SERVE-HF – Was treating a central neurological disturbance of breathing control by a mechanism initially designed to keep open an obstructed airway always doomed to fail?

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On May 24th this year at the Heart Failure Association meeting in Seville, Spain I had the pleasure of chairing a special session at which Martin Cowie, chairman of the Steering Committee, presented the results of SERVE-HF, the largest ever trial of treatment of predominant central sleep apnoea (CSA) in chronic heart failure (CHF). The final results were not presented at this session, for these were embargoed until presented at the European Society of Cardiology Meeting in London on September 1st, with simultaneous publication of the main results paper in New England Journal of Medicine[1]. Despite that, it was still a fascinating overfilled session, such was the interest in the heart failure community. What we did hear, however, was that 11 days prior (on May 13) the sponsor of SERVE-HF, Resmed had issued a press release stating *"ResMed (NYSE: RMD) today announced that SERVE-HF, a multinational, multicenter, randomized controlled Phase IV trial did not meet its primary endpoint. SERVE-HF was designed to assess whether the treatment of moderate to severe predominant central sleep apnea with Adaptive Servo-Ventilation (ASV) therapy could reduce mortality and morbidity in patients with symptomatic chronic heart failure in addition to optimized medical care. The study did not show a statistically significant difference between patients randomized to ASV therapy and those in the control group in the primary endpoint of time to all-cause mortality or unplanned hospitalization for worsening heart failure (based on a hazard ratio [HR] = 1.136, 95 percent confidence interval [95% CI] = (0.974, 1.325), p-value = 0.104). A preliminary analysis of the data identified a statistically significant 2.5 percent absolute increased risk of cardiovascular mortality for those patients in the trial who received ASV therapy per year compared to those in the control group. In the study, the cardiovascular mortality rate in the ASV group was 10 percent per year compared to 7.5 percent per year in the control group."* In answer to many very lively questions Prof Cowie revealed at that stage that there was 2.5 percent absolute increased annual risk of CV mortality - 10.0 % p.a. in ASV group, 7.5 % p.a. in control group, (HR =1.335, 95% CI's 1.070 - 1.666, p= 0.010) and furthermore that they had found no subgroup who had benefitted from treatment in terms of the primary end-point of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock), or unplanned hospitalization for worsening heart failure. They had also seen no improvement in LVEF, quality of life (QOL) or patient preference, but that sleep architecture had improved, with more REM sleep. He stated verbally that there was an increased hazard in lower LVEF patients, and that the more the patient used a mask (days per week and hours per night) the worse the hazard, but that excess deaths did not appear to occur during use of the mask based therapy at night, rather they were daytime and apparently sudden. Also that ICD's did not protect fully against the excess of "sudden" deaths in the treated group. The results were the buzz of the meeting for they were almost totally unexpected.

I must admit to an interest here, for I have held a long term fascination with reflex control systems in the syndrome of CHF, performing some of the first studies of the modern era on chemoreflex sensitivity, periodic breathing (PB) and Cheyne-Stokes respiration (CSR) in CHF. We found that both were surprisingly common in CHF patients and both were associated with augmented chemoreflex sensitivity, so much so that, not only was there an extremely high correlation between the power of the oscillatory pattern of breathing and chemosensitivity[2], but that switching off chemoreflex firing with inspired oxygen, rapidly and reproducibly abolished the oscillatory breathing pattern. We and close colleagues also later showed even in normals we could mimic periodic breathing and even generate a pattern close to Cheyne-Stokes respiration by manoeuvres such as voluntary hyperventilation followed by rest, as a way to mimic virtually unopposed chemoreflex control of the circulatory and respiratory rhythms. Indeed I had earlier set up the London heart

