Title : **In-vivo and in-vitro Evaluation of the 5 French Neonatal Gastric Tonometer**

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DECLARATION

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Abstract

Introduction - Gastrointestinal tonometry has been widely used in adult practice for the early detection of shock and multi-organ failure. Its application in paediatrics has been limited by unsuitably large tonometers and doubt about the accuracy of measurements when saline is used as a tonometric fluid / vehicle for carbon dioxide (CO_2) equilibration.

Objective - To evaluate the accuracy and reliability of the newly developed saline 5 French (5F) neonatal gastric tonometer.

Study Design - (a) Direct in-vivo comparison of the 5F 0.9%saline tonometer (NST) with the recirculating gas tonometer (RGT) [the current reference standard in adult practice] in 10 Paediatric intensive care unit (PICU) patients, measuring tonometric PCO_2 ($PtCO_2$) and gastric intramucosal PCO_2 ($PiCO_2$).

(b) In-vivo comparison of $PiCO_2$ measurements from two 5F tonometers in 10 PICU patients in unfed and fed state.

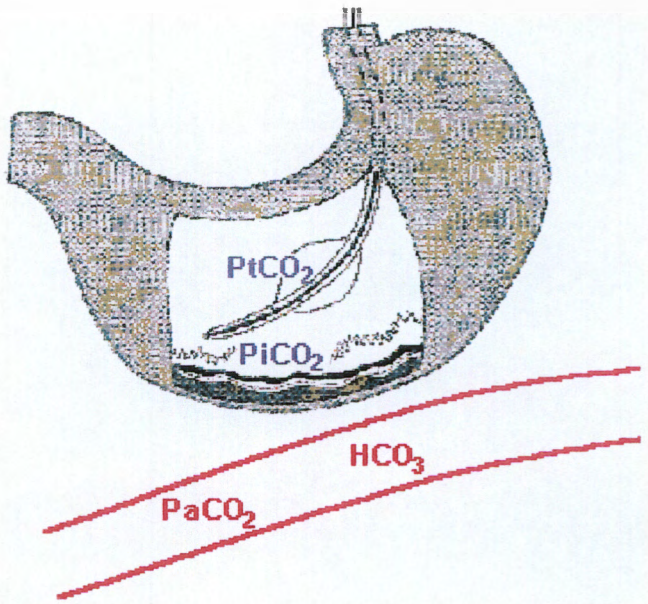
(c) In-vitro comparison of reference PCO_2 to $PtCO_2$ values obtained using 0.9%saline and phosphate buffered saline in 5F tonometers, and the RGT.

Results - (a) Comparing the 5F NST to RGT in 50 paired simultaneous measurements over $PtCO_2$ range 3.0 - 9.7kPa, the mean bias was -1.44kPa; limits of agreements (LOA) ±1.45kPa. The mean values of $PtCO_2$-derived gastric intramucosal pH (pHi) and $PiCO_2$-$PaCO_2$ difference differed significantly by -0.11 and +1.10kPa respectively ($p<0.0001$).

(b) 100 paired 5F NST measurements (50 fed / 50 unfed) over $PtCO_2$ range 2.48-11.1kPa were assessed. No significant difference was observed in $PtCO_2$: mean difference(standard deviation) - unfed 0.05kPa (0.36) ($p=0.36$); fed 0.05kPa (0.42) ($p=0.43$).

(c) 20 consecutive measurements of $PtCO_2$ were obtained from the 5F NST, 5F phosphate buffered saline tonometer (PBST) and RGT at constant reference PCO_2's of 2.5, 5.0, 7.5, 10.0kPa. The 5F NST underestimated the reference PCO_2 by a mean bias of 58% (LOA ±20%); the 5F PBST by 6% (LOA ±26%); while the RGT performed best with a mean bias of 5.7% and tight LOA ±1.5%.

Conclusion - There are inherent problems in the methodology of the saline tonometry utilised in the 5F neonatal gastric tonometer. The use of the saline 5F neonatal gastric tonometer to monitor gut perfusion in neonates and children should be interpreted with caution. Recirculating gas tonometry is the most accurate method of tonometry studied.



- $PiCO_2 = PtCO_2$ X time-dependent factor

- gastric intramucosal pH = pHi

- $pHi = 6.1 + \log \frac{[\text{arterial } HCO_3]}{0.03 \text{ X } PiCO_2}$

- gastric intramucosal-arterial PCO_2 difference = $PiCO_2$-$PaCO_2$ difference = PCO_2 gap

Background and Literature Review

Gastrointestinal tonometry is a simple, minimally invasive technique of monitoring hepatosplanchnic perfusion which has been widely used in adult practice for the early detection of shock and multi-organ failure[1-4], and which may be a better prognostic indicator than either conventional biochemical parameters or haemodynamic indices[4]. Tonometry is based on the principle that, at equilibrium, the partial pressure of a diffusible gas, such as carbon dioxide (CO_2), is the same in both the wall and the lumen of a viscus. Gastric tonometry can therefore measure the gastric intramucosal partial pressure of CO_2 ($PiCO_2$) by measuring the intraluminal PCO_2. During steady state, $PiCO_2$ reflects the balance between CO_2 production by gastric tissue and CO_2 removal (washout) by gastric/splanchnic blood flow. Decreases in splanchnic blood flow, with associated decreases in gut perfusion, can result in tissue hypoxia, anaerobic glycolysis, and tissue acidosis reflected in the intestinal and gastric mucosa by increases in tissue concentrations of Hydrogen ions (H^+) + CO_2 [5].

Gastric tonometry involves the sampling of CO_2 from a semi-permeable silicone balloon sited within the stomach on a blind-ending dual lumen nasogastric tube. Because of the easy diffusibilty of CO_2, the balloon PCO_2 ($PtCO_2$) becomes equal to the gastric intramucosal PCO_2 ($PiCO_2$) after a period of equilibration[1 3]. The length of this period of equilibration depends on the vehicle (e.g. 0.9%saline, air) used to carry the CO_2, as well as the diffusion properties of the balloon itself[1]. The $PiCO_2$ may be used to calculate the gastric intramucosal pH (pHi) according to the Henderson-Hasselbalch equation[1 3] : pHi = 6.1 + log[arterial bicarbonate/(0.03 X $PiCO_2$)].

The pHi has been shown in many studies to hold prognostic value[1-4 6-9 25 26]. Unfortunately pHi relies on the often incorrect assumption that gastric mucosal bicarbonate (HCO_3) always equilibrates the systemic arterial HCO_3 [5]. $PiCO_2$ is also influenced directly by the systemic arterial PCO_2 ($PaCO_2$). The gastric intramucosal-arterial PCO_2 difference ($PiCO_2$-$PaCO_2$ difference) is believed to be more accurate than pHi[10], as it is not changed by remote systemic acid-base metabolic disturbances. The $PiCO_2$-$PaCO_2$ difference is assumed to have the same prognostic value as pHi.

Gastric tonometry has traditionally utilised saline as the CO_2 vehicle within the tonometer balloon, but due to inherent errors in the measurement of dissolved CO_2, this method has been largely superseded by recirculating gas tonometry (utilises air as the CO_2 vehicle) as the reference standard in adult practice[3 11 12]. Further critical analysis of the methodology of gastric tonometry is addressed later in the "Discussion". It is better sited there as reference can be made to the present study as well.

An adapted 7 French (7F) tonometer, originally designed for adult sigmoid placement, has been employed in children in place of the impractical larger standard adult 14 French (14F) tonometer. Only a few reports have evaluated gastric tonometry in paediatric practice (table 1), with the total number of paediatric cases studied in the literature being 228. All these studies have used saline as the CO_2 vehicle and all have used the adapted 7F tonometer.

Nearly all the paediatric tonometry studies have used pHi changes as their predictor of prognosis or outcome[8 9 13 – 17]. This is essentially for historical reasons. When these studies were performed, pHi was the accepted predictive marker in adult practice. Four of the six paediatric studies using pHi as a measure of outcome found it to hold predictive value[8 9 13 15]. In the studies of Hatherill M[8] (24 patients – septic shock), Casado-Flores J[9] (51 patients – post surgery, sepsis, trauma, respiratory), and Krafte-Jacobs B[13] (8 patients – septic shock) mean pHi values of < 7.30 – 7.32 were predictive of poor outcome. Calvo C[15] (30 patients – mostly post cardiac surgery) found a mean pHi < 7.30 at any stage to be predictive of serious haemodynamic complications, such as shock or cardiac arrest.

Two studies, Duke TD[16] (19 septic patients) and Wippermann CF[17] (35 post cardiac surgery patients), found pHi to be of no predicitve value. Duke TD[16] found that neither the pHi values, nor the trends, predicted outcome. In fact, they found that raised lactate levels (> 3mmol/L) within the first 24 hours of admission a better marker of outcome. In the post cardiac surgery patient group of Wippermann CF[17], the pHi values did not differentiate for patients developing post-operative organ dysfunction.

Only one 'enlightened' paediatric study used $PiCO_2$-$PaCO_2$ difference as a predictive marker – Duke T[18]. All 20 paediatric patients were receiving extra-corporeal membrane oxygenation (ECMO) therapy during the study period (i.e. a highly selective and ill patient group). 12 of the 20 children died, 7 during ECMO and 5 thereafter (2 - 30 days post ECMO). Duke T[18] found a high mean $PiCO_2$-$PaCO_2$ difference (23.6 mmHg; 95% confidence intervals: ± 9.4 mmHg) predictive of mortality. Compared to this, survivors had a much lower mean $PiCO_2$-$PaCO_2$ difference (4.7 mmHg; 95% confidence intervals: ± 5.4 mmHg). Animal and adult studies have shown $PiCO_2$-$PaCO_2$ difference values > 25 – 35 mmHg to indicate gut ischaemia[5 10]. The normal range for $PiCO_2$-$PaCO_2$ difference in adults is 3 – 10 mmHg[10 35]. Future paediatric studies will undoubtedly concentrate on $PiCO_2$-$PaCO_2$ difference as a predictive index.

