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Sendaway capillary NT-proBNP in pulmonary hypertension

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ABSTRACT

Background N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a biomarker of cardiac ventricular wall stress that is incorporated into pulmonary hypertension (PH) risk stratification models. Sendaway sampling may enable patients to perform NT-proBNP tests remotely. This UK-wide study aimed to assess the agreement of sendaway NT-proBNP with standard venous NT-proBNP and to assess the effect of delayed processing.

Methods Reference venous NT-proBNP was collected from PH patients. Samples for capillary and venous sendaway tests were collected contemporaneously, mailed to a reference laboratory and processed at 3 and 7 days using a Roche Cobas e411 device. Differences in paired measurements were analysed with Passing-Bablok regression, percentage difference plots and the % difference in risk strata.

Results 113 patients were included in the study. 13% of day 3 capillary samples were insufficient. Day 3 capillary samples were not equivalent to reference samples (Passing Bablok analysis slope of 0.91 (95% CI 0.88 to 0.93) and intercept of 6.0 (95% CI 0.2 to 15.9)). The relative median difference was −7% and there were acceptable limits of agreement. Day 3 capillary NT-proBNP accurately risk stratified patients in 93.5% of cases. By comparison, day 3 venous results accurately risk stratified patients in 90.1% of cases and were equivalent by Passing-Bablok regression. Delayed sampling of sendaway tests led to an unacceptable level of agreement and systematically underestimated NT-proBNP.

Conclusions Sendaway NT-proBNP sampling may provide an objective measure of right ventricular strain for virtual PH clinics. Results must be interpreted with caution in cases of delayed sampling.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a biomarker that is released in proportion to the extent of cardiac ventricular wall stress and has become established for use in risk assessment for patients with pulmonary arterial hypertension, incorporated into all contemporary pulmonary hypertension (PH) risk stratification models. Sendaway tests, through capillary sampling, can be performed by patients at home and are sent for processing at a central laboratory with results sent either directly to the patient or the referring medical team.

WHAT THIS STUDY ADDS

⇒ This UK-wide study aimed to assess the agreement of sendaway NT-proBNP with standard venous NT-proBNP and to assess the effect of delayed processing on the results. When capillary NT-proBNP was compared with standard venous NT-proBNP, there were acceptable limits of agreement and capillary NT-proBNP accurately risk stratified patients in 93.5% of cases, however, capillary results were not equivalent to standard results. Delayed sampling of sendaway tests led to an unacceptable lack of agreement and systematically underestimated NT-proBNP.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Sendaway testing may allow patients to perform an NT-proBNP blood test at home, without having to travel to a healthcare facility. This could provide an objective measure of right ventricular strain during virtual clinics. PH specialist teams could incorporate this test into a virtual clinic model.

BACKGROUND

Pulmonary arterial hypertension (PAH) is a rare and progressive form of pulmonary hypertension (PH) which if untreated may progress to right heart failure and death.[1 2] PAH and certain other aetiologies of PH are diagnosed and managed in specialist pulmonary vascular units. Dysfunction of the right ventricle (RV) is the primary driver behind the symptom burden in PH, leading to exercise intolerance, exertional dyspnoea, fatigue and RV failure as the disease progresses with fluid retention, chest pain and syncope.[3 4] The assessment of right ventricular function is used to risk stratify patients at the point of diagnosis and to monitor the response to treatment.[1] B-type natriuretic peptide (BNP) and N-terminal prohormone of BNP (NT-proBNP) are biomarkers that are released in proportion to the extent of cardiac ventricular wall stress.[5 6] NT-proBNP

has become established as a surrogate marker of RV function and is incorporated into all contemporary PAH risk stratification models.[1 7–11] In current practice at UK PH centres, samples are collected as venous serum or plasma blood through venepuncture at the time of a patient' face-to-face assessment and results are commonly available ≥24 hours. NT-proBNP has superior stability than BNP but is still prone to degradation, especially at higher temperatures.[6]

Remote risk assessment in PH heralds benefits such as reducing lengthy transport to specialist centres, reducing patient exposure to nosocomial infections and allowing ad hoc assessments at home.[12] The majority of PH patients in the UK have a travel time of >1 hour to attend clinic appointments, are concerned about contracting COVID-19 while in hospital and 93% would be happy for some of aspects of their PH care to be remote.[13] During the COVID-19 pandemic, the role of virtual consultations rapidly expanded in PH, yet consultations were often bereft of objective data, such as NT-proBNP.[14 15] It remains that NT-proBNP data are often unavailable at the time of virtual clinic appointments due to the restrictions on the use or funding for these tests within primary care networks and the lack of a global remote blood monitoring facility within the National Health Service (NHS).[16 17]