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failure clinic from which Martin Cowie had recruited some of the first CHF patients to be studied for this therapy of CSA and did some of early studies jointly with another SERVE-HF author and sleep expert, Dr. Anita Simmonds. Based on our, and many other groups' pathophysiological and epidemiological studies central sleep apnoea (CSA), as opposed to obstructive (OSA), is seen mainly to be a complication of CHF. Pathophysiologically it is associated with increased chemosensitivity, a slowed circulation and reduced baroreflex and other cardiopulmonary reflex sensitivities. Using mathematical modelling we predicted that CSA would occur exactly in these circumstances due to the characteristic behaviour of stable/unstable feedback loops in any controlled servo-adjusted feedback loop system (which the body is for many of the parameters it attempts to keep stable over time)[3]. In the situation of CHF many factors predict an harmonic oscillation of breathing drive is likely to develop. At its most extreme this behaviour of the "system" leads to cyclical swings of periodic hyperventilation and apnoea, recognised since classical times as a sign of severe illness and near death. Full blown CSR, sub-apnoeic oscillatory periodic breathing (PB) and nocturnal CSA are three manifestations of the same oscillatory behaviour in the breathing control system. Apart from CHF the other main causes of CSA or CSR are neurological disorders or severe multi-organ failure in which central respiratory control becomes very disordered.

So what happened in SERVE-HF? It should have been a positive not a negative trial. CSR, CSA and PB had all been shown to be negative prognostic markers in CHF, as had the analogous pattern of exercise-induced oscillatory ventilation (EOV). All are inter-related and all owe their genesis to the same physiology. Heightened chemoreflex sensitivity, exaggerated ventilatory drive, an increase in the ventilatory response to exercise measured as the Ve/VCO2 slope during cardiopulmonary exercise testing, chemoreflex-dependent very low frequency rhythms (VLF) in heart rate variability and exercise-induced oscillatory ventilation (EOV)[4] had been repeatedly shown to be associated with an increased risk of death in CHF. Thus the target was an appropriate one, a predominant central pattern sleep apnoea in CHF. The trial used an effective therapy. For years patients with OSA had received relief of obstructive sleep apnoeas by the use of positive airway pressure masks in the form of continuous positive airway pressure (CPAP). This therapy had been modified to deal also with central sleep apnoeas by modifying the airway pressure to "even-out" variations in breathing intensity by a servo-controlling level of positive airway pressure; the Resmed system being called, auto-set Assisted Servo-Ventilation (or ASV), and these systems were shown to reduce the frequency of central apnoeas in CHF patients with CSA. It should have been a "slam-dunk" that the SERVE-HF trial would have shown a reduced mortality. It didn't. The results went the wrong way. Why?

Lets first review what SERVE-HF was and what it showed. The aim of SERVE-HF was to investigate the effects of adding ASV to guideline-based medical management on survival and cardiovascular outcomes in patients with heart failure with reduced ejection fraction and predominant CSA[5]. It was of randomized, controlled parallel group, event-driven design. ASV was commenced in the hospital using Polygraphy or Polysomnography and commenced with the mask on its default settings. Expiratory PAP was increased to treat any coincident OSA and the airway pressure support was up-titrated to treat CSA. Patients were recruited from 91 centres in Europe and 1325 patients were enrolled over 5 years. Most measured sleep parameters were improved by therapy when it was being used, with the overall and central apnoea/hypnoea indices (AHI) both being significantly reduced. Yet the adverse effects on patients' outcomes described above still occurred, and yet worse was reported. Cardiovascular death without prior worsening of heart failure, a surrogate for sudden death, was significantly made more likely by ASV, with a hazard ratio of 2.6 (95%CI's: 1.5-4.4, $p<0.001$). In the world-wide discussion that has followed three theories for why these adverse effects were seen have emerged:

1. CSA (in the form of CSR) is a beneficial compensatory mechanism that should be allowed to persist
2. Intermittent use of the therapy was harmful
3. Positive pressure delivered by ASV was harmful

