

Chronic hypoxaemia and gender status modulate adiponectin pathway in severe COPD patients: new endotypic presentation?

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Abstract

Background: Disease progression in COPD patient is associated to lung function decline, leading to a higher risk of hypoxaemia and associated comorbidities, notably cardiovascular diseases (CV). Gender is also known to influence CV risk. Adiponectin (Ad), a cardio-protective hormone, was suggested as a biomarker for COPD risk management. However, determinants and consequences of Ad pathway modulation in COPD are unknown and gender specificities are poorly understood. We postulated that hypoxaemia and gender could influence Ad pathway and contribute to the appearance of a distinct endotype associated to an altered CV risk.

Methods: The Ad plasmatic (Ad_{pl}) level and proportion of its different forms were evaluated in hypoxemic and non-hypoxemic COPD men or women. The relationship between these measures and BMI, blood gas analysis (PaO_2 , $PaCO_2$), or lung function (FEV1, FEV1/FVC, TL_{CO} , TLC, RV) were tested.

Results: Despite similar age, BMI and obstruction severity, women had a higher TLC and RV than men. Ad_{pl} level was higher in women and negatively associated with hyperinflation and hypercapnia. The proportion of the most active forms of Ad (HMW) is increased in hypoxemic women but not in men. A positive correlation between TL_{CO} and HMW form proportion was observed in hypoxemic men, whereas a negative correlation was detected in non-hypoxemic men.

Conclusion: Physiopathology of COPD seems to be gender specific. Hypoxaemia, hypercapnia and hyperinflation are associated to gender-specific Ad pathway alterations. Given CV properties of Ad, the impact of such modulation on co-morbidities development have to be considered in future studies.

Background

Chronic obstructive pulmonary disease (COPD) is a progressive affection associated to lung function decline and to comorbidities such as cardiovascular diseases (CV). By inducing secondary erythrocytosis, endothelial dysfunction, and pulmonary arterial hypertension, hypoxaemia in severe COPD patients was suggested to contribute to the increased CV risk in these patients (1,2). The prevalence of the disease is increasing among women due to the higher smoking rate (3,4). Moreover, sex-differences were reported in the course of the disease. Women were described to exhibit a greater susceptibility to tobacco, faster annual decline of lung function and worse quality of life (3,4). This increased effect of tobacco smoke on women was suggested to be due to gender difference in airway structure (5–7), but inflammatory response to tobacco smoke was also suspected to differ at the level of the small airways (8) and to be at the origin of a more extensive airway remodelling (9). The prevalence of co-morbidity also varied with gender in COPD patients and men were described to be more susceptible to CV and diabetes mellitus (10).

Adiponectin (Ad), a 30kDa protein mainly secreted by adipose tissue, is well described for its anti-inflammatory, anti-atherogenic and anti-diabetic effects (11). The physiological plasmatic concentration

of this adipokine is higher in women (12). Ad circulates in the blood in 3 different isoforms: low (LMW), medium (MMW), and high molecular weight forms (HMW). HMW forms are described as the most active isoforms: they are better correlated to insulin sensitivity and circulating glucose concentration (13,14). A reduced Ad plasmatic (Ad_{pl}) level is associated to multiple metabolic and CV disorders (15). In COPD patients, conflicting results regarding Ad_{pl} level were observed in previous studies (16–18) and could be explained by the heterogeneity of the disease. Several factors, such as exacerbation rate, BMI, disease severity and progression were associated to differences in Ad_{pl} level in COPD (16,19–22). In addition, exposure to chronic hypoxia was also shown to altered Ad expression in adipocytes *in vitro*, and in adipose tissue *in vivo* (23–25).

Adiponectin was previously proposed as a biomarker for COPD risk management, and its pathway was suggested as a potential therapeutic target. However, COPD is a complex and heterogeneous disease that could interact in a variety of ways with adiponectin pathway. In this study, we therefore evaluated the adiponectin pathway in COPD patient, with a special attention to gender and hypoxaemia effects. Potential relationships between these data and lung function were also evaluated.

Methods

Subjects

COPD patients were recruited from the outpatient clinic of a tertiary University Hospital and were referred for evaluation of need for oxygen therapy or for the adaptation of this treatment. COPD was diagnosed according to the ACCP/ATS/ERS guidelines (27).

Patients with concomitant confounding diseases such as malignant or endocrine disorders, liver disease, gastrointestinal and primitive cardiovascular abnormalities, or recent surgery were excluded. All subjects were >40 years of age. This study was approved by the Erasme Hospital Ethics Committee and conducted in accordance with Helsinki Declaration.

