Research Article

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A Comparison of Capillary Versus Venous N-Terminal Prohormone Brain Natriuretic Peptide

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ABSTRACT

Background: The natriuretic peptides B-type natriuretic peptide and N-terminal fragment B-type natriuretic peptide provide a relatively low-cost and accessible screening tool for heart failure. Point of care testing using finger prick capillary blood samples has been developed for BNP. We compared capillary versus venous N-terminal fragment B-type natriuretic peptide measurements using a commercially available point of care testing assay.

Methods: A cross-sectional prospective sub-analysis of a study screening 67 patients with stable chronic obstructive pulmonary disease for cardiovascular disease using N-terminal fragments of B-type natriuretic peptide was performed. Capillary and venous blood samples for each patient were analysed using a point of care testing N-terminal fragment B-type natriuretic peptide whole blood assay. Correlation between capillary and venous N-terminal fragment B-type natriuretic peptide levels was assessed. The probability of heart failure was classified based on age-stratified N-terminal fragment B-type natriuretic peptide levels.

Results: Mean capillary versus venous N-terminal fragment B-type natriuretic peptide values were similar, 236±530pg/mL vs. 237±512 (n=67), with high linear correlation (R2 = 0.96, P<0.05). Capillary testing reclassified 5 of the 39 patients (13%) designated low probability of HF by venous testing as having intermediate values, mainly in elderly patients. No patients designated as having a moderate or high probability of having venous testing were reclassified by capillary testing.

Conclusion: There is a good correlation between N-terminal fragment B-type natriuretic peptide levels in capillary and venous samples, which suggests there may be a role for point of care testing of N-terminal fragment B-type natriuretic peptide using capillary blood samples. These findings need to be confirmed in larger populations, including more patients with heart failure.

KEYWORDS: Heart failure; Natriuretic peptide; Point of care testing

ABBREVIATIONS: BNP: B-type Natriuretic Peptide; COPD: Chronic Obstructive Pulmonary Disease; HF: Heart Failure; LVSD: Left Ventricular Systolic Dysfunction; NT-proBNP: N-terminal Fragment B-Type Natriuretic Peptide; POCT: Point of Care Testing

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INTRODUCTION

Heart failure (HF) is a worldwide epidemic that causes frequent hospitalizations and high health-care costs. Prognosis remains poor despite numerous medications and devices which improve symptoms and prolong survival [1]. Therapies halt or even reverse left ventricular systolic dysfunction (LVSD). This process, termed left ventricular remodeling, occurs over years. Early detection and treatment of HF are therefore paramount [2,3]. Symptoms and signs alone exhibit low diagnostic accuracy for HF, which requires an objective demonstration of cardiac dysfunction. This is typically provided by imaging such as echocardiography, which presents barriers in terms of access and costs [4]. The natriuretic peptides (NP) B-type natriuretic peptide (BNP) and N-terminal fragment BNP (NT-proBNP) are released in response to ventricular stretch in patients with HF. High and low NP levels suggest a high and low probability of HF respectively, the latter having high negative predictive value. Natriuretic peptides provide a relatively low-cost and accessible method to screen patients for confirmatory imaging and to initiate therapy [1,4-6].

Natriuretic peptides were traditionally assayed in laboratories using venous blood samples. Development of Point of Care Testing (POCT) has enabled expedited measurement and management [4]. However, most POCT still requires venous blood and thus phlebotomy services, which limits availability [7,8]. Recently, several commercial BNP POCT assays have been tested on capillary 'finger-prick' samples with encouraging results [8-11]. Treatment with angiotensin receptor blocker-neprilysin inhibitors, which increase BNP levels, has increased demand for NT-proBNP compared to BNP testing [12,13]. We therefore aimed to compare capillary versus venous NT-proBNP measurements using a commercially available POCT assay based on the RAMP® technology platform.

MATERIALS AND METHODS

Design and Population

The cross-sectional study was prospectively designed as a sub-analysis of a study screening ambulatory patients with stable chronic obstructive pulmonary disease (COPD) for cardiovascular disease using NT-proBNP from February 2017 to July 2018. Consecutive patients with stable COPD attending pulmonary clinics at Vancouver General Hospital and St. Paul's Hospital The inclusion criteria were: 1) clinical diagnosis of COPD with confirmatory spirometry; 2) stable respiratory state for at least 4 weeks, i.e. no recent hospitalization attributed to COPD, no respiratory tract infections requiring antibiotics or steroids, and unchanged doses of concomitant respiratory therapy. Patients with established heart failure were excluded.

