 begins to rectify at 0 mV. Consequently, TWIK-1 carries significant
outward currents between −60 and 0 mV. HIR is distinguished by its relatively small single-channel conductance (10 pS under symmetrical K⁺ conditions), much less than the other IRKs hIRK (36 pS), TWIK-1 (34 pS), and HH-IRK1 (30 to 49 pS).1–3

Potential Role of Differential IRK Abundance in Native Iₖᵢ Heterogeneity
Iₖᵢ has been studied in many species, including rat, guinea pig, rabbit, and human. A common observation is that atrial Iₖᵢ has a smaller outward current carrying capacity and a smaller current density. Differences in Iₖᵢ are believed to be important in contributing to characteristic differences between atrial and ventricular action potentials, particularly the less negative resting potential and slower terminal repolarization typical of atrial cells. We found that the mRNA concentration of TWIK-1 is 13 times higher in ventricle than in atrium. Because TWIK-1 shows less rectification than the other IRK clones, it is possible that its relative absence in atrium accounts for the small outward current of atrial Iₖᵢ; however, distinct currents typical of TWIK-1 were not detected. HIR transcripts were 12 times more abundant in atrium versus ventricle. The single-channel conductance of HIR is approximately one third less than that of other IRKs, raising the possibility that the greater preponderance of HIR contributes to the smaller macroscopic Iₖᵢ conductance in atrium.

Native Iₖᵢ has been found to show considerable complexity at the single-channel level. Wible et al. demonstrated the presence of four discrete Iₖᵢ channels in human heart tissue. A 21-pS channel was seen in 77% of patches, a 35-pS channel in 60% of patches, a 41-pS channel in 36%, and a 9-pS channel in only 4%. Although these conductances most resembled those of HH-IRK1, TWIK-1, hIRK, and HIR, respectively, none of the native channels were identical to any of the heterologously-expressed cloned channels. In 2 other studies in human atrial cells, only 27-pS channels were described, but open times differed substantially. Our experiments provide evidence for the presence of four different IRKs in both human atrium and ventricle, with distinct differences between atrium and ventricle; however, functional heterogeneity may be produced not only by differences in IRK species but also by heteromultimer formation. Further studies of cardiac IRK protein expression and coassembly are warranted.

IRK Levels in Failing Ventricle
The only other publication on ion channel mRNA concentrations in the failing human ventricle that we were able to identify found that the level of mRNA encoding the DHP receptor was decreased by 47% in patients with heart failure compared with normal control subjects and the number of DHP binding sites was decreased by 35% to 48%. A study in abstract form compared levels of various K⁺ channel mRNA, including Iₖᵢ (IRK clone not specified), in normal and failing human hearts. In agreement with our findings, message levels for Iₖᵢ were not altered in failing hearts. Because IRK mRNA concentrations do not appear to decrease in the failing ventricle, posttranscriptional factors may be important in decreasing Iₖᵢ density.

Potential Limitations
Changes in steady-state levels of mRNA often parallel alterations in protein production and provide insights into underlying molecular mechanisms. For example, Levitan et al. reported parallel inhibition by depolarization of Kv 1.5 voltage-gated K⁺ channel gene transcription and protein expression in pituitary cells. Parallel changes in Kv 2.1 and Kv 4.2 mRNA levels and protein expression were also found in rat ventricles after experimental myocardial infarction. On the other hand, there are well-demonstrated instances of a lack of correlation between mRNA and protein expression. For example, although Kv 1.4 mRNA is present in rat cardiac cells, no proteins corresponding to Kv 1.4 could be found in the membrane. The inward rectification of Iₖᵢ is the consequence of voltage-dependent blockade by Mg²⁺ and polyamines, and the differences in the rectification between atrium and ventricle could be due to different block of Iₖᵢ by Mg²⁺ and polyamines in the 2 tissue types. Thus although the differences in IRK mRNA expression that we found may be important in contributing to differences between atrial and ventricular Iₖᵢ, they are unlikely to be the only factors involved and further research is necessary to evaluate other potential components.

Acknowledgments
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2428  IRK mRNA Quantification in Human Heart


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