Central Sleep Apnoea during CPAP therapy
First insights from a big data analysis

April 2018
• Lexicon

• Introduction to Big Data

• The findings of the “Trajectories of Emergent Central Sleep Apnea during Continuous Positive Airway Pressure Therapy” article

• The findings of the “Adherence to positive airway therapy after switching from CPAP to ASV: a big data analysis” article

• Summary
Complex Sleep Apnoea (CompSA)
is a form of CSA that manifests during CPAP therapy. CompSA is the usual term used in Sleep Medicine to refer to any CSA during CPAP therapy.

Transient CSA is a type of CompSA, and the term indicates that CSA was, at least partially, present at the diagnosis of SDB and disappears during CPAP therapy.

Persistent CSA is a type of CompSA, and the term indicates that CSA was, at least partially, present at the diagnosis of SDB, but does not disappear during CPAP therapy.

Emergent CSA is one kind of CompSA. The term indicates that the CSA has appeared during CPAP therapy. This term is more precise as it specifies that the CSA is due to the CPAP therapy. Emergent CSA is the only category of CompSA recognised by The International Classification of Sleep-Disorders-Third Edition.

Obstructive Sleep Apnoea (OSA)
is sleep disordered breathing (SDB) caused by partial or complete obstruction of the upper airways.
### Introduction to Big Data

**Real-life, massive data: A new way to explore clinical challenges**

<table>
<thead>
<tr>
<th>Big data</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big data looks to include as broad a sample as possible and can explore questions of clinical relevance that cannot be answered using small patient populations found in clinical trials 1,2,3</td>
<td>Clinical trials offer a very controlled environment for examining hypotheses and minimising uncertainties</td>
</tr>
<tr>
<td>Huge databases can identify signals or trends, undetectable in smaller data samples, and generate hypotheses</td>
<td>RCT criteria exclude most patients seen in routine clinical practice, and the findings rarely mirror clinical practice</td>
</tr>
<tr>
<td>Difficult to rule out unidentified confounders, uncertainties cannot be eliminated</td>
<td>Clinical trials define a precise patient population</td>
</tr>
</tbody>
</table>

**These two approaches are complementary** and together can provide a better understanding of the question at hand and **minimise the limitations of each methodology**

**References:**
“Trajectories of Emergent Central Sleep Apnea during Continuous Positive Airway Pressure Therapy”
1. A study looked at anonymous data from PAP device telemonitored patients in the US

- A study of CSA/CompSA led by an external international committee of experts (Jean-Louis Pépin (France), Holger Woehrle (Germany), Atul Malhotra (USA) and Peter Cistulli (Australia)) appointed by ResMed looked at anonymous data from 189,946 telemonitored patients treated for SDB with ResMed Positive Airway Pressure devices in the US.

- Data were de-identified and aggregated.

1. A study looked at anonymous data from PAP device telemonitored patients in the US

- Data were collected from a **US PAP devices telemonitoring database** (AirView, ResMed) on patients who **started CPAP or APAP from 1 January 2015 to 2 October 2015**.

- **Patients accepted to be telemonitored.**

- As US data protection laws¹ **allow the use of device data for scientific purposes if de-identified**, an **institutional review board waiver was provided** and patient informed consent was not necessary in this study.

Reference:
1. The United States Privacy Act, the Safe Harbor Act and the Health Insurance Portability and Accountability Act.
2. Complex Sleep Apnea, an area with many clinical challenges and uncertainties

- Research and analysis explored a challenging clinical issue—the natural history of CompSA—to provide insights about CSA during CPAP therapy
  - What has been previously called CompSA is now referred to as emergent CSA
  - The International Classification of Sleep-Disorders-Third Edition\(^1\) and the ERS task force document on central breathing disorder recognised\(^2\) **emergent CSA as a new category of CSA**
  - ERS and AASM use the word **persistent CSA** in their guidelines and statements to identify patients who might require alternative therapy, such as ASV

References:
3. Looking at 133,000 patients, this “big data” analysis provides new information about the natural history of CompSA

