What are the reasons for divergent outcomes of the SERVE-HF vs ADVENT-HF?

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Arkansas Slep Meeting, 2024

Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The American Academy of Sleep Medicine and the Sleep Professionals of Arkansas & Washington Regional Center for Sleep Disorders. The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Conflict of interest

Shahrokh Javaheri, MD disclosed a financial relationship with

Zoll Respicardia (consultant), ResMed, and Phillips (received honorarium within the prior 24-months)

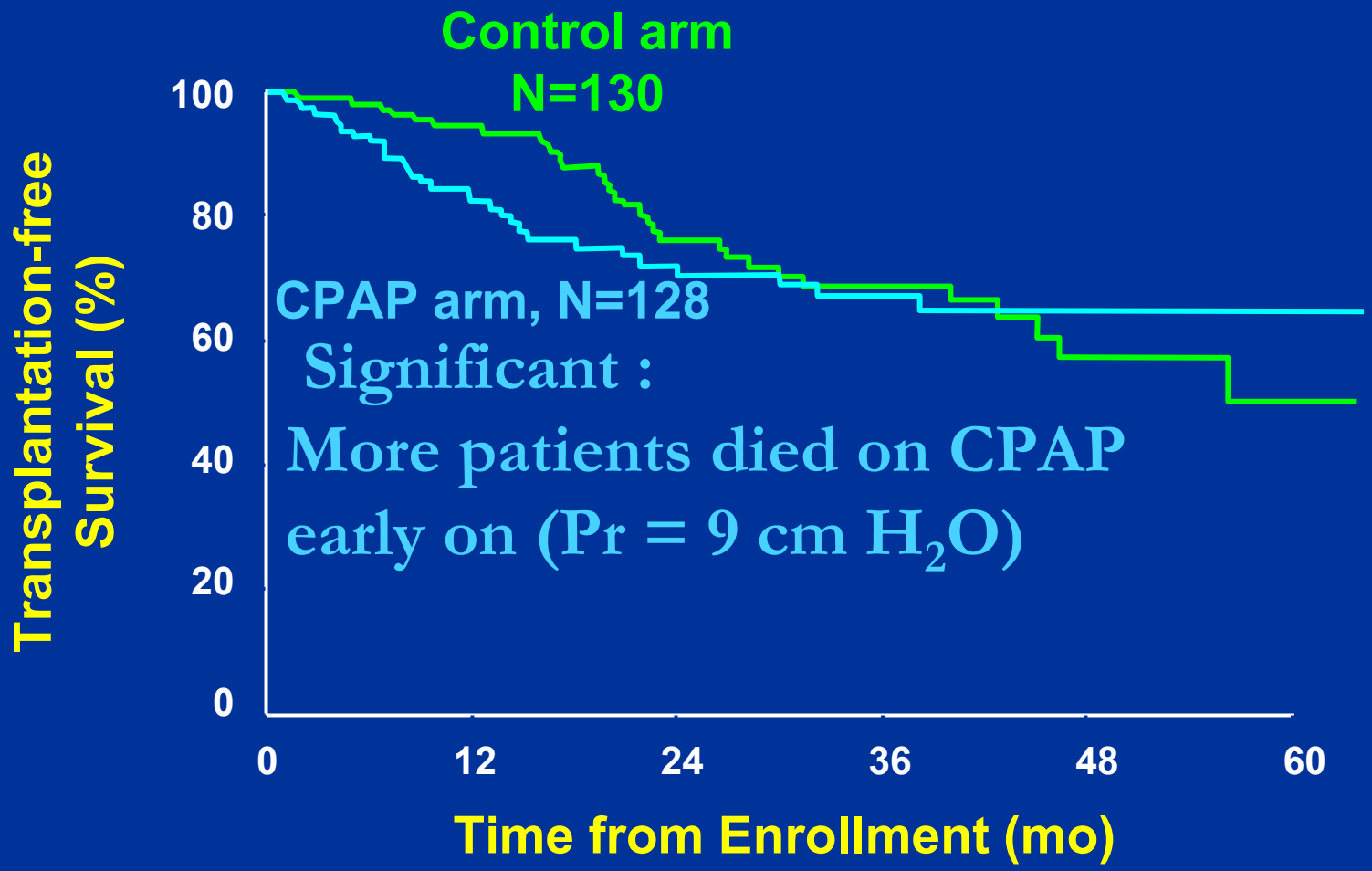
The relevant financial relationships listed for this individual have been mitigated.

Learning Objectives

Upon completion of this course, attendees should be able to…

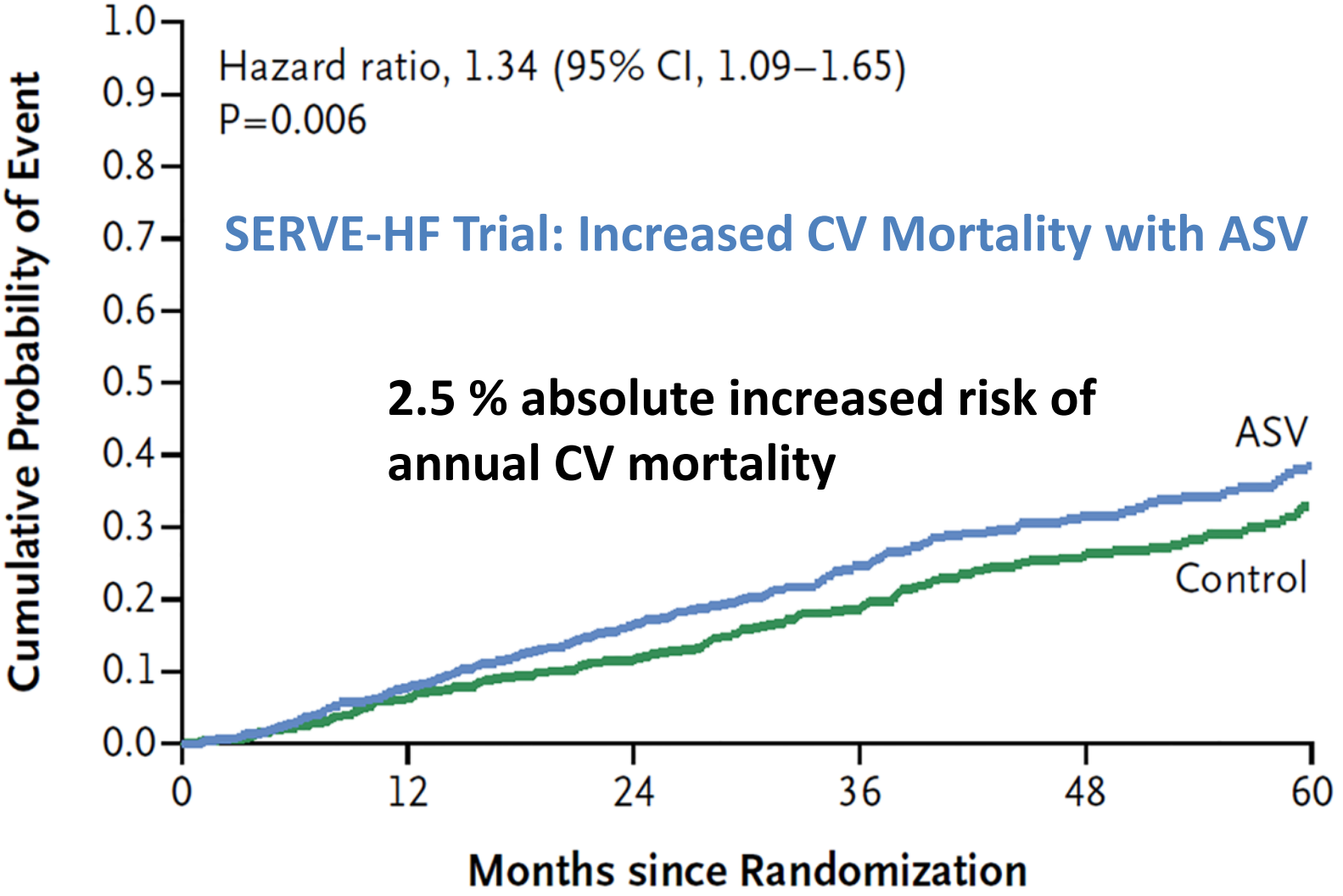
- Identify why the SERVE-HF resulted in excess mortality in the ASV arm
- Gain an understanding on the differences between SERVE-HF and the ADVENT trial
- Gain an understanding on the algorithm of ASV devices

