The effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes

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Abstract

The effects of continuous positive airway pressure (CPAP) for obstructive sleep apnoea (OSA) on insulin resistance are not clear; trials have found conflicting results and no appropriate control groups have been used.

Methods: Forty two men with known type 2 diabetes and newly diagnosed OSA (>10, >4% SaO_2 dips/hour) were randomised to receive therapeutic (n=20) or placebo CPAP (n=22) for 3 months. Baseline tests were performed and repeated after 3 months. The study was double blind.

Results: Results are expressed as mean (SD). CPAP improved the Epworth sleepiness score significantly more in the therapeutic group than the placebo group (-6.6 (4.5) vs. -2.6 (4.9), p=0.01). The maintenance of wakefulness test improved significantly in the therapeutic group, but not in the placebo group (+10.6 (13.9) vs. -4.7 (11.8) mins, p=0.001). Glycaemic control and insulin resistance did not significantly change in either the therapeutic or placebo groups: HbA1c (-0.02 (1.5) vs. +0.1 (0.7), p=0.7, 95% CI -0.6% to +0.9%), euglycaemic clamp (M/I: +1.7 (14.1) vs. -5.7 (14.8), p=0.2, 95% CI -1.8 to +0.3 $l/kg/min^{1000}$), HOMA-%S (-1.5 (2.3) vs. -1.1 (1.7), p=0.4, 95%CI -0.3 to +0.08%) and adiponectin (-1.1 (1.2) vs. -1.1 (1.3), p=0.2, 95% CI -0.7 to +0.6 ug/ml). Body mass index, bioimpedance and anthropometric measurements were unchanged. Hours of CPAP use per night were: therapeutic 3.6 (2.8) vs. placebo 3.3 (3.0), p=0.8. There was no correlation between CPAP use and the measures of glycaemic control or insulin resistance.

Conclusion: Therapeutic CPAP does not significantly improve measures of glycaemic control or insulin resistance in men with type 2 diabetes and OSA.

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Introduction

Obstructive sleep apnoea (OSA) is characterised by recurrent upper airway obstruction during sleep, recurrent apnoeas and arousals. It is associated with central obesity and affects approximately 4% of men (1). Population studies have found OSA is associated with insulin resistance, and the more severe the OSA, the greater the insulin resistance, independent of general obesity (2;3). Insulin resistance occurs when the metabolic effect of insulin is reduced, leading to a lack of hepatic and peripheral tissue response to insulin-mediated glucose metabolism (4). This most closely correlates with central obesity, and the greater the visceral fat, the greater the insulin resistance (5). The insulin resistance in OSA is postulated as being due not only to visceral obesity, but also due to increased sympathetic drive from the frequent arousals, hypoxia and sleep fragmentation - all thought to impair glucose tolerance (6;7).

Insulin resistance is frequently observed in pre-diabetes and type 2 diabetes develops when normoglycaemia is no longer maintained, due to inadequate pancreatic beta-cell compensation and insulin production. Insulin resistance is affected by many variables, including changes in weight, body fat distribution (with visceral fat causing more insulin resistance than subcutaneous fat), exercise, drugs, smoking. Studies of longitudinal change in insulin resistance as an outcome need to include a control group, to allow for such confounders. Insulin resistance is measurable by several techniques, including the homeostatic model assessment (HOMA) for basal assessment (8) and the euglycaemic clamp for stimulated insulin assessment (9).

There has been interest in whether the treatment for OSA, continuous positive airway pressure (CPAP), can improve the insulin resistance found in OSA. If the hypoxia,

arousals and increased sympathetic drive found in OSA were adequately treated, would the insulin resistance and hence the glycaemic control improve? Several studies have tried to answer this, but thus far, the available data have not led to a conclusive answer, as the significance of any changes cannot be assessed without a control group (10-14). We therefore performed a randomised controlled trial, using therapeutic and placebo CPAP, to assess the effect of CPAP on glycaemic control (glycosylated haemoglobin, HbA1c) and insulin resistance (determined by euglycaemic clamp and HOMA), in men with established type 2 diabetes and newly diagnosed OSA.

Methods

Subjects

Subjects were recruited via the Oxford Sleep Clinic between June 2004 and August 2005. Eligible subjects were men aged between 18 and 75, with established type 2 diabetes (on diet, oral hypoglycaemic agents or insulin therapy). They had excessive daytime sleepiness (Epworth Sleepiness Score (ESS) $\geq$ 9) and were due to start CPAP for OSA, established from overnight laboratory sleep studies (VisiLab, Stowood Scientific Instruments, Oxford, UK). The entry criterion for OSA was greater than ten oxygen saturation (SaO_2) dips of greater than 4% per hour on an overnight sleep study. Patients were excluded if they required urgent CPAP or if they had unstable diabetes (requiring an escalation in treatment). Additional details are provided in an online data supplement.

