Efficacy of ventilator waveforms observation for detection of patient–ventilator asynchrony during non-invasive ventilation. An international multicenter study

Online Supplement

EXPANDED MATERIALS AND METHODS

The study was performed in 8 ICUs from China (Nanjing, Wuhu, ZhenJiang), Italy (Bologna, Novara, Roma, Vercelli) and the Netherlands (Nijmegen). The local ethics committees approved the study and informed consent or waived consent was obtained according to national regulations.

Patients and Protocol

Flow, airway pressure (Paw), and diaphragm electrical activity (EAdi) were obtainned using a dedicated software[1] from 40 patients enrolled in previous studies [2-4], who had received NIV, 20 through facial masks (FreeMotion RT041 Non Vented Full Face Mask, Fisher and Paykel, Auckland, New Zealand; Ultra Mirage FFM-NV, ResMed, San Diego, CA, USA or PerforMax Face Mask, Philips Respironics, Murrysville, PA, USA) and 20 through helmets (Castar R, Intersurgical, Mirandola, Italy or Castar NEXT, Intersurgical, Mirandola, Italy) for treatment of Acute Respiratory Failure (ARF) of varied aetiologies. All patients were ventilated with a Servo-I ventilator (Maquet Critical Care, Solna, Sweden) equipped with a NIV software for air-leaks. Patient's characteristics at enrolment are reported in Table E1 (in the ESM). EAdi was obtained through a nasogastric feeding tube with a multiple array of electrodes placed at its distal end (EAdi catheter; Maquet Critical Care, Solna, Sweden). Catheter placement and verification of correct positioning were done as previously described[1, 3]. Airflow, Paw, and EAdi were acquired from the ventilator through a RS232 interface at a sampling rate of 100 Hz, recorded by means of dedicated software (Nava Tracker Version 3.0; Maquet Critical Care), stored in a hard disk and processed using a customized software based on Microsoft Excel (Microsoft, Redmond, WA).

Positive end-expiratory pressure (PEEP), pressure support (PS) and expiratory cycling settings were those applied by the attending physicians, as clinically indicated (see Table E1, in the ESM). The inspiratory rise time was set at the fastest rate of pressurization. One 5-minute epoch of data was randomly extracted from all 40 recordings, whose overall durations were 20 to 30 minutes.

The flow-time and Paw-time tracings were scaled to simulate the waveforms available on most ventilator screens and uploaded on a dedicated online website. Data were reviewed and scored on the online website by all participants, and automatically collected and stored for further analysis in a database not visible to the other participants.

Seventy physicians were drawn by chance from the medical staff of 8 ICUs (3 in the Chinese Republic, 4 in Italy and 1 in the Netherlands)[5]. In particular, group 1 included 35 expert physicians (Ex), *i.e.;* ICU physician in staff for ≥3 years and familiar with the application of NIV, whereas group 2 included 35 ICU residents who had received at least 6 months of ICU training, considered to be non expert (N-Ex). All of them were familiar with NIV. Physicians were asked to independently identify patient-ventilator asynchronies according to previously published criteria[6-8].

We considered the following asynchronies: 1) ineffective effort (IE), as defined by a drop in Paw and a positive deflection of expiratory flow not triggering ventilator support; 2) auto-triggering (AT), identified by a ventilator cycle without a preceding Paw deflection; 3) double-triggering (DT), *i.e.;* one properly triggered breath followed by a second ventilator insufflation after a time lower than 50% of the inspiratory time. Physicians were requested to mark and label online IEs, ATs, or DTs. To simulate bedside condition, physicians had a maximum of 5 minutes to analyze each report.

Data Analysis

Three examiners (F.L., D.C., P.N.) with a specific expertise in patient-ventilator interaction independently reviewed the tracings on a booklet including the EAdi tracings. EAdi swings were considered efforts when exceeding 1.5 μV and was at least twice as high as the ground noise level[5]. The predefined criterion for considering an event asynchronous was the agreement between no less than two examiners. This analysis was considered the gold standard and used for reference[5]. Accordingly, the AI of each tracing was calculated as as the number of asynchronous events divided by the overall breath count, *i.e.;* the sum of ventilator cycles and non-triggered breaths[6]. Reports were graded as asynchrony-free, or, based on the 10% AI threshold, either severely (≥10%) or mildly(<10%) asynchronous[6].