CANPAP Trial
Increased CV mortality with CPAP



Bradley TD et al., *N Engl J Med* 2005

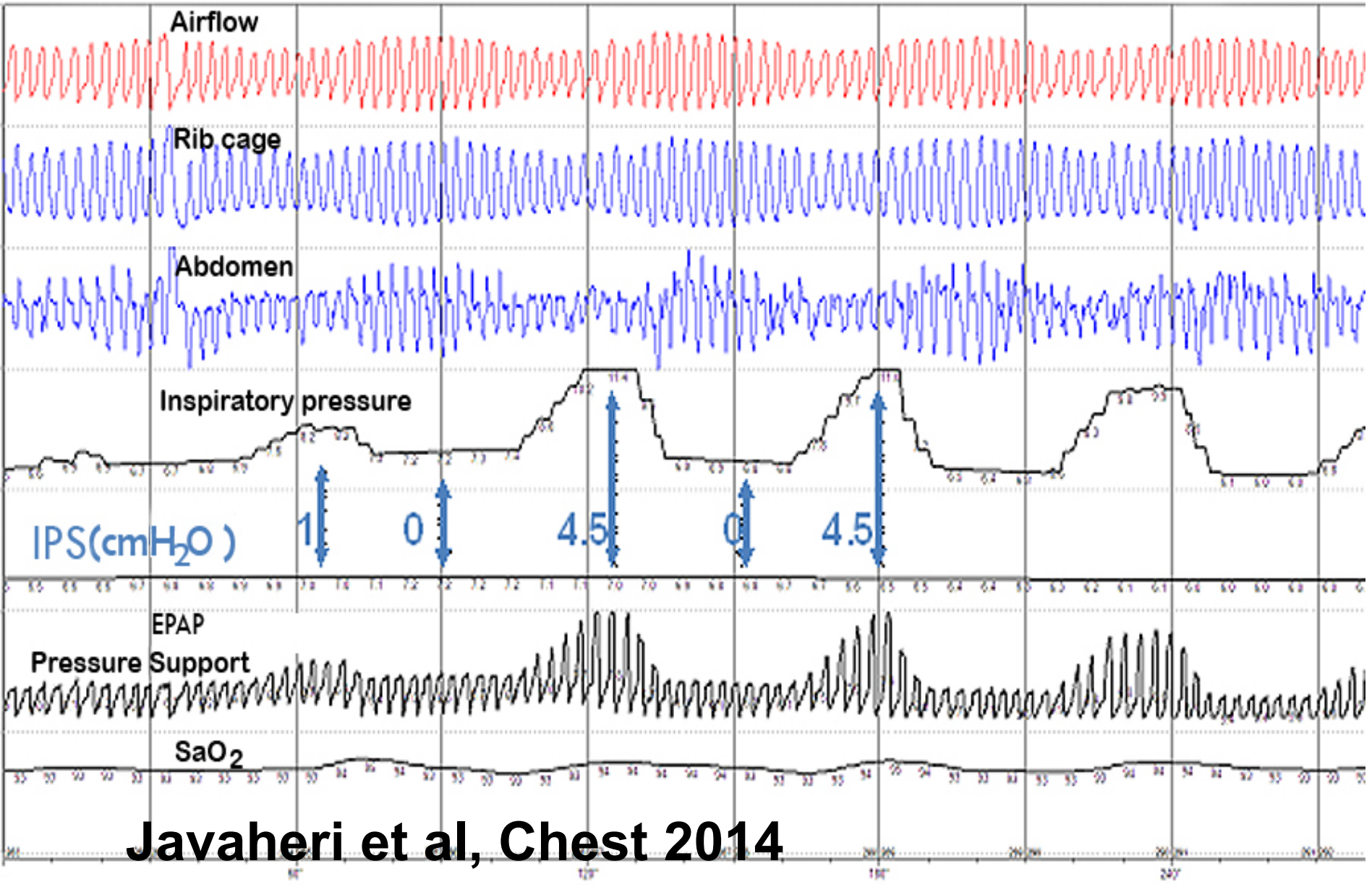
Death from Cardiovascular Causes



No. at Risk

Control	659	563	493	334	213	117
ASV	666	555	466	304	189	97

Changes in inspiratory pressure support during Hunter-Cheyne-Stokes breathing



Javaheri et al, Chest 2014

SERVE-HF

1300 patients with chronic HF with LVEF ≤45% NYHA class III or IV, or NYHA class II with ≥1 hospitalization for HF in the previous 24 months with predominant central SDB defined as an AHI ≥15 events/h with ≥50% central events and a central AHI ≥10 events/h, derived from PG or PSG were randomized to ASV or UC

NEJM, 2015, Cowie et al.

Design of SERVE-HF

NEJM online

666 patients were assigned to ASV, of whom 21 and did not receive the device: 666-21 = 645. Of these 82 withdrew, 2 discontinued ASV and one lost to follow-up: 645-85= 560.

Of 560, 168 patients discontinued ASV:

560-168 = **392** who should have completed

Meanwhile 87 patients from the control arm began using PAP device, mostly ASV

In intention to treat analysis one considers all patients in the arm they were allocated to and this includes those who did not use ASV.

Design of SERVE-HF

NEJM online

Statistical analysis

The primary analysis was conducted in the intention-to-treat population consisting of all the patients who underwent randomization with adjudication of all the events (651) that occurred before database was locked

Design of SERVE-HF

NEJM online

666 patients were assigned to ASV, and 659 to control arm

Centers, PSG and PG

70% of all patients from Germany, all with PSG
30% from the remaining 10 centers, all PG

Then, PSG AHI, normalized to total recording time

Design of SERVE-HF NEJM online

LVEF issues

Inclusion criteria: ≤ 45%

Mean LVEF= 32%

Range: ASV arm: 10% to 54%

Control arm 9% to 71%

Missing LVEF:

ASV arm: 130 (N= 666, 20%)

Control arm: 126(N=659, 19%)

SERVE_HF

ASV started in hospital with full face mask

Standard ASV settings

It is recommended that major mask leaks should be avoided if possible

The target is to reduce AHI to 10/h within 14 days of starting ASV. If this is shown not to be the case at clinic visits (based on the data downloaded) then proper mask fitting is again undertaken and device settings adjusted for each patient

Patients contacted by telephone at 6 and then every 12m.

SERVE-HF Outcomes

Primary

All cause mortality, cardiovascular mortality, and planned hospitalization for worsening heart failure, resuscitation of cardiac arrest, appropriate ICD shock for ventricular arrhythmia and cardiac transplantation

Secondary

New York heart association, Epworth Sleepiness Scale and Minnesota living with heart failure

SERVE-HF trial did not meet its primary z int

SERVE-HF : Primary Outcome Neutral

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

HR = 1.136

95% CI = 0.974, 1.325

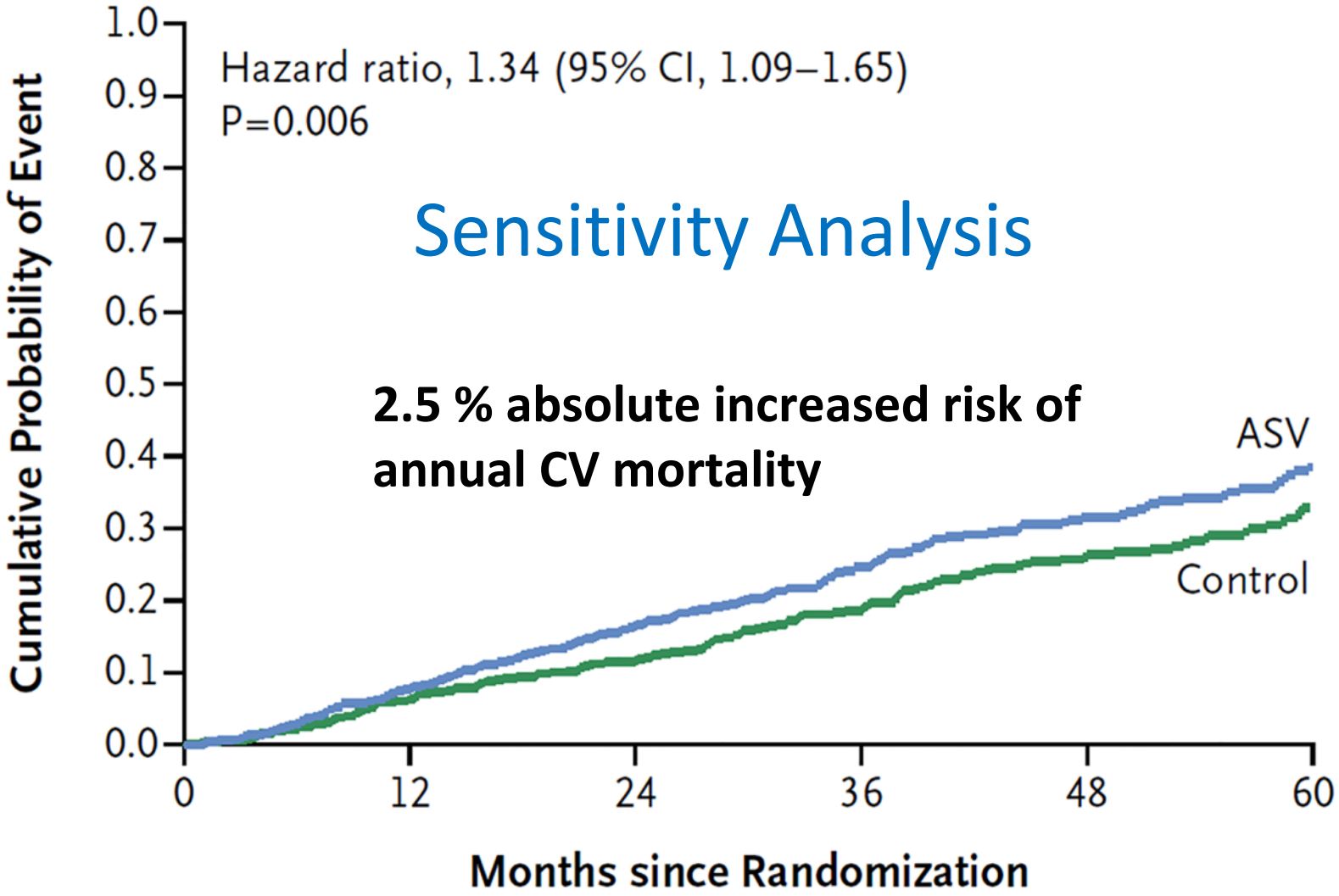
p-value = 0.104

SERVE-HF –Secondary outcomes

Comparing ASVmv arm to the control group, sleep architecture including sleep stages and arousal index did not change significantly

Similarly, other secondary endpoints including New York heart association, Epworth Sleepiness Scale and Minnesota living with heart failure were not significantly different

Death from Cardiovascular Causes



Sensitivity Analysis

2.5 % absolute increased risk of annual CV mortality

No. at Risk						
Control	659	563	493	334	213	117
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In the largest randomized control trial, Cowie and colleagues tested the hypothesis that in well treated patients with HFrEF, treatment of CSA with ASVmv, would improve CSA and the hard outcomes as well as patient's symptomatology. A total of 1325 patients were randomized to receive ASV versus untreated control group

