Chronic Electrical Stimulation of the Carotid Sinus Baroreflex Improves Left Ventricular Function and Promotes Reversal of Ventricular Remodeling in Dogs With Advanced Heart Failure

Hani N. Sabbah, PhD, FAHA; Ramesh C. Gupta, PhD; Makoto Imai, MD; Eric D. Irwin, MD; Sharad Rastogi, MD; Martin A. Rossing, BSEE; Robert S. Kieval, VMD, PhD

Background—Autonomic abnormalities exist in heart failure and contribute to disease progression. Activation of the carotid sinus baroreflex (CSB) has been shown to reduce sympathetic outflow and augment parasympathetic vagal tone. This study tested the hypothesis that long-term electric activation of the CSB improves left ventricular (LV) function and attenuates progressive LV remodeling in dogs with advanced chronic heart failure.

Methods and Results—Studies were performed in 14 dogs with coronary microembolization-induced heart failure (LV ejection fraction \( \approx 25\% \)). Eight dogs were chronically instrumented for bilateral CSB activation using the Rheos System (CVRx Inc, Minneapolis, Minn) and 6 were not and served as controls. All dogs were followed for 3 months, and none received other background therapy. During follow-up, treatment with CSB increased LV ejection fraction 4.0 \( \pm 2.4\% \) compared with a reduction in control dogs of 2.8 \( \pm 1.0\% \) (\( P < 0.05 \)). Similarly, treatment with CSB decreased LV end-systolic volume 2.5 \( \pm 2.7\) mL compared with an increase in control dogs of 6.7 \( \pm 2.9\) mL (\( P < 0.05 \)). Compared with control, CSB activation significantly decreased LV end-diastolic pressure and circulating plasma norepinephrine, normalized expression of cardiac \( \beta_1 \)-adrenergic receptors, \( \beta \)-adrenergic receptor kinase, and nitric oxide synthase and reduced interstitial fibrosis and cardiomyocyte hypertrophy.

Conclusions—In dogs with advanced heart failure, CSB activation improves global LV function and partially reverses LV remodeling both globally and at cellular and molecular levels. (Circ Heart Fail. 2011;4:65-70.)

Key Words: heart failure ■ ventricular remodeling ■ gene expression ■ baroreflex function

Clinical Perspective on p 70

Studies in conscious resting normal dogs by Vatner et al \(^{17} \) showed that activation of the carotid sinus reflex through electric stimulation can decrease HR and can also decrease sympathetic constrictor tone during exercise. Studies in patients by Eckberg et al \(^{18} \) showed that electric stimulation of the carotid baroreflex can prolong the R-R interval secondary to augmented parasympathetic activity. These modulation of HR and sympathetic tone are at present recognized as important therapeutic targets in HF. Chronic carotid sinus nerve stimulation has also been shown to be effective in the reversal of systemic arterial hypertension \(^{19} \) and the relief of angina pectoris. \(^{20} \) In the present study, we tested the hypothesis that chronic activation of the CSB through electric stimulation of the carotid sinus nerve will lead to improved LV systolic function, attenuation of progressive LV remod-
eling, decreased sympathetic outflow and normalization of components of the cardiac β-adrenergic receptor, and nitric oxide signal transduction pathways.

Methods

The canine model of coronary microembolization-induced chronic HF used in this study was previously described in detail.21,22 In the present study, 14 healthy mongrel dogs, weighing between 20 and 30 kg, underwent serial coronary microembolization to produce HF. Embolization was performed 1 to 2 weeks apart and was discontinued when LV ejection fraction (EF), determined angiographically, was approximately 25%. All the procedures were performed during cardiac catheterization, under general anesthesia and sterile conditions. Induction of anesthesia was initiated with intravenous administration of hydromorphone (0.22 mg/kg) and diazepam (0.17 mg/kg), and a plane of anesthesia was maintained with 1% to 2% isoflurane. The study was approved by Henry Ford Health System Institutional Animal Care and Use Committee and conformed to the National Institute of Health “Guide and Care for Use of Laboratory Animals.”

