Origin of Oscillatory Kinetics of Respiratory Gas Exchange in Chronic Heart Failure

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Background—Respiratory gas exchange measurements in patients with chronic heart failure (CHF) at rest and during exercise commonly reveal prominent slow oscillations in ventilation (\(\dot{V}_E\)), measured oxygen uptake (\(\dot{V}_O_2\)), and carbon dioxide production (\(\dot{V}_C0_2\)), whose origin is not clear. Voluntary simulation of periodic breathing (PB) in normals has been reported to generate a different pattern of oscillations in gas exchange from that seen in spontaneous PB. This necessitates hypothesizing that PB is caused by a primary oscillation in tissue metabolism or in cardiac output.

Methods and Results—We developed an automated method by which normal controls could be guided to breathe according to a PB pattern. The resultant metabolic oscillations closely matched those seen in spontaneous PB and had several interesting properties. At low workloads (including rest), the oscillations in \(\dot{V}_O_2\) were as prominent as those in \(\dot{V}_E\) in both spontaneous PB (\(\alpha_{\dot{V}_O_2}/\alpha_{\dot{V}_E}=0.92\pm0.04\)) and voluntary PB (0.93±0.07). However, at increased workload, the oscillations in \(\dot{V}_O_2\) were because less prominent than those in \(\dot{V}_E\) in spontaneous PB (intermediate workload 0.63±0.05, high workload 0.57±0.04; \(P<0.001\)) and voluntary PB (intermediate 0.66±0.03, high 0.48±0.03; \(P<0.001\)). There was no difference in the relative size of metabolic oscillations between voluntary and spontaneous PB at matched workloads (\(P>0.05\) at low, intermediate, and high workloads). Furthermore, \(\dot{V}_O_2\) peaked before \(\dot{V}_E\) in both spontaneous and voluntary PB. This time delay varied from 6.4±0.4 s at low ventilation, to 11.3±0.9 s at high ventilation (\(P<0.0001\)).

Conclusions—The magnitude and phase pattern of oscillations in gas exchange of spontaneous PB can be obtained by adequately matched voluntary PB. Therefore, the gas exchange features of PB are explicable by primary ventilatory oscillation. (Circulation. 1999;100;1065–1070.)

Key Words: heart failure ■ ventilation ■ metabolism

During exercise testing of some chronic heart failure (CHF) patients, marked periodic oscillations in measured oxygen uptake (\(\dot{V}_O_2\)), measured carbon dioxide production (\(\dot{V}_C0_2\)), and ventilation (\(\dot{V}_E\)) have been recognized, with a period of approximately one minute,\(^1\) a manifestation of periodic breathing (PB). The origin of these oscillations is unclear. There are several possibilities, and these may be conveniently grouped into (1) ventilatory and (2) metabolic-hemodynamic.

The ventilatory hypothesis is that there is a primary cyclic fluctuation in the homeostatic systems which regulate ventilation, which results from the time delay between detection of a disturbance and its correction. Fluctuating ventilation causes variations in the body’s gas stores, which manifest as oscillations in \(\dot{V}_O_2\) and \(\dot{V}_C0_2\) as determined by respiratory gas exchange.

Three lines of evidence oppose this hypothesis. First, it has been reported that the amplitude of \(\dot{V}_O_2\) oscillation in spontaneous PB during exercise is more prominent than the concomitant oscillation in ventilation.\(^2\) This has been given as evidence of an underlying oscillation in metabolism, driving that in ventilation. Second, the metabolic oscillations do not coincide in time with those in ventilation. The third (and most persuasive) finding opposing a ventilatory origin is that control subjects who volitionally simulated PB failed to reproduce the magnitude and phase of the metabolic oscillations seen in spontaneous PB.\(^3\) This can be viewed as proof that primary ventilatory oscillations cannot be the cause of the oscillations observed in \(\dot{V}_O_2\) and \(\dot{V}_C0_2\) in patients with PB.

