14/226/07_NAIROS_HTA Final Report. Supplementary materials, File 1. Nasal patency measurements report

Author/work lead: **Alison Bray** (corresponding author), Lead Healthcare Scientist, [redacted]
Supervisor/reviewer: **Michael Drinnan**, Head of Clinical Engineering
Date: **11/08/2021**, Version: **v1**

Purpose

This document describes nasal patency data collection and analysis for the NIHR HTA-funded Nasal airway obstruction study (NAIROS) (funder reference 14/226/07), led by the Northern Medical Physics and Clinical Engineering (NMPCE) directorate of The Newcastle upon Tyne Hospitals NHS Foundation Trust.

Summary

Methods

NAIROS participants performed two types of nasal patency measurements at baseline and at six and 12 months post-randomisation. These were peak nasal inspiratory flow (PNIF) using a mechanical device, and rhinospirometry, using a device that measured airflow through each nostril independently. Measurement protocols were devised through literature reviews and discussions with the trial management group. Rhinospirometry data were monitored throughout the study to assess quality and adherence to the measurement protocol, and issues resolved.

The following five baseline, per-patient parameters are proposed for use in NAIROS secondary analysis:

1. Post-decongestant PNIF (maximum of three post-decongestant values) from a forced sniff.
2. Absolute, post-decongestant, tidal breathing, nasal partitioning ratio (NPR) – an indication of the symmetry of airflow through the nostrils.
3. The change in absolute NPR following decongestant – structural obstruction may be less likely than an irritative/allergic cause to respond to decongestant.
4. Post-decongestant, tidal breathing tidal volume, which is likely to relate to bother.
5. Post-decongestant, tidal breathing maximum flow rate, which is also likely to relate to bother.

MATLAB was used to analyse rhinospirometry data files and extract these parameters. Calculations were validated by comparison to Rhinospirometer software values. Parameter distributions were presented and discussed.

Results

Seven-hundred-and-twenty baseline rhinospirometry files were received. Thirty-five files were excluded due to having too few or too many measurements. Sixty-four further files were excluded or corrected following visual inspection of flow and volume measurements; the reasons for this are described.

Data validity and observations are discussed, including noisy flow, saturated measurements, flow calibration, and patient/operator compliance.

Per-measurement and per-patient parameters exhibited the expected distributions. Parameters 2 and 3 above were moderately correlated. Parameters 4 and 5 above were very strongly correlated.

Abbreviations

Abbreviation	Meaning
CRF	Case report form
HTA	Health Technology Assessment
NAIROS	Nasal airway obstruction study
NCTU	Newcastle Clinical Trials Unit
NIHR	National Institute for Health Research
NMPCE	Northern Medical Physics and Clinical Engineering
NPR	Nasal partitioning ratio
PHSI-BRG	Population Health Sciences Institute Biostatistics Research Group
PNIF	Peak nasal inspiratory flow
SNOT-22	Sino-nasal outcome test 22
TMG	Trial management group

Contents

Background

NAIROS is multicentre, mixed-methods, open label, randomised controlled trial of septoplasty versus medical management for adults with a deviated septum and reduced nasal airway. The primary outcome measure is a patient reported outcome score (SNOT-22) at six months post-randomisation. A small number (up to five) of parameters from baseline nasal patency data will feed into analyses conducted by the trial statisticians from the Population Health Sciences Institute Biostatistics Research Group (PHSI-BRG).

Further analyses of unblinded and follow-up data may be performed by NMPCE at a later date, subject to agreement from the NAIROS trial management group (TMG).

Methods

Nasal patency measurement and data collection protocols

The nasal patency measurement and data collection protocols were devised through a combination of:

- Review of the scientific literature and equipment manufacturer's user information (GM Instruments, Irvine, UK) [1, 2, 3, 4]
- Consultation with the NAIROS TMG
- Consultation with a representative of the NV1 Rhinospirometer manufacturer (Eric Greig)

These protocols are described in full in the following documents:

- Rhinospirometer software installation guide [5]
- Nasal patency measurements protocol [6]
- NAIROS protocol publication [7]

Site staff were trained in these protocols in person during site initiation visits, were provided with a training video [8], and had access to ad-hoc support from NMPCE and GM Instruments.

In short, measurements of nasal patency took place at all three study visits (baseline, and six months and 12 months post-randomisation). At each visit, following at least 20 minutes' acclimatisation, measurements were made both before and 5-60 minutes after decongesting with xylometazoline.

Two types of measurements were made:

1. Peak nasal inspiratory flow (PNIF) rate, using a PNIF meter (GM Instruments). This is a mechanical device providing one measurement read from a scale ranging from 0-370 L/min (0-6 L/s) (*Figure 1*). A forced sniff manoeuvre is performed.
2. Rhinospirometry, using a NV1 Rhinospirometer (GM Instruments) (*Figure 2*). This device comprises mechanics, electronics and software. It provides readings on the front of the device of the total volume of air inhaled through the left and right nostrils separately. A file is saved using the software, which contains flow rate time series data. The limit of volumes displayed on the front of the NV1 Rhinospirometer is 4.5 L ± approximately 2% (4.41-4.59 L). The limit in the software is determined by a setting [5], set for NAIROS to be 5 L. The flow rate limit is 0.8 L/s [4]. In fact, the measurement saturates at around 1.24 L/s (and –0.9 L/s), but is only specified to be linear to ±0.8 L/s [4].

Three measurements of PNIF were made. For rhinospirometry, three maximal inhalation measurements (slow inhalation of the full capacity of the lungs) followed by one tidal breathing measurement (normal breathing in and out) were made.

Figure 1. PNIF meter.