Study design

Eligible subjects were seen for their baseline study visit ten days prior to commencing CPAP. Subjects were asked not to change their diet or exercise habits for the duration

of the study, and their primary care physicians were asked not to change their medications, unless essential. Following baseline studies, each subject was randomised to receive either therapeutic or placebo CPAP for three months in a double blind fashion. Randomisation was by means of a balanced computer programme (MINIM version 1.5, Evans S). CPAP was first used overnight at home, following an afternoon training session, which is standard practice in our unit. Two weeks after CPAP initiation, all patients were seen in the nurse-led CPAP clinic. The nurses involved in the randomisation, CPAP initiation and ongoing CPAP care were separate to the study investigators. After three months of CPAP treatment, the baseline studies were repeated. At the end of the study, all subjects receiving placebo CPAP were changed to therapeutic CPAP. Subjects gave written informed consent and the study was approved by the local ethics committee.

CPAP

Those subjects receiving therapeutic CPAP had autotitrating machines (Autoset Spirit, ResMed UK). Those receiving placebo CPAP had the same machines, set to their lowest pressure, with a flow-restricting connector inserted at the machine outlet and six extra 4mm holes inserted in the collar of the main tubing to allow air escape and to prevent rebreathing of carbon dioxide. A pressure of <1cm and >0cm H_20 was delivered, insufficient to hold open the pharynx. These methods of placebo CPAP provision have been used previously (15;16). The data from the CPAP machines were downloaded at the second study visit.

Measures of insulin resistance

Insulin resistance was assessed by both HOMA and euglycaemic hyperinsulinaemic clamp on a single day. Studies were carried out after an overnight fast and omission of the morning oral hypoglycaemic agents or insulin. Baseline blood samples were collected for the determination of glucose and insulin for HOMA. Following the basal sampling, subjects underwent a hyperinsulinaemic euglycaemic clamp (17). Subjects were kept awake for the duration of the clamp, in order to avoid any confounding effects of sleep on glucose metabolism.

Other blood tests

HbA1c, lipids (cholesterol, HDL-cholesterol, triglycerides), adiponectin and highly sensitive CRP were measured.

Measures of body composition

Subjects had their height and weight recorded, body mass index (BMI) calculated and neck, waist and hip measurements made. Body composition was measured using bioelectrical impedance analysis (Bodystat 1500, UK).

Measures of sleepiness and activity

Subjective sleepiness was measured by the ESS, and objective sleepiness measured once at the same time of day, using a modification of the Maintenance of Wakefulness test (OSLER) (18). The Short Sleep Apnea Quality of Life Index (Short SAQLI) was completed (19). These variables were measured to confirm patients were responding to therapeutic CPAP, compared to the placebo group. Physical activity was assessed at baseline and at the end of the study using wrist worn actiwatches (electronic devices

containing accelerometers, which measure and record intensity, amount and duration of physical movement (Cambridge Neurotechnology Ltd, UK)).

Analysis

The primary end point was the change in HbA1c measured after 3 months of therapeutic or placebo CPAP. Secondary end points were changes in insulin sensitivity measured by HOMA and euglycaemic clamp. Differences between groups (using the change from baseline as the outcome variable) were assessed with unpaired student's t-test. A Chi-squared test was used to compare the proportions in each group on different diabetes therapy and duration of diabetes. Non-normally distributed data were logarithmically transformed before applying parametric statistical tests and data are reported as geometric means. Activity data was analysed using non-parametric tests. A p value of <0.05 was considered to be statistically significant. Analysis was performed with SPSS version 12.0.

Study size

The study was powered not to miss a difference of 0.8 in HbA1c (assuming a within subject SD of 0.8) (20) at a significance level of 5% and with a power of 90%, which required 20 subjects in each treatment group.

Results

Figure 1 shows a flow chart of the study. Forty-eight men were considered for entry to the study: four declined, two were unsuitable, thus 42 were enrolled. Twenty-one men were randomised to receive therapeutic CPAP, 21 to receive placebo CPAP. One patient randomised to therapeutic CPAP had a defective machine which delivered