The alternative metabolic-hemodynamic hypothesis is, therefore, that the fluctuations in \(\dot{V}_O_2\) and \(\dot{V}_C0_2\) in patients with spontaneous PB result not from fluctuations in ventilation but instead from true fluctuations in gas exchange of the tissues of the body.\(^2\) Because tissue \(\dot{V}_O_2\) is equal to blood flow multiplied by arteriovenous difference in oxygen content, there must be either an underlying oscillation in cardiac output or in tissue metabolic rate. Changes in either of these can modulate ventilation\(^4\) through the action of chemoreceptors\(^4\) and metaboreceptors,\(^5\) thus causing periodic fluctuations in ventilation.
The rejection of the ventilatory hypothesis is based on the failure of voluntary PB to adequately match spontaneous PB. However, one drawback is that voluntary PB is difficult to perform and therefore may not match spontaneous PB well. A second drawback is that without appropriate guidance, controls find it difficult to simulate PB at low mean ventilation rates. It has been assumed that volitional simulation of the qualitative pattern of PB forms an adequate control group, even if the mean ventilation and workload are much higher than those of patients with spontaneous PB. There has been no study to date which assesses the effect of changing workload on the inter-relationships between metabolism and ventilation.

We therefore developed a computer program that could visually guide controls to simulate PB at different ventilation rates to suit rest and different exercise levels. We could thus examine the effect of different workloads on the inter-relationships between ventilatory and measured metabolic oscillations.

Methods

Subjects
We studied 13 patients with CHF who exhibited oscillatory breathing at rest and during clinical exercise testing (spontaneous PB) and 8 normal controls who performed voluntary PB at rest and during exercise. Patients had an average left ventricular ejection fraction of 34±10%. Six had ischemic heart disease, 1 had primary valvular disease, and the remaining 6 had idiopathic dilated cardiomyopathy. The patients were aged 52±20 years, and controls were aged 31±4 years. All subjects gave informed consent.

Exercise Studies
Patients and controls were studied for a short period at rest and then during treadmill exercise, which followed a Bruce protocol modified by the insertion of an initial stage of 0.5 mph at 5% gradient. An Amis 2000 metabolic monitoring system (Innovision), which used a heated pneumotachograph and respiratory mass spectrometer, obtained breath-by-breath on-line calculations of $V_E$, oxygen uptake $V_{O_2}$ and carbon dioxide production $V_{CO_2}$.

Voluntary Periodic Breathing
To enable volunteers to simulate PB, the signal from the pneumotachograph was also monitored by a second computer system (Carrera) with custom-designed software which displayed, for the volunteer, a moving bar representing their breathing in association with a target. We could program this system with a fluctuating ventilatory pattern, whose tidal volume varied sinusoidally with a period of oscillation of 1 minute, and with a controllable mean and amplitude. The software compared the volunteer's respiratory rate and tidal volume with those of the programmed target. It continuously computed and cumulated the difference between intended and actual ventilation. It used this information to modify the target presented to the volunteer. Thus the subject was guided to correct undershoots or overshoots (of rate and/or volume). The result achieved was a close approximation to a sinusoidal ventilation pattern.

Quantification of Oscillation
For each cycle of oscillation, we calculated the mean and amplitude (half the difference between peak and trough). We defined the relative amplitude of the oscillation ($\alpha$) as the ratio between amplitude and mean. For example, if ventilation varied between 15 and 25 L/min with mean 20 L/min, then the amplitude would be 5 L/min and the relative amplitude, $\alpha$, would be $5/20=0.25$. We calculated $\alpha_{V_{O_2}}$ and $\alpha_{V_{CO_2}}$ in a similar manner.

Ventilatory oscillations in spontaneous PB become less prominent (lower $\alpha_{V_{O_2}}$) at higher workloads. This must be taken into account when comparing the sizes of metabolic oscillations at different workloads. We therefore calculated the ratio between $\alpha_{V_{O_2}}$ and $\alpha_{V_{E}}$. For example, if $\alpha_{V_{E}}$ is 0.25 and $\alpha_{V_{O_2}}$ is 0.20, then the size of the metabolic oscillation in comparison to the ventilatory oscillation is $\alpha_{V_{O_2}}/\alpha_{V_{E}}=0.8$. This ratio was also calculated for oscillations in $V_{CO_2}$.

Statistics
The distribution of continuous variables is described by their mean and SD. When means of samples are being compared, each mean is qualified by its standard error (SE). Statistical analysis was carried out using Statview 4.5 (Abacus Concepts). Comparisons between patients and controls, and/or across different workloads, were made using ANOVA. $P<0.05$ was significant.