The analysis performed online on a dedicated website by the 70 physicians on every breath of the 40 reports, *i.e.;* presence (yes or no) and type of asynchrony (IE, AT, DT) was matched with the reference, referred to as Breath Analysis (BA)[5]. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were calculated for each physician and tracing. The physician's performance in detecting asynchronies was also assessed by evaluating their ability to detect the reports with AI ≥10%, referred to as Report Analysis (RA). The AI based on the scores for each report was calculated for all physicians and compared with the reference for determining Sensitivity, specificity, PPV and NPV[5].

For each waveform analysis by every single observer, a Double "True" index (DTI) was calculated as the ratio between the sum of true positive and true negative, and the overall breath count (*i.e.;* the sum of ventilator cycles and IEs). DTI represents the ability of properly identifying both synchronous and asynchronous breaths, and ideally should be 100%.

Ventilator cycling (RR_{mec}) and inspiratory duty cycle ($TI/TTOT_{mec}$) were determined from the flow tracing, while patient's (neural) respiratory rate (RR_{neu}) and inspiratory duty cycle ($TI/TTOT_{neu}$) from the EAdi tracing[3]. Inspiratory tidal volume (V_T) was obtained by digital integration of the flow[1]. EAdi amplitude from baseline to peak ($EAdi_{peak}$) and EAdi-time product (EATP) were computed to assess the neural drive[9-10]. The inspiratory trigger delay ($Delay_{TR\text{-}insp}$) was calculated as the time lag between onsets of EAdi and commencement of ventilator support[3]. Air-leaks were calculated as the difference between inspiratory and expiratory minute volume divided by expiratory minute volume, and expressed in percent[3].

Statistics

Fleiss' kappa coefficient was computed to calculate the degree of agreement in classification for the gold standard analysis between the three examiners. The normal distribution was ascertained by means of the Kolmogorov-Smirnov test. To assess the ability of ICU physicians to detect patient-ventilator asynchrony, sensitivity, specificity, PPV and NPV were calculated for both BA and RA and overall reported as mean ± standard deviation (SD) or median and interquartile range [25th-75th percentile], as indicated. Data were then grouped according to: 1) level of experience (Ex and N-Ex), 2) interface (mask and helmet) and 3) geographic origin (Asia and Europe). The Mann-Whitney U-test or t-Student was applied to assess statistical differences between groups, as appropriate. The linear regression was used to assess the correlation between the mean DTI (mean value from all observers) of each tracing and the corresponding AI, both overall and separately for the mask and helmet subgroups. The χ-square test for linear trends was applied to ascertain the influence of the level of PS, RR_{mec}, V_T and $EAdi_{peak}$ on both AI and ability to properly recognize asynchronies (*i.e.;* sensitivity). For all the tests, the null hypothesis was rejected for values < 0.05.

Table S1. Patients characteristics

Patient	Gender	Age	BMI	Admission Pathology	SAPSII	PEEP	PS	Interface
1	F	78	27.8	Pneumonia	34	12	10	Helmet
2	M	62	28.1	Septic shock	37	10	12	Helmet
3	M	57	23.5	Polytrauma	32	12	8	Helmet
4	M	67	23.2	Pneumonia	39	11	8	Helmet
5	F	75	28.4	Septic shock	46	10	10	Helmet
6	M	69	25.1	Pancreatitis	68	11	10	Helmet
7	M	31	21.1	Chest trauma	18	12	10	Helmet
8	F	45	21.0	Post-surgical ARF	25	11	10	Helmet
9	F	37	21.2	Chest trauma	18	12	10	Helmet
10	M	56	22.2	Septic shock	30	12	10	Helmet
11	M	74	23.8	Septic shock	40	12	10	Helmet
12	F	76	25.5	Pneumonia	34	14	11	Helmet
13	F	73	24.5	Pneumonia	33	12	12	Helmet
14	F	63	22.4	Post-surgical ARF	32	10	13	Helmet
15	M	59	22.9	Septic shock	33	12	10	Helmet
16	M	68	25.1	Pancreatitis	68	14	13	Helmet
17	F	76	28.4	Septic shock	46	14	11	Helmet
18	F	32	17.2	Polytrauma	33	12	10	Helmet
19	M	56	28.4	Polytrauma	40	9	10	Helmet
20	M	63	20.3	Pneumonia	30	9	10	Helmet
21	M	72	24.5	Congestive Heart failure	43	9	15	Mask
22	F	78	29.1	Septic shock	49	8	11	Mask
23	M	72	26.8	COPD exacerbation	36	13	13	Mask
24	M	43	24.1	Polytrauma	33	6	9	Mask
25	F	65	26.5	COPD exacerbation	30	7	14	Mask
26	F	69	25.9	Septic shock	48	9	10	Mask
27	F	55	25.4	Septic shock	22	11	13	Mask
28	M	59	26.4	Septic shock	35	9	11	Mask
29	M	64	28.7	Septic shock	40	5	8	Mask
30	F	78	27.8	COPD exacerbation	38	5	8	Mask
31	M	67	29.1	COPD exacerbation	34	10	14	Mask
32	M	77	23.7	Pneumonia	28	12	15	Mask
33	M	64	28.2	Septic shock	37	5	9	Mask
34	M	58	24.5	Polytrauma	44	5	12	Mask
35	M	28	26.1	Polytrauma	29	8	14	Mask
36	F	78	23.5	Pneumonia	38	6	10	Mask
37	F	72	25.7	Pneumonia	38	6	15	Mask
38	M	71	22.0	Pneumonia	27	12	14	Mask
39	M	84	24.1	COPD exacerbation	39	6	12	Mask
40	F	85	19.5	Pneumonia	56	6	15	Mask