Point-of-care testing (POCT) for NT-proBNP has been studied in the left heart failure population[18] and in the REPEAT-PAH study in PH[19 20] both with acceptable agreement to standard NT-proBNP. However, it remains that POCT requires patients to travel to a healthcare facility. Sendaway tests, through capillary sampling, can be performed by patients at home and are sent for processing at a central laboratory with results sent either directly to the patient or the referring medical team. Sendaway samples may allow PH centres to obtain NT-proBNP results in a telemedicine setting. Capillary samples are obtained through fingerpick blood draw, similar to how capillary blood glucose measurements are obtained and collected in serum microtainer bottle. Venous sendaway sampling could enable patients to have blood drawn locally, such as by a general practitioner, with the result funded and followed by a specialist team.

This UK-wide study aimed to assess the agreement of sendaway NT-proBNP with standard venous NT-proBNP and to assess the effect of delayed processing on the results.

METHODS

Inclusion criteria

Participants ≥16 years old with PH (mean pulmonary artery pressure≥25 mm Hg, regardless of pulmonary vascular resistance) and from any clinical classification, were included.[21] Therapy with anticoagulation or antiplatelet medication was not considered an exclusion. Participants provided informed consent.

Study structure

Samples were collected between April 2022 and April 2023 over seven of the adult national centres for PH in Great Britain. During a single visit (day 0), during patients' standard care, blood was drawn in sequence, following 30 min of rest and without participant exertion between tests, as below;

1. 1x reference venous NT-proBNP—transported by Royal Mail post to a reference laboratory and analysed on arrival.
2. 1x local venous NT-proBNP—analysed as per standard protocol at the laboratory based at each participating site.
3. 2x sendaway venous NT-proBNP.
4. 2x sendaway capillary NT-proBNP—each with 600 µL of blood from different fingers.

Sendaway samples were obtained using kits from Thriva (London, UK), sent to the Thriva lab by Royal Mail post and analysed using Thriva infrastructure at day 3 and day 7 from the day of the blood draw. Sendaway samples were analysed using a Roche Cobas e411 device (Roche, Switzerland) with a 4.2%–6.3% coefficient of variation (online supplemental table S1). In cases where one sample was insufficient, the day 3 sample was prioritised. Reference samples were performed at the Royal Brompton Hospital (London) using a Roche Cobas e411 device and Elecsys proBNP II assay. This method was chosen for the reference sample to maintain reproducibility. Postal samples were sent immediately and were not refrigerated prior to postage.

Aims

The primary outcome was the agreement between reference and day 3 Capillary NT-proBNP results. Secondary outcomes included the assessment of (1) agreement between reference and day 3 venous sendaway NT-proBNP results and (2) the effect of delayed processing (stability) on capillary and venous sendaway NT-proBNP results by comparing the agreement between reference and day 7 results.

Statistical analysis

Continuous variables are presented as mean±SD, median (IQR) or number (%). Significance was set at the $p<0.05$ level. Where results were reported below the analytical range, they were analysed using the value closest to the reporting limit (eg, <10 was analysed as 9).

The Shapiro-Wilk test was used to assess the normality of the data. The relationship between the reference and study NT-proBNP was assessed in several ways: (1) median difference (IQR), (2) traditional Bland-Altman plots,[22] (3) percentage difference plot (4) Passing-Bablok regression[23] with (5) Spearman's r correlation.[24] Reference NT-proBNP results were assigned a risk status based on the COMPERA 2.0 thresholds[7] and the proportion of patients who would have been assigned a different risk stratum based on study NT-proBNP results was