Reinosa-Barbero F[19] set out to establish a normal reference range for pHi in children. All the 17 patients were in good health and underwent short minor surgical procedures. Normal pHi was reported as 7.35 ± 0.06 (mean / SD).

Although 12 of the 20 ECMO patients in the study of Duke T[18] were in the neonatal age group, the only study using a specifically neonatal patient group was that of Booker PD[14]. 24 neonates with congenital heart disease (age range: 3 – 57 days; mean weight 3.35kg) were studied before, during and after cardiac surgery with cardiopulmonary bypass. They concluded that neonates requiring aortic arch surgery may be at risk of gut hypoxia in the peri-operative period. They forwarded a pHi < 7.33 as indicating gut mucosal hypoxia.

All the paediatric studies thus far have been observational studies, with none evaluating management strategies based on gastric tonometer measurements. No complications of gastric tonometry have been reported in any of these paediatric studies.

It has recently been suggested that gastric tonometry may provide neonatologists with an "early warning" monitoring tool for the detection of necrotising enterocolitis (NEC)[20 21]. A case report by Hatherill M, Tibby SM et al [20] described a 2 day old term neonate (birth weight 3.2kg) with Hypoplastic Left Heart Syndrome whose persistently low pHi (< 7.32) predated the clinical onset of NEC by 4 – 6 hours.

This has coincided with the development of a 5 French (external diameter 1.7mm) gastric tonometer (Tonometrics, Datex-Engstrom Division, Helsinki, Finland), which because of its appropriately small size, is suitable for neonatal use. The new 5 French (F) gastric tonometer has the added advantage that it has a double lumen, so that along with the tonometer, it also contains an independent feeding/aspiration lumen and port. Thus negating the need for a separate nasogastric tube in these patients. The new 5F neonatal device relies upon saline as the CO_2 vehicle. The small size of this 5F gastric tonometer's balloon (1cc) has made it technically impossible at this stage for recirculating gas tonometry to be utilised. Its size therefore necessitates the use of saline as the CO_2 vehicle. It is marketed as a saline gastric tonometer.

Table 1: Published results from Gastric tonometry in Paediatric practice

Authors et al	No. patients	Patient group	Comment/Prediction
Krafte-Jacobs B [13] 1995	8	Septic shock Paediatric	Non-survivors: mean pHi 7.32 +/-0.18* Survivors: mean pHi 7.48 +/-0.07*
Booker PD [14] 1996	24	Cardiac surgery Neonatal	Neonates undergoing aortic arch surgery at risk of gut hypoxia following cardiopulmonary by-pass
Calvo C [15] 1997	30	Post surgery, sepsis Paediatric	pHi < 7.30 a predictor of haemodynamic complications
Duke TD [16] 1997	19	Septic shock Paediatric	Neither absolute pHi nor trend in the first 48 hours was predictive of outcome
Wippermann CF [17] 1997	35	Cardiac surgery Paediatric	pHi did not differentiate for patients who developed post-operative organ dysfunction
Duke T [18] 1997	20	on ECMO Paediatric	High mean $PiCO_2$-$PaCO_2$ difference was a good predictor of death (23.6 mmHg +/-9.4†)
Hatherill M [8] 1998	24	Septic shock Paediatric	Persistent pHi < 7.32 at 6 hours of PICU admission associated with poor prognosis
Casado-Flores J [9] 1998	51	Critically ill Paediatric	At any time pHi < 7.30 : predictor of mortality
Reinosa-Barbero F [19] 1998	17	Minor surgery Paediatric	Normal pHi 7.35 +/-0.06*

* *mean / SD*

† *mean / 95% confidence interval*

Plate 1 shows the adult 14F tonometer, the 7F tonometer and the new 5F gastric tonometer

In view of the potential application of this device to neonatal and paediatric practice, the accuracy and reliability of the 5F saline tonometer has been evaluated, in the first instance by direct in-vivo comparison with the current reference standard[3 10 12], the recirculating gas tonometer (Datex-Ohmeda, Helsinki, Finland), in a heterogeneous group of critically ill infants and children. Based on these findings, the sources of error in the measurement of $PiCO_2$ using this device, including the influence of gastric content, sampling technique, CO_2 vehicle, and the CO_2 analyser have been further investigated, both in-vivo and in an in-vitro model. Clarification of these issues may help standardise the interpretation of tonometric data before the 5F gastric tonometer becomes widely used in neonates and infants.

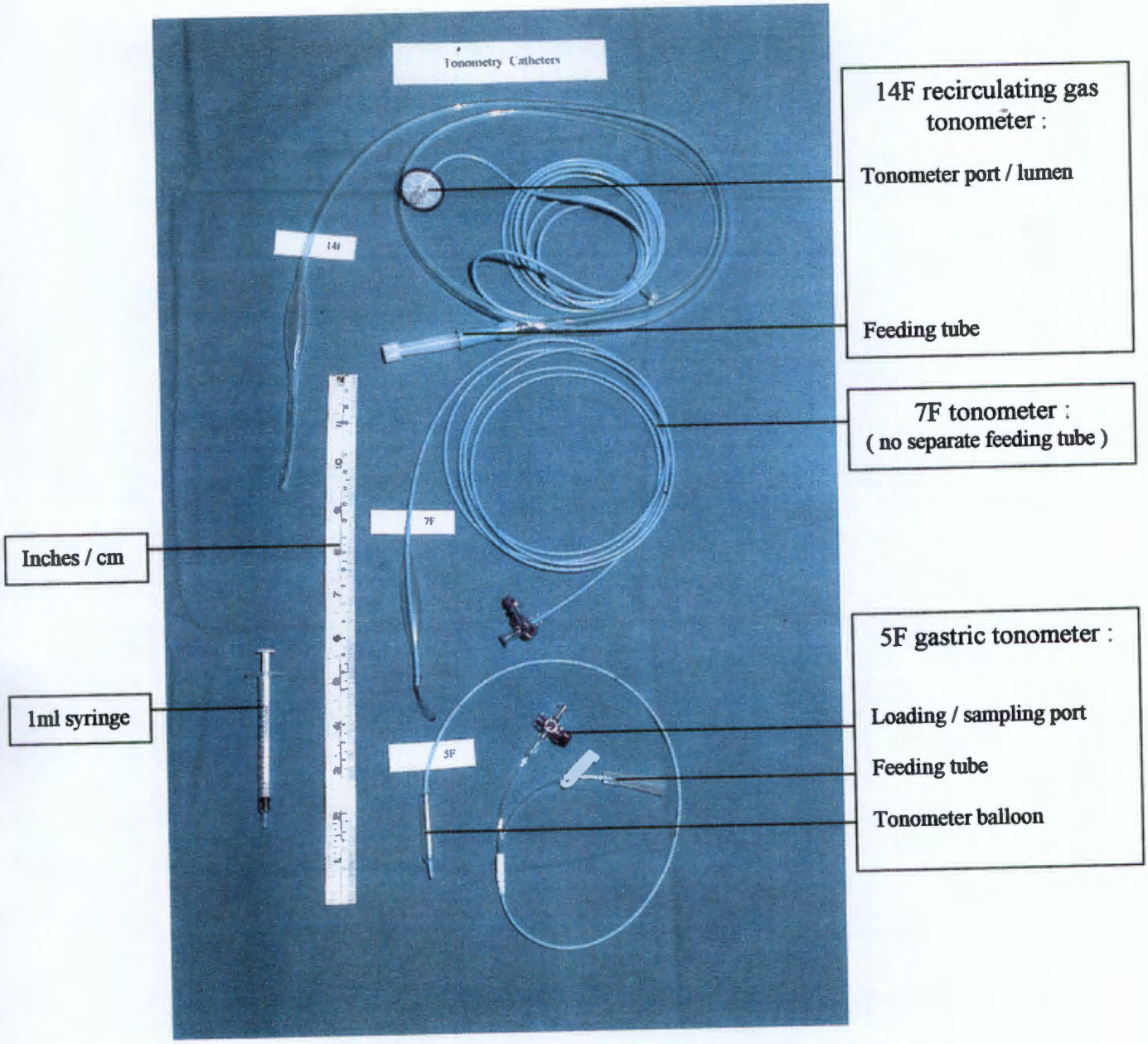


Plate 1: An adult 14F gastric tonometer, a 7F tonometer and the new 5F gastric tonometer

Patients and Methods

The study was approved by the Guy's Hospital's Ethics Committee, and the Postgraduate Programmes Committee of the Faculty of Medicine of the University of Cape Town.

The study comprised 3 stages:

a) 5F 0.9%saline tonometer vs recirculating gas tonometer in vivo.

b) Dual 5F 0.9%saline tonometers in vivo, both with and without enteral feeding.

c) 5F 0.9%saline tonometer, 5F phosphate-buffered saline tonometer and recirculating gas tonometer vs known reference PCO_2 in vitro.

The in-vivo components of the study were performed in the Caleb Paediatric Intensive Care Unit at Guy's Hospital in London :- 16 bed unit (with capacity to ventilate 16 patients) encompassing all aspects of medical, surgical and cardiac paediatric intensive care, including extra-corporeal membrane oxygenation (ECMO).

Informed parental consent was obtained prior to the in-vivo components.

Plate 1 illustrates the different gastric tonometers used in the study so an appreciation of their relative sizes may be gained (with a 1ml syringe on the left for comparison).