Table S2: Breathing pattern, respiratory drive and air-leaks values of the tracings

Track #	RR_{mec} (breaths/min)	RR_{neu} (breaths/min)	$TI/TTOT_{mec}$	$TI/TTOT_{neu}$	$Delay_{TR\text{-}insp}$ (sec)	$EAdi_{peak}$ (μV)	EATP (μV*sec)	Air-leaks (%)
1	19	25	0,23	0,33	0,42	17,9	1070	5
2	11	10	0,12	0,19	0,43	7,1	308	2
3	20	20	0,23	0,29	0,48	14,6	775	0
4	21	19	0,26	0,41	0,44	22,6	1172	3
5	9	9	0,19	0,16	0,34	29,2	1933	5
6	17	13	0,18	0,21	0,33	14,6	642	9
7	23	23	0,40	0,38	0,17	17,4	1216	1
8	11	11	0,16	0,17	0,09	9,8	429	2
9	18	15	0,18	0,31	0,25	5,8	190	2
10	25	28	0,27	0,37	0,39	19,2	807	1
11	33	33	0,33	0,40	0,43	34,0	1472	2
12	21	21	0,23	0,32	0,30	12,7	649	1
13	22	23	0,24	0,40	0,54	48,3	2141	3
14	18	19	0,20	0,40	0,64	40,3	1930	4
15	25	24	0,23	0,27	0,40	14,6	624	0
16	34	36	0,25	0,32	0,36	29,0	992	3
17	30	35	0,27	0,24	0,24	35,1	1501	0
18	37	36	0,30	0,33	0,32	8,9	347	3
19	18	25	0,23	0,37	0,40	10,5	518	6
20	12	11	0,19	0,18	0,12	8,2	522	4

21	22	21	0,29	0,43	0,52	11,7	695	7
22	21	21	0,32	0,43	0,35	14,4	938	1
23	21	21	0,29	0,41	0,39	15,8	913	1
24	29	28	0,28	0,27	0,03	6,8	274	1
25	27	26	0,24	0,32	0,21	14,7	584	0
26	25	25	0,27	0,33	0,23	14,7	649	2
27	26	25	0,26	0,31	0,10	10,0	362	1
28	21	20	0,33	0,31	0,02	8,8	442	6
29	21	20	0,32	0,32	0,08	5,5	267	5
30	20	19	0,36	0,34	0,11	7,8	438	7
31	29	29	0,30	0,39	0,25	23,0	932	9
32	32	31	0,39	0,37	0,09	15,0	658	6
33	26	25	0,31	0,38	0,26	34,2	1554	0
34	16	17	0,27	0,30	0,41	21,9	1400	6
35	22	21	0,30	0,39	0,34	29,7	1708	3
36	20	20	0,30	0,41	0,41	13,9	871	1
37	20	19	0,28	0,35	0,32	7,6	450	1
38	23	37	0,28	0,28	0,10	12,0	419	1
39	23	22	0,31	0,45	0,39	14,1	818	7
40	20	20	0,30	0,38	0,32	10,7	645	4

RR_{mec}, mechanical respiratory rate; RR_{neu}, neural respiratory rate; $TI/TTOT_{mec}$, ventilator duty cycle; $TI/TTOT_{neu}$, patient's own duty cycle; $Delay_{TR\text{-}insp}$, inspiratory trigger delay; EAdi, Electrical Activity of the diaphragm; $EAdi_{peak}$, peak of EAdi; EATP, EAdi-time product.

