S1 - Methodology of Position paper: Search strategy for identification of studies

It is debated whether guidelines should be prepared only on the basis of rigorous methodologies [1-3] categorizing the strength of available evidence according to rigid criteria [4;5].

A rigid approach appears particularly difficult to follow when evaluating information on the link between OSA and hypertension, an area in which data from randomized controlled trials of sufficient power and their meta-analyses are still limited. Nonetheless, the writing Committee made a great effort to provide objective recommendations, through extensive retrieval of published data, and by establishing task forces to prepare and discuss separate documents on specific topics (See appendix 1S as supplemental material on the Journal website).

Methodology of data search, Published documents have been identified from the following sources by means of the specified search strategies : Cochrane Library Systematic review, National Library of Medicine's MEDLINE database (from 1966) through use of MESH terms, and Elsevier's EMBASE database (from 1980). An evaluation of reference lists from identified articles to find additional references was also performed. Unpublished documents have also been searched by through consultation of disease-specific websites and by interviewing investigators and experts in the field.

In preparing the Consensus Document, information form existing Guidelines has been also derived. The available material was addressed in a draft document and was reviewed by all the Writing Committee members during a few consensus conferences.

According to the approach followed in preparing the ESH-ESC Hypertension Management Guidelines, also in preparing this Consensus Document the Writing Committee decided not to perform any formal grading of the evidence.

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-Diagnosing OSA in patients with hypertension.

-Diagnosing hypertension in patients with OSA: Assessment of OSA contribution to resistant hypertension

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-Effects of other specific OSA treatments besides CPAP (surgical procedures and oral devices) on BP reduction

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-Problems and perspectives

S2 Patient history and questionnaires

Clinical symptoms suggestive for co-morbid OSA(S) may be divided into daytime and nighttime symptoms (table 4) [6]. A structured interview or specific questionnaires are particularly helpful in the routine assessment of these clinical features of OSA(S) in patients with arterial hypertension [7;8]. The assessment of increased daytime sleepiness is of particular interest as data indicate that OSA has a stronger impact on blood pressure regulation in patients with concomitant daytime sleepiness and thereby expressing the clinical syndrome termed OSAS [9]. However, it is a difficult task to assess excess daytime sleepiness by simple measures due to the fact that sleepiness may be masked by various coping behaviors or a personal perception of normal or abnormal levels of alertness. One often used and validated tool for the systematic assessment of impaired daytime alertness in the context of OSA is the Epworth Sleepiness Scale [10] (see file S.4 pdf). This questionnaire contains eight questions regarding the occurrence of unintended sleep periods during certain monotonous situations during daily life which have to be answered by the patient. A sum score of >10 out of 24 points indicate a clinically relevant impaired daytime wakefulness. However, a score of 10 points or below does not exclude a relevant impairment of vigilance. An additional method for the assessment of daytime sleepiness is the Multiple Sleep Latency Test (MSLT). The patient undergoes four to five 20 minute periods of quiet bed rest between 8 am and 4 pm with a simultaneous sleep EEG recording and is asked to fall asleep during these periods. The method aims to detect pathologically short latencies for sleep onset as an objective measure of increased daytime sleepiness. A variant of this test is the Multiple Wakefulness Test (MWT). In the MWT patients are asked to stay awake during periods of 40 minutes lying in bed in a dark and quite environment. Both methods are time consuming, costly, and therefore restricted to specific clinical questions. Data from patient's history and physical status alone has been used to predict polysomnographically verified OSA(S). It has been clearly demonstrated that sensitivity and specificity for the daytime assessment of OSA(S) is insufficiently low [7;11].

S 3 - Specific Blood Pressure Monitoring data in the general population and in OSA patients

Most studies in the general population looking at the relationship between SDB and hypertension have used clinic BP measurements [12-15]. In few studies, however, ABPM has also been used. In a small sample of the general population (n= 82) longitudinal observations have been obtained on how measures of SDB may predict changes in 24-h ABPM profile [16]. 24-h mean arterial pressure (MAP) and mean 24-h DBP were each best predicted by change in RDI, explaining 5% of the variance in these 24-h ABP parameters, and by current smoking status. After accounting for these variables, BP was not predicted by any of the other potential confounders. Mean RDI (averaged between t5 and t1) was associated with night-time average MAP and SBP, and by maximal SBP measured during sleep [16].

ABPM has been used in clinical settings to assess BP changes in OSA for more than 15 years [17]. However, the question still under debate is the added value of ABPM compared to clinic measurement in diagnosing HT in OSA.