Data on each patient including age, gender, BMI were collected and analyses were performed anonymously. Arterial blood sample was obtained at rest, with the patient in sitting position, while breathing room air. Arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) partial pressures were measured and recorded. Spirometry, lung volumes and single-breath determination of carbon monoxide uptake were then evaluated according to the ATS guidelines (28–30) (M.E.C PFT systems Body™ and Diff™, Belgium). FEV1 (forced expiratory volume in one second) and FVC (forced vital capacity), FEV1/FVC ratio carbon monoxide transfer factor (TL_{CO}), total lung capacity (TLC), and residual volume (RV) were recorded. As patients did not interrupt their medical treatment before medical appointment, these measures could be reasonably considered as post-bronchodilation data. TLC and RV have not been obtained from 2 non-hypoxemic women and 5 men because they were unable to perform plethysmography in a reproducible way.

Adiponectin plasmatic level measurement

Ad_{pI} level was measured according to the manufacturer's instructions (DRP300: Human Total Adiponectin/Acrp30 Quantikine ELISA Kit, R&D Systems).

Adiponectin oligomer distribution determined by Western blot

The relative amounts of LMW, MMW and HMW Admer were evaluated as previously described in Pierard et al.(31).

Statistical analysis

Patients were divided into two groups: hypoxic group corresponded to severely hypoxic patients with a PaO₂ ≤ 55mmHg and non-hypoxic group with a PaO₂ > 55mmHg while breathing room air. This cut-off was based on ATS/ERS statement in which severe hypoxaemia in COPD patients is defined as a PaO₂ ≤ 55mmHg. A Rank-Sum test was used to evaluate differences between groups. In table, results were represented as median and 5th-95th percentiles. In the graphs, all data were represented as boxplot (5th-95th percentiles; dots are outliers). Pearson's coefficient was used for correlation analysis. Pearson correlation coefficient (R) was calculated for each parameter (supplementary data 1). Differences were considered statistically significant at a P value < 0.05.

Results

Characteristics of subjects

100 COPD patients with moderate (16%), severe (43%) or very severe obstruction (41%) were included in this study. 61% of the cohort were male. 46% were not severely hypoxemic and allocated to the non-hypoxemic group (**Table 1**). Hypoxemic and non-hypoxemic patients exhibited the same age, BMI and disease severity based on FEV1 value. Both groups had a significant air trapping (increased RV). The alteration of TL_{C0} was more severe in hypoxemic patients and these patients were more hypercapnic than non-hypoxemic counterparts. When the cohort was separated according to gender, no difference was observed for age, BMI, FEV1, PaCO₂ or TL_{C0}. However, we found an increased TLC and RV in women compared to men.

Table 1: Clinical characteristics of COPD subjects separated according to gender or hypoxaemia status.

	Non-hypoxemic (n=46)	Hypoxemic (n=54)
Age (year)	68 [65 - 76]	71,5 [64 - 77]
BMI (kg/m ₂)	24,34 [20,2 - 30,48]	25,84 [22,39 - 30,12]
PaCO ₂ (mmHg)	41 [37 - 44]	45,5 [39 - 53] *
FEV ₁ (%pred)	34,5 [29 - 46]	31 [25 - 44]
FEV ₁ /FVC	46,77 [38 - 58]	46,28 [39,5 - 52]
TLCO (%pred)	39,5 [32,45 - 49,5]	29,5 [23 - 42,8] *
TLC (% pred)	91 [79 - 104,8]	97,5 [82 - 109,8]
RV (%pred)	143 [117,5 - 171]	152, 65 [114 - 202,5]
	Men (n=61)	Women (n=39)
Age (year)	72 [66,75 - 77,25]	67 [60 - 74,75]
BMI (kg/m ₂)	25,61 [22,39 - 30,48]	24,84 [20,29 - 30,58]
PaCO ₂ (mmHg)	42 [37 - 47]	45 [40 - 50]
FEV ₁ (%pred)	32 [25,75 - 44,25]	34 [27,25 - 46]
FEV ₁ /FVC	47 [39,68 - 55,25]	45,78 [39,04 - 54,76]
TLCO (%pred)	35 [26,6 - 50,5]	32,9 [24 - 43,35]
TLC (% pred)	87,35 [74,5 - 102,5]	105,4 [90 - 116] **
RV (%pred)	132,3 [104 - 179]	166,25 [138 - 195] *

Data were represented as median [25th and 75th percentiles]. * p<0.05; Rank-Sum test.

Effect of hypoxaemia on Ad_{pI} level and HMW forms

We postulated that hypoxia could modulate Ad pathway in COPD patients. However, we did not observe any difference in Ad_{pI} level and in HMW form proportion between hypoxemic and non-hypoxemic patients (**Figure 1A-B**). We found that Ad_{pI} level was negatively correlated with BMI in both groups but were not correlated with other parameters (**Figure 1C-D**). We detected a significant negative correlation between BMI and HMW form proportion in non-hypoxemic patients, but not in the hypoxemic group. Moreover, a negative correlation was observed between HMW form and TL_{CO} in non-hypoxemic patients. In the hypoxemic group, these parameters were positively correlated but without reaching a statistically significant level (p=0.055).

