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Flow–volumes indices as means to discriminate between intra- and extrapulmonary restrictive disease

Pieter Zanen[a,*], Hans Folgering[b], Jan-Willem J. Lammers[a]

[a]*Department of Pulmonary Diseases, University Medical Center, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*
[b]*Department of Pulmonology Dekkerswald, University of Nijmegen, Nijmeegsebaan 31, 6561 KE, Groesbeek, The Netherlands*

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Summary Restrictive lung disease comes in two major categories: (1) intrapulmonary (= parenchymal) disease caused by fibrotic reactions or (2) extrapulmonary (= compression), like in heart failure. In the first category the conducting airways, tethered in stiffened structures, are less likely to be compressed during forceful expiration and expiratory flows hence are expected to remain high. This could serve as a cheap and easy diagnostic, avoiding more complicated measures. A database was build containing 624 patients suffering from either intra- and extrapulmonary disease. The flow–volume curve indices of restrictive patients (with a total lung capacity <-1.96 SD of reference) were compared and it was shown that in primary fibrotic disease and in leukaemia, indeed, the PEF and $MEF_{75/50/25}$ were significantly higher compared to the heart failure group ($P \leqslant 0.001$). The diabetes mellitus vs. heart failure differences were much less ($P > 0.05$). The area under the ROC to discriminate extra- from intrapulmonary disease was a low 0.607 and 0.606 for the PEF and MEF_{75}, respectively. For the peakflow an optimal cut-off point was found at 65.8% of the reference value. The positive/negative predictive value of a peakflow $<65.8\%$ to detect extrapulmonary disease was 30.1% and 82.2%, respectively.

Introduction

Restrictive lung disease is frequently diagnosed by either a high FEV_1/VC ratio, a lowered TLC via bodyplethysmography and/or helium dilution measurements. Two categories of restrictive disorders can be recognised: (1) intrapulmonary

*Corresponding author. Tel.: +31 30 2506150; fax: +31 30 2505421.
E-mail address: p.zanen@azu.nl (P. Zanen).

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(= parenchymal) disease of the lungs, leading to fibrosis, etc. or (2) extrapulmonary disease leading to lung compression, like cardiac enlargement due to (longstanding) heart failure. This difference in aetiology reflects itself in an absence or presence of stiffening of the lung: the latter is not expected in heart failure. All theories explaining flow limitation during forced expiration (like the equal pressure point theory) take into account the compression of the conducting airways, causing an increase of airway resistance. The fact that when a FEV_1/VC ratio is high indicates that the FEV_1 is reduced to a same degree as the VC: the less outspoken compression of the stiffened airways being responsible. In case of extrapulmonary disease, these phenomena do not occur and one would expect that the reduced airway diameter could easily lead to even more outspoken compression phenomena: expiratory flows are expected to be lower(ed).[1]

The consequences of the different behaviour is that in extrapulmonary restrictive disease, the peakflow and other parameters of the flow–volume curve would be lower compared to the 'fibrotic' restrictive disease. This difference could hence function as an easy means to discriminate between extra/intrapulmonary restrictive disease. In places where additional diagnostic measures like high resolution CT scanning is not readily available, the analysis of the flow–volume curves might be helpful in differentiating intra- versus extrapulmonary restrictive disease.

Methods

Database

A database was build containing those patients, who are likely to develop a restrictive lung disease: Table 1 lists the diagnoses of these patients. The diagnosis was established by the treating physician and/or the pulmonologist. Patients with a (co-)diagnosis at risk for an obstructive or obstructive/restrictive lung disease were excluded. The latter means that subjects over 40 years of age and a history of $\geqslant$10 pack years were not included in the database.[2] Smokers with a clinical diagnosis of COPD or those in which HRTC-scanning showed loss of alveolar tissue, defined as $>5\%$ of the total lung volume consists of areas with a density <-910 Hounsfield units were also not included.[3,4] The database was completed with spirometry and bodyplethysmography data. Bodyplethysmography and spirometry were performed at the same day.

Lung function data

Bodyplethysmography and spirometry were carried out in a Jaeger bodyplethysmograph (also suited for spirometry) according to ERS guidelines.[5] Measured variables were TLC, RV, RV/TLC, FEV_1, VC_{in}, FEV_1/VC, PEF and $MEF_{75/50/25}$. The measured values were expressed as a percentage of the reference value and a value outside the 95% confidence interval was labelled as 'diseased'.[5]

Statistics

The next step was to select those measurements where the TLC could be labelled as 'restrictive' because the value was below the lower limit of the 95% confidence interval. The values of all other lung function parameters were subsequently compared between the intra/extrapulmonary disease groups using one-way analysis of variance. The heart failure group was used as reference group, because of the difference in aetiology. The diagnostic value of the lung function parameters to discriminate between intrinsic–extrinsic restriction was approached via calculation of the area under

Table 1 Summary of selected diagnoses for patients at risk to develop restriction, type of restriction and the number of subjects present in database.

