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Original Article

The SERVE-HF safety notice in clinical practice – experiences of a tertiary sleep center

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ABSTRACT

Background: In May 2015, the results of the SERVE-HF trial – addressing adaptive servoventilation (ASV) in chronic congestive heart failure (CHF) patients with central sleep apnea (CSA) – prompted a field safety notice. It was recommended to identify CHF patients treated with ASV and to advise the discontinuation of the treatment. We aimed to analyze the identification process and effect of ASV discontinuation on affected patients.
Methods: 126 patients treated with ASV on May 13th, 2015 at our institution were retrospectively analyzed. Treatment decisions, effect of ASV discontinuation and clinical course were followed for a year. Patients on ASV with CHF were compared to those without CHF.
Results: The risk criteria of the safety notice were fulfilled by 10.3% of patients (13/126). Additional echocardiographies were performed in 38%. ASV was discontinued in 93% of patients without adverse events (emergency hospitalization in n = 1). CSA reappeared immediately. Day- or nighttime symptoms were reported by 61%. Symptomatic patients were started on alternative treatments. CHF and non-CHF patients differed in cardiac function and type of SDB. CHF patients had shorter overall treatment duration. Compliance to ASV was similar in both groups with a median usage of 412 min (269; 495)/night in the CHF group and 414.5 min (347; 480) in the non-CHF group.
Conclusion: Identification of patients "at risk" is feasible but outcome of discontinuation of ASV cannot be evaluated based on these data. ASV withdrawal in patients with stable chronic CHF and CSA leads to an immediate return of sleep disordered breathing. Symptomatic patients may ask for alternative treatment options.

1. Introduction

In May 2015, the results of the SERVE-HF study, a large multicenter randomized controlled trial addressing adaptive servoventilation (ASV) in chronic congestive heart failure (CHF) patients with central sleep apnea (CSA), showed an unexpectedly higher risk of cardiovascular mortality in CHF patients who were treated with ASV compared to the control group [1]. This prompted field safety warnings by the manufacturers of the ASV devices, legal authorities, and sleep and respiratory societies [2–5]. The safety notice recommended to immediately stop the prescription of ASV devices to patients with symptomatic heart failure with a reduced ejection fraction (HFrEF) of ≤45% and central sleep apnea. Physicians were also advised to identify and contact prior patients with symptomatic heart failure who were already treated with ASV in order to discuss the study results [2–5]. It was suggested to "strongly reconsider recommending that they stop ASV treatment," initially irrespective of the indication for ASV [2]; the exact means for identifying or counseling the patients who were already treated with ASV was not predefined [2,6]. In August 2015 the contraindication of ASV therapy was narrowed to patients with symptomatic, chronic heart failure (NYHA 2–4) with reduced LV-EF≤ 45% and moderate to severe predominant central sleep apnea [2].

The SERVE-HF study raised many questions on how ASV might have caused the increased risk of cardiovascular death in patients with heart failure and reduced ejection fraction LV-EF≤ 45% [7–9]

Abbreviations: AASM, American association of sleep medicine; AHI, Apnea hypopnea index; ASV, Adaptive servoventilation; CPAP, Continuous positive airway pressure; CHF, Congestive heart failure; CSA, Central sleep apnea; ESS, Epworth sleepiness scale; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; OSA, Obstructive sleep apnea; SDB, Sleep disordered breathing; SpO2, Oxygen saturation.

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and the discussions included concerns on the study methodology and performance. Nevertheless, the recommendations of the safety notices to stop ASV were clear and put the treating clinicians in the position to discontinue ASV without additional information on whether an abrupt discontinuation of the ASV would be safe in the heart failure patients or how to choose potential alternative treatment options. Further, due to the then urgent warning, national or international registries had not been established and it was difficult to obtain information on how to proceed in daily practice. We therefore aimed to retrospectively analyze the process of ASV discontinuation and observe the clinical course of affected patients after ASV withdrawal at our institution.

2. Methods

In a retrospective single-center study we reviewed the clinical course of all patients who were treated with ASV devices on May 13th, 2015 in our department, observed their clinical course in the year after the ASV safety notice and compared patients with CHF with non-CHF patients. The study was approved by the institutional review board and the Cantonal Ethics Committee Bern (REC No: 2016-00592).

