Desipramine improves upper airway collapsibility and reduces obstructive sleep apnoea severity in patients with minimal muscle compensation.

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ONLINE DATA SUPPLEMENT

Supplemental results

Relationship between the AHI and the gap between activeV_0 and Varousal.

Consistent with a previous study (1), the AHI values were related to the gap between Varousal and activeV_0 ($r=0.62$, $p<0.001$ for both placebo and desipramine nights, figure E1). This relationship suggests that physiological measurements and AHI calculation are reliable despite the fact that they were performed over only a portion of the night.

Post-hoc analysis:

1. *Change in phenotypic traits and AHI on and off the drug*

Figures E2-E5 show the diagrams of the four ventilatory parameters calculated on and off the drug for comparison in each of the 14 subjects analyzed. Subjects were grouped for the same type of response to the drug. Figure 2 shows subjects 1, 2, 4, 5 and 14 who had an improvement in both ventilatory traits (passive and activeV_0) and AHI on desipramine compared to placebo. Figure 3 shows subjects 3, 7, 10 and 13 who showed an improvement in physiology but not in AHI on desipramine compared to placebo. Figure 4 shows subjects 8, 9 and 11 who had a worsening in physiology consistent with an increase in AHI on desipramine compared to placebo. Figure 5 shows subjects 6 and 12 who had a mild degree of sleep apnea: changes in AHI and physiology in these subjects were more likely due to night-to-night variability (2) rather than to desipramine effect.

Table E1 shows the comparison between baseline ventilatory traits in the group of responders (n=5) vs non-responders (n=7) and the correlation between the change of these parameters and the change in AHI. Only patients with moderate-to-severe OSA (n=12) were included in this analysis. Responders were considered those patients whose AHI was reduced at least by 20 events/hour on desipramine compared to placebo.

Table E1. Physiological determinants of response to despiramine in moderate-to-severe OSA (n=12)

	Sub-group analysis			Correlation with ΔAHI	
	Responders (n=5)	Non-responders (n=7)	P	R	P
Placebo					
Veupnoea, L/min	7.5 [3.4]	7.2 [1.7]	>0.5	0.22	0.50
Varousal, L/min	5.0 [1.2]	3.8 [2.3]	0.43	0.13	>0.50
Active V_0, L/min	0.4 [3.9]	2.7 [2.8]	0.10	0.59	0.07
Passive V_0, L/min	-0.3 [4.0]	1.4 [4.9]	>0.5	0.07	0.81
Loop Gain	0.7 [0.4]	0.6 [0.2]	>0.5	0.24	0.47
Varousal-Active V_0, L/min	4.2 [4.7]	0.5 [3.9]	0.03	0.45	0.14
Muscle compensation, L/min	1.5 [2.9]	2.4 [3.7]	<0.01	0.72	<0.01
Change with desipramine					
Veupnoea, L/min	0.3 [1.5]	-0.2 [0.9]	>0.5	0.28	0.37
Varousal, L/min	0.7 [0.8]	0.3 [1.1]	0.34	0.28	0.34
Active V_0, L/min	4.1 [3.5]	-0.2 [5.4]	0.02	0.73	<0.01
Passive V_0, L/min	1.8 [3.5]	0.1 [5.0]	0.27	0.41	0.17
Loop Gain	-0.2 [0.9]	0.0 [0.1]	>0.5	0.00	0.94
Varousal-Active V_0, L/min	-3.8 [4.3]	0.0 [4.7]	0.02	0.70	0.01
Muscle compensation, L/min	2.1 [3.5]	-0.5 [0.4]	0.02	0.71	<0.01

V eupnoea, eupnoeic ventilation; V arousal, ventilation that leads to arousals; Passive V_0, ventilation at a nasal pressure of 0 cmH_2O when the pharyngeal muscles are passive; Active V_0, ventilation at a nasal pressure of 0 cmH_2O when the pharyngeal muscles are active; L/min, liters per minute.
Data are expressed as median [interquartile range].

