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Measurement of exhaled nitric oxide fails to predict left atrial pressure assessed by E/e ratio in elderly patients

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Abstract:

Background: During left-sided heart failure, left atrial and pulmonary venous pressure increase, which may lead to pulmonary congestion. Previous cohort studies examining participants with symptomatic heart failure or rheumatic heart disease suggest a relationship between increased left atrial pressure (LAP) and fractional exhaled nitric oxide (FeNO).

Aim: In this study, we examined the strength of association between FeNO and echocardiographic assessment of LAP by the E/e' ratio to determine if FeNO could be used to identify those with elevated LAP. Office-based diagnostic testing for heart failure could be improved if such a relationship exists, as FeNO can be measured using a portable hand-held analyser.

Design and Setting: This cross-sectional cohort study examined a subset of the OxVALVE cohort aged >65 years. Data collection was undertaken in primary care practices in central England.

Method: Each participant underwent a focused cardiovascular history and clinical examination. Standard transthoracic echocardiographic (TTE) assessment was performed on all participants, with the E/e' ratio calculated to obtain a validated surrogate of LAP. FeNO was measured in 227 participants.

Results: FeNO was higher in men and no different in participants with asthma, chronic obstructive airways disease, or using inhaled steroids. Participants with a high E/e' (>14) were older with a higher proportion of women. There was no relationship between E/e' and FeNO, either when measured as a continuous variable or in the group with high E/e'.

Conclusion: FeNO is not an accurate predictor of elevated left atrial pressure in a primary care setting.

Keywords: Cardiology, Heart Failure, Primary Health Care, General Practice, Family Practice

How this fits in:

Previous cohort studies examining patients with symptomatic heart failure or rheumatic heart disease suggest a relationship between increased left atrial pressure (LAP) and fractional exhaled nitric oxide (FeNO). High LAP can frequently be reduced with diuretic therapy, so a simple method of predicting LAP could help guide management in outpatient settings. As FeNO can be measured with a hand-held analyser, a diagnostic test for heart failure in primary care could be developed if such a relationship exists. We found that E/e' ratio measured on echocardiography is not associated with FeNO in a population based setting - FeNO does not predict LAP in primary care.

Introduction

Heart failure (HF) is a major cause of morbidity and mortality in the United Kingdom and worldwide.[1,2] Approximately 50 percent of patients with HF present with a left ventricle that essentially contracts normally, termed HF with preserved left ventricular ejection fraction (HFpEF).[3] Early diagnosis of HF is difficult despite its high prevalence, particularly in the elderly, with symptoms of heart failure, such as fatigue and shortness of breath, being frequently seen due to other diagnoses.[4] Assessment of left atrial pressure (LAP) in these patients is traditionally carried out by echocardiography or invasive cardiac catheterisation. Formal echocardiography requires specialist training and expertise, and is therefore not widely used in the primary health care setting. Furthermore, even when left ventricular ejection fraction (LVEF) is measured using point of care echocardiography, LAP assessment requires Doppler measurement that is often unavailable on point of care devices. A simple cost-effective test for elevated LAP requiring minimal expertise could therefore lead to improved HF diagnosis and identify those patients most likely to benefit from medical therapy.

Fractional exhaled nitric oxide (FeNO) may be a suitable diagnostic marker for elevated LAP. In left-sided HF (whether due to reduced ejection fraction [HFrEF) or preserved ejection fraction [HFpEF]), the left ventricle is unable to adequately pump blood to the systemic circulation, leading to elevated LAP[5] and a subsequent increase in pulmonary venous pressure, resulting in pulmonary congestion and a possible increase in FeNO.[6] Nitric oxide (NO) is a potent vasodilator[7] whose production may be "a compensatory response to increased flow in the pulmonary venous circulation" in left-sided HF.[6] Measurement of FeNO is frequently used for the assessment of inflammatory airways disease and portable hand-held FeNO analysers are now inexpensive and reliable,[8] allowing testing in the primary health care setting. If FeNO is a reliable predictor of elevated LAP, it could be used as a simple adjunct to current HF assessment algorithms. We therefore sought to determine whether FeNO can identify subjects with an elevated LAP (E/e ratio).

