SUPPLEMENTARY INFORMATION

N_2MBW MEASUREMENT SETUP

Flow was measured by a mainstream ultrasonic flowmeter which derives tidal volumes. Gas concentrations were measured by a sidestream oxygen (O_2) sensor, main-stream carbondioxide (CO_2) sensor, and the N_2 fraction was calculated indirectly from O_2, CO_2 and the estimated Argon fraction. During the measurement children were breathing through a snorkel mouthpiece attached to a bacterial filter, wearing a nose clip. N_2MBW measurements were stopped after three breaths below 1/40th of the N_2 starting concentration. FRC and LCI were calculated at 2.5% (1/40th) of normalized N_2 starting concentration as currently recommended [20]; the formulae are provided below.

FORMULAE

Formula 1: Calculation formulae of FRC [l] and LCI according to Spiroware (Eco Medics AG, Duernten, Switzerland). Cet = expiratory N_2 concentration, CEV= cumulative expired volume [l], DS= dead space [l].

$$FRC = CumVolN_2/(CetStart - CetEnd)$$

$$LCI = (CEV - DS)/FRC$$

$$DS = (pre\text{-} + postcap.Volume) * \#Breath$$

$$VolN_2Netto = VolN_2exp - VolN_2reinsp$$

$$CumVolN_2 = \sum VolN_2Netto$$

Formula 2: Example of calculation of a pre-capillary expiratory continuous leak of 10% tidal volume, performed breath-by-breath for every tidal breath of washout.

$VolN_2exp *0.9 = VolN_2exp\ leak$

$CEV*0.9 = CEV\ leak$

Formula 3: Example of calculation of an intra-capillary side-stream continuous leak where end-tidal N_2 concentration [%] is overestimated by 1% N_2 performed breath-by-breath for every tidal breath of an extended washout. Accordingly, $CumVolN_2$ was altered, resulting in new FRC and LCI values.

$Cet + 1 = Cetleak$

$VolN_2exp + 0.01*Volexp = VolN_2exp\ leak$

TABLES

Table S1: Modeling of pre-capillary expiratory continuous leak into the original N_2MBW trace

Breath #	Cet [%]	FRC [l]	FRC leak 20%[l] whole washout	FRC leak 20%[l] after 1/2 washout	VolExp [l]	VolExp -20% [l]	CEV-DS [l]	CEV-DS-20% [l] whole washout	CEV-DS-20% [l] after 1/2 washout	VolN2Exp [ml]	VolN2Exp -20%[ml]	VolN2Netto -20%[ml]	CumVolN2Netto [ml]	CumVolN2Netto -20%[ml] whole washout	CumVolN2Netto -20%[ml] after 1/2 washout
1	59.547	2.768	2.192	2.768	1.139	0.911	1.093	0.865	1.093	545.255	436.204	415.043	524.094	415.043	524.094
2	46.473	2.723	2.155	2.723	1.008	0.807	2.055	1.626	2.055	363.431	290.745	274.795	871.576	689.839	871.576
3	36.495	2.841	2.250	2.841	1.144	0.915	3.154	2.495	3.154	332.220	265.776	254.638	1192.657	944.476	1192.657
4	29.408	2.986	2.365	2.986	1.199	0.960	4.307	3.409	4.307	283.576	226.861	216.004	1465.376	1160.480	1465.376
5	23.519	3.049	2.414	3.049	1.177	0.942	5.438	4.305	5.438	220.807	176.645	166.295	1675.832	1326.775	1675.832
6	18.847	3.089	2.446	3.089	1.161	0.929	6.553	5.188	6.553	173.944	139.155	131.528	1842.149	1458.303	1842.149
7	15.132	3.112	2.463	3.112	1.128	0.902	7.635	6.044	7.635	135.017	108.014	102.106	1971.259	1560.409	1971.259
8	12.342	3.128	2.476	3.128	1.059	0.848	8.648	6.845	8.648	102.489	81.991	77.141	2068.898	1637.550	2068.898
9	10.057	3.160	2.501	3.160	1.207	0.965	9.809	7.764	9.809	96.981	77.584	73.976	2162.270	1711.526	2162.270
10	8.190	3.185	2.521	3.185	1.206	0.965	10.969	8.683	10.969	80.312	64.250	60.622	2238.954	1772.148	2238.954
11	6.801	3.214	2.544	3.195	1.223	0.979	12.147	9.616	11.902	67.532	54.025	51.426	2303.887	1823.574	2290.380
12	5.629	3.244	2.568	3.209	1.337	1.069	13.437	10.640	12.925	61.806	49.445	47.144	2363.392	1870.718	2337.524
13	4.742	3.263	2.583	3.216	1.148	0.918	14.539	11.512	13.798	44.474	35.579	33.545	2405.832	1904.263	2371.069
14	4.043	3.283	2.599	3.226	1.204	0.963	15.697	12.429	14.715	40.020	32.016	30.076	2443.912	1934.339	2401.145
15	3.463	3.302	2.614	3.236	1.215	0.972	16.867	13.355	15.641	34.664	27.732	26.306	2477.151	1960.645	2427.451
16	2.997	3.322	2.629	3.248	1.258	1.007	18.079	14.316	16.602	31.806	25.445	23.926	2507.438	1984.571	2451.377
17	2.729	3.345	2.647	3.263	1.207	0.966	19.240	15.236	17.522	27.569	22.055	20.603	2533.554	2005.173	2471.980
18	2.458	3.363	2.661	3.275	1.155	0.924	20.349	16.114	18.400	23.872	19.097	17.977	2556.306	2023.151	2489.957
19	2.292	3.380	2.675	3.287	1.046	0.837	21.349	16.905	19.191	19.574	15.660	14.604	2574.825	2037.755	2504.561
20	2.177	3.401	2.692	3.303	1.186	0.949	22.489	17.807	20.093	21.212	16.970	15.973	2595.041	2053.728	2520.535
21	2.062	3.418	2.705	3.316	1.047	0.838	23.490	18.599	20.885	17.631	14.105	13.238	2611.805	2066.966	2533.773
22	1.946	3.433	2.717	3.327	1.003	0.802	24.447	19.355	21.641	16.224	12.979	12.078	2627.127	2079.044	2545.850
23	1.927	3.454	2.734	3.343	1.130	0.904	25.531	20.213	22.499	17.987	14.390	13.617	2644.342	2092.661	2559.467
24	1.895	3.474	2.749	3.359	1.110	0.888	26.595	21.055	23.341	17.154	13.723	12.817	2660.590	2105.478	2572.284
25	1.767	3.490	2.762	3.371	1.183	0.946	27.732	21.956	24.241	17.773	14.219	13.287	2677.432	2118.765	2585.571
26	1.735	3.508	2.776	3.384	1.051	0.841	28.737	22.750	25.036	15.359	12.287	11.521	2692.025	2130.286	2597.093
		without leak	20% precapillary exspiratory leak												
			whole washout	after 1/2 washout											
LCI (CEV-DS/FRC)		7.12	7.12	6.5											