	Type of disease	Type of restriction	Number of subjects
Leukaemia and lymphoma	All sorts of leukaemia, Hodgkin, non-Hodgkin, myeloma, Kahler, including treatment effects	Parenchymal	90
Diabetes mellitus	Excluding cardiac involvement	Parenchymal	89
Fibrotic disease	Collagen diseases, SLE, sarcoidosis, alveolitis, rheumatoid arthritis, Raynaud, post-inflammation fibrosis	Parenchymal	270
Cardiac disease	Heart failure, cardiomegaly	Compression	175

the curve of the ROC curve: an AUC value of 0.7 was considered as useful. α-value was set at 0.05.

Results

The database contained data on 624 subjects in whom 1749 measurements were made: in Table 2 the mean (SD) TLC are listed. Eight hundred and ninty-eight measurements (51.3%) showed a TLC below the 95% CI lower limit and were selected. Analysis of variance showed significant differences between the disease groups, where especially the fibrotic/leukaemia groups showed significantly higher PEF and $MEF_{75/50/25}$ values compared to the heart failure/diabetes mellitus group (Table 3 and Fig. 1).

When the three intrapulmonary disease groups were combined and compared to the heart failure group via an unpaired *T*-test, the peakflow and the MEF_{75} showed the largest differences. The peakflow, respectively, MEF_{75} 95% CI of the parenchymal/heart failure difference was 6–14.5% and 7.3–17% of the reference value. The AUC of the ROC curve for peakflow, respectively, MEF_{75} proved to be 0.607 ($P<0.001$) and 0.606 ($P<0.001$), which is below the value of 0.7. In this database, the highest combination of sensitivity and specificity for the peakflow was found at a cut-off point of 65.8% of the reference value. The positive predictive value of a peakflow $<65.8\%$ of reference to detect extrapulmonary restriction was 30.1% and the negative predictive value proved to be 82.2%.

Discussion

We could show that in restrictive lung disease due to intrapulmonary pathology, the peakflow and several other flow–volume curve indices were indeed higher compared to extrapulmonary restrictive lung disease, as in heart failure. This conclusion is especially true for fibrotic parenchymal disease, as seen in alveolitis, sarcoidosis, etc. The differences however were not that large that they constitute a useful diagnostic criterion.

The most probable cause for this phenomenon is a difference in the compliance of the airways.[1] Airways are deformed (= compressed) during forceful expiration due to a pressure difference over

Table 2 Mean (SD) of the TLC as percentage of reference and demographics data in the four disease groups.

	Mean TLC (% of reference)	Height (cm)	Age (years)	% Female	% Restrictive
Leukemia's and related diseases	80.0 (15.1)	176.7 (10.8)	43.6 (15.2)	26.7	47.8
Diabetes mellitus	**86.8 (16.3)**	171.9 (10.8)	57.9 (16.1)	36.0	29.1
Heart failure	78.7 (17.1)	173.2 (9.5)	63.8 (15.4)	21.7	55.6
Fibrotic diseases	**74.7 (15.8)**	172.7 (10.1)	53.9 (16.3)	41.5	58.6

Bold data indicate a significant TLC difference versus the heart failure group.

Table 3 Mean values of several lung function parameters (% reference) as function of the underlying disease entity and overall between group significance level.

Parameter	Leukaemia and lymphoma	Diabetes mellitus	Heart failure	Fibrotic disease	*P*-value for between group difference
RV	91.8	**97.9**	86.5	**78.6**	<0.001
RV/TLC	**132.5**	**133.2**	121.1	117.4	<0.001
VC	59.5	62.5	60.1	61.9	0.283
FEV_1	57.6	54.7	56.3	**59.8**	0.028
FEV_1/VC	96.7	**87.4**	93.5	**98.0**	<0.001
PEF	**77.1**	62.3	63.4	**74.8**	<0.001
MEF_{75}	**70.1**	50.2	54.3	**68.5**	<0.001
MEF_{50}	**56.9**	39.4	45.2	**55.7**	<0.001
MEF_{25}	45.8	**32.3**	40.0	**45.1**	0.001

Bold data indicate a significant post hoc difference versus the heart failure group.