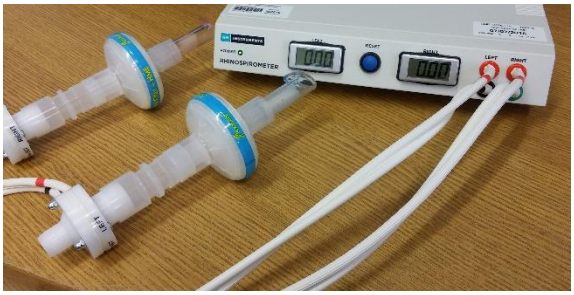

Figure 2. NV1 Rhinospirometer.

A summary of this measurement schedule is as follows:

- Baseline visit (immediately prior to randomisation)
  - Pre-decongestant
    - 3 × peak nasal inspiratory flow
    - Rhinospirometry
      - 3 × maximal inspiration
      - 1 × tidal breathing
  - Post-decongestant: as for *Pre-decongestant*
- 6 months post-randomisation: as for *Baseline visit*
- 12 months post-randomisation: as for *Baseline visit*

The readings from the PNIF meter and from the front of the NV1 Rhinospirometer were written by the research nurse onto a case report form (CRF) [9] and then uploaded to the NAIROS database along with the files from the NV1 Rhinospirometer software (one pre-decongestant and one post-decongestant file). The NAIROS database specification is given in [10].

A naming convention was specified for the NV1 files that identified the data by participant screening ID, visit, and whether pre- or post-decongestant [6]. Newcastle Clinical Trials Unit (NCTU) checked that filenames conformed to this convention and resolved any issues with sites. NMPCE also received files on a roughly monthly basis so that data quality and compliance with the protocol could be checked, and any issues resolved.

Selection of parameters to feed into NAIROS secondary analyses

The following parameters, derived from NV1 Rhinospirometer data files from baseline data only, were discussed during a meeting between members of the TMG:

1. Nasal partitioning ratio (NPR). This is an indication of the asymmetry of airflow through the nostrils, ranging from –1 (total left side obstruction) to 1 (total right side obstruction), given by *Equation 1* (where VL = left side volume and VR = right side volume). The normal range for NRP from slow exhalation of the vital capacity of the lungs through the nose, determined from a study of 100 healthy volunteers, was 0.30 to –0.34 [11].

$$Nasal\ partitioning\ ratio = \frac{VL-VR}{VL+VR} \quad \textit{Equation 1}$$

2. Change in NPR following decongestant. Structural obstruction may be less likely than an irritative/allergic cause to respond to decongestant, so this metric may separate those groups.
3. Tidal volume, which is likely to relate to patient bother.
4. Maximum flow rate, which is likely to relate to patient bother.
5. An exploratory parameter relating to flow-volume curves.

This left decisions of whether to use pre- or post-decongestant data (except for 2 above, which uses both), maximal inhalation or tidal breathing, and inhalation and/or exhalation data. In line with previous reporting of rhinospirometry data from the scientific literature [2], post-decongestant data were chosen. Tidal breathing measurements were chosen as they are more likely to be representative of patients' normal breathing and therefore their symptoms, and they provide a tidal volume measurement. Inhalation data was chosen over exhalation data because measured inhalation volumes tended to be larger than exhalation volumes, implying that more flow is being captured during inhalation. This phenomenon was noticed during quality control data reviews throughout data collection. It may occur because inhalation pulls the rhinospirometry nosepieces towards the nostrils, creating a seal, whereas exhalation pushes them away, resulting in more air escaping.

Finally, parameter 5 above, being the most speculative, was excluded in favour of including one derived from PNIF measurements. PNIF data are held by NCTU/PHSI-BRG. The suggested parameter is the maximum of the three post-decongestant, baseline PNIF measurements [1]. PNIF normal ranges (although without decongestion) by age, gender and height, are given in [12].

Receipt of rhinospirometry data

Following data lock, all NV1 rhinospirometry files were sent by NCTU to NMPCE. In addition, PHSI-BRG provided a list of NV1 volumes entered onto the database that exceeded 4.5 litres.

Filename format check

The filename formats were checked and any issues resolved with NCTU.

Extracting and processing flow rate, time and volume data

Analyses described from this point were performed using a MATLAB version R2019 script [13, 14]. The MATLAB workspace variables created by the script are given in [15]. Technical descriptions of certain aspects of data analysis are given in Appendix I. For each baseline NV1 rhinospirometry file:

1. The file was read into MATLAB and separated into measurements.
2. A frequent error was to save the post-decongestant measurements into the same file as the pre-decongestant measurements, giving a file with eight measurements instead of four. Files with eight measurements were corrected by:
    a. For pre-decongestant files: deleting the second four measurements.
    b. For post-decongestant files: deleting the first four measurements.
3. Files with fewer than four measurements were excluded from further analysis.
4. Files with more than eight measurements were viewed using the Rhinospirometer software (version 3.0.0.381) to determine whether they could be corrected to contain three maximal inhalations and one tidal breathing, or should be excluded from further analysis.
5. Files were organised into a MATLAB structure by participant and whether pre- or post-decongestant, as identified by the filename.
6. Left and right flow and time data were extracted from the measurements.
7. The following additional time series were calculated:
    a. Filtered flow, to smooth high frequency noise and give more reliable calculation of maximum flow rate.
    b. Inhalation only flow, by setting flow rate samples with a value less than zero to zero.
    c. Exhalation only flow, by setting flow rate samples with a value above zero to zero.
    d. Total flow, by adding left flow to right flow.
    e. Volume, by integrating flow.
8. The following per-measurement parameters were calculated:
    a. Total volume.

   b. Maximum flow rate.
   c. Mean flow rate.
   d. Nasal partitioning ratio.
   e. Measurement duration.
9. Flow rate and volume time series data were plotted to enable visual inspection.
10. Histograms of the per-measurement parameters extracted above were plotted.

