Respiratory Systolic Pressure Variability During Atrial Fibrillation and Sinus Rhythm

Maria Vittoria Pitzalis, Francesco Massari, Cinzia Forleo, Agnese Fioretti, Roberto Colombo, Cataldo Balducci, Filippo Mastropasqua, Paolo Rizzon

Abstract—Previous studies have found that respiratory variations of ventricular response in atrial fibrillation are infrequent and inconsistent. This asynchrony between heart rate and respiration may characterize the physiological mechanisms coupling heart rate and systolic blood pressure oscillations in the respiratory band. The aim of this study was to evaluate whether synchronous variations in systolic blood pressure and respiration depend on a simultaneous change in heart rate. Univariate and bivariate spectral analyses were made of the R-R interval, systolic blood pressure, and respiratory signals during controlled respiration (16 breaths/min) in 24 patients with atrial fibrillation before and after efficacious electrical cardioversion and in 24 age- and sex-matched control subjects. During atrial fibrillation, the spectral coherence between respiration and heart rate was low (0.18 ± 0.03), but there was a high level of coherence between respiration and systolic blood pressure (0.67 ± 0.05). After cardioversion, the coherence between respiration and heart rate increased to 0.86 ± 0.04, whereas the geometric mean values of the concomitant respiratory systolic blood pressure oscillations decreased by 72% (from 21.1 to 5.9 mm Hg², P < 0.001), which was similar to that observed in the control group (5.7 mm Hg²). These results confirm the inconsistent effect of respiration on heart rate response during atrial fibrillation and demonstrate that respiratory sinus arrhythmia is not a prerequisite for systolic blood pressure oscillations but may play an antioscillatory role in respiratory systolic blood pressure variability, which is probably mediated by arterial baroreflex mechanisms. (Hypertension. 1999;34:1060-1065.)

Key Words: arrhythmia • blood pressure • heart rate

The clinical hallmark of atrial fibrillation (AF) is an irregular ventricular rhythm. Few studies have investigated the respiratory oscillations of ventricular rhythm during AF,1–3 and only 2–4,5 have made use of spectral analysis. These last 2 studies reported the presence of respiratory arrhythmia during AF in a small percentage of patients, but none measured respiration as a factor of analysis.

The mechanisms underlying the origin of respiratory sinus arrhythmia (RSA) are still debated, but 2 main and not mutually exclusive theories have been put forward: One considers it to be the effect of cycling respiratory stimulation on arterial baroreceptors (the “peripheral” theory), and the other emphasizes the direct role of central respiratory drive (the “central” theory). Bivariate spectral analyses may quantify the relations between the heart period (R-R interval) and systolic blood pressure (SBP) but do not build causality between 2 signals: The spontaneous relation between the R-R interval and SBP fluctuations is a closed loop, and cross-spectral analysis is unable to separate the mechanical R-R–SBP feedforward by baroreflex feedback from SBP to R-R.6

A number of methods7–11 and models12–15 for exploring the fundamental relations between R-R and SBP oscillations in the respiratory band have been suggested, but their results are conflicting.

Random ventricular rhythm during AF may represent a unique model for investigating the origin of RSA because the absence of respiratory-related oscillations in ventricular rhythm may make it possible to characterize respiratory-related SBP oscillations. Furthermore, comparison of respiratory-related oscillations in SBP before and after the restoration of sinus rhythm may make it possible to understand whether or not the variations in blood pressure synchronous with respiration depend on simultaneous changes in heart rate.

The aim of this study was to establish the relations between cardiorespiratory signals during AF and after the restoration of sinus rhythm. In particular, we considered 2 complementary questions (1) Does respiration have consistent effects on ventricular rhythm during AF; and (2) if not, does the magnitude of respiratory-related SBP oscillations during AF change after cardioversion to sinus rhythm?
Methods

Study Patients
The study population consisted of 24 patients (14 men and 10 women; mean age 54±8 years; range 36 to 68 years) hospitalized for elective electrical cardioversion of AF. The median time since the diagnosis of AF was 60±456 days (range 27 to 2190). Patients with intraventricular conduction disturbances, sick sinus syndrome, frequent premature ventricular contractions, or pacemaker-induced rhythms were excluded, as were those who showed any period of atrial flutter or premature ventricular contractions >1/min during signal acquisition. The clinical characteristics of the patients are summarized in Table 1. Care was taken to perform the precadioversion and postcardioversion evaluations while maintaining the same medications, if any. The study also included a control group of 24 normal subjects (14 men and 10 women, age 54±9 years; range 36 to 69) in whom the presence of any disease had been ruled out by means of history, physical examination, routine laboratory tests, ECG, echocardiography, and exercise test. None of them were receiving any medication. The study was approved by the local ethics committee, and all of the participants gave their informed consent.

