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Development of Baroreflex Control of Heart Rate in Swine

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ABSTRACT. The purpose of this study is to describe the developmental course of arterial baroreflex control of heart rate in swine. Tests of baroreflex function were performed with eight conscious piglets serially over their first 2 mo of life. Systemic blood pressure was raised with phenylephrine (pressor test) and lowered with nitroprusside (depressor test), and stimulus-response curves relating heart rate to mean blood pressure were constructed. Baroreflex sensitivity was determined as the slope of the linear portion of the curve. Baroreflex sensitivity decreased with increasing age. Baroreflex sensitivity was not different between pressor and depressor tests except when the piglets were >52 d old and sensitivity was greater with the depressor test. The heart rates at threshold and saturation, and therefore the heart rate response range, shifted to lower heart rates with increasing age. This shift was more than can be accounted for by the simultaneously decreasing resting heart rate. (*Pediatr Res* 27: 148–152, 1989)

Arterial baroreceptors maintain hemostasis in the circulatory system by buffering acute alterations in arterial blood pressure with adjustments in cardiac output and peripheral vascular resistance. These acute alterations in blood pressure happen with common occurrences such as changes in posture, emotions, and exercise, and the ability of the newborn organism to tolerate these and other stressful disturbances depends on the functional state of the arterial baroreflex. Several investigators have demonstrated immaturity or decreased function of the arterial baroreflex in neonatal animals (1–4) and humans (5, 6). However, other investigators have not demonstrated immaturity (7–11). This conflict may in part reflect the fact that different components of the arterial baroreflex, *i.e.* cardiac output or vascular resistance control mechanisms, mature at different rates. When one examines a single component, such as the heart rate response, conflicting results may in part be due to differences in species, in modes of stimulation, in methods of response analysis, and in state of consciousness, *i.e.* anesthetized *versus* unanesthetized.

The purpose of our study is to describe the developmental course of arterial baroreflex control of heart rate in conscious infant swine. Swine were chosen as the experimental animals because a body of work, mostly from Gootman and colleagues (2, 12–16), indicates that in this species maturation of cardiovascular reflexes occurs over the first weeks of life. Our study with swine is unique in that the same animals are followed serially through the first 2 mo of life, and all studies are performed with conscious animals. The unaltered integrated baroreflex response can be fully evaluated only in a conscious state because anesthesia depresses the reflex at multiple peripheral and central sites (17, 18).

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MATERIALS AND METHODS

Animal preparation. Experiments were performed with eight farm piglets from three litters (spotted China-Poland breed). The animals were weaned and brought to the research facility at 3 d of age. Chronic indwelling vascular catheters (Vascular-Access-Ports, Access Technologies, Skokie, IL) were placed in the right common carotid artery and left internal jugular vein as previously described (19). Briefly, Vascular-Access-Ports consist of a catheter and a reservoir that are totally implanted in the subcutaneous tissue. The reservoir contains a self-sealing rubber septum that is pierced by a deflected-point Huber needle to gain access to the vascular system. The ports were placed in the animals under general halothane anesthesia using aseptic surgical technique. Two reservoirs were placed in the dorso-lateral neck, one on each side of the mid-line. The catheters were tunneled to the ipsilateral ventral neck and inserted into either the carotid artery or jugular vein. For arterial access, the right common carotid artery was cannulated with a 3.5 Fr. polyurethane catheter and the tip was passed to the abdominal aorta. For venous access, the left internal jugular vein was cannulated with a 5 Fr. silicone catheter and the tip was passed to the right atrium. The carotid catheter was secured in the vessel with non-occluding ligatures, but because of its relatively large size in comparison to the vessel, the catheter partially occluded flow to the right common carotid artery and right carotid sinus. Because of a potential pressure differential between the right carotid sinus and the rest of the systemic circulation due to the occlusion, the right carotid sinus was denervated. Denervation was accomplished as follows: the carotid bifurcation was identified just distal to the occipital artery; then the carotid sinus and contiguous regions of the internal and external carotid arteries were stripped of adjoining tissue; finally, the carotid sinus nerve was cut at its point of exit from the sinus region. The catheters were coiled in the subcutaneous layer at two sites, near the entrance to the vessel and also near the reservoir, to provide additional length to accommodate growth of the animals. The animals were allowed to recover from general anesthesia for at least 36 h before baroreflex testing was initiated.