Table 1 Participant demographics

	Mean±SD n (%)
Diagnosis, n (%)	Total=113
Group I—pulmonary arterial hypertension (PAH)	67 (59)
► Idiopathic PAH	30 (27)
► Hereditary PAH	4 (4)
► Pulmonary veno-occlusive disease	1 (1)
► Connective tissue disease PAH	22 (19)
► Drug-induced PAH	1 (1)
► Congenital heart disease PAH	7 (6)
► Portopulmonary hypertension	2 (2)
Group II—PH due to left heart disease	6 (5)
Group III—PH due to chronic lung disease and/or hypoxia	16 (14)
Group IV—chronic thromboembolic pulmonary hypertension (PH)	21 (19)
Group V—PH due to miscellaneous causes undefined	2 (2)
	1 (1)
Age (years)	60±14.8
Male, n (%)	39 (35)
Reference NT-proBNP, pg/mL	514 (167–1890)
Estimated glomerular filtration rate <60 (mL/min/1.73 m^2)—n (%)	20 (18)
Haemoglobin (g/L)	139±20

Data are presented as mean±SD or actual number (%) unless where stated.
NT-proBNP, N-terminal pro-B-type natriuretic peptide.

calculated. The relationship between the local lab and study NT-proBNP was additionally assessed with the above analyses and the results and are included in online supplemental material. The viability of sendaway sampling was measured by assessing the number and causes of invalid samples. Analysis was performed on GraphPad Prism (V.9.3.0 for Windows, GraphPad Software, San Diego, California, USA) and MedCalc (V.22.003 for Windows, MedCalc Software, Ostend, Belgium).

Sample size calculation

The power requirement was based on agreement using Bland-Altman analysis. Using the criteria for NT-proBNP of a mean change of 5 pg/mL with an SD of 10 pg/mL and a maximum difference of 30 pg/mL, using a power of 0.8 and a significance level of 0.95, an estimated of 83 participants was required.[18 19]

Patient and public involvement

Patients were not directly involved in the design of this study. However, this study is designed to demonstrate the utility of remote NT-proBNP testing, which could lead to benefits for patients.

RESULTS

Participant demographics

Participant demographics are shown in table 1. 114 participants were recruited into the study with one patient with CTEPH excluded as they were unable to produce sufficient blood for either capillary or venous samples. The median NT-proBNP was 514 (IQR 167–1890). The range of NT-proBNP results from all study data sets is shown in table 2; all were non-parametrically distributed (p<0.0001; online supplemental figure S1).

Invalid samples

Valid results were obtained for all reference samples, 81% of day 3 capillary samples, 74% of day 7 capillary samples and 88% of day 3 and day 7 venous samples. Of the invalid results, 13% of day 3 capillary, 19% of day 7 capillary and 1% of day 3 venous samples were not processed due to an insufficient quantity of blood in the container. One patient with severe Raynaud's was unable to provide any quantity of capillary blood yet was able to provide venous blood. Overall, 24 samples were delayed in the postal service, and therefore, not suitable for processing. Four samples were received by Thriva laboratories but were not processed, one sample was incorrectly labelled and two samples did not arrive to Thriva for reasons unknown. There was no significant difference in the proportion of invalid samples obtained during the summer months (April–September) when compared with the winter months (October–March).

Sendaway capillary NT-proBNP

As shown in figure 1, the median relative difference between reference and day 3 capillary NT-proBNP was −7% (IQR −15% to 0%; (b) Passing-Bablok regression showed an estimated slope of 0.9 (95% CI 0.88 to 0.93), intercept of 6.0 (95% CI 0.2 to 15.9) and an r of 0.99 (p<0.0001) indicating there was excellent correlation yet the measures were not equivalent and (c) Bland-Altman analysis further demonstrates that day 3 capillary results were systematically lower than reference results (bias

Table 2 NT-proBNP dataset overview

			Sendaway capillary		Sendaway venous	
Data set	Reference	Local lab	Day 3	Day 7	Day 3	Day 7
Median (IQR)	514 (167–1890)	546 (171–2039)	494 (166–1770)	404 (139–1586)	516 (184–2252)	441 (152–1938)

All units are pg/mL.
NT-proBNP, N-terminal pro-B-type natriuretic peptide.