Electrical Cardioversion
External cardioversion was performed in all of the patients according to the best-known established methods.16 Under the supervision of an anesthesiologist, deep narcosis was induced by means of the nonresistive breathing at a rate of 16 breaths/min for 5 minutes. Tidal volume was not controlled or measured because it has negligible effect on respiratory-mediated autonomic oscillations.17 The test was performed during AF and 24 hours after successful electrical cardioversion while continuously and simultaneously acquiring ECG (R-R intervals), respiration (RESP), and noninvasive SBP data, as previously described.18,19 The respiratory signal was derived from thorax ECG electrodes by means of an impedance pneumograph (Hewlett-Packard model 78354C) and blood pressure from the finger with the use of a Finapres unit (model 2300, Ohmeda) in accordance with Imholz’s suggestions.20 Periods of 200 to 300 beats were selected from the tachogram, systogram, and respirogram time series for spectral analysis (Figure 1).

Spectral Analysis
Power spectral analysis was performed on the R-R intervals, SBP, and respiratory signals by means of an autoregressive technique with the Levinson Durbin algorithm; Anderson’s test was used to check the validity of the model,21 and the model order was selected by use of the Akaike Information Criterion,22 starting from a minimum order of 7. A spectral decomposition algorithm23 was used to measure the centered frequency and the area below the spectral peaks in the respiratory band (near 0.27 Hz). The respiratory oscillations in the R-R interval (ie, RSA) and SBP (ie, Ludwig waves, SBP-HF) spectra were identified by means of cross-spectral analysis24 (expressed in ms² and mm Hg², respectively).

Cross-Spectral Analysis
To assess the relations between signals in the respiratory band, we performed autoregressive bivariate spectral analyses between the R-R intervals and RESP (R-R–RESP), SBP and RESP (SBP–RESP), and R-R intervals and SBP (R-R–SBP) as in previous studies24,25 by use of the squared coherence function (K²) to evaluate the phase stability between the oscillations of 2 signals (range: 0, no relation to 1, close relation) at any frequency and phase function (Φ; range −180° to +180°). When Φ was negative, the first signal was considered as following the second, and vice versa. Φ was expressed in both degree and seconds.26 Furthermore, we calculated the spectral baroreflex gain in the high-frequency band (αHf) as the square root of the ratio of the R-R and SBP variabilities (ms/mm Hg).26

Statistical Analysis
The data are given as mean values±SEM or, when the distribution was strongly skewed, as geometric means and ranges. A Student’s t test for paired data was used to evaluate the differences within the patient group, and an unpaired t test was used for the differences between the patients in sinus rhythm and the control group. A value of P<0.05 was considered significant.

Results
All of the subjects completed the paced breathing test, with none of them having any difficulty in controlling their respiration. Respiratory power was always centered at ≈0.27 Hz in all subjects and under all conditions (Table 2).

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics of Study Patients</th>
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<tbody>
<tr>
<td>Underlying heart disease, n</td>
</tr>
<tr>
<td>Lone arrhythmia</td>
</tr>
<tr>
<td>Systemic hypertension</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Valvular disease</td>
</tr>
<tr>
<td>No medication, n</td>
</tr>
<tr>
<td>Concomitant medication, n</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>β-Adrenergic blocker</td>
</tr>
<tr>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Left atrial diameter, cm</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
</tr>
</tbody>
</table>

Figure 1. Time series of RESP, SBP, and R-R interval signals during AF and after cardioversion to sinus rhythm (SR), a.u. indicates arbitrary units.

<table>
<thead>
<tr>
<th>AF</th>
<th>SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESP (a.u.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>R-R interval (ms)</td>
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</table>

Pitzalis et al Respiratory-Related Systolic Pressure Fluctuations 1061

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Sinus rhythm was restored by means of electrical shocks in all of the patients. The mean number of shocks was 1.3 and the mean delivered energy was 231 J.