Experimental protocol. This study was approved by the Medical College of Wisconsin Animal Care and Use Committee. During each experiment the animal rested quietly in an upright position supported in a sling. Some animals in their first 2 wk of life slept during the experiment. Resting heart rate and blood pressure were recorded for at least 2 min with the animal in a quiet and unmedicated state. Then baroreflex control of heart rate was tested using a modification of the methods of Smyth

and Pickering and coworkers (20, 21). Intravenous infusions of phenylephrine (Neo-Synephrine HCl, Winthrop-Breon Laboratories, New York, NY), 167 μg/mL in a solution of 5% dextrose and 0.2% normal saline, and nitroprusside (USP LyphoMed, Inc., Rosemont, IL), 100 μg/mL in the same type dextrose solution, were alternated to raise and lower blood pressure throughout the range of baroreceptor activity. Drug doses were titrated to change the blood pressure at an approximate rate of 20 mm Hg/min. The doses of phenylephrine used were 12 ± 5 μg/kg/min (mean ± SD) and the doses of nitroprusside used were 10 ± 4 μg/kg/min (mean ± SD). The blood pressure was raised or lowered until there was no further change in heart rate. This was generally achieved within 1–2 min. The drugs were alternated with phenylephrine infused first to raise blood pressure until heart rate reached a minimum plateau. Then phenylephrine was discontinued and when blood pressure began to decrease, nitroprusside was infused to lower blood pressure until heart rate peaked. Then phenylephrine was infused again, and so on until at least three tests free of artifact for each drug were obtained. In this manner multiple replications were obtained for statistical analysis, and the possibility of obtaining biased data due to acute baroreceptor resetting or to change in background autonomic activity (secondary to other stimuli) was minimized.

Measurements. Direct arterial blood pressure, electrocardiogram, and heart rate were continuously displayed by a polygraph (model 7, Grass Instrument Co., Quincy, MA). The blood pressure transducer (DTX, Spectramed, Inc., Oxnard, CA) was calibrated with a mercury manometer. A lead of the ECG that clearly displayed P waves was monitored, and the heart rhythm was sinus for all data used for analysis. The arterial blood pressure wave form and ECG were also continuously displayed on an oscilloscope (model 5113, Tektronix, Beaverton, OR) and recorded on magnetic tape (Vetter model D Instrumentation Recorder, Redersburg, PA). Blood pressure was electronically meaned using a second order Bessel low pass filter with an averaging window of 2 s. R-R interval was measured by setting a voltage threshold on the R wave of the ECG such that levels exceeding this threshold generated rectangular voltage pulses. The time between successive pulses was measured using an 8-bit counter/timer with D/A output, providing a continuous reading of R-R interval with a resolution of 5 ms. For each blood pressure maneuver, mean blood pressure and R-R interval were sampled at 5 Hz using a Hewlett-Packard 310 computer (Hewlett-Packard Co., Palo Alto, CA) equipped with an Infotek AD 200 12 bit A/D converter. R-R- interval was converted to heart rate and both signals were stored in floppy disk files for later graphical and statistical analysis. Rectal temperature was monitored for piglets that weighed less than 10 kg and kept in the normal range (38–39°C) with an overhead radiant heater.

Baroreflex analysis. To evaluate baroreflex control of heart rate, the relationship between heart rate and mean systemic blood pressure was examined. This relationship is sigmoidal and exhibits threshold, a linear range, and saturation. Stimulus-response curves relating mean blood pressure and heart rate were constructed for each blood pressure manipulation (Fig. 1). Baroreflex sensitivity is the slope (bpm/mm Hg) of the linear portion as determined by the method of least squares linear regression. Only regressions with correlation coefficients ≥0.8 were used in statistical analysis. The steeper the slope, or the greater the change in heart rate per change in blood pressure, the greater the baroreflex sensitivity. Threshold and saturation blood pressures and the heart rates at threshold and saturation were also noted. These define the operating ranges for the heart rate response.

