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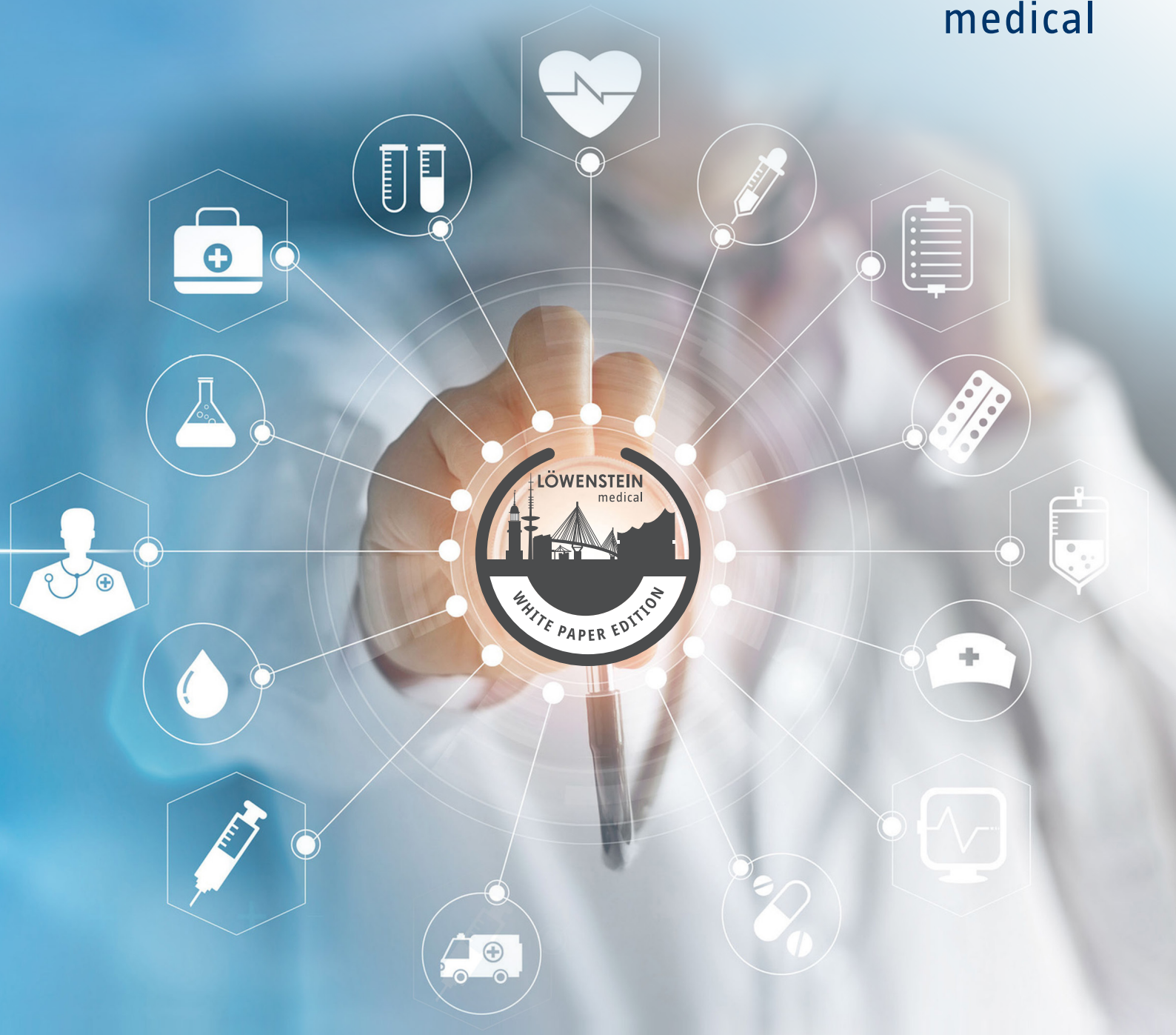


Central Respiratory Events during CPAP/APAP Therapy

Challenges and therapeutic solutions

With people in mind

Central Respiratory Events during CPAP/APAP Therapy

Challenges and therapeutic solutions

Central respiratory events during CPAP/APAP therapy occur in a relevant percentage of Obstructive Sleep Apnea (OSA) patients. They pose a risk to therapy adherence or to existing comorbidities. New scientific findings indicate that the central apneas are frequently closed in nature.