Assay, Sampling and Data Collection

A POC NT-proBNP whole blood assay was supplied by Response Biomedical Corporation (RAMP® kit and Reader). Venous (1-2ml) and capillary (a few drops of finger-stick sample collected by a small pipette) blood samples were drawn from each patient. An aliquot (75µL) from each sample was mixed 10 times with the buffer solution and applied to a single-use disposable cartridge. Baseline demographics, medical history, medications, physical examination and clinical parameters of interest were recorded. All data was stored in an electronic case report form using REDCap.

Statistical Analyses

Baseline characteristics of patients are presented as means with standard deviations for continuous variables or by frequencies and percentages for categorical variables. Venous and capillary values are presented by means of a scatter plot with a correlation coefficient. The proportion of patients with low, medium or high NT-proBNP levels was calculated based on the recommended lower exclusionary threshold of 300pg/mL, and age specific upper cut-points from the International Collaborative of NT-proBNP dataset: <50 years 450pg/mL; 50-75 years 450–900pg/mL; >75 years >900pg/mL [14]. The proportion of patients misclassified using capillary compared to the gold standard of venous blood was calculated. Bland-Altman difference plots were constructed to assess the limits of agreement. The study was approved by the University of British Columbia Research Ethics Board. All analyses were performed using SPSS for Windows v21.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline Characteristics

Table 1: Baseline characteristics.

Demographics	Mean ± SD or Frequency (%)
Male	46 (68.7%)
Age	71.5 ± 10.0
Body mass index (BMI)	29.2 ± 14.1
Overweight (25 ≤ BMI < 30)	20 (29.9%)
Obese (BMI ≥ 30)	24 (35.8%)
Chronic Obstructive Pulmonary Disease (GOLD classification)	
I Mild	2 (3.0%)
II Moderate	37 (55.2%)
III Severe	24 (35.8%)
IV Very severe	1 (1.5%)
Cardiovascular Risk Factors	
Smoking	62 (92.5%)
Diabetes	13 (19.4%)
Hypertension	25 (37.3%)
Dyslipidaemia	27 (40.3%)
Cardiovascular Disease	
Atrial fibrillation	7 (10.4%)
Angina	12 (17.9%)
Coronary artery disease	13 (19.4%)
Myocardial infarction	7 (10.4%)
History of valve disease	2 (3.0%)
Transient ischemic attack or stroke	4 (6.0%)
Comorbidities	
Anaemia	16 (23.9%)
Malignancy	21 (31.3%)
Electrocardiogram	
Atrial fibrillation	5 (7.5%)
ST depression or elevation	4 (6.0%)
Non-specific ST changes	6 (9.0%)
T wave inversion	3 (4.5%)

Laboratory results	
NT-proBNP (venous) (pg/mL)	237.2 ± 512.0
NT-proBNP (capillary) (pg/mL)	235.7 ± 530.3
Haemoglobin (g/L)	137.5 ± 18.0
Creatinine (µmol/L)	86.0 ± 25.9
Glomerular filtration rate (ml/min)	74.1 ± 19.2
eGFR > 90 (ml/min)	16 (23.9%)
60 ≤ eGFR < 90 (ml/min)	37 (55.2%)
30 ≤ eGFR < 60 (ml/min)	7 (10.4%)
eGFR < 30 (ml/min)	2 (3.0%)
Total cholesterol (µmol/L)	4.3 ± 0.8
LDL cholesterol (µmol/L)	2.1 ± 0.7
HDL cholesterol (µmol/L)	1.6 ± 0.6

Mean ± SD or frequency (%).

67 patients with COPD were enrolled, mostly moderate (55.2%) and severe (35.8%) based on GOLD classification (Table 1). Patients were predominantly male (68.7%), elderly (71.5±10.0 years), and overweight (66% with BMI ≥25). Cardiovascular risk factors were common, including smoking (93%), hypertension (37%), dyslipidemia (40%) and diabetes (19%). Cardiovascular disease was also notable, including atrial fibrillation (10%), coronary disease (19%) and previous myocardial infarction (10%). Anemia and mild renal impairment were common, 24% and 55% respectively. Moderate or severe renal disease was less frequent (13%).

Correlation

Mean venous versus capillary values of NT-proBNP were similar, 237±512 vs. 236±530pg/mL. The scatter-plot illustrates the linear correlation between the venous and capillary values (Figure 1), which were highly correlated with the coefficient of determination (R2) of 0.96 (P<0.05). The slope was 1.01; 95% CI [0.96, 1.07], with an intercept of -4.91; 95% CI [-33.87, 24.05].