Impact of gender difference on Ad_{pI} level and HMW forms

As gender differences in total and HMW Ad levels were previously observed in many studies (32,33), we evaluated these parameters in men and women and correlated these values with lung function parameters. We found a higher Ad_{pI} level in women compared with men (**Figure 2A-B**). As previously, in both groups, Ad_{pI} level was negatively correlated with BMI (**Figure 2C-D**). In women, we observed a

significant negative correlation between Ad_{pl} level and TLC, as well as with $PaCO_2$. These observations were in accordance with the decrease of Ad_{pl} level in hypercapnic women ($PaCO_2 > 45$ mmHg) compared with normocapnic women ($p < 0.05$). A reduced Ad_{pl} level was also observed in women characterized by hyperinflated lungs (TLC $> 115\%$ of the predicted value (%pv)) (**Figure 2E-F**). Concerning HMW form proportion, no gender difference and no correlation with BMI, arterial gas values, or lung parameters were detected.

Effect of combined gender difference and hypoxia on Ad_{pl} level and HMW forms

Since differences on Ad_{pl} level between men and women could reflect different mechanisms of regulation, we separated the cohort according to gender and to the presence, or not, of hypoxaemia. We did not observe any modification in total or HMW Ad level between hypoxemic and non-hypoxemic men (**Figure 3**). In women, hypoxaemia did not modify total Ad_{pl} level but increased HMW form proportion. As previously, whatever the gender, Ad_{pl} level is negatively correlated with BMI in hypoxemic and non-hypoxemic group (**Figure 4**). A negative correlation between total Ad_{pl} level and TLC was statistically significant in non-hypoxemic women, and borderline in hypoxemic women ($p = 0.07$). Regarding HMW forms, we observed a positive correlation between HMW proportion and RV in non-hypoxemic men. We also detected an opposed relationship between TL_{CO} and HMW level in hypoxemic and non-hypoxemic men. While a positive correlation was observed in hypoxemic men, a negative correlation was detected in non-hypoxemic men. This relationship did not appear in women. Although, we observed that HMW level was negatively associated with RV in hypoxemic women.

Discussion

To identify potential mechanisms involved in COPD-related co-morbidity, we considered the impact of gender and hypoxaemia on Ad_{pl} level and HMW form proportion. In our study, a gender difference in Ad_{pl} level was observed. Women exhibited a higher Ad_{pl} level compared with men. While this discrepancy was previously described (34,35), the mechanism underlying this divergence is still investigated. Testosterone level (36–39) and the different adipose tissue distribution in men and women were previously mentioned (40). For a given BMI, men exhibited higher lean mass, and women had a higher adiposity and Ad_{pl} level (40). In addition, muscle is well-known to be affected by COPD and in this context, muscle dysfunction was more intense in women than in men (41–43). This phenomenon could also contribute to increase Ad_{pl} level in women.

In addition to the gender difference in Ad_{pl} , we observed a gender divergence in TLC and RV, without any difference in BMI. These data suggested that, for a given FEV1, women had a more pronounced air trapping (increase of RV) or hyperinflation (increase of TLC) than men, while hyperinflation was quite limited in our study (mean TLC was 105%pv in women and 87%pv in men). These results contrasted with previous studies in which men exhibited more emphysema than women. By using CT scan, previous studies observed that the percentage of low attenuation area was higher in men than in women (44,45).

Using the same method, Martinez et al. also found that emphysema was less extensive in women (46). However, the study group consisted in patients evaluated for lung volume reduction surgery. Therefore, emphysema was a predominant feature in the population studied, contrary to our population. Moreover, in Martinez et al. study, women had a greater FEV1 (%pv) than men, so we cannot exclude that the predominance of emphysema in men was associated to disease severity. This is consistent with the study of Hardin et al. (47) highlighting that gender difference in CT-determined emphysema is dependent on the severity of airway obstruction (GOLD classification). Despite of these considerations, it is interesting to note that the difference in radiological emphysema did not appear in functional hyperinflation in Martinez's study. Indeed, TLC %pv was not significantly higher in men (value of women tended to be higher). Moreover, inspiratory capacity (IC) to TLC ratio was even significantly smaller in women. These results underlined the contrast between radiological evaluations in favour of more emphysema in men, and functional measures reflecting probably a higher air trapping in women.

