S.Ü.Tıp Fakültesi Dergisi Cilt: 8 Sayı: 4 Sayfa: 617-621 (1992)

THE EFFECTS OF NIFEDIPINE ON PULMONARY ARTERIAL ATRIAL NATRIURETIC PEPTIDE IN CHRONIC HYPOXEMIC PATIENTS WITH PULMONARY HYPERTENSION

Dr. Mecit SÜERDEM*, Dr. Hüseyin ŞENOCAK**, Dr. M. Ramazan YİĞİTOĞLU***

Dr. Ümit ÖZBEK**, Dr. Sebahattin ATEŞAL**, Dr. Ebubekir BAKAN***

ÖZET

Pulmoner Hipertansiyonlu Kronik Hipoksemik Hastalarda Pulmoner Arteryal Atrial Natriüretik Peptid Üzerine Nifedipinin Etkisi

Kronik obstrüktif akciğer hastalığına (KOAH) bağlı pulmoner hipertansiyonlu 21 hastaya sağ kalb kateterizasyonu esnasında sublingual 10 mg nifedipin verilerek pulmoner arteryal atrial natriüretic peptid (ANP) ile hemodinami üzerine etkileri araştırıldı. ANP seviyeleri ile ortalama pulmoner arter basınçları ve sağ atrium basınçları arasında direkt korelasyon tespit edildi (Sırasıyla; r=0.50, p<0.05 ve r=0.47, p <0.05). Nifedipin sonrasında ortalama pulmoner arter, sağ atrium ve pulmoner kapiller saplama basıncında önemli değişim olmadı. Ancak, nifedipin pulmoner arter plazma ANP seviyesinin 127.9 dan 216.3 pg/ml değerine çıkmasına neden oldu (p<0.05). Bu bulgu KOAH'lı hastalarda nifedipinin ANP salınımı için bir stimülan olduğunu göstermektedir.

Anahtar Kelimeler : Atrial natriüretik peptid, nifedipin, pulmoner hipertansiyon

SUMMARY

Nifedipine was given, 10 mg sublingually, to 21 patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD), and its effects on hemodynamics, and pulmonary arterial atrial natriuretic peptide (ANP) level were investigated during right heart catheterization. The levels of ANP correlated directly with mean pulmonary arterial pressure (r=0.50;p<0.05) and right atrial pressure (r=0.47;p<0.05). After nifedipine, no significant changes were observed in mean pulmonary arterial, right atrial, and pulmonar capillary wedge pressure. However, the nifedipine caused an increase in the median pulmonary arterial plasma ANP level from 127.9 to 216.3 pg/ml (p<0.05). These data indicate that nifedipine is a stimulus for ANP release in patients with COPD.

Key Words : Atrial natriuretic peptide, nifedipine, pulmonary hypertension

INTRODUCTION

Atrial natriuretic peptide (ANP), which has potent natriuretic, diuretic and vasorelaxant effects, is released into the circulation from both human atria (1). ANP also inhibits the secretion of renin, aldosterone, and vasoconstrictive action of catecholamines (2,3). The predominant stimulus for ANP secretion appears to be direct atrial stretch (4). These findings strongly suggest that ANP is probably involved in blood volume homeostatis and in arterial blood pressure regulation.

Specific receptors for ANP have been identified in pulmonary vascular tissue (5), and ANP has pulmonary arterial relaxant activity by direct effects (6,7). The vasorelaxant activity of ANP was shown to be 10 times more potent on pulmonary arteries than on renal arteries (8). Thus, these observations led us to the hypothesis that ANP could serve as an endogenous regulator of the pulmonary vascular tone. Some reports have shown that ANP may be released in response to pulmonary hemodynamic alterations and may play a significant pathophysiological role in the control of pulmonary

Haberleşme Adresi: Doç. Dr. Mecit SÜERDEM, S. Ü. T. F. Göğüs Hastalıkları Anabilim Dalı, KONYA

circulation in hypoxic state (9,10,11). Moreover, administration of synthetic human ANP to patients with chronic obstructive puymonary disease (COPD) causes pulmonary vasodilation (12). Data obtained in patients with COPD suggest that enhance secretion of ANP may represent a hormonal counterregulatory mechanism against to pulmonary hypertension. But, the mechanism and pathophysiological role of ANP release during hypoxia has not been clarified. We attempted to assess the stimulus for realese of ANP by changing pulmonary hemodynamics acutely through nifedipine given sublingually in chronic hypoxemic patients with pulmonary hypertension.

