PULMONARY ARTERY AND CAPILLARY PROSTAGLANDIN LIKE ACTIVITY IN CASES WITH PULMONARY HYPERTENSION OF VARIOUS ETIOLOGY

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SUMMARY: The determination of PGLA by bioassay method from the Pa and Pc blood samples of patients -20 with passive pulmonary hypertension due to valvular heart disease, 3 with primary pulmonary hypertension, 1 with chronic constrictive pericarditis and high pulmonary pressure, 1 with pulmonary hypertension due to pulmonary branch stenosis, totally 25, and 13 cases who had pulmonary hypertension due to pulmonary disease (chronic cor pulmonale)- were performed. Twenty-one persons who had cardiac catheterization of various reasons were used as control group and the values were compared. In control group PaPGLA values were significantly high ($p<0.0001$) from PcPGLA, while the group with pulmonary hypertension of mechanical factors had an unversed and significant ratio ($p<0.05$) and the difference in the group of chronic cor pulmonale was insignificant ($p<0.05$). In our opinion while the lung is a PG metabolizing organ normally in pulmonary hypertension, if parenchymal disease does not exist, it acts as a PG releasing organ.

Key Words: Prostaglandins, pulmonary hypertension.

INTRODUCTION

Prostaglandins (PGs), first described in 1930s, are lipid compounds in unsaturated fatty acid nature released from many tissues of the body by various impulses (1, 3, 9, 10, 14, 17, 18, 20, 24, 26). The released PGs are demolished 95% in lungs except PGI_2 (7, 10, 19).

The lungs are a filter for PGs in normal conditions and protect the body from their systemic effect, they may become PG released by various pulmonary hypertension producing impulses. These events are observed in anaphypoxis (1, 24, 26). In human beings, when two principal pulmonary hypertensive reasons like hypoxia and pulmonary venous hypertension are present, there is not a study showing the effects of the lungs on PGs. In this study we tried to compare the determined prostaglandin like activity (PGLA) taken from the entry (pulmonary artery, Pa) and the exit (pulmonary capillary, Pc) of the lung in normal ones and patients with pulmonary hypertension of various reasons.

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MATERIALS AND METHODS

This study contains 46 cases from Ankara University, Medical Faculty Cardiology section who were catheterized and 13 cases of chronic cor pulmonale, 3 from Ankara University Medical Faculty Cardiology section and 10 from thoracal diseases and tuberculosis division. The catheterizations were made for diagnosis of rheumatic disease and for preoperative preparation in cases who described a rheumatic past. The diagnosis of chronic cor pulmonale was made by the criteria of WHO (22). Total of 59 cases were observed in three groups;

Group 1: 21 cases of pulmonary artery mean pressure (Pa mean) below 20 mmHg in catheterization.

Group 2: 25 cases of Pa mean over 20 mmHg.

Group 3: 13 chronic cor pulmonale cases.

Eight of the chronic cor pulmonale cases, and all of the group 1 and 2 had catheterization in A. U. Medical Faculty

Hemodynamics laboratory of Cardiology section. Five of the chronic cor pulmonale cases had micro catheterization in A. U. Thoracal diseases and Tuberculosis section because of low effort capacity and excessive respiratory distress.

When blood pressures by right cardiac catheterization were performed, blood samples for PGLA determination were taken from arteria pulmonalis and pulmonary capillaries (the region where the blood oxygen saturation was similar to arterial and the pulmonary capillary pressure are able to be recorded).

For the determination of PGLA's from plasma, the extraction of PGs by Gilmore method was first made (12). Then PGLA in fundus of the stomach of rat was detected by bioassay method (27). In this method, other substances that influence the fundus muscles like PG, where it is antagonized and the preparation was made stable; then various doses of standard PG were given and the responses recorded (Figure 1). The dose-response curve for each experiment was taken (Figure 2). Then extract, diluted with 1 cc of Tyrode solution, and added 0.05 or 0.1 cc to the preparation. The responses so taken (Figure 3) were compared with the standard PGE 2 responses. By looking at the dose-response-curve, PGLA in 1 cc was estimated.

Statistical method

The importance control of the difference of mean values made by 't' test. In every group PGLA in pulmonary artery (PaPGLA) and PGLA in pulmonary capillary (PcPGLA) differences were combined and compared by 't' test again.