All patients were monitored by routine gastric tonometry. The gastric tonometer, which is essentially a modified dual lumen nasogastric tube, is inserted into the stomach via the nasogastric or orogastric route as one would insert a feeding tube. The length for insertion is measured by the same standard methods used for nasogastric or orogastric feeding tubes. Confirmation of placement in the stomach is by the usual aspiration of acidic gastric contents and/or radiological confirmation. No analgesia, anaesthesia nor sedation is required for the insertion or monitoring of there tonometers. In fact the separate feeding/aspiration lumen of the 5F gastric tonometer functions as the nasogastric or orogastric tube for the patient.

The design of this study evaluated the new 5F neonatal gastric tonometer and was not primarily involved in determination of clinical outcome.

a) ***5F 0.9%Saline tonometer (NST) vs recirculating gas tonometer (RGT) in vivo.***

Ten intubated and ventilated children, median age 13 months (range 1 day - 6 years) and median weight 10.2 kg (range 4.1 - 20 kg), were enrolled after stabilisation in the paediatric intensive care unit (PICU). Their diagnoses included meningococcal disease (n=4), pneumonia (n=2), cardiac surgery (n=3), and head injury (n=1). Patients were haemodynamically stable and had no active interventions nor ventilatory changes performed during the 6 hour study period. In each patient a 5F NST and a 7F RGT were placed in the stomach by the orogastric route, inserted as one would insert an orogastric feeding tube. The ends of the two tonometers were tethered together to ensure that the silicone balloons were sited in the same area in the stomach, and their position was confirmed radiologically prior to commencement of the study.

The 7F RGT was used in place of the significantly larger standard 14F adult RGT because of the small size of our patients. The 7F RGT and the 14F RGT have been shown to behave similarly and give the same measurements when compared with each other[31].

Plate 2 illustrates the positions and size of the two tonometers in one of the study patients.

All patients, when not enterally fed, received sucralfate but not histamine-2 (H-2) antagonists.

The balloon of the NST was loaded according to the manufacturer's instructions with 1 ml normal saline. After a 60 minute equilibration period the first 0.4ml was aspirated and discarded to account for dead space. Gastric intramucosal CO_2 ($PiCO_2$), equivalent to the tonometer CO_2 ($PtCO_2$), was measured in the remaining 0.6ml aspirate, using the IL BGE blood gas analyser (Instrumental Laboratories, Lexington, USA). A strict anaerobic sampling technique was maintained to minimise CO_2 loss. Meticulous care was taken not to introduce any air into the sample and to remove any immediately. All samples were analysed within 2 minutes of aspiration. The same person took all the samples. All saline $PtCO_2$ measurements were then corrected by the 60 minute time-dependent factor of 1.13 recommended by the manufacturer[22] to allow for incomplete equilibration. Full equilibration for normal saline takes 90 minutes[22]. The manufacturer has derived time-dependent factors by directly measuring the PCO_2 within the tonometer balloon over time against known external PCO_2 values.

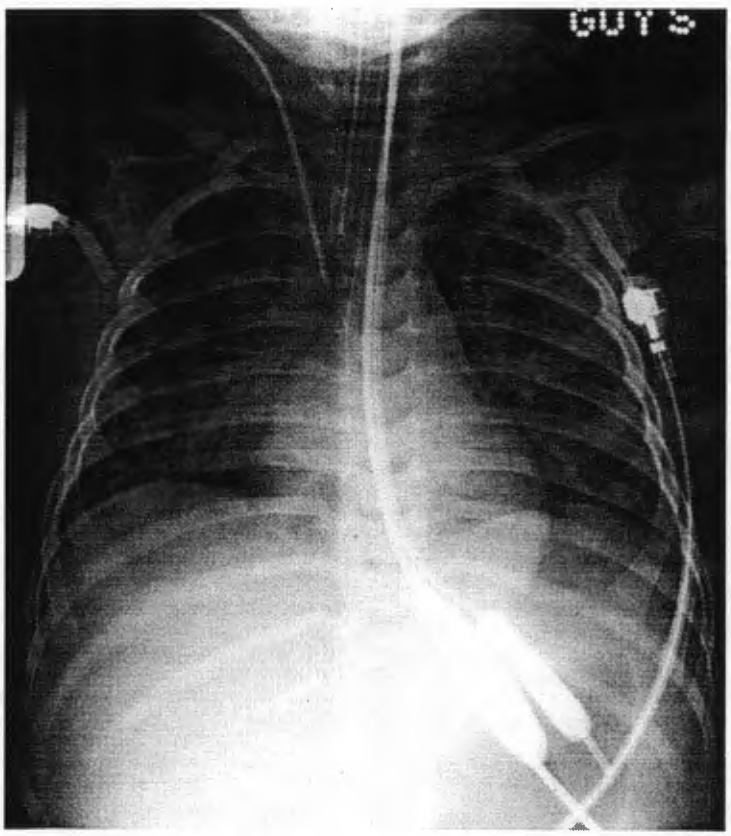


Plate 2: Xray showing a 7F and a 5F tonometer (contrast enhanced) in-situ in one of the study patients.

In the case of the RGT, a specialised capnograph (Tonocap, Datex, Helsinki, Finland) utilising infrared absorbence spectrometry was used to measure the PCO_2 of the 6ml of air it re-circulated through the tonometer balloon, following a 10 minute dwell time (i.e. equilibration period). No time-dependent factor is required for RGT. The average RGT measurement was taken for the 60 minute equilibration period required for the NST.

Five simultaneous paired measurements, each following a 60 minute equilibration period, were taken in each patient. With each paired tonometer reading, an arterial blood gas was taken anaerobically for corresponding arterial CO_2 ($PaCO_2$) and serum bicarbonate (HCO_3) levels, and measured by the same blood gas analyser. All saline and blood samples were temperature corrected when processed in the blood gas analyser. A total of 50 paired tonometer readings were taken. Gastric intramucosal pH (pHi) and the $PiCO_2$-$PaCO_2$ difference (PCO_2 gap) were derived from the measured $PiCO_2$ values using each modality (NST and RGT).

(b) ***Dual 5F 0.9%saline tonometers (NST) in vivo, before and after enteral feeding***.

A further 10 intubated and ventilated PICU patients were studied, median age 3.25months (range 1 day - 11months) ; median weight 3.5kg (range 2.5 - 5.5kg). Diagnoses included cardiac surgery (n=5), bronchiolitis (n=3), pneumonia (n=1), and pre-operative hypoplastic left heart syndrome (n=1). Two 5F NST's with their ends tethered together were placed in the stomach by the orogastric route as previously described.

Plate 3 illustrates the position and size of the two 5F NST's in one of the study patients.

Ten simultaneous paired measurements were taken, each following a 60 minute equilibration period, 5 with the patient unfed and 5 after the institution of enteral feeding - median feed volumes 2ml/kg/hour (range 1 - 4ml/kg/hour). Measurements were taken on average 8 hours (range 6-12 hours) after feeding had been established. A total of 100 paired $PiCO_2$ measurements were taken (50 unfed and 50 fed), along with the corresponding arterial blood gas parameters, and corrected by the time equilibration factor as described.

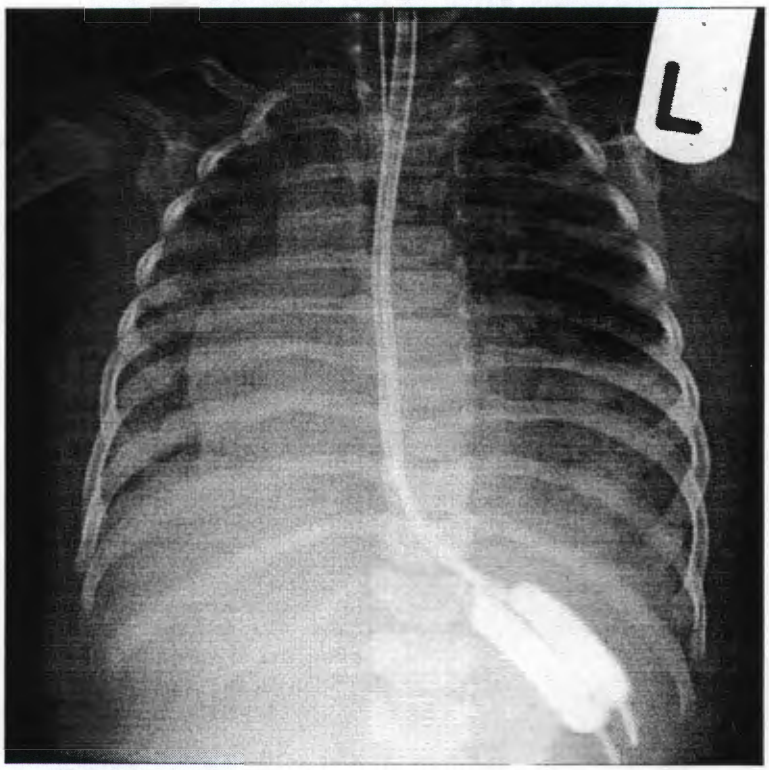


Plate 3: Xray demonstrating two 5F tonometers (contrast enhanced) in-situ in one of the study patients.

c) ***5F 0.9%Saline tonometer (NST), 5F phosphate-buffered saline tonometer (PBST) and recirculating gas tonometer (RGT) vs reference PCO_2 in vitro.***

A sealed equilibration chamber containing 0.9% Saline was maintained at 37°C. CO_2 was bubbled through the saline and kept at constant reference PCO_2's of 2.5, 5.0, 7.5 and 10.0 kPa. The PCO_2 was monitored and maintained at these levels using a Paratrend 7 probe (Biomedical Sensors, High Wycombe, UK) in the chamber saline.