Carotid Sinus Stimulation and Study Protocol

Eight of 14 dogs were selected at random and chronically instrumented for CSB activation using the Rhoes System (CVRx, Inc, Minneapolis, Minn) and 6 were not and served as controls. The implant procedure and stimulation of the CSB was carried out as previously described.10,23 Briefly, stimulating electrodes were implanted circumferentially around both carotid sinuses and connected to the implantable pulse generator. Efficacy of the stimulation algorithm and proper placement of the electrodes were confirmed at the time of surgery by 3 to 4 acute stimulation runs performed 3 to 5 minutes apart and each confirming an acute drop of blood pressure and a reduction of HR. A period of at least 2 weeks was allowed to ensure that the electrodes had healed into place. Dogs assigned to the CSB treatment group received a predetermined voltage with 0.5- to 1.0-ms square wave pulses at 50 to 100 Hz at a duty cycle of 9 minutes on and 1 minute off. This was maintained unchanged for the 3-month duration of the therapy. Hemodynamic, ventriculographic, echocardiographic, Doppler, ECG, and plasma norepinephrine measurements were made before initiating therapy (pretreatment) and after completing 3 months of therapy or follow-up (after treatment). All hemodynamic and ventriculographic measurements were made during cardiac catheterization. After completing the last catheterization and while under general anesthesia, the dog’s chest was opened; the heart was rapidly removed, and LV tissue was prepared for histological and biochemical evaluation.

Hemodynamic, Ventriculographic, and ECG Measurements

In all instances, CSB therapy was turned off for the duration of the cardiac catheterization for hemodynamic evaluation. Aortic and LV pressures were measured with catheter-tip micromanometers (Millar Instruments, Houston, Tex). Left ventriculograms were obtained with the dog placed on its right side and recorded on 35-mm cine film at 30 frames per second during the injection of 20 mL of contrast material (RENO-M-60 Squibb, Princeton, NJ). Correction for image magnification was made with a radiopaque calibrated grid placed at the level of the LV. LV end-diastolic pressure (EDP) and LV end-diastolic volume (LVEDV) were calculated from LV cineangiograms using the area-length method,24 and LVEF was calculated as previously described.25 Cardiac output was calculated as the product of stroke volume and HR. Extrasystolic and postextrasystolic beats were excluded from any of the angiographic analysis. Ventriculograms were evaluated unblinded because of device visualization. To minimize bias, random ventriculograms were selected for review by a second reader for concordance. All dogs underwent a pretreatment and a posttreatment 24-hour ambulatory ECG Holter monitoring study. Full Holter disclosures were used to measure maximum, minimum, and average HR and exclude any proarrhythmic potential of CSB therapy. Levels of norepinephrine in plasma extracted from peripheral venous blood samples was measured by competitive ELISA.26

Echocardiographic and Doppler Flow Measurements

Echocardiographic and Doppler studies were performed using a 77030A ultrasound system (Hewlett-Packard) with a 3.5-MHZ transducer. All echocardiographic measurements were made with the dog placed in the right lateral decubitus position and recorded with a 30-frame per second during the injection of 20 mL of ECG Measurements

Hemodynamic, Ventriculographic, and echocardiographic, Doppler, ECG, and plasma norepinephrine measurements were made before initiating therapy (pretreatment) and after completing 3 months of therapy or follow-up (after treatment). All hemodynamic and ventriculographic measurements were made during cardiac catheterization. After completing the last catheterization and while under general anesthesia, the dog’s chest was opened; the heart was rapidly removed, and LV tissue was prepared for histological and biochemical evaluation.

Histomorphometric Measurements

From each heart, 3 transverse slices (approximately 3 mm thick), 1 each from basal, middle, and apical thirds of the LV, were obtained. From each slice, transmural tissue blocks were obtained and embedded in paraffin blocks. Transmural tissue blocks were also obtained from the free wall segment of the slice, mounted on cork using Tissue-Tek embedding medium, and rapidly frozen in isopentane precooled in liquid nitrogen and stored at −70°C until used. For each histomorphometric measure, the multiple slices obtained from each animal were averaged, and that single average was used to represent each animal in the analysis. The volume fraction of replacement fibrosis (VFRF), volume fraction of interstitial fibrosis (VFIF), myocyte cross-sectional area (MCSA), a measure of cardiomyocyte hypertrophy, capillary density (CD), and oxygen diffusion distance (ODD) were measured as previously described.29,30 LV tissue from 6 normal dogs was processed in an identical manner as above and the results used for comparisons.