Table 1: Findings of group 1 (patients with normal pulmonary arterial pressure).

Case No.	Diagnosis	Pa. mean (mmHg)	PGLA (ng/ml)		
			Pa	Pc	Pa/Pc
1	Pulmonary stenosis	16	14.0	6.8	2.05
2	ASD	16	17.0	1.0	17.0
3	Pulmonary stenosis	14	7.6	3.8	2.0
4	ASD	18	1.8	1.9	0.9
5	RHD (Aortic stenosis)	15	6.0	1.6	3.7
6	Pulmonary stenosis	14	6.4	2.6	2.4
7	Pericardial and aortic calcification	14	16.1	3.6	4.4
8	Pulmonary stenosis	15	5.9	3.2	1.8
9	Pulmonary stenosis	15	12.0	5.5	2.1
10	RHD (Mitral insufficiency)	18	8.2	3.3	2.4
11	Pulmonary stenosis	14	4.3	2.0	2.1
12	Cardiomyopathie	19	21.3	3.33	6.3
13	VSD	12	4.0	2.0	2.0
14	Normal	14	4.2	2.4	1.7
15	Pulmonary stenosis	17	6.5	4.0	1.6
16	VSD	12	6.0	3.5	1.7
17	Subclavian steal syndrome	10	5.8	3.9	1.5
18	Coarctation of aorta	15	7.4	4.0	1.8
19	Pericardial cyst	12	1.0	1.6	0.6
20	Pulmonary stenosis	14	6.2	2.8	2.3
21	Arteriovenous	15	14.0	0.8	17.5

ASD: Atrial Septal Defect
RHD: Rheumatic Heart Disease
VSD: Ventricular Septal Defect

RESULTS

The peculiarities of group 1, 2 and 3 are shown in Tables 1, 2 and 3. The PaPGLA is found to be high from PcPGLA in 19 of 21 cases of group 1. The difference between the mean values of PaPGLA is significant (Table 4). In the whole group the PaPGLA/PcPGLA ratio is 1 (3.70±1.019) (Table 5). The mean Pa value of this group is 14.714±0.499 (Table 6).

In contrary to group 1, PcPGLA is greater than PaPGLA in 21 of 25 cases of group 2 (84%) and the difference between PcPGLA and PaPGLA mean values is found to be significant (Table 4). The mean ratio of PaPGLA/PcPGLA is 1 for the whole group (0.858 ±0.188) (Table 5). The mean pulmonary artery pressure of the group is 39.68 ± 3.802, and the differences between the values of group 1 is significant (Table 6).

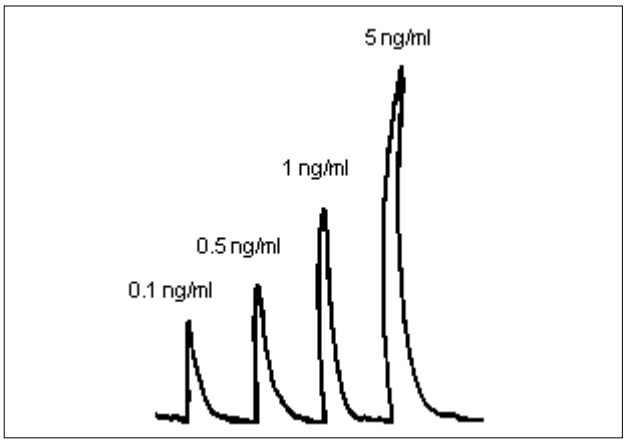
The PaPGLA/PcPGLA values of group 3 remained same in 3 cases, PcPGLA decreased in four of them (similarity to group 1) and PcPGLA increased in 6 cases (similarity to group 2). The difference between the mean PaPGLA and PcPGLA values of the whole group is insignificant (Table 4). The mean PaPGLA/PcPGLA ratio for the whole group is 1.177±0.395 and the difference between the normal group (1) is insignificant (Table 5). The mean pulmonary artery pressure of the group is 32.038 ± 3.494 and the difference with the normal group is significant (Table 6).