In APAP therapy with FOT (Forced Oscillatory Technique) such events trigger a pressure increase which intensifies pressure-related leaks and side effects and can adversely affect sleep quality and CPAP compliance.

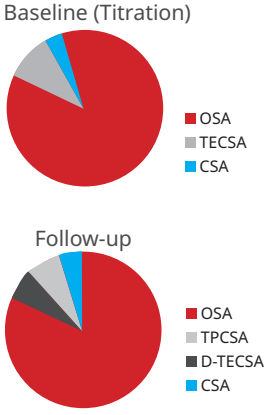
Devices from the latest prisma generation offer an adjustable maximum pressure limit (Pmax oA) in response to closed apneas. Therapy can be optimized for each patient, depending on the presence of obstructive or closed central apnea.

In therapy monitoring the presence of closed apnea above the set threshold can be seen in the high pressure Apnea Index hPr AI and targeted intervention can be carried out.

Definition and Frequency

Definition:

- If central respiratory events (cAI > 5 / h) occur during CPAP therapy after mostly obstructive events (> 50%) in the diagnosis night, the disorder is referred to as **TECSA** (treatment emergent central sleep apnea) (Morgenthaler, Kagramanov, Hanak, & Decker, 2006; Nigam, Riaz, Chang, & Camacho, 2018).
- If the elevated central AHI during therapy persists after several weeks of acclimation to positive pressure therapy, **TPCSA** (treatment persistent central sleep apnea) is said to exist.
- If the elevated central AHI does not occur immediately but rather after weeks or months of therapy, the problem is referred to as **D-TECSA** (delayed treatment emergent central sleep apnea).
- Then there are patients with predominant Central Sleep Apnea (**CSA**) at the time of diagnosis.



Paper	n	% TECSA	Follow-up Period	% TPCSA	% D-TECSA
cassel 2011	675	12,4	3 months	3.2	3.7
Javaheri 2009	1286	6.5	1 month	1.5	Not assessed
Liu 2017	133.006	2.8	3 months	0.7	6.9
Morgenthaler 2006	223	15	Not assessed	Not assessed	Not assessed
Endo 2006	1312	5	Not assessed	Not assessed	Not assessed
Kuzniar 2008	200	6.5	28 weeks	3	Not assessed
Neu 2017	263	9.1	Not assessed		Not assessed

Figure 1: Frequency of central apnea (cAI > 5 / h) in OSA patients during CPAP therapy

Frequency:

- The frequency at which TxCSA occurs varies per study. Reports have been made of connections to gender, age, leakage, opioid intake and comorbidities, but a relation to the level of CPAP pressure has not yet been confirmed.
- The frequency of CSA is influenced mainly by the referral structure and comorbidities among patients in a sleep lab [Rowley 2017]. An attempt to treat CSA with CPAP/APAP is recommended and, for non-responders, ASV therapy as long as no HFrEF with LVEF < 45% is present (Dellweg, Kerl, Hoehn, Wenzel, & Koehler, 2013; Heider et al., 2018; Morgenthaler et al., 2014; Randerath et al., 2017).
- In CPAP therapy central respiratory events often occur in bundles during falling-asleep phases, NREM phases or toward morning.

