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# Validation of the use of foreign gas rebreathing method for non-invasive determination of cardiac output in heart disease patients

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**Abstract:** Objective: To compare a new device (Innocor) for non-invasive measurement of cardiac output (CO) by foreign gas rebreathing method with conventional techniques used in the measurements of cardiac function. Methods: Cardiac outputs measured by Innocor ($CO_{RB}$) were compared with CO obtained by echocardiography ($CO_{EC}$), Swan-Ganz thermodilution ($CO_{TD}$), and left ventricle radiography ($CO_{LVR}$) in 34 patients subjected to cardiac catheterization. Values obtained from the four methods were analyzed by linear regression and paired values were compared by the method of Bland and Altman in SPSS. Results: There was strong positive correlation ($r$=0.94) between Innocor cardiac output values and the corresponding values obtained by thermodilution and between $CO_{EC}$ and $CO_{LVR}$ values. Thermodilution appears to overestimate cardiac output when compared to the values obtained with Innocor by (0.66±0.22) L/min ($P$<0.0001). There was no correlation between data obtained by Innocor and the corresponding $CO_{EC}$ and $CO_{LVR}$ values. Conclusion: Innocor $CO_{RB}$ is an easy, safe and well established method for non-invasive measurement of cardiac output with good prospects for clinical application in heart disease patients.

**Key words:** Indirect Fick (foreign gas rebreathing), Swan-Ganz, Cardiac output, Left ventricle radiography, Echocardiography
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## INTRODUCTION

In the arsenal of cardiac functional parameters, cardiac output (CO), cardiac index (CI), and stroke volume (SV) are potentially important determinants of hemodynamics, the measurement of which relies on complicated and sometimes invasive techniques. In the case of congestive heart failure, non-invasive methods to provide accurate measures of these parameters during exercise stress testing would add significant objectiveness to the test result. This could be of considerable importance for precise risk stratification and for adjustment of therapy. In general, non-invasive measurements are inaccurate and the invasive measurements (thermodilution, direct Fick) are clinically unacceptable in the exercise stress test.

The foreign gas rebreathing method (Sackner *et al*., 1975) has been known for more than 50 years and validated against invasive methods (dye dilution, thermodilution and direct Fick). The principle of the foreign gas rebreathing method is to let the patient breath a gas mixture containing two inactive compounds, one being blood soluble and the other being blood insoluble in a closed rebreathing assembly. When the blood soluble gas comes in contact with the blood in the lung capillaries it is dissolved and is thus washed out by the blood perfusing the lungs. The pulmonary blood flow (cardiac output) is therefore proportional to the rate of washout of the blood soluble compound, which is measured continuously by a gas analyzer. The blood insoluble compound is used to determine the lung volume, which is also required in the equation used to calculate cardiac output for the measured washout curve of the blood soluble compound. Previous validations of the foreign gas rebreathing method showed that the method gives very

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accurate measurements of cardiac output in both rest and exercise. However, until recently the method depended on the use of a medical mass spectrometer, which is expensive and quite complicated to operate and maintain.

Recently, a new product, Innocor, was introduced using foreign gas rebreathing to measure cardiac output. This product is based on a newly developed insert rebreathing gas analyzer, which is significantly less expensive than a mass spectrometer and much less complex to apply in a clinical environment.

The present study is a validation of Innocor by comparison with the standard methods used in clinical practice: thermodilution, echocardiography and left ventricle radiography.

## METHODS

### Subjects

Study subjects were recruited from 20 male and 14 female patients with average age of (62.32±7.87) years undergoing cardiac catheterization with measurement of CO for diagnostic purposes. The clinical characteristics of the patients are listed in Table 1.