The first I call the Naughton theory following a very prescient editorial published by Matt. Naughton some years ago in which he said CSA was a good thing and should not be treated[6]. He quoted several potential mechanisms for this that I will not go into detail here. But I do not agree with him. As I have reviewed above so much of the pathophysiology underlying CSA and CSR is harmful and associated with a poor prognosis that for it to be beneficial to the patients would require a compensatory protective mechanisms so powerful it overcame the undoubted adverse prognostic features of having these abnormalities in the first place. Numerically speaking if any of the abnormalities I describe as being characteristic of CSA/CSR confer anything like a doubling in the risk of death (and many observational studies suggest even more that this), then the protective effect of CSA must be even greater than this for its removal to be associated with an increase mortality. We just never see such a powerful protective effect for any therapy. But my simple "black-box" approach to test if CSA is good for and should not be treated at all is the following, to see what happens when you do treat it away or when it remains despite your treatment. The earlier CANPAP trial of the simpler mask therapy CPAP in CHF with CSA was neutral[7]. But importantly for our thought experiment a later post-hoc analysis showed that the worst prognosis was seen in two groups, those with CSA who were not treated and those with CSA who were treated but in whom the CSA persisted[8]. Those who were treated but whose CSA was suppressed did far and away the best. Thus the theory that the CSA is essential to patients' survival is fiercely contradicted by this earlier trial analysis. What about the second theory, of the on-off effects of ASV being harmful. It cannot be that there was simply not enough ASV to show a benefit; that would have lead to a reduced benefit or a neutral result; somehow harm was introduced. It could be speculated that somehow the intermittent use of ASV was harmful when more prolonged use would have been helpful, I simply feel this is unlikely even though we do not have the data available to investigate this at present. The third theory is my favourite, that the positive pressure in the airways was the baddy. This makes some sense. A positive airway mask system developed initially to keep a collapsing airway open and later adapted to servocontrol variations in the airway flow, came to be applied in a condition characterised by neurological abnormalities in breathing control and oscillatory reflex control systems, without thought whether this is the most appropriate way of treating this condition. What does positive airway pressure do? In OSA it may be helpful. The CHF patients with OSA may have increased left ventricular wall stress and impaired LV functional reserve. To this is added very high negative intra-thoracic pressure swings as the patients gasp against a closed airway in a futile attempt to get air into the lungs. The very high negative intra-thoracic pressure is added to the LV intramural pressure to create the LV wall stress and this can shoot up dramatically and harm and impair LV systolic function. Studies of positive airway pressure (PAP) in OSA have shown this. In CSA by contrast the negative intra-thoracic pressure is not so marked, and is slowly cyclical, being

zero as often as it is marked. If the mask now generates even higher levels of PAP especially during the respiratory cycle and often much higher than that used in OSA then the net effect may be a reduced LV transmural pressure gradient but much more adverse effects on the right side of the circulation, with a likely impairment of right ventricular function in those at risk. The often-impaired RV function combined with reduced venous return and increased afterload due to left sided filling pressures being increased by the positive intra-thoracic pressure mean the RV may fail to adequately perfuse the lungs. This may cause ventilation-perfusion mismatch and further worsening of long term RV function and can set up a background to opportunistic ventricular arrhythmias. In support of this notion were some interesting secondary analyses of SERVE-HF seen only in the online appendix and not published in the main paper. Of 10 sub-groupings analysed (including AHI, NYHA class, aetiology, age, gender, eGFR, LVEF, beta-blockers, BMI and LVEF) only one showed a significant treatment sub-group interaction (in fact highly significant, p=0.006) and that was the percentage of CSA episodes that were defined as true CSR, i.e. the more florid form. As stated earlier there is considerable overlap between OSA and CSA with many patients having a mixed pattern. If treatment of OSA is good but ASV treatment of CSA is harmful then one might expect that the milder forms of CSA, such as one would see in a mixed pattern, may get some benefit or at least little harm. Those patients with a high % of true CSR would be more likely pure central apnoea patients with the myriad of reflex abnormalities I described above, and very little OSA would be less likely to benefit from ASV, whereas those with a lower % of true CSR would be more like OSA patients and get less harm and possibly more benefit - this is precisely what was seen in SERVE-HF.

Conclusions

I am left to conclude that ASV treats OSA well, and can suppress CSA (but is not necessarily doing this in a helpful way). ASV is not logical in pure CSA or in its more exaggerated form CSR where it can lead to persistent and increasing use of positive airway pressures, which in turn may have deleterious effects on right sided preload and RV function. This mix may actually increase mortality in patients at risk. We should not abandon attempts to treat CSA or CSR but we should look at the effects of ASV that may have caused harm and devise therapeutic interventions to achieve the benefit of less CSA without such harm. Many trials remain to be performed, not least repeating the ambition of SERVE-HF with other therapies and investigating the haemodynamic effects of positive airway pressure and alternative strategies in different sub-sets of patients with different haemodynamic profiles.

Statement of ethical publishing

The authors agree to abide by the requirements of the "Statement of publishing ethics of the International Cardiovascular Forum Journal"[9].

Conflict of interest:

The author has received consulting and lecture fees from Resmed and Respicardia

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