The primary endpoint was all cause mortality, CV mortality, and planned hospitalization for worsening heart failure, resuscitation of cardiac arrest, appropriate ICD shock for ventricular arrhythmia and cardiac transplantation Secondary outcomes included Minnesota living with heart failure questionnaire, Epworth Sleepiness Scale, New York heart association class and sleep quality

Comparing the 2 arms : Neutral

However, a sensitivity analysis showed that use of ASV was associated with excess cardiovascular mortality


May 13, 2015
CSA is protective
ASV-related CV Mortality

Conclusions from the SERVE-HF trial

ASV was associated excess cardiovascular mortality

1. CSA is protective
   Treatment of CSA was the cause of mortality

2. Mortality was due to excess pressure by ASV

SERVE-HF

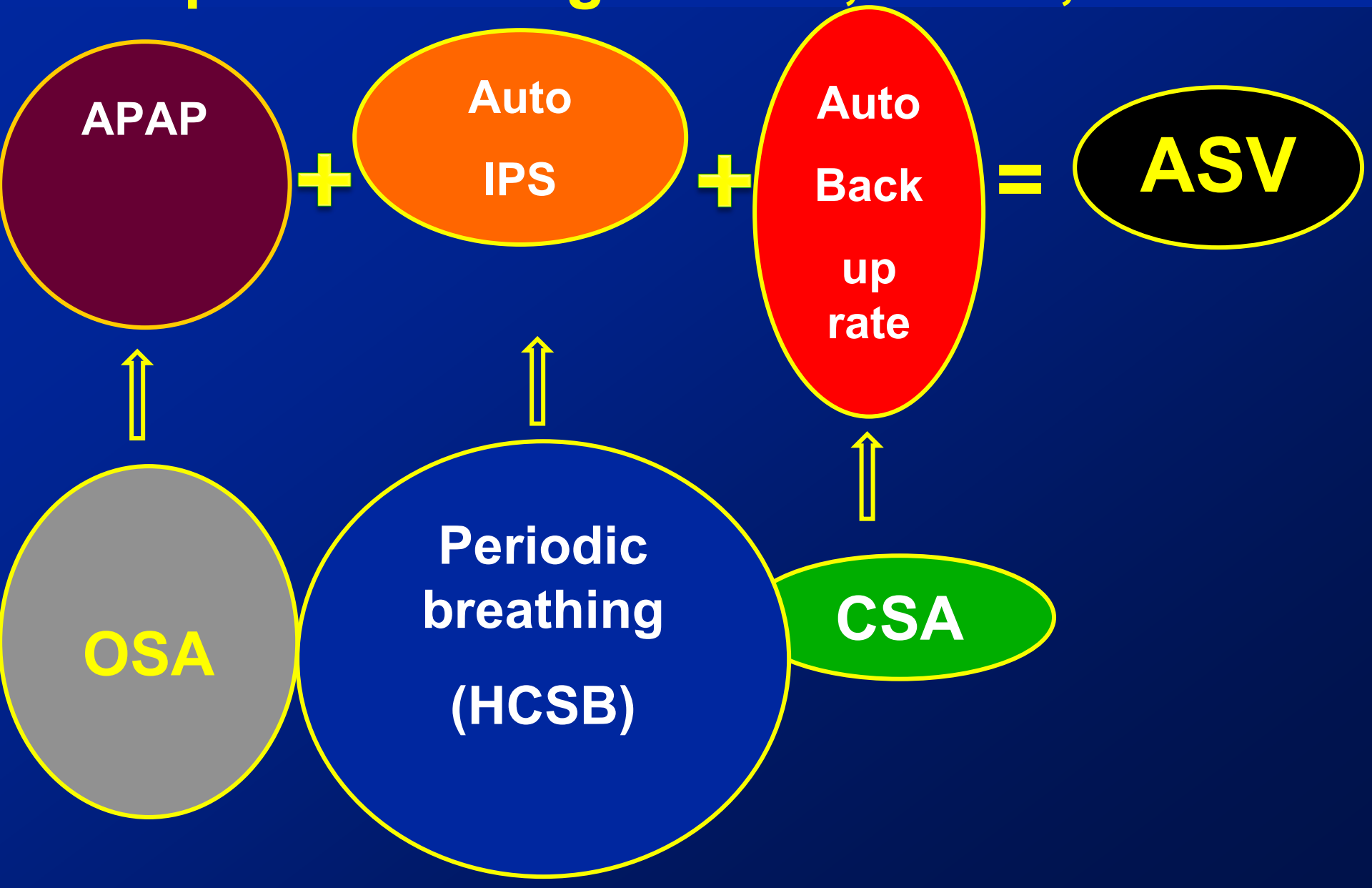
Randerath W, Khayat R, Arzt M, Javaheri S
Missing links: Sleep Medicine. 2015

Javaheri S, LK. Brown LK, Randerath W, Khayat R
More Questions Than Answers: Chest 2016

Javaheri et al. STATE-OF-THE-ART REVIEW:
Sleep Apnea Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardiol 2017

Randerath et al. Adaptive Servoventilation in Clinical Practice - Beyond SERVE-HF? ERJ Open Res 2017

Components of ASV devices
Operational algorithms, Chest, 2014



SERVE-HF
"ASV effectively treated sleep apnea"

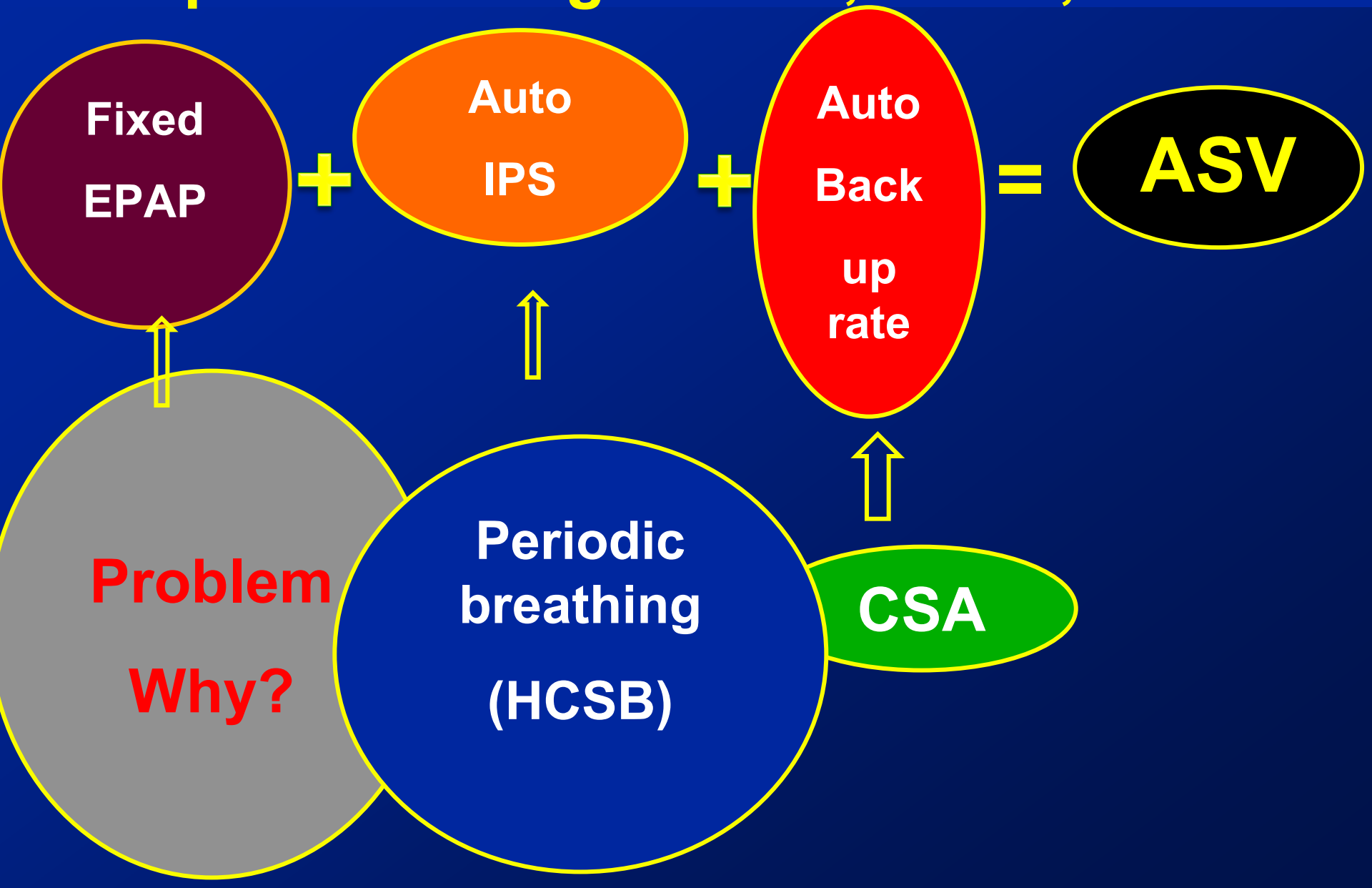
	Baseline	3m	12 m	24m	36m	48m
AHI, mean	31	7	7	6	7	7
AHI, range	10-115	0-72	0-51	0-46	0-61	0-38

SERVE-HF : ASV data; NEJM
"ASV effectively treated sleep apnea"

	Baseline
AHI, mean (SD)	31±13
Central AHI/total AHI	81 %
Obstructive AHI/total AHI	19%

30% PG: Javaheri S. Rapoport DM, Schwartz AR
Distinguishing Central from Obstructive Hypopneas on a Clinical Polysomnogram
J Clin Sleep Med 2023;19(4):823-834