**Effects of Sinus Rhythm Restoration**

As expected, the R-R intervals were shorter during AF than during sinus rhythm. The difference in SBP before and after the restoration of sinus rhythm was not statistically significant (Table 2), whereas diastolic blood pressure was statistically lower after cardioversion as a consequence of the longer run-off time. The PR interval in the patient group was 184 ± 6 ms (range 140 to 240 ms).

During AF, ventricular rhythm was decoupled from respiration because of the low degree of $K^2$ between the two signals (0.18 ± 0.03), but this value significantly increased with the reappearance of sinus rhythm (0.86 ± 0.04) (Table 3). Similarly, the relation between the R-R interval and SBP variabilities was low during AF (0.27 ± 0.04) and high after cardioversion (0.8 ± 0.05) (Table 3). The respiratory oscillations in SBP, whose $K^2$ during AF was 0.67 ± 0.05, significantly decreased by 72% during sinus rhythm (Table 2), with a concomitant increase in $K^2$ (0.93 ± 0.03); sinus node restoration had no effect on the $F$ between these 2 signals (Table 3). Examples of spectral analysis are reported in Figure 2 and Figure 3.

**Differences Between Patients and Control Subjects During Sinus Rhythm**

The values of the R-R intervals and systolic and diastolic blood pressures did not differ between the 2 groups (Table 2). The RSA and $aHF$ values were lower in the patients than in the control subjects, but this difference was not statistically signif-

### Table 2: Cardiorespiratory Variables and Their Oscillations in Patients With Atrial Fibrillation Before and After Cardioversion and in Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Group</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AF</td>
<td>SR</td>
<td>Control Group</td>
<td>AF vs SR</td>
<td>SR vs C</td>
<td></td>
</tr>
<tr>
<td>Breathing rate, Hz</td>
<td>0.274±0.002</td>
<td>0.273±0.003</td>
<td>0.275±0.003</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>708±29</td>
<td>885±22</td>
<td>865±19</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>124±4.7</td>
<td>128±4.9</td>
<td>128±3.3</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>65±3.2</td>
<td>59±2.5</td>
<td>62±2.6</td>
<td>0.045</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>RSA, ms²</td>
<td>...</td>
<td>125 (8.6–458)</td>
<td>514 (16–4993)</td>
<td>...</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SBP-HF, mm Hg²</td>
<td>21.1 (4.7–81)</td>
<td>5.9 (1.4–31.8)</td>
<td>5.7 (1.3–19.8)</td>
<td>&lt;0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>$aHF$, ms/mm Hg</td>
<td>...</td>
<td>6 (1.6–17.6)</td>
<td>8.8 (2.4–26)</td>
<td>...</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates during atrial fibrillation; SR, during sinus rhythm; C, control group; R-R–RESP, cross-spectral analysis between R-R interval and respiration signal; SBP–RESP, cross-spectral analysis between systolic blood pressure and respiration signal; R-R–SBP, cross-spectral analysis between R-R interval and systolic blood pressure; $K^2$, spectral coherence; $F$, spectral phase. Values are mean ± SEM.

### Table 3: Cross-Spectral Analysis of Cardiorespiratory Variables in Patients With Atrial Fibrillation Before and After Cardioversion and in Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Group</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AF</td>
<td>SR</td>
<td>Control Group</td>
<td>AF vs SR</td>
<td>SR vs C</td>
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</tr>
<tr>
<td>R-R–RESP</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$K^2$</td>
<td>0.18±0.03</td>
<td>0.86±0.04</td>
<td>0.96±0.02</td>
<td>&lt;0.0001</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>$\phi$, degrees</td>
<td>...</td>
<td>−98.9±26</td>
<td>−100±18</td>
<td>...</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>$\phi$, s</td>
<td>...</td>
<td>−0.93±0.1</td>
<td>−0.98±0.2</td>
<td>...</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SBP–RESP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K^2$</td>
<td>0.67±0.05</td>
<td>0.93±0.03</td>
<td>0.96±0.01</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>$\phi$, degrees</td>
<td>−80±9.2</td>
<td>−77±12</td>
<td>−78±20</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>$\phi$, s</td>
<td>−0.82±0.09</td>
<td>−0.8±0.12</td>
<td>−0.76±0.2</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>R-R–SBP</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$K^2$</td>
<td>0.27±0.04</td>
<td>0.8±0.05</td>
<td>0.94±0.02</td>
<td>&lt;0.0001</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>$\phi$, degrees</td>
<td>...</td>
<td>−8±14</td>
<td>−9±5.8</td>
<td>...</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>$\phi$, s</td>
<td>...</td>
<td>−0.09±0.7</td>
<td>−0.1±0.6</td>
<td>...</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates during atrial fibrillation; SR, during sinus rhythm; C, control group; R-R–RESP, cross-spectral analysis between R-R interval and respiration signal; SBP–RESP, cross-spectral analysis between systolic blood pressure and respiration signal; R-R–SBP, cross-spectral analysis between R-R interval and systolic blood pressure; $K^2$, spectral coherence; $\phi$, spectral phase.