Results
Examples of the ventilatory and metabolic data obtained are shown in Figure 1A (spontaneous PB) and Figure 1B (voluntary PB). The fine line indicates ventilation, whereas the thick line shows measured oxygen uptake. The 13 patients demonstrated a total of 84 cycles of PB, and the normal controls performed a total of 170 cycles of voluntary PB. Overall workload and ventilation rates were comparable between the 2 groups, as shown in Table 1.

The mean workload of each cycle was categorized into low ($V_{O_2}<6$ mL·kg$^{-1}$·min$^{-1}$, which included the resting state), intermediate (6–12 mL·kg$^{-1}$·min$^{-1}$), and high (>12 mL·kg$^{-1}$·min$^{-1}$), so that similar numbers of cycles of spontaneous PB were in each group. The same categorization was applied to the cycles of voluntary PB.
Magnitude of Oscillations in $\dot{V}O_2$
The relative size of the oscillations in oxygen uptake, in comparison to those in ventilation ($\alpha_{\dot{V}O_2}/\alpha_{\dot{V}E}$) averaged 0.74 (SE 0.03) in the spontaneous PB of the patients. It was not significantly different in the controls performing voluntary PB (mean $\alpha_{\dot{V}O_2}/\alpha_{\dot{V}E}$ 0.71, SE 0.03, $P>0.5$). However, the means of $\alpha_{\dot{V}O_2}/\alpha_{\dot{V}E}$ for all subjects at different workloads were 0.93 (SE 0.05) at low, 0.67 (SE 0.03) at intermediate, and 0.52 (SE 0.03) at high workload (Figure 2A). The differences in $\alpha_{\dot{V}O_2}/\alpha_{\dot{V}E}$ were all significant (low versus intermediate, $P<0.0001$; intermediate versus high, $P=0.003$; low versus high, $P<0.0001$).

Considering the spontaneous and voluntary PB cycles separately (Figure 2B) revealed a similar pattern. Among the spontaneous cycles, the means of $\alpha_{\dot{V}O_2}/\alpha_{\dot{V}E}$ were 0.92 (SE 0.04) at low, 0.69 (SE 0.05) at intermediate, and 0.57 (SE 0.04) at high workload. The differences were significant for low versus intermediate ($P=0.0003$) and low versus high ($P<0.0001$) and close to significant for intermediate versus high ($P=0.057$). Among the voluntary cycles, the means of $\alpha_{\dot{V}O_2}/\alpha_{\dot{V}E}$ were 0.93 (SE 0.07) at low, 0.66 (SE 0.03) at intermediate, and 0.48 (SE 0.03) at high workload. All the differences were significant: low versus intermediate, $P<0.0001$; intermediate versus high, $P=0.01$; low versus high, $P<0.0001$.

Magnitude of Oscillations in $\dot{V}CO_2$
The relative size of the oscillations in CO$_2$ production, in comparison to those in ventilation ($\alpha_{\dot{V}CO_2}/\alpha_{\dot{V}E}$) was greater overall than the corresponding measure for oxygen uptake: mean $\alpha_{\dot{V}CO_2}/\alpha_{\dot{V}E}$ 0.87 (SE 0.02) versus mean $\alpha_{\dot{V}CO_2}/\alpha_{\dot{V}E}$ 0.72 (SE 0.02), $P<0.0001$. This difference persisted across different workloads: at low workload, 1.04 (SE 0.05) versus 0.93 (SE 0.05), $P<0.0001$; at intermediate 0.83 (SE 0.02) versus 0.67 (SE 0.03), $P<0.0001$; at high 0.70 (SE 0.03) versus 0.52 (SE 0.03), $P<0.0001$. There was no significant difference in $\alpha_{\dot{V}CO_2}/\alpha_{\dot{V}E}$ between spontaneous (0.81, SE 0.03) and voluntary PB (0.89, SE 0.03), $P>0.05$. Figure 3A shows the variation of $\alpha_{\dot{V}CO_2}/\alpha_{\dot{V}E}$ with workload. Its mean value was 1.04 (SE 0.05) at low, 0.83 (SE 0.02) at intermediate, and 0.70 (SE 0.03) at high workload. These differences were all significant: low versus intermediate, $P<0.0001$; intermediate versus high, $P=0.009$; low versus high, $P<0.0001$. Again, this difference in $\alpha_{\dot{V}CO_2}/\alpha_{\dot{V}E}$ was seen when spontaneous and voluntary cycles were considered separately (Figure 3B).
spontaneous PB cycles (mean $T_{\text{VO2-VE}}$ 6.7, SD 4.4 seconds) and in voluntary PB cycles (mean $T_{\text{VO2-VE}}$ 9.1, SD 4.4 seconds) as shown in Figure 4, although both were significantly different from zero ($P<0.0001$ for both).