Components of ASV devices
Operational algorithms, Chest, 2014



CAHI/AHI %

Baseline	3m	12m	24m	36m	48m
81	53	49	40	43	40

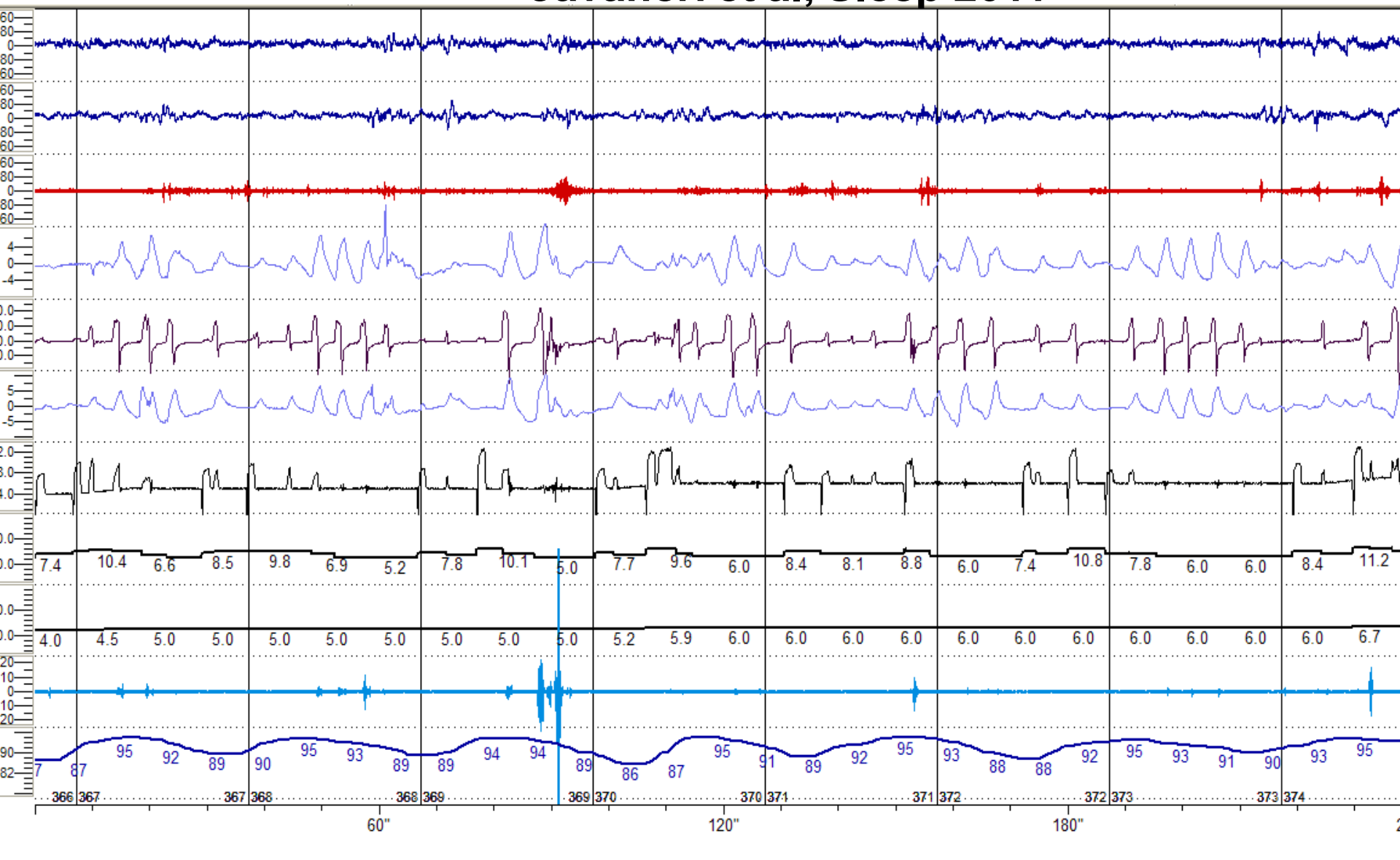
OAH?AHI

19	47	51	60	57	60

AHI, range

10-115	0-72	0-51	0-46	0-61	0-38

Operation of EPAP during obstructive disordered breathing ev
in BiPap auto SV Advanced
Javaheri et al, Sleep 2011



Range of P parameters ASVmv used in SERVE-HF

Parameter	Minimum	Maximum	Default
ASV mode			
EEP (cm H_2O)	4	15	5
MIN PS (cm H_2O)*	3	6	3
MAX PS (cm H_2O)*	8	16	15

	First ASV night	3 m	12 m	24 m	36 m	48 m
IPAP Median	**9.7 (5 ,17)**	**9.6 (6, 17)**	**9.8 (7, 18)**	**9.9(7, 17)**	**10 (7., 17)**	**10 (7, 16)**
95th percentile	**14 (7, 22)**	**14 (7, 22)**	**14 (7, 21)**	**14 (9, 21)**	**14 (8, 21)**	**14 (10, 20)**
EPAP Median	**5.5 (3, 11)**	**5.5 (3, 11)**	**5.7(3, 12)**	**5.8 (4, 11)**	**6.0 (4, 11)**	**6.1 (4, 11)**
95th percentile	**5.6 (4, 11)**	**5.6 (4. 15)**	**5.7 (3, 12)**	**5.8 (4, 12)**	**6.1 (4, 12)**	**6.1 (4, 11)**

Max Pr of this ASV is 25 cm of H_2O

SERVE-HF

ASV (old generation)

What are the shortcomings in the algorithm regarding dynamics of IPS of the device used in SERVE-HF and why is it important?

Javaheri et al. Positive airway pressure therapy with adaptive servo-ventilation (Part 1: Operational)algorithms). Chest 2014

OSA not suppressed by the fixed EPAP

The algorithm of the ASV device used was was designed progressively to *aggressively* increase the IPS in an attempt to open the closed airway

However, once the airway opened, IPS needed to drop considerably, yet the algorithm had a relatively long decay in lowering IPS. This resulted in excessive and excess ventilation and excessive rise in intrathoracic pressure with consequent adverse chemical and hemodynamic effects until IPS dropped to its lowest level which was not zero

After airway opened:

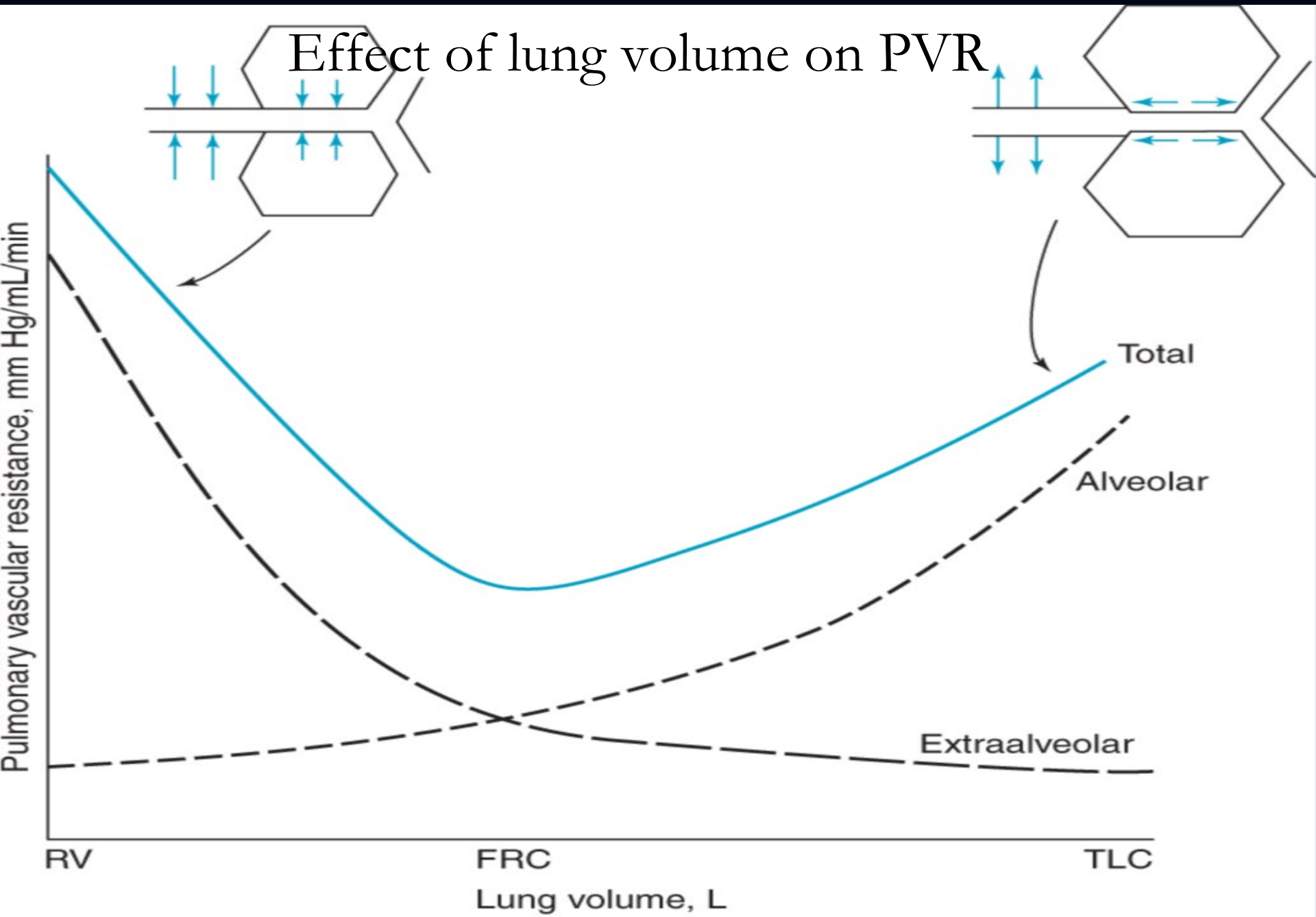
Excessive IPS

1. Decreased RV preload
2. Increased RV afterload

Excessive Ventilation

1. worsening hypocapnia
2. Excessive arousals

Effect of lung volume on PVR



After airway opened:

Excessive Ins Pressure

1. Decreased RV preload
2. Increased RV afterload

Excessive Ventilation

1. worsening hypocapnia

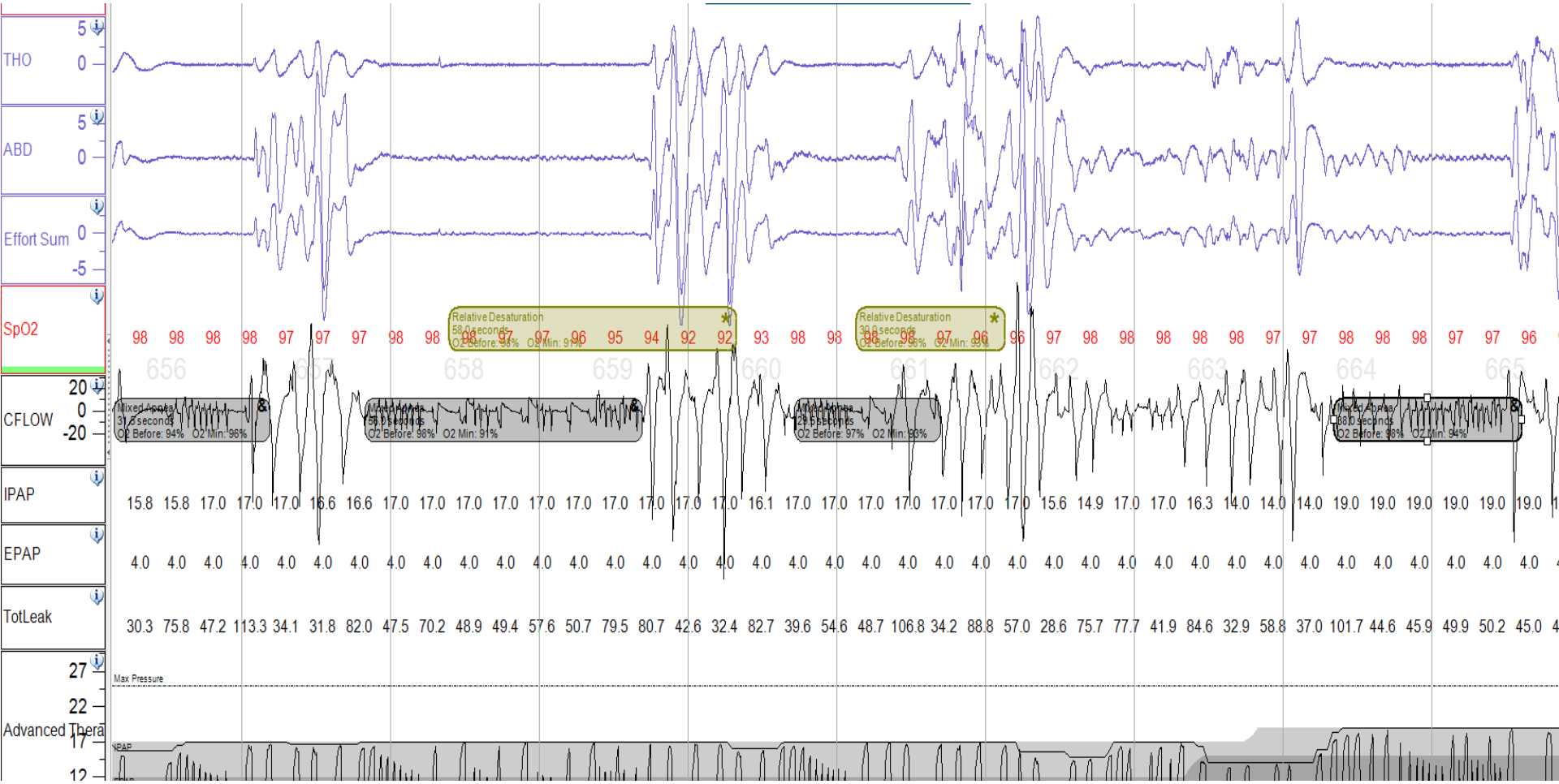
CSA with closed upper airway

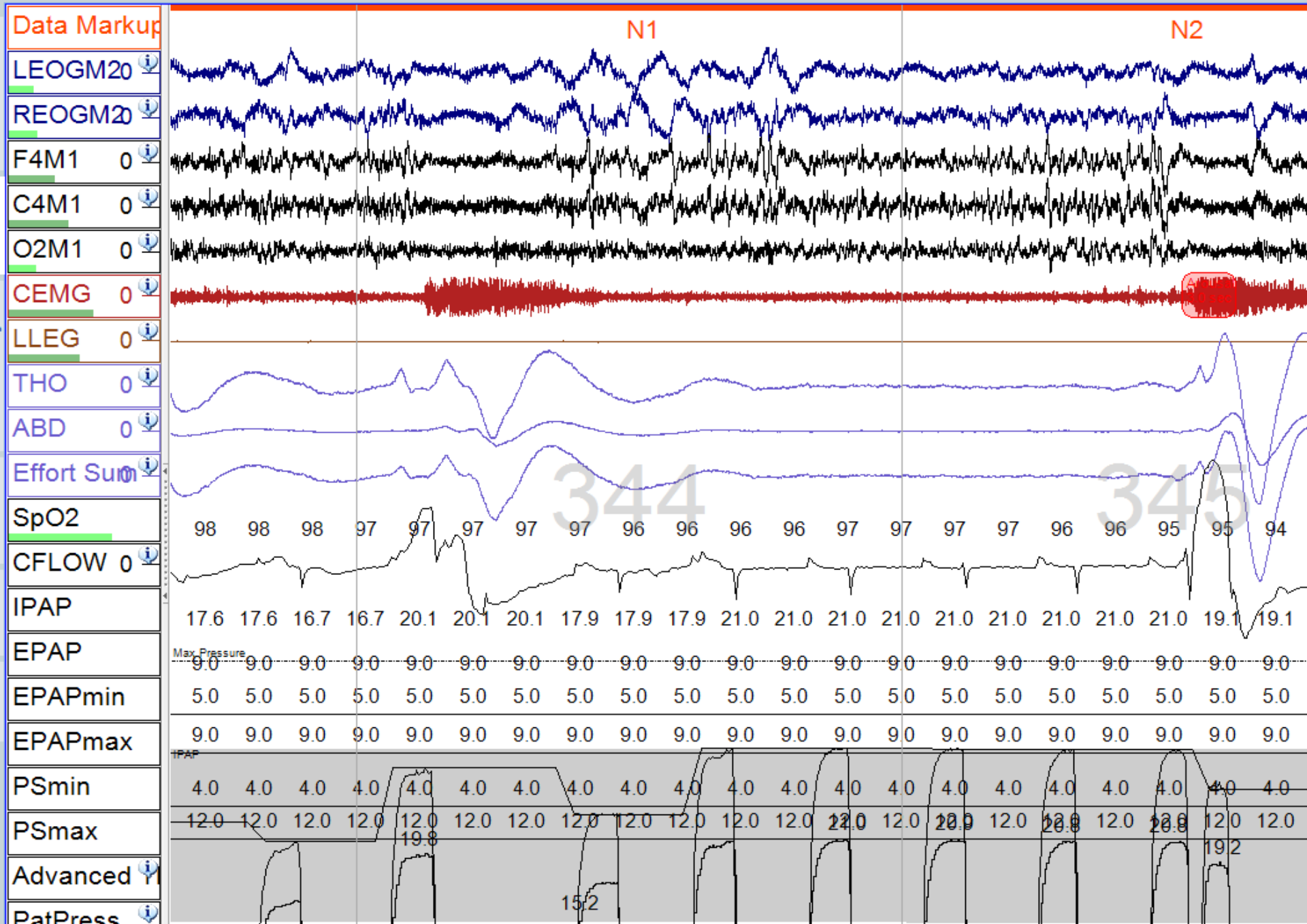
Arrhythmogenic

2. Excessive arousals

Arrhythmogenic

sleep fragmentation


THO
ABD
Effort Sum
SpO2
CFLOW
IPAP
EPAP
TotLeak
Advanced Thera
Max Pressure
IPAP
Relative Desaturation
58.0 seconds
O2 Before: 98% O2 Min: 91%
Relative Desaturation
30.0 seconds
O2 Before: 96% O2 Min: 93%
Mixed Apnea
31.0 seconds
O2 Before: 94% O2 Min: 96%
Hypopnea
75.0 seconds
O2 Before: 98% O2 Min: 91%
Hypopnea
23.0 seconds
O2 Before: 97% O2 Min: 93%
Mixed Apnea
88.0 seconds
O2 Before: 98% O2 Min: 94%


Data Markup
LEOGM2 0
REOGM2 0
F4M1 0
C4M1 0
O2M1 0
CEMG 0
LLEG 0
THO 0
ABD 0
Effort Sum 0
SpO2
CFLOW 0
IPAP
EPAP
EPAPmin
EPAPmax
PSmin
PSmax
Advanced
PatPress
N1
N2
344
345
98 98 98 97 97 97 97 97 96 96 96 96 97 97 97 97 96 96 95 95 94
17.6 17.6 16.7 16.7 20.1 20.1 20.1 17.9 17.9 17.9 21.0 21.0 21.0 21.0 21.0 21.0 21.0 21.0 21.0 19.1 19.1
Max Pressure
9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0
5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0 5.0
9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0 9.0
IPAP
4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0 4.0
12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0
19.8
15.2
19.2

