Determination of the degree of pulmonary artery hypertension by plasma atrial nateiuretic peptide levels and pulmonary perfusion imaging

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Abstract

To evaluate the degree of pulmonary artery hypertension (PAH) and its significance, pulmonary perfusion tomographic imaging (PPTI) and radioimmunoassay of plasma atrial nateiuretic peptide (ANP) levels were examined in different stages of rabbit PAH models, controlled with cardiac catheterization. When the PAH was mild, ANP levels were not significantly changed (t=1, p >0.05). The mean pulmonary artery pressures (mPAP) measured by catheterization had no significant change, but there was a significant increase of the ratio of dorsal/abdominal counts using pulmonary perfusion tomographic imaging (PPTI) (t=2.5, p <0.05). The ANP levels rose when PAH was moderate or severe, and the difference was significant compared with the control group (t=4 and 6.5, p <0.05). The other two methods also showed significant changes (p <0.01). There was positive correlation between the results of ANP/PPTI, ANP/catheterization, and PPTI/catheterizations (p <0.01). These results suggest that ANP levels can assess the degree of the PAH as a simple method, but it is not as sensitive as that of the PPTI in mild PAH.

Keywords Atrial nateiuretic peptide, Catheterization, Pulmonary artery hypertension, Pulmonary perfusion imaging

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1 INTRODUCTION

Selecting non-invasive methods for judging the level of pulmonary artery pressure (PAP) in time and accurately is a popular subject of present research. It has important clinical significance in the early diagnosis and therapy of lung or heart diseases during slight increase of PAH. Using different stages of rabbit PAH models, we examined the pulmonary perfusion imaging and plasma arterial nateiuretic peptide (ANP) levels, controlled with cardiac catheterization to observe the relationship among ANP, pulmonary perfusion imaging and PAH staging.

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2 MATERIALS AND METHODS

2.1 Experimental animals

27 Japan big ear rabbits, 3.0~3.5 kg weight, 17 females, 10 males, were selected randomly. Normal control group: 13 rabbits were taken pulmonary perfusion imaging, among them 5 rabbits were taken (right cardiac) catheterization.

2.2 Preparation of animal models

(1) Anoxia under normal pressure (10 rabbits): A chamber lacking oxygen was made according to the method of Xue Qian-Fu.[1] The rabbits were put into the anoxia chamber for 8 hours per day in 6 consecutive days followed by one-day rest. Pulmonary perfusion tomographic imaging, catheterization and examination of ANP were carried out in the 3rd and 6th week respectively. Then, 3 rabbits were moved to the next group.

(2) Drug injection group (20 rabbits): One percent solution was made by adding $FeCl_3$ 4.15 g into 250 mL sterilized water and filtered by biomembrane. This solution was injected into rabbit ear border vein 2~3 times every week and the dose increased gradually from 1.0 mL to 5.0 mL. When the total dosage reached 40 mL, 80 mL and 120 mL, respectively, catheterization and pulmonary perfusion tomographic imaging were taken and 1.5 mL of blood was taken from the ear border vein for ANP measurement. These procedures were completed within 2 days.

2.3 Detecting methods

Measurement of plasma ANP level:

(1) Specimens: 1.5 mL of blood was drawn from rabbit ear border vein, anticoagulated and kept in -70°C freezer.

(2) Instrument: GAMMA-C12 counter made by Depu Company, Tianjin.

(3) Reagents: ANP radioimmunoassay kits provided by the China Institute of Beijing.

(4) Detecting method: Operated according to the instruction of ANP kits. Sensitivity: 0.05mg/L.

Pulmonary artery pressure measured by catheterization:

(1) Manometer: Six leads (HELLIGE SERVOMED AMR 155-9) made in Germany.

(2) Pipe: The diameter is 3.6 mm.

(3) X-ray machine: Daojin HDI50G-12 100MA made in Japan.

(4) Procedure of operation: After anesthesia by ip. (Sodium pentothal 0.1 g/kg), a pipe (anticoagulated by 1 ‰ heparine solution) was inserted from the thigh vein into the main pulmonary artery under the help of X-ray screening. 76% meglucamine diatrizoate was injected and after the pulmonary was seen, the pressure was measured by connecting the pipe with the sensor of manometer.

Pulmonary artery pressure measured by pulmonary perfusion tomographic imaging:

(1) Instrument: GCA-7200/DI SPECT made by Toshiba, Japan.

(2) Procedure: After sedating by injection of 5mg diazepine, ^{99m}Tc-MAA 148 MBq was administered. A two-head camera equipped with a low-energy, high-resolution collimator was used. Data were acquired in a 128×128 matrix, one frame per 3 degree, 30~50 kilocounts per frame. The data were computer reconstructed. The clearest frame on sagittal slice was chosen, and the average counting rates of the regions of interest (ROI) at dorsal and abdominal lung were acquired respectively. The same pixels in two ROIs were required. The distribution ratio of dorsal to abdominal was then calculated.

Statistical methods: All values were given as $(x \pm s)$ and the group difference was compared by group t-test. The correlation between different methods was analyzed by using linear regression and was judged for significance with the correlation coefficient r.