Visual inspection and correction of flow rate and volume data

11. Each measurement plot was inspected visually.
12. Data issues were identified and either corrected, or the data excluded if that was not possible.

Per-measurement calculation validation

13. Measurements calculated both by the Rhinospirometer software and using MATLAB, listed below, were compared manually for one file chosen at random from each site, in order to validate the MATLAB analyses. This was done by viewing each measurement in the Rhinospirometer software (version 3.0.0.1436, which corrected an issue in version 3.0.0.381 resulting in incorrect calculation of peak flow rates) and recording the values into a table, then comparing these to results from MATLAB. Differences in volume of 10 mL or more, and in flow of 10 mL/s or more, were investigated further.
    - Left side volume (unfiltered, inhalation only)
    - Left side average (mean) flow rate (unfiltered, inhalation only)
    - Left side peak (maximum) flow rate (unfiltered, inhalation only)
    - Right side volume (unfiltered, inhalation only)
    - Right side average (mean) flow rate (unfiltered, inhalation only)
    - Right side peak (maximum) flow rate (unfiltered, inhalation only)
    - NPR (unfiltered, inhalation only)
    - Duration

Extraction of per-patient parameters

14. The chosen parameters were calculated from each dataset as follows:
    a. Absolute NPR (baseline, post-decongestant, tidal breathing, inhalation only data). The absolute rather than signed value was chosen so that across its range, from 0 to 1, the change was from symmetric to asymmetric flow.
    b. Absolute pre-decongestant NPR minus absolute post-decongestant NPR (baseline, tidal breathing, inhalation only data).
    c. Maximum flow rate (baseline, post-decongestant, tidal breathing, inhalation only, filtered flow rate data).
    d. Tidal volume (baseline, post-decongestant, tidal breathing, inhalation only data).

Per-patient calculation validation

For a random sample of five patients, the four per-patient measurements were extracted (14.a), calculated (14.b), or estimated (14.d), or an upper limit calculated (14.c), using the NV1 Rhinospirometry software. These values were compared to the MATLAB calculations.

Per-patient parameter histograms, scatter plots, correlations

Histograms of the per-patient parameters were plotted, as were scatter plots of each parameter versus the others (giving six comparisons). The correlation between each parameter was calculated, and statistical significance assessed according to a conservative Bonferroni-adjusted P value threshold ($0.05/6 = 0.008$).

Results

Receipt of rhinospirometry data files, file name check and correction

Following data lock, 1488 rhinospirometry data files were received from NCTU on 05/02/2021 (these are stored on the NMPCE server in [16]) followed by 17 replacement files with corrected file names on 10/03/2021 (stored in [17]). Filename corrections are detailed in [18].

File summary

The number of files received by site and visit is shown in *Table 1*. Due to the COVID-19 pandemic, no nasal patency measurements took place after March 2020, so a large number of follow-up datasets are missing, especially at 12 months.

Table 1. The number of rhinospirometry files received by site and visit.

Site	Baseline	6 months	12 months	Total
ABD	74	65	36	175
AIN	54	26	6	86
BFD	20	2	0	22
BIR	26	22	9	57
CAR	22	16	11	49
DAR	18	8	8	34
DEE	40	28	20	88
GYM	44	38	30	112
LDN	28	14	0	42
LDS	52	36	24	112
LNK	40	24	12	76
NCL	150	118	74	342
NWT	26	16	10	52
PLY	25	17	12	54
SAL	29	20	18	67
SPT	36	18	2	56
WGN	36	18	10	64
Total	720	486	282	1488

Correction or exclusion of files with the wrong number of measurements

Unless stated, only baseline data (720 files) were included from this point. One-hundred-and-two baseline files had fewer or more than four measurements:

- 14 files had fewer than four measurements. These were excluded because in most cases it was unclear from visual inspection which measurements were maximal inhalation and which were tidal breathing.
- 52 files had eight measurements:
  - 8 of these were pre-decongestant files and so were corrected by removing the second four measurements.
  - 44 of these were post-decongestant files and so were corrected by removing the first four measurements.
- 36 files had more than four measurements (but not eight), ranging from five to 27:
  - 15 were corrected where it was clear from visual inspection which measurements should be removed (for example if there were measurements with no breathing).
  - 21 were excluded where this was unclear.

Exclusion or correction of these files is detailed in [19]. The remaining 685 files from 350 patients used for subsequent analysis are stored in [20].

Correction or exclusion of data following visual inspection of flow and volume

Results from visual inspection of these data are detailed in [21] and summarised in *Table 2*. Flow plots for datasets subsequently excluded or corrected are given in [22]. Volume and flow plots for each patient following these exclusions and corrections are given in [23].

Table 2. Summary of file exclusions and corrections following visual inspection of flow and volume data. 'PRE' refers to the pre-decongestant file, and 'POST' refers to the post-decongestant file.