Effects of desipramine on EMG_{GG} activity during CPAP manipulation. We performed a post-hoc analysis to evaluate the effect of desipramine on EMG_{GG} activity during optimum CPAP, during rapid CPAP dial downs, and at the end of slow CPAP dial downs to investigate the possible link between increased EMG_{GG} activity and reduced upper airway collapsibility on desipramine. The average optimum CPAP on both placebo and desipramine nights was 8±3 cmH_2O in these OSA patients. Measurements were performed during sleep in the supine position and normalised for baseline EMG_{GG} values during optimum CPAP. We found that immediately following rapid CPAP dial downs, there was no difference in tonic (1.1 [0.2] on placebo vs 1.2 [0.5] $\%_{max}/cmH_2O$ on desipramine, p>0.5) or phasic activity (1.2 [1.2] on placebo vs 1.2 [1.0] $\%_{max}/cmH_2O$ on desipramine, p>0.5). However, on desipramine, compared to placebo, phasic EMG_{GG} activity was higher during slow CPAP dial downs (2.0 [2.5] on placebo vs 3.8 [2.6]

$\%_{max}/cmH_2O$ on desipramine, p=0.035) while tonic EMG_{GG} activity was not significantly changed between nights (1.5 [1.7] on placebo vs 1.7 [1.6] on desipramine, p>0.5). These data suggest that the reduced collapsibility when upper airway muscles were in active conditions during desipramine night was likely mediated by increased phasic activity of these muscles.

Supplemental figures

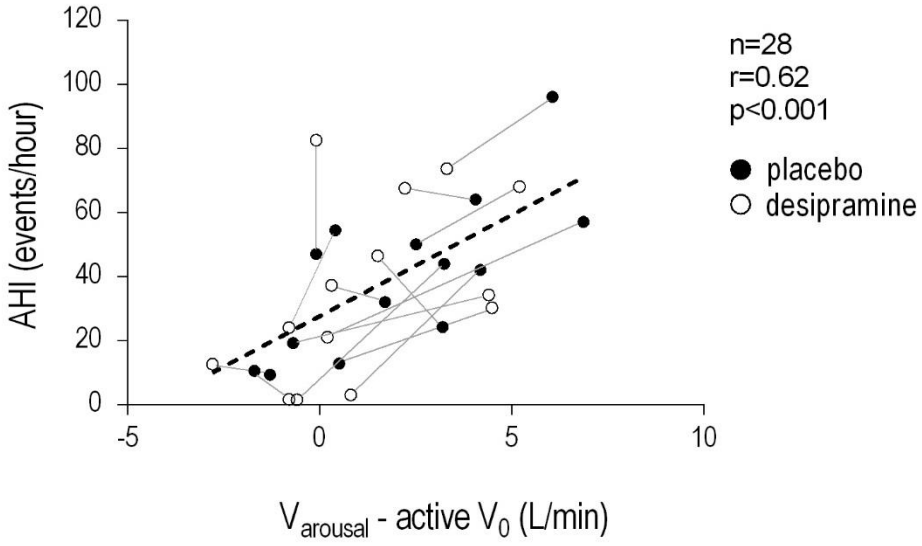

Figure E1. The "gap" that must be overcome to achieve stable breathing, quantified by the difference between the minimum tolerable ventilation and the maximum achievable ventilation (Varousal-ActiveV_0, *x* axis) correlated with the severity of OSA (r=0.62, p<0.001). Black dots represent the gap associated with an AHI value on placebo nights and white dots represent the same parameters on desipramine nights. Data from the same subject are connected by a gray line.