Example of breath-by-breath modelling of a pre-capillary expiratory continuous leak of 20% during the whole washout and after ½ washout in a breath table of a quality controlled washout measurement of a healthy adolescent. Columns for lung turnover (TO = CEV/FRC), Cet Start, CEV, DS, N2InspMean, VolN2Netto, VolN2Reinsp are not illustrated for better overview. Calculations are based on the above named formulae online supplement. Names and abbreviations of columns are analog to Spiroware (Eco Medics AG, Duernten, Switzerland).

FIGURES

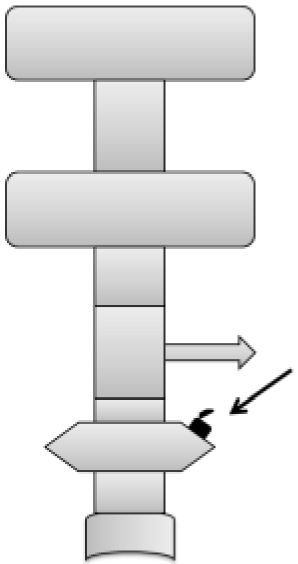
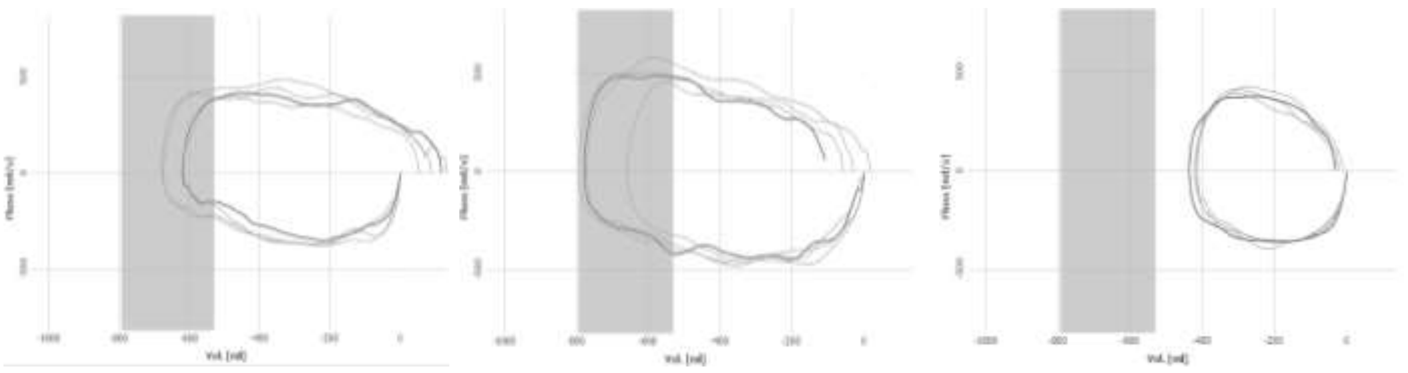