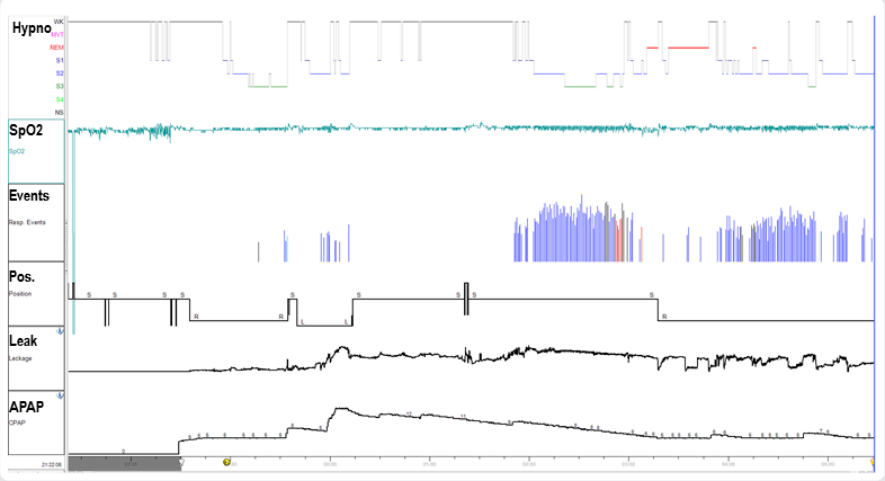


Figure 2: Appearance of central events in a TECSA patient on the first night of APAP therapy

Clinical relevance

- Persistent TECSA puts CPAP compliance and a possible discontinuation of therapy at risk (Liu et al., 2017; Mulgrew et al., 2010). Consequently, the effectiveness of the therapy is reduced. If this risk arises, it is recommended that the patient is treated with ASV mode in order to improve adherence to therapy (Pépin et al., 2018).
- Patients with TECSA experience a less pronounced improvement in symptoms (sleepiness) under CPAP therapy (Cassel et al., 2011).
- Furthermore, TECSA occurs more frequently in the presence of comorbidities such as cardiopulmonary diseases (Hong, Yoon, Cho, Won, & Shin, 2017), which influence the loop gain of the respiratory regulation (Sands et al., 2011). For purposes of therapy monitoring or telemonitoring, attention should be paid to an elevated central AHI.

Challenges in recognizing central apnea with PAP devices

- Modern PAP devices equipped with FOT technology can measure the resistance in the upper airways and distinguish between open and closed apneas. In automatic therapy modes, pressure that acts as a splint is increased only in the presence of closed apnea.
- Pathophysiological studies have shown, however, that central apneas too are often closed. In such cases when a closure is concurrent with a lack of respiratory drive, the upper airways remain closed. (Morrell, Badr, Harms, & Dempsey, 1995), (Badr, F, B, & J, 1995), (Badr, 1996), (Jobin et al., 2012). Respiratory drive and closure of the airways are shown below in four quadrants:

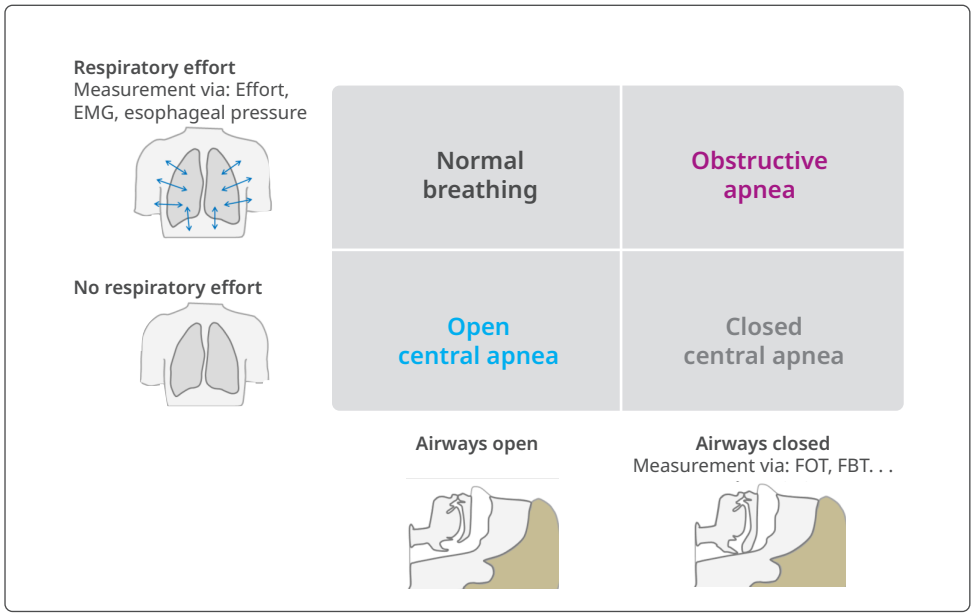


Figure 3: Apnea classification dependent upon respiratory effort and closure of upper airways