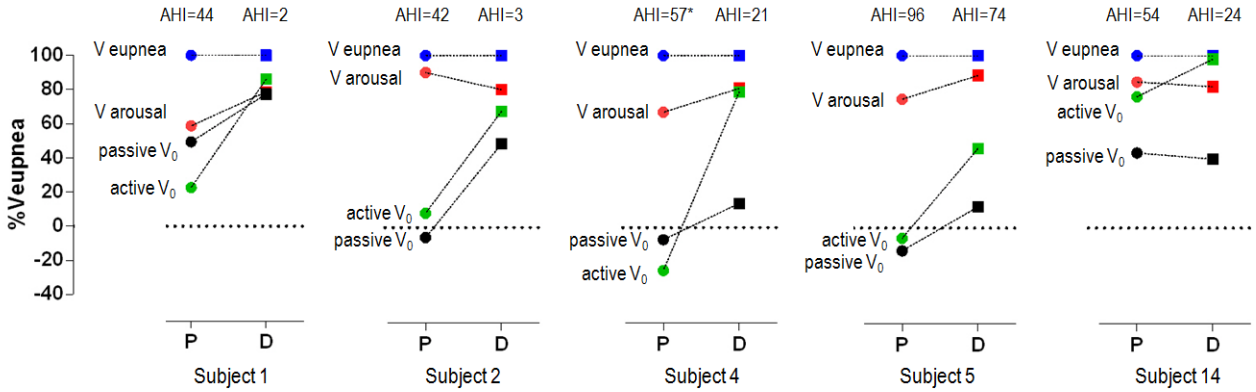

Figure E2. Graphical display of the four ventilation parameters on placebo and desipramine nights in subjects that showed an improvement in physiology and a consistent reduction in AHI on despramine (D) compared to placebo (P) night. In subjects 1 and 2 the improvement in passiveV_0 and activeV_0 led to a complete resolution of OSA. Subjects 1 and 4 showed on placebo night a bad upper airway muscle compensation with upper airway progressively more closed with successive breaths as respiratory drive increased (activeV_0 was lower than passiveV_0). During desipramine night, important improvements in muscle compensation led to resolution of OSA in subject 1 and to a reduction of AHI by 63% baseline in subject 4. Subjects 5 had a 23% improvement in AHI consistent with the increased passive and activeV_0 from placebo to desipramine night. Subject 14 had a reduction in AHI of 56%, associated to an increase of activeV_0 on desipramine. Although in subject 14 several mild hypopneas were scored on desipramine night, these were not associated with oxygen desaturation and the oxygen desaturation index (ODI) went from 28 on placebo to 0 events/hour on desipramine.
Values of ventilatory parameters are expressed as %eupnea to facilitate comparison between subjects.

* Indicates that the AHI value was calculated from an additional polysomnography night and not from the same night of physiology measurements as for the other subjects (see main manuscript for explanation).