**Table 1 Clinical data of the patients**

| Patients No. | Age (year) | Sex | Postoperative diagnosis | NYHA (degree) | *PAP* (mmHg) | *LVP* (mmHg) | $S_{aO_2}$ (%) | *PAWP* (mmHg) | *CVP* (mmHg) | *HR* (bpm) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | F | CAD | II | 25/15 (19) | 104/12 | 92 | 15 | 16/10 (13) | 82 |
| 2 | 60 | F | Normal | I | 24/8 (14) | – | – | 7 | 4/–2 (1) | 75 |
| 3 | 54 | F | Normal | II | 24/7 (15) | 153/–6 | 92 | 9/3 (6) | 6/0 (3) | 63 |
| 4 | 71 | M | Normal | I | 27/8 (14) | 157/2 | 98 | 8/4 (5) | 10/0 (4) | 60 |
| 5 | 60 | F | DCM | III | – | – | 96 | – | – | 62 |
| 6 | 75 | M | CAD | III | 53/25 (36) | 139/20 | 95 | – | 12 | 99 |
| 7 | 75 | M | CAD | II | 18/9 (12) | 123/11 | 98 | 11/6 (8) | 4 | 83 |
| 8 | 52 | M | CAD | III | 18/4 (10) | 128/–1 | 94 | 6/2 (4) | 3/–2 (0) | 61* |
| 9 | 52 | M | Normal | I | 18/9 (12) | 110/–6 | 97 | 9/5 (6) | 7/4 (5) | 76 |
| 10 | 57 | F | Normal | II | – | – | 98 | – | – | 73 |
| 11 | 65 | M | CAD | I | 22/10 (15) | 158/10 | 99 | 11/6 (8) | 6/3 (4) | 67 |
| 12 | 58 | F | CAD | II | 28/13 (19) | 135/6 | 98 | 12 | 5 | 87 |
| 13 | 66 | M | Normal | I | – | – | 95 | – | – | 59 |
| 14 | 57 | F | CAD | I | 25/16 (20) | 104/8 | 98 | 9 | 6 | 87 |
| 15 | 79 | M | Normal | I | – | – | 98 | – | – | 59 |
| 16 | 74 | F | CAD | I | 31/14 (19) | 165/22 | 96 | 10/6 (8) | 5/1 (3) | 98 |
| 17 | 41 | F | Normal | I | – | – | 98 | – | – | 88 |
| 18 | 75 | M | CAD | II | 29/11 (18) | 134/6 | 94 | 18/7 (9) | 5 | 76 |
| 19 | 51 | M | Normal | I | 24/10 (16) | 105/5 | 97 | 12/8 (10) | 7/4 (6) | 62 |
| 20 | 60 | F | Normal | I | 26/10 (16) | 163/9 | 98 | 12/6 (8) | 7/3 (5) | 66 |
| 21 | 71 | M | CAD | II | 16/2 (7) | 88/10 | 97 | –3 | 3/0 (1) | 75 |
| 22 | 43 | M | Normal | I | 35/18 (25) | 134/13 | 98 | 25/15 (19) | 16/7 (12) | 75 |
| 23 | 60 | M | CAD | I | 30/13 (19) | 124/7 | 98 | 16/10 (12) | 10/4 (7) | 67 |
| 24 | 59 | F | Normal | I | 30/24 (27) | 158/24 | – | 19 | 6 | 66 |
| 25 | 75 | M | CAD | II | 31/21 (27) | 161/17 | 98 | 20/10 (18) | 16/11 (14) | 73 |
| 26 | 61 | M | CAD | III | 22/16 (19) | 173/14 | 99 | 14 | 10 | 64 |
| 27 | 61 | M | CAD | II | 26/11 (17) | 136/19 | 98 | 9/6 (7) | 9/2 (6) | 92 |
| 28 | 75 | F | Normal | I | 26/11 (17) | 140/6 | 99 | 13/6 (9) | 4 | 80 |
| 29 | 65 | F | CAD | I | 29/10 (17) | 163/9 | 98 | 26/16 (20) | 17/6 (13) | 85 |
| 30 | 66 | M | Normal | I | 29/13 (19) | 136/–2 | 99 | 14 | 7/5 (6) | 65 |
| 31 | 43 | M | PPH | II | 56/27 (39) | 104/12 | 95 | 53/40 (44) | 20/15 (18) | 73 |
| 32 | 65 | M | DCM | III | 28/16 (20) | 150/13 | 97 | 14 | 4 | 94* |
| 33 | 71 | F | Normal | I | 20/7 (12) | 112/1 | 97 | 16/5 (7) | 6 | 92 |
| 34 | 63 | M | CAD | II | 30/25 (27) | 155/3 | 98 | 19/6 (9) | 8/6 (7) | 68 |