Prior validation of the Paratrend 7 probe against known concentrations of CO_2 in saline using in-line capnography (Ultima, Datex-Ohmeda, Helsinki, Finland) gave an equation of :

$y = 0.91x + 0.49$ ($r^2 = 0.99$).

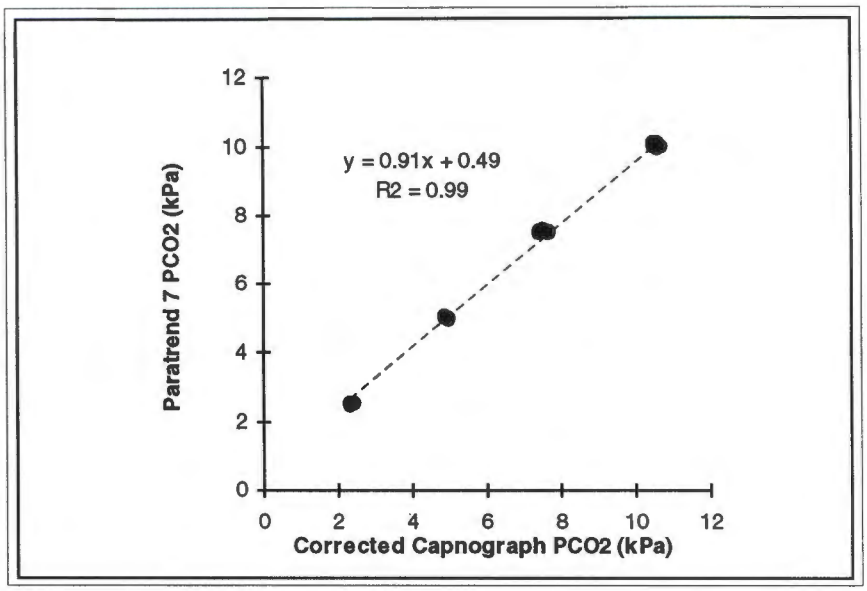


Figure 1 : Correlation plot of capnographic PCO_2, corrected for humidification, against the PCO_2 measured by the Paratrend 7 in the equilibration chamber saline

The Paratrend 7 probe is a multi-parameter intra-arterial sensor (MPIAS) that allows continuous accurate and reliable intra-arterial monitoring of temperature, pH, PO_2 and PCO_2. A signal light beam is sent down optic fibres and a stainless steel mirror at its tip reflects the altered light beam back up the optic fibres to the detectors - i.e. a miniature spectrophotometer. The CO_2 sensor is enclosed within a gas-only permeable membrane and encapsulated within is a bicarbonate solution containing phenol red dye as an indicator. CO_2 diffuses across the membrane and alters the pH of the solution. The PCO_2 is measured by measuring the absorbency of green light by the red dye.

Two 5F neonatal gastric tonometers and a standard adult 14F RGT were positioned in the saline chamber with their distal ends tethered together. Normal saline (0.9%) was utilised as the CO_2 collection vehicle in the first 5F tonometer (NST) and phosphate-buffered saline in second 5F tonometer (PBST). The PBST fluid contained NaH_2PO_4 44mmol and Na_2HPO_4 6mmol, adjusted to pH 6.0 (saline has pH 6.2). The 14F RGT was used as this tonometer is the established reference standard in adult practice[3 11 12].

Figures 2 and 3 illustrate the in-vitro study apparatus.

Loading, sampling and $PtCO_2$ analysis for saline and gas tonometers was as previously described.

Twenty consecutive measurements of $PtCO_2$, each following a 60 minute equilibration period, were obtained from the NST, PBST, and the RGT, with a constant reference PCO_2 of 2.5 kPa in the saline chamber as determined by the Paratrend 7 sensor. This process was repeated for equilibration chamber / bath saline reference PCO_2 levels of 5.0, 7.5, and 10kPa respectively. All NST and PBST PCO_2 readings were corrected by the manufacturer's (Tonometrics) 60 minute time-dependent factor of 1.13 and 1.11 respectively[22]. With each $PtCO_2$ measurement, a sample of the bath saline was anaerobically aspirated and PCO_2 was measured by the same blood gas analyser. The bath saline PCO_2 values were not corrected, as the time-dependent factors relate to equilibration periods of the saline tonometers only.

Statistical Analysis :

In-vivo: Data were analysed using Student's paired t-test, Mann-Whitney U test and the Chi square test. Comparison of recirculating gas tonometry with saline tonometry was by the Bland and Altman method[23].

In-vitro: Data were analysed by linear regression and the Bland Altman method[23], and were logarithmically transformed where appropriate.