- A random sample representing 30% of the database population that began CPAP or APAP in 2015 was analysed for 5 types of data
  - Patient demographic data, treatment usage, clinical metrics, respiratory events, pressure settings
- The definition used for residual CSA was CAI ≥ 5/h, calculated in 1-week assessment windows
- This differs from previous research because it introduces repeated measures based on real-life telemonitoring data rather than single “snapshots” of CSA
- Of the initial patient population, 133,006 used a PAP device ≥1 day with use ≥1 hour in Week 1 and Weeks 10-13 (inclusion criteria)

3. Looking at 133,000 patients, this “big data” analysis provides new information about the natural history of CompSA.

<table>
<thead>
<tr>
<th>Study flow</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% sample of US patients starting between January 1, 2015 and October 2, 2015, and using only AirSense/AirCurve 10 devices with AHI/CAI reporting</td>
<td>N = 189,946</td>
</tr>
<tr>
<td>≥1 day with usage ≥1 hour</td>
<td>N = 188,368</td>
</tr>
<tr>
<td>Valid data entry</td>
<td>N = 187,825</td>
</tr>
<tr>
<td>First device mode: CPAP</td>
<td>N = 175,326</td>
</tr>
<tr>
<td>Continue CPAP for ≥90 days</td>
<td>N = 137,924</td>
</tr>
<tr>
<td>≥1 day with usage ≥1 hour in Week 1</td>
<td>N = 136,725</td>
</tr>
<tr>
<td>≥1 day with usage ≥1 hour in both Weeks 1 and 13</td>
<td>N = 133,006</td>
</tr>
<tr>
<td>All days with usage &lt;1 hour</td>
<td>N = 1,578</td>
</tr>
<tr>
<td>Invalid data entry*</td>
<td>N = 543</td>
</tr>
<tr>
<td>First device mode: bilevel or ASV</td>
<td>N = 12,499</td>
</tr>
<tr>
<td>Terminate CPAP within 90 days</td>
<td>N = 37,402</td>
</tr>
<tr>
<td>Usage &lt;1 hour all days in Week 1</td>
<td>N = 1,199</td>
</tr>
<tr>
<td>Usage &lt;1 hour any day in Week 13</td>
<td>N = 3,719</td>
</tr>
</tbody>
</table>

*Invalid data entry = age implausible (n = 497), or received data and session date not synchronized (n = 46)

4. OSA plus three categories of CompSA were identified: Emergent, transient, and persistent CSA

- Patients with OSA had an average CAI that remained consistently well below the threshold of 5 CSA events per hour
- Patients with transient CSA began above the threshold but then gradually normalised over the 90-day period
- Patients with emergent CSA began below the cut-point of 5, but rose gradually over time
- Patients with persistent CSA remained consistently well above the cut-point

5. Three categories of CompSA were identified: Emergent, transient, and persistent CSA

- New wording has been coined for what we previously called CompSA based on the difference in the CAI during the first 3 months of CPAP therapy

- Only one of the terms, emergent CSA, is currently recognised by the International Classification of Sleep-Disorders Third Edition and the ERS task force document on central breathing disturbances

References:
6. Each category of CompSA is associated with decreased compliance

- Average daily usage hours in the first 90 days were lower in those with any kind of CSA during CPAP therapy than in those without

<table>
<thead>
<tr>
<th>SDB SUBTYPE</th>
<th>CPAP DAILY USAGE (HOURS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA (no CSA)</td>
<td>5.97</td>
</tr>
<tr>
<td>Transient CSA</td>
<td>5.75</td>
</tr>
<tr>
<td>Persistent CSA</td>
<td>5.87</td>
</tr>
<tr>
<td>Emergent CSA</td>
<td>5.66</td>
</tr>
</tbody>
</table>

6. Each category of CompSA is associated with therapy termination

Compared with the OSA group, patients with any CSA during CPAP were less likely to continue using therapy.

The estimated probability of continuing CPAP therapy on day 300 was 83% for OSA, and 79%, 76% and 72% for the transient CSA, persistent CSA and emergent CSA.

6. Each category of CompSA is associated with increased therapy drop-out risk

- Patients with any CSA during CPAP were significantly more likely to terminate therapy after 90 days than those without CSA
  - Patients with emergent CSA were nearly 2 times more likely to terminate CPAP therapy than OSA patients on day 90
  - Hazard ratio [HR] 1.3 for transient; 1.5 for persistent; 1.7 for emergent

This analysis has been done according to the US definition of residual or persistent CSA, which is CAI ≥ 5/h. The recent European Respiratory Society (ERS) task force states that patients with persistent CSA with a residual AHI ≥15/h should be switched to ASV.