MATERIALS AND METHODS

Subjects

The study group consisted of 21 patients (Table 1) affected by pulmonary hypertension and COPD. There were 16 men and 5 women (age range, 44 to 66 years). The patients were diagnosed as COPD on the basis of the criteria of American Thoracic Society (13). All patients were in a stable phase of their disease. Chest roentgenograms were compatible with chronic bronchitis and variable degrees of emphysema. To be included in the study, the patients had to have: (1) resting, supine mean pulmonary pressure> 20 mmHg, (2) irreversible airflow obstruction, (3) no history systemic hypertension or any condition that would affect the left heart and no echocardiographic ventricular dysfunction, (4) no resting or exercise ECG abnormality indicating cardiac ischemia, (5) no clinical evidence of right heart failure at the time of study, (6) no use of diuretics, vasodilators, corticosteroids or antihypertensive drugs.

Table 1. Demographic, spirometric, and blood gas data on the 21 patients.

Patient No.	Sex	Age (yr)	FEV_1 (%FVC)	$Pa0_2$ (mmHg)	$PaCO_2$ (mmHg)
1	M	55	64	45	42
2	F	62	75	55	40
3	M	57	44	44	48
4	M	44	71	55	54
5	M	49	42	48	43
6	M	49	50	57	41
7	M	66	33	49	46
8	F	58	56	50	39
9	M	51	57	43	45
10	M	45	40	57	40
11	M	64	65	58	41
12	M	60	62	56	46
13	F	49	69	57	39
14	F	62	57	51	43
15	M	56	54	81	35
16	M	63	38	73	43
17	M	46	47	52	51
18	M	51	59	56	45
19	F	48	58	57	47
20	M	65	61	55	44
21	M	58	50	55	39
Mean		55.1	54.8	54.9	43.3
SE		1.5	2.4	1.8	0.9

Protocol

Patients were studied at supine position after overnight fasting. All medications and supplemental oxygen had been stopped for at least 12 h. Seven F Cournand catheter was inserted into right atrium and pulmonary artery via the antecubital vein under scopy. Measurements of right atrial, pulmonary arterial, and pulmonary capillary wedge pressure were recorded by averaging the values over three normal respiratory cycles. Heart rate was determined from an electrocardiographic lead, which was monitored continuously. Blood samples for analysis of ANP were obtained sisimultaneously from the pulmonary artery. These samples (usually 5 ml) were drawn on chilled tubes containing dipotassium EDTA and aprotinin (400 kallikrein inactivator units per mililiter), placed on ice. The same procedure was repeated 15 min after 10 mg nifedipine was given sublingually and then catheter removed from peripheral vein.

Analysis of atrial natriuretic peptide

Bood samples were centrifuged immediately at 4 °C. Plasma samples were stored at -30 °C until assayed. Plasma ANP levels were determined using a commercial radio-immunoassay (INCSTAR, USA). Rabbit anti-ANP serum bound to sepharose particles was used for plasma ANP immunoextraction from a 0.5 ml plasma aliquot in coloumn. The chromatography coloumns were shaken up upside down gently for 1 h at room temperature. Plasma was drained through the coloumns into the pan, then each

coloumn was washed 3 times with 1 ml aliqouts of 0. 85 % saline. The ANP was eluted by pipetting 250 µl of 0.025 N Hcl into the coloumns and was let stand for 1 min before forcing the acid solution through the coloumns into the 13x100 mm tubes using a rubber bulb. Each eluate was well mixed and placed on crushed ice. Then, the eluate was immediately assayed by RIA procedure and results were obtained from the standart curve.

Statistics

Data are expressed as the mean ± SE. Statistical analysis was performed using Student's t test. The relationships between ANP levels and other measurements were analyzed by linear regression procedure. Probabilites of less than 0.05 were considered significant.

RESULTS

Meun values of pulmonary arterial pressure ranged from 20 to 65 mmHg (mean, 31.8 ± 2.4 mmHg). Mean right atrial pressure was normal (mean, 6.0 ± 0.4 mm Hg), and only 3 patients had slightly elevated right atrial pressure (range, 3 to 10 mmHg). All the patients had normal pulmonary capillary wedge pressure (mean, 6.0 ± 0.5 mmHg).

The hemodynamic effects of nifedipine are summarized in Table 2. After nifedipine intake, pulmonary arterial pressure had fallen unsignificantly from 31.8 ± 2.4 to 26. 2 ± 1.9 mmHg ($p>0.05$). Pulmonary arterial pressure remained unchanged in 2 patients, whereas a drop was obtained in others with nifedipine. Right atrial and pulmonary capillary wedge pressure were unchanged as compared with baseline values. No significant difference was also observed between measurements of heart rate and systemic arterial pressure before and after nifedipine.