minimal pressure, so his data were therefore analysed with the placebo group. The two groups were well matched at baseline, with no significant difference in age (mean (range): therapeutic 58 (29-74), placebo 55 (24-66)), >4% SaO_2 dips/hour (therapeutic 33.1 (11.0-87.9), placebo 39.1 (10.8-82.2), BMI (therapeutic 36.6 (26.2-49.2), placebo 36.8 (29.2-47.1)) or HbA1c (therapeutic 8.5 (6.5-12.1), placebo (8.4 (6.0-13.6)). For diabetes, five subjects were treated with diet only, 23 with oral hypoglycaemic agents (OHA), 23 with insulin and OHA, and four with insulin alone; the proportions of subjects receiving these treatment categories were not significantly different between the two groups (Chi-square, p=0.6). The mean duration of diabetes was 7.3 years in the therapeutic CPAP group and 6.5 years in the placebo group (Chi square, p=0.3). There are completion data on 40 men: one patient receiving therapeutic CPAP did not attend his second study visit, as he was admitted to hospital for emergency cardiac surgery and one patient withdrew from the study because he was unwilling to continue using CPAP (randomised to placebo). Patients who attended and had poor or negligible CPAP usage were included and analysed on an intention to treat basis. Euglycaemic clamps were performed on 33 of the study participants; technical difficulties meant these were not performed in the first nine participants. There were no adverse events in either of the groups.

Measures of daytime sleepiness and SAQLI score

Subjective sleepiness, measured by the ESS improved in both groups following CPAP treatment (table 1), but the change was significantly greater in the group receiving therapeutic CPAP ($p<0.01$). Objective sleepiness, measured by the modified MWT, improved significantly only in the group receiving therapeutic CPAP, by a mean of +10.6 minutes ($p<0.001$). This change in MWT was similar to our previous randomised

controlled trial in this area (+7.0 mins), and the change in ESS was of an effect size (1.9), nearly as large as this previous study (2.2), in which the patients had less comorbidity (15). The mean short SAQLI score improved following CPAP treatment in both groups, but the change between the groups was significantly different, in favour of therapeutic CPAP (p=0.04).

Clamp characteristics

The mean (SD) blood glucose concentrations over the last 20 minutes of baseline euglycaemic clamp were 5.9 (0.5) mmol/l in the therapeutic CPAP group and 5.9 (0.5) mmol/l in the placebo group (p=0.8); and in the repeat clamp were 6.1 (0.8) mmol/l and 5.9 (0.5) respectively (p=0.5).

Table 1. Baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP.

	BASELINE		**CHANGE FROM BASELINE (Δ)**		95% CI between groups	P (for Δ)
	Therapeutic CPAP n=20	**Placebo CPAP n=22**	**Therapeutic CPAP n=19**	**Placebo CPAP n=21**		
Age	57.8 (10.4)	54.5 (9.4)				
>4% SaO2 dips/hr	33.1 (21.6)	39.1 (24.8)				
ESS	14.7 (3.5)	13.6 (3.5)	-6.6 (4.5)	-2.6 (4.9)	-7.0 to -0.9	0.01
MWT (Osler) (mins)	21.9 (12.8)	32.0 (10.8)	+10.6 (13.9)	-4.7 (11.8)	+6.5 to +23.9	0.001
BMI (kg/m^2)	36.6 (4.9)	36.8 (4.6)	-0.2 (1.0)	-0.2 (1.1)	-0.6 to +0.7	1.0
SAQLI	4.3 (1.1)	4.4 (0.9)	+0.8 (1.0)	+0.03 (1.2)	-1.5 to +0.04	0.04
Neck size (cm)	46.2 (2.6)	47.0 (2.6)	+0.04 (1.2)	-0.06 (1.4)	-0.7 to +0.9	0.8
Waist to hip ratio	1.0 (0.06)	1.1 (0.06)	0 (0.3)	0 (0.4)	-0.03 to +0.02	0.5
Impedance	426.4 (91.3)	404.9 (39.5)	-3.8 (28.4)	+9.3 (31.2)	-32.6 to +6.4	0.2
Fasting glucose (mmol/l)	10.1 (3.6)	10.0 (4.5)	+0.3 (2.1)	-0.2 (2.1)	-0.9 to +1.8	0.5
HbA1c (%)	8.5 (1.8)	8.4 (1.9)	-0.02 (1.5)	+0.1 (0.7)	-0.9 to +0.6	0.7
Fasting plasma insulin (pmol/l)	93.3 (52.2)†	100.0 (71.5)†	+1.3 (1.6)	+1.1 (1.7)	-0.2 to +0.09	0.4
HOMA-%S	47.9 (1.6)†	44.7 (1.7)†	-1.5 (2.3)†	-1.1 (1.8)†	-0.3 to +0.08	0.2
M/I: euglycaemic clamp ($l/kg/min^{1000}$)	26.5 (14.4)	27.8 (17.9)	+1.7 (14.1)	-5.7 (14.8)	-3.2 to +18.1	0.2
Adiponectin ug/ml	3.7 (2.2)†	2.8 (1.5)†	-1.1 (1.2)†	-1.1 (1.3)†	-0.7 to +0.6	0.2

Data are shown as mean (SD), †geometric mean (SD). There was no significant difference in any of the baseline data between the groups (p range 0.3 to 0.9), except for MWT, $p<0.01$ and adiponectin, $p=0.05$.