DISCUSSION

The mammarial cells are known to release PGs with even very little impulses which can be physiologic, pathologic or mechanical and the released PGs have local regulating endocrine effects (28). The releasing function is much above the real content of the cell and its aim is thought to be to protect the cell wall effected by the impulse (20, 21). For this reason it is possible to say that an impulse irritating any cell wall is forcing that cell to produce and release PGs. By this idea PGs are thought to be the defensive means of the cell (20). Virtually, noradrenaline release by the innervation of spleenic nerve is inhibited by PGE_2 (13). Considering that the PGE_2 is released from the contracted spleen by innervation (10), it may be said that the contracted muscle cell is trying to reduce the effect of the impulse which causes it to contract by this way with negative feed-back mechanism (20).

The presence of PGs in the venous return of the organs is a reminder of possible general effect of them, in addition to their local regulating effects. In this case PGs have to keep their activity till the target organ. PGs released from spleen or intestine are inactivated 90% in the liver when they enter the portal system, and they can not make a systemic effect except the target organ is the liver. The lungs also have a very important function in this affair. PGs passing the liver barrier are inactivated 95% in the lungs in one circulation period (10, 19). Only PGI_2 is out of this effect and enters the systemic circulation without being inactivated (7, 10). In normal conditions the lungs are the most important inactivation places (10) to protect the cardiovascular system and the other organs from the systemic effect of PG (4, 16). For this reason PcPGLA should have to be lower than PaPGLA and the ratio of PaPGLA/PcPGLA greater than 1 in normal people. Truly, animal experiments by giving exogenous PG (10, 19) and some studies on humans are correcting this idea (8).

Figure 1: Recorded responses to standard PGE_2 doses in isolated rat stomach fundus muscle.



In group 1; 21 cases with normal Pa mean (Table 6), the mean PaPGLA is greater than the mean PcPGLA and the difference between the two values has a statistical significance ($p<0.001$) (Table 4). The PaPGLA/PcPGLA ratio is also 1 as expected (3.70 ± 1.019) (Table 5).

The lung, which acts as a filter for PGs released by other systems and tissues, also releases PG with various impulses (1, 3, 9, 14, 17, 18, 20, 21, 24, 26) by these kind of impulses which generally causes pulmonary hypertension, the lung may become a PG producing organ and not inactivate PG any more. In this point of view, the lungs are thought to be an endocrine organ (18). When pulmonary hypertension is produced in isolated lung by particle infusion, PGE_2 release in perfusion solution has been detected (14). In spite of this vasodilator PG, constrictor PGs like TxA_2 have not been found (15). The same results are also obtained in pulmonary hypertension

caused by anaphylaxis and particle infusions of different diameters (18). In these experiments, it is shown that the lung weight increases (congestion) in addition to pulmonary hypertension is also needed for PGLA release (20). The mentioned animal experiments are only acute pulmonary hypertension examples caused by pulmonary embolism. There is no animal experiment similar to mitral stenosis in humans of passive pulmonary hypertension cases which produces pulmonary venous hypertension on first, and then pulmonary hypertension.

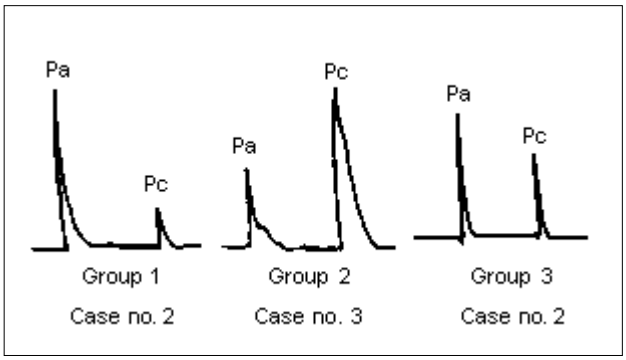
The group 2 of our study are cases of this type. The findings of these cases are completely contrary to group 1. PcPGLA values are over the values of PaPGLA, which means the lungs have begun to release PGs. The difference between the PaPGLA PcPGLA values is significant ($p<0.05$) (Table 4). PaPGLA/PcPGLA ratio is 1

Table 2: Findings of group 2 (patients with normal pulmonary arterial pressure).