The baseline level of ANP in pulmonary arterial plasma was found 127.9 ± 10.3 pg/ml (range, 68 to 217 pg/ml). Atrial natriuretic peptide levels were positively related to pulmonary arterial pressure ($r = 0.50$; $p<0.05$) and to right atrial pressure ($r = 0.47$; $p < 0.05$). Plasma ANP did not correlate with changes in PaO_2, $PaCO_2$ and pulmonary capillary wedge pressure. After nifedipine, plasma ANP level increased to 216.3 ± 33.5 pg/ml and was significantly higher than the baseline level ($P<0.05$), values varying largely among patients from 78 to 696 pg/ml. No relationship was observed between ANP levels and any of the hemodynamic variables studied after nifedipine administration.

Table 2. Hemodynamic determinations before and 15 minutes after 10 mg nifedipine given sublingually in 21 patients with COPD.

	Baseline	Nifedipine	p value
HR, beats/min	81 ± 1.2	94 ± 1.3	NS
Psa, mmHg	98 ± 0.5	93 ± 0.5	NS
Pra, mmHg	6.0 ± 0.4	5.1 ± 0.3	NS
Ppa, mmHg	31.8 ± 2.4	26.2 ± 1.9	NS
Ppcw, mmHg	6.0 ± 0.5	6.3 ± 0.5	NS

DISCUSSION

This study demonstrated that 10 mg nifedipine was given sublingually to 21 patients with pulmonary hypertension secondary to COPD caused slight but not significant decrease in pulmonary arterial pressure and significant increase in pulmonary arterial ANP levels. Several studies performed in patients with chronic pulmonary arterial hypertension have indicated that plasma ANP levels were positively related to changes in pulmonary arterial pressure (9,10), as also observed in the present study, Thus, the enhanced release of ANP in response to an elevated pulmonary arterial pressure may appear as an appropriate physiologic response that could limit the increased pressure load developed on the right ventricle during hypoxia. Increased atrial pressure and atrial stretch or distension are thought to be the most significant factors for the secretion of ANP (4). Pressure loading on the right

atrium caused by an increase in the right ventricular end-diastolic pressure stimulate the secretien of ANP from the right atrium and raise the plasma ANP levels. This may be an auto-compensatory mechanism of the heart to decrease pre-and after-loading.

It has been suggested that atrial enlargement may be a stimulus for ANP release because chronic right ventricular overload may result in right atrial enlargement in the absence of increased right atrial pressure (9,14). In addition, catecholamines are released from the isolated heart during hypoxia (15) and have been reported that catecholamines stimulate ANP secretion in a variety of in vitro systems (16, 17). Moreover, Lew and Baertschi (18) demonstrated that alpha-and beta-adrenergic stimulation are responsible for approximately half of the hypoxia-induced ANP release from the isolated heart. It has also been show that activation of the sympathetic nervous system can enhance ANP secretion in isoladet rat atria (17).

It is well known that nifedipine stimulates a reflex sympathetic discharge (19, 20). However, inhibitor effect of nifedipine of hypoxic pulmonary hypertension is independent of the reflex adrenergic discharge (21). It is therefore possible that nifedipine can be a indirect stimulus for ANP secretion through activation of the sympathetic nervous system. Recently, Sei and Glembotski (22) demostrated that atrial cardiocytes require both extracellular and intracellular calcium to support maximal rates of stimulated ANP secretion, and that intracellular calcium pools may be used during the early phase of secretion, while the extracellular source of calcium may be important for the sustained phase of secretion. A preliminary report suggested that nifedipine administration (10 mg sublingually) to hypertensive patients induced a significant decrease in blood pressure and increase in urinary sodium, urine volume and creatinine clearance, and a significant rise in ANP levels at 60 and 90 min (23).

In conclusion, nifedipine can enhance ANP release in patients with COPD by an as yet unknown mechanism. Further studies will be needed to determine effects of calcium channel antagonists on ANP secretion and pathophysiological role of these effects.