HbA1c and insulin sensitivity

Results are shown in table 1. HbA1c did not change significantly following CPAP treatment in either of the groups. There was no significant change in insulin sensitivity in either the therapeutic or placebo CPAP groups after three months of treatment. The plasma insulin concentrations during the baseline and final euglycaemic clamps were not significantly different between groups. The geometric mean (SD) plasma insulin concentrations over the last 30 minutes of the baseline clamp were 1405 (239) pmol/l in the therapeutic CPAP group and 1436 (335) pmol/l in the placebo group ($p = 0.6$); and in the repeat clamp geometric mean (SD) plasma insulin concentrations were 1453 (339) pmol/l and 1481 (327) pmol/l respectively ($p=0.8$). Insulin sensitivity (M/I) is expressed as the quantity of glucose metabolised (M) per unit of plasma insulin concentration (I), data obtained from the euglycaemic clamp. At the end of the study, M/I had changed by +1.7 (14.1) in the therapeutic CPAP group compared with -5.7 (14.8) in the placebo CPAP group ($p=0.2$). A positive change indicates an improvement in insulin resistance. HOMA-%S, changed by -1.5 (2.3) in the therapeutic group and -1.1 (1.8) in the placebo group ($p=0.2$). Adiponectin did not change significantly following CPAP treatment in either of the groups (therapeutic -1.1 (1.2), placebo -1.1 (1.3), $p=0.3$). There were no correlations between change in M/I with change in weight, BMI, waist to hip ratio, bioelectrical impedance, HbA1c, %S, adiponectin or change in physical activity.

Other blood tests

There were no significant changes in any of the measures of fasting lipids or highly sensitive CRP over the three month period in either of the two groups.

Measures of body composition

There was no significant change in any of the measures of body mass index, waist to hip ratio, neck size or bioelectrical impedance over the three month period in either of the two groups (table 1).

Actigraphy

The average activity for the most active ten hours (M10, usually representing wakefulness) and the least active five hours (L5, usually representing sleep) per day over a seven day period were calculated. The activity levels were found to be highly variable and changes after CPAP in those receiving therapeutic CPAP did not reach statistical significance (M10, p=0.4; L5, p=0.1). (Mean change (SD) M10: Therapeutic +13.3 (68.3), Placebo +0.7 (5.9), 95%CI -43.0 to +17.7; Mean change (SD) L5: Therapeutic -0.3 (0.8), Placebo -0.4 (1.6), 95% CI -1.0 to +0.8 arbitrary units/1000).

CPAP use

There was no significant difference between the two groups in the mean number of hours for which CPAP was used on the nights it was worn, (table 2). In the therapeutic CPAP group, there was no correlation between the hours of CPAP usage per night and the change in M/I, %S or HbA1c. Three subjects in the placebo CPAP group (14%), and five in the therapeutic CPAP group (26%), had, on average, below one hour per night of CPAP use per night worn, over the last one month and three months. The main analyses were repeated with these poor compliers removed (i.e. per protocol) and remained non-significant, with no suggestion of an improvement in the therapeutic group.

Table 2. CPAP use

	Therapeutic CPAP n=19	Placebo CPAP n=21	P value
Mean hours on nights used over last month	3.6 (2.8)	3.3 (3.0)	0.8
% nights used over last month	74.8 (30.2)	65.4 (28.5)	0.4
Mean hours on nights used over last 3 months	3.3 (2.6)	3.5 (2.8)	0.9
% nights used over last 3 months	74.5 (29.3)	69.3 (26.6)	0.6
% with compliance <1 hour/night used	26	14	
Mean hours on nights used in those with >1hour/night compliance over last month	4.8 (2.3)	4.1 (2.7)	0.4
Mean hours on nights used in those with >1 hour/night compliance over last 3 months	4.4 (2.0)	4.2 (2.6)	0.8

Discussion

This double blind randomised controlled trial, using therapeutic and placebo CPAP for three months, in men with type 2 diabetes and obstructive sleep apnoea, has not shown any significant improvement in glycosylated haemoglobin or insulin resistance measured by euglycaemic clamp and HOMA. As anticipated, subjects receiving therapeutic CPAP experienced significant improvements in their subjective and objective sleepiness and sleep apnoea quality of life scores, similar to our previous studies, indicating that CPAP was effectively treating their OSA, but this was not accompanied by improvements in glycaemic control or insulin resistance.