Number of files	Exclusion/correction details	Files
12	Excluded because all measurements were invalid. The volume measurements changed linearly from 0 to ±5 L rather than measuring actual flow. This can happen if the USB cable is not plugged in, or if the Rhinospirometer is not reset before the measurements (user error). For example, SCN0001BIR (page 1 [22]).	SCN0001BIR PRE SCN0001BIR POST SCN0002BIR PRE SCN0002BIR POST SCN0002LNK PRE SCN0002LNK POST SCN0003LNK PRE SCN0004LNK PRE SCN0004LNK POST SCN0005LNK PRE SCN0005LNK POST SCN0011PLY PRE
3	Individual invalid measurements excluded.	SCN0003DEE PRE SCN0013BIR PRE SCN0016BFD POST
2	Excluded because they were identical, so it was not known which patient's data they were. SCN0027PLY and SCN0087PLY are shown on page 29 and 31 respectively [22].	SCN0027PLY POST SCN0028PLY POST
6	Excluded because pre- and post-decongestant data were identical, so it was not known which the data were. For example, SCN0002DAR (page 5 [22]).	SCN0002DAR PRE SCN0002DAR POST SCN0010NCL PRE SCN0010NCL POST SCN0014SAL PRE SCN0014SAL POST
30	Corrected to reverse the direction of left and right flow. Reversed flow is clear from the data because the maximal inhalation flow is negative, and results from both flowheads being connected the wrong way round (see **Reversed flow** below). For example, SCN0001LDN (page 2 [22]).	All files from site LDN SCN0009NCL PRE SCN0009NCL POST
2	Corrected to reverse the direction of right flow for the reason above. SCN0021AIN is shown on page 28 [22].	SCN0021AIN PRE SCN0021AIN POST
5	Corrected to reorder measurements so that maximal inhalations and tidal breathing were in the correct positions. For example, SCN0010CAR PRE (page 19 [22]).	SCN0001SAL POST SCN0010CAR PRE SCN0013BIR PRE SCN0017CAR PRE SCN0031ABD POST
4	Corrected to swap the right side time and right side flow, which were swapped in the data. For example, SCN0005NCL (tidal breathing measurements) (page 14 [22]). This appears to be a software glitch causing the data to contain an extra sample.	SCN0005NCL PRE SCN0005NCL POST SCN0016LDS PRE SCN0060NCL POST
64	**Total**	

Measurement issues and observations

Reversed flow

Figure 2 shows two tubes connecting the Rhinospirometer to each of the two white plastic flowheads. The left side tubes are colour-coded red and black, and the right side tubes are colour-coded red and green. If these tubes are connected to the Rhinospirometer the wrong way round, inhalation and exhalation will be swapped.

For one site (LDN), all their measurements were reversed in this way, implying that the device was set up incorrectly to begin with, and remained that way throughout the study. Two other sites had one instance of one (SCN0021AIN, page 28 [22]) or both (SCN0009NCL, page 18 [22]) sides being reversed, implying that the tubes were disconnected for cleaning/storage, or accidently, and reconnected the wrong way round as a one-off error.

If the left and right flowheads were swapped at the connections to the Rhinospirometer, or placed on the wrong nostrils, left and right measurements would be swapped, and there would be no way of detecting this from the data. The NPR would then have the correct magnitude, but the wrong sign, so the direction of asymmetry indicated would be wrong.

Exhalation during maximal inhalation measurements

Anti-viral filters were used for NAIROS rhinospirometry measurements because both inhalation and exhalation was measured. The NV1 Rhinospirometer User Guide Version 10 [4] states that:

> *A typical test should involve inspired room air only and last a few seconds. If expired air is to be passed through the flowhead, adding the recommended anti-viral filter will protect it from the effects of humidity and from infection.*

However, our data show that even when patients are instructed only to inhale, there is often also exhalation, shown by the grey flow below 0 mL/s for many instances of maximal inhalations in flow plots [23]. Therefore, we recommend that anti-viral filters always be used.

Noisy/erratic flow

Noisy flow was observed in several measurements, prompting filtering of flow before calculation of maximum and mean values. Discussions with GM Instruments and members of the TMG indicated that this is unlikely to be an artefact such as electromagnetic interference, and more likely to be a genuine finding of a disturbed flow pattern. SCN0006AIN (page 103 [23]), for example, shows consistent, bilateral, high-frequency flow changes, which is reduced following decongestant. Some patients, such as SCN0016LDS (page 271 [23]), exhibited erratic flow, the reason for which is unclear.

Flow saturation

In quite a few cases, almost all of which were maximal inhalations, the flow measurement saturated at 1.24 L/s (or at –0.9 L/s for corrected reversed measurements). For example, all maximal inhalations for SCN0030GYM (page 443 [23]). Saturated flow measurements are marked with ‘S’ in [21]. It is unlikely that measurements from –0.9 to –0.8 L/s and 0.8 to 1.24 L/s are significantly non-linear, and as there are several hundred of these, they have been retained. Those above the saturation threshold, however, are artificially limited.

Flow outwith these limits may genuinely reflect slow/normal breathing, meaning that the Rhinospirometer is not capable of measuring flow rate for maximal inhalations and, in a few cases, tidal breathing, across the full physiological range. Alternatively, high flow rates may result from patients forcing flow, as for PNIF measurements, rather than as instructed, especially for maximal inhalations.

Peak flow has been reported to be 130 ± 16 L/min (mean ± standard deviation) (2.2 ± 0.3 L/s) in 60 patients diagnosed with nasal septum deviation [24]. This was the highest value of three attempts, with patients instructed to "*make a strong inspiration after making a powerful expiration while the mouth is closed*". Decongestion was not mentioned so presumably was not done. This implies that on average the peak flow rate through each nostril was around 1.1 L/min for a forced manoeuvre.

Part-captured flow

Some maximal inhalation measurements appear to start part way through the breath, meaning that not all volume was captured, and the point of maximum flow may have been missed. For example, SCN0057AIN (page 599 [23]). This results from operator and/or patient error. It is less of an issue for tidal breathing measurements, which involve several breaths. The per-patient tidal volume parameter, which is based on breaths, excludes the first and last in case they are partial (see Appendix I).