The investigators also performed a post-hoc analysis using this definition to look at any differences.

When using this more restrictive ERS task force criteria, prevalence of residual CSA differs slightly (1.2%) from the previous finding (3.5%).

Of this 1.2% with residual CSA:
- 52.3% had transient CSA
- 21.9% had emergent CSA
- 25.8% had persistent CSA

All other findings were similar: The same trajectories impact compliance or therapy termination risk similarly whether identified using ERS task force criteria or US criteria.

* ASV therapy is contraindicated in patients with chronic, symptomatic heart failure (NYHA 2-4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) and moderate to severe predominant central sleep apnoea.

7. These findings remain consistent using either the ERS or the US definition of persistent CSA (AHI ≥15/h or CAI >5/h) 

The same trajectories impact compliance or therapy termination risk similarly whether identified using ERS task force criteria or US criteria

“Adherence to positive airway therapy after switching from CPAP to ASV: a big data analysis”
8. Switching from CPAP to ASV in patients with emergent or persistent CSA may improve adherence

- A second analysis was performed with a random sample representing 30% of the database population that had begun CPAP therapy or ASV therapy from 1 Jan to 2 Oct 2015 plus all who switched from CPAP to ASV over the same period.
- Adherence (US Medicare definition*) and device usage were determined for 3 groups.

* Adherence to CPAP is defined as usage greater or equal to 4 hours per night on 70% of nights during a consecutive 30 days anytime during the first 3 months of initial usage.

8. Switching from CPAP to ASV in patients with emergent or persistent CSA may improve adherence

**Average PAP usage hours before vs after CPAP to ASV switch**

8. Switching from CPAP to ASV in patients with emergent or persistent CSA may improve adherence

**Average AHI before vs after CPAP to ASV switch**

![Graph showing average AHI before and after CPAP to ASV switch]

17.34 (15.17, 19.41) vs 4.10 (3.30, 4.89)

8. Switching from CPAP to ASV in patients with emergent or persistent CSA may improve adherence

- These data suggest that normalisation of CSA during CPAP (transient CSA) may contribute to better long-term adherence to CPAP therapy

- However, if there is persistence of CSA after 2 weeks*, then the patient fits within the trajectory of emergent or persistent CSA as shown by these data and will probably require a switch to ASV

* Similar trends were observed when day-by-day values of CAI and AHI over the first 2 weeks of therapy were analyzed

Summary

• Big data analysis provides a new way of investigating questions of clinical importance

• The big data study of CSA/CompSA characterised the SDB landscape, differentiating OSA from CSA and the various CSA subtypes—transient, emergent, and persistent—from each other

• All forms of CSA negatively impact CPAP therapy, decreasing compliance and increasing therapy drop-out risk

• Patients who experience emergent or persistent CSA while on CPAP therapy may benefit from a switch to ASV

• Patients who experience transient CSA with subsequent normalisation may continue on CPAP

• This analysis, the biggest ever done in CompSA, may challenge the current definition of Central Sleep Apnea and clinical practice; furthermore, the scientific community may consider updating the guidelines according to these new findings
ResMed remains committed to ASV

- ResMed is the sponsor of two major registries with ASV:
  - The FACE registry is looking at new evidence in a population of 500 patients with heart failure with preserved ejection fraction (HFpEF) eligible for ASV
  - The READ-ASV registry will look at the current indications for ASV in routine clinical practice across Europe and collect data on ASV impact on daytime symptoms, sleep quality and quality of life (QoL)

- ResMed is funding the French Sleep Society registry FACIL-VAA, which will look at ASV therapy impact on QoL, treatment efficacy and health care costs in a population of 520 CSA patients with all CSA aetiologies (CompSA, post stroke, opioid-induced CSA, neurological disease, HFpEF)

References:
1. FACE registry: clinicaltrials.gov Identifier: NCT01831128
2. FACIL-VAA registry: clinicaltrials.gov Identifier: NCT02835638
3. READ-ASV registry: clinicaltrials.gov Identifier: NCT03032029