In the present study, we also observed that the increased TLC %pv in women was associated with a reduced Ad_{pl} level. As pro-inflammatory cytokines were previously demonstrated to reduce Ad expression in adipocytes (48), it could be hypothesised that inflammatory state in these patients modulated Ad_{pl} level. Indeed, Rubinsztajn et al. observed that patients with hyperinflation had elevated inflammatory markers (21). Another explanation supporting this hypothesis could be the gender difference in inflammatory processes (49–51). The exact mechanism remains unclear. Rathod et al. showed that a divergent hormonal status could be involved in this regulation (50), whereas the study of Casimir et al. observed that some genes on X chromosome, involved in the inflammatory cascade, were overexpressed in women (49). While this divergence in the inflammatory state was not previously described in COPD, this phenomenon is well known in patients with asthma, with a more pronounced inflammatory responses within the airway wall in women (52–54). Therefore, more studies are necessary for elucidating the potential role of inflammation in the association between Ad_{pl} level and TLC %pv in women with COPD.

The increase of TLC and RV %pv observed in women in our study was observed in other recent studies (43,55,56). Grabicki et al. observed that COPD women had more hyperinflation, air trapping and comorbidities, inducing a higher risk of mortality (55). In women, this increased air trapping also led to the development of hypercapnia (57). In Martinez's study, women had a decreased IC/TLC ratio compared to men and was also more hypercapnic and hypoxemic, in spite of a higher mean FEV1 %pv. We also observed a significant difference between men and women for PaCO₂. Moreover, in women, Ad_{pl} level was negatively associated with TLC and PaCO₂, especially in hypoxic subgroup. Previous studies found a decreased Ad_{pl} level and a higher PaCO₂ in mice with acute lung injury (58) or in patients with hypoventilation syndrome (59). However, a potential correlation between these parameters was not evaluated. Dimoulis et al. studied this association as well as the effect of non-invasive ventilation (NIV) on Ad_{pl} level in stable hypercapnic COPD (60). They observed that Ad_{pl} level was negatively correlated with bicarbonate level. In addition, NIV reduced PaCO₂, increased PaO₂, and Ad_{pl} level was also increased from the first month of intervention, without any change in BMI (61). In addition to physiological gender

difference in Ad_{pI} level, our study suggested that functional alteration such as hyperinflation, air trapping and impaired gas exchange also modulated Ad_{pI} level in COPD patients.

In addition to its potential modulation of Ad_{pI} level through its association with hypercapnia, hypoxaemia was associated to an increased HMW form level in women. Interestingly, these observations were in accordance with our previous study in which an increased HMW form proportion in a murine model of hypoxaemia was observed (62). In this model, the only difference between the active and control group was the exposure to hypoxia. However, we also observed that the increased HMW form proportion was associated to a decreased AdipoR protein level in different tissues (63,64). Further studies are therefore needed to better understand the impact of an increased HMW form level in hypoxemic women. No modulation of Ad_{pI} level or HMW form proportion were observed among hypoxemic and non-hypoxemic men, suggesting that Ad pathway is modulated by different mechanisms in men and women. One explanation could be the presence of a gender-difference in the inflammatory response, as previously mentioned. Indeed, in different pathological contexts, previous studies reported that women were affected to a more extended level by a pro-inflammatory state but respond more vigorously (65–67).

This study has some limitations. As we evaluated the effect of the hypoxaemia component in COPD patient, we separated our cohort according to the PaO_2 (≤ 55 mmHg). However, patients in such condition received LTOT in order to reduce the risk of complications and mortality. It is therefore difficult to justify a washing period from oxygen therapy for those already on this treatment at the inclusion time. Treatment naïve patients should be selected and Ad pathway modulation could then be studied before and after LTOT in the same patient.

Conclusions

All together, these data suggested that men and women with severe hypoxaemia exhibited a different physiopathology of COPD, which is linked to an Ad pathway modulation. Indeed, an increased Ad_{pI} level was observed in COPD women and was associated with a distinct pattern of functional alteration (for the same age, BMI or obstruction severity): women had more hyperinflation, air-trapping and hypercapnia, which, in association with hypoxaemia, could contribute to a modulation of Ad_{pI} level. These variations were accompanied with an increased HMW form level in hypoxaemic women. All these results suggested the development of a distinct endotypic presentation, based on gender, with a more pronounced bronchiolar damage possibly associated with an inflammatory state, leading to an increased air-trapping. Consequently, a long-term study should be realized to evaluate if these modulations of total Ad_{pI} and HMW forms are associated with a better vital survival or with lower risk of comorbidities.

Abbreviations

Ethics approval and consent to participate

This study was approved by the Erasme Hospital Ethics Committee. All procedures were conducted in accordance with ACCP/ATS/ERS guidelines. All patients had previously given their written informed consent for this study.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional file.

Competing interests

The authors declare that they have no conflict of interest regarding the publication of this paper. Each author meets the criteria for authorship and assumes the corresponding responsibility.

