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Research Article

Pulmonary Vessels Remodelling in Chronic Obstructive Pulmonary Disease

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Abstract

Our aim was to measure the loss and the compliance of the pulmonary vessels in the different GOLD stages of COPD and to assess the relationship between these and the Pulmonary Artery Pressure (PAP).

Patients affected by COPD with Pulmonary Hypertension (PH) (n=39, FEV1 39±15%, PaO_2 60±12 mmHg, $PaCO_2$ 46±10 mmHg, PAP 33±8 mmHg) and without PH (n=39, FEV1 43±21%, PaO_2 62±12 mmHg, $PaCO_2$ 39±9 mmHg, PAP17±5 mmHg) were studied in stable state and divided in three groups belonging to stage I-II, III and IV GOLD stage respectively. Each subset was compared to healthy people (n=13). PAP and pressure / flow relationship (PAP/Q) were measured by catheterization of pulmonary artery and effort test. Vessels loss was measured by perfusive scintigraphy.

Lung vessels loss is significant even in former stages, showing a progressive trend (20±4, 28±4, 30±5 in stages I-II, III and IV resp.; 3±1% in healthy people (h.p.)) and a significant relationship with airways obstruction. In patients with PH it was higher even in I stage (30%). The apico-basal gradient of perfusion was significantly inverted (1.87±0.4 in COPD, 1.86±0.6 in COPD+PH and 0.625±0.2 in h.p.). Compliance was slightly higher in PH (PAP/Q= 1.8+1.2 mmHg/L/m *vs* 1.6+0.9 in COPD and h.p.). Vessels loss was found not to be significantly related to PH. Under effort higher pressures due to lesser vessel recruitment and a leftward shift of P/Q trace could be observed. Vascular rarefaction is an early feature of COPD. PH looks not dependent solely upon vessels loss but upon different pathways such as organic remodelling and vasospastic response to hypoxia.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) affects primarily the ventilatory units [1-9], an involvement of the vascular bed with pruning of vessels is evident with imaging methods, such as computed tomography or lung scintigraphy [10]. Damage to the vessels is initially attributed to a disease of the small peripheral arteries, whose changes determine Pulmonary Vascular Resistance (PVR) and compliance (PAP/Q) [8,11-15]. Both the loss of compliance and the development of an elevated mean Pulmonary Artery Pressure (PAP) overload the right ventricle because of the increased workload necessary to overcome the downstream pressure. This can ultimately lead to right-sided heart failure and determines worse clinical features, such as life expectancy, effort tolerance and outcome during acute respiratory failure [1-8]. The development of a pre capillary Pulmonary Hypertension (PH) is observed in about 45% of patients and it is associated with a worst prognosis [4-7]. PAP is moderately elevated, although it reaches values close to those observed in primary Pulmonary Artery Hypertension in about 5% of cases [1-7]. The presence of PH characterizes three different clusters of patients: the former one with airways obstruction and normal PAP, the second one with increased PAP proportional to the degree of airways obstruction, the third one with limited impairment of lung mechanics but fairly advanced PH, labelled as "out of proportion" PH [4-8]. The pathophysiology underlying PH development depends upon vessels changes of both central and peripheral arteries ; the former ones are the dilation and diminished pulsatility of Pulmonary Artery (PA), the second ones are Hypoxemic Pulmonary Vasospasm (HPV) and organic remodelling, consisting of vascular bed loss, intimal thickening, hypertrophy of muscle layer and thrombosis [1-7]. The damage of vessels is documented by perfusive scintigraphy in pulmonary embolism and expressed as the number of "segmental defects", while in COPD it is rather referred as "arterial deficiency" by imaging methods such as computed tomography. In literature, no measure of the entity of vessels loss and no such study about the link between vessel rarefaction and the onset and development of PH in each GOLD stage are available. Our aim is to measure in patients affected by COPD in different stages the loss and the compliance of the pulmonary vessels and to assess the relationship between these and the PH.