Methods

Subjects

This cross-sectional cohort study examined a subset of the original OxVALVE cohort recruited in 2014 and 2015.[9] The OxVALVE participants are an extensively characterised population-based cohort aged 65 years and older who were invited to attend screening examination and echocardiography at their local primary care (general) practice in central England, UK. Those with a previous diagnosis of valvular heart disease, a terminal illness, excessive frailty, or inability or unwillingness to provide consent were excluded.[9] This subset of participants was recruited consecutively (once the appropriate testing equipment was available) to examine this specific study question, with no additional inclusion or exclusion criteria applied. Four separate general practices took part in this substudy. All participants provided written consent and the study was approved by the local research ethics committee (Southampton, UK; REC Ref: 09/H0502/58).

Clinical and echocardiographic assessment

Demographic and clinical information was collected from each participant, combined with a focused cardiovascular history and clinical examination. The cardiovascular history consisted of past medical conditions (such as asthma, chronic obstructive pulmonary disease [COPD], diabetes and hypertension, past surgical procedures (such as coronary artery bypass grafting [CABG] and percutaneous coronary intervention [PCI]), smoking history (never smoked, ex-smoker [quit >1 year ago] or current smoker [smoked in last 12 months]), current medications (including inhaled steroids), and the presence of HF symptoms (New York Heart Association classification [NYHA]). Clinical examination included blood pressure, heart rate, height and weight.

Standard transthoracic echocardiography (TTE) was performed on all participants by a British Society of Echocardiography (BSE) accredited sonographer or physician using a Vivid-Q portable

echocardiographic machine. The reference standard for FeNO was the E/e' ratio, a validated measure of LAP,[5] calculated by dividing the TTE-derived mitral E velocity (E) by the septal e' velocity (e'). Mitral E velocity measures mitral valve flow velocity in early diastole, while septal e' measures tissue velocity at the mitral valve annulus and is an assessment of vertical relaxation of the base of the heart during diastole. Both measurements were performed using standard methods in the apical four-chamber view, with E velocity measured using pulse wave Doppler at a sample volume placed between the mitral leaflet tips, and septal e' velocity measured using pulse wave tissue Doppler imaging at a sample volume in the basal septum.

A consecutive subset (nested within the main OxVALVE cohort) of 277 participants underwent FeNO measurement in parts per billion (ppb) using a portable electrochemical analyser (NIOX VERO Airway Inflammation Monitor, Aerocrine AB, Råaundavägen 18, SE-169 67, Sweden) and variables with a previously observed association with FeNO examined. E/e' ratio was grouped into normal (<8), intermediate (8-14) and high (>14) strata.[10]

Statistical analysis

Due to non-normal distribution, FeNO was compared in participants matched according to clinical factors (sex, asthma, COPD, smoking status, diabetes mellitus, use of inhaled steroids) previously identified as affecting FeNO levels (see Discussion) using a Mann-Whitney U-test (or Kruskal-Wallis test for the three-level smoking variable). FeNO was compared across E/e' strata using a Kruskal-Wallis test. Categorical variables are expressed as proportions and percentages, and were compared across E/e' strata using a Chi-square test. Associations between FeNO and age, and FeNO and E/e' (as a continuous variable) were assessed using univariate linear regression. No multivariate adjustment was performed since there were so few significant univariate associations between FeNO and demographic, echocardiographic and HF risk factors. Statistical analysis was performed using the R statistical computing package (version 3.5.1) and a P-value <0.05 considered significant.

Results

FeNO and clinical characteristics

The OxVALVE subset was predominately white, with a mean age of 73.5 ± 6.3 years and 45% female ***(Table 1)***. There were 8 (2.9%) current smokers, 20 (7.2%) participants with asthma and 16 (5.8%) participants with COPD. Only 10 (3.6%) participants were in NYHA Class III/IV. Measurement of FeNO was attempted in a total of 277 consecutive participants and successful in 227 (82%). There were no significant differences in major demographic variables between those who could and could not successfully complete a FeNO measurement (supplementary table 1).