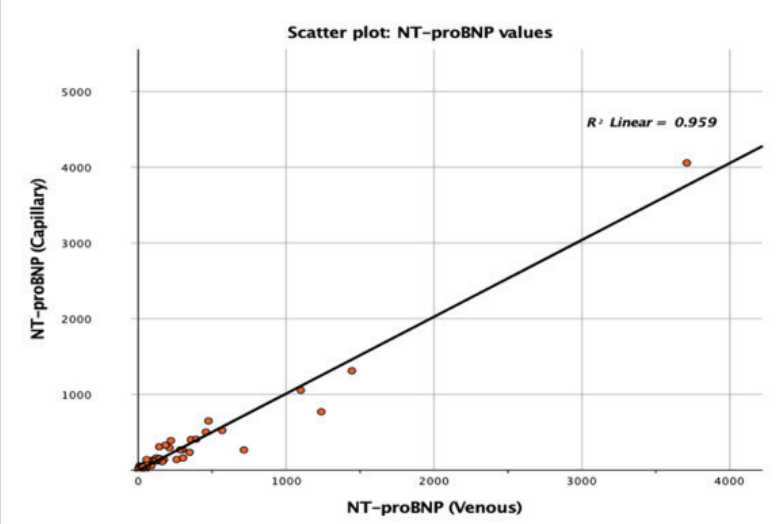

Figure 1: Scatter plot comparing venous versus capillary NT-proBNP measurements.

Reclassification

Table 2: Proportion of patients with low, medium or high NT-proBNP according to standard thresholds based on venous versus capillary measurement.

Age	Low	Medium	High
< 50 years (n=2)	**<300 pg/mL**	**300 – 450 pg/mL**	**>450 pg/mL**
Venous	2	0	0
Capillary	2	0	0
50 – 75 years (n=43)	**<300 pg/mL**	**300 – 900 pg/mL**	**>900 pg/mL**
Venous	26	15	2
Capillary	25	16	2
> 75 years (n=22)	**<300 pg/mL**	**300 – 1800 pg/mL**	**>1800 pg/mL**
Venous	11	11	0
Capillary	7	15	0
Total	**<300 pg/mL**	**Medium (age-specific)**	**High (age-specific)**
Venous	39	26	2
Capillary	34	31	2

In terms of reclassification, capillary and venous sampling was identical in identifying two middle-aged patients with probable heart failure (NT-proBNP >900pg/mL) (Table 2). However, capillary testing reclassified 5 of the 39 patients (13%) designated low probability by venous testing as having intermediate values, mainly elderly patients.

Level of Agreement

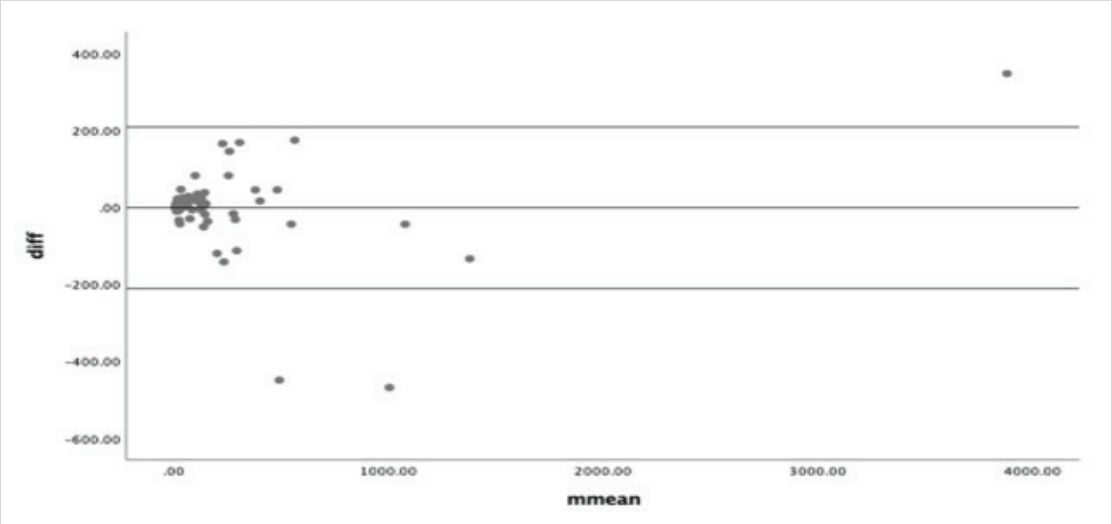

Figure 2: Bland-Altman plot.
The Bland-Altman plot visualizes the limits of agreement between venous and capillary values. It indicates that the agreement interval (-211.12 to 208.32) within which 95% of the differences of the capillary method, compared to the venous one fall. After a linear regression analysis, there is no proportional bias pointing out that there is no trend being above or below the mean difference line.