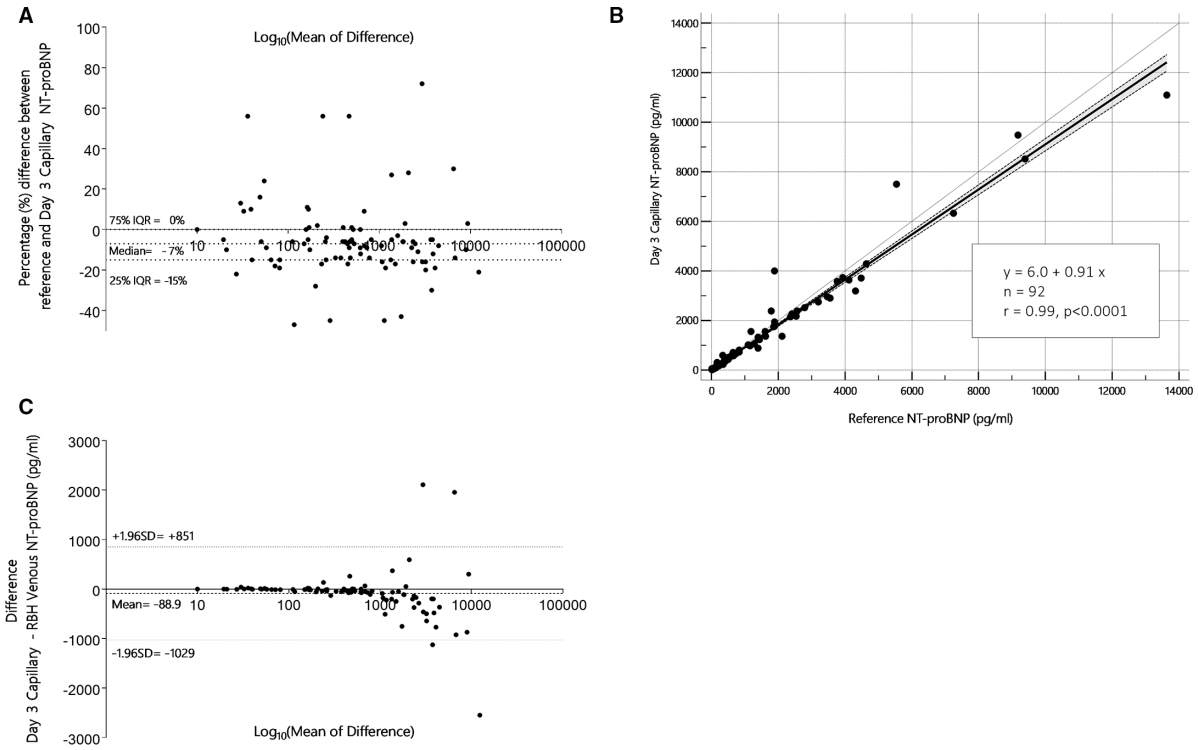

Figure 1 Analysis comparing reference and sendaway day 3 capillary NT-proBNP (pg/mL) using (A) percentage difference plot demonstrating a median difference of −7%, (B) Passing-Bablok regression showing strong correlation (r=0.99), with a slope of 0.91 (95% CI 0.88 to 0.93) and intercept of 6.0 (95% CI 0.2 to 15.9) and (C) Bland-Altman plot showing a bias of −89.9 with limits of agreement −1029 to 851. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

−88.9, SD 479.6 pg/mL) with limits of agreement from −1029 to 851 pg/mL. Although the absolute differences were greater at higher values, the performance of the percentage difference was uniform across the range of values. The median absolute difference was −30 pg/mL (IQR −137 to 0 pg/mL; online supplemental figure S2). Differences between reference and day 3 capillary results led to a different assignment of risk strata in 6 of 92 (6.5%) cases, of which 5 underestimated the risk status (figure 2).

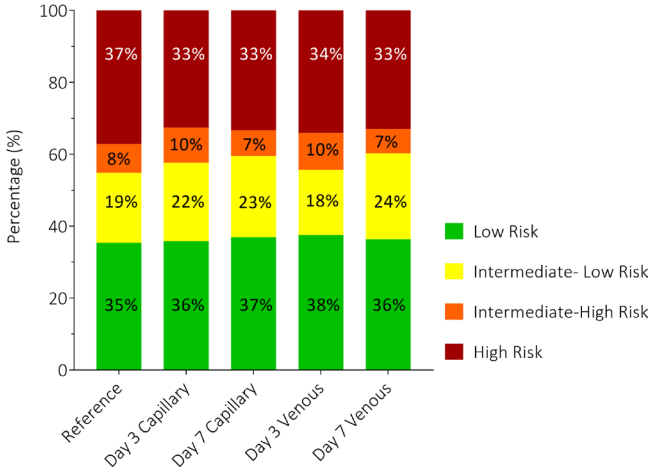

Figure 2 Percentage of patients as classified by four-strata risk based on reference and study NT-proBNP results. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Sendaway venous NT-proBNP