In those participants with a successful FeNO measurement, the mean FeNO was 24.2 ± 15.6 ppb (median 20 ppb, interquartile range [IQR] 14-29). Selected variables previously observed to correlate with FeNO are illustrated in ***Figure 1*** and the relationship between FeNO and age shown in ***Figure 2A***. In the OxVALVE subset, only sex had a statistically significant association with FeNO (p = 0.003), with male participants having higher levels compared with females (median 22 and 18 ppb, respectively). There was no correlation with age (univariate linear regression beta 0.28, 95% confidence interval -0.05 - 0.61, p=0.09), and no statistically significant differences in FeNO in participants with asthma (p=0.78), COPD (p=0.45), or diabetes mellitus (p=0.20), those using inhaled steroids (p=0.82), and no relation to smoking status (p=0.56).

FeNO and echocardiographic variables

Echocardiographic measurements are displayed in ***Table 1*** and demonstrate a median E/e' ratio of 10.7 (IQR 9.1-13.5), which lies within the intermediate range (8-14) of population levels.[10] Relationships between E/e' and FeNO are displayed in ***Figure 2B*** and show no association of E/e' ratio with FeNO (univariate linear regression beta -0.03, 95% confidence interval -0.06 - 0.01, p=0.10). As a sensitivity analysis, when assessment was restricted to those with breathlessness

(NYHA class II/III, n=99), there remained no significant association between E/e' and FeNO (univariate linear regression beta -0.08, 95% confidence interval -0.17 - 0.0, p=0.06).

Clinical and echocardiographic characteristics of the normal, intermediate and high E/e' strata are displayed in ***Table 2*** with mean FeNO levels of 23.8 ± 11.4, 24.1 ± 16.1, and 22.5 ± 13.7 ppb in the normal, intermediate and high E/e' groups, respectively (p=NS). Those with high E/e' were older than those with normal E/e' (76.8 ± 7.4 years vs. 72.0 ± 5.5 years, p<0.001) and the proportion of females in the high E/e' range was greater than in the normal E/e' range (58.6% vs 35.9%, p=0.05). There were no other statistically different clinical and echocardiographic characteristics across the E/e' strata.

Discussion

In this population cohort study of primarily asymptomatic participants, we demonstrate no significant association between the echocardiographically derived E/e' ratio (a reference standard for LAP) and FeNO, and conclude that FeNO does not predict the presence or absence of HF in the primary care setting.

Strengths and limitations

This is the largest study to assess the presence or absence of an association between FeNO and E/e'. A major strength of the study is that investigation was undertaken in primary care where such a test would prove most useful. In addition, the study was conducted prospectively in consecutive participants and OxVALVE participants are representative of the wider primary care population.[11] Furthermore, participants were aged 65 years and older, the cohort most frequently affected by HF.

The cross-sectional design of this study means important day to day intra-individual variation in expired nitric oxide was not assessed.[12] In addition, potential confounders such as caffeine and alcohol consumption were not recorded, limiting our ability to adjust for these variables.[13,14]

FeNO measurement was unsuccessful in 18% of participants tested. Reasons for unsuccessful measurement were mainly related to inability of the patient to follow instructions or maintain constant expiration of approximately 50 mL/s. Consistent with previous studies,[15] we demonstrate that FeNO measurement is not feasible in all individuals, which limits its use as a diagnostic test.