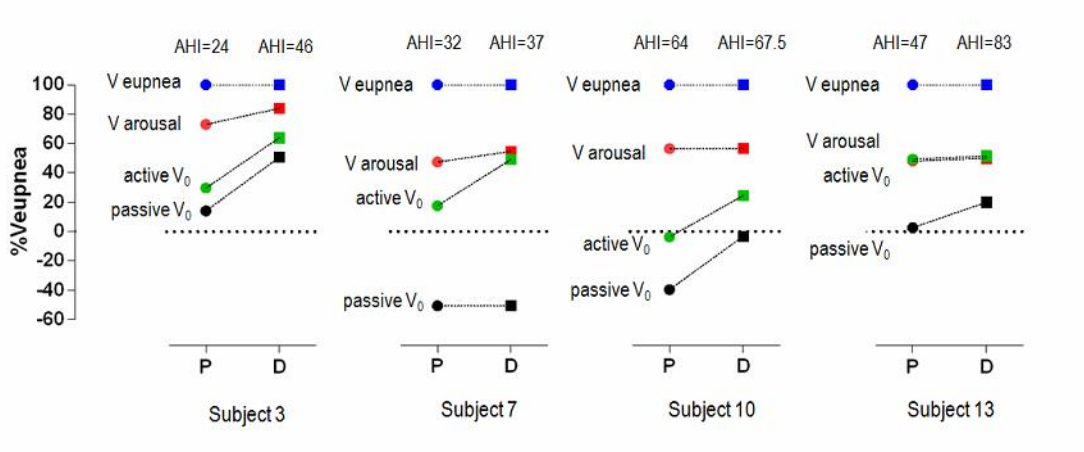

Figure E3. Graphical display of the four ventilation parameters on placebo and desipramine nights in subjects that showed an improvement in physiology but not an AHI reduction on despramine compared to placebo. Despite an increase in passiveV_0 and activeV_0 , subject 3 had a worsening of AHI. Notably, more than 50% of respiratory events were of central origin on desipramine night while all events were obstructive on placebo night. This was the only subject who showed an increased number of central events on desipramine night. AHI was almost unchanged in subject 7 and subject 10 despite an increase in activeV_0 and in both passiveV_0 and activeV_0, respectively. Subject 13 showed an increase in AHI on desipramine compared to placebo. The mean lenght of the apneas and hypopneas was shorter on desipramine night compared to placebo night (apneas went from 36 s on placebo to 21 s on desipramine while hypopneas went from 31 s on placebo to 27 s on desipramine). The reduced lenght of the events might partially explain the increase in AHI on desipramine in this subject.

Values of ventilatory parameters are expressed as %eupnea to facilitate comparison between subjects.

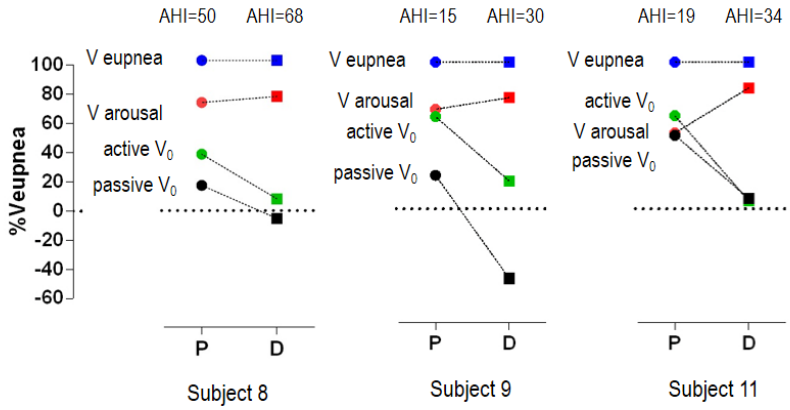

Figure E4. Graphical display of the four ventilation parameters on placebo and desipramine nights in subjects that showed a worsening in physiology parameters consistent with an AHI increase on desipramine night compared to placebo night. In subjects 8, 9 and 11 a worsening of activeV_0 and passiveV_0 was associated with a worsening in OSA severity. These subjects had the highest reduction in arousal threshold (measured as the epiglottic pressure swing prior to arousal during an obstructive apnea/hypopnea) in the group which could be responsible for this worsening in collapsibility parameters and AHI.

Values of ventilatory parameters are expressed as %eupnea to facilitate comparison between subjects.