Flow zero calibration

Some flow measurements had a non-zero baseline, indicated by flat portions of flow not equal to zero when breathing had apparently stopped. For, example SCN0005LDS (page 93 [23]). For the first and third maximal inhalations, both left and right flow return to zero once the breath has ended. However, for the second maximal inhalation, the left and right flow measurements return to different, non-zero baselines. The reason for this is unclear. Calibration errors such as this result in flow and volume measurements being incorrect by this offset. This appears to be the most significant issue with reliability of the data, and is only obvious if there are portions of flow with no breathing.

Data sample rate

For one site (LDS), the data sample rate was 32.05 Hz rather than 50 Hz, the latter being the default software setting and that specified in the software installation guide [5]. The reason for this is unclear.

Unequal inhaled and exhaled tidal breathing volume

Tidal inhaled volume must equal exhaled volume, otherwise a positive or negative pressure would quickly build up in the lungs. This was not always the case, as illustrated by studies where bidirectional volume drifted upwards or downwards. This may result from the flow saturation and/or calibration issues described above. However, it also occurred in cases such as SCN0003LDS (pre-decongestant, page 49-50 [23]) where the flow measurement appears to start from a zero baseline. This may result from more flow being captured in one direction due the patient's technique with the nosepieces, as discussed earlier.

Volume values displayed on the Rhinospirometer

The list of 72 NV1 volumes entered onto the database exceeding 4.5 litres is given in [25]; this included six and 12 month follow-up data. These were compared to the volumes shown in the Rhinospirometer software. The findings are described in [26]. In summary:

- Nineteen matched within 0.1 L. Nine of these exceeded the device display limit of 4.59, so were probably read from the software rather than the device.
- Fifteen had no corresponding data file, so could not be checked.
- Twelve were between 4.5 and 4.59 L, which is within the range of the device display.
- Six were data entry errors (the decimal in the wrong place). These were incidental findings and there may be other data entry errors for values below 4.5 L.
- Four measurements related to data files with more than four measurements, so they could not be matched in order to check the volume.
- For the remaining 16, the database values were all higher than the software values, and all between 4.52 and 4.59 L. This may be due to a delay between the measurement being made,

and being read and written on the CRF, during which time the measurement shown on the Rhinospirometer display drifted upwards to its limit.

The database should have been configured to reject values above 4.6 L (rather than warning above 8 L and rejecting above 10 L [10]). This appears to be an error in the specification/approval of the nasal patency aspects of the database by NMPCE. The software limit should also have been set to the same limit, to ensure that database and software values matched. However, these issues can be overcome by using the software rather than database values in further analyses; the software values are more reliable for reasons described in the list above.

Validation of calculations

Per-measurement parameters

All 136 volume measurements, and 265 of the 272 flow measurements, agreed within 10 mL and 10 mL/s respectively. The seven flow measurements that did not agree within 10 mL/s were all due to rounding differences. All NPRs agreed within 0.001 and all durations agreed within 0.05 seconds. The results are given in [27].

Per-patient parameters

All NPRs agreed, all NPR differences agreed within 0.01, all total maximum flow rates were below the upper limits, and all estimated tidal volumes agreed within 0.1 L. The results are given in [28].

Per-measurement parameters

Per-measurement parameters are given in [29, 30]. Histograms showing the distributions of the per-measurement parameters for all patients pooled together are given in [31], where left hand plots show all maximal inhalation values, right hand plots show all tidal breathing values, upper plots show pre-decongestant, and lower plot show post-decongestant. The number of bins is the square root of the number of measurements included. Comments on these distributions are given in *Table 3*. Four volumes values above 5 L were excluded. These occurred for reversed, corrected measurements, which ended when exhaled volume reached 5 L, by which time inhaled volume was above 5 L.

Table 3. Comments on the distributions of per-measurement parameters shown in [18].

Per-measurement parameter	Comments
Left/Right End Volume Pre Filter Inhalation (page 1-2 [31])	Limited to 5 L due to software limit. Peak for tidal breathing at around 3 L due to protocol instruction to stop measurement if 3 L reached on either side. Slightly higher post-decongestant values on average.
Left/Right Maximum Flow Pre Filter Inhalation (page 3-4 [31])	Peak at zero, especially for maximal inhalation, due to one-sided flow associated with patient population. Peak at measurement limit of 1.24 L/s for maximal inhalation only, implying that patients often forced this manoeuvre. Peak at around 0.2 L/s for tidal breathing. Slightly higher post-decongestant values on average.
Left/Right Maximum Flow Filtered Inhalation (page 5-6 [31])	As above, shifted slightly towards lower flow rates due to filter effect.

Per-measurement parameter	Comments
Total Maximum Flow Filtered Inhalation (page 7 [31])	Peak at around 0.5 L/s, except for pre-decongestant tidal breathing, which is lower. No peak at zero due to contribution from both nostrils. Higher post-decongestant values on average.
NPR Pre Filter Inhalation (page 12 [31])	Distribution with three peaks at –1, 0 and 1. Two distributions combined; one centred on zero from patients with symmetric flow (perhaps those with inflammatory obstruction), and another with peaks at –1 and 1, and a trough at zero, from patients with asymmetric flow (perhaps those with one-sided structural obstruction). Post-decongestant values shifted towards zero.
Measurement Duration (page 13 [31])	Peak at 6 seconds for pre-decongestant maximal inhalation, slightly lower for post-decongestant. Peak at 60 seconds (software limit) for tidal breathing.

Per-patient parameters

The per-measurement parameters are given in [32, 33]. Histograms showing their distributions are given in *Figure 3*.

Table 4. Comments on the distributions of per-patient parameters shown in Figure 3.