Participants from the OxVALVE population cohort were recruited from their local general practice (rather than hospital in/outpatients) and were consequently relatively healthy. However, this is the population in whom a simple screen for LAP would have greatest value. There were low numbers of current smokers (2.9%), participants with asthma (7.2%), COPD (5.8%), or cardiovascular risk factors such as diabetes (13.7%), which may have reduced study power. Furthermore, there is a significant difference in the severity of population level asthma, which may be controlled or seasonal, and that of asthmatics presenting to secondary care. Previous associations of FeNO with conditions such as asthma may not be relevant in less severe disease.[16–18]

Comparison with existing literature

The mean FeNO in this cohort was 24.2ppb, which is slightly higher than that observed in previous population studies using a flow rate of 50 mL/s. Population studies in Japan,[19] Germany,[20] United States,[21] and New Zealand[22] all observed lower mean FeNO. However, these studies were in younger cohorts than the OxVALVE subset. A previously reported association between older age and increased FeNO may explain the differences in mean FeNO between studies.[20] Our study aligns with previous population studies that demonstrated higher mean FeNO levels in men compared with women.[19,21–23]

Previous research has suggested an association between various clinical conditions and FeNO, including asthma,[16–18] COPD,[24,25] and diabetes.[26] Current and previous smoking habit,[23,25,27] inhaled steroid use,[28–30] and low and high BMI[31] have also been associated with low FeNO. However, no such associations were observed in the OxVALVE subset.

Previous smaller studies have suggested a relationship between FeNO and elevated LAP. A study of 34 chronic symptomatic HF patients found increased FeNO levels post exercise, although no association with echocardiographic measures was observed at baseline.[6] Conversely, a study comparing compensated (n=30) and decompensated (n=7) HF patients to normal controls (n=90) observed increased FeNO in HF patients.[32] In addition, a study comparing subjects with rheumatic heart disease (n=74) and normal controls (n=27) found significantly increased FeNO in patients with pulmonary hypertension,[7] suggesting a relationship between pulmonary congestion and FeNO (since pulmonary hypertension is almost universally due to high LAP in rheumatic heart disease). However, these studies were undertaken in selected younger cohorts with HF and rheumatic heart disease. OxVALVE is a population-based study in subjects aged 65 years and older and the lack of any association between FeNO and E/e' ratio may be more relevant in an unselected older population.

Implications for research and/or practice

This study contributes to current research that examines the relationship between FeNO and LAP, with particular focus on the elderly population, a group that bears the greatest burden of morbidity and mortality related to HF. Despite evidence suggesting elevated FeNO may be a marker of LAP, our study provides evidence that there is no significant relationship between the two. As such, FeNO would not be a clinically appropriate test for elevated LAP in HF within this patient cohort. There remains an unmet need for improved assessment of potential HF patients in the primary care setting. In patients with previously diagnosed heart failure, the clinical decision as to whether adjustment of current management approach would improve symptoms is often difficult to assess, with complex interactions between cardiac and non-cardiac contributors to symptoms.[33] Beyond the assessment of symptoms, there has also been a move towards more objective methods to guide management.[34] Natriuretic peptides may help in this scenario, but require additional patient contact for blood testing and adjustment of treatment. Further research should examine whether bedside testing (using point

of care ultrasound to assess the lungs or inferior vena cava, for example) would help to refine clinical management.

Conclusion

FeNO is not an accurate predictor of elevated E/e' in predominantly asymptomatic primary care patients.

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Ethics approval: Local research ethics committee (Southampton, UK; REC Ref: 09/H0502/58).

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Table 1: Clinical characteristics, heart failure risk factors, and echocardiographic measurements in the OxVALVE subset

Characteristic	Total cohort
n	277
Age* (years)	73 (68 – 78)
Sex†	
Male	152 (54.9)
Female	125 (45.1)
Ethnicity†	
European	269 (97.1)
Asian	5 (1.8)
Black	2 (0.7)
Mixed	1 (0.4)
Smoking status†	
Non-smoker	133 (48.0)
Ex-smoker	136 (49.1)
Current	8 (2.9)
BMI* (kg/m^2)	27.6 (24.5 – 30.4)
Asthma†	20 (7.2)
COPD†	16 (5.8)
Inhaled steroids†	12 (4.3)
Atrial fibrillation†	39 (14.1)
Diabetes†	38 (13.7)
Hyperlipidaemia†	134 (48.4)
Hypertension†	149 (53.8)
Myocardial infarct†	12 (4.3)
PCI†	11 (4.0)
CABG†	5 (1.8)
Chronic kidney disease†	35 (12.6)
NYHA class	
I	178 (64.3)
II	89 (32.1)
III	10 (3.6)
Socioeconomic class†	
1 (least deprived)	67 (24.2)
2	65 (23.5)
3	85 (30.7)
4	36 (13.0)
5 (most deprived)	21 (7.6)
Missing	3 (1.1)
Ejection fraction*	69% (66-73%)
E velocity*	0.60 (0.51-0.71)
Septal e' velocity*	0.05 (0.04-0.07)
E/e'*	10.7 (9.1-13.5)
FeNO (ppb)‡	24.2 (15.6)