As shown in figure 3, the median relative difference between reference and day 3 venous NT-proBNP was 0% (IQR −4.5% to 7.4%), (b) Passing-Bablok regression showed an estimated slope of 1.0 (95% CI 0.9 to 1.02), intercept of 0.0 (95% CI −5.4 to 6.1) and an r of 0.99 (p<0.0001) indicating measurements were equivalent and (c) Bland-Altman analysis showed day 3 venous results were systematically higher than laboratory results (mean 76.6, SD 497 pg/mL) with limits of agreement from −897.5 to 1051 pg/mL. The median absolute difference was −4 pg/mL (IQR −85 to 13; online supplemental figure 2). Differences between reference and day 3 venous results led to a different assignment of risk strata in 8 of 88 (9.1%) cases, of which 6 underestimated the risk status (figure 2).

Stability of sendaway NT-proBNP

Capillary and venous samples at day 7 had poorer agreement to the reference NT-proBNP, when compared with the day 3 results and systematically underestimated the reference NT-proBNP. There was not a significant difference in results when assessed for winter and summer months (data not shown).

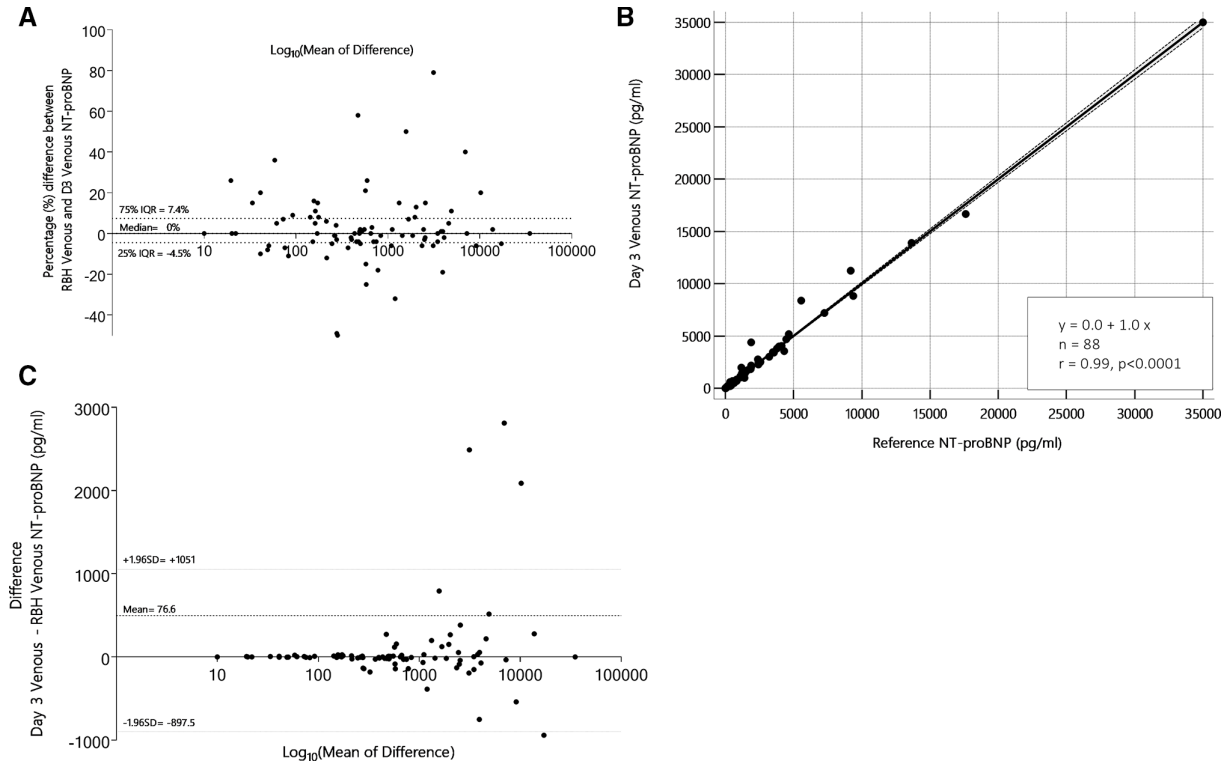

Figure 3 Analysis comparing reference and sendaway day 3 venous NT-proBNP (pg/mL) using (A) percentage difference plot demonstrating a median difference of 0%, (B) Passing-Bablok regression showing strong correlation (r=0.99), with a slope of 1.0 (95% CI 0.9 to 1.0) and intercept of 0.0 (95% CI −5.4 to 6.1) and (C) Bland-Altman plot showing a bias +76.6 with limits of agreement −897.5 to 1051. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