Values are mean ± SEM.
There was no difference between the 2 groups in terms of the magnitude of respiratory SBP variability (Table 2).

The phase lag between the considered signals and the $K^2$ between respiration and SBP were similar in the two groups (Table 3), whereas the $K^2$ between the R-R intervals and SBP, as well as that between respiration and the R-R intervals, was significantly higher in the control group (Table 3).

### Discussion

The main findings of the present study are that (1) respiration has inconsistent effects on ventricular rhythm during AF; and (2) respiratory modulation of heart rate, which is virtually absent during AF, plays an antioscillatory role in SBP variability, probably as a result of arterial baroreflexes.

### Effects of Respiration on Ventricular Rhythm and SBP During AF

Considerable interest has been shown in the possibility of identifying any “regularity” in the irregular ventricular rhythm characterizing AF and in evaluating whether this “regularity” is related to the influence of autonomic nervous system activity. This interest is due to the fact that it has been suggested that reduced heart rate variability during AF may be associated with an adverse prognosis in patients with nonischemic mitral regurgitation or advanced heart failure. Cardiac vagal activity fluctuates with respiration during sinus rhythm, thus leading to the quantifiable phenomenon of RSA, which is associated with parallel changes in atrioventricular conduction. Previous studies have provided evidence indicating the presence of vagal influences on ventricular rhythm in patients with AF, and demonstration of the effect of respiratory oscillations on ventricular rhythm in such patients may provide a noninvasive measure of cardiac vagal activity.

Few studies have so far investigated the possible respiratory effect on ventricular rhythm during AF. In 1920, Kilgore reported respiratory oscillations in 6 of 9 patients with AF, and in 1989, Rawles et al demonstrated the same phenomenon in 14% of patients by means of cosinor analysis. Chandler and Trewby and Nagayoshi et al found that only a small percentage of patients showed respiratory modulation of heart rate during AF (10.5% and 18%, respectively) but, although these are the only studies that used spectral techniques, they have the major limitation that respiration was not measured. The presence of a peak in the R-R interval spectrum at a similar respiratory rate does not necessarily imply a relation with breathing; furthermore, to verify the relation between 2 signals, it is necessary to perform cross-spectral analysis, as shown in Figure 4.
Effects of Sinus Rhythm Restoration

During sinus rhythm, the high coherence values between the considered signals made it possible to evaluate vagal activity on the sinoatrial node by calculating RSA and the αHF. After cardioversion, the magnitude of Ludwig waves decreased by 72%, and there was a synchronous reappearance of RSA. The only explanation for this phenomenon is represented by the mechanical influence of respiration on cardiac output; in particular, respiration modulates venous return, whose modification is transmitted to the left ventricle and causes a variation in arterial pressure. These changes are rapidly buffered by the vagal arm of the arterial baroreflex. Therefore, the reduction in respiratory SBP variability found in the present study appears to be due to the buffering action of the baroreflex on these oscillations: An increase in blood pressure is associated with an increase in R-R intervals. This model is also supported by the value of the phase relation between the R-R interval and SBP (−8°) after cardioversion and in the control group: The fluctuations in the R-R interval appeared to follow SBP fluctuations, and an increase in SBP was associated with a concomitant lengthening in R-R intervals. On the other hand, Taylor and Eckberg’s positive finding of respiratory-related blood pressure oscillations. As expected, no relation was associated with a concomitant lengthening in R-R intervals. On the other hand, Taylor and Eckberg’s positive finding of respiratory-related blood pressure oscillations.

We cannot exclude that lower baroreflex sensitivity in patients as compared with control subjects could be due to 1 or more of the following: drug treatment; systemic hypertension; or an altered activation of atrial cardiopulmonary receptors secondary to a “mechanical stunning” of atrial systolic function, which could interact with arterial baroreflex responsiveness. Moreover, we cannot exclude that the lower stroke volume during atrial fibrillation may cause greater respiratory-related blood pressure oscillations.