The Bland-Altman plot (Figure 2) demonstrates the limits of agreement (-211.12 to 208.32pg/mL) in which 95% of the differences between capillary compared to venous values are expected. There was no trend above or below the mean difference line after linear regression analysis, confirming a high level of agreement.

DISCUSSION

We report several key findings in this comparison of capillary versus venous NT-proBNP measurement using a commercially available POCT assay. Overall, mean capillary and venous NT-proBNP values were similar with high correlation. Detection of high NT-proBNP levels was identical. However, capillary compared to venous NT-proBNP reclassified five patients from "low" to "moderate" risk.

Relatively few studies have examined the clearance of BNP from human blood, but those that do provide a potential explanation for capillary samples' overestimating BNP [15]. There is a significant ateriovenous gradient of BNP between the femoral artery and femoral vein, implying a degree of BNP clearance in peripheral tissue [16]. This could account for higher BNP levels in the upstream capillaries compared to veins. The proposed mechanism is a combination of receptor mediated breakdown and extra-cellular proteolysis of BNP. NT-proBNP clearance is less reliant on receptor mediated breakdown and extra-cellular proteolysis. However, a significant arteriovenous gradient is still evident between the femoral artery and vein as well as across the liver, renal, head, and neck tissue [17]. This perhaps reflects the less rapid overall clearance of NT-proBNP (half-life 120 minutes vs. 20 minutes for BNP) [18].

Our study of NT-proBNP was prompted by previous studies comparing capillary and venous BNP. In a cohort of 111 patients with stable HF, overall capillary and venous BNP levels correlated strongly (r=0.94). However, this diverged at BNP levels greater than 1500 pg/mL, at which point capillary testing tended to overestimate BNP with a bias of 46.9pg/mL seen on Bland-Altman analysis [8]. A similar correlation between capillary and venous BNP levels was observed in 98 healthy adult subjects and patients diagnosed with systolic HF in another single centre study (r=0.96). There was a non-significant trend towards bias with the capillary method overestimating BNP by 14.9 +/- 40.5% (p=0.04) [19]. Finally, in a similar sized, single-centre study (n=117), capillary was consistently higher than venous BNP, with a regression slope (i.e. correction factor) of 1.48. Limited information was provided in the study, though such differences may typically be attributable to differences in sample handling, sample anticoagulation, and assay platforms [20].

Overall, the strong correlation between capillary and venous NT-proBNP values in our study suggests there may be a role for capillary NT-proBNP POCT for diagnosis and monitoring of HF. In five instances, capillary blood samples generated higher NT-proBNP readings than venous samples, resulting in a reclassification from low to moderate BNP levels. Potentially higher capillary values could lead to false positive diagnoses of HF and thus decrease the positive predictive value. This would require increased use of confirmatory imaging, though not necessarily impact the negative predictive value and utility as a screening tool. Further validation studies are needed to assess whether higher cut-off values for HF diagnosis or a correction factor, as seen in prior studies, are needed for capillary NT-proBNP measurements [20].

A finger prick blood sample is collected via pipette, mixed 10 times with a buffer solution, and then applied to a single-use

disposable cartridge to use the RAMP® kit and reader. This process introduces opportunities for blood clotting and other errors. A more streamlined process in which blood from a finger prick is applied directly to a cartridge would be preferable. This exists for BNP testing and was shown to be feasible for home monitoring in the HABIT study [21]. To our knowledge this is not currently available for NT-proBNP testing.

There are several limitations to our study. The sample size of 67 is relatively small. The COPD population limits the generalizability to other target populations, such as patients presenting with unexplained dyspnea. However, similar results were seen in both stable HF patients and healthy adult volunteers using BNP (8,19,20). The lack of imaging limits our ability to determine the accuracy and predictive values of capillary NT-proBNP POCT as compared to the gold standard for the diagnosis of HF.

Further research is required to clarify the role of capillary NT-proBNP POCT for the diagnosis and management of HF. Larger sample sizes, including more patients with elevated NP levels and HF, are needed to clarify the reclassification at the upper threshold for probable HF. Including a gold standard would allow assessment of the accuracy of the parameters and recalibration of diagnostic thresholds if necessary. Nonetheless, this is an encouraging first step in the incorporation of NT-proBNP POCT.

CONCLUSION

There is a good correlation between NT-proBNP levels in capillary and venous samples, which suggests there may be a role for NT-proBNP POCT using capillary blood samples. These findings need to be confirmed in larger and more diverse populations, including more patients with HF.

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