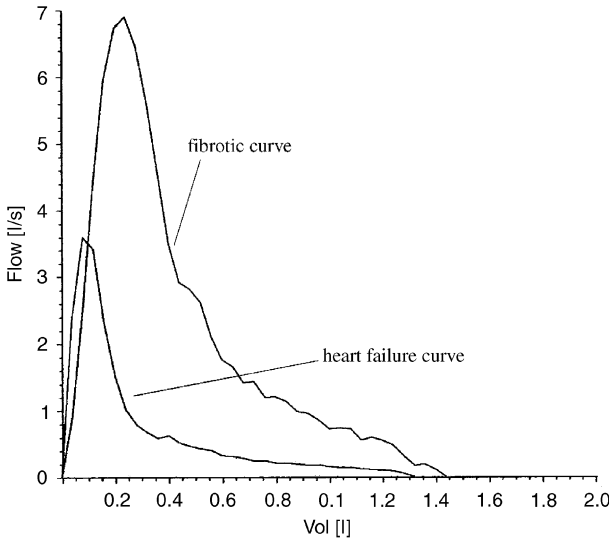

Figure 1 Two flow–volume curves showing a higher peak flow for the fibrotic patient in comparison to the heart failure patient. Note that the FVC for both subjects is identical.

the airway wall and/or to the Bernoulli effect.[6] The airways in fibrotic lungs are tethered in stiffened parenchymal structures and these fibrotic pathological changes render the airways more resilient against deformation and hence airflow tends to be/remain higher.[7] In heart failure such a tethering in stiffened structures is less probable: deformation of the airways during forceful expiration is to be expected and hence lowered flow–volume curve indices.

The large airway parameters (PEF and MEF_{75}) differed strongest between extra- and intrapulmonary disease. We can point at several mechanisms to explain this. First of all mechanical compression/deformation of the large airways caused by the enlarged heart can play a role: the diameter of the large airways will be reduced and they will be therefore more compression prone. Secondly, the PEF and MEF_{75} are parameters sensitive to low intrathoracic pressure build up and it is conceivable that during the start of the expiration more blood than usual will flow out of the enlarged heart back into the systemic veins and so a part of the pressure build up is buffered.

We could report expected differences between intra/extrapulmonary disease, but they do not constitute a highly useful diagnostic tool: the differences are not large enough. This can be explained in several ways: (a) the 'flow preserving' effect in fibrosis is not strong enough, (b) heart failure lungs may also show a reduced compliance. Some indeed described a lower compliance in heart failure.[8,9] One explanation was the stiffening effect of overfilled pulmonary blood vessels in heart failure. Next to that it is frequently reported that in heart failure the capillary blood volume is reduced to vasoconstriction, so overfilling should be a large vessel phenomenon.[10] It is unknown whether large vessel overfilling only could lead to stiffening of the lungs. On the other hand, it is known that in heart failure alveolar damage is present as indicated by a reduced $D_{m,CO}$. That damage could serve as an alternative explanation for the reported reduced compliance.[11] So it is possible that the lung mechanics in heart failure are indeed moving towards a reduced compliance, although it is not altered as much as in intrapulmonary fibrotic disease.

The restricted diabetes mellitus patients also do not show the degree of preservation of flow as in leukaemia and fibrotic. The lung function in a systemic disease like diabetes mellitus is claimed in some reports to have an obstructive component and it is very well possible that the restrictive patients suffer from such an obstructive component.[12,13] Benbassat reported an increased RV/TLC ratio.[14] The fact that the leukaemia group showed preserved flow–volume curve indices is most probably due to the fact that most patients are treated with either cytostatics and/or irradiation of the lungs. This leads to a well-charted fibrotic reactions with restriction.[15] However, the RV/TLC ratio is increased although combined with a normal FEV_1/VC ratio. Close examination showed that a few subgroups in this 'leukaemic' cohort (Hodgkin, acute lymphatic leukaemia, acute/chronic lymphoid leukaemia and bone marrow transplants) were largely responsible for this increase. Lung function disturbances in these diseases are hardly described in the literature, so we cannot say whether this is a confirmed disease related or a local phenomenon.

Despite the highly significant differences, the diagnostic value of the flow–volume curve indices for differentiation of types of restrictive disease is low. Generally a parameter is considered as a useful diagnostic, when the area under its ROC curve is >0.7 and none of the indices in our study reached that level, not even the peakflow or MEF_{75}. More useful was the negative predictive value of 82%, to detect an externally caused restriction which means that a peakflow larger than the cut-off value of 65.8% of reference frequently excludes extrapulmonary restriction. The positive predictive value to detect extrapulmonary restriction is too low to be of any practical value: a peakflow $<65.8\%$ indicates only in a minority externally caused restriction.

In conclusion we can confirm that in restrictive lung disease due to intrapulmonary disease the peakflow is less disturbed compared to extrapulmonary disease: in our material, a peakflow of $>65.8\%$ of reference frequently excludes extrapulmonary restriction, but a peakflow lower than that value does occur with both extra- and internal pulmonary restriction.

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