NYHA: New York Heart Association functional class; PAP: Pulmonary artery pressure; LVP: Left ventricular pressure; $S_{aO_2}$ : Arterial $O_2$ saturation of hemoglobin; PAWP: Pulmonary artery wedge pressure; CVP: Centre venous pressure; HR: Heart rate; CAD: Coronary arterial disease; DCM: Dilated cardiomyopathy; PPH: Primary pulmonary hypertension; *: The patient's heart rhythm is atrial fibrillation

**Study protocol**

Cardiac catheterization was performed on the subjects complaining of chest discomfort and dyspnoea after conventional non-invasive Electrocardiogram, Echo and treadmill test had failed to make a correct CAD (coronary arterial disease) diagnosis. In parallel, coronary arteriography, $CO_{RB}$, LVR and $CO_{TD}$ measurements were made. Written consent was obtained from all patients following a full explanation of the purpose and nature of the study and the potential risks and discomforts associated with participation. The test was done in an environment of constant room temperature of 27 °C and 65 % room humidity.

**Foreign gas rebreathing technique**

The patient, lying in supine position on the examination table used for cardiac catheterization, breathed through a hermetically closed circuit system (Innocor, INNOVISION A/S) containing a gas mixture of 0.1% (*V*/*V*) $SF_6$ (blood insoluble gas), 0.5% (*V*/*V*) $N_2O$ (blood soluble gas), 28% (*V*/*V*) $O_2$ in $N_2$ in a 4-L rubber bag. Rebreathing was performed over 30 s with a gas volume of 300% of the predicted tidal volume and a breathing rate of 18 $min^{-1}$. Gas was sampled continuously from the mouthpiece for analysis by the IR gas analyser of Innocor. A constant ventilation rate was ensured by having the subject breathe in synchrony with a graphical tachometer on the computer screen, and a constant ventilation volume was ensured by requesting the subject to empty the rebreathing bag completely with each breath. The rebreathing system software calculated $CO_{RB}$ from the rate of uptake of $N_2O$ into the blood (slope of the regression line through logarithmically transformed expiratory $N_2O$ concentration plotted against time). After correction for system volume changes using $SF_6$ concentration the first two or three breaths were excluded from the analysis due to initial incomplete gas mixing.

For the majority of patients without pulmonary arterial-venous shunt ($S_{aO_2} \geq 98\%$) the measured $CO_{RB}$ value was considered equal to cardiac output (Friedman *et al*., 1984; Petrini *et al*., 1978), whereas for patients with a pulmonary shunt, the shunt was calculated and added to $CO_{RB}$. Shunt fraction was calculated according to the equation:

$$\text{Shunt fraction}=(C_{capO_2} - C_{aO_2})/(C_{capO_2} - C_{vO_2})$$

where $C_{aO_2}$ is arterial $O_2$ content; $C_{vO_2}$ is venous $O_2$ content $C_{capO_2}$ (capillary $O_2$ content) can be calculated using the following formula:

$$C_{capO_2} = 1.34[HB] \times S_{capO_2} + P_{capO_2} \times 0.003.$$

where [HB] is concentration of hemoglobin, $S_{capO_2}$ (saturation of capillary $O_2$) was set to 0.98 and $P_{capO_2}$ (pressure of capillary $O_2$) was estimated as the alveolar oxygen tension ($P_{AO_2}$). $P_{AO_2}$ was calculated from the formula:

$$P_{AO_2} = [F_{iO_2} \times (PB - 47)] - \{P_{aCO_2} \times [F_{iO_2} + (1 - F_{iO_2}/RQ)]\}$$

where *PB* denotes the barometric pressure, $F_{iO_2}$ is $O_2$ fraction in inspired air and $P_{aCO_2}$ is the measured arterial $CO_2$ tension. $CO_2$ excretion and the respiratory quotient (RQ) were determined with a special software program using standard formulae.

**Thermodilution technique**

In a 27 °C constant room temperature and a 65% room humidity environment, cardiac output was measured via a floating Swan-Ganz catheter inserted in a branch of the pulmonary artery and connected to a Baxter CCO computer. After injected 10 ml, 27 °C, 0.9% saline solution in right atrium, automated $CO_{TD}$ measurements were generated by the computer approx in 5 s. There were 5 times measurements in every case, and averages of the automated readings over the time interval of interest were used in paired comparisons.