2.1. Risk stratification

Within the clinical routine all patients on ASV are seen at our institution at least once per year. Immediately after the safety warning, patients were pragmatically triaged into three risk categories based on their medical records: ("potentially at risk," "potentially no risk," and "unclear risk"). The consultations of those patients who were potentially affected by the safety notice or in whom the risk was unclear were moved forward to inform, reassess, and counsel the patients. The other patients were reassessed at their scheduled clinical routine visit. Patients were initially classified as being "potentially at risk" if they had a history of heart failure, known LV-EF $\leq$45% or if they had fulfilled the SERVE-HF inclusion criteria [1] when ASV was started. In our country, all patients with HFrEF who used ASV devices were included in the first safety notice released on May 13th 2015 [3]. Therefore CHF patients with a LV-EF $\leq$45% who were treated with ASV for treatment emergent central sleep apnea or coexisting OSA and CSA were initially also classified as "potentially at risk", reassessed as a priority and ASV discontinuation discussed with these patients. The "potentially no risk" category applied if patients did not fulfil the SERVE-HF criteria, had no history of any cardiac disease or a known heart disease with a recent LV-EF of >45%. Patients were classified as "unknown risk" if there was no sufficient information on cardiac function and symptoms in their medical records. After the reassessment patients were still classified as "at risk" if they fulfilled the SERVE-HF inclusion criteria [1] when ASV was initially started or if they had a reduced LV-EF $\leq$45% at the reassessment and no available baseline information on cardiac function. The criteria for "no risk" were similar to "potentially no risk" with the addition of no change in symptoms if no additional echocardiography was performed that confirmed a LV-EF >45%.

2.2. Chart review and data extraction

Clinical information for the analyses was obtained from sleep medicine consultations, echocardiography reports, respiratory polygraphies, polysomnographies, and ASV machine read outs. The following parameters were evaluated: demographics, clinical symptoms, baseline sleep disordered breathing (SDB), medical history, echocardiography and/or cardiac catheter data, date of ASV initiation, adherence data as well as ventilator settings and residual respiratory events measured by the ASV machines. The number of medical tests and treatment modifications that were initiated after the safety warning were also recorded. The following outcome parameters were also assessed in those patients who were advised to stop the ASV treatment and agreed to a discontinuation: clinical symptoms and results of repeated sleep studies after ASV discontinuation, type and effectiveness of the initiated alternative treatment modalities, and clinical course and treatment one year after the safety notice.

2.3. Statistics

Results are expressed as frequencies, median followed by interquartile ranges in parenthesis or as mean $\pm$ SD unless indicated otherwise. Mann-Whitney-U tests were used for the comparison of groups. The significance level of all analyses was set to 0.05. Data was analyzed using SPSS Version 21 (Chicago, USA).

3. Results

3.1. Risk classification and reassessment

On May 13th, 2015 when the SERVE-HF safety notice was first released, overall 126 patients were treated with ASV devices at our institution. The indications for ASV use were treatment emergent central sleep apnea (n = 51 patients, 40.5%), co-existing OSA and CSA, insufficiently controlled with CPAP (n = 27 patients, 21.4%), or CSA (n = 48 patients, 38.1%). CSA was related to a cardiovascular disease with or without HFrEF (n = 33), neurological disorders including stroke (n = 13) or medication (n = 2). According to the risk classification based on the initial chart review 75 patients (59.5%) were classified as "potentially no risk" whereas 24 patients (19%) were identified as being "potentially at risk". In 27 patients (21.4%) the risk could not be determined from the records only (Fig. 2).

121 patients (96%) were reassessed in clinical consultations. Four patients had moved abroad, or did not respond to the invitations. One "at risk" patient died from a cerebral hemorrhage not related to the ASV treatment or a cardiac disease before his prescheduled clinical visit in May 2015. After the clinical reassessment the majority of patients (n = 104, 82.5%) could be classified as "no risk", due to a LV-EF >45% and continued the ASV treatment. 17 patients (13.5% of the cohort) were still in the "at risk" group (Fig. 1). Strictly speaking, only 13 patients (10.3%) fulfilled all of the SERVE-HF inclusion criteria, the other four at risk patients had treatment emergent central sleep apnea (n = 2) or co-existent OSA and CSA (n = 2) and a LV-EF <45%.

3.2. CHF and non-CHF patients

As expected, the 17 "at risk" patients differed from the 104 "no risk" patients in cardiac function, history of heart disease, and type of SDB. The CHF patients also had a significantly shorter overall treatment duration than the "no risk" group. Demographics, data on heart disease, SDB and ASV treatment are depicted more detailed in Table 1.

3.3. Additional examinations

Patients who were already treated for HFrEF usually had an echocardiography performed within the last 12 months. Other patients with a cardiac co-morbidity had no recent echocardiography or complained of dyspnea, which led to the initiation of 48 echocardiographies because of the safety notice. Nine patients who were initially classified as "potentially at risk" had no baseline