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Two is better than one: the double diffusion technique in classifying heart failure

Background

Heart Failure (HF) is a chronic condition characterised by inefficient myocardial performance that results in reduced blood supply to the body. In patients with HF, there can be a significant impairment in pulmonary gas exchange due to an excessive difference in alveolar-arterial oxygen tension (*P*A–aO2) and arterial oxygen tension (*P*aO2). The diffusing capacity of the lung for carbon monoxide (DLCO) and nitric oxide (DLNO) measurements can serve as potential indicators of pulmonary dysfunction. This study aimed to investigate whether combining DLNO and DLCO measurements can enhance the predictive value and classification of HF compared to DLCO alone.

In the context of HF, DLNO measurements are particularly useful because they correlate with *P*A–aO2, predominantly measuring the diffusion between the alveolar-capillary membrane and red blood cell membrane, while DLCO reflects the pulmonary capillary blood volume and the oxygen-binding capacity of haemoglobin. This reflects pulmonary vascular/blood volume impairments. Together, these measurements provide a comprehensive view of the diffusion pathways.

Methods

Study Design

The retrospective secondary data analysis collected data from four prior studies that utilised single-breath nitric oxide-carbon monoxide (NO-CO) double diffusion technique for lung function assessment.

Study Cohort and Participant Characterisation

The study included 140 ambulatory patients diagnosed with Class II HF with low ejection fraction (<40%) and 50 controls without HF which were assumed to be free of cardiovascular or pulmonary dysfunction. Patients with HF were, on average, four years older and had a 2.5kg/m^{-2} higher mean BMI than those without HF.

Data Collection and Variables

DLNO and DLCO measurements were obtained for each patient. Z-scores for DLNO, DLCO and combined DLNO+DLCO were calculated using reference equations from the European Respiratory Society Technical Standards Munkholm et al., and Zavorsky and Cao. These z-scores were adjusted for age, sex, height, altitude, and lung function device.

Statistical Analysis

The statistical analysis compared diffusing capacities between HF and non-HF groups using t-tests and calculated odds ratios for DLCO, DLNO and combined DLCO+DLNO models. Bayesian Information Criterion was used to determine model fit and Matthews Correlation Coefficient evaluated the ability of each model to classify HF. Confidence intervals (CI) were used to determine estimate uncertainty. SPSS Statistics and R software analysed data at $p<0.05$ significance.

Limitations

Limitations of the study include the retrospective nature of the analysis, the potential biases inherent in secondary data analysis and the homogeneity of the study population (primarily caucasian adults). In addition, conditions such as anaemia, polycythaemia or elevated carboxyhemoglobin levels were not accounted for in the models.

Results

A total of 140 patients with Class II HF (113 males, 27) females and 50 control subjects (26 males, 24 females) were included in the study. The mean baseline diffusing capacity testing breath-holding time (BHT) was 5.5±0.5 s. Approximately 50% of HF patients exhibited obstructive or restrictive patterns on spirometry, compared to 20% in those patients without HF ($p<0.001$). This is suggestive of a higher prevalence of impaired lung function among patients with HF.

There were significant differences in diffusing capacities between individuals with and without HF (z-scores in non-HF: DLCO= -1.03 ± 0.84, DLNO= -1.30 ± 0.91, combined z-scores= -2.33 ± 1.45; z-scores in HF: DLCO= -2.18 ± 1.32, DLNO= -2.35 ± 1.19, combined z-scores= -4.53 ± 2.34).

Moreover, the prevalence of DLNO and DLCO impairment was notably higher in HF patients, with 65% and 69% respectively, exhibiting mild, moderate, or severe impairment in gas diffusion. In contrast, only 36% of patients without HF showed a mild impairment in DLNO and 24% in DLCO. This was shown to be statistically significant with a p-value of <0.001 between groups.

The absolute values for both DLCO and DLNO were lower in patients with HF than those without. However, the DLNO/DLCO ratio did not differ significantly between the two groups (p-value 0.36), indicating it cannot be used to reliably distinguish between those with and without HF.

Researchers analysed 12 models to assess their efficacy in predicting the likelihood of HF. Odds ratios revealed significant reductions in HF risk with increased DLCO z-scores. Furthermore, patients with HF had significantly higher odds of having z-scores below the lower limit of normal (LLN) when using the combined z-scores. These findings underscore the utility of combined scores and specific reference equations in predicting HF risk and increasing classification accuracy.

Discussion

This study evaluated the combined effectiveness of DLNO and DLCO z-scores in predicting and classifying Class II HF patients from controls. Results showed that combined z-scores outperformed individual ones in predicting HF. Metrics such as Matthews Correlation Coefficient highlighted the superiority of combined z-scores. Analysis revealed that DLNO and DLCO z-scores share around 53% of their variance in HF patients, suggesting the importance of measuring both to capture all variances. Although DLNO technically proved superior to DLCO, the combined approach proved to be most reliable in HF classification. Despite the strength of combined z-scores, established screening tools such as echocardiography remain superior. The study places emphasis on the complementary role of DLNO z-scores alongside DLCO z-scores in specific circumstances, offering a comprehensive insight into gas diffusion pathways in HF.

Conclusion

In conclusion, combined DLNO + DLCO z-score models outperform single z-score models in predicting HF. HF classification benefits from using combined z-scores over individual DLCO or DLNO LLN cut-offs. However, only 32% of HF variance in predicting HF can be explained by the combined z-scores. This discourages its use as a HF screening tool. It is instead recommended that an NO-CO double diffusion technique (currently only used in research, not TGA approved) be used for gas exchange assessment and improved classification in patients with HF.

Article Reference

Zavorsky GS, Agostoni P. Two is better than one: the double diffusion technique in classifying heart failure. ERJ Open Res 2024; 10: 00644-2023 [DOI: 10.1183/23120541.00644-2023].