Fundings

FRMH (Fonds pour la Recherche Médicale dans le Hainaut) provided funding in order we performed molecular analysis. MP held PhD fellowships from the University of Mons.

Authors' contributions

MP carried out the molecular studies, participated in the design of the study, drafted the manuscript and performed data recording, data analysis, and the statistical analysis. AT participated in the conception of the study and in its design and coordination. AT also supervised molecular studies, critically revised the manuscript and found sustaining funds for project. AL1 participated in study coordination, data recording and analysis. AL2 conceived of the study, and participated in its design and coordination, helped to draft the manuscript and to perform statistical analysis. All authors read and approved the final manuscript.

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Declarations

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MP carried out the molecular studies, participated in the design of the study, drafted the manuscript and performed data recording, data analysis, and the statistical analysis. AT participated in the conception of the study and in its design and coordination. AT also supervised molecular studies, critically revised the

manuscript and found sustaining funds for project. AL1 participated in study coordination, data recording and analysis. AL2 conceived of the study, and participated in its design and coordination, helped to draft the manuscript and to perform statistical analysis. All authors read and approved the final manuscript.

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Figures

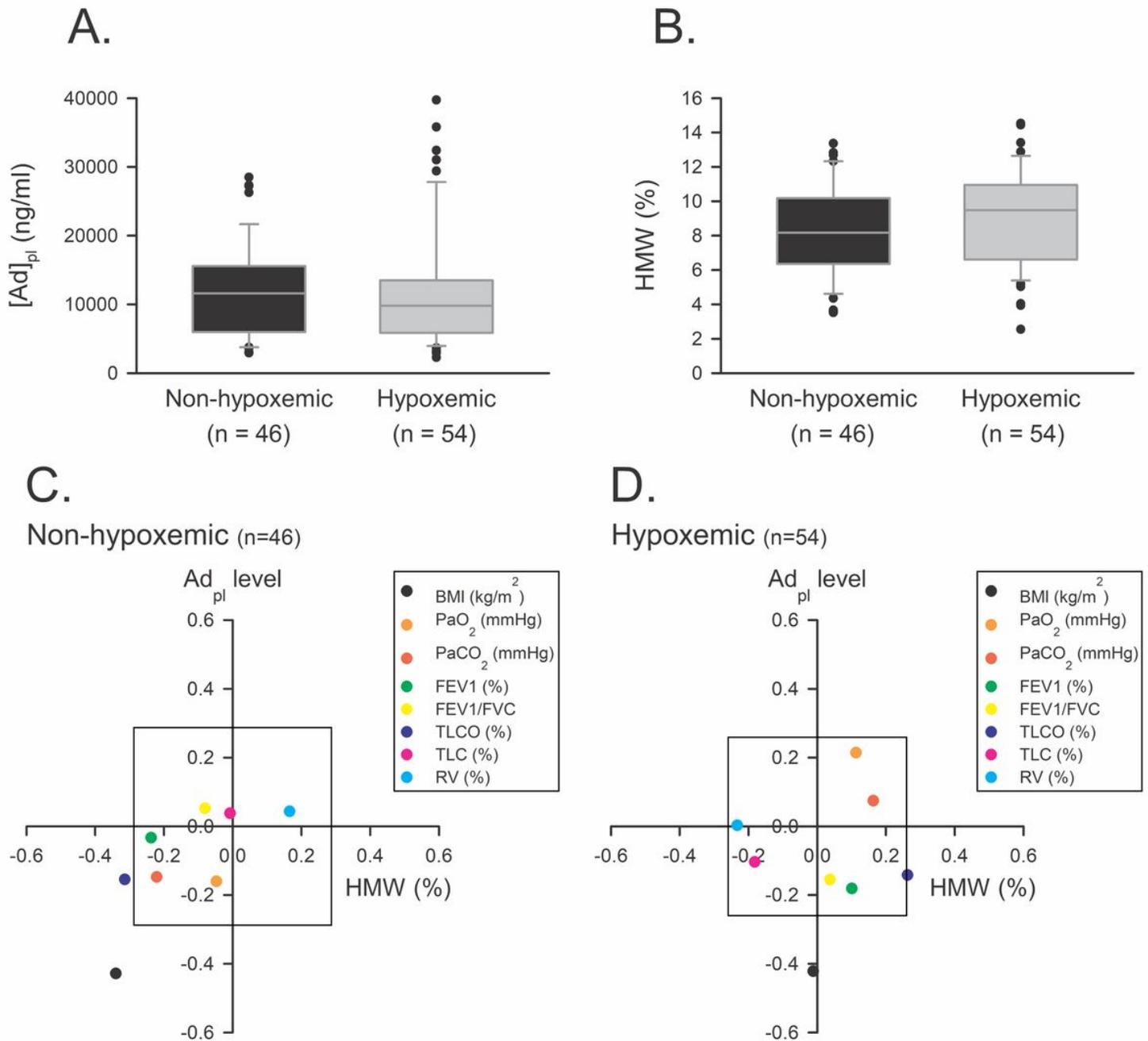


Figure 1

(A-B) $[Ad]_{pl}$ level (A) and HMW form proportion (B) in non-hypoxemic and hypoxemic COPD patients. Data were represented as boxplot (5th and 95th percentiles). Rank-Sum test: NS. (C-D) Correlation between lung function parameters and $[Ad]_{pl}$ level (vertical) or HMW form proportion (horizontal), in non-hypoxemic (C) and hypoxemic (D) COPD patients. Pearson correlation coefficients (R) between every parameter and either $[Ad]_{pl}$ level or HMW form proportion were calculated and represented as a point on the graph. The box in the graph represented the critical value for Pearson correlation coefficient to obtain a $p < 0.05$.

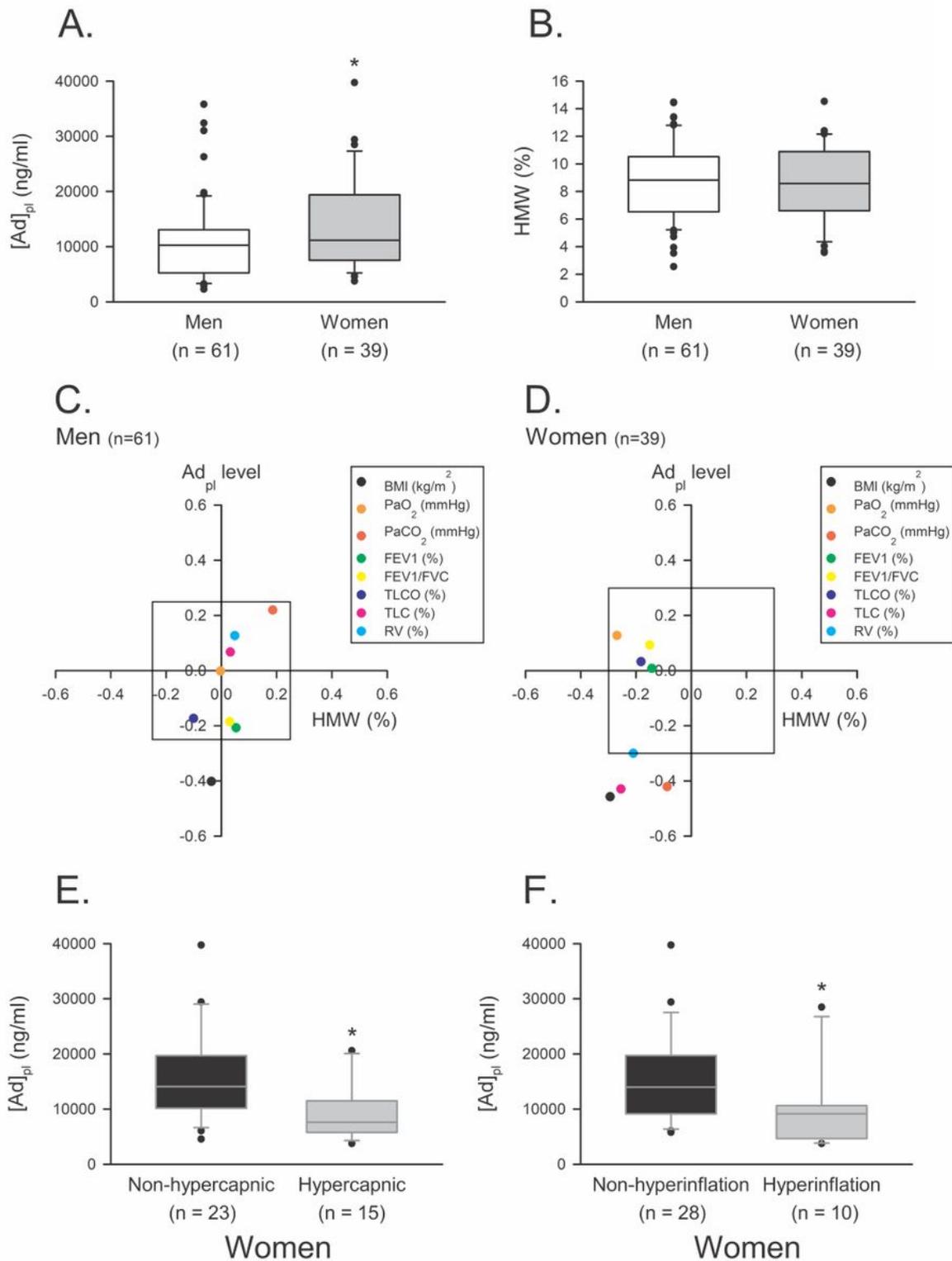


Figure 2

(A-B) Adpl level (A) and HMW form proportion (B) in men and women COPD patients. Data were represented as boxplot (5th and 95th percentiles). * $p < 0.05$; Rank-Sum test. (C-D) Correlation between Adpl level, (vertical) or HMW form proportion (horizontal) and lung function parameters in men (A) and women (B) COPD patients. Pearson correlation coefficients (R) between every parameter and either Adpl level or HMW form proportion were calculated and reported as a point on the graph. The box in the graph