Table S3. Sensitivity, specificity, Positive Predictive Value and Negative Predictive Value for ineffective efforts, autotriggering and double triggering with mask and helmet.

Asynchronies	Mask (n=20)	Helmet (n=20)	P value
IE			
Sensitivity	0.04 [0.01; 0.08]	0.13 [0.05; 0.22]	p<0.001
Specificity	0.96 [0.93; 0.98]	0.92 [0.86; 0.95]	p<0.001
PPV	0.03 [0.01; 0.06]	0.06 [0.04; 0.10]	p<0.001
NPV	0.96 [0.96; 0.96]	0.95 [0.95; 0.96]	p<0.001
AT			
Sensitivity	0.06 [0.01; 0.17]	0.01 [0.0; 0.11]	p<0.001
Specificity	0.98 [0.97; 0.99]	0.99 [0.97; 0.99]	p<0.001
PPV	0.14 [0.04; 0.26]	0.03 [0.00; 0.13]	p<0.001
NPV	0.94 [0.94; 0.95]	0.96 [0.96; 0.96]	p<0.001
DT			
Sensitivity	0.47 [0.19; 0.71]	0.04 [0.00; 0.18]	p<0.001
Specificity	0.97 [0.95; 0.98]	0.97 [0.96; 0.98]	p=0.002
PPV	0.41 [0.20; 0.58]	0.03 [0.00; 0.10]	p<0.001
NPV	0.97 [0.95; 0.99]	0.98 [0.98; 0.98]	p<0.001

IE, ineffective effort; AT, autotriggering; DT, double triggering; PPV, positive predicted value; NPV, negative predicted value. Data are expressed as median [25th-75th interquartile range].

Table S4. Rate of undetected ineffective efforts, autotriggering and double triggering expressed both overall and separately for mask and helmet

	IE	AT	DT	p Value
Overall (%)	91 [84; 97]	94 [85; 99]	62 [45; 83]$^{*\wedge}$	p<0.001
Mask (%)	96 [92; 99]	94 [83; 99]	53 [29; 81]$^{*\wedge}$	p<0.001
Helmet (%)	87 [76; 95]	99 [89; 100]$^{\$}$	96 [82; 100]*	p<0.001

IE, ineffective effort; AT, autotriggering; DT, double triggering; $^{\$}$p<0.001, AT *vs* IE; *p<0.001, DT *vs* IE; $^{\wedge}$p<0.001, DT *vs* AT. Data are expressed as median [25th-75th IQR].

Table S5. Influence of support level, breathing pattern and respiratory drive on sensitivity and prevalence of asynchronies with mask NIV

Variables	Range*	Sensitivity ≥0.28	Linear trend for sensitivity	AI≥10%	Linear trend for prevalence
PS (cmH_2O)	<10	0.0%	*p*=0.884	33.3%	*p*=0.172
	10-14	50.0%		66.6%	
	>14	40.0%		60.0%	
V_T (ml)	<518	40.0%	*p*=0.047	40.0%	*p*=0.999
	518-637	60.0%		60.0%	
	>637	0.0%		60.0%	
RR_{mec} (breath/min)	<20	75.0%	*p*=0.344	50.0%	*p*=0.712
	20-26	45.5%		63.6%	
	>26	0.0%		40.0%	
$EAdi_{peak}$ (μV)	<9	60.0%	*p*=0.095	60.0%	*p*=0.330
	9-16	63.6%		63.6%	
	>16	0.0%		25.0%	

*as defined by percentiles.

NIV, noninvasive ventilation; PS, inspiratory pressure support; V_T tidal volume; RR_{mec}, ventilator rate of cycling, $EAdi_{peak}$, peak value of electrical activity of the diaphragm.