Per-patient parameter	Comments
Absolute post-decongestant NPR	Unsigned equivalent of *NPR Pre Filter Inhalation* row in *Table 3*. 167/331 (50%) are greater than 0.3.
Absolute pre-decongestant NPR minus absolute post-decongestant NPR	The peak at zero is patients whose flow symmetry is unchanged by decongestant. This could include patients who are obstructed on one side pre-decongestant, and obstructed by the same amount on the other side post-decongestant. Those above zero are more symmetrical when decongested (around two thirds). Those below zero more asymmetrical when decongested (around a third).
Total maximum flow rate	See *Total Maximum Flow Filtered Inhalation* row in *Table 3*.
Tidal volume	Peak at around 0.6 L. This is close but higher than the average values of 0.4 and 0.5 L reported for healthy, adult, females and males respectively [34]. This may indicate that the manoeuvre tended to be slightly forced. Unusually low or high values may result from flow calibration issues, as calculation of tidal volume uses flow sign change to differentiate inhalation from exhalation.

Scatter plots showing the relationship between each per-patient parameter are given in *Figure 4*. ρ and P values are for correlation analysis according to Spearman's rank. Comments on these relationships are given in *Table 5*.

Table 5. Comments on the relationships between per-patient parameters shown in Figure 4.

Parameter 1	Parameter 2	Comments
Absolute post-decongestant NPR	Absolute pre-decongestant NPR minus absolute post-decongestant NPR	Moderate, statistically significant negative correlation. As expected, those with more symmetric post-decongestant flow were those in whom decongestant improved flow symmetry more.
Absolute post-decongestant NPR	Total maximum flow rate	Weak, statistically significant negative correlation: more symmetric post-decongestant flow in those with higher maximum flow rate.
Absolute post-decongestant NPR	Tidal volume	No relationship.
Absolute pre-decongestant NPR minus absolute post-decongestant NPR	Total maximum flow rate	No relationship.
Absolute pre-decongestant NPR minus absolute post-decongestant NPR	Tidal volume	No relationship.
Total maximum flow rate	Tidal volume	Very strong, statistically significant positive correlation. Those with higher maximum flow rates had higher tidal volumes; both are likely to depend on body mass, and could be could be corrected for mass to give flow rate in L/kg·s and volume in L/kg.

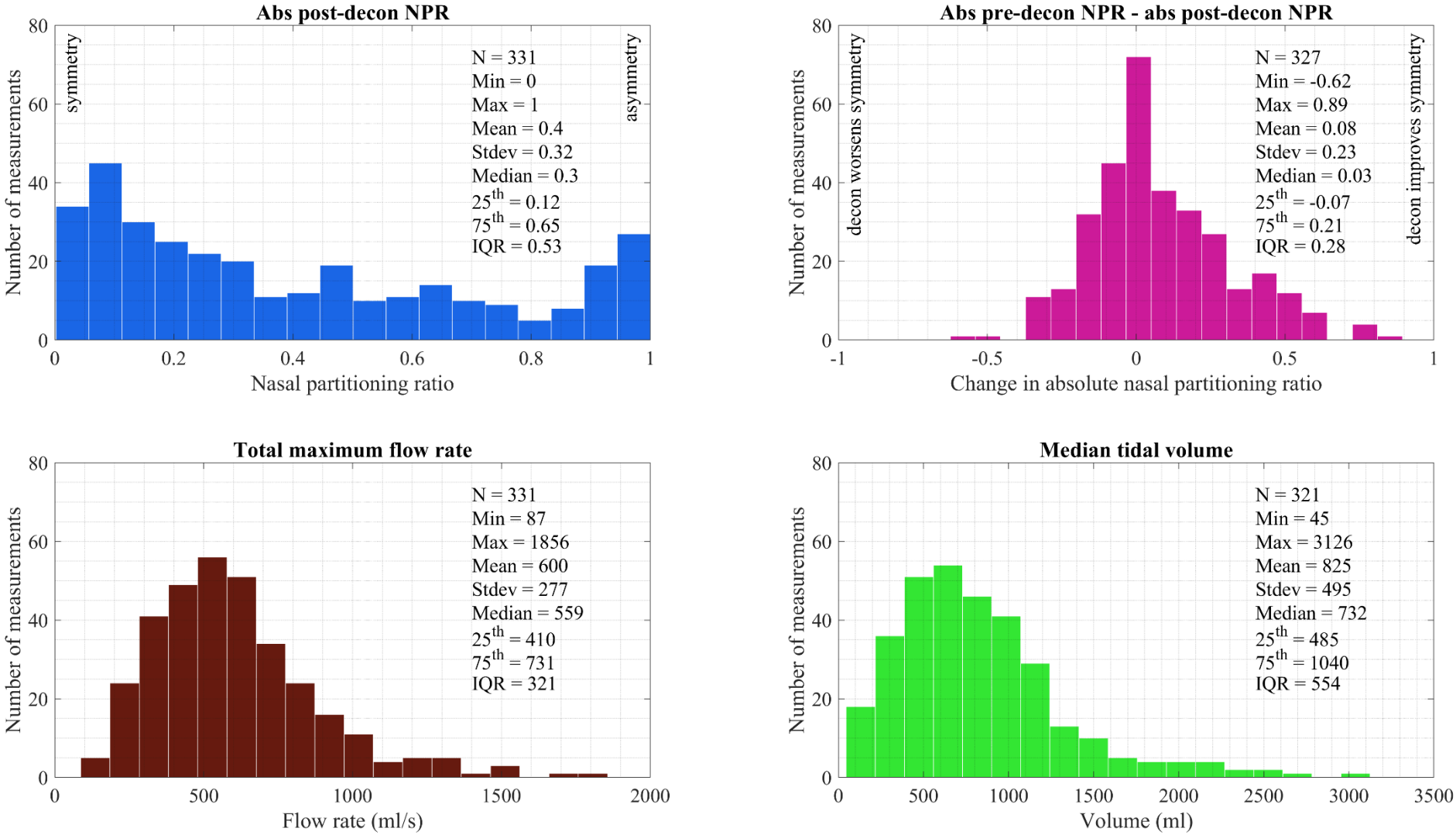

Figure 3. Histograms showing the distributions of the per-patient parameters. The number of bins is the square root of the number of measurements included.