- The frequency of closed central apneas varies greatly from patient to patient and lies between 0 and 100 percent of all central apneas. The mean frequency reported is 30 to 50 percent (Morrell et al., 1995), (Jobin et al., 2012). The exact causes for the occurrence of closed and open central apneas have not yet been settled conclusively. It is suspected that closed central apneas arise when the loop gain of the upper airways (UALG) is larger than or equal to the loop gain of the respiratory drive (Bosi et al., 2018).
- An exact individualized differentiation of an event within the four quadrants can be made during therapy monitoring only by means of P(S)G combined with the stored FOT value.
- The presence of cardiogenic oscillations in the respiratory mask during apnea has been identified as a very specific but less sensitive indicator of a lack of respiratory drive (Ayappa, Norman, & Rapoport, 1999), which does not correlate with closure of the upper airways during apnea (Morrell et al., 1995).

Interaction with therapy pressure

- Diverse physiological effects can lead to patient-specific increases or decreases in the frequency of central respiratory events at rising therapy pressures (Salloum et al., 2010), (Orr, Malhotra, & Sands, 2017).
- Data from a Löwenstein Medical Technology APAP study (work in progress) with n=55 patients, including six with TECSA, show no connection between APAP pressure and the relative frequency of central apnea.
- However, the data show that closed central apneas cannot be opened by increasing the APAP pressure. The closures of the upper airways do not appear to be passive obstructions but rather active constrictions. In contrast, obstructive apneas can be eliminated quickly by increasing the therapy pressures. Under effectively functioning APAP regulation, obstructive apneas also occur considerably less frequently than open or closed central apneas.

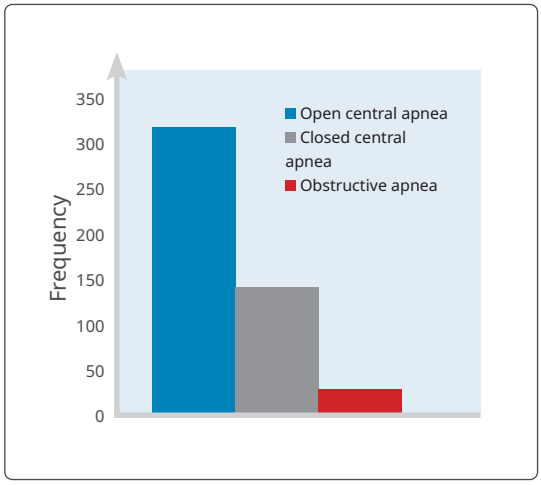


Figure 4a: Frequency of apnea types with an effectively functioning APAP therapy; differentiation of central and obstructive apnea according to PSG scoring; differentiation of open and closed apnea based on FOT technology.

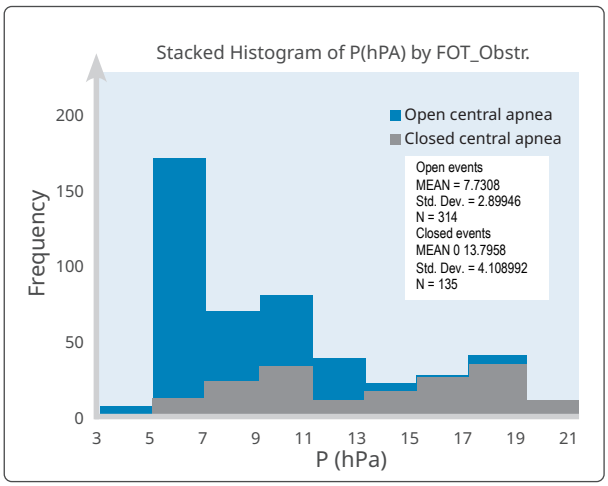


Figure 4b: Distribution of open and closed apneas over therapy pressure.