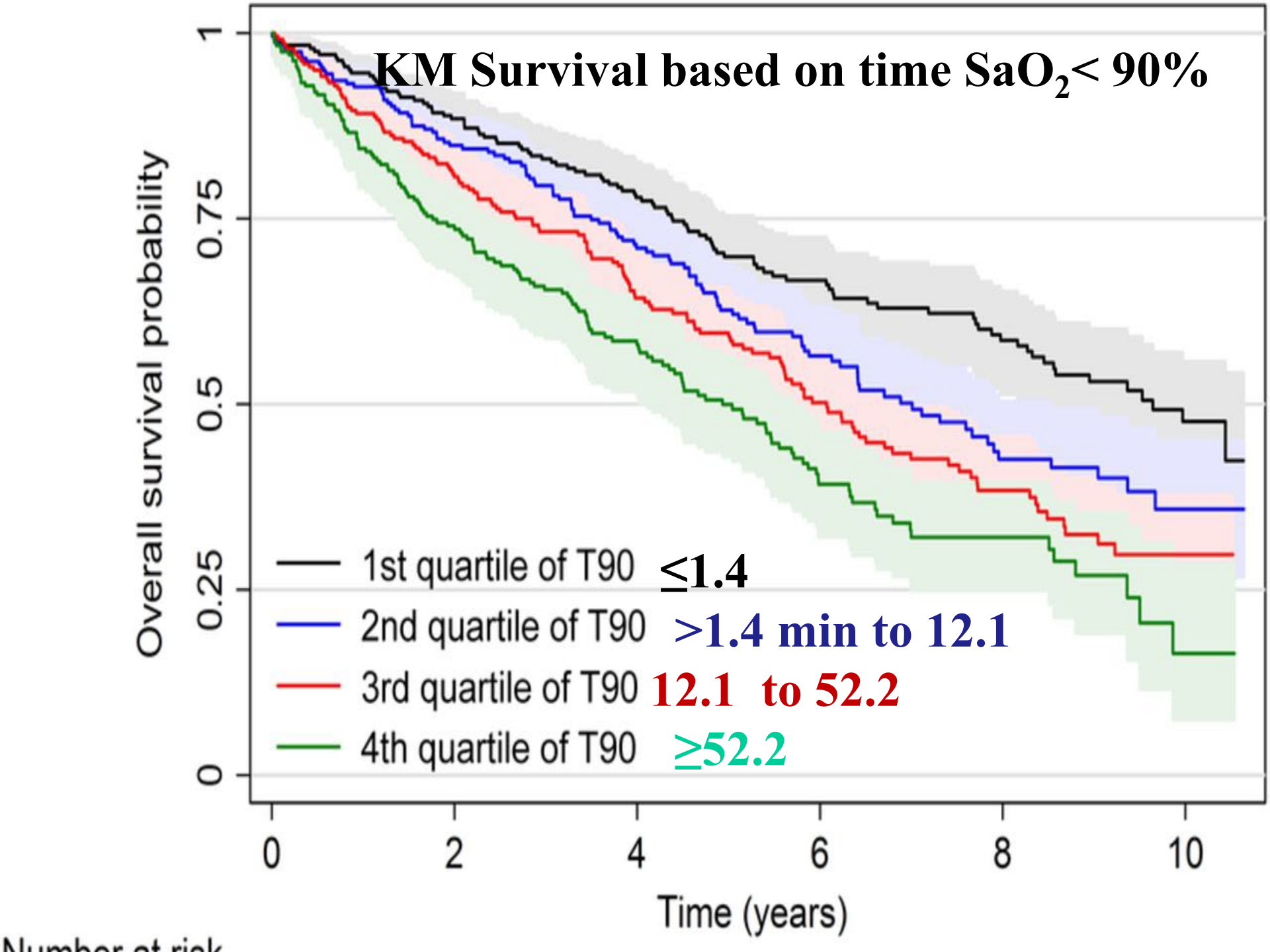
Association of Smoking, Sleep Apnea, and Plasma Alkalosis With Nocturnal Ventricular Arrhythmias in Men With HFrEF

Variable	OR	95%CI	p value
ArI	1.05	1.02-1.08	.001
$[H^+]$	0.8	0.64-0.99	.04
Age	1.1	1.03-1.19	.008
Smoking	9.96	1.93-51.5	.006

Javaheri et al, Chest 2012

SERVE-HF
"ASV effectively treated sleep apnea"

	Baseline	3m	12 m	24m	36m	48m
AHI, mean	31	7	7	6	7	7
AHI, range	10-115	0-72	0-51	0-46	0-61	0-38
SaO_2< 90%	51	19	20	18	19	25
min range	0-459	0-344	0-268	0-285	0-291	0-278


KM Survival based on time SaO2< 90%
Overall survival probability
1
0.75
0.5
0.25
0
1st quartile of T90 ≤1.4
2nd quartile of T90 >1.4 min to 12.1
3rd quartile of T90 12.1 to 52.2
4th quartile of T90 ≥52.2
0
2
4
6
8
10
Time (years)
Number at risk

The Enigma: Daytime Death

1. Combined respiratory and metabolic alkalosis + hypokalemia (caused by diuretics and K-H exchange across cell membranes leading to arrythmias

2. Cumulative effects of hypoxemia and hemodynamic consequences + alkalemia and hypocapnia leading to myocardium and conduction system remodeling

3. Daytime napping without ASV and death during sleep

4. CSA is compensatory and that is why they died.
If so, and ASV effectively treated CSA, death should have occurred mostly at night

SERVE-HF

Randerath W, Khayat R, Arzt M, Javaheri S
Missing links: Sleep Medicine. 2015

Javaheri S, LK. Brown LK, Randerath W, Khayat R
More Questions Than Answers: Chest 2016

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ADVENT Trial

The findings of the SERVE-HF are somewhat divergent from those in the ADVENT trial

Use of ASVpf was not associated with excess CV mortality (no harm)

In the ADVENT trial there was improvement in sleep architecture including reduction in N1 light sleep and increased in deep sleep, N3 (leading to overnight favorable changes in autonomic activity)

Patient centered outcome also improved significantly when compared to control. There was reduction in arousal index.

Therefore, the question remains as to what account for these differences.

In the largest randomized control trial, Cowie and colleagues tested the hypothesis that in well treated patients with HFrEF, treatment of CSA with ASVmv, would improve CSA and the hard outcomes as well as patient's symptomatology. A total of 1325 patients were randomized to receive ASV versus untreated control group

The primary endpoint was all cause mortality, CV mortality, and planned hospitalization for worsening heart failure, resuscitation of cardiac arrest, appropriate ICD shock for ventricular arrhythmia and cardiac transplantation Secondary outcomes included Minnesota living with heart failure questionnaire, Epworth Sleepiness Scale, New York heart association class and sleep quality

Comparing the 2 arms : Neutral

However, a sensitivity analysis showed that use of ASV was associated with excess cardiovascular mortality

Endpoints in ADVENT trial

1. The primary endpoint included all cause mortality/heart transplantation/LVAD implantation, CV hospitalizations, appropriate ICD shock and new onset A-fib requiring anticoagulation

2. Secondary outcomes included sleep quality improvement in Minnesota living with heart failure questionnaire, Epworth Sleepiness Scale and New York heart class

Similar to that of SERVE-HF

ADVENT trial

1. Control group: 375 patients with HFrEF and sleep apnea, AHI ≥ 15/hour of sleep, (PSG)

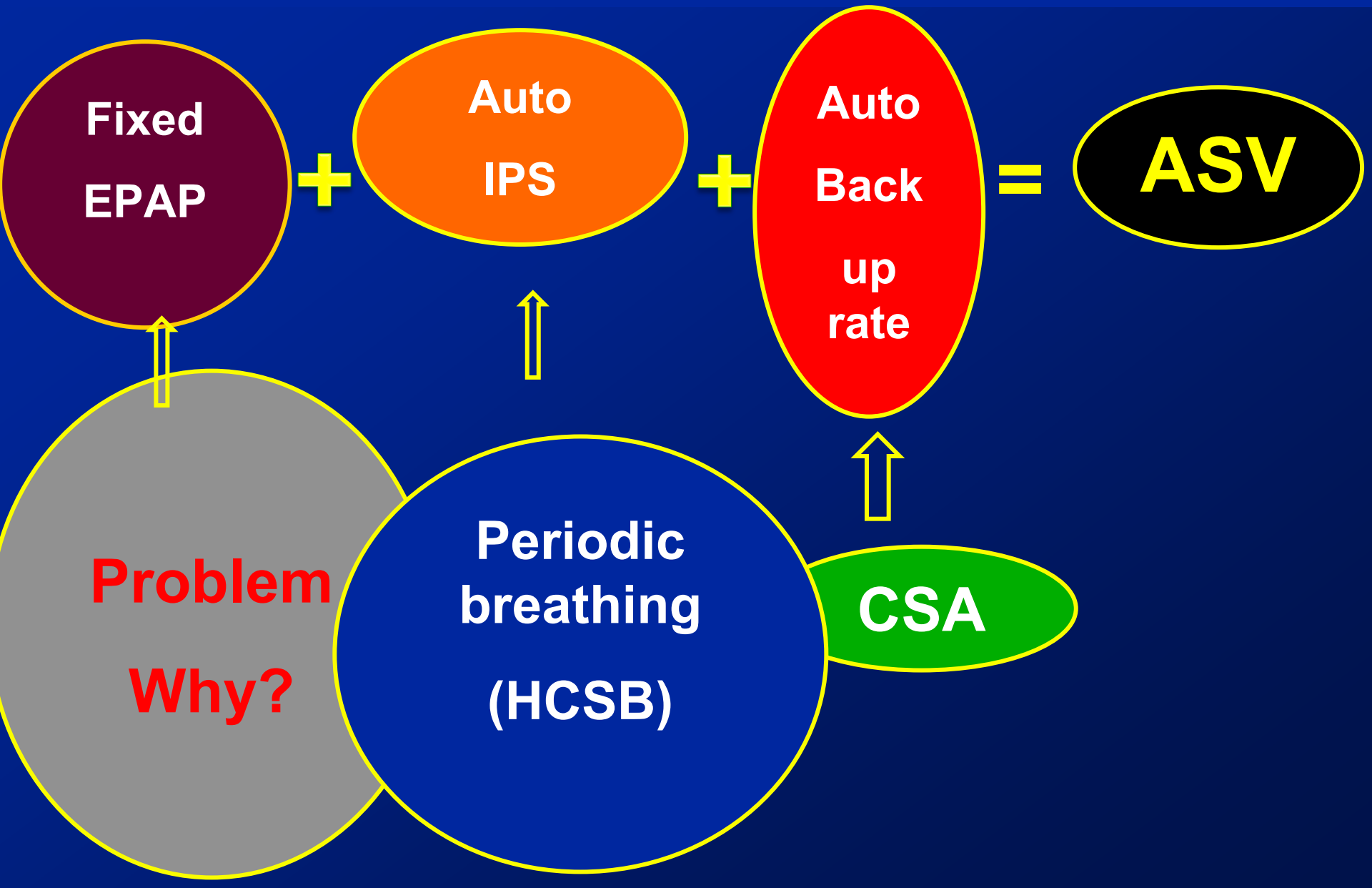
ASV group: 356 patients with sleep apnea, AHI ≥ 15/hour of sleep, (PSG) and otherwise well matched.