Case No.	Diagnosis	Pa. mean (mmHg)	PGLA (ng/ml)		
			Pa	Pc	Pa/Pc
1	MS-TI	38	7.0	10.4	0.6
2	MS-MI-TI	63	16.0	36.0	0.4
3	MS-TI	36	2.0	17.0	0.1
4	P. Hyp	81	2.6	5.8	0.4
5	Pulmonary branch stenosis	24	11.6	16.0	0.7
6	MS-TI	73	2.0	8.0	0.25
7	MS-MI-AI	25	3.0	5.8	0.5
8	MS-MI	28	2.8	6.0	0.4
9	MI-AI	57	2.4	3.9	0.4
10	Constrictive Pericarditis	27	1.8	2.0	0.9
11	P. Hyp	73	18.0	19.0	0.9
12	P. Hyp	55	5.6	11.0	0.5
13	MS-MI-TI	20	2.8	2.3	1.2
14	TS-P. Hyp.	50	4.0	5.2	0.7
15	MS-MI-AS	28	1.9	4.0	0.4
16	MS	20	1.6	4.8	0.3
17	MS-MI-TI	24	8.6	2.33	3.7
18	MS-MI	48	4.5	6.8	0.6
19	MI	22	8.6	2.2	3.9
20	MS-AI-AS	61	6.0	9.6	0.6
21	MS-MI	27	2.0	14.8	0.1
22	AS-MS-TI	28	2.5	2.7	0.9
23	MI-TI	27	11.0	7.0	1.5
24	MS-AI	22	10.5	13.0	0.8
25	MS-AI-TI	35	1.3	2.6	0.5

MS: Mitral stenosis, TI: Tricuspid insufficiency, MI: Mitral insufficiency, P. Hyp: Pulmonary hypertension, AI: Aortic insufficiency, TS: Tricuspid stenosis, AS: Stenosis

Figure 2: Responses to examples taken from pulmonary artery (PA) and pulmonary capillary (Pc) of one case with normal pulmonary arterial pressure (Group 1), one with pulmonary hypertension (Group 2), and one chronic cor pulmonale (Group 3) case.



(0.858 ± 0.188) and comparing this with group 1, the difference between the mean values is significant ($p<0.05$) (Table 5). The results of these cases are fitting to the results of animal experiments mentioned above (18, 20). Remembering that the PGs released in pulmonary hypertension of animal experiments are mostly vasodilator kind (20), in spite of the existence of some contrast evidence (2), it may be thought that the released PGs in our studies are not responsible from pulmonary hypertension and may be directed to decrease the pulmonary arterial pressure which can increase more. In an indirect experiment in persons who have passive pulmonary hypertension due to mitral stenosis, it is shown that the treatment by PG inhibitors does not decrease the pulmonary hypertension level (5). This finding also reminds that PGs are not pulmonary hypertension making mediators at least in mechanically caused pulmonary hypertension. The lungs weight increase which is necessary for the release of PGLA with pulmonary hypertensions in animal experiments (20), is present in our cases by means of pulmonary venous congestion. For the three primary pulmonary hypertension cases in this group, it is difficult to perform a discussion because there is no similar animal experiment; but they show similarity to mitral patients for releasing PGLA. However, there is not lung weight increase in these cases; consequently, the condition seen in animal experiments is not necessary for this group of cases, and may be not for all pulmonary hypertension.

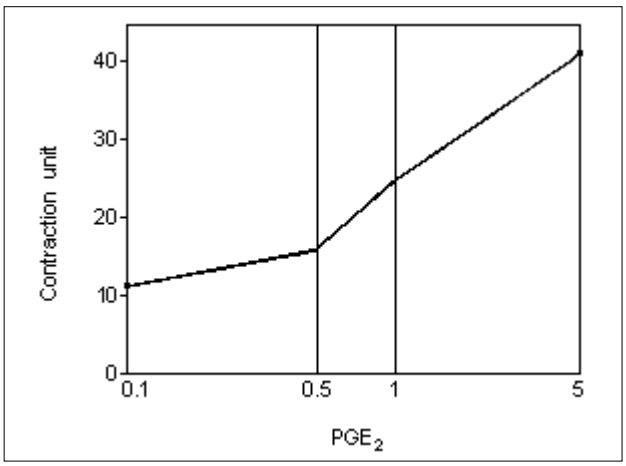
The lung also releases PG in pulmonary hypertension caused by hypoxia or anoxia increases the perfusion pressure in the perfused lung (6). It is shown that there is PGLA release with pulmonary hypertension in hypoxia in

Table 3: Findings of group 3 (patients with chronic cor pulmonale).