In a non-selected group of OSA patients, the occurrence of a HT condition was dramatically underestimated by clinic BP measurements [18]. In a small cohort of OSA patients unknown as being hypertensive and without any cardiovascular history or cardiovascular treatment, 42% had clinic hypertension whilst 58% had daytime hypertension and 76% had night-time hypertension, using 24-h ABPM. All patients with daytime hypertension also had night-time hypertension. Overall, 80% were hypertensive either in the clinic or over the 24h based on ABPM data. Diastolic and systo-diastolic hypertension, were the prominent types of hypertension observed both by clinic or ambulatory measurements, particularly in the more severe apneic patients according to AHI [18].

When considering a clinical cohort of OSA patients, ABPM is able to detect a significant number of patients who exhibit normal clinic BP but have high ambulatory BP. This is defined as masked hypertension. Masked HT seems to be associated with significant target organ damage [19;20] and increased rate of cardiovascular events [21]. This has been demonstrated both for treated hypertensive patients in whom, even when using antihypertensive medications, uncontrolled out-of office HT is persistent in presence of controlled office BP, and for untreated subjects in the general population [22]. Thus, masked HT subjects should be considered as a subgroup of patients at high risk for cardiovascular diseases. In OSA, masked hypertension is more prevalent than in the general population. Clinic systolic BP of more than 125 and diastolic BP of more than 83 mmHg are associated with a relative risk of 2.7, and have a 90% positive predictive value, for the occurrence of masked hypertension [23].

S4 Epworth Sleepiness Scale : see file pdf

TABLE S1

Summary data on randomized controlled trials on the effects of CPAP treatment on blood pressure in OSA patients ordered by duration of CPAP treatment

Author	Type of study	CPAP duration	Mean CPAP use	Sample size	AHI at diagnosis	NT/HT	BP by:	Outcome: BP during sleep	Outcome: BP during daytime	Comments
Dimsdale et al, 2000 [24]	sham – effective CPAP	1 week	>5	39 pts	RDI 53.6±23 CPAP/ 41.7±25 sham	CPAP: 15 NT/6 HT; sham 14 NT/4 HT	ABPM	↓ MBP (-5 mmHg) in CPAP group	↓ MBP in both groups	
Norman et al, 2006 [25]	CPAP vs placebo vs O2	2 wks	> 6	46 pts (15-18-13)	66±29 CPAP; 54±30 placebo; 61±29 O2	NA	ABPM	↓ MBP and SBP only in CPAP group	↓ MBP and SBP only in CPAP group	
Engleman et al, 1996 [26]	crossover CPAP vs placebo tablets	3 wks	4.3	13 pts	49±9	8 NT/5 HT (4 treated)	ABPM	5 pts non-dippers on placebo became dipper on CPAP	NA	Mean BP in 24-h unchanged on CPAP
Faccenda et al, 2001 [27]	CPAP vs placebo tablets	4 wks	3.3 h	68 pts	35 (range 15-129)	All NT	ABPM	↓ DBP with CPAP between 2 and 10 am	No change	Mean 24-h DBP ↓ by 1.5 mmHg; SBP/DBP ↓ in pts with high desat, index; DBP ↓ in pts using CPAP for >3.5 h/night
Campos-Rodriguez et al, 2006 [28]	sham – effective CPAP	4 wks	CPAP: 5.0 h; sham: 4.4 h	68 pts	CPAP: 58±25; sham: 59±22	All HT on treatment	ABPM	CPAP vs sham: similar BP, trend for increased dipping	CPAP vs sham: no difference	Pts with refractory HT showed similar results on therapeutic CPAP
Kohler et al. 2009 [29]	sham – effective CPAP	4 wks	Sham3.9 ± 2.5 h. Effective 4.7 ± 2.1 h	102 pts	ODI sham 42.7 ± 21.6 effective 41.9 ± 25.4	Subtherapeutic: HT 25.5% Therapeutic HT 21.6%	ABPM + office BP	BP changes during sleep failed to achieve statistical significance	↓ SBP e DBP on CPAP, but no differences in office BP	Decreased sympathetic markers and increased BRS after active treatment
Pepperell et al, 2002 [30]	sham – effective CPAP	1 month	4.7 h	118 pts	DI: 37±20	59 NT/11 HT in each group	ABPM	↓ MBP (-3 mmHg)	↓ MBP (-4 mmHg)	BP MBP ↓ in both NT and HT, especially if CPAP use >5 h and DI>33