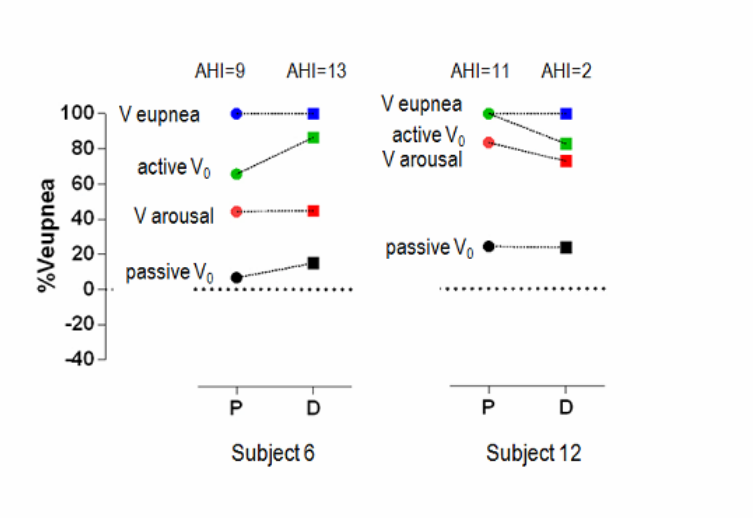

Figure E5. Graphical display of the four ventilation parameters on placebo and desipramine nights in subjects who showed a mild degree of OSA in both nights. Changes in AHI in subjects 6 and 12 are likely more dependent on night-to-night variability rather than on changes in physiologic parameters or on a drug effect. Despite a bad anatomy (low passiveV_0) these two subjects have a low AHI because of a high muscle compensation (activeV_0 – passiveV_0).

Values of ventilatory parameters are expressed as %eupnea to facilitate comparison between subjects.

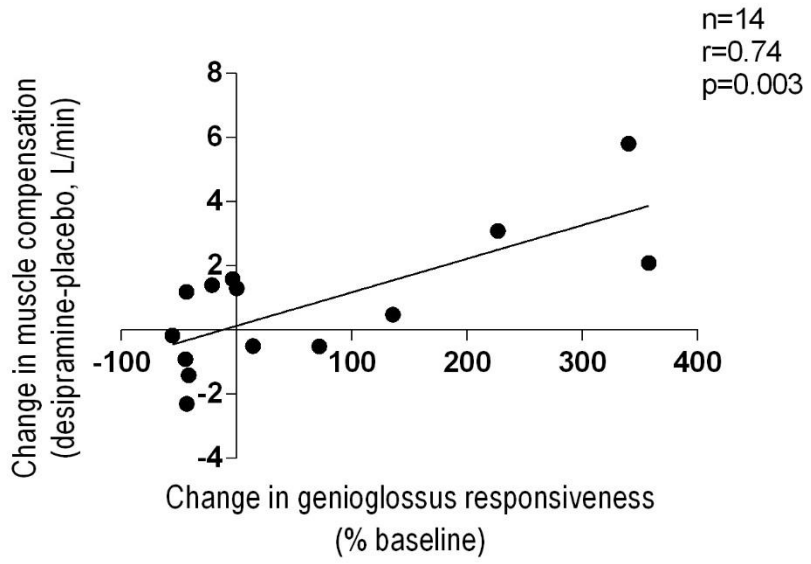

Figure E6. The improvement in muscle compensation (V_0active – V_0passive) is related to the change in genioglossus responsiveness to progressively-greater epiglottic pressure swings measured with intramuscular electromyography (EMG_{GG}). Notably, changes in muscle responsiveness can account only for 50 % of the changes in muscle compensation. This finding reflect the partial dissociation between EMG amplitude and muscle force generation, muscle shortening or tissue displacement previously described in literature (3-5). Other factors such as the mechanical coordination and efficiency of upper airway muscle contraction could be responsible for the increased ventilation.