Case Numbers	Pa. mean (mmHg)	PGLA (ng/ml)		
		Pa	Pc	Pa/Pc
1	57	14.4	7.2	2.0
2	33	11.6	2.0	5.8
3	32	25.0	26.0	0.96
4	22	2.4	3.5	0.6
5	25	2.33	2.33	1.0
6	38	4.8	4.5	1.1
7	21	1.0	4.0	0.2
8	25	6.2	12.6	0.5
9*	36	2.8	6.8	0.4
10*	24	2.8	4.6	0.6
11*	33	12.2	11.6	1.1
12*	52	6.4	10.75	0.6
13*	19	16.4	20.0	0.8

*: Catheterization performed by microcatheter.

Figure 3: An example to dose/response curve obtained by placing the responses taken to standard PGE_2 doses on logaritmic paper.



isolated rat lung (24, 26). The pulmonary hypertension level formed by hypoxia in anesthetized cats (25), dogs (29), and piglets (3) increases after PG inhibitors, or it does not decrease at least (23).

It is said that in hypoxia pulmonary hypertension, this condition is caused by the inhibition of secondary released vasodilator PGs (3, 30). There are no similar studies in human beings. But there is some indirect evidence that vasodilator PGs can be released by the lungs in patients with pulmonary hypertension caused by chronic inflammatory pulmonary diseases (11).

In chronic cor pulmonale cases of examples of hypoxia pulmonary hypertension which makes our group 3, the difference between the mean values of PaPGLA and PcPGLA is found insignificant ($p>0.05$) in spite of the presence of serious pulmonary hypertension (Table 6). Also the ratio of PaPGLA/PcPGLA of this group does not show important differences comparing to the cases of group 1 ($p>0.05$) (Table 5). This condition in our opinion may be due to reduced lung tissue because of parenchymal disease, or enzymes necessary for the biosynthesis of PGs.

As a result; pulmonary hypertensions except chronic cor pulmonale cases can be determined noninvasively by determining the arterial and venous PGLA levels and PG inhibitors should not be recommended to the patients with pulmonary hypertension.

Table 4: PaPGLA and PcPGLA means in the three groups of patients.

	Group 1	Group 2	Group 3
PaPGLA	8.367±1.160	5.606±0.938	8.333±1.979
PcPGLA	3.030±0.314	8.329±1.504	8.668±1.875
	$p<0.001$	$p<0.05$	$p>0.05$

Table 5: PaPGLA/PcPGLA means in the three groups of patients.

Group 1	Group 2	Group 3
3.700±1.091	0.858±0.188	1.177±0.395

$p<0.01$

$p>0.05$

Table 6: Mean pulmonary arterial pressures (PaMean) in the three groups of patients.

Group 1	Group 2	Group 3
14.714 ± 0.479	39.680 ± 3.802	32.038 ± 3.494

$p<0.001$

$p<0.001$

REFERENCES

1. Badesch DB, Orton EC, Zapp LM, Westcott JY, Hester J, Voelkel NF, Stenmark KR : Decreased arterial wall prostaglandin production in neonatal calves with severe chronic pulmonary hypertension. Am J Respir Cell Mol Biol, 1:489, 1989.

2. Barst RJ, Stalcuo SA : Endothelial function in clinical pulmonary hypertension. Chest, 88:2168, 1985.

3. Belik J, Sienko A, Light RB : The effect of repeated intermittent hypoxia on pulmonary vasoconstriction in the newborn. Can J Physiol Pharmacol, 68:355, 1990.

4. Boot JR, Cockerill AF, Dawson W, Mallen DNB, Osborne DJ : Modification and successive immunological challenges from Guinea-pig lung. Archs Allergy Appl Immune, 57:159, 1978.

5. Dabiel J, Szczeklik A : Effect of indomethacin on pulmonary vasomotor response in patients with mitral stenosis. Pol Eur Cardiol, 6:53, 1977 (Excerpt Med Int Med 39:433, 1978).