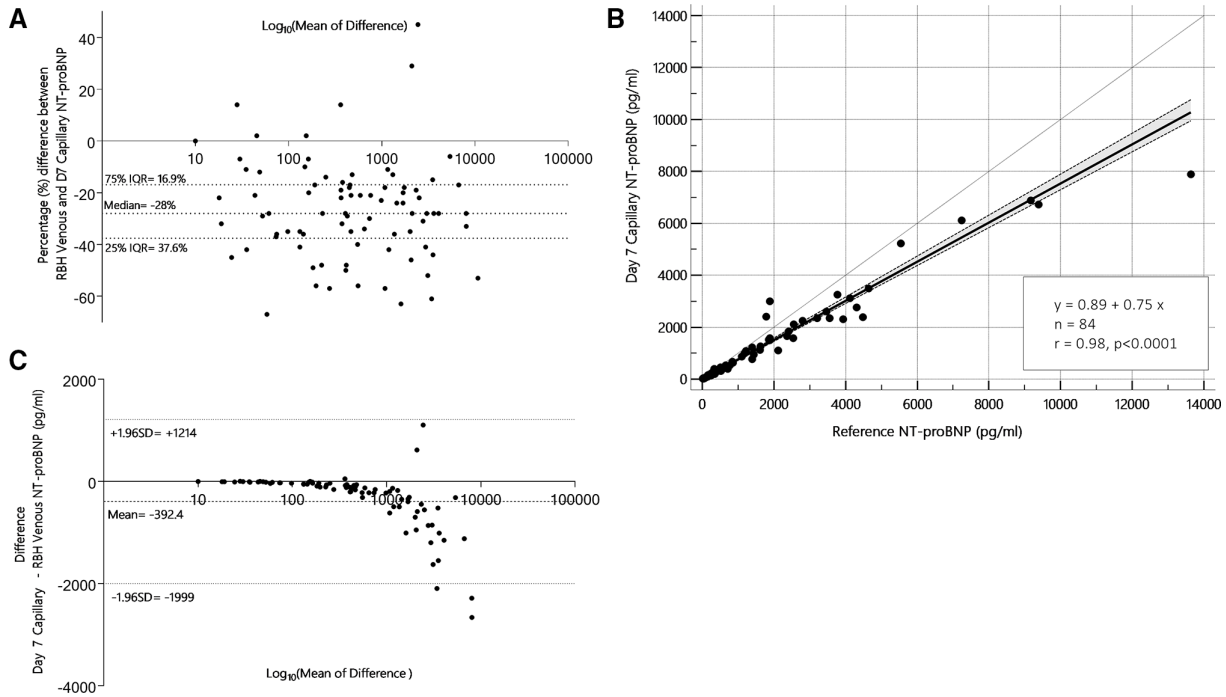

Figure 4 Analysis comparing reference and sendaway day 7 capillary NT-proBNP (pg/mL) using (A) percentage difference plot demonstrating a median difference of −28%, (B) Passing-Bablok regression showing strong correlation (r=0.98), with a slope of 0.75 (95% CI 0.73 to 0.79) and intercept of 0.89 (95% CI −5.2 to 7.09) and (C) Bland-Altman plot showing a bias of −392.4 with limits of agreement −1999 to 1214.