There were no significant changes in any of the other variables which were measured, despite the clinical response of improvement in OSA. Adiponectin is an adipocyte derived peptide with insulin sensitizing properties. It is decreased in adiposity and

increases after weight reduction and higher levels correlate with increased insulin sensitivity (21). A previous study had shown large and significant changes in adiponectin, along with significant changes in M/I, following treatment with pioglitazone (22). Adiponectin is therefore another marker, along with %S and M/I, which can be used to determine if there is a change in insulin resistance, but in our study, it did not significantly change. The fact that neither the primary outcome measure of HbA1c, nor any of the other variables associated with insulin resistance changed, adds validity to the consistent findings of this study. The euglycaemic clamp is widely accepted as the gold standard for assessing insulin resistance; as markedly supra-physiological insulin concentrations are achieved, this method is applicable over a wide range of insulin sensitivities and glucose tolerances, from normal to diabetes (23). Whatever the insulin resistance, agents that change the sensitivity tend to show effects with the euglycaemic clamp. The clamp data (Vmax effect) are concordant with the HOMA data (basal effect) (8, 23), so it is unlikely that a real change was observed with these two methods.

For comparison, a similar double blind randomised controlled trial was carried out in 30 subjects with diet controlled type 2 diabetes, to assess the effects of pioglitazone on glycaemic control and insulin resistance (22). Following three months of pioglitazone compared to placebo treatment, HbA1c significantly improved (-0.6%, p=0.003), as did HOMA-%S (+23%, p=0.02), M/I (+12 $l/kg/min^{1000}$, p=0.009) and adiponectin (3.8ng/ml, p=0.00004). These results demonstrate that larger, significant improvements in all these measures are achieved with pioglitazone, whereas the small improvements in HbA1c and M/I found in the CPAP group in our study are not statistically significant and are unlikely to be clinically significant. The validity characteristics of the euglycaemic clamp (mean and SD of the measures of blood glucose concentrations over

the last 20-30 minutes and SD of M/I) in our study were comparable to those in this pioglitazone study, as was the variation in the repeat measurements of HbA1c, HOMA %S, and M/I between the two time points.

The patients studied all had well established type 2 diabetes. The development of type 2 diabetes reflects progressive decline in pancreatic beta-cell function rather than increasing insulin resistance (24). The patients had a range of ages, from 24-74, and were receiving different treatments for their diabetes; neither age nor diabetes treatment was significantly different between the two groups. In a comparison depending on a change following an intervention, with within subject comparisons being made, homogeneity of groups is not of the same importance as it is in a cross sectional comparison. Wider recruitment can therefore be seen as an advantage.

Studies of drug therapy in patients with type 2 diabetes receiving different therapies have shown significant improvements in insulin resistance, typically within three months (25;26). The use of CPAP for three months would therefore seem to be long enough for any changes in insulin resistance or glycaemic control to occur. It would be difficult to justify ethically giving placebo CPAP for longer than three months in this symptomatic group. It is possible that CPAP might be effective in a pre-diabetic group, by improving insulin resistance via an improvement in the activity of the still functioning beta-cells; this will be an area for future research.

It could be argued that the mean CPAP compliance figures of less than 4 hours use per night in our study might account for the lack of improvement in glycaemic and insulin resistance variables. If subjects had used their CPAP for longer, decreasing the number

of apnoea-related arousals and the resultant sympathetic nervous system activation, would they have improved their insulin resistance? We do not think this is the case. First, the mean CPAP compliance was clearly great enough in the therapeutic group to improve the OSA, making a significant difference to sleepiness (measured by ESS, MWT and SAQLI), whereas the placebo group experienced no significant improvement. Since the sleepiness improved, the number of apnoea-related arousals were likely to have decreased, along with the associated sympathetic nervous system hormone surges. Second, there was a range of mean compliance over the preceding month, from zero use to 9.1 hours per night, with poor and good compliers being found in both the therapeutic and placebo groups. A per protocol analysis of these good compliers did not change the results, neither could we could find a correlation between any of the measures of insulin resistance or HbA1c and CPAP compliance. We would have expected positive correlations if improvements in insulin resistance were associated with compliance. Indeed, even the study by Harsch et al showed no correlation between CPAP use and the improvements in insulin resistance (13). This is surprising, given that the treatment of OSA is thought to lead to the improvements in insulin resistance via decreased sympathetic nervous system activation. We are clear that the outcome of our study is not due to lack of CPAP use.

The inclusion of a control group treated with placebo CPAP is particularly important in a study of insulin resistance. It is likely that glycaemic control and insulin resistance would be influenced by taking part in a study, regardless of the intervention, as people are more likely to modify their behaviour, knowing they are being monitored. It would be impossible in an uncontrolled study to attribute any changes purely to the intervention concerned. There have been several studies published assessing the effect

of CPAP on insulin resistance. None have used a control group, which leads to concern regarding the interpretation of the results. Harsch et al treated 40 patients with therapeutic CPAP and performed euglycaemic clamp studies prior to CPAP, after 2 days and after 3 months (13). A significant improvement in insulin sensitivity (the reciprocal of insulin resistance) was found after 2 days of CPAP treatment, which was sustained at 3 months (p=0.001). Mean BMI did not change during the study. The sub-group of patients with a BMI of >30 kg/m^2 showed no significant change in insulin sensitivity at 2 days but a significant improvement at 3 months (p=0.03). There was no correlation between improvement in insulin sensitivity and CPAP use. The investigators hypothesised that the early changes in insulin sensitivity after 2 days were due to improvements in sleep disordered breathing and associated decreases in nocturnal sympathetic drive, as well as improvements in the hypothalamic-pituitary-adrenal function due to improvements in sleep and hypoxia. The later changes in the patients with BMI>30 kg/m^2 may have been due to changes in body fat distribution.