mRNA Expression

mRNA expression of the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH), cardiac β-adrenergic receptor and β-arrestin, β-adrenergic receptor kinase, adenylyl cyclase, angiotsinogen, endothelial nitric oxide synthase (eNOS), and inducible nitric oxide synthase (iNOS) was measured in LV tissue from all study dogs and from LV tissue of 6 normal dogs for comparison. Total RNA with an absorbance ratio (260 nm/280 nm) above 1.7 was isolated from frozen LV tissue, and approximately 4 to 10 μg of RNA was reverse-transcribed into cDNA in an assay volume of 80 μL, as described previously.29,31 Fluorescent band intensity was quantified using a Bio-Rad GS-670 imaging densitometer and expressed in densitometric units.

Statistical Analysis

Within-group comparisons of hemodynamic, ventriculographic, echocardiographic, Doppler, and ECG variables were made between measurements obtained at pretreatment and measurements made at posttreatment after completion of 3 months of therapy using Wilcoxon signed rank tests with a significance set at P<0.05. To ensure that all study measures were similar at pretreatment, between or intergroup comparisons were made using a Wilcoxon rank sum test with α set at 0.05. To assess treatment effect, the change (Δ) in each measure from pretreatment to posttreatment was calculated for each of the 2 study arms. To determine whether significant differences in Δ were present between the control group and the CSB treatment groups, Wilcoxon rank sum tests were performed with α set at 0.05.
Comparisons of Treatment Effect

Between-group comparisons of the change between pretreatment and posttreatment measurements are shown in Table 2.

### Results

**Within-Group Changes of Hemodynamic, Ventriculographic, and Echocardiographic, and Plasma Norepinephrine Measures**

Hemodynamic, ventriculographic and plasma norepinephrine results obtained at pretreatment and posttreatment in CSB-treated dogs and controls are shown in Table 1. There were no significant differences between the 2 study groups in any of the measurements obtained at pretreatment. Comparisons of hemodynamic, angiographic, echocardiographic, Doppler, and neurohormonal measures between pretreatment and posttreatment in control dogs and dogs treated with CSB are shown in Table 1. In untreated control dogs, LV EDV and ESV measured from ventriculograms increased, and EF, also measured from ventriculograms, decreased significantly at posttreatment compared with pretreatment (Table 1). In contrast, in dogs treated with CSB, LV EDV was unchanged, ESV decreased, and EF increased significantly at posttreatment compared with pretreatment (Table 1).

**Comparisons of Treatment Effect**

Between-group comparisons of the change between pretreatment and posttreatment measurements are shown in Table 2.

There were no significant differences in HR (obtained under anesthesia) and mean aortic pressure between the 2 study groups. Compared with controls, CSB activation decreased LV end-diastolic pressure and increased both stroke volume and cardiac output. CSB activation therapy also significantly decreased EDV and ESV measured from ventriculograms and increased LVEF, also measured from ventriculograms, compared with control. It also significantly increased both EDSI and ESSI, indicating some physiological restoration of LV shape. Along with improvement in LV systolic function and global LV remodeling, active CSB therapy also improved LV diastolic function, as evidenced by a significant reduction of EDWS, a significant increase of the ratio of peak mitral flow velocity in early diastole (PE) and peak mitral inflow velocity during left atrial contraction (PA); EDWS, circumferential end-diastolic wall stress; MR, functional mitral regurgitation; and PNE, plasma norepinephrine.