represented the critical value for Pearson correlation coefficient to obtain a $p < 0.05$. (E-F) Adpl level in women with or without hypercapnia (E) or lung hyperinflation (F). Data were represented as boxplot (5th and 95th percentiles). * $p < 0.05$; Rank-Sum test.

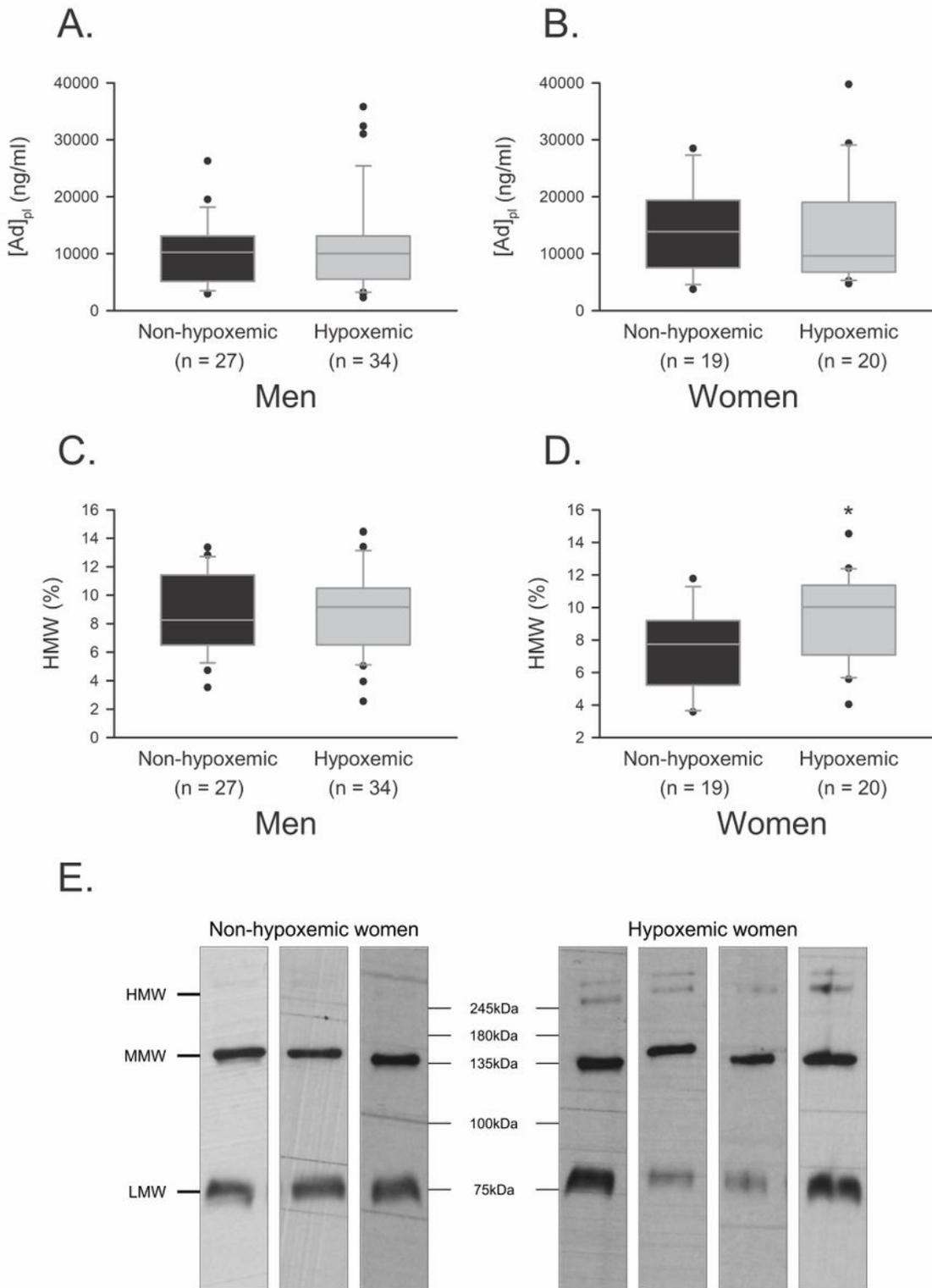


Figure 3

Adpl level (A-B) and HMW form proportion (C-D) in hypoxemic and non-hypoxemic men and women COPD patients. Data were represented as boxplot (5th and 95th percentiles). * $p < 0.05$; Rank-Sum test. (E)

Representative blots.