No relationship was seen between $T_{\text{VO2-VE}}$ and workload. However, there was a clear relationship between $T_{\text{VO2-VE}}$ and ventilation level, as shown in Figure 5A. At low ventilation levels ($<300 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) $T_{\text{VO2-VE}}$ averaged 6.4 s (SE 0.4), at intermediate (300–600 mL · kg$^{-1}$ · min$^{-1}$) it was 9.1 s (SE 0.4), and at high (>600 mL · kg$^{-1}$ · min$^{-1}$) it was 11.3 s (SE 0.9). The comparisons between these are all statistically significant: low versus intermediate, $P<0.0001$; intermediate versus high, $P=0.011$; low versus high, $P<0.0001$.

Separate analysis of spontaneous and voluntary PB cycles also showed a similar result (Figure 5B). For spontaneous cycles, the $T_{\text{VO2-VE}}$ at the 3 ventilation levels averaged 4.8 (SE 0.7), 7.3 (SE 0.6), and 10.8 (SE 1.4) s, respectively. These differences were all significant: low versus intermediate, $P=0.008$; intermediate versus high, $P=0.015$; low versus high, $P<0.0001$. For voluntary cycles, the $T_{\text{VO2-VE}}$ means were 7.3 (SE 0.5), 9.8 (SE 0.5) and 11.5 (SE 1.1). The differences between low and intermediate ($P=0.0005$) and low and high ($P=0.0002$) were significant, although that between intermediate and high ventilation was not ($P=0.11$).

**Discussion**

Periodic breathing, the waxing and waning of ventilation with a period of about one minute, has been a recognized feature of CHF for almost 2 centuries. Lately the development of on-line respiratory gas exchange analysis has demonstrated associated fluctuations in measured metabolic rates ($\text{VO}_2$ and $\text{VCO}_2$). Whether these fluctuations in $\text{VO}_2$ and $\text{VCO}_2$ are cause or effect of the ventilatory oscillations is as yet an unresolved question.

Under the metabolic-hemodynamic hypothesis, the $\text{VO}_2$ and $\text{VCO}_2$ oscillate because of a primary fluctuation in tissue metabolism or in cardiac output. In support of this are echocardiographic and radionuclide studies which demonstrate fluctuations in stroke volume. CHF is associated with weakened baroreflex regulation of heart rate, and experimental interference with baroreflex function has been shown to enhance the natural fluctuations in arterial blood pressure. Indeed, blood pressure and even cerebral blood flow have been shown to oscillate during PB. Moreover, there is a potential animal model in the Mayer wave phenomenon seen with experimental hemorrhage: ventilation and blood pressure, as well as directly-measured sympathetic and phrenic nerve activity are all seen to oscillate together. In fact, many lines of evidence support the concept of simultaneous ventilatory and metabolic-hemodynamic fluctuations during PB. But the most important clinical evidence showing that the ventilatory oscillations could not be the prime mover has been the failure of voluntary PB to reproduce the pattern of metabolic oscillation seen in spontaneous PB.

Our study is, to our knowledge, the first in which volunteers had not simply an oscillatory target but also automated feedback of the cumulative error in their ventilation, so that they could adapt their rate and depth appropriately. It is also unique in that it considered the effect of different workloads upon the observed metabolic oscillations, in both patients and controls. The central finding is that as workload increases, there is a marked decline in size of the measured metabolic oscillations in relation to the ventilatory ones (a falling $\alpha_{\text{CO2}/\text{VE}}$ ratio). This occurs both in patients with spontaneous PB and in normal controls with voluntary PB. This key $\alpha_{\text{CO2}/\text{VE}}$ ratio does not differ between patients and controls whether all cycles are considered together or grouped by workload level. The other available measure of metabolic rate, $\text{VCO}_2$, also undergoes oscillations during periodic breathing. Again, the relative size of these oscillations ($\alpha_{\text{VCO2}/\text{VE}}$ ratio) is comparable between spontaneous and voluntary PB.