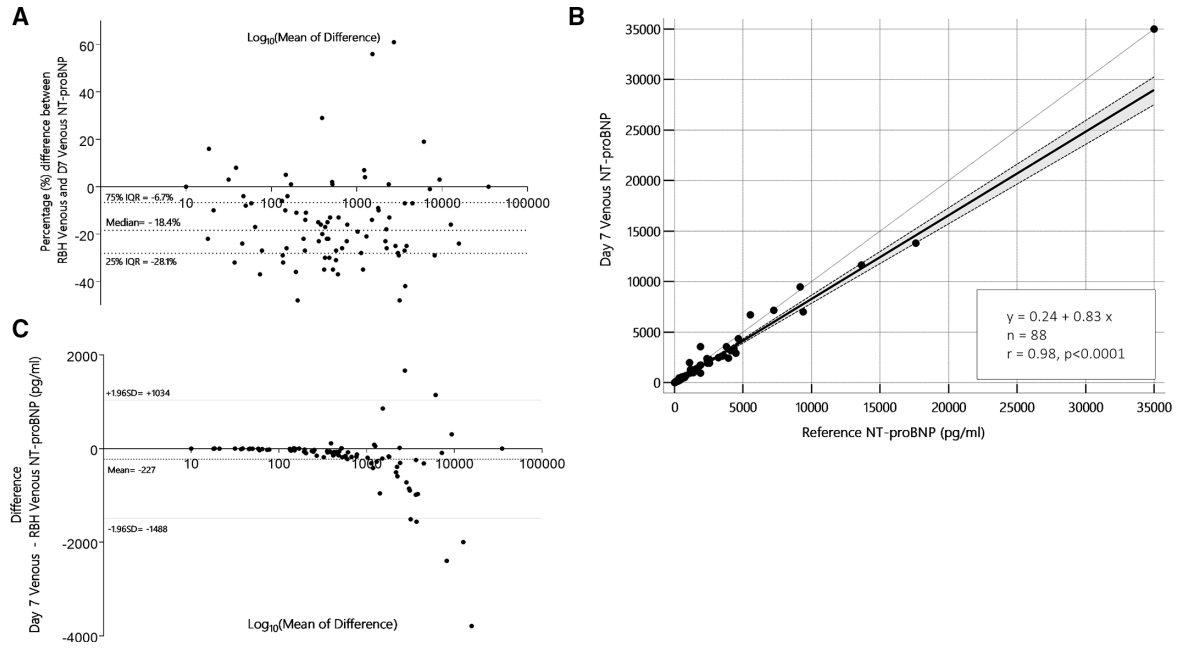

Figure 5 Analysis comparing reference and sendaway day 7 venous NT-proBNP (pg/mL) using (A) percentage difference plot demonstrating a median difference of −18.4%, (B) Passing-Bablok regression showing strong correlation (r=0.98), with a slope of 0.83 (95% CI 0.78 to 0.86) and intercept of 0.24 (95% CI −9.6 to 8.0) and (C) Bland Altman plot showing a bias of −227 with limits of agreement −1488 to 1034. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Day 7 capillary: As shown in figure 4, the median relative difference between reference and day 7 capillary NT-proBNP was −28% (IQR −37.6% to −16.9%,), (b) Passing-Bablok regression showed that results were significantly different to the reference with greater deviation when compared with day 3 capillary results and (c) Bland-Altman analysis demonstrated a mean difference of −392.4 pg/mL (SD 819) and limits of agreement −1999 to 1214 pg/mL. The median absolute difference was −122 pg/mL (IQR −483 to −28 (online supplemental figure S2). Differences between reference and day 7 capillary results led to a different assignment of risk strata in 10 of 84 (11.9%) cases, of which all 10 underestimated the risk status (figure 2).

Day 7 venous: As shown in figure 5, the median relative difference between reference and day 7 venous NT-proBNP was −18.4% (IQR −28.1% to 6.7%), (b) Passing-Bablok regression showed that results were significantly different to the reference with greater deviation when compared with day 3 venous results and (c) Bland-Altman analysis demonstrated a mean difference of −227 pg/mL (SD 643) and limits of agreement −1488 to 1034 pg/mL. The median absolute difference was −87.5 pg/mL (IQR −325.5 to −10.8 (online supplemental figure S2). Differences between reference and day 7 venous results led to a different assignment of risk strata in 12 of 88 (13.6%) cases, of which 11 underestimated the risk status (figure 2).

Local NT-proBNP: The agreement between the local and day 3 and day 7 venous and capillary NT-proBNP were performed and results are included in (online supplemental figure 3–6). The agreement between the local and study NT-proBNP was similar yet slightly poorer compared with analysis using the reference NT-proBNP.

DISCUSSION

The study investigated the agreement of sendaway capillary NT-proBNP when compared with a standard venous NT-proBNP. The main findings were (1) sendaway day 3 capillary NT-proBNP demonstrated good agreement as assessed for proportional difference and would accurately risk stratify patients as per COMPERA 2.0 thresholds in 93.5% of cases and yet was not equivalent to standard venous NT-proBNP using Passing-Bablok analysis, whereas (2) sendaway day 3 venous results accurately risk stratified patients in 90.1% of cases and yet were equivalent by Passing-Bablok regression; (3) delayed sampling of sendaway tests led to an unacceptable level of agreement with a systematic underestimation of NT-proBNP and (4) a high proportion (13%) of day 3 capillary samples were insufficient.