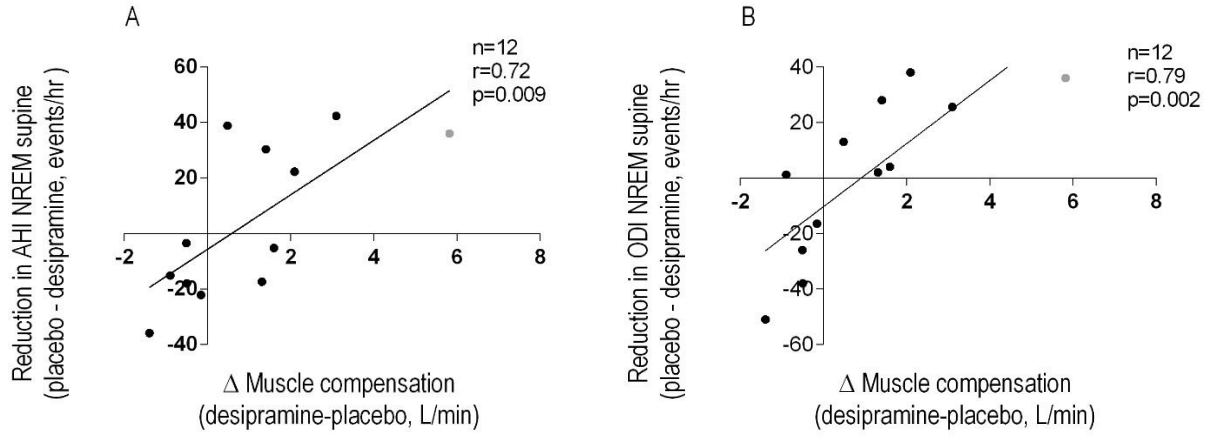

Figure E7. Relationship between the difference in muscle compensation (activeV_0 – passiveV_0) on desipramine vs placebo night and the reduction in AHI (A) or reduction in ODI (B) from placebo to desipramine. The improvement in muscle compensation was more tightly related with the reduction in ODI rather than with the reduction in AHI. One possible explanation is that an increase in muscle compensation leads to overall increase in the mean ventilation. This increase would be expected to reduce the severity of any desaturations associated with hypopneas. However, this ventilatory compensation is probably not enough to completely eliminate the respiratory event. Only 12 subjects with moderate-to-severe OSA were included in the analysis.

● Indicates that the AHI value of placebo night was calculated during an additional diagnostic night (see main text for explanation). It is noteworthy that this relationship persists even when this subject is excluded.

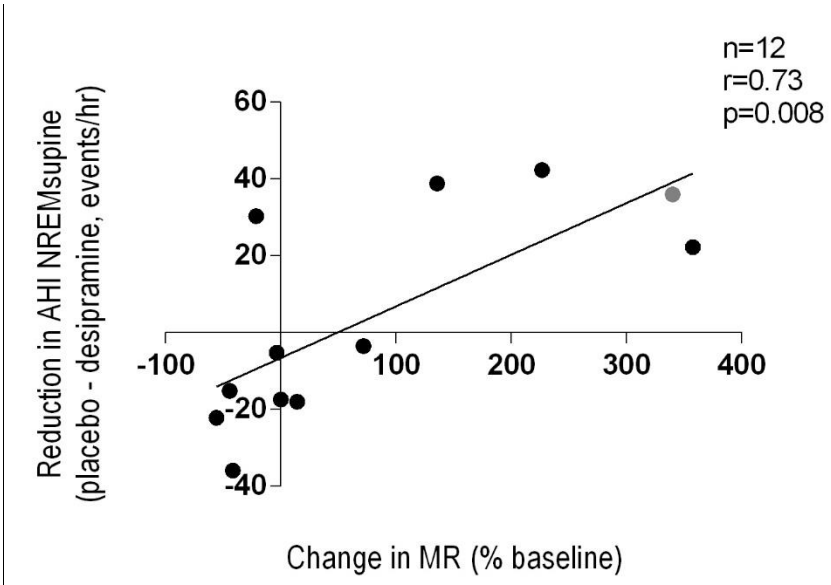

Figure E8. Relationship between the change in genioglossus muscle responsiveness (MR) to progressively-greater epiglottic swings during slow CPAP dial downs on desipramine night and the reduction in AHI from placebo to desipramine. Only 12 subjects with moderate-to-severe OSA were included in the analysis.

● Indicates that the AHI value of placebo night was calculated during an additional diagnostic night (see main text for explanation). Note: this relationship persists even when this subject is excluded.

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