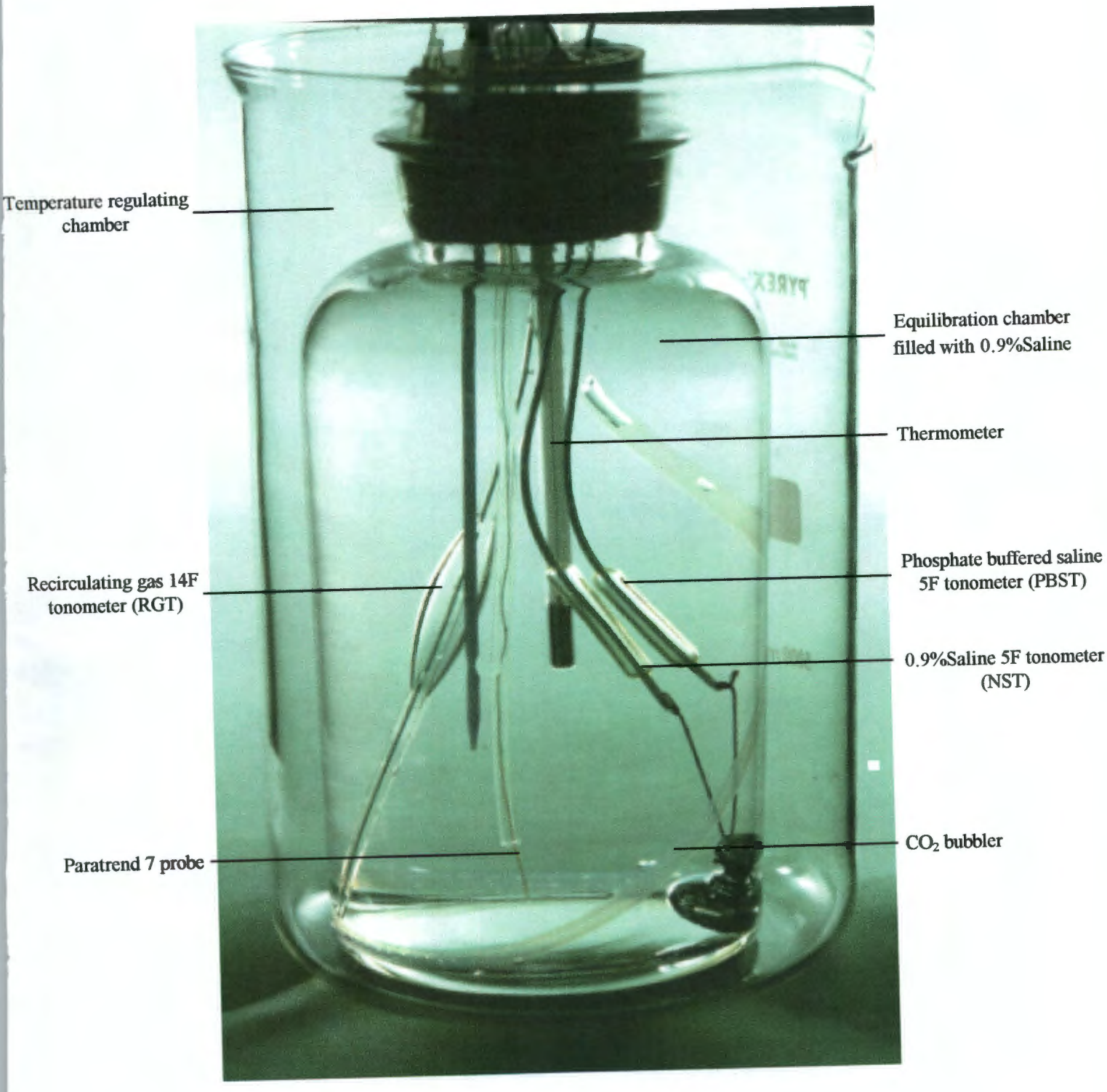


Figure 2 : In-vitro study apparatus - close-up view

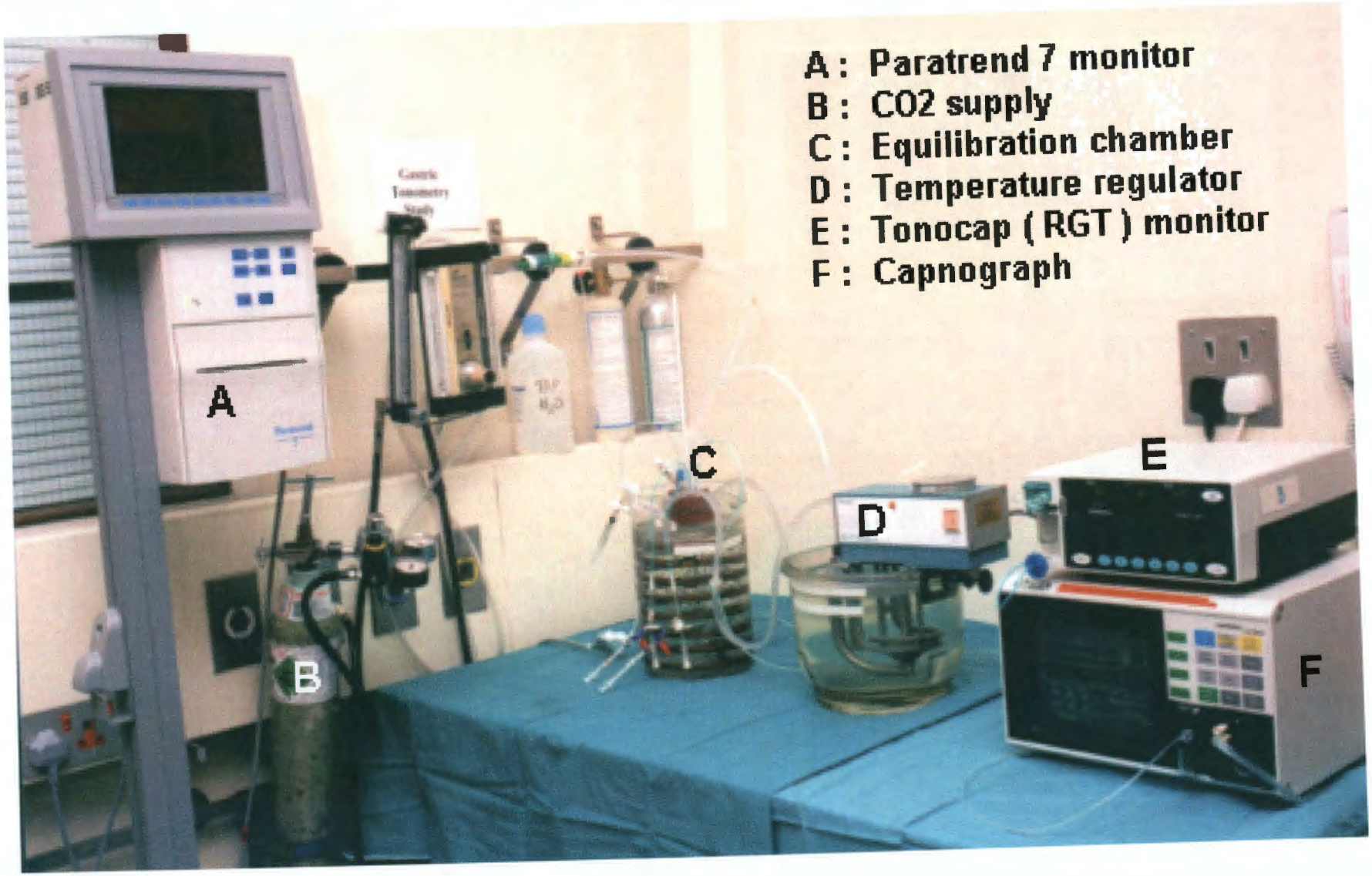


Figure 3 : Overview of the in-vitro study apparatus

Results

a) ***5F 0.9%Saline tonometer (NST) vs recirculating gas tonometer (RGT) in vivo.***

Figure 4 illustrates the Bland-Altman plot of $PiCO_2$ for the RGT (reference standard) against those simultaneously measured by the 5F NST over the range 3.0 - 9.7kPa. The figure shows poor agreement between the two methods, with a wide scatter across the range measured (Mean bias: -1.44kPa; 95% confidence interval of mean bias: -1.65 to -1.23; with limits of agreement (LOA) ±1.45kPa).

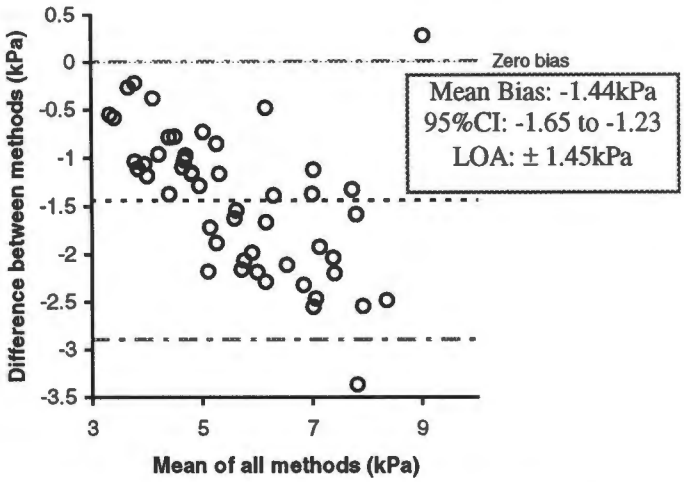


Figure 4 : Bland Altman plot of gastric intramucosal PCO_2 ($PiCO_2$) for the recirculating gas tonometer (RGT) against the 5F 0.9%saline tonometer (NST).
95%CI = 95% confidence interval of the mean bias LOA = limits of agreements

Table 2 shows the mean [standard deviation/SD] tonometric PCO_2 ($PtCO_2$ = $PiCO_2$) along with its derived pHi and $PiCO_2$-$PaCO_2$ difference (PCO_2 gap) for RGT and NST. Comparing RGT to NST, the mean values differed significantly by: $PtCO_2$ +1.44kPa; pHi -0.11; PCO_2 gap +1.10kPa. Both tonometers did however demonstrate similar increased or decreased trends in their $PiCO_2$ in 95% (38/40) of cases.

Table 2 : Comparison of tonometer PCO_2 ($PtCO_2$), their derived pHi and $PiCO_2$-$PaCO_2$ difference (PCO_2 gap) between the recirculating gas tonometer (RGT) and 5F 0.9%saline tonometer (NST) - shown as: mean [± 1 standard deviation]

	RGT	NST	Difference	p Value
$PtCO_2$ (kPa)	6.38 [±1.67]	4.94 [±1.28]	1.44 [±0.74]	0.0001
pHi	7.26 [±0.13]	7.37 [±0.12]	0.11 [±0.04]	0.0001
PCO_2 gap (kPa)	1.79 [±1.20]	0.73 [±0.70]	1.06 [±1.01]	0.0001

b) ***Dual 5F 0.9%saline tonometers (NST) in vivo, before and after enteral feeding.***

In the unfed state, over the range of tonometric $PiCO_2$ 2.42 - 11.1kPa (median 4.73 kPa), the mean difference between the two saline tonometers was 0.05 kPa (SD 0.36kPa) . In the fed state over the range 2.48 - 8.71 kPa (median 4.71 kPa), the mean difference between the tonometers was 0.05 kPa (SD 0.42kPa). There was no significant difference noted between the tonometers in either the unfed or fed state (p=0.36 and p=0.43 respectively). Both tonometers followed the same increased or decreased trend in their $PiCO_2$ in 75% (30/40) of cases in the unfed state, and in 68% (27/40) of cases in the fed state (Chi^2 p = 0.82).

c) ***In-vitro: 5F 0.9%Saline tonometer (NST), 5F phosphate-buffered saline tonometer (PBST) and recirculating gas tonometer (RGT) vs reference pCO_2.***

The performance of the 3 tonometers is shown in figures 5, 6, 7, 8 ; table 3 and table 4.

Figure 5 shows a correlation plot of reference PCO_2 against $PtCO_2$ of RGT, PBST, NST and the Bath saline. Linear regression of $PtCO_2$ values derived from each modality yields equations of $y = 0.97x-0.13$ ($r^2 = 0.99$) for the RGT, $y = 0.78x+0.82$ ($r^2 = 0.97$) for the PBST, $y = 0.59x+0.18$ ($r^2 = 0.98$) for the NST, and $y = 0.61x+0.25$ ($r^2 = 0.97$) for Bath saline.

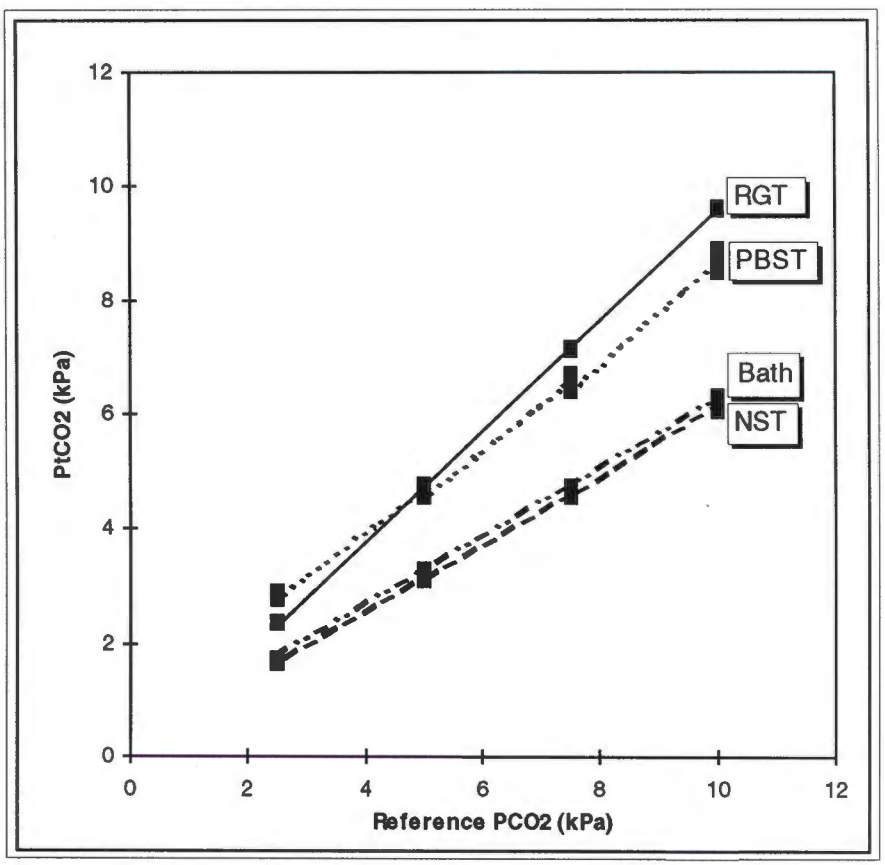


Figure 5 : Correlation plot of reference PCO_2 against the recirculating gas tonometer (RGT), 5F phosphate buffered saline tonometer (PBST), 5F 0.9%saline tonometer (NST) and bath saline (Bath)

Figures 6, 7 and 8 illustrate the Bland Altman plots for RGT, PBST and NST respectively against the reference PCO_2 values.