To determine the maturation pattern of baroreflex control of heart rate, each piglet was tested at weekly or biweekly intervals over the first 2 mo of life. At the time of initial testing their ages ranged from 5 to 9 d and they weighted 1.9 ± 0.2 kg (mean ± SD). Ages and wt at the time of final testing were 54.5 ± 5.5 d and 15.3 ± 3.2 kg (mean ± SD), respectively. The animals were healthy throughout the experimental period as judged by activity,

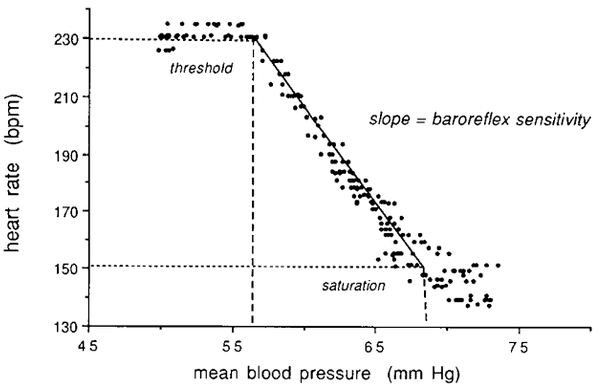

Fig. 1. Stimulus-response curve for 6-d-old piglet. The regression line for the linear portion of the curve is displayed. Baroreflex sensitivity is the slope of the line. Threshold and saturation are the minimum and maximum pressures, respectively, of the line. Heart rates at threshold and saturation are also indicated.

feeding, growth, resting heart rate, and blood pressure (Fig. 2), and arterial pH and blood gas tensions (22–25).

Statistical analysis. Pressor and depressor curves exhibit hysteresis of the linear portion (20), so baroreflex sensitivity was analyzed separately for these tests. A multifactor analysis of covariance (26) with replication was used to test for the effect of age on baroreflex sensitivity. Because baroreflex sensitivity is effected by other factors that change with age, *i.e.* resting blood pressure (27–33) and resting heart rate (34, 35), interaction between these variables was examined by analysis of covariance using age as the last sequential covariate. With this method an adjustment is made for the effects of resting blood pressure and resting heart rate by eliminating the variability in baroreflex sensitivity due to these factors. This allows an examination of the residual variability due to age alone. For analysis of covariance, data for each animal were treated as a continuous function of age and the age groups presented in Figures 2–5 are for graphical representation of trends and do not represent statistical grouping.

To determine at which age(s) changes occur in baroreflex sensitivity, the effect of age on baroreflex sensitivity was also tested using the Waller-Duncan multiple comparisons test. For this test the animals were grouped by age: 5–9 d (n = 8), 12–19 d (n = 3), 22–32 d (n = 8), 36–45 d (n = 6), and 54–57 d (n = 7). For each age group baroreflex sensitivity was also compared between pressor and depressor tests. Statistical significance is defined as $p < 0.05$.

A multifactor analysis of covariance with replication was also used to test for the effect of age on resting heart rate, resting blood pressure, heart rates at threshold and saturation, and threshold and saturation blood pressures. Interactions between heart rate at threshold, age and resting heart rate, and between heart rate at saturation, age, and resting heart rate were examined as described above in order to eliminate the effect of the resting variable. Similarly, interactions between threshold blood pressure, age, and resting blood pressure, and between saturation blood pressure, age, and resting blood pressure were also examined. Threshold blood pressure and heart rate at saturation were determined from the phenylephrine pressor test, and saturation blood pressure and heart rate at threshold were taken from the nitroprusside depressor test. These values represent heart rates after maximal change and blood pressures at initiation of heart rate change and for their respective tests.

RESULTS

Baroreflex sensitivity decreased with age between 5 and 59 d of age for both the phenylephrine pressor test and the nitroprus-

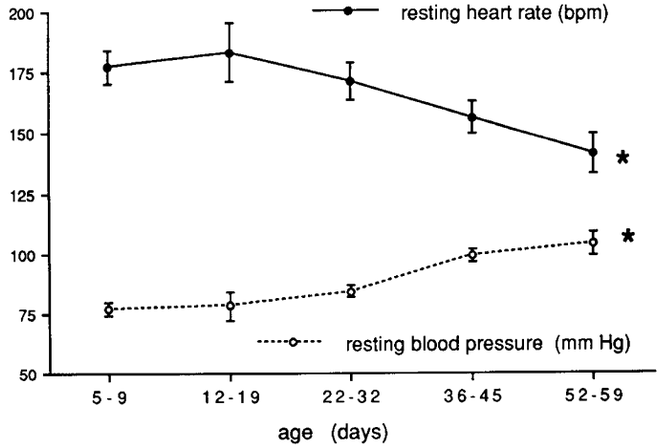

Fig. 2. Resting heart rate and resting blood pressure. *, significant change over age range 5 to 59 d ($p < 0.0001$). Values are mean ± SEM.