**Echocardiography and left ventricle radiography**

While being subjected to cardiac catheterization, the patients were subjected to an echocardiography examination. Here, the Teichholz technique was used for the measurements of EDV (end diastolic volume), ESV (end systolic volume), SV (stroke volume), EF (ejection fraction) and CO (cardiac output). We use the Teichholz technique because this technique is used in most patients in our hospital. It is easy to implement and is accurate. We also chose to apply the modified Simpson's Rule to those CAD patients, whose NYHA (New York Heart Association functional class) are worse than II degree. Below are the formulas for the measurements.

$$V=[7.0/(2.4+D)]D3$$
$$EF=(EDV-ESV)/EDV$$
$$SV=EDV-ESV,\ CO=SV\times HR$$

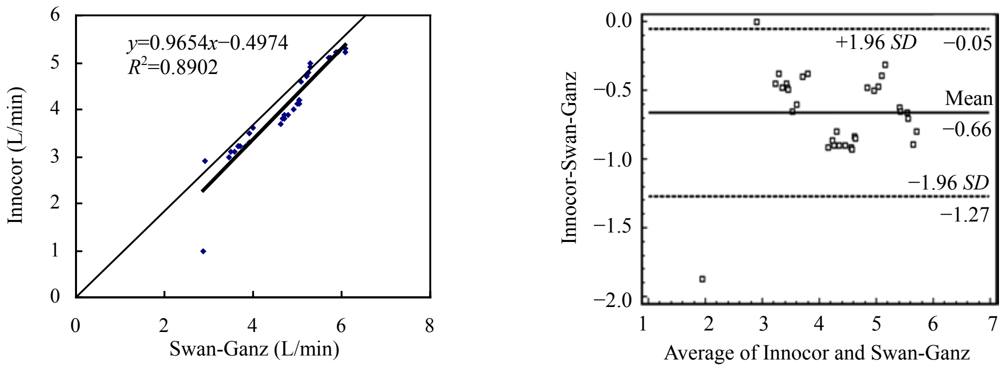
where $D$ is chamber diameter; $V$ is chamber volume and $HR$ is heart rate.

Double blind analysis was performed by the same technicians.

LVR radiography, as a currently used method is a useful approach for coronary arteriography and cardiac function study. A pigtail catheter is guide-wired into the left ventricle and connected to a high pressure syringe after air bubble cleaning. Synchronously with the rapid contrast media infusion at 12 ml/s into the left ventricle, Digital Subtraction Angiography is performed. SV, EDV and ESV were calculated by a single observer with Rx using the single-plane area-length Sandler-Dodge method in the 30° right anterior oblique projection. Hicom software automated analyser (Coroskop T.O.P Siemens) was used. Double blind analysis was done by the same technicians.