- The higher the therapy pressure, the more likely the closure detected by FOT is a closed central apnea rather than an obstructive apnea.
- If the therapy device reacts with a pressure increase in each case, the upper pressure limit Pmax will be reached quickly in phases with closed central respiratory events occurring in bundles.
- Excessive pressure increases can intensify leakage and side effects of PAP therapy and impair therapy compliance. Therefore, they should be prevented to ensure good therapy results.
- A general limitation of Pmax, however, can lead to an increased residual obstructive AHI or residual flow limitations in other phases of the night (e.g., REM sleep or supine position) and with an increase in the patient's pressure requirements.

Solution: Adjustable pressure limit (Pmax oA) for closed apneas

The newest generation of prisma devices offer a solution aimed at improving therapy results with residual apneas under APAP therapy.

The setting parameter Pmax oA can be individually defined to a maximum pressure to be reached in response to closed apnea.

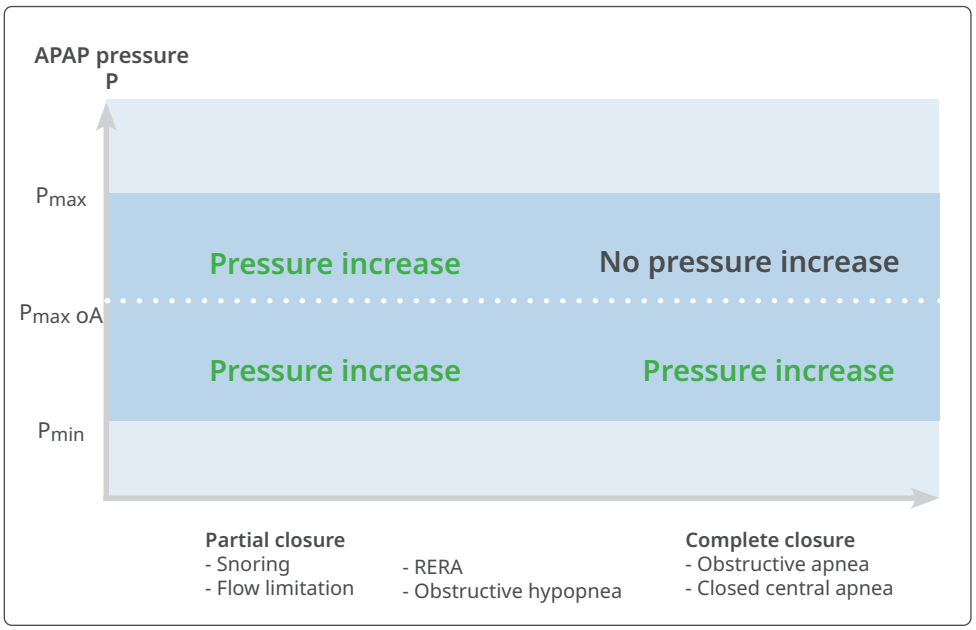


Figure 5: APAP regulation dependent upon the three adjustable limits Pmin, Pmax oA, Pmax

- The factory settings of Pmax oA = 13 hPa or Pmin = + 7hPa effectively meet the therapeutic needs of most patients. Obstructive apneas very rarely occur at this pressure. If the pressure increase is caused by closed central events, the pressure remains moderate.
- If oH, flow limitations and snoring occur, the complete pressure range up to the individually set Pmax can be used.
- If obstructive apneas occur at high pressures, the Pmax oA can be increased by raising Pmin to over 6 hPa. In phases without obstructive events, pressure is again reduced to Pmin.

Monitoring with prismaTS and prisma CLOUD

Closed apneas above the threshold Pmax oA are marked in APAP mode as **"**apnea at high pressure**"** or **"**hPr A**"**. In the case of an elevated high pressure Apnea Index (hPr AI), it is recommended that the following be checked by means of P(S)G:

- whether obstructive apnea is present
  ➜ increase Pmax oA (over Pmin) or switch to BiLevel S
- whether closed central apnea is present
  ➜ consider switching to AcSV or treat comorbidities to improve the outcome.

Conclusion

The recognition of central closed apneas and adequate pressure regulation, particularly in the high pressure range, present a great challenge to providing effective therapy with a PAP device. In these cases the prisma series devices offer a solution for effective therapy and high compliance by means of an adjustable pressure up to defined maximum in response to closed apnea.

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