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**Figure 4.** Histograms showing the distribution of phase difference between peak in oxygen uptake and peak in ventilation in spontaneous and voluntary PB. Positive times indicate oxygen uptake peaks before ventilation.

**Figure 5.** Time difference between peak in oxygen uptake and peak in ventilation at differing levels of ventilation. A, Overall relationship; B, distinguishes spontaneous from voluntary cycles.
and reduces with increasing workload in both groups. The phase of the metabolic oscillations also changes with level of ventilation; as mean ventilation rises, the \( \dot{V}_O_2 \) peak moves to a progressively earlier time with respect to the ventilatory peak in both spontaneous PB and voluntary PB.

How can we reconcile these findings with the previous clinical studies\(^5\) of voluntary PB which showed that the metabolic oscillations measured during voluntary PB differ dramatically from those occurring in spontaneous PB? We propose that in fact there is no contradiction. In previous work, the spontaneous PB cycles occurred at a relatively low workload, with average oxygen uptake of about 8.7 mL · kg\(^{-1}\) · min\(^{-1}\) (obtained by calculating an average of 653 mL/min from the published data and dividing by a notional weight of 75 kg). In contrast, nearly 3-fold higher a workload (approximately 23.9 mL · kg\(^{-1}\) · min\(^{-1}\)) was applied to the normal controls carrying out their voluntary PB cycles. Those volunteers manifested a relatively smaller oscillation in \( \dot{V}_O_2 \) (in comparison to the oscillation in VE) than did the patients; this was interpreted as a sign of an underlying metabolic oscillation driving spontaneous PB. Our study now offers an alternative explanation for the lower value of \( \alpha_{\dot{V}O_2}/\alpha_{VE} \) seen in volunteers in previous work: their workload was far higher, which we have now shown leads to smaller \( \alpha_{\dot{V}O_2}/\alpha_{VE} \) ratios in both patients and controls. When workload is instead matched, \( \alpha_{\dot{V}O_2}/\alpha_{VE} \) is higher and equivalent in patients and controls.

The same study also reported a large 39-degree phase discordance (equivalent to \( \approx 6.5 \) seconds) between spontaneous and voluntary PB with regard to timing of metabolic oscillation in relation to ventilatory oscillation. This has also been interpreted as evidence against a purely ventilatory origin for spontaneous PB. Yet it can now be explained by the marked difference in ventilation between those patients (which can be estimated at 387 mL · kg\(^{-1}\) · min\(^{-1}\)) and their controls (740 mL · kg\(^{-1}\) · min\(^{-1}\)). The evidence from our study shows that such higher ventilation can itself cause the observed metabolic fluctuations to move earlier in phase in relation to the ventilatory fluctuations. The difference in phase between low and high ventilation in our patients alone was as high as 6 s.

Our study demonstrates that the metabolic oscillations seen in association with spontaneous PB can be closely emulated by voluntary PB. It removes the need to hypothesize an underlying hemodynamic or metabolic oscillation. Application of Occam’s razor (the preference for minimal complexity in scientific explanations) obliges us to consider pure ventilatory oscillation an adequate primary driving force for spontaneous PB. Ventilation is dependent on arterial blood and tissue gas tensions, which in turn (after a circulation-time lag) are determined by lung gas concentrations whose levels themselves fluctuate according to ventilation.\(^{16}\) This sequence of relationships forms a closed circuit which may develop self-sustaining oscillations if the gains of the various linkages are high enough and the time-delays are adequate.\(^{17}\) In CHF, there is enhanced ventilatory sensitivity to both central\(^8\) and peripheral\(^9\) chemoreceptor stimulation. Chronically increased ventilation results in reduction in arterial concentration of both CO\(_2\) and bicarbonate,\(^{20}\) which weakens the blood’s power to buffer against changes in CO\(_2\) levels so that the same change in ventilation yields a larger change in arterial pCO\(_2\) and pH. Circulation time is also prolonged in CHF. CHF patients with spontaneous PB manifest more severe forms of these abnormalities of chemoreflex control,\(^{21}\) circulation time,\(^{22}\) and blood buffering capacity.\(^{20}\) Modifying the levels of inspired oxygen\(^{23}\) and CO\(_2\) have been found to attenuate PB, as have procedures that may shorten circulation time such as valve operations,\(^{25}\) heart transplantation,\(^{26}\) and administration of cardiovascular drugs such as milrinone\(^{27}\) or theophylline.\(^{28}\) Thus a wide body of observational, interventional, and theoretical studies support the concept of a primary oscillation in ventilation resulting from harmonic interactions between reflexes of the ventilatory control system and cardiopulmonary physiology.\(^{22}\) The cardiovascular fluctuations that have been documented to occur during PB may well exist, in both patients and controls, as a consequence of this primary oscillation in respiratory physiological control.