2. In the control group there were 375 people 265 with OSA and 106 patients with CSA

3. In the ASV arm a 264 with OSA and 92 with CSA

4. CSA group: 106 in the control group and 92 in the ASV group

ASV Used in SERVE-HF



SERVE-HF

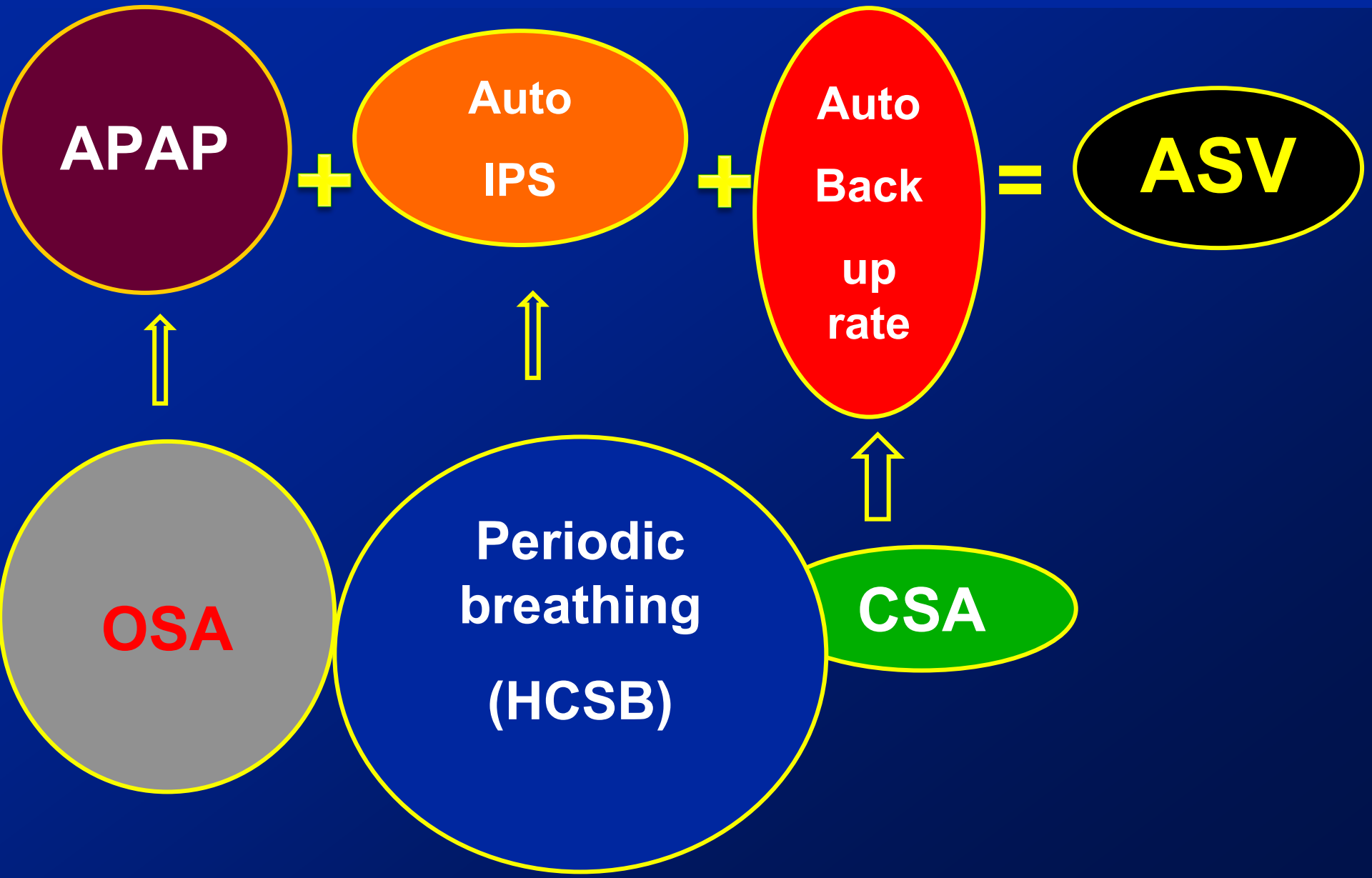
ASV (old generation)

1) Fixed EPAP
2) Shortcomings in the algorithm of dynamics of IPS

Both improved in the new generation

Javaheri et al. Positive airway pressure therapy with adaptive servo-ventilation (Part 1: Operational algorithms). Chest 2014

ASV Used in ADVENT-HF



ADVENT trial (n= 731, 5 years FU)

Control 375 ASV356

All cause mortality: 87 in Control, 76 in ASV

OSA, n= 533

52 deaths in Control 51 in deaths in ASV

CSA, n= 198

Cumulative Incidence of mortality

55 deaths in Control 35 ASV

HR=0.78 ,CI: 0.47,1.3, p=0.34

Differences between SERVE vs ADVENT trials: The ASV differences

	ADVEN	SERVE
Device	ASVpf	ASV mv
EPAP	Automatic	Fixed
PS min	0.0	4 cm H_2O(Default)
PS max	15	10 (lowest 8 cm above min PS, max 21)
ASV titration	Yes(PSG in sleep lab)	Yes (PSG/polygraphy)(Default)
Mask	Nasal	FF mask (75%)(9% unknown)

Do these differences impact the outcomes?

Characteristic Patients with HFrEF

ADVENT (n= 730)

NYHA

B. Objective evidence of minimal cardiovascular disease.
Mild symptoms and slight limitation during ordinary activity
Comfortable at rest

C. Objective evidence of moderately severe cardiovascular disease.
Marked limitation in activity due to symptoms, even during less-than-ordinary activity
Comfortable only at rest

SERVE-HF (n=1325)

NYHA class III or IV heart failure, or
NYHA class II heart failure with at least one heart failure–related hospitalization within the 24 months before randomization