FeNO measurement was unsuccessful in 50 participants – these participants' data is included in all variables outside of FeNO.

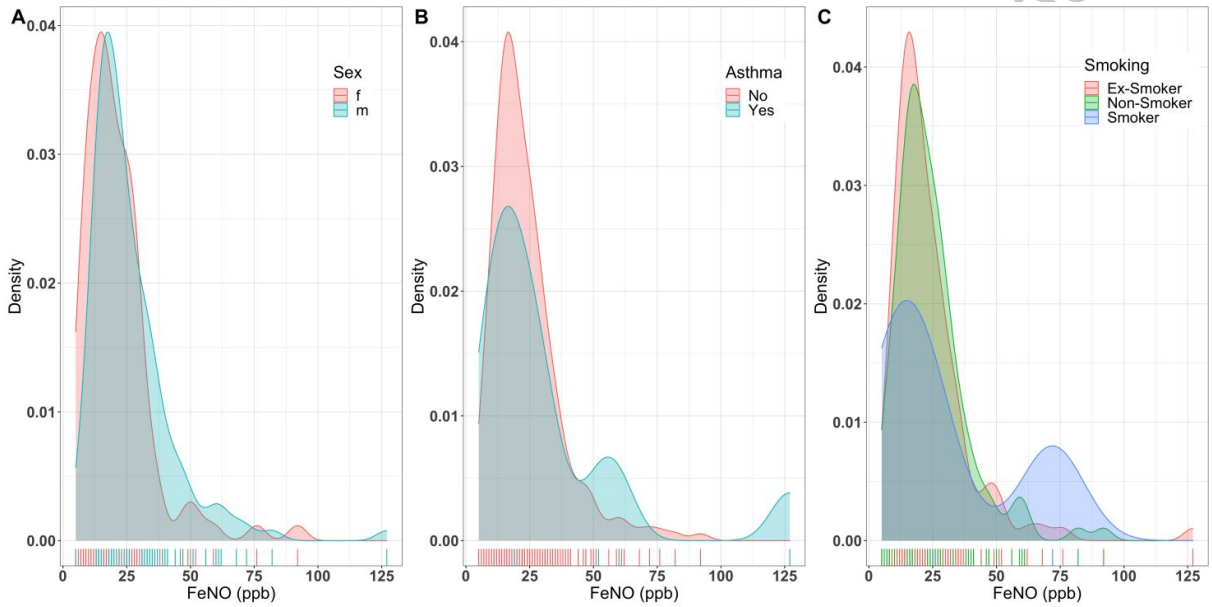
*Median (interquartile range), †Counts(%), ‡Mean(SD)
Abbreviations: BMI = body mass index, CABG =coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, SEC Quintile = measure of socioeconomic deprivation (Quintile 1= least deprived, Quintile 5= most deprived), ppb = parts per billion, Ethnicity = other includes African, Asian and Mixed origin

Table 2: Clinical characteristics of the OxVALVE subset stratified according to E/e' ratio

Characteristic	Normal E/e' (<8)	Intermediate E/e' (8-14)	High E/e' (>14)	P-value
n	39	173	58	-
Age*	71 (68-76)	72 (68-77)	76 (71-83)	<0.001ˆ
Sex†				0.045º
Male	25 (64.1)	100 (57.8)	24 (41.4)	-
Female	14 (35.9)	73 (42.2)	34 (58.6)	-
NYHA class†				0.098º
I	25 (64.1)	121 (69.9)	29 (50.0)	-
II	12 (30.8)	47 (27.2)	26 (44.8)	-
III	2 (5.1)	5 (2.9)	3 (5.2)	-
Ejection fraction*	69% (65-72%)	69% (66-73%)	68% (65-74%)	0.97ˆ
FeNO (ppb)*	19 (17-31)	21 (14-29)	19 (14-27)	0.74ˆ