3 RESULTS

(1) The relationship of the ANP level and the pulmonary artery pressure: As showed in Table 1, there was no significant difference in the ANP level between the group with slightly increased pulmonary artery pressure and the control group (r=1.0, p >0.05). But there was significant difference in the ANP levels between the pulmonary artery pressure moderately or seriously increased group and the normal control group (t=4.0, 6.5, p <0.05, 0.01, respectively).

Table 1 Relationship of the ANP level and the pulmonary artery pressure (mg/L)

Subject	Number	ANP
Normal group	13	3.88± 1.03
Group of slight PAH	8	3.57±1.14(1.0)
Group of moderate PAH	13	16.84± 5.32$^{(1)}$(4.0)
Group of severe PAH	5	29.06±3.51$^{(1)}$(6.5)

$^{(1)}p$ <0.01 (the number in the parentheses represents t value)

(2) The ratios of dorsal versus abdominal pulmonary counting rates are shown in Table 2.

Table 2 Dorsal/abdominal cpm ratio of rabbit lung (%)

Subject	Number	Dorsal/abdominal cpm ratio of rabbit lung
Normal group	13	87.26± 3.58
Group of slight PAH	8	107.88± 2.20$^{(1)}$ (2.58)
Group of moderate PAH	13	114.01±6.96$^{(2)}$(4.3)
Group of severe PAH	5	132.58±2.25$^{(2)}$ (7.1)

$^{(1)}p$ <0.05, $^{(2)}p$ <0.01 (the number in the parentheses represents t value)

(3) The results of pulmonary artery pressure measured by catheterization are shown in Table 3.

Table 3 The results of pulmonary pressure measured by catheterization (kPa)

Subject	Number	Pressure
Normal group	13	1.71± 0.16
Group of slight PAH	8	1.80± 0.16
Group of moderate PAH	13	$2.64\pm0.38^{(1)}$(3.5)
Group of severe PAH	5	$3.99\pm0.33^{(1)}$(7.9)

$^{(1)}p<0.01$ (the number in the parentheses represents t value)

(4) The relationship among the ANP level, pulmonary perfusion tomographic imaging and catheterization. The correlation coefficients were positive between the various examining methods. Between ANP and catheterization, $r=0.82$, $t=3.5$, $p<0.01$; between ANP and the nuclide distribution ratio of pulmonary dorsal to abdominal cpm, $r=0.70$, $t=3.0$, $p<0.01$; between catheterization and the nuclide distribution ratio of pulmonary dorsal to abdominal cpm, $r=0.89$, $t=4.5$, $p<0.01$.

4 DISCUSSION

The above study suggested that ANP level could to certain degree assess the degree of PAP. When PAP went up gently, the ANP level was not significantly different from the control group ($t=1.0$, $p>0.05$). When PAP went up obviously (moderate or severe increment), there was significant difference compared with normal group ($t=4.0$ and 6.5, $p<0.05$ and 0.01, respectively). Perreault[2] and Adnot[3] reported that compared with healthy person, patients with PAH had a significant increment of plasma ANP level and the ANP level was positively relative to PAP and pulmonary vessel resistance. It has been suggested that anoxia and increased blood viscosity causes disturbance of pulmonary dynamic, increment of pulmonary vessel resistance and increase of vasoconstrictors such as histamine, etc. In order to antagonize contraction of pulmonary artery and bronchial spasm caused by histamine, lung tissue synthesized, restored and released ANP-like substance. Finally, it led to increment of plasma ANP levels, which maintained the normal level of PAP[4~6].

Moreover, our results suggested that pulmonary perfusion tomographic imaging could assess mild increment of PAP. The probable mechanism was that the pulmonary radiodistribution was positively related to the amount of pulmonary blood flow. Anoxia, increasing of blood viscosity and constriction of blood vessel, caused the increase of PAP. Capillaries of the lung apex, which were not open in normal condition, opened gradually, so the blood flow of the lung apex increased. Thus, the blood flow of lung apex increased gradually from less than to equal to and even to more than that in normal lung bottom.

Because the animals stand on four-feet and the human beings stand on two-feet, the back and abdominal side of rabbit are equivalent to the apex and bottom of human lung. In our results, there was significant difference in the nuclide distribution ratio of rabbit pulmonary dorsal to abdomen side between the group with mild PAH the normal control group. The pulmonary perfusion tomographic imaging was not influenced by artificial factors, so it could reflect the change of PAP objectively and could assess the change of PAP sensitively, even in the condition of gentle increment PAP[7].

In summary, the ANP level could determine the degree of PAH and the method was simple, but it was not as sensitive as pulmonary perfusion tomographic imaging in mild PAH.

References

1 Xue Q F, Xie J M, Hu C G *et al.* Chinese J Tuberculosis and Respiration, 1989, **12**:350~352
2 Perrault T, Baribeau J, Gosselin S *et al.* Am J Physiol, 1997, **273**:289-295
3 Adnot S, Andirvet P, Chabrier P E *et al.* Clin Invest, 1989, **83**:986
4 Cargill R I, Batt C S, Coutic W S *et al.* Thorax, 1994, **49**:1247~1249
5 Butkowsks J, Cantin M, Benest J *et al.* FEBS Lett, 1987, **214**:17~20
6 Qin Q N, Zhao D G, Xia S Y *et al.* Chin Circul J, 1994, **9**:142~144
7 Zhang C X, Li J M, Li Z J *et al.* Chin J Nucl Med, 1998, **18**:243~244