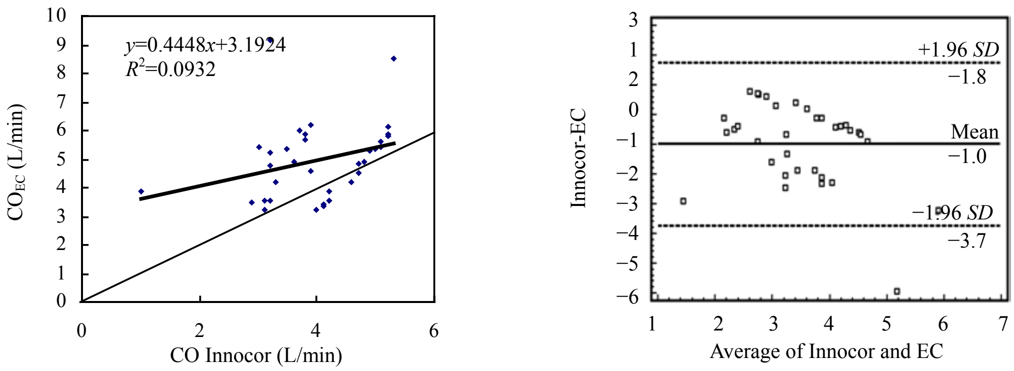
## RESULTS

As Fig.1 shows, the relationship between cardiac output measured by thermodilution and CO measured by Innocor. There is a strong positive correlation and the difference between the two methods ($CO_{TD}$-$CO_{RB}$) was (0.66±0.22) L/min (mean±$SD$) ($P$<0.0001). Fig.2 shows that there is no correlation between $CO_{EC}$ and $CO_{RB}$ and Fig.3 shows that there is no correlation between $CO_{LVR}$ and $CO_{RB}$. Their $r$ are 0.305 and 0.41, respectively. Fig.4 is a scatterplot of $CO_{EC}$ against Swan-Ganz ($r$=0.284), while Fig.5 is a scatterplot of $CO_{EC}$ against LVR, which shows approximately positive correlation between $CO_{EC}$ and $CO_{LVR}$ (PCI) ($r$=0.929; $P$=0.038).



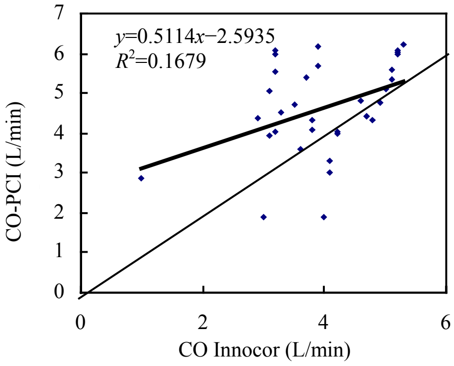

(a) (b)

**Fig.1 (a) Scatterplot of $CO_{TD}$ against $CO_{RB}$; (b) Bland and Altman plot of $CO_{TD}$ against $CO_{RB}$**

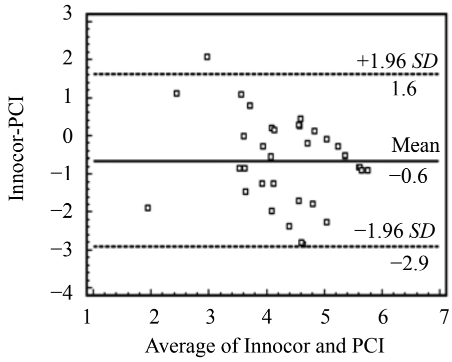



(a) (b)

**Fig.2 (a) Scatterplot of $CO_{RB}$ against $CO_{EC}$; (b) Bland and Altman plot of $CO_{RB}$ against $CO_{EC}$**



(a)



(b)

**Fig.3 (a) Scatterplot of $CO_{RB}$ against LVR; (b) Bland and Altman plot of $CO_{RB}$ against LVR**

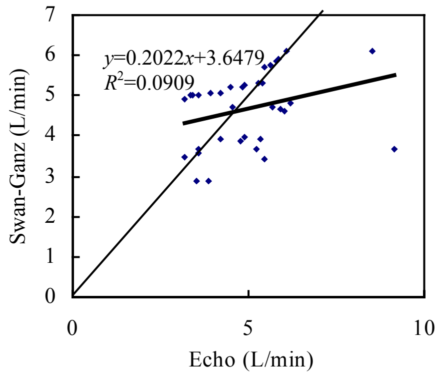


**Fig.4 Scatterplot of $CO_{EC}$ against Swan-Ganz**

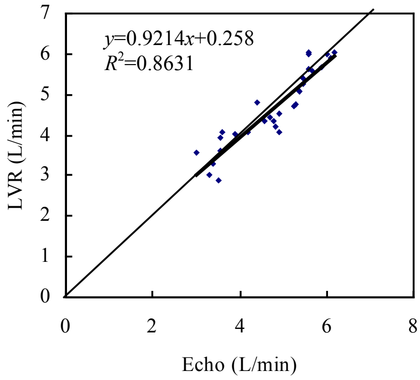


**Fig.5 Scatterplot of $CO_{EC}$ against LVR**

## DISCUSSION

The foreign gas rebreathing method with continuous analysis of respiratory gas concentrations, is a quick, safe and easy technique to apply for measurements of CO, whereas the direct Fick method (gold standard) requires cardiac catheterization which is associated with potential risk of adverse events. Although, the direct Fick method is the gold standard of cardiac output measurement, it is rarely accepted by clinical doctors or patients because of its risk and complexity. After all, few hospitals have an expensive mass spectrometer. Clinical physicians choose Swan-Ganz (thermodilution method) as substitution so that Swan-Ganz becomes "gold standard".