6. Duke H, Lee G de J : The regulation of blood flow through the lungs. Brit Med Bull, 19:71, 1963.

7. Dusting GJ, Moncada S : Disappearance of prostacyclin (PGI_2) in the circulation of the dog. Brit J Pharmacol, 62:414, 1978.

8. Ekici E, Olguntürk R, Ilhan M, Ozme S : Possible relationship between pulmonary hypertension and prostaglandins. Prostaglandins, Med 7:71, 1981.

9. Farber HW, Fairman RP, Rounds S, Millan JE, Glauser FL : Pulmonary hypertensive response to foreign body micro emboli. Prostaglandins Leukot Essent Fatty Acids, 39:151, 1990.

10. Ferreira SH, Vane JR : Prostaglandins: Their disappearance from and release into the circulation. Nature, 216:683, 1967.

11. Gavrisiuk VK, Diachenko AP, Krasnostup NA, Iachnik AI, Draga NP : Vasoconstrictor action of ibuprofen in treating patients with pulmonary hypertension. Vrach Delo, 1:62, 1989.

12. Gilmore N, Vane JR, Wyllie JH : Prostaglandins released by the spleen. Nature, 218:1135, 1968.

13. Hedqvist P : Control by Prostaglandins E_2 of sympathetic neurotransmission in the spleen. Life Sci, 9:269, 1970.

14. Lindsey HE, Wyllie JH : Release of Prostaglandins from embolized lungs. Brit J Surg, 57:738, 1970.

15. Moncada S, Higgs EA, Vane JR : An enzyme isolated from arteries transforms Prostaglandins endoperoxides an unstable substance that inhibits platelet aggregation. Nature, 263:663, 1976.

16. Moncada S, Flower RJ, Vane JR : Prostaglandins, prostacyclin and thromboxane A2. Goodman and Gilman's the Pharmacological Basis of Therapeutics. Sixth Ed, MacMillan Publishing Co Inc, New York, p 668, 1980.

17. Palmer MA, Piper RJ, Vane JR : Release of vasoactive substances from by injection of particles. Brit J Pharmacol, 40:547, 1970.

18. Piper JP, Vane JR : Release of additional factors in anaphylaxis and its antagonism by anti-inflammatory drugs. Nature, 223:29, 1969.

19. Piper JP, Vane JR, Wyllie JH : Inactivation of Prostaglandins by the lungs. Nature, 225:660, 1970.

20. Piper JP, Vane JR : The release of Prostaglandins from lung and other tissues. Ann NY Acad Sci, 18:363, 1971.

21. Ramwell PW, Shaw JE : Biological significance of the prostaglandins. Recent Prog Hormone Res, 26:139, 1970.

22. Report from WHO : Chronic cor pulmonale. Circulation, 27:594, 1963.

23. Rouse E, Hales C, Kazemi H : Role of prostaglandins in the pulmonary vasoconstrict response to alveolar hypoxia. Clin Res, 23:351 A, 1975.

24. Said SI, Yoshida T, Kitamura S, Vreim C : Pulmonary alveolar hypoxia: Release of prostaglandins and other humeral mediators. Science, 185:1181, 1974.

25. Said SI, Hara N, Yoshida T : Hypoxia pulmonary vasoconstriction in cats: Modification by aspirin and indomethacin. Federation Proc, 34:238, 1975.

26. Vaage J, Hague A : Prostaglandins and the pulmonary vasoconstrictor response to alveolar hypoxia. Science, 189:899, 1975.

27. Vane JR : The use of isolated organs for detecting active substances in the circulating blood. Brit J Pharmacol, 23:360, 1964.

28. Watson J : The influence of intracellular levels of cyclic nucleotides on cell proliferation and the induction of antibody synthesis. J Exp Med, 141:97, 1975.

29. Weit EK, Reaves JT, Grover RF : Meclofenomate and indomethacin augment the pulmonary presser response to hypoxia and exogenous Prostaglandins F_2 (PGF_2). Physiologist, 17:355, 1975.

30. Zou AP, Cheng G, Pi YQ, Wang WH, Yu SB, Wang DX : The role of lipoxygenase and cyclooxygenase metabolites in acute hypoxia pulmonary vasoconstriction in piglets. J Tongji Med Univ, 9:239, 1989.

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