### Ambulatory ECG Holter Monitoring

Twenty-four-hour ambulatory ECG Holter monitoring obtained at pretreatment and posttreatment showed no de novo ventricular arrhythmias in dogs treated with CSB activation therapy. In control dogs, maximum HR increased from 119 ± 40 to 158 ± 32 bpm, average HR increased from 69 ± 22 to 76 ± 15 bpm, and minimum HR increased from 39 ± 11 to 45 ± 11 bpm. None of these increases reached statistical significance. In CSB-treated dogs, maximum HR decreased from 161 ± 40 to 122 ± 47 bpm, average HR decreased from 92 ± 19 to
Table 2. Treatment Effect (Δ) Comparison Between Controls and Dogs Treated With CSB Activation

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6)</th>
<th>CSB Activation (n=8)</th>
<th>Wilcoxon P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHR, bpm</td>
<td>5 ± 6</td>
<td>0 ± 6</td>
<td>0.154</td>
</tr>
<tr>
<td>ΔmAoP, mm Hg</td>
<td>13 ± 18</td>
<td>−2 ± 15</td>
<td>0.106</td>
</tr>
<tr>
<td>ΔLVEDP, mm Hg</td>
<td>2 ± 4</td>
<td>−4 ± 3</td>
<td>0.008</td>
</tr>
<tr>
<td>ΔCO, L/min</td>
<td>0.00 ± 0.14</td>
<td>0.23 ± 0.23</td>
<td>0.045</td>
</tr>
<tr>
<td>ΔSV, mL</td>
<td>−1.2 ± 1.6</td>
<td>3.1 ± 2.2</td>
<td>0.003</td>
</tr>
<tr>
<td>ΔLVEF, %</td>
<td>−2.8 ± 1.0</td>
<td>4.0 ± 2.4</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔLVEDV, mL</td>
<td>5.5 ± 3.5</td>
<td>0.6 ± 2.9</td>
<td>0.016</td>
</tr>
<tr>
<td>ΔLVESSV, mL</td>
<td>6.7 ± 2.9</td>
<td>−2.5 ± 2.7</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔLVEDS</td>
<td>−0.05 ± 0.05</td>
<td>0.03 ± 0.04</td>
<td>0.012</td>
</tr>
<tr>
<td>ΔLVEDS, mg</td>
<td>−0.07 ± 0.06</td>
<td>0.02 ± 0.04</td>
<td>0.014</td>
</tr>
<tr>
<td>ΔOT, ms</td>
<td>−5.7 ± 5.1</td>
<td>10.6 ± 14.6</td>
<td>0.070</td>
</tr>
<tr>
<td>ΔPE/PA</td>
<td>−0.12 ± 0.11</td>
<td>0.29 ± 0.44</td>
<td>0.010</td>
</tr>
<tr>
<td>ΔLVEDWS, g/cm²</td>
<td>11.2 ± 9.8</td>
<td>−11.0 ± 11.0</td>
<td>0.005</td>
</tr>
<tr>
<td>ΔMR, %</td>
<td>5.1 ± 4.7</td>
<td>−4.1 ± 4.8</td>
<td>0.007</td>
</tr>
<tr>
<td>ΔPNE, pg/mL</td>
<td>70 ± 125</td>
<td>−121 ± 121</td>
<td>0.12</td>
</tr>
</tbody>
</table>

mAoP indicates mean aortic pressure; LVEDP, LV end-diastolic pressure; CO, cardiac output; SV, stroke volume; LVEF, LVEF from ventriculograms; EDV, end-diastolic volume from ventriculograms; ESV, end-systolic volume from ventriculograms; ESSV, end-systolic sphericity index from ventriculograms; EDSV, end-diastolic sphericity index from ventriculograms; PE/PA, ratio of peak mitral flow velocity in early diastole (PE) and peak mitral inflow velocity during left atrial contraction (PA); EDWS, circumferential end-diastolic wall stress; MR, functional mitral regurgitation; and PNE, plasma norepinephrine.

64 ± 18 bpm, and minimum HR decreased from 54 ± 18 to 38 ± 11 bpm. None of these reductions of HR reached statistical significance. Treatment effect comparisons between groups showed a marked reduction of maximum, average, and minimum HR after CSB therapy compared with control, but again this reduction did not reach statistical significance.

Histomorphometric Findings

Histomorphometric findings are shown in Table 3. Compared with normal dogs, control HF dogs showed a significant increase in VFRF, VFIF, ODD, and MCSA and a significant decrease in CD (Table 3). Compared with control, treatment with CSB activation resulted in a significant reduction of VFRF, VFIF, ODD, and MCSA and a significant increase in CD (Table 3).