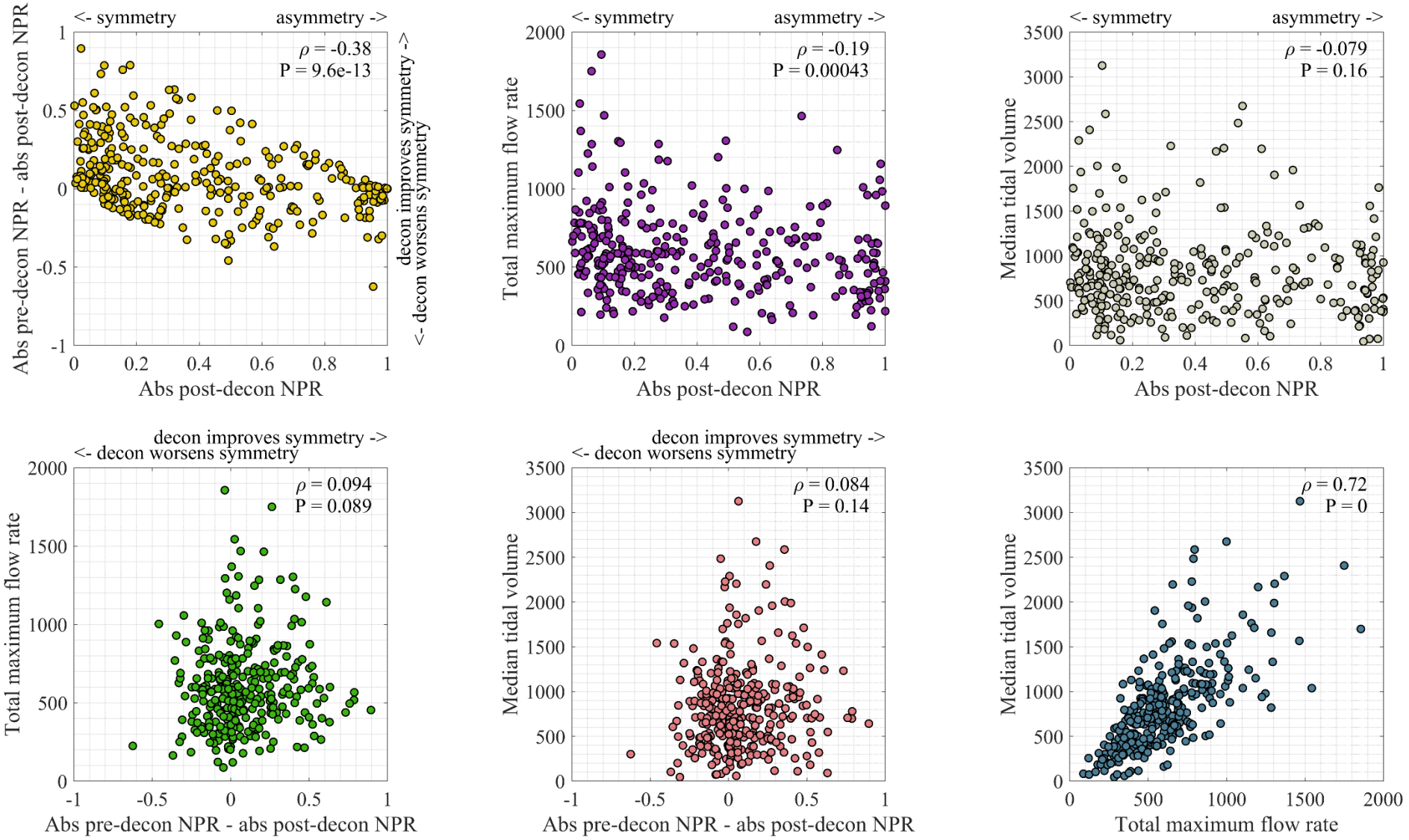

Figure 4. Scatter plots showing the relationship between each per-patient parameter. ρ and P values are correlation analysis according to Spearman's rank.