Table S6. Influence of support level, breathing pattern and respiratory drive on sensitivity and prevalence of asynchronies with helmet NIV

Variables	Range*	Sensitivity ≥0.10	Linear trend for sensitivity	AI≥10%	Linear trend for prevalence
PS (cmH_2O)	<9	50.0%	*p*=0.999	50.0%	*P*=0.315
	9-12	37.5%		50.0%	
	>12	50.0%		0.0%	
V_T (ml)	<763	80.0%	*p*=0.525	80.0%	*p*=0.525
	763-1067	20.0%		40.0%	
	>1067	60.0%		60.0%	
RR_{mec} (breath/min)	<17	20.0%	*p*=0.099	80.0%	*p*=0.087
	17-25	45.5%		36.4%	
	>25	75.0%		25.0%	
$EAdi_{peak}$ (µV)	<10	40.0%	*p*=0.999	60.0%	*p*=0.525
	10-29	50.0%		40.0%	
	>29	40.0%		40.0%	

*as defined by percentiles.

NIV, noninvasive ventilation; PS, inspiratory pressure support; V_T tidal volume; RR_{mec}, ventilator rate of cycling, $EAdi_{peak}$, peak value of electrical activity of the diaphragm.

Table S7. Effects of varying Asynchrony Index thresholds on sensitivity and specificity

Cut-off	Overall	Mask	Helmet
Cut-off 10%			
Sensitivity	0.10 [0.05; 0.25]	0.18 [0.00; 0.36]	0.00 [0.00; 0.00]
Specificity	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]
Cut-off 15%			
Sensitivity	0.08 [0.00; 0.08]	0.11 [0.00; 0.11]	0.00 [0.00; 0.00]
Specificity	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]
Cut-off 20%			
Sensitivity	0.00 [0.00; 0.17]	0.00 [0.00; 0.25]	0.00 [0.00; 0.00]
Specificity	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]
Cut-off 25%			
Sensitivity	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]
Specificity	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]

INSTRUCTION TO THE STUDY PARTICIPANTS

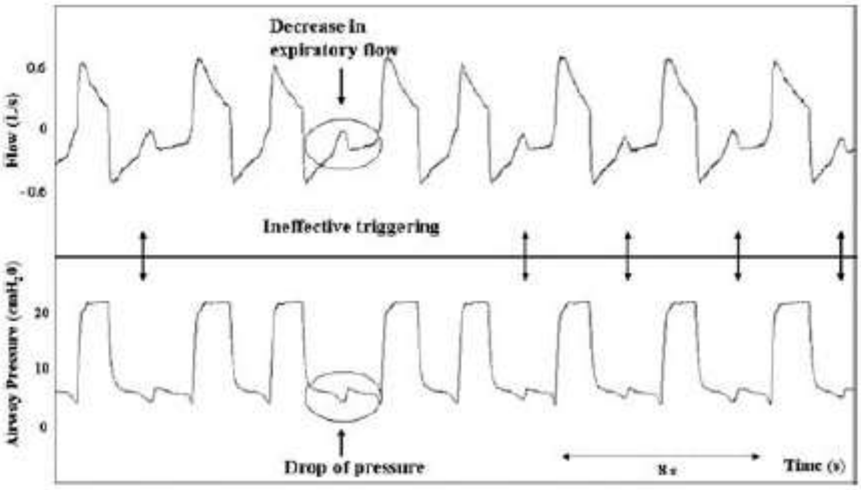
Manual

In the present study we ask you to evaluate flow and airway pressure waveform recorded from a ventilator, to detect possible asynchronies according to the literature.
We remind you that waveforms that you will observe are all from patients undergoing non invasive ventilation, applied with both mask and helmet. Moreover every waveform is 5 minutes long: we therefore ask you to not take more than this time to observe each waveform.
For every asynchrony we ask you to recognize them as reported.

Ineffective triggering (IE)

This asynchrony is a patient effort not supported by the ventilator. They can be either in inspiratory or expiratory (more frequently) ventilator phase.

1. In the expiratory ventilatory phase, they are defined by a drop in air way pressure (> 0.5 cmH_2O) with a flow reduction, without any ventilatory support.