The primary focus of the present study was to compare foreign gas rebreathing method with thermodilution method. Researchers (Kallay *et al*., 1987; Hoeper *et al*., 1999) reported that there were positive correlation between direct Fick and themodilution techniques and that the thermodilution technique overestimated the cardiac output (obtained by direct Fick method) by (0.8~1.3) L/min (Gabrielsen *et al*., 2002), probably because 27 °C, 0.9% saline solution absorbs not only the heat energy of blood in the right ventricular but also that of muscle and connective tissue around the heart, so that blood temperature in the pulmonary artery is higher than it should be. The results of our study also showed overestimation of $CO_{TD}$ compared to $CO_{RB}$ (Fig.1). We suggest further research should be conducted on direct Fick and rebreathing methods.

Echo and LVR are recognized as useful methods for determination of cardiac function; especially as Echo is reputed to be a synonym of cardiac function in medical clinics. Echo and LVR are visible, physicians can see the heart motion and structure. To many patients, Echo and LVR are good methods. And $CO_{EC}$ and $CO_{LVR}$ are correlated to direct Fick, if mitral regurgitation or a ventricular aneurysm can be excluded (Sweet *et al*., 1975). But it is not easy because many critical patients have valvular regurgitation.

Theoretically speaking, in Echo (Type M Teichholz technique), the left ventricle is regarded as a cylindrical cone whose the volume can be estimated from the ventricle inner diameter: ESV at the end cardiac contraction phase and EDV at the end diastolic phase. In combination with the measured HR, SV, CO and EF can be calculated (see the formulas in Method echocardiography). The modified Simpson's Rule may be more accurate than the Teichholz technique in CAD patients, who have segmental LV wall motion. We apply Simpson's Rule to CAD patients, whose NYHA are worse than II degree. The same measurements can be obtained with LVR. Both these methods have another big problem in that they depend on absence of cardiac valve regurgitation (Sweet *et al.*, 1975). The larger the regurgitation is, the larger the errors in the estimated values are. The partial blood regurgitation that often occurs between chambers and aorta of patients invariably cannot be calculated in cardiac output. Another problem is heart rate, so that if $CO_{EC}$ and $CO_{LVR}$ can be multiplied with the heart rate? And skill and experience of technician is also a problem. There are other problems such as ventricular aneurysm and ventricular wall asymmetry, etc., which can influence the result. Consequently, for these patients, the test results are often uncertain. This may be part of the explanation for the lack of correlation to the thermodilution measurements and also may explain the positive correlation between Echo and LVR, which are expected to be influenced by this error source to the same extent, because the problems of Echo are also the same problems of LVR.

In contrast to Echo and LVR, $CO_{TD}$, which is based on the law of energy conservation, is calculated from temperature curves recorded in the right ventricle and pulmonary artery, so it is more accurate. The foreign gas rebreathing method is based on the law of conservation of matter using the gas balance in a closed respiratory system. It is just what the base of direct Fick (gold standard) is. They have nothing to do with regurgitation or ventricular aneurysm.

The foreign gas rebreathing method dose not need a medical mass spectrometer. This is a huge practical advantage because the mass spectrometer is bulky and expensive, and requires frequent calibrations and maintenance (Reinhart *et al.*, 1979; Sackner, 1987; Clemensen *et al.*, 1994; Morten and Peter, 2005), it virtually impossible to be used in routine clinical applications. Our study showed that the foreign gas rebreathing method gives cardiac output measurements that are as accurate as can be obtained with invasive thermodilution measurements. $CO_{RB}$ is an easy, safe and well established method for non-invasive measurement of cardiac output with good prospects for clinical application in heart disease patients. And we expect more research and application of the foreign gas rebreathing method.

## CONCLUSION

Innocor $CO_{RB}$ provided at least as good an estimate of cardiac output as did the thermodilution technique.

The foreign gas rebreathing technique is an easy, safe and well established method for non-invasive measurement of cardiac output with good prospects for clinical application in heart disease patients.

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