

Anxiety Disorders



- Anxiety disorders affect 19 million US citizens annually
- Current therapies (e.g. benzodiazepines, buspirone, SSRIs) have significant limitations
 - Side-effects including sedation, nausea, muscle relaxation, memory impairment
 - Development of tolerance, dependence and withdrawal symptoms
 - Slow onset of action for buspirone and SSRIs
- Need for an anxiolytic that has a rapid onset and does not cause sedation and memory impairment or induce dependence
- Registration trials require large numbers of patients due to placebo effects
- Potential for Experimental Medicine studies to select best compound(s) for late stage trials

CO₂ Inhalation as a Model of Anxiety



- Extensively documented in published literature
- Exploratory pilot study of 35% CO₂ carried out at University of Bristol (1999)
 - Marked response with rapid recovery
 - HPA activation – stress response
- Aim to develop and validate a model to study the performance effects of fear
 - 7.5% CO₂ inhaled for 20 minutes
- How do we ‘measure’ a stressful or anxious response in healthy humans?

A collaboration with David Nutt and Jayne Bailey, University of Bristol

Visual Analogue Rating Scale (VAS)



At this moment I feel.....

0 10 20 30 40 50 60 70 80 90 100

Not at all
Anxious

A little
Anxious

Quite
Anxious

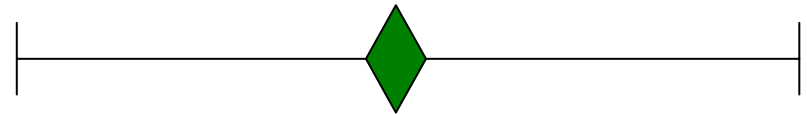
Very
Anxious

The most
Anxious

Palm Pilot (M105)



Not at all Moderately Extremely



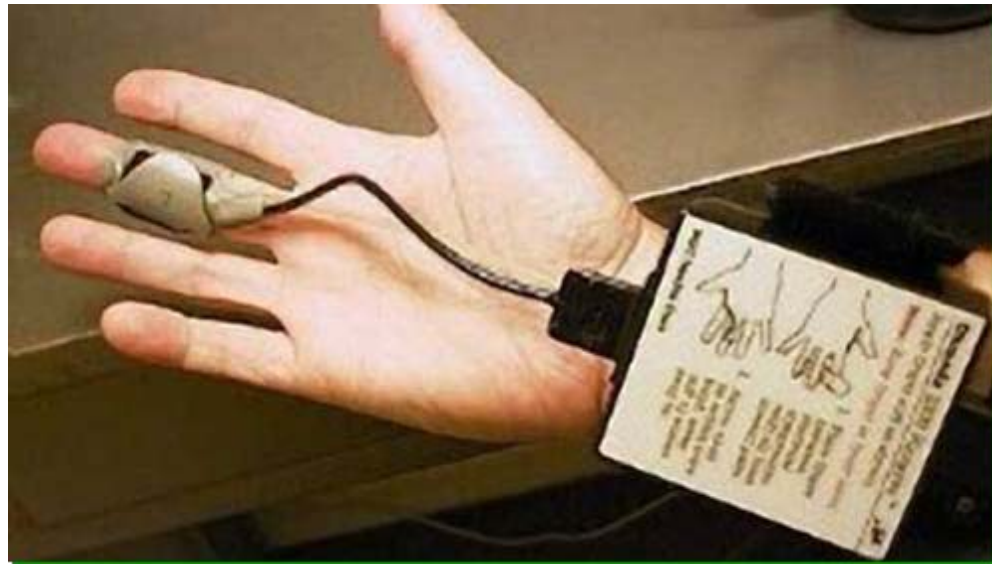
Cursor movement
required to register
response

Cardiovascular Measures



The Finapres:

- Cuff detects pressure in finger
- Measures every beat
- Good for assessing change



CO₂ Inhalation Procedure



(subjects gave verbal consent to use image in presentations)

Why Use 7.5% CO₂



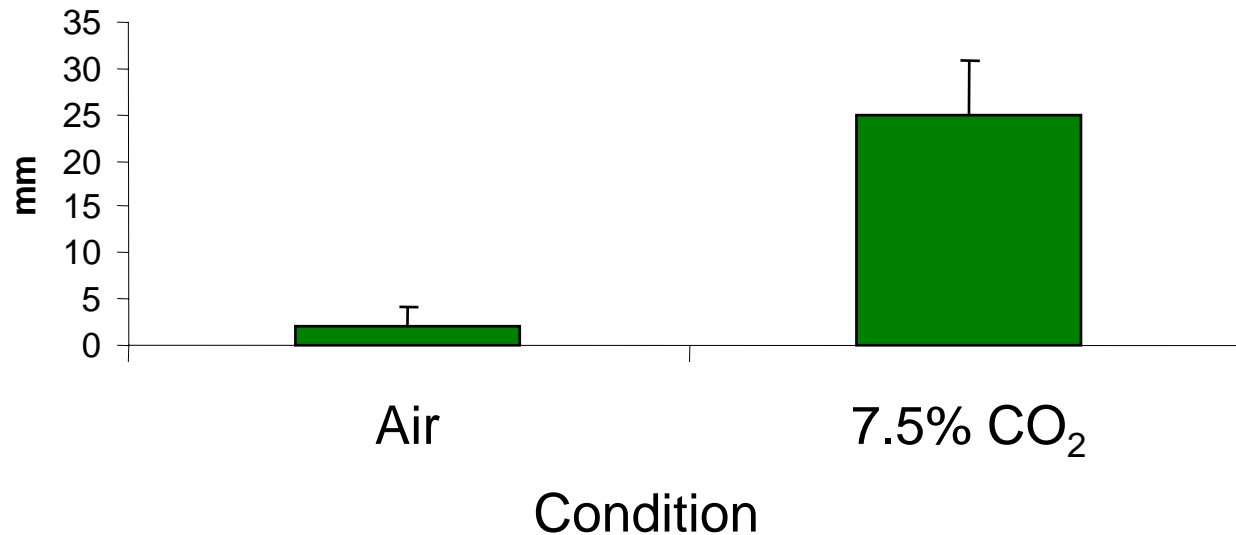
	Bristol Study	Woods et al., 1988	Woods et al.,1988
	7.5% CO ₂ , n= 8 mean (± sem)	7.5% CO ₂ , n=8 mean (± sem)	5% CO ₂ , n=11 mean (± sem)