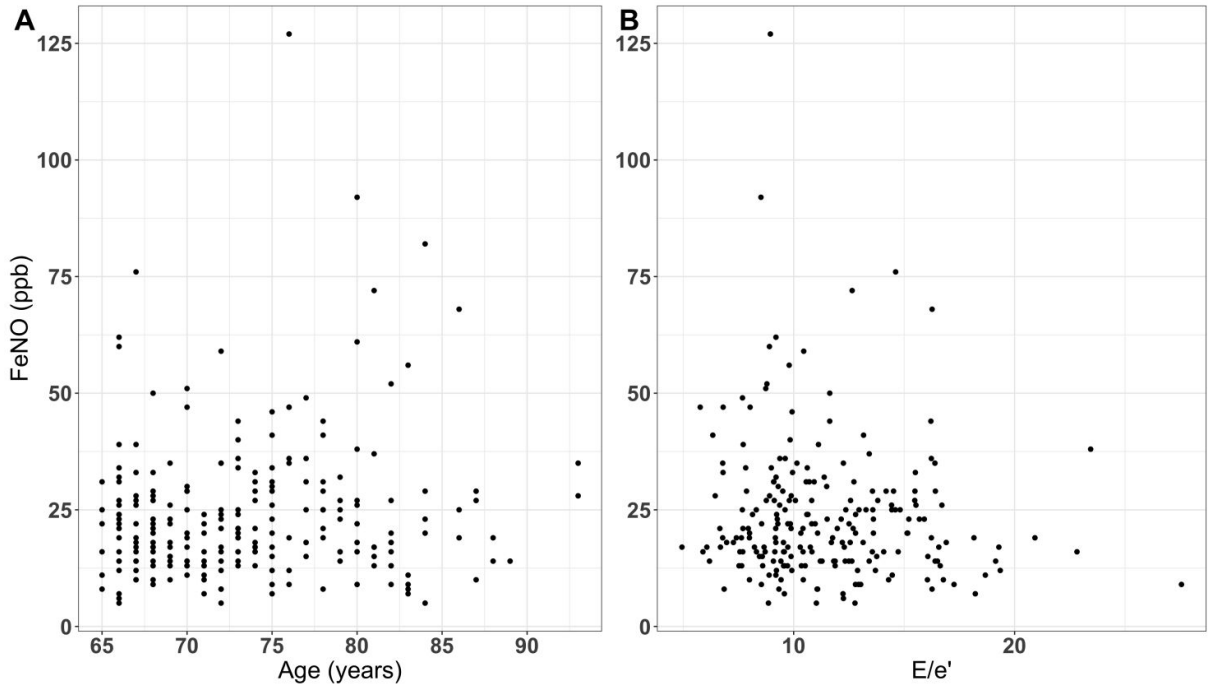
Note: 7 (of 277) participants did not have E/e' measured.
Abbreviations: *Median (interquartile range), †Yes(%), ˚Chi-square test for independent association of categorical variables with E/e' strata, ˆKruskal-Wallis test for independent association of continuous variable with E/e' strata, EF = ejection fraction, FeNO = fractional exhaled nitric oxide, NYHA = New York Heart Association

Figure 1: FeNO distribution according to clinical characteristics



A: Distribution of FeNO stratified by sex. Red = female, Blue = male
B: Distribution of FeNO stratified by presence of asthma. Red = no asthma, Blue = asthma
C: Distribution of FeNO stratified by smoking status. Red = ex-smoker (quit >1 year ago), Green = non-smoker (never smoked), Blue = current smoker (smoked within past 1 year)

Figure 2: FeNO according to (A) age and (B) E/e' ratio



Abbreviation: ppb, parts per billion