Table 3. Histomorphometric Findings at the End of 3 Months in Normal Dogs, Control Dogs, and Dogs Treated With CSB Activation

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=6)</th>
<th>Control (n=6)</th>
<th>CSB Activation (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFRF, %</td>
<td>0.0 ± 0.0</td>
<td>21.0 ± 2.6*</td>
<td>15.7 ± 3.8*†</td>
</tr>
<tr>
<td>VFIF, %</td>
<td>3.7 ± 0.2</td>
<td>12.3 ± 1.4*</td>
<td>9.9 ± 0.7*†</td>
</tr>
<tr>
<td>MCSA, μm²</td>
<td>409 ± 26</td>
<td>736 ± 57*</td>
<td>585 ± 22*†</td>
</tr>
<tr>
<td>CD, cap/fiber</td>
<td>1.00 ± 0.0</td>
<td>0.95 ± 0.05*</td>
<td>1.03 ± 0.05†</td>
</tr>
<tr>
<td>ODD, μm</td>
<td>8.9 ± 0.5</td>
<td>11.6 ± 0.4*</td>
<td>10.5 ± 0.3†</td>
</tr>
</tbody>
</table>

Cap/LL indicates capillary density for fiber; CD, capillary density based on capillary-to-fiber ratio (cap/fiber); MCSA, myocyte cross-sectional area; ODD, oxygen diffusion distance; VFRF, volume fraction of interstitial fibrosis; and VFRF, volume fraction of replacement fibrosis.

mRNA Expression Findings

Results from mRNA expression analyses are shown in Table 4. As expected, expression of GAPDH was the same in controls and CSB-treated dogs. Compared with normal dogs, mRNA expression of cardiac β1-adrenergic receptor, adenyly cyclase, and eNOS decreased significantly in untreated HF control dogs, whereas expression of cardiac β-adrenergic receptor kinase, angiotensinogen, and iNOS increased significantly. There was no difference in the expression of cardiac β1-adrenergic receptor between normal dogs and HF controls. Treatment with CSB activation partially normalized expression of all the dysregulated genes (Table 4).

Discussion

The sustained increase in sympathetic outflow in HF along with the ensuing vasoconstriction has long been thought to precipitate a positive feedback mechanism that leads to worsening of HF evidenced by progressive deterioration of LV function, progressive LV remodeling, end-organ damage, and ultimately, death.1–5,32 Therapies that target a reduction of sympathetic overdrive and enhance parasympathetic drive are desirable in the management of chronic HF. Results of this study indicate that long-term therapy with CSB improves global LV systolic and diastolic function in dogs with advanced HF. The improvement of LV function was accompanied by improvement in global LV remodeling evidence by reduced LV size and partial restoration of LV shape to one that is more ellipsoidal rather than spherical.

In the present study, chronic carotid sinus electric stimulation or CSB therapy in dogs with chronic HF resulted in partial normalization of components of the cardiac β-adrenergic signal transduction specifically, upregulation of β1-adrenergic receptors and adenyly cyclase, and downregulation of β-adrenergic receptor kinase. This was accompanied by a significant reduction of circulating plasma norepinephrine. Chronic CSB therapy also resulted in downregulation of angiotensinogen and hence a possible partial deactivation of the vasoconstrictive influence of the tissue renin-angiotensin- adosterone system. Interestingly, CSB therapy also normalized nitric oxide signaling, evidenced by normalization of
both eNOS and iNOS. Normalization of the nitric oxide pathway can have important benefits on the progression of HF through vascular effects related to afterload reduction and reduced myocardial oxygen consumption. In the present study, normalization of signal transduction pathways was associated with improved systolic and diastolic global LV function and partial reversal of LV global and cellular remodeling. The latter also was evidenced by a reduction of VFRF, VFIF, ODD, and MCSA and an increase of capillary density. CSB therapy also tended to decrease HR in conscious HF dogs, providing some supportive evidence for CSB as a modulator of parasympathetic activity.