It has been noted previously that the clamp procedure itself increases sympathetic nervous system activity, presumably because patients are uncomfortable and anxious and this is likely to increase insulin resistance (27). Control patients who underwent a clamp procedure, but received only saline, had increases in plasma norepinephrine similar to the increases found in patients undergoing a euglycaemic clamp with insulin and glucose. By a second clamp, patients are likely to have acclimatized to the situation, and insulin resistance is hence reduced (28), and by the third clamp this acclimatization would be greater. This effect makes the inclusion of a control group mandatory, so that changes in insulin resistance are not falsely attributed to the intervention concerned. One study, assessing change in insulin resistance in people with type 2 diabetes

commenced on either pioglitazone or placebo, showed that insulin resistance (measured by euglycaemic clamp) improved in both groups after three months, although the improvement was greater in the pioglitazone group (41% vs. 10% in controls) (22). The control group improvement was likely to be due at least in part to acclimatization to the clamp procedure itself, as well as other factors such as better adherence to diet and medication, or increased exercise. We did not see such improvements in either group in our study, possibly because the subjects were encouraged not to alter diet or activity. It could be questioned whether the 18% and 31% improvement found in insulin resistance by Harsch after 2 days and 3 months respectively might not in fact be due to CPAP, but due to clamp acclimatisation, study effect or confounding variables (13).

The other studies published in this area have had small numbers of patients ($n \leq 10$) and have also not had control groups. A study of ten subjects by Brooks et al showed a non-significant improvement in insulin sensitivity following three months of CPAP (28%, $p=0.06$) (12). A further study in nine people with type 2 diabetes by Harsch et al showed a significant improvement in insulin sensitivity after three months of CPAP (42%, $p=0.04$) (14). Both of these results could have been due to the effect of acclimatisation on the second clamp, study effect or biological variation in insulin sensitivity, as well as the confounders which affect insulin resistance. Another study by Saarelainen et al found no significant effect of three months treatment with CPAP on euglycaemic clamp measures in ten people with OSA (11), as did another by Smurra et al in ten patients with OSA treated for two months with CPAP (10). Babu et al, looked at HbA1c and 72 hour continuous glucose monitoring before and after approximately three months of CPAP treatment (29). No significant improvement in overall HbA1c was found ($p=0.06$), but HbA1c significantly improved in those patients in whom it was

initially above 7% (p=0.02, likely to be due to regression to the mean) and there were some improvements in post-prandial glucose (p=0.05). Again, without a control group, it is difficult to attribute these improvements in glycaemic control solely to CPAP and not to the effect of being monitored in a study.

Conclusion

Obstructive sleep apnoea, insulin resistance and type 2 diabetes are all increasing in prevalence as population obesity levels increase. Our randomised, placebo-controlled study adds evidence that CPAP does not improve insulin resistance and glycaemic control in men with established type 2 diabetes and obstructive sleep apnoea. Routine treatment of OSA in patients with type 2 diabetes is unlikely to result in improved diabetic control or a reduction in treatment requirements through a direct effect on insulin resistance.