Long- term ASV adherence in patients with HFrEF and CSA in SERVE-HF trial

% Patients using ASV

	2W	3M	1y	2y	3y	4y	5y
< 1 h	17	22	29	31	40	39	33
> 4 h	59	45	47	51	43	44	52

Cowie et al, NEJM, 2015 online Supplement

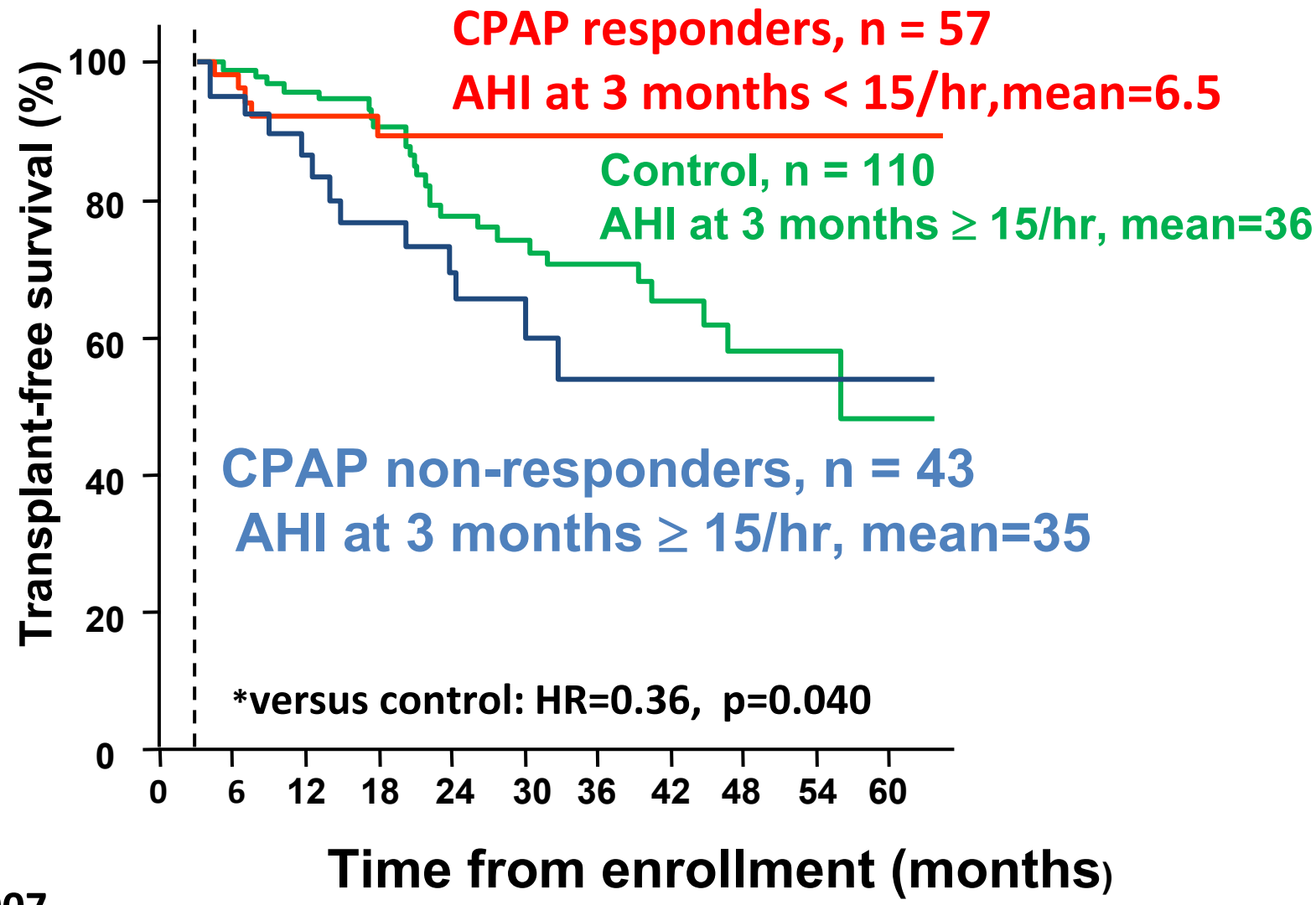
ASV Adherence

Average use of ASVmv in the SERVE-HF = 3.7 h

Average use of ASVpf in the ADVENT trial = 4.3 h

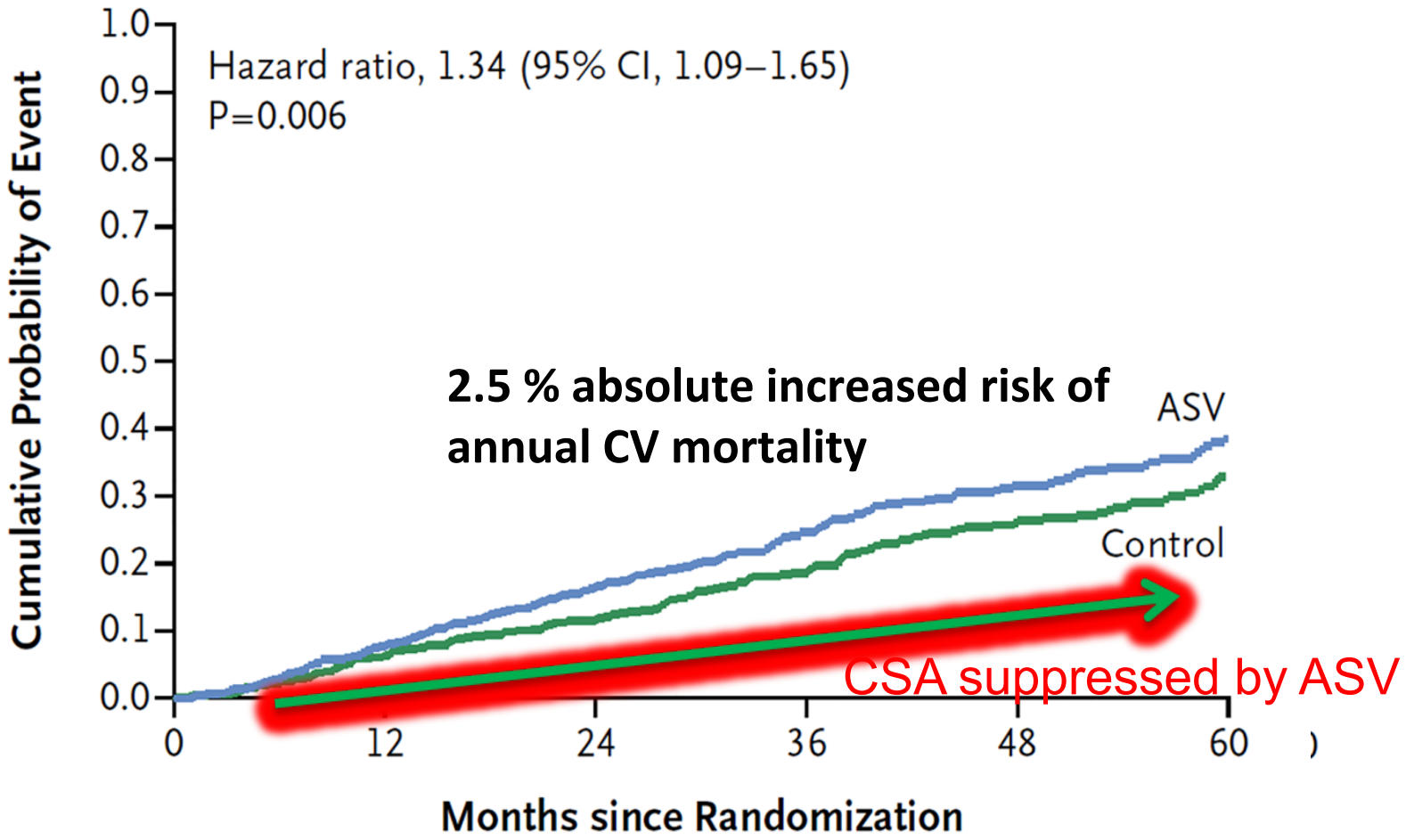
What now?

Transplant-free survival in the control group and according to effect of CPAP on CSA



Artz , Circ,2007

Death from Cardiovascular Causes



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Javaheri et al. Positive airway pressure therapy with adaptive servo-ventilation (Part 1: Operational algorithms). Chest 2014

What now?

1. Another ASV trial with current ASV

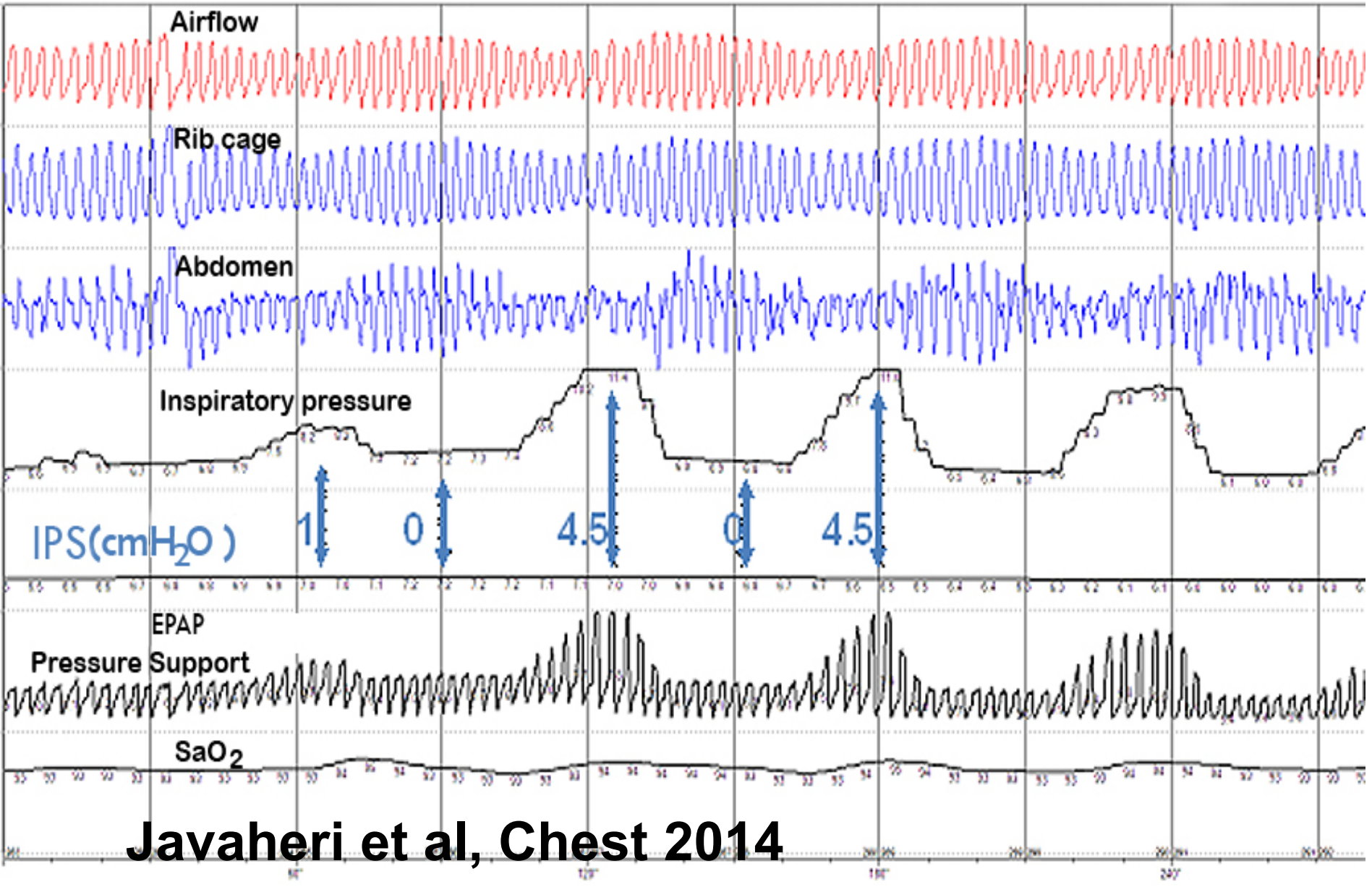
   ASVmv ASVpf

PNS. Already approved for CSA including HF

Oxygen trial (terminated)

Other medications

Changes in inspiratory pressure support during Hunter-Cheyne-Stokes breathing



Javaheri et al, Chest 2014