REFERENCES

1. Yamaji T, Ishibashi M, Takaku F. Atrial natriuretic factor in human blood. Clin Invest 1985; 76: 1705-9.
2. Laragh JH. Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure electrolyte homeostatis. N Egl J Med 1985; 313: 1330-40.
3. Sowers JR, Mohanty PK, Thames MD, Goldstein DS, Atlas S. Effects of atrial natriuretic factor on urinary concentration of catecholamines and renin secretion in dogs. Biochem Biophys Res Commun 1988; 156: 1070-6.
4. Rodeheffer RJ, Tanaka I, Imada T, Hollister AS Robertson D, Nagami T. Atrial pressure and secretion of atrial natriuretic factor into the human central circulation. J Am Coll Cardiol 1986; 8: 18-26.
5. Sakamoto M, Nakao K, Moril N, Sugawara A, Yamada T, Itoh H, et al. The lung as a possible target organ for atrial natriuretic polypeptide secreted from the heart. Biochem Biophys Res Commun 1986; 135: 515-20.
6. Igarro LJ, Wood KS, Harbison RG, Kadowitz PJ. Atriopeptin II relaxes and elevates cGMP in bovine pulmonary artery but not vein. J Appl Physiol 1986; 60: 1128-33.
7. Jin H, Yang RH, Thornton RM, Chen YF, Jakson R, Oparil S. Atrial natriuretic peptide lowers pulmonary atrial pressure in hypoxia-adapted rats. J Appl Physiol 1988; 65: 1729-35.
8. Jansen TLTA, Morice AH, Brown MJ. A comparison of the vasodilator responses to atrial peptides in the pulmonary and renal arteries of the pig in vitro. Br J Pharmacol 1987;91:687-91.
9. Adnot S, Chabrier PE, Andrivet P, Viossat I, Piquet J, Brun-Buisson C, et al. Atrial natriuretic peptide concentrations and pulmonary hemodynamics in patients with pulmonary hpyertenison. Am Rev Respir Dis 1987; 136: 951-6.
10. Burghuber OC, Hartter E, Punzengruber C, Weissel M, Voloszozuk W. Human atrial natriuretic peptide secretion in precapillary pulmonary hypertension. Chest 1988; 92:31-7.
11. Adnot S, Chabrier PE, Brun-Buisson C, Viossat I, Broquet P. Atrial natriuretic factor attenuates the pulmonary response to hypoxia. J Appl Physiol 1988; 65: 1975-83.
12. Adnot S, Andrivet P, Chabrier PE, Piquet J, Plas P, Braquet P, Roudot-Thoraval F, Brun-Buisson C. Atrial natriuretic factor in chronic obstructive lung disease vith pulmonary hypertension. Physiological correlates and response to peptide infusion. J Clin Invest 1989; 83: 986-93.
13. America Thoracic Society. Standarts for the diagnosis and care of patients with chronic obstructive pulmonary disease and asthma. Am Rev Respir Dis 1987; 136: 225-43.
14. Winter RJD, Davidson AC, Treacher D, Rudd RM, Anderson JV, Meleoqros L, Bloom SR. Atrial natriuretic peptide concentrations in hypoxic secondary pulmonary hypertension: relation to haemodynamic and blood gas variables and response to supplemental oxygen. Thorax 1989; 44: 58-62.
15. Wollenberger A, Shahab L. Anoxia-induced release of noradrenaline from the isolated perfused heart. Nature Lond 1965; 207: 88-9.

16. Currie MG, Newman WH. Evidence for alpha-1 adrenergic receptor regulation of atriopeptin release from the isolated rat heart. Biochem Biophys Res Commun 1986; 137: 94-100.

17. Bchiebinger RJ, Baker MZ, Linden J. The effect of adrenergic and muscarinic cholinergic agonists on atrial natriuretic peptide secretion by isolated rat atria: a potential role of the autonomic nervous system in modulating atrial natriuretic peptide secretion. J Clin Invest 1987; 80:1687-91.

18. Lew RA, Baertschi AJ. Mechanism of hypoxia-induced atrial natriuretic factor release from rat hearts. Am J Physiol 1989; 257: H 147-56.

19. Beer N, Gallegos I, Cohen A, Klein N, Sonnenblick E, Frishman W. Efficacy of sublingual nifedipine in the acute treatment of systemic hypertension. Chest 1981; 79: 571-4.

20. Moses J, Wertheimer JH, Bodenheimer NM, Banka VS, Feldman M, Heifant RH. Efficacy of nifedipine in rest angina refractory to propranolol and nitrates in patients with obstructive coronary artery disease. Ann Intern Med 1981; 94: 425-9.

21. Kennedy T, Summer W. Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. Am J Cardiol 1982; 50:864-8.

22. Sei CA, Glembotksi CC. Calcium dependence of phenylephrine, endothelin, and potassium chloride stimulated atrial natriuretic factor secretion from long term primary neonatal rat atrial cardiacytes. J Biol Chem 1990; 265:7166-72.

23. Rappelli A, Dessi-Fulgheri P, Madeddu P, Glorioso N. Studies on the natriuretic effect of nifedipine in hypertensive patients: increase in levels of plasma atrial natriuretic factor without participation of the renal kalliklerin-kinin system. J Hypertension 1987; 5: S 61-5.