Figure S1: Example pre-capillary leak performed in practice with open valve of Pediatric slimline® filter. Other leaks are incorporated similarly by opening valves or lue locks on different locations in the system.



A B C

Figure S2: Practical examples of flow-volume loops due to leaks. The grey area denotes the measured weight based target VT (10-15ml/kg measured weight).according to the manufacturer. Figure S2A: In a pre-capillary inspiratory leak the expiratory volume appears to be larger than inspiratory volume. Figure S2B: In a pre-capillary expiratory leak the inspiratory volume appears to be larger than expiratory volume. Figure S2C: In the pre-capillary inspiratory and expiratory leak the tidal volume deviates largely from the grey “normal” area and is also underestimated as compared to S2A and S2B.

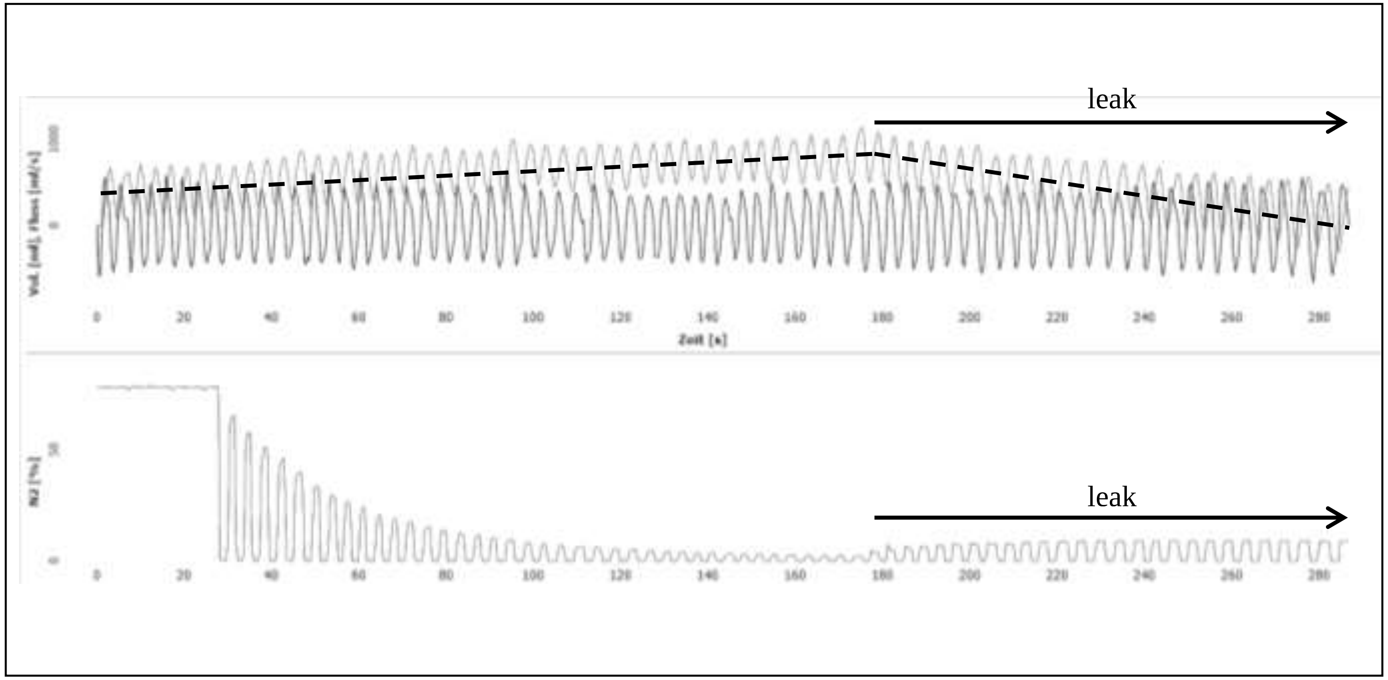


Figure S3: Sudden step change in volume trace and premature rise in N2 signal due to continuous pre-capillary inspiratory and expiratory leak (trial did not reach washout criteria due to stabilization of elevated N2 concentration).