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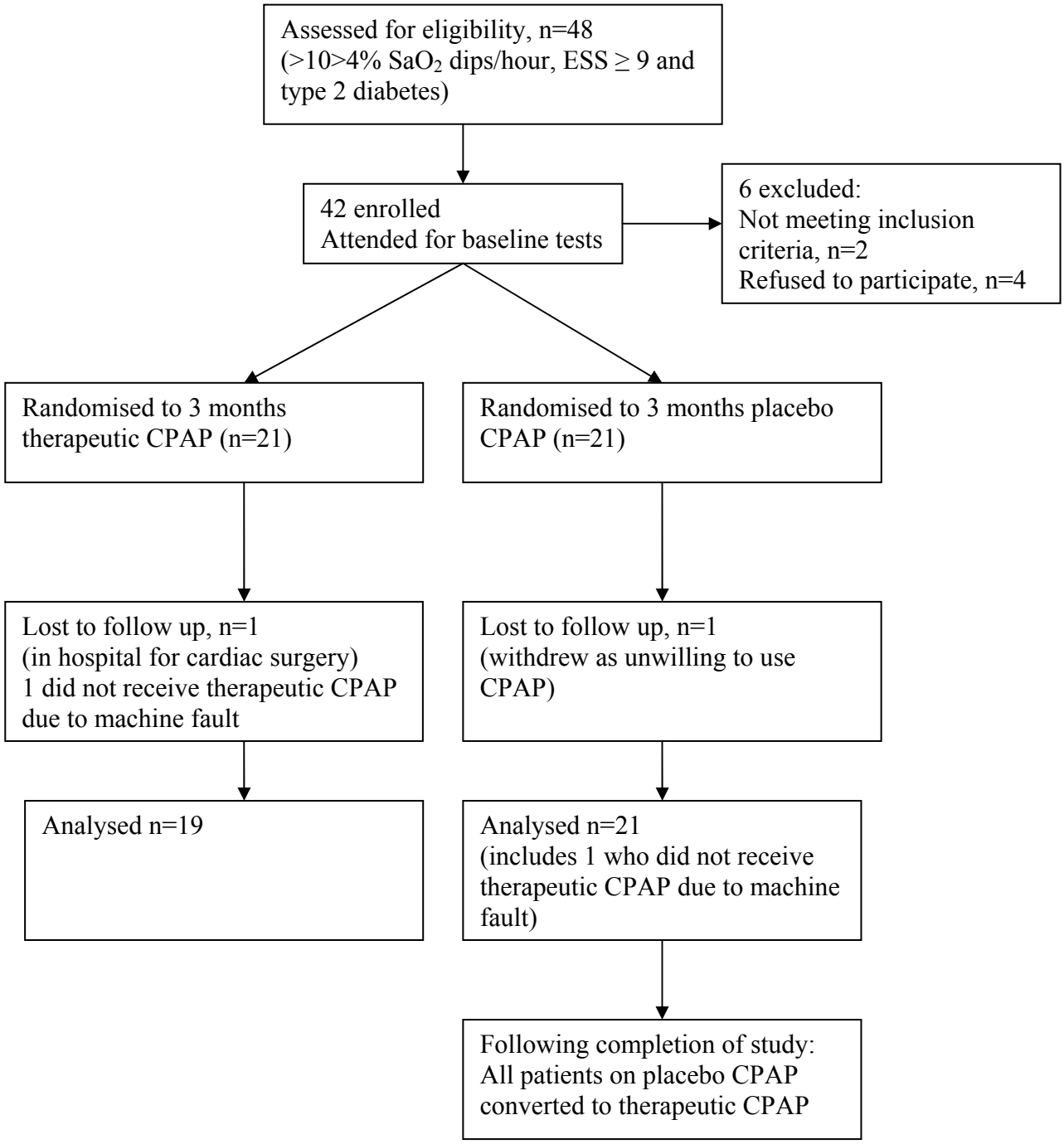
Figure 1. Flow chart of study



Online data supplement

The effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes

Sophie D West, Debby J Nicoll, Tara M Wallace, David R Matthews, John R Stradling

Subjects

Eligible subjects were men aged between 18 and 75, with established type 2 diabetes (on diet, oral hypoglycaemic agents or insulin therapy). They had excessive daytime sleepiness (Epworth Sleepiness Score (ESS) ≥ 9) and were due to start CPAP for proven OSA. The diagnostic criteria for OSA were greater than ten, oxygen saturation (SaO_2) dips of greater than 4% per hour on either a one-night hospital respiratory polysomnography sleep study or an unsupervised one-night home sleep study. The hospital sleep study took place in a hospital room decorated and furnished to resemble an ordinary bedroom. Subjects' body movements, heart rate and pulse transit time (PTT) changes were recorded as measures of arousal from sleep. The PTT signal and body movements derived from video are robust markers of arousal (1). Arterial oxygen saturation measurements, snoring and increases in the respiratory effort (from the PTT) were used as markers of breathing pattern and respiratory effort (Win-Visi monitoring system, Stowood Scientific Instruments, Oxford UK). The PTT swing is a sensitive index of respiratory effort that accurately predicts change in pleural pressure and differentiates between central and obstructive apnoeas (2). The results of the sleep study were scored automatically, with manual review to ensure accuracy of the data. OSA was diagnosed from a review of all the data. The severity of the sleep apnoea

was quantified as the number of dips in oxygen saturation of greater than 4% for every hour of the study, confirmed as being caused by upper airway obstruction. This index is one of the best predictors of therapeutic response to nasal CPAP (1) and a recent study has also shown oximetry to be at least as good as conventional EEG-based polysomnography at predicting response to CPAP (3). In the home sleep study, body position, body movement, nasal pressure via nasal cannula, oximetry, pulse rate, plus respiratory effort via thoracic and abdominal bands were measured to give a validated AHI and automatic calculation of oxygen desaturation events per hour (Embletta PDS 3.0, Flaga Medical, Iceland). Areas of artefact were manually edited. Good agreement between Embletta home sleep studies and in hospital polysomnography has been shown previously in the diagnosis of OSA (4). Patients were excluded if they required urgent CPAP due to respiratory failure or to prevent job loss due to excessive daytime sleepiness, or if they had unstable diabetes (requiring an escalation in treatment).