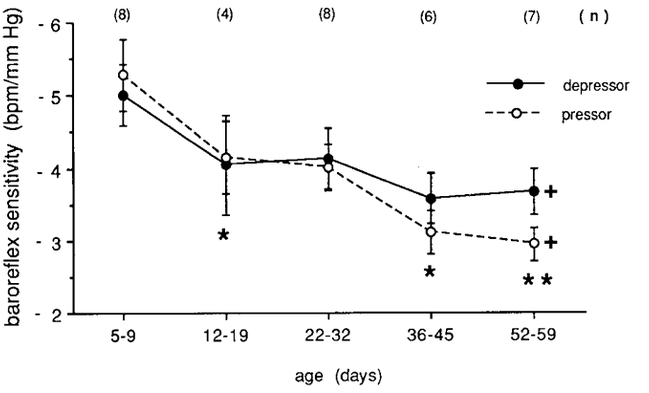

Fig. 3. Baroreflex sensitivity and age. +, significant decrease over age range 5 to 59 d (analysis of covariance, $p < 0.0001$). *, significant difference from preceding age group for both pressor and depressor tests (Waller-Duncan, $p < 0.05$). **, significant difference between pressor and depressor tests for age group (Waller-Duncan, $p < 0.05$). Values are mean ± SEM.

side depressor test ($p < 0.0001$) (Fig. 3). For the pressor test sensitivity decreased from −5.28 ± 0.48 to −2.95 ± 0.23 bpm/mm Hg (mean ± SEM), and for the depressor test sensitivity decreased from −5.00 ± 0.42 to −3.67 ± 0.31 bpm/mm Hg (mean ± SEM). These relationships persisted when adjustments (as described above) were made for the effects of resting blood pressure and resting heart rate on baroreflex sensitivity ($p < 0.001$). Significant changes were found for both pressor and depressor tests between 5 to 9-d-old and 12 to 19-d-old groups, and between 22 to 32-d-old and 36 to 45-d-old groups ($p < 0.05$). Baroreflex sensitivity was greater for the depressor test than the pressor test in the oldest group (52–59 d old) ($p < 0.05$). In other age groups, baroreflex sensitivity was not different between pressor and depressor tests.

Heart rate at threshold decreased with age from 211 ± 10 to 175 ± 8 bpm (mean ± SEM) ($p < 0.0001$) and heart rate at saturation decreased with age from 140 ± 9 to 114 ± 6 bpm (mean ± SEM) ($p < 0.001$) (Fig. 4). These relationships persisted when adjustments were made for the effect of resting heart rate ($p < 0.001$). Resting heart rate was within the heart rate response range.

Threshold blood pressure increased with age from 57 ± 2 to 90 ± 3 mm Hg (mean ± SEM) ($p < 0.0001$) and saturation blood pressure increased with age from 66 ± 2 to 101 ± 2 mm Hg (mean ± SEM) ($p < 0.0001$) (Fig. 5). These relationships persisted when adjustments were made for the effect of resting blood pressure ($p < 0.001$). Resting heart rate decreased with age from 177 ± 20 to 141 ± 22 bpm (mean ± SEM) ($p < 0.0001$) (Fig. 2). Resting mean blood pressure increased with age from 77 ± 3 to 104 ± 5 mm Hg (mean ± SEM) ($p < 0.0001$) (Fig. 1).