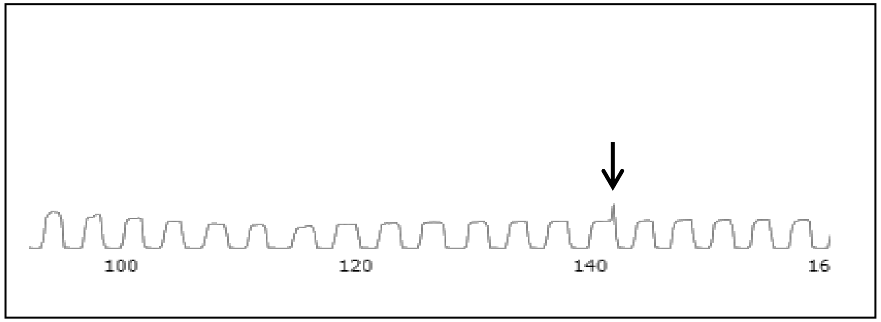


Figure S4: Sudden spike in N_2 concentration during inspiration due to continuous pre-capillary inspiratory and expiratory leak (trial did not reach washout criteria due to stabilization of elevated N2 concentration).

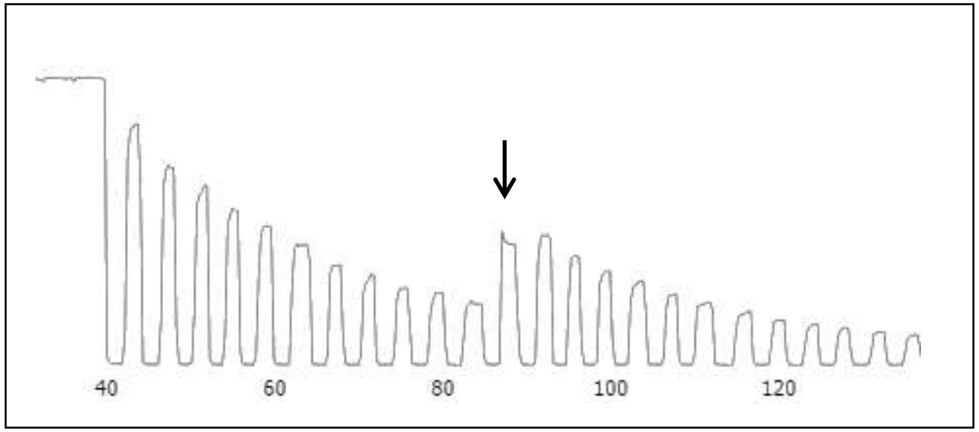


Figure S5: Step-up in end-tidal N_2 concentration due to isolated pre-capillary inspiratory and expiratory leak over two tidal breathes resulting in an increase in FRC and LCI.

Figure S6: Practical example of leveling of end-tidal N_2-concentration due to leak

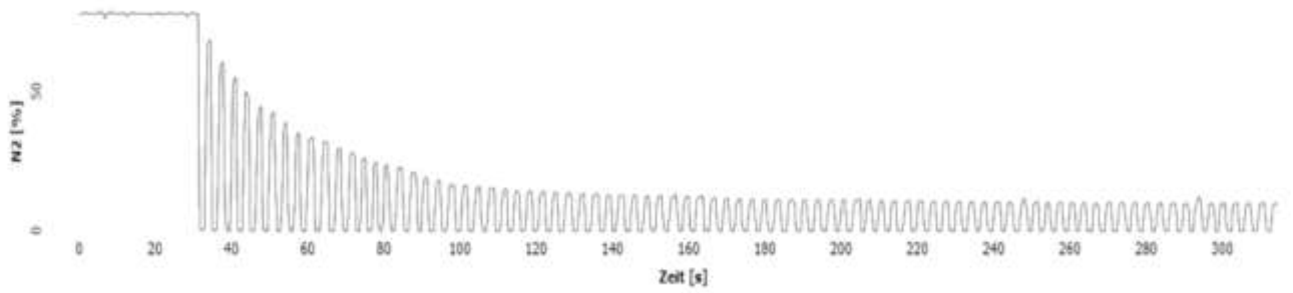


Figure S6: Stabilization of end-tidal N_2 concentration at 10% due to continuous pre-capillary inspiratory and expiratory leak. The washout could not be completed because the end-tidal N_2 concentration does not fall below 2.5%. In MBW measurements, it can be difficult to differentiate between elevated N_2 concentrations due to a continuous leak or increased ventilation inhomogeneity as a result of lung disease.