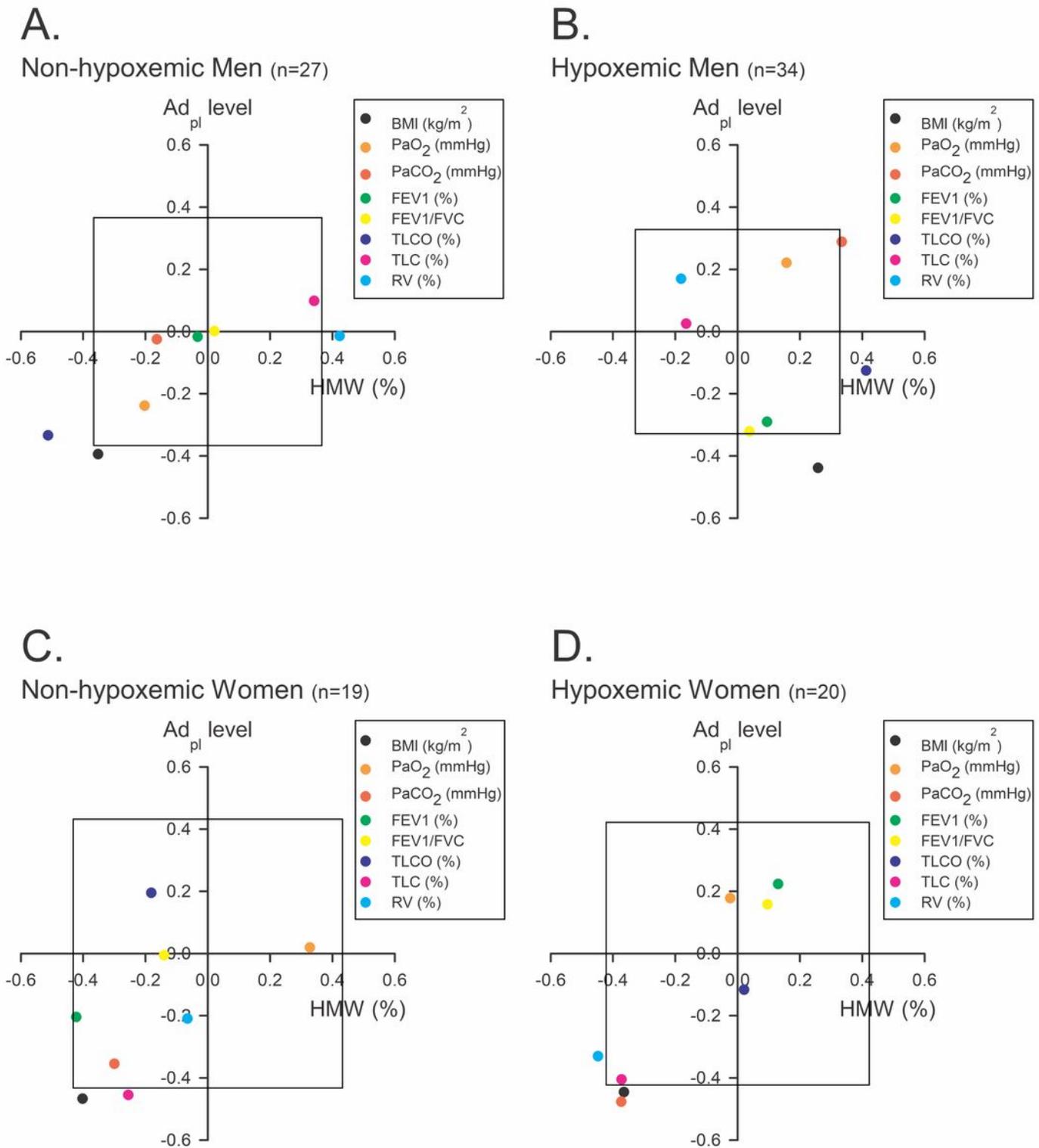


Figure 4

Relationship between Adpl level, (vertical), HMW form proportion (horizontal) and lung function parameters in non-hypoxemic men (A), hypoxemic men (B), non hypoxemic women (C) and hypoxemic women (D) COPD patients. Pearson correlation coefficients (R) between every parameter and either Adpl

level or HMW form proportion were calculated and were represented as a point on the graph. The box in the graph represented the critical value for Pearson correlation coefficient to obtain a $p < 0.05$.

Supplementary Files

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