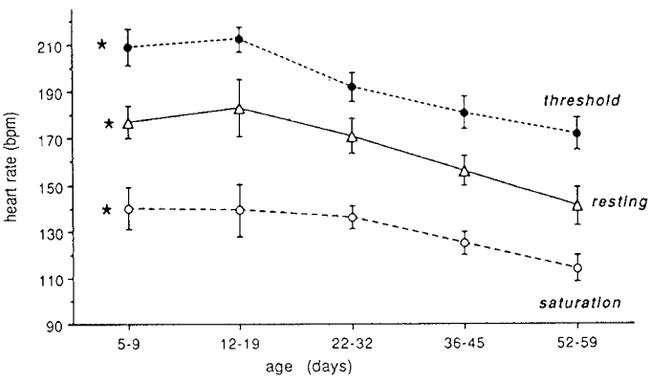

Fig. 4. Heart rate and age. Threshold and saturation indicate heart rates at threshold and saturation blood pressures. *, significant decrease over age range 5 to 59 d ($p < 0.0001$). Values are mean ± SEM.

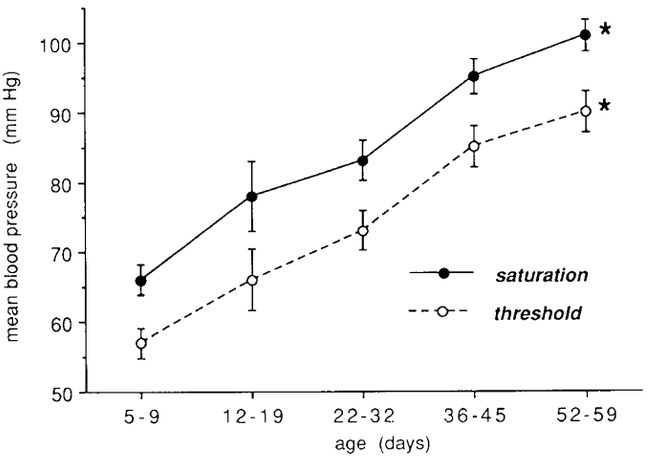

Fig. 5. Blood pressure and age. Threshold and saturation delineate the blood pressure range over which the heart rate reflexly changed. *, significant increase over age range 5 to 59 d ($p < 0.0001$). Values are mean ± SEM.

DISCUSSION

This report demonstrates that neonatal maturation of baroreflex control of heart rate in piglets is characterized by decreasing baroreflex sensitivity. Significant decreases in baroreflex sensitivity occurred during approximately the 2nd and 5th wk of life. Similar changes were demonstrated with both pressor and depressor tests, and sensitivity was not different between the two tests except for the oldest animals (52–59 d old) in whom depressor sensitivity was more than pressor sensitivity. This maturational course has not been previously demonstrated for baroreflex control of heart rate, but it has been demonstrated for the afferent limb of the carotid sinus reflex (36, 37).

Blanco *et al.* (36) recorded afferent discharge from carotid sinus nerves in fetal and newborn lambs and found decreasing baroreflex sensitivity with advancing age. The baroreflex response range also shifted to higher blood pressures with increasing age. Also, Tomomatsu and Nishi (37) demonstrated decreasing baroreflex sensitivity and resetting to higher blood pressure with increasing age for the afferent limb of the carotid sinus reflex in newborn rabbits.

Our data demonstrate that heart rates at threshold and satu-

ration, and therefore the heart rate response range, shifted to lower heart rates with increasing age. The shift was more than can be accounted for by the simultaneously decreasing resting heart rate. Resting heart rate was within the baroreflex heart rate response range at all ages, implying that the heart rate responds in a range encompassing the resting value. The mechanism for this shift in heart rate range in unknown, but may be similar to mechanisms (see below) that cause shifts in resting heart rate with development.

Threshold and saturation blood pressures shifted to higher pressures with increasing age. This indicates that the the blood pressure range over which the heart rate reflexly changes increases with age. Because blood pressure and peripheral vascular resistance were exogenously controlled, this experiment does not measure the animals' ability to regulate blood pressure.

In this study resting blood pressure increased and resting heart rate decreased with age. This confirms previous reports by others (24, 25, 38, 39). The change in heart rate is neither reflex nor mediated by the autonomic nervous system because the inverse relationship between age and heart rate persists after autonomic blockade (40). The change in blood pressure is secondary to increasing peripheral resistance (38). These changes occur concurrently with other developmental changes in the cardiovascular system, such as decreasing oxygen consumption and cardiac output (41).