The present study cannot provide a definitive mechanism for the observed improvement of LV systolic and diastolic function from chronic CSB therapy. A paramount observation of this study was a reduction in sympathetic activity and normalization of the cardiac β-adrenergic receptor signal transduction pathway. Cardiac sympathetic dysfunction is a prime therapeutic target in HF, and successful use of β-adrenergic blockers in HF is a testament to this. Another possible mechanism is attenuation of the enhanced activity of the peripheral renin-angiotensin-aldosterone system. In a study in dogs with pacing-induced HF, Zucker et al. suggested that the improvement in survival seen in their study may also be due in part to enhanced endothelial function mediated by chronic CSB therapy. They postulated that this benefit may have resulted from reduced levels of circulating plasma norepinephrine and angiotensin II seen also in their study. In the present study, we observed a normalization in the expression of cardiac endothelial and inducible nitric oxide synthases, enzymes that catalyze the production of nitric oxide from L-arginine. Nitric oxide plays a vital role in several biological processes that include modulation of the immune system and vasodilatation of blood vessels. Finally, another possible contributor to the improvement of LV function with chronic CSB therapy is the observed reduction of HR in treated dogs. Even though this reduction of HR did not reach statistical significance, the magnitude of the reduction is in line with reduction seen after chronic therapy with β-blockers in patients with HF.

There are limitations to the study that warrant discussion. Whereas the absence of background therapy with angiotensin-converting enzyme inhibitors, β-adrenergic receptor blockers, and/or aldosterone antagonists focuses attention on the direct effects of CSB therapy, it does limit extrapolation of the results to patients who would surely be receiving established HF therapy. The present study is also limited by the absence of data on the effects of CSB on exercise tolerance, a measure often used to assess the efficacy of therapy in patients with HF.

In conclusion, the results of the present study indicate that long-term therapy with CSB improves global LV systolic and diastolic function in dogs with advanced HF. The improvement of LV function was accompanied by improvement in global LV remodeling evidenced by reduced LV size and partial restoration of LV shape to one that is more ellipsoidal rather than spherical. Global LV remodeling was also accompanied by structural remodeling at the cellular level as well as by correction, albeit in part, of molecular abnormalities characteristic of the HF state, as evidenced by normalized expression of cardiac β1-adrenergic receptor and nitric oxide signal transduction pathways along with and reduced interstitial fibrosis and cardiomyocyte hypertrophy. These experimental results support the initiation of clinical trials in patients with systolic HF. At present, the CSB Rheos System used in the present study is being tested in a clinical trial in patients with refractory hypertension, titled “Device-Based Therapy for Hypertension” (DEBuT-HT), and in a trial in patients with HF and preserved LVEF, titled “Rheos Health Outcomes Prospective Evaluation for Heart Failure with EF ≥40%” (HOPE4HF).

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Disclosures
Dr Sabbah has received grant funding from and was a consultant to CVRx, Inc; Dr Erwin is a consultant to CVRx, Inc; and Drs Rossing and Kieval are full-time employees of CVRx, Inc.

References
Despite major advances in the development of new drugs for the treatment of chronic heart failure, the mortality and morbidity from this disease syndrome remain unacceptably high. In some patients, the use of life-saving standard pharmacological therapy such as angiotensin-converting enzyme inhibitors, β-adrenergic receptor blockers, and aldosterone antagonists is suboptimal because of poor tolerability. Even in patients with heart failure who have over the years tolerated and benefited from these pharmacological therapies, a time is reached when their effectiveness wanes and symptomatology from the disease increases, and new therapeutic interventions are needed. In the present study, we tested a novel device-based therapy that can potentially be used in the treatment of such patients. The approach, termed chronic activation of the carotid sinus baroreflex, which acts via electric stimulation of the carotid sinus nerve, was tested as monotherapy in dogs with experimental heart failure. Compared with no therapy at all, chronic carotid sinus baroreflex treatment resulted in improved left ventricular systolic and diastolic function and attenuation of left ventricular remodeling. The improvement in ventricular function was associated with reduced left ventricular filling pressure, reduced left ventricular size, and lowering of heart rate, along with normalization of components of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the nitric oxide signaling pathway. All of these benefits argue in favor of carotid sinus baroreflex therapy, which is likely to provide benefit to patients with advanced chronic heart failure. Translation of the results of this study to the clinical setting, however, must be used with care, given that the experimentation was conducted in the absence of standard background medical therapy, as would certainly be the case in patients.
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