Barbé et al, 2001 [31]	sham – effective CPAP	6 wks	CPAP: 5 h; sham: 4 h	54 pts with ESS≤10	CPAP: 54±3; sham: 57±4	NA	ABPM	CPAP vs sham: no difference in BP or dipping status	CPAP vs sham: no difference in BP	Most pts were NT, number of HT unspecified but treated HT similar in both groups
Coughlin et al, 2007 [32]	crossover effective vs. sham CPAP	6 wks for each treatment	CPAP: 3.9 h; sham: 2.6 h	34 pts	40±14	7 NT/27 HT	ABPM	NA	NA	↓ 24-h MBP, SBP, DBP
Cross et al, 2008 [33]	Crossover effective vs. sham CPAP	6 wks for each treatment	CPAP: 4.5h; sham: 3.1 h	29 pts	Desaturators: 63±5; non-desaturators: 20±1	NT	Intra-arterial daytime BP	NA	CPAP vs sham: no difference in BP	Vascular function worse in desaturators; recovery after effective CPAP
Pépin et al. 2010 [34]	crossover CPAP vs. Valsartan 160 mg/die	8 wks for each treatment, 4 wks washout in between	4.8±2.1	23 pts	29±18	All HT	ABPM	Valsartan more effective than CPAP	Valsartan more effective than CPAP	RCT followed by an open study in 11 pts, treated with both CPAP and Valsartan, with further reduction in BP compared to Valsartan alone
Becker et al, 2003 [35]	sham – effective CPAP	9 wks	5.5 h	32 pts	Pre-CPAP: 64; post: 3 CPAP/ 33 sham	CPAP: 8 NT/8 HT; sham: 3 NT/ 13 HT	Portapres	↓ SBP and DBP (-10 mmHg)	↓ SBP and DBP (-10 mmHg)	Large number of dropouts
Hui et al, 2006 [36]	sham – effective CPAP	12 wks	5.1 h CPAP/ 2.6 h sham	46 pts	CPAP: 33±3 (SE); sham: 30±3 (SE)	CPAP: 11 NT/17 HT; sham: 17 NT/11 HT	ABPM	↓ MBP and SBP only in CPAP group	No change	↓ 24-h MBP and DBP; trend for larger effect in HT
Barnes et al, 2004 [37]	crossover CPAP vs. OA vs. placebo	3 months for each treatment	CPAP: 3.6 h; OA: 5.5 h	110 pts, 80 pts for all 3 arms	21.5±2	94 NT/ 16 HT; 44 nondippers	ABPM	Unchanged BP on CPAP	Unchanged BP on CPAP	No Δ in dipping/non-dipping status on CPAP
Lozano et al. 2010 [38]	CPAP+HT treatment vs HT treatment alone	3 months	5.6 ± 1.52 h	75 pts	52.67 ± 21.5 conventional treatment: 46.78 ± 21.43 CPAP treatment 59.79 ± 19.71	All with resistant HT	ABPM	No difference between CPAP and conventional treatment . in patients with high CPAP compliance (>5.8 h) ↓ nocturnal SBP and DBP	↓24 h diastolic BP in CPAP group in patients with high compliance also ↓ diurnal DBP and 24h SBP	Largest BP decrease in pts using CPAP for >5.8 h/night ↓ number of non-dipping patients in the CPAP group, no significant changes in the conventional treatment group

Duran-Cantolla et al, 2010 [39]	sham – effective CPAP	3 months	CPAP: 4.5± 1.7 h, Sham 4.2± 1.8 h	340 pts with HT and OSA (AHI>15)	43.5±24.5	All HT	ABPM	↓ MBP, SBP, AND DBP only in CPAP group	↓ MBP, SBP, AND DBP only in CPAP group	Change in BP statistically significant but small (<3 mmHg)
Drager et al, 2011 [40]	CPAP vs no treatment	3 months	5.2 ± 0.7	36 pts. with pre-HT or masked HT	AHI: 56±22	Pre-HT :control 17%, CPAP 17%. Masked HT: 7% control , 7% CPAP. Nondipping: 6% control, 9% CPAP.	Office BP, ABPM	↓ nocturnal SBP and DBP at ABPM in CPAP group	↓ office SBP, ↓ diurnal SBP and DBP at ABPM	
Barbé et al, 2010 [41]	CPAP vs no treatment for OSA	L, 1998	4.7± 2	359 non-sleepy OSA pts (178 CPAP, 181 conservative)	AHI: 45±20	All HT	Office BP	NA	At 3 months, no differences. At 12 months ↓ SBP, ↓ DBP	Largest BP decrease in pts using CPAP for >5.6 h/night
Robinson et al, 2006 [9]	crossover CPAP vs. sham CPAP	1 month	CPAP: 5.2 h; sham: 4.3 h	35 pts with ESS≤10	DI: 28 (range 18-38)	35 HT, 27 on anti-HT treatment	ABPM	CPAP vs sham: no difference	CPAP vs sham: no difference	

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