Other conditions, *i.e.* hypertension, old age, and exercise (27–33, 42), exhibit a similar pattern of decreasing baroreflex sensitivity and resetting to higher blood pressures. Two mechanisms that have been implicated in baroreflex changes in these conditions may also have implications in developmental changes. They are: 1) changes in mechanical properties of arterial vasculature (27, 29, 30, 32, 33), and 2) alterations in autonomic influences on the sinus node (29, 30, 32, 33, 42).

Arterial vasculature undergoes maturational changes in puppies that consist of decreasing cellularity, increasing connective tissue content, and increasing arterial wall stiffness (43). Increasing arterial wall stiffness has been implicated in decreasing baroreflex sensitivity with hypertension and old age (27, 29, 30, 32, 33).

Alterations in autonomic influences on the sinus node influence baroreflex responses (31). The bradycardic response to baroreceptor stimulation is mediated by vagal mechanisms. The tachycardic response to baroreceptor deactivation is largely mediated by the vagus, but sympathetic mechanisms also contribute. Alteration in autonomic tone or balance, with reduction in preponderance of vagal tone, has been implicated in decreasing baroreflex sensitivity with exercise (42) and old age (29, 30, 32, 33). Similar alterations in autonomic tone and influences on the sinus node have been reported with development (13). Whereas both branches of the autonomic system are immature at birth, the parasympathetic is initially dominant and the sympathetic matures later. Therefore, with maturation there is reduction in the preponderance of vagal tone and increase in sympathetic tone. The asynchronous maturation of the two branches of the autonomic nervous system may also be a factor in the divergence of pressor and depressor sensitivities for the oldest animals.

Our study did not produce results comparable to those of Gootman (12) who demonstrated a greater change in heart rate in 2-mo-old than in 2 to 4-d-old piglets (26 *versus* 19 bpm, respectively) with phenylephrine injections that produced equal changes in blood pressure (30 mm Hg). This discrepancy is possibly due to differences in modes of stimulation and state of consciousness/anesthesia. For our animals, changes in blood pressure of approximately 13 to 18 mm Hg produced changes in heart rate of approximately 60 to 80 bpm (Figs. 4 and 5).

We chose to use drug infusion tests to quantitate baroreflex control of heart rate because with this technique the response is mediated through all arterial baroreflexes (carotid sinus and aortic) with a small contribution from cardiopulmonary baroreceptors (30). The heart rate response to phenylephrine is entirely reflex in origin because it is abolished after autonomic blockade (3, 30, 31, 35, 44). Similarly, nitroprusside directly relaxes arteriolar and venous smooth muscle (45), and reflexly alters heart rate. In this experiment pressor and depressor drug infusions were alternated to raise and lower blood pressure throughout the range of baroreceptor activity. This method of blood pressure manipulation was chosen to derive the full sigmoidal baroreflex function and to avoid the use of subthreshold or suprasaturation points in the analysis.

We chose heart rate rather than pulse interval to measure the cardiac cycle because we anticipated that initial heart rate would change with age. Several authors have discussed the use of heart rate *versus* R-R interval in physiologic analysis (42, 46, 47). Briefly, the relationship between heart rate and R-R interval is hyperbolic, and for a given change in heart rate, the corresponding change in R-R interval will be less if the initial heart rate is high than if it is low. When using heart rate, the numerical baroreflex slope is dependent on the initial heart rate and when initial heart rates are different, plotting blood pressure *versus* R-R interval may suggest a change in sensitivity where none actually exists. We believe it is important to consider variation in initial heart rate in developmental studies and therefore used heart rate and not R-R interval in our study.

Some animals slept during baroreflex testing in their first 2 wk of life, and this may have altered baroreflex response. Although one study suggested that for human adults baroreflex sensitivity is increased by sleep (21) a subsequent study by the same group (28) did not confirm this, and others (1) have demonstrated no change in baroreflex sensitivity with sleep in fetal lambs.

The heart rate component of the baroreflex, when tested sequentially in maturing conscious piglets, exhibits a pattern of decreasing sensitivity and resetting to lower heart rate and higher blood pressure. These changes may be due to changes in mechanical properties of the arterial vasculature, alterations in autonomic influences on the sinus node, or other mechanisms. Further studies are necessary to elucidate which factors are involved in these changes in baroreflex control of heart rate in developing piglets.

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