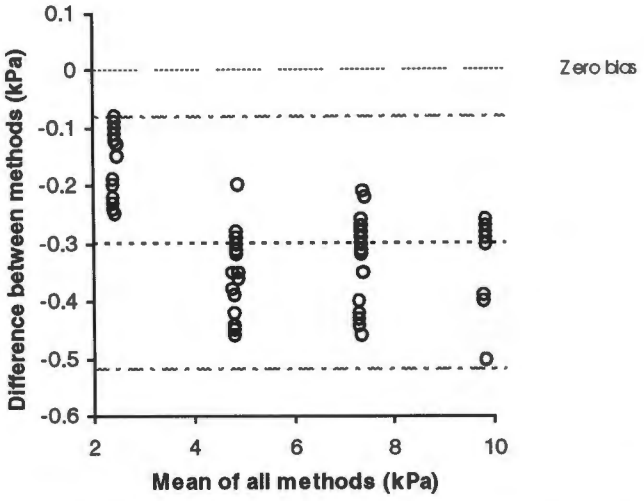


Figure 6 : Bland Altman plot of $PtCO_2$ of RGT against the reference PCO_2 values

Figure 6 shows good agreement between the $PtCO_2$ for RGT and the reference PCO_2, noting that the y-axis (difference between RGT and reference PCO_2) is in units of only 0.1kPa.

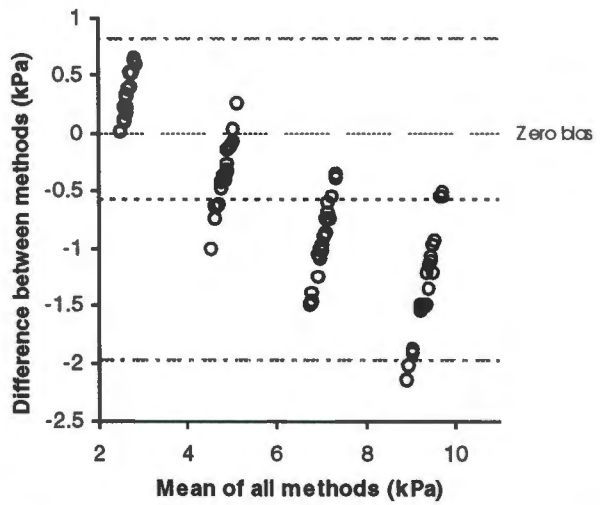


Figure 7 : Bland Altman plot of $PtCO_2$ of PBST against the reference PCO_2 values

Figure 7 shows initial moderate agreement between PBST and the reference PCO_2, with increasing underestimation and widening scatter as the reference PCO_2 increases past 5kPa.

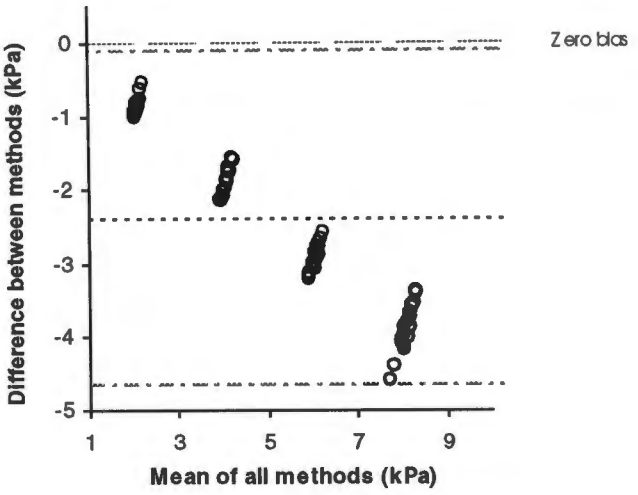


Figure 8 : Bland Altman plot of $PtCO_2$ of NST against the reference PCO_2 values

Figure 8 shows poor agreement, progressively worsening negative bias and scatter of NST $PtCO_2$ measurements as the reference PCO_2 increases.

Both PBST and especially NST demonstrate increasing underestimation/negative bias of $PtCO_2$, along with widening limits of agreements (LOA), with increasing reference PCO_2 levels (table 3). The corresponding measurement of the bath saline PCO_2, measured simultaneously with the tonometric $PtCO_2$'s, was also consistently lower than the reference PCO_2, and very similar to the performance of NST (figure 5 and table 3).

Table 3 : Mean PCO_2, mean bias, limits of agreement (LOA), in kPa, of each tonometer and Bath saline for each of the reference PCO_2 groups and overall

pCO2 group	2.5 kPa	5 kPa	7.5 kPa	10 kPa	Overall
RGT (mean)	2.36	4.67	7.14	9.63	5.96
Mean Bias	-0.15	-0.34	-0.37	-0.38	-0.31
LOA ±	0.17	0.11	0.22	0.22	0.25
PBST (mean)	2.84	4.67	6.55	8.7	5.69
Mean Bias	0.33	-0.34	-0.96	-1.31	-0.57
LOA ±	0.33	0.6	0.68	0.94	1.4
NST (mean)	1.68	3.16	4.6	6.15	3.95
Mean Bias	-0.83	-1.85	-2.91	-3.86	-2.36
LOA ±	0.22	0.35	0.39	0.63	2.27
Bath (mean)	2.04	3.43	4.84	6.31	4.15
Mean Bias	-0.47	-1.58	-2.67	-3.7	-2.11
LOA ±	0.21	0.29	0.34	0.72	2.41

After logarithmic transformation to compensate for the heteroscedasticity (lack of uniformity of variance), the overall relative bias of the NST, PBST and RGT compared to the reference PCO_2 values is shown in table 4, expressed as percentages for better clarity.

Table 4 : Mean bias, 95% confidence interval of mean bias (95% CI), limits of agreement (LOA) of the tonometric PCO_2 ($PtCO_2$) measurements from the recirculating gas tonometer (RGT), 5F phosphate buffered saline tonometer (PBST) and 5F 0.9%saline tonometer (NST) compared to the reference PCO_2 over the entire range of values

	Mean Bias	95% CI	LOA
RGT	5.7%	5.2 to 6.2%	± 1.5%
PBST	6%	3.0 to 9.0%	± 26%
NST	58.6%	56.4 to 60.8%	± 20%

Discussion

The principle of tonometry was first reported in 1959 by Boda and Muranyi who estimated $PaCO_2$ levels in ventilated children with polio by measuring intraluminal gastric CO_2 levels[24]. Since then the further application and clinical development of this technique has almost exclusively been in adult patients. Gastric tonometry has been widely used in adult practice to monitor the adequacy of hepatosplanchnic perfusion, using parameters such as $PiCO_2$, pHi or the $PiCO_2$-$PaCO_2$ difference, as indicators of shock, organ failure or mortality[6 10 25 26].

Recently adult physicians have begun to express concern over the use of 0.9%saline as the vehicle for tonometric studies, and phosphate buffered saline has been used in some centres to decrease the loss of dissolved CO_2[11 22 27]. It was also noted that underestimation of PCO_2 in saline varied with the type of blood gas analyser used[11 22 27 28]. For these reasons gastric tonometry in adult practice is changing from the saline vehicle to the recirculating gas technique[3 11 12 29].

Tonometry in infants and children has been limited by the size and construction of the available devices and all studies have used 0.9%saline in the balloon. It has been suggested that gastric tonometry may be used to detect the onset of necrotising enterocolitis in neonates[20 21]. For this reason the development of a 5F tonometer suitable for neonatal use is particularly welcome. This study sought to evaluate this neonatal 5F saline-based tonometer, both in-vivo and in an in-vitro model, in order to clarify the areas of difficulty highlighted by the adult experience[30]. Whether feeding influences their accuracy and reliability was also investigated.

In vivo (a) using the RGT as the reference standard, it was shown that NST consistently underestimates the $PiCO_2$ across the studied range (3.0 - 9.7kPa) by a mean bias of 1.44kPa (LOA ±1.45kPa). Accordingly the $PiCO_2$-$PaCO_2$ difference and pHi, which are derived from the $PiCO_2$, were both significantly different between RGT and NST ($p=0.001$). This is important to note since it is tonometer-derived pHi that has been shown to hold prognostic value[7 8 9 26]. Thus creating confusion as to which of the methods should be used for prognostication.

Whilst NST underestimated $PiCO_2$ compared to RGT, they both still paralleled the same trends in PCO_2. Therefore it might be more appropriate to follow trends in $PiCO_2$ rather than absolute values when utilising the NST.

Several factors may play a role in the apparent lack of accuracy in the measurement of $PiCO_2$ using the 5F neonatal NST. Dissolved CO_2 can be lost during aspiration from the tonometer balloon, especially if air is introduced into the sample. The natural instability of CO_2 in the saline medium allows for it to be easily and readily lost from solution. There is systematic underestimation of saline PCO_2 by the blood gas analyser. This may be due to calibration problems, insensitivity of the CO_2 probe to saline PCO_2, or the loss of dissolved CO_2 as the sample passes through the analyser. It was therefore attempted to isolate some of these components in our further evaluation of the device.