Why does the relationship between measured metabolism and ventilation change as exercise progresses? We speculate that at low workloads and associated low ventilations, lung O\(_2\) stores are relatively stable. Consequently, periodic fluctuations in ventilation produce proportional changes in respiratory exchange of oxygen (\( \alpha_{\dot{V}O_2}/\alpha_{VE} \) close to unity). As ventilation approaches its peak, the difference in O\(_2\) concentration between air and the lung begins to fall. Because \( \dot{V}_O_2 \) is the product of alveolar ventilation and O\(_2\) concentration difference between air and lung, it peaks slightly before ventilation. This explains the small but significant time delay between peak \( \dot{V}_O_2 \) and peak \( V_E \), which in our study averaged 6 s at rest and minimal exercise. With gradually increasing exercise, the mean ventilation rises, generating swifter changes in lung gas stores in response to cyclic fluctuations in ventilation. The nadirs in air-lung O\(_2\) concentration difference more closely match the peaks in ventilation. This has 2 effects. First, the peak in \( \dot{V}_O_2 \) (which is related to the product of the 2) occurs even sooner (because the air-lung \( \dot{O}_2 \) concentration difference between air and lung, it peaks slightly before ventilation). Second, the amplitude of oscillation of \( \dot{V}_O_2 \) is attenuated, because the 2 contributory components are almost in antiphase. Carbon dioxide has a slightly different quantitative physiology; whereas oxygen can be considered to be extracted from the lung into pulmonary blood at a relatively constant rate irrespective of lung O\(_2\) fluctuations, carbon dioxide is effectively buffered by the passage of pulmonary blood, whose CO\(_2\) concentration can vary in response to lung CO\(_2\) concentration. The result is that end-tidal CO\(_2\) is relatively more stable in the face of irregular breathing than is end-tidal O\(_2\). For the reasons given above, this leads to relatively larger oscillations in \( \dot{V}CO_2 \) than in \( \dot{V}_O_2 \), particularly at the higher workloads where the pulmonary blood flow (and consequently the buffering effect on CO\(_2\) levels) is greater.

One important implication of this study is that planning of future investigations of the periodic breathing phenomenon should incorporate the knowledge that workload affects not only the overall size of the ventilatory oscillations\(^1\) but also...
the magnitude and phase of the observed relationships. Studies focusing purely on resting patients or exercising patients may thus have reason to demonstrate divergent results. Furthermore, when control subjects are involved, they should be matched with the patient group for workload and ventilation, if the comparison is to be appropriate.

In conclusion, this study shows for the first time that the oscillations measured in oxygen uptake and CO₂ production in patients with spontaneous periodic breathing can be reproduced by appropriate voluntary periodic breathing in normal controls. We make the novel observations that the relative size of the metabolic oscillations becomes smaller with increasing workload, and that rising ventilation leads to a shift of oxygen uptake to a phase further ahead of that of ventilation itself. Finally, these changes occur not only in spontaneous periodic breathing but also in voluntary periodic breathing, which explains discrepancies observed in previous studies of this phenomenon. It is therefore not necessary to hypothesize a primary metabolic oscillation in the genesis of spontaneous periodic breathing of CHF. Harmonic fluctuations in reflex control, resulting from enhancement of chemoreflex sensitivity, slowed hemodynamics, and increased instability of blood gas stores, are an adequate explanation.

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