Study design

CPAP was first used overnight at home, following an afternoon training session, which is standard practice in our unit. Two weeks after CPAP initiation, all patients were seen in the nurse-led CPAP clinic. If the patients had problems after this two-week visit, they were instructed to telephone the sleep nurses for advice. The nurses involved in the randomisation, CPAP initiation and ongoing CPAP care were separate to the study investigators. At the end of the study, all subjects receiving placebo CPAP were changed to therapeutic CPAP. Subjects gave written informed consent and the study was approved by the local ethics committee (04/Q1605/5).

CPAP

Those subjects receiving therapeutic CPAP had autotitrating machines (Autoset Spirit, ResMed UK). Autotitrating machines adjust pressure according to inspiratory flow limitation, snoring and apnoeas, and are as effective as polysomnography at performing overnight CPAP titration (5). They have been used to initiate CPAP treatment, either at home or in hospital, or for long-term therapy (6-9). The data from the CPAP machines were downloaded at the second study visit to give the usage (hours CPAP used per 24 hours, measured as mask-on time, on nights worn, and number of nights used) and treatment pressure (over the time period during mask-on time).

Measures of insulin resistance

Insulin resistance was assessed by both a euglycaemic hyperinsulinaemic clamp and homeostasis model assessment (HOMA) on a single day. Studies were carried out after an overnight fast. Baseline blood samples were collected for the determination of glucose and insulin for HOMA. An antecubital vein was cannulated for blood sample collection. The contralateral antecubital vein was cannulated for glucose and insulin infusions. The arm from which blood samples were taken was heated to obtain arterialized samples. Three basal blood samples were obtained at 5 minute intervals for glucose and insulin determination (Abbott Aeroset Analyser, UK and Dako Cytomation, UK). Following the basal sampling, subjects underwent a hyperinsulinaemic euglycaemic clamp (10). Blood glucose was measured every 3 minutes by HemoCue Glucose 201 (HemoCue AB, Sweden). A priming insulin infusion of 600mU min^{-1} m^{-2} for 10 minutes was followed by a maintenance infusion at a rate of 100mU min^{-1} m^{-2} (Human Actrapid 100iμ/ml, NovoNordisk, Denmark). A

variable rate glucose infusion (glucose intravenous 20% w/v, Fresenius Kabi, UK) was administered to maintain euglycaemia (6.0mmol/l). The infusion rate was adjusted at 3 minute intervals on the basis of blood glucose concentrations which were entered into an iterative computer programme (11). The euglycaemic clamp was continued for 150 minutes to achieve steady state. Plasma samples were collected at five minute intervals for the last 30 minutes of the clamp for determination of insulin concentrations. Plasma glucose and HbA1c were analysed fresh. Other blood samples were placed on ice immediately and following centrifugation, plasma samples were stored at -70ºC. Homeostasis model assessment (HOMA) is a structural mathematical model which interrelates fasting plasma insulin and glucose to derive a measure of insulin sensitivity (%S) (12). HOMA-%S was calculated from plasma glucose and insulin concentrations, using the computer model (13). The model is adjusted to yield median 100%S in normal subjects. All the studies were performed by the same two investigators (SW & DN).

Other blood tests

HbA1c (Menarini 8140 Analyser, UK), fasting lipids (cholesterol, HDL-cholesterol, triglycerides) (Abbott Aeroset Analyser, UK), adiponectin (AutoDelfia 1235 Analyser, Perkin Elmer, Finland) and highly sensitive CRP (Dade-Behring BN II Analyser, Germany) were measured at baseline and at the end of the study.

Measures of sleepiness and activity

Subjective sleepiness was measured by the ESS, and objective sleepiness measured once, using a modification of the Maintenance of Wakefulness test (OSLER), a behavioural sleep resistance challenge, where the patient is required to stay awake in a

darkened sound protected room (14). The Short Sleep Apnea Quality of Life Index (Short SAQLI) was completed, which measures the effects of sleep apnoea on a person's quality of life (15). Daily activity levels were assessed at baseline and at the end of the study. Activity was quantified using wrist worn actiwatches (electronic devices containing accelerometers, which measure and record intensity, amount and duration of physical movement (Cambridge Neurotechnology Ltd, UK)). Automatic activity analysis was completed for seven consecutive days following the baseline tests and following the second study visit after three months of CPAP. The same weekdays were analysed in each period. This activity analysis included sleep and wake times and gave a mean 24 hour activity score.

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