In vivo (b) two saline 5F neonatal tonometers were compared using an identical technique, to minimise the influence of the individual variation of each tonometer due to CO_2 loss. Recently presented adult work has suggested there may be a large discrepancy (in excess of 2.5kPa) between simultaneous measurements from two tonometers in the same stomach[31]. In this study population there was no significant difference between simultaneous NST measurements either in the unfed (mean difference 0.05kPa, SD 0.36kPa; p=0.36) or fed (mean difference 0.05kPa, SD 0.42kPa; p=0.43) state. Feeding did not appear to affect the two tonometers' ability to mirror each others trends in $PiCO_2$ ($Chi^2 = 0.82$).

There has also been controversy over the influence of gastric contents and H-2 antagonists on the measurement of $PiCO_2$[32-36]. It is not our unit's usual policy to place children who are nil per mouth on H-2 antagonists because of the perceived risk of nosocomial infection[37 38]. Their mandatory use is still contested[32 36]. The study patients were given sucralfate, which does not interfere with the interpretation of pHi measurements[39 40].

In vitro (c) it was demonstrated that the best method of tonometry studied is RGT (mean bias -5.7% LOA ±1.5%). NST underestimates PtCO2 by a large bias of 58% (LOA ±20%). It may be inferred that even with meticulous attention to sample handling the low stability of CO_2 in saline allows for easy loss from CO_2 in the sample. Although the considerable bias in the NST measurement of $PtCO_2$ is specific to the IL BGE blood gas analyser, other studies have demonstrated that other types of blood gas analyser may perform even less accurately with 0.9% saline[22 27].

Both the directly aspirated bath saline PCO_2 and the NST $PtCO_2$ were underestimated by a similar magnitude (figure 5 and table 3). This finding infers that this systematic error is related to CO_2 loss from the sample, and/or underestimation by the blood gas analyser, rather than the physical properties of the 5F neonatal tonometer.

It has been suggested that use of a phosphate buffered saline vehicle allows greater CO_2 solubility and stability, thus minimising CO_2 loss[11 22 27 28]. Although PBST only underestimated by a mean bias of 6%, the limits of agreement were even larger than NST (26% vs 20%), and considerably more than RGT (1.5%). In view of the difficulties involved in using PBST, such as preparation time and degradation of the solution, and its poor performance in-vitro, one may suggest that the phosphate buffered saline has little practical advantage over normal saline.

In comparison to both the NST and the PBST, RGT demonstrates both a small bias (5.7%) and tight limits of agreement (±1.5%), reiterating the adult experience that recirculating gas tonometry does not suffer from the problems encountered in saline tonometry[11 12 29]. This may also be due to the advantages of the in-built capnograph, which is reliable, easily recalibrated and accurate. The standardisation of these specially adapted capnographs (Tonocap monitors) has also allowed tonometric data from different centres to be comparable and baseline values to be set in adult practice.

Possible other solutions to overcome the problems in the saline tonometric technique are :-

1. The specific calibration of a specially designated blood gas analyser to be used solely for measuring saline samples.
2. The calculation (from linear regression equations) of correction equations specific to each blood gas analyser being used, to account for its inherent underlying bias.

Both of these solutions are essentially impractical.

3. Its use to monitor trends within the individual patient, rather than absolute or one-off values.

Although the 5F gastric tonometer was designed for use in neonates, it is also suitable for all ages and sizes. The size of the tonometer balloon does not affect its accuracy[11 22 31].

The 5F gastric tonometer has many advantageous features:-

Its size allows for tonometric monitoring of patients from 800 - 900grams body weight upwards;

It can easily be placed in the stomach by the nasogastric route (unlike the larger tonometers which require orogastric placement);

Its separate feeding/aspiration lumen and port serves as a conventional nasogastric tube;

It is made from polyurethane, which allows it to left in-situ for an extended period.

Conclusion :

This study has highlighted the problems inherent in the methodology of saline tonometry with the 5F neonatal gastric tonometer. It has shown that $PiCO_2$, and the derived variables pHi and $PiCO_2$-$PaCO_2$ difference, differ considerably depending on the method of tonometry.

Although recirculating gas tonometry is presently the most reliable and accurate method of tonometry, it is currently unavailable for neonates and small infants. Until this technology is developed, the use of saline tonometry to monitor gut perfusion in neonates or children should be interpreted with caution.

Indeed, it suggests that the saline technique, which is utilised in these 5F neonatal gastric tonometers, makes the interpretation and comparison of tonometric data from different centres virtually impossible, seeing that each centre's $PiCO_2$ results/measurements will be specific to their unit's blood gas analyser.

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Addendum

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Data (a) In-vivo RGT-NST

	NST uncor	cNST	RGT	PaCO2	art HCO3	Art pH	
							1
1	4.13	4.67	5.4	4.21	20.6	7.35	R.D.
2	4.29	4.85	5.7	4.5	21.9	7.36	Meningococcal disease
3	4.44	5.02	7.3	5.24	19.2	7.29	
4	3.79	4.28	6	3.4	16.3	7.41	
5	3.04	3.44	4.5	3	13.2	7.37	6 yrs old / 19.8kg
							2
6	5.73	6.47	7.6	7.34	30.4	7.34	T.N.
7	4.97	5.62	7	5.78	24.9	7.36	Pneumonia
8	8.12	9.18	8.9	6.75	24.3	7.28	Sickle Cell
9	4.35	4.92	7.1	5.26	24.1	7.39	
10	4.23	4.78	6.4	4.63	23.7	7.44	2 yrs old / 17kg
							3
11	5.6	6.33	7.7	4.15	22.5	7.46	J.B.
12	3.56	4.02	6.2	4.34	23.1	7.45	Meningococcal disease
13	3.7	4.18	5.2	3.74	22.5	7.51	
14	3.3	3.73	5.1	3.19	19.4	7.51	
15	4.11	4.64	6.8	6.31	22.1	7.27	10 months old / 10kg
							4
16	4.72	5.33	7	4.51	18.4	7.34	C.P.
17	4.86	5.49	7.6	4.36	17.6	7.34	Meningococcal disease
18	4.35	4.92	6.9	4.58	18.8	7.34	
19	4.3	4.86	6.4	4.5	17.8	7.33	
20	4.19	4.73	5.9	3.86	16.4	7.36	9 months old / 10.2kg
							5
21	3.74	4.23	5.2	4.69	29.6	7.53	J.A.
22	3.02	3.41	4.6	3.65	23.2	7.53	Pneumonia
23	3.82	4.32	5.6	5.73	23.9	7.35	ALL
24	4.19	4.73	6.8	6.04	26.3	7.37	Sepsis
25	6.21	7.02	8.6	6.29	27.5	7.37	3 yrs old / 14.9kg
							6
26	5.03	5.68	8	5.84	18.2	7.22	Y.P.
27	5.58	6.31	8.5	5.52	17.3	7.22	Meningococcal disease
28	5.89	6.66	9.2	5.15	16.5	7.24	
29	5.43	6.14	9.5	6.24	17.2	7.17	
30	6.3	7.12	9.6	6.67	17.8	7.15	16 months old / 10.1kg
							7
31	2.89	3.27	4.3	4.16	24.3	7.5	J-K. C.
32	3.55	4.01	4.8	4.05	20.3	7.43	TGA Switch
33	3.63	4.10	5.2	3.98	21	7.45	
34	3.76	4.25	5.4	4.51	25	7.47	
35	3.75	4.24	5.4	3.75	19.4	7.44	1 day old / 4.1kg

cNST = time-dependent factor corrected values

Data (a) In-vivo RGT-NST

	NST uncor	cNST	RGT	PaCO2	art HCO3	Art pH	
							8
36	2.76	3.12	3.7	3.06	20.9	7.44	T.C.
37	2.7	3.05	3.6	3.46	17	7.42	Rastelli procedure
38	3.13	3.54	3.8	2.97	15.5	7.45	PA/VSD/MAPCAS/PDA
39	3.31	3.74	4.7	3.51	15	7.36	
40	2.91	3.29	4.4	3.62	16	7.38	2 yrs old / 10.4kg
							9
41	6.26	7.07	8.4	4	20	7.43	K.Y.
42	5.47	6.18	8.1	4.14	20.9	7.41	Head Injury
43	5.63	6.36	8.4	4.84	20.3	7.35	Leg #
44	5.17	5.84	8.3	4.75	20.5	7.36	
45	5.09	5.75	8.3	3.77	19	7.43	5 yrs old / 20kg
							10
46	5.24	5.92	6.4	5.37	16.1	7.3	O.M-J.
47	3.47	3.92	4.3	3.78	19.9	7.45	Fallots Repair
48	3.26	3.68	3.9	3.86	19.5	7.43	Junctional Tachycardia
49	3.65	4.12	4.9	4.25	18.7	7.37	Pleural Effusions
50	3.82	4.32	6.2	4.41	18.1	7.34	10 months old / 7.3kg

cNST = time-dependent factor corrected values

Data (b) In-vivo NST-NST (kPa)