References

1. *20170118 Review of peak nasal flow protocols.pdf*
2. *20170105 Review of rhinospirometry protocols.pdf*
3. *20130919 NV1 Rhinospirometer Software Manual V10.pdf*
4. *20160914 NV1 User Guide V10.pdf*
5. *20171002 NV1 software installation guide v1.1.pdf*
6. *20180822 Nasal patency measurements protocol v4.pdf*
7. Rennie KJ, O'Hara J, Rousseau N, Stocken D, Howel D, Ternent L, Drinnan M, Bray A, Rooshenas L, Hamilton DW, Steel A, Fouweather T, Hynes AM, Holstein EM, Oluboyede Y, Abouhajar A, Wilson JA, Carrie S; NAIROS Study Group. *Nasal Airway Obstruction Study (NAIROS): a phase III, open-label, mixed-methods, multicentre randomised controlled trial of septoplasty versus medical management of a septal deviation with nasal obstruction.* Trials. 2020 Feb 13;21(1):179. doi: 10.1186/s13063-020-4081-1. PMID: 32054508; PMCID: PMC7020359.
8. NAIROS study team. 30/05/2017. *NAIROS: A guide to measurements of nasal patency.* YouTube. https://youtu.be/ZuK66Jf_iGc
9. *20183001 Nasal patency CRF v1.2 NCL.pdf*
10. *8302-NAIROS-Database Specification-2020-03-27-V9.0-14.1.4.2.xlsx*
11. Roblin DG, Eccles R. *Normal range for nasal partitioning of airflow determined by nasal spirometry in 100 healthy subjects.* Am J Rhinol. 2003 Jul-Aug;17(4):179-83. PMID: 12962185.
12. Ottaviano G, Scadding GK, Coles S, Lund VJ. *Peak nasal inspiratory flow; normal range in adult population.* Rhinology. 2006 Mar;44(1):32-5. PMID: 16550947.
13. *NAIROS_NV1_Analyses_20210611.m*
14. *NAIROS_NV1_Analyses_20210611.pdf*
15. *NAIROS_NV1_Workspace_20210611.pdf*
16. T:\Clinical Research\Projects\P201603 NAIROS\Nasal patency measurements\Data\Final dataset from CTU\Final download for AB_2021-02-05 (only accessible from NMPCE server)
17. T:\Clinical Research\Projects\P201603 NAIROS\Nasal patency measurements\Data\Final dataset from CTU\Final download for AB_2021-03-10 (only accessible from NMPCE server)
18. *20210504 NAIROS NV1 file name corrections.pdf*
19. *20210504 NAIROS NV1 files with other than 4 measurements.pdf*
20. T:\Clinical Research\Projects\P201603 NAIROS\Nasal patency measurements\Data\Final dataset from CTU\Final dataset corrected - baseline only (only accessible from NMPCE server)
21. *20210504 NAIROS NV1 visual inspection results.pdf*
22. *20210506 NV1 measurements to exclude or correct.pdf*
23. *20210518 NV1 volume flow plots.pdf*
24. Sahin C. *Evaluation of Patient Satisfaction After Nasal Septoplasty Operation Using Peak Nasal Inspratuar Flow and Nasal Obstruction Symptom Score Questionare*. J Craniofac Surg. 2016 Jul;27(5):1289-91. doi: 10.1097/SCS.0000000000002748. PMID: 27391500.
25. *20210311 NPR out of spec (limit 4.5 litres).xls*
26. *20210316 NAIROS NV1 out of range database volumes.pdf*
27. *20210602 NAIROS baseline per measurement parameter validation.pdf*
28. *20210610 NAIROS baseline per patient parameter validation.pdf*
29. *20210506 NAIROS baseline per measurement parameters.xlsx*
30. *20210506 NAIROS baseline per measurement parameters.pdf*
31. *20210506 Per measurement NV1 parameter histograms.pdf*
32. *20210506 NAIROS baseline per patient parameters.xlsx*
33. *20210506 NAIROS baseline per patient parameters.pdf*
34. Hallett S, Toro F, Ashurst JV. *Physiology, Tidal Volume*. [Updated 2020 Jun 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482502/

Appendix I. Data processing technical descriptions

Reading data and separating measurements

- The file was read into MATLAB as 8 bit unsigned integers (i.e. bytes). This enabled non-measurement parts of the data (representing patient initials and NAIROS screening ID) to be identified (these are stored as bytes) and separated from the measurements themselves.
- The data were extracted excluding the first 45 samples (bytes) representing the patient initials and NAIROS screening ID.
- The data were converted to 16 bit signed integers, giving flow rate and time data in real world units (millilitres per second and milliseconds respectively), one measurement after the other. Because time data were stored as unsigned rather than integers, this resulted in overflow of time data, corrected as described below.
- The number of measurements that existed in the file were counted (identified by the presence of a 151-sample stamp, samples 25-150 of which were identical, at the beginning of each).
- Files were separated into measurements (without the stamp described above).

Extracting flow and time data

- Measurements were separated into left side (the first half of samples) and right side (the second half of samples).
- Left side and right side data were separated into their flow rate (odd-numbered samples) and time (even-numbered samples) components.
- For measurements longer than 1638 samples, the 1639th time sample fell by 65516 and then began counting up again, caused by the way in which the data were saved and read (unsigned time data read as signed). This was corrected by adding 65516, plus the mean of the difference between the first 1638th samples rounded to the nearest integer, to the 1639th sample onwards.
- Time data were divided by 1000 to give units in seconds rather than milliseconds.
- The sample rate was calculated by dividing 1 by the mean of the differentiated time series.

Filtering flow data

- Flow data were filtered forwards and then backwards with a 0.2 second, unity gain triangle filter (using MATLAB's *filtfilt* function). The number of samples in the filter kernel was 0.2 multiplied by the sample rate, rounded to the nearest integer. The filter kernel was created using MATLAB's *triang* function for this many samples, then divided by its sum to give unity gain.

Calculating volume

- Volume data were calculated by integrating unfiltered flow rate data with respect to time series data using MATLAB's *cumtrapz* function.

Calculating tidal volume

- For total, filtered, inhalation only flow data, the sample numbers where flow equalled zero (i.e. exhalation samples set to zero in 7.b above) were extracted and differentiated. Those where the differentiated value did not equal 1 gave the sample numbers of the starts of inhalations.
- This was repeated for total, filtered, exhalation only flow data, giving the starts of exhalations (i.e. the ends of inhalations).
- The start and end samples were combined with those identified above.

- Unfeasibly fast transitions, i.e. those where the inhalation lasted less than 1 second, were removed by excluding the second sample in pairs closer together than that.
- The first and last samples were removed in case the flow measurement started and/or ended part way through an inhalation.
- This gave the sample numbers of transitions between full inhalations and exhalations.
- The unfiltered, bi-directional flow rate data was then integrated between each pair of samples to give the volume between each.
- The tidal volume was calculated as the median value of those where this volume was above zero (inhalations).