Limitations of the Study

We cannot exclude that lower baroreflex sensitivity in patients as compared with control subjects could be due to 1 or more of the following: drug treatment; systemic hypertension; or an altered activation of atrial cardiopulmonary receptors secondary to a “mechanical stunning” of atrial systolic function, which could interact with arterial baroreflex responsiveness. Moreover, we cannot exclude that the lower stroke volume during atrial fibrillation may cause greater respiratory-related blood pressure oscillations.

Figure 4. Example of spectral and cross-spectral data obtained from a subject during AF. In the power spectrum of R-R interval, variability is evident a prominent component (dark area) centered at same frequency of RESP. At first analysis, we may conclude that in this case, respiration influences ventricular rhythm. However, cross-spectral analysis between the 2 signals shows a very low coherence (near 0). Therefore, the variability of R-R interval corresponding to the frequency of breathing is not related to respiration.

We found a low degree of coherence between respiration and heart rate variability during AF (always <0.47), which makes it possible to conclude that the effects of respiration on heart rate variability are weak and inconsistent in this condition. If we had taken the widely accepted cutoff point of 0.5 to define the $K^2$, a statistically reliable measure, none of our patients would have shown any respiratory modulation of R-R intervals during AF.

The absence of respiratory arrhythmia during AF in our patient population was not related to reduced vagal activity; respiratory arrhythmia was found after the restoration of sinus rhythm, and this was not the effect of drugs because medication was the same at both evaluations. On the other hand, SBP oscillated widely during AF, and there was a good level of $K^2$ with respiration, which, in the absence of a synchronous oscillation in heart rate, clearly demonstrates a direct effect of respiration on blood pressure. As expected, no relation was found between R-R intervals and SBP variabilities. These findings suggest that respiratory fluctuations in SBP do not depend on changes in R-R intervals. Similar results have been reported in studies of respiratory-related blood pressure variability in normal subjects after pharmacological autonomic blockade and in heart transplantation patients. When RSA is eliminated, the respiratory modulation of SBP persists.

Effects of Sinus Rhythm Restoration

During sinus rhythm, the high coherence values between the considered signals made it possible to evaluate vagal activity variability in normal subjects after pharmacological autonomic blockade and in heart transplantation patients. These findings suggest that respiratory fluctuations in SBP do not depend on changes in R-R intervals. Similar results have been reported in studies of respiratory-related blood pressure variability in normal subjects after pharmacological autonomic blockade and in heart transplantation patients. When RSA is eliminated, the respiratory modulation of SBP persists.

The role of baroreceptors in influencing SBP is still unclear despite the fact that various studies have attempted to analyze this relation with different models and methods: Some have eliminated RSA by means of pharmacological autonomic blockade or fixed cardiac pacing; others have studied cardiac denervation in heart transplantation patients or in those with autonomic failure. However, the results obtained in these studies are discordant for a number of different reasons, including the presence or absence of cardiac disease, the use of drugs, and the fact that the analyses were performed during controlled breathing.

The importance of the present study is that it is the first to explore the relation between RSA and Ludwig waves with the use of a model in which the R-R intervals are virtually random in the respiratory band.

Limitations of the Study

We cannot exclude that lower baroreflex sensitivity in patients as compared with control subjects could be due to 1 or more of the following: drug treatment; systemic hypertension; or an altered activation of atrial cardiopulmonary receptors secondary to a “mechanical stunning” of atrial systolic function, which could interact with arterial baroreflex responsiveness. Moreover, we cannot exclude that the lower stroke volume during atrial fibrillation may cause greater respiratory-related blood pressure oscillations.
Conclusions
Analysis of cardiorespiratory interactions in patients during AF and after the restoration of sinus rhythm shows that (1) respiratory modulation of heart rate during AF is inconsistent and should therefore be considered virtually absent; and (2) AF represents a unique human model in which respiratory oscillations in heart rate are eliminated, thus making it possible to study the synchrony of SBP oscillations and respiration. The restoration of sinus rhythm is associated with the reappearance of RSA and a marked reduction in SBP oscillations. These findings suggest that in a supine resting position, respiratory sinus arrhythmia may represent the baroreflex buffering of arterial SBP.

References
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