	cNST 1	cNST 2	PaCO2	Patient	cNST 1	cNST 2	PaCO2	
1	3.1	2.9	4.28	H.K.	3.1	2.68	4	1 week old
2	3.06	2.94	4.19	Coarctation	3.02	3.01	4.03	3kg
3	3.48	2.72	3.86	Repair	2.92	2.48	4.4	
4	2.81	2.42	4.6		2.81	2.64	4.28	
5	2.82	2.59	4.68	NPM	3.14	3.02	4.76	FED
6	4.57	4.47	5.53	R.S.	5	4.2	4.69	4 months old
7	5.17	4.85	6.01	Fallots Repair	4.19	4.11	4.37	4kg
8	4.82	4.67	5.9	CHARGE	4.05	4.25	4	
9	5.46	5.11	7.42		4.36	4.06	4.72	
10	6.17	6	7.9	NPM	5.27	5.41	6.1	FED
11	6.02	5.65	6.94	R.L.	5.02	4.96	6.09	2 months old
12	5.22	5.6	7.1	TAPVD	4	4.82	6.9	3.1kg
13	5.16	6.03	6.07	RSV+	4.69	4.6	6.91	
14	3.65	3.84	6.1		4.75	3.64	6.75	
15	4.55	4.08	6.77	NPM	4.47	4.11	7.18	FED
16	4.45	3.74	5.76	A.M.	4.69	4.37	5.12	1 day old
17	3.66	4.24	6.8	Hypoplastic	4.3	4.63	4.25	2.5kg
18	3.77	3.52	3.89	Left Heart	4.55	4.73	6.1	
19	3.89	3.92	5.39		2.48	2.73	5.87	
20	4.11	4.16	5.35	NPM	4.08	4.16	5.87	FED
21	4.84	4.84	5.12	M.K.	6.44	6.34	4.8	2 months old
22	5.39	6.07	5.54	AVSD Repair	5.97	6.37	6.02	2.7kg
23	4.25	4.23	5.03	LAI/DextraCardia	4.57	4.39	4.53	
24	3.58	3.86	4.03		3.52	3.9	5.4	
25	3.89	3.93	4.26	NPM	3.61	3.83	4.3	FED
26	3.91	4.76	5.17	D.L.	4.46	5.05	6.28	7 days old
27	4.77	4.42	5.23	Mitral Stenosis	5.53	5.04	5.56	2.87kg
28	4.55	4.64	4.9	Valve Repair	6.71	6.22	6.35	
29	4.72	4.6	5.41	PulmHT	5.64	5.33	5.23	
30	5.41	4.98	5.25	NPM	5.22	5.62	5.2	FED
31	3.36	3.28	3.96	S.J.	4.15	4.06	3.69	6 months old
32	3.67	3.49	3.75	TGA	4.47	4.81	4.5	4.74kg
33	3.6	3.47	3.91	Switch Surgery	4.64	5.04	4.71	
34	9.67	9.62	8.31		4.8	5.13	5.22	
35	4.81	5.11	7.18	NPM	6.17	6.48	5.61	FED

cNST = time-dependent factor corrected values

Data (b) In-vivo NST-NST (kPa)

	NST 1	NST 2	PaCO2	Patient	NST 1	NST 2	PaCO2	
36	4.56	4.64	7.57	A.S.	5.75	5.36	7.65	3 months old
37	5.63	5.89	7.87	ChLD	5.44	5.99	6.68	3.5kg
38	6.29	6.24	7.06	RSV+	4.37	3.86	6.38	
39	5.27	5.26	7.41		4.73	4.86	5.75	
40	5.98	6.13	8.2	NPM	6	6.14	6.34	FED
41	9.12	8.71	12.2	K.I.	7.12	6.81	10	11 months old
42	11.13	10.18	11.51	Pulm Dysplasia	7.67	7.05	7.33	5.5kg
43	7.01	6.77	7.5	RSV+	6.97	6.14	8.06	
44	6.6	6.63	8.7		8.71	8.34	8.92	
45	6.46	6.88	8.3	NPM	6.23	5.99	6.2	FED
46	5.02	4.98	5.8	S.L.	4.18	4.34	6.35	3.5 months old
47	4.93	5.02	4.74	Pneumonia	4.34	5.04	6.11	2.9kg
48	4.54	4.86	4.9	PAPVD	5.55	4.77	6.42	
49	4.79	4.38	5.76		4.79	5.04	5.84	
50	4.74	4.7	5.4	NPM	4.28	4.34	5.46	FED

cNST = time-dependent factor corrected values

Data (c) In-vitro study (kPa)

Paratrend	RGT	NST	PBST	cNST	cPBST	Bath
2.53	2.3	1.56	2.48	1.76	2.75	2.07
2.55	2.4	1.49	2.84	1.68	3.15	1.98
2.5	2.3	1.47	2.46	1.66	2.73	1.99
2.5	2.4	1.52	2.83	1.72	3.14	2.13
2.49	2.4	1.48	2.52	1.67	2.80	2.11
2.5	2.4	1.38	2.27	1.56	2.52	1.82
2.52	2.4	1.51	2.36	1.71	2.62	1.98
2.5	2.4	1.46	2.82	1.65	3.13	1.79
2.51	2.4	1.42	2.83	1.60	3.14	2.08
2.52	2.4	1.49	2.46	1.68	2.73	1.96
2.49	2.3	1.44	2.54	1.63	2.82	2.08
2.53	2.4	1.35	2.43	1.53	2.70	2.09
2.52	2.4	1.37	2.74	1.55	3.04	2.01
2.49	2.4	1.66	2.45	1.88	2.72	2.14
2.48	2.4	1.72	2.71	1.94	3.01	2.18
2.55	2.3	1.45	2.4	1.64	2.66	2.06
2.5	2.3	1.5	2.6	1.70	2.89	2.07
2.52	2.3	1.58	2.63	1.79	2.92	2.19
2.52	2.3	1.46	2.36	1.65	2.62	2.04
2.54	2.3	1.43	2.45	1.62	2.72	2.02
4.99	4.6	2.88	4.16	3.25	4.62	3.46
4.95	4.6	2.88	3.88	3.25	4.31	3.53
4.98	4.7	2.89	4.05	3.27	4.50	3.56
5.01	4.7	2.81	3.85	3.18	4.27	3.62
4.98	4.7	3.05	4.36	3.45	4.84	3.38
4.99	4.7	2.91	4.53	3.29	5.03	3.53
5.05	4.6	2.82	4.19	3.19	4.65	3.49
5.06	4.6	2.64	4.27	2.98	4.74	3.26
5.02	4.6	2.56	4.29	2.89	4.76	3.24
5.04	4.6	2.84	3.64	3.21	4.04	3.47
4.98	4.6	2.78	4.72	3.14	5.24	3.22
5.05	4.7	2.73	4.49	3.08	4.98	3.3
5.02	4.7	2.68	4.43	3.03	4.92	3.34
5.06	4.7	2.81	4.26	3.18	4.73	3.37
5.02	4.6	2.66	3.97	3.01	4.41	3.4
4.98	4.7	2.87	4.1	3.24	4.55	3.72
5.01	4.7	3.04	4.18	3.44	4.64	3.46
5	4.7	2.89	4.54	3.27	5.04	3.31
5	4.8	2.58	3.93	2.92	4.36	3.48
4.99	4.7	2.54	4.38	2.87	4.86	3.53

cNST + **cPBST** = time-dependent factor corrected values

Data (c) In-vitro study (kPa)

Paratrend	RGT	NST	PBST	cNST	cPBST	Bath
7.48	7.2	3.97	6.19	4.49	6.87	5.04
7.51	7.3	3.95	5.45	4.46	6.05	5.05
7.52	7.3	4.21	6.42	4.76	7.13	4.61
7.5	7.2	4.17	6.44	4.71	7.15	4.95
7.5	7.2	3.83	6.13	4.33	6.80	4.97
7.46	7.2	3.84	5.77	4.34	6.40	4.77
7.48	7.2	4.27	5.84	4.83	6.48	4.86
7.47	7.2	4.16	6.06	4.70	6.73	4.91
7.51	7.2	4.24	5.96	4.79	6.62	4.95
7.49	7.2	4.1	5.88	4.63	6.53	4.69
7.52	7.1	4.39	5.79	4.96	6.43	4.88
7.53	7.1	3.98	5.86	4.50	6.50	4.76
7.54	7.1	4.03	5.67	4.55	6.29	4.77
7.55	7	4.08	6.02	4.61	6.68	4.79
7.5	7.1	4.14	5.51	4.68	6.12	4.99
7.5	7	3.82	5.4	4.32	5.99	4.92
7.55	7	4.13	5.47	4.67	6.07	4.86
7.5	7.1	4.36	6.26	4.93	6.95	4.74
7.56	7.1	3.97	6.15	4.49	6.83	4.44
7.52	7	3.81	5.79	4.31	6.43	4.77
10	9.7	5.85	8.54	6.61	9.48	6.2
9.97	9.7	5.41	8.49	6.11	9.42	6.63
9.96	9.7	5.67	7.88	6.41	8.75	6.89
10	9.7	5.73	8.52	6.47	9.46	6.7
9.97	9.7	5.83	7.63	6.59	8.47	6.41
9.98	9.7	5.34	7.96	6.03	8.84	6.34
10	9.7	5.33	8.13	6.02	9.02	6.67
10	9.7	5.56	7.28	6.28	8.08	6.63
9.99	9.7	5.59	8.03	6.32	8.91	6.59
10	9.7	5.68	7.64	6.42	8.48	6.34
10.1	9.5	5.26	7.87	5.94	8.74	6.45
10.1	9.5	5.25	7.75	5.93	8.60	6.25
10.1	9.6	5.51	7.73	6.23	8.58	6.21
10	9.5	5.69	8.01	6.43	8.89	6.36
10	9.6	5.51	7.07	6.23	7.85	5.89
9.99	9.6	5.26	7.17	5.94	7.96	6.3
10	9.6	4.96	7.62	5.60	8.46	5.52
9.99	9.6	4.78	7.31	5.40	8.11	5.46
10	9.6	5.24	8.17	5.92	9.07	5.93
10.1	9.6	5.39	8.01	6.09	8.89	6.43

cNST + **cPBST** = time-dependent factor corrected values