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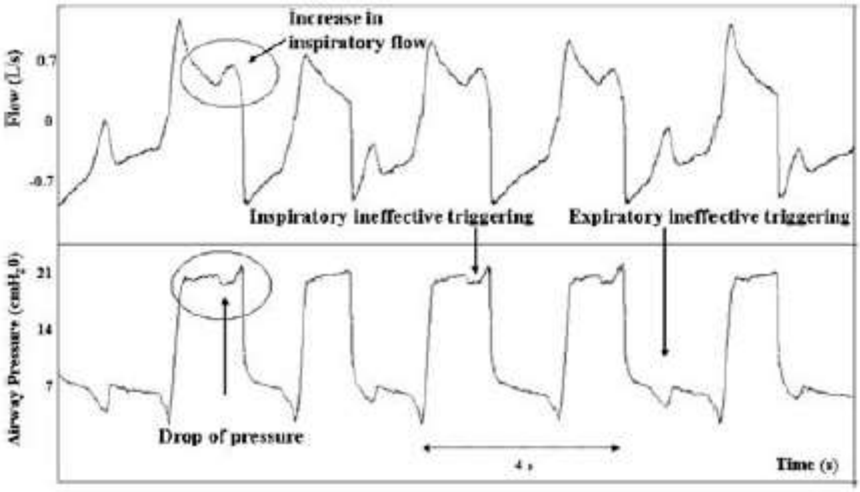
2. In the inspiratory phase, there is a drop in the air way pressure with an incremented inspiratory flow.



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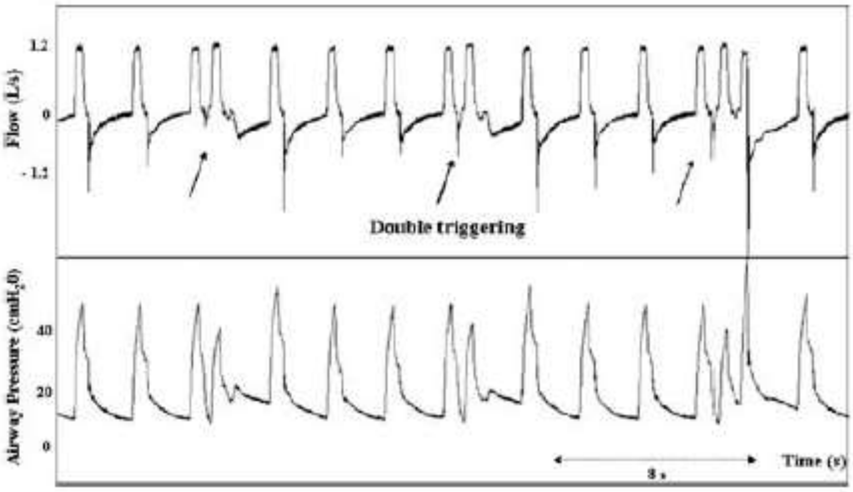
Double triggering (DT)

They are defined by two mechanical breaths divided by an expiratory time smaller than an half of the mean inspiratory time, on the airway pressure tracing.



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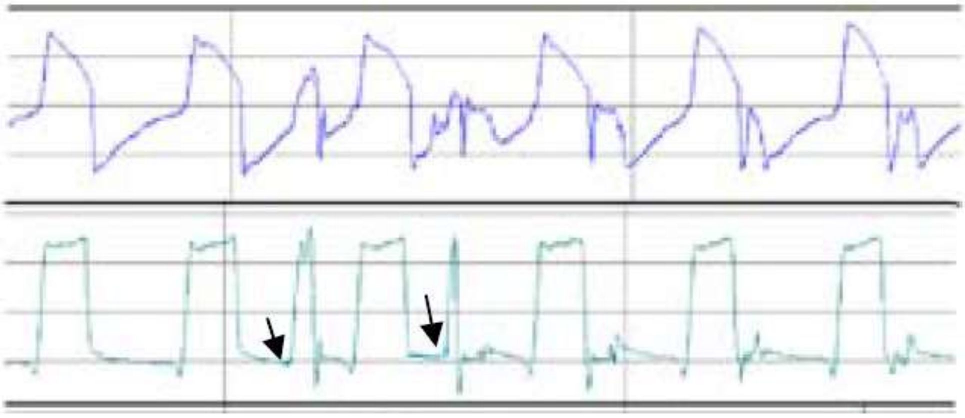
Autotriggering (AT)

It is defined by a ventilator respiratory cycle without any drop of airways pressure, i.e. without a patient trigger. It can be due to cardiac movement or to excessive air-leaks during non invasive ventilation.



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