The level of agreement and agreement of risk stratification for day 3 capillary samples would likely be acceptable for a virtual clinic, although clinicians would need to take into account the unreliability of delayed samples. This is especially pertinent as patients are more likely to be misclassified into a lower risk category, and hence the situation may arise where the opportunity for a treatment escalation is missed as a patient is erroneously misclassified as low risk. Remote capillary sampling could be best used for PAH patients in lower risk strata, where remote tests are used to confirm stability, and a significant rise in NT-proBNP would prompt urgent face-to-face assessment.

The systematically lower capillary NT-proBNP results are likely due to the reduced stability of NT-proBNP over time,[5 6] as further shown by the poorer agreement when compared between day 3 and day 7 results.

There was a high proportion of insufficient capillary samples (13%), with feedback from the healthcare practitioners performing the test commenting that obtaining the required 600 µL of blood could be occasionally difficult. Furthermore, 24 samples were delayed in the postal service, although it was noted that the study took place during a period of UK Royal Mail industrial action between August and December 2022.[25] The high number of invalid results in a real-world setting may reduce the overall utility of sendaway capillary testing and further disruption to the postal service may jeopardise this model.

One patient was unable to provide any capillary samples due to severe Raynaud's. However, this study included a high proportion of patients with CTD-PAH, potentially demonstrating that some patients with poor peripheral perfusion due to scleroderma are able to perform capillary testing. However, this study did not collect data on whether patients with scleroderma subsequently experienced adverse effects, such as digital ulceration, and future work should include this.

Previous studies have investigated the use of NT-proBNP POCT. In left heart failure, POCT has been extensively studied for use in screening, overall demonstrating acceptable agreement when samples were tested contemporaneously.[16 18 26–28] The REPEAT-PAH study investigated the agreement between reference and POCT NT-proBNP in patients with PH using a Quidel Triage MeterPro device, where a capillary sample is obtained by a healthcare professional with a result available within 20 min. Between reference and POCT NT-proBNP, the intraclass correlation coefficient was 0.98 and Bland-Altman analysis demonstrated the bias increased proportional to the magnitude of reference NT-proBNP, as seen in this study.[19 20] The effect of delayed processing was investigated (mean delay 2.6 days) with an ICC of 0.99 between results.

This study was limited by the lack of a patient feedback questionnaire on the process of capillary sampling. As this was primarily an agreement study, capillary samples were obtained by healthcare professionals, not by patients, and hence the feasibility of fingerpick samples at home in this population is unknown. This is clearly relevant given the high proportion of insufficient capillary samples in the study. Furthermore, an assessment of intratest reliability was not performed as only one capillary sample was taken for day 3 and day 7 results, respectively. This study relied on the UK national postage service, and therefore, may not be applicable in all countries. Future work will focus on implementing capillary NT-proBNP sampling in a group of patients in an existing virtual clinic to assess the following (1) feasibility, (2) patient perceptions and (3) adverse effects of capillary sampling. Future work should aim to reduce the number of invalid samples by increasing patient education of how to perform the test and allowing 'practice runs' in order to refine the fingerpick technique.

In conclusion, capillary sendaway NT-proBNP sampling may allow specialist PH teams to incorporate an assessment of right ventricular function into virtual clinics, without requiring patients to travel. Capillary results were within acceptable limits of agreement and accurately risk stratified patients in the majority of cases, however, they must be interpreted with caution in cases of delayed sampling. Venous sendaway NT-proBNP demonstrated superior statistical agreement with the reference values yet with similar accuracy of risk stratification, and therefore, can also be relied on. These could be obtained by patients attending their local health provider.

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Contributors HS: methodology, patient recruitment, formal analysis, investigation, data curation, writing–original draft, conceptualisation, project administration; MJ: methodology, supervision, writing–review and editing; SW: methodology, patient recruitment, investigation, conceptualisation, supervision, writing–reviewing and editing, project administration, approval of the final draft for submission. All other authors: patient recruitment, writing–review and editing. SW: responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study was approved by the London–Fulham Research Ethics Committee (Ref 22/LO/0097). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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