Methods

Selection of Patients

All the patients were affected by COPD (diagnosed according to ATS statement and GOLD criteria)

[16] and they were examined immediately as they consecutively arrived in the ward of the pulmonary division. Patients were assigned to a specific GOLD stage, according to relevant guidelines [16]. Inclusion criteria was as follows: (a) presence of COPD, (b) written informed consent and motivation, (c) level of dyspnoea higher than 2 on the MRC scale, (d) ex smoker or not smoker, (e) male gender and (f) stable phase of the disease in the last month. Exclusion criteria consisted of: (a) significant cardiac diseases as valvulopathies or cardiac failure (echocardiographic ejection fraction lesser than 50%), (b) presence of other pulmonary diseases as pulmonary fibrosis, tuberculosis or chronic embolic disease (diagnosed by scintigraphy). Enrolled patients were examined by clinical check, functional testing, blood gas analysis, echocardiography, Right Heart Catheterization (RHC) and lung scintigraphy within two consecutive days. Patients with PAP higher than 25mm Hg and Pulmonary Wedge Pressure (Pw) lesser than 15 mmHg during RHC were assumed as affected by pre capillary PH (COPD+PH). Within one year only 13 patients with PH and COPD in stage I-II could be enrolled ; therefore we chose to enroll the first 13 patients belonging to each consecutive GOLD stage (III and IV) both with and without PH (39 patients in each group). Each GOLD stage was compared to a group of 13 healthy people (h.p.) with biometry overlapping the features observed in the patients, while performing RHC and scintigraphy were wrong suspects of pulmonary embolism or PH.

Selection of Methods

The evaluation of pulmonary blood vessels was obtained by scintigraphic lung perfusion imaging.

RHC allowed for the measure of PAP, PAP/Q and the vasodilation (dPAP) induced by Nitric Oxide (NO). The relationship between loss sustained to lung vessels and airway obstruction was assessed by the regression between scintigraphic unperfused areas and the spirometric deficits, as well as by dividing patients into different subsets according to the GOLD levels. The relationship between vascular damage and haemodynamic features could be accomplished by dividing patients with and without PH and by the regression between unperfused areas and PAP/Q, dPAP, PAP and PVR.

Physiologic measures

Forced Vital Capacity (FVC), FEV_1, maximal expiratory flow at 50% (Mef50%), Functional Residual Capacity (FRC) and ventilation (V'e) were determined by whole body plethysmograph Autobox6200, Sensormedics, USA) and referred to ERS normal standards [37]. Arteria1 oxygen tension, content and saturation (PaO_2, CaO_2, SaO_2), carbon dioxide tension ($PaCO_2$) and acidemia (pH) were measured by blood gas analysis by arterial puncture whilst breathing room air at rest and automated analyzer (Rapidlab 405, Bayer Health Care, FRG). The same measures were repeated on mixed venous samples drawn by cardiac catheterization. Eight channel polysomnograph (Healthdyne Nightwatch, USA) allowed for the measure of overnight saturation and assessment of apneas. OSAS was defined by Apnea-Hypopnea Index (AHI) higher than 15/h.

Haemodynamics

Pulmonary Artery Pressures (systolic =PAPs, diastolic= PAPd, mean = PAP) and Pulmonary Wedge Pressures (Pw) were measured by Swan Ganz catheters (Baxter, USA), electronic transducers(Baxter, USA) and monitors (Passport, USA) [38]. Patients with Pw higher than 15 mmHg were discarded. Cardiac output was measured by using the Fick method, measuring oxygen consumption by gas analyzer (Cortex, FRG) ($Q'=V'O_2 / (CaO_2-CvO_2)$. PVR was obtained by dividing pressure drops across pulmonary arteries by cardiac output (PAP-Pw/Q). The Trans Pulmonary Pressure Gradient (TPPG) is defined by the difference between PAP and Pw [17]. Efforts in the supine position with the ergometer (Siemens, Germany) allowed the measures of PAP ad Q' under effort at 15 Watt and at 45 Watt, for working periods lasting 2' each. The relationship PAP/Q' was obtained by best fitting procedures. The inhalation of NO at 20 ppm for ten minutes allowed the measure of pressure drop under vasodilator, and was assumed as reversibility of PH (dPAP) [18].

Lung Perfusion Imaging

Segmental deficits of perfusion were measured by perfusion scintigraphy, injecting albumin labelled 99Tc (2mCu =74 Mbeq) and by acquiring scintigraphic images in six views (anterio-posterior, post-anterior, lateral and oblique anterior ones) by gamma camera (Montesta XIRT General Electric, USA) equipped with high resolution energy collimators. Computer allowed for the definition of areas of interest over upper, middle and lower fields with computation of regional perfusion, while the patients were held in sitting position to allow the effect of gravity on the gradient of blood perfusion [19,20]. Segmental defects were appreciated by multiple views; overall lung inhomogeneity and intra-segmental defects were computed as the percentage of unperfused pixels referred to the lung area, delineated as region of interest. The lungs were divided in upper, middle and lower lung fields: the apico-basal ratio of lung perfusion was the ratio of the percentage of perfusion in upper lung fields by the amount measured over lower ones.

Analysis and Ethical Advice

Statistical analysis was performed by software package (Epistat and Graphpad, USA). The mean number was compared by Student's T test and frequencies by chi square analysis. The significance of the relationship between variables was assessed by the least square method analysis applied to linear fitting procedures. Differences were reported as significant for a p level less than 0.05 (*) and highly significant if less than 0.00 l (**). Informed consent and favorable advice from an ethical committee were obtained. Data is reported as mean± standard deviation.

Results

Patient Features

Patients showed (Tables 1 and 2) almost normal biometrics with mild overweight. Biometrics and co morbidities were overlapping within COPD with PH, as well as within COPD without PH and in healthy people; only the obstructive apneas syndrome was more prevalent in patients with COPD + PH (Table 1).

Patients were affected by borderline desaturation and hypoxaemia (Table 2), diminution of ventilatory volumes with marked airways obstruction, slight policythemia, raised global ventilation, normal cardiac output and mildly reduced vascular compliance. Comparing patients affected by COPD to the patients with COPD and PH (Table 2) we could appreciate that in PH a significant increase of PAP, RVP,

Table 1: Biometrics and co-morbidity.

	Units	COPD	Sign Diff	COPD+PH	Healthy subjects
Age	Years old	70± 10	Ns	70± 7	65± 5
Height	Cm	165± 5	Ns	164± 4	167±3
Weight	Kg	72± 15	Ns	75± 12	75± 7
BMI	Mt^2/kg	29± 4	Ns	28± 3	27± 4
Hyp.cardiop.	%	15	Ns	15	15
OSAS	%	12	P<0.001	18	12
Diabetes	%	15	Ns	14	15

COPD +PH= patients with Pulmonary Hypertension; BMI= Body Mass Index; Hyp Cardiop. = percentage of patients affected by Hypertensive Cardiopathy; OSAS = % of patients with Obstructive Apnea Syndrome; diabetes= % of patients affected by diabetes; mean± standard deviation. Ns= difference between COPD and COPD+PH not significant.

Pw, $PaCO_2$, and within unperfused areas. Night time desaturation and PAP/Q exhibited higher levels of PH, but did not reach a significant threshold.

Comparing stage by stage and each set of patients to the healthy control (Table 3), it was possible to appreciate that FEV_1 progressively and significantly declined, and PaO_2 as well was shown to diminish thus reaching a significant threshold since stage III; $PaCO_2$ increased significantly in PH under stage III and IV.

Measures of Vessels Loss

The analysis of the number of affected segments was not possible, since the wasting was scattered, uneven, and mainly intrasegmental, therefore the most objective measure was the percentage. Unperfused Lung Areas (ULA) (Table 2) was significantly increased in all the patients. In patients without PH, ULAs were progressively higher as GOLD stages worsened and they were significantly related to airway obstruction (ULA = 35-0.241 FEV_1 %; ±4; r2 0.53, p<0.05). In patients with "Out of Proportion" PH the ULAs were significantly higher than in patients without PH, while in advanced airway obstruction (stage III and IV) the ULAs were not different between the patients with or without PH.

The vascular wasting was associated with an upward redistribution of lung perfusion with inversion of apico basal gradient of perfusion even in patients without PH since early stages, and not different between patients (apex 45±7%, middle field 27±3 % and base 24±5% of lung perfusion in both sets).

Vascular Compliance, Pulmonary Artery Pressure, Reversibility

PAP did not increase significantly under different GOLD stages with worsening degrees of obstruction (Table 2 and 3) in COPD. This is confirmed by the lack of a clear correlation between PAP and FEV_1 and the degree of respiratory failure in the patients with PH, although it was higher in GOLD stage IV. The slope PAP/Q showed a steeper slope in patients with COPD with PH, as compared to healthy people and COPD without PH. However the difference was not significant, due to a wide transvariance of distributions. The inhalation of a selective vasodilator such as NO induced borderline not significant changes both in healthy people and in COPD (dPAP about 2 mmHg). The effect was seen to be more relevant in PH

Table 2: Functional Data.

	Units	COPD	Difference COPD*vs*+PH	COPD+PH	Healthy subjects
PaO_2	mmHg	62± 12	Ns	60± 12	80± 3
$PaCO_2$	mmHg	39± 9	Ns	46± 10	40± 2
$Sa0_2$	%	90± 5	Ns	89± 7	98±2
SaO_2night	%	90± 4	Ns	85± 5	98± 2
Hct	%	49±2	Ns	50±3	40±2
FVC	% of pred.	56±23	Ns	47± 17	97±5
FEV_1	% of pred	43±21	Ns	39±15	98±4
Mef5O%	% of pred	25±15	Ns	22± 15	95±10
PAPs	mmHg	35± 8	$<1x10^{-6}$	52±13	22±4
Pw	mmHg	6± 2	$<1x10^{-5}$	10±2	6± 3
PAP	mmHg	16.8±5.4	$<1x10^{-5}$	33± 8	15±3
PAPeff 15W	mmHg	22± 5	$<1x10^{-4}$	38± 6	17± 3
PAP/Q	mmHg/L/m	1.6± 1	Ns	1.8±1.2	1.5±.9
PAPvasod	mmHg	16± 4	$<1x10^{-5}$	28± 5	13± 2
CI	Lt/m/m2	2.8±.5	Ns	2.7±.65	2.9±.5
PVR	Dynes/L sec^{-5}	155± 50	<.001	386± 148	120± 10
ULA	%	25±6	<.045	30±2	3± 1
apico/basal	U	1.87± .4	Ns	1.86±.6	.625± .2
V'e	L/m	10± 2	Ns	10±2	7±1
subjects	N	39		39	13

COPD = COPD without Pulmonary Hypertension; COPD+PH = COPD with Pulmonary Hypertension; PAPs Systolic Pulmonary Artery Pressure; Pw =Pulmonary Wedge Pressure; PAP =mean Pulmonary Arterty Pressure; PAP vasodil =PAP under 20 ppm NO; % ; PAPeff=PAP during arm loading at 15 watts; ULA=percentage unperfused scintigraphic areas; SaO_2 night mean SaO_2 during overnight study; Hct =Haematocrit value; apico/basal =apico /basal gradient of lung perfusion; PAP/Q =slope of PAP/Q relationship.

Table 3: Functional values according to the stage of COPD and the presence of pulmonary hypertension.

	Stage I-II	Stage III	Stage IV	Healthy people	Units
FEV_1 PH-	66± 16*	40± 7* 35± 5*	25± 6* 24± 6*	98± 4	%
PH+	64± 10*	n.s.	n.s.		
PH- *vs* PH+	n.s.				
PaO_2 PH-	73± 13	59±9	54± 7	80± 3	mmHg
PH+	65± 12	59± 12	57± 14		
PH- *vs* PH+	(*)	n.s.	n.s.		
$PaCO_2$ PH-	38± 7	41± 9	42± 4	40± 2	mmHg
PH+	40± 6	45± 12	55± 7		
PH- *vs* PH+	n.s.	n.s.	(*)		
PAP PH-	17± 8	16± 2	18± 2	15± 3	mmHg
PH+	29± 4*	30± 6*	36± 10*		
PH- *vs* PH+	(**)	(**)	(**)		
TTPG PH-	11± 3	10± 2	12± 2	1± 2	mmHg
PH+	22± 4*	22± 3*	26± 3*		
PH- *vs* PH+	(**)	(**)	(**)		
ULA PH-	20± 4* 30± 4*	28± 4* 29± 4*	30± 5* 31± 3*	3± 1	%
PH+	(**)	n.s.	n.s.		
PH- *vs* PH+					

Number of observations = 13 in each set; +PH = COPD with pulmonary hypertension, ULA= unperfused scintigraphic areas; * = significant difference between healthy people and subset of patients; TTPG= transpulmonary gradient; PH- *vs* PH+ = Difference between patients affected by COPD and COPDand PH (*) =p<0.05, (**)=p<-0.001,n.s.=not significant

(average dPAP 5 mmHg); although in no patient did the PAP reach normal values under NO breathing. Taking into account an average difference of PAP of about 15 mmHg in COPD+ PH as referred to COPD; increased vascular tone is likely to account for the 30% of the increase of PAP.

Discussion

Our data show for the first time a relevant loss of pulmonary perfusion (about 30%) from early stages of the disease and that the damage is related to obstruction of airways, although the worsening is limited in progressive GOLD stages. Moreover in patients with "out of proportion" PH a pronounced vascular wasting is evident even in early stages with no relationship to airways obstruction. These features and the limited contribution of vasospasm to the increase of PAP indicate that PH is determined by pathways different than the combined action of loss of vessels units together with HPV.

The main limitations of the study are the limited number of observations, the invasive option of measurements of haemodynamics, the vascular imaging method, the variance within the patients. The limited number of observations is due to the low prevalence of PH in former stages of COPD, as already mentioned (5, 27 and 53% in GOLD stages II, III and IV, respectively) [12]. Current data can be regarded as preliminary to be confirmed in more extensive multicentric studies. We chose the invasive RHC instead of not invasive ultrasounds because of the difficulties to find a suitable acoustic window in patients affected by pulmonary hyperinflation. RHC remains essential for the management of PH since it confirms the diagnosis, determines the type of pulmonary hypertension, its severity, its vasoreactivity as well as response to therapeutic interventions [1-7]. Effort was chosen as a more physiologic method to induce an increase of perfusion to obtain P/Q, as compared to the infusion of low doses of dobutamine [13,20]. The standardization, the widespread availability and the computer facilities render perfusive scintigraphy preferable as compared to tomography or magnetic resonance imaging. A possible bias could be the lack of correction of the measured perfusion by the ventilated volumes; but this procedure must be applied only in studies concerning V'/Q' relationship, such as the diagnosis of emboli, that are not the scope of the current investigation. Lastly, the heterogeneity of patients with PH depends on two different subgroups: the "out of proportion" group in the former stages (referred as due to the co-existence of PH and COPD) [4-7], the group of patients with hypercapnic hypoxemic respiratory failure with progressive vascular worsening and HPV due to respiratory failure.

According to literature reports [4-7], pulmonary blood flow is characterized by a low pressure and resistance pattern with high compliance, due to the recruitment and distensibility of vascular bed. Under effort the PAP/Q relationship is characterized in normal people by wide variance (due to gender, age, load and time), variability of the point of onset of increase of PAP (mainly due to a variable recruitment), straight slope (expression of PVR) and time dependence (diminution of PVR upon time) [21,22]. Patients affected by COPD show a normal distribution of PAP ranging 15 to 55 mmHg with a mode centered on the values of 23-25 mmHg. PAP shows a slow progressive trend over time (0.8 mmHg/year) and marked elevations during sleep, efforts and acute relapses. The PAP/Q' trace is leftward shifted, curvilinear, with a steeper slope in the initial phase (as expression of reduced distensibility or increased PVR) and a flatter one under higher flows. This last feature looks dependent upon a decrement of PVR at higher loads, referred as due to the overcome of the alveolar vessels compression by the increased PAP. Time dependence is lacking [21-24]. Our results, according to literature [1-9] identify different clusters of patients such as patients without PH even in advanced stages, patients with "Out of Proportion" PH, patients with PH, advanced airways obstruction and respiratory failure: in all the patients an early and significant vascular damage was shown due to both organic and functional changes.

Within functional changes, HPV is claimed as the most important determinant of PAP under acute hypoxemic challenge. HPV is present in denervated lung and in smooth muscle cells denudated by epithelium and determined by sensors located in the gas exchange vessels in arteriolar side close to alveolar units; acute HPV depends mainly on Ca^{++} entry due to Ca^{++} and K^{+} channels activation and it is inhibited by Ca^{++} channel blockers, diminished by endothelin inhibitors and arginine [4-10,20]. Current evidence indicates that vasospasm accounts only for about 30% of the increase of PAP.

Within the organic changes, the vessels loss can be appreciated by scintigraphic imaging as an early and a common feature of COPD associated with an inversion of apico basal gradient of lung perfusion. The vascular damage is due to post inflammatory fibrosis, vascular compression or obstruction or blockage of vascular endothelial growth factor pathway and it accounts for about one third of vascular units with a modest progression over stages in COPD, proportional to airways obstruction. The damage is dependent upon a marked and scatters intra segmental heterogeneity of perfusion (already shown by positron emission tomography or single photon tomography) [27-29]. It looks disproportionately greater than airflow limitation in GOLD stage I (as already found by inert gases method) [30], suggesting that COPD initially involves significantly the smallest airways, parenchyma, and pulmonary vessels even when the spirometric disturbances are still minimal [9,31-33]. Although the damage is early, the progression of both vascular rarefaction and perfusion inequality along different stages with worsening severity is modest: it may reflect that the pathogenic processes reduce both local ventilation and blood flow in the same regions through consensual involvement of airway, alveolar disease and capillary. The inversion of the apico-caudal gradient of lung perfusion is likely dependent on damage of basal vessels with recruitment of apical ones or diversion of blood flow due to arteriolar vasoconstriction in basal regions, although in our observations there was no relationship between dPAP and apico/basal ratio.

The haemodynamic consequences of vascular rarefaction on the circulation of blood can be studied using a multiscale mathematical model that can predict blood flow and pressure in the systemic and pulmonary arteries [34-38]. According to our results and literature reports [19-22], vascular rarefaction does not seem to determine PH is resting patients but taking into account that about 30% of vascular bed is involved, the blood flow is diverted in the remaining units with a proportional overflow, leading to a leftward shift of PAP/Q, because of the already exhausted exploitation of recruitment and distensibility (likely cause of inversion of perfusion gradient), and a consequent increase of PAP under effort [23-27]. Increasing after load of right ventricle ultimately leads to a decrease of systolic ejection in advanced stages. In the patients with PH the pulmonary

rarefaction is worst in earlier stages and the PAP/Q is steeper, due to higher PVR: this can explain the reported positive predictive power of effort induced PH upon the onset and development of PH [7-10,26]. However PAP/Q slopes do not separate clearly the subsets of patients because of the transvariance of distributions, thus the slopes are more useful in the evidence of PH in initial phases and to assess the effects of pharmacologic treatments [28]. The causes of variance are the phenotype of disease [35], the left ventricle cardiac performance (leading to increased capillary pressures in case of altered diastolic filling or systolic failure), and the degree of respiratory failure and the presence of OSAS determining HPV.

The topic of whether vessel loss is responsible for PH can be addressed taking into account that the lack of a significant relationship between vascular rarefaction and PAP indicates that PH at rest is likely dependent upon different pathways, although under effort rarefaction renders PH more probable. In our study, HPV accounts only for a limited amount, thus other factors different than simple vessels loss or HPV play a relevant role, such as intrinsic changes of vessels lumens, the proliferation of muscle cells layers with muscolarization of arteries, associated with PH and related to hypertrophy of right ventricle and chronic hypoxia [34] and referred to as due to an imbalance of mythogenic and vasospastic mediators over vasodilators and anti-proliferative ones as response to oxidant load and inflammation.

Conclusion

In conclusion our preliminary data, to be confirmed by more extensive and multicentric studies, suggest an early vascular loss in COPD, evident even when pulmonary function testing is not sensitive, coherent with the reported [23] wasting of V'/Q' relationship, associated with an abnormal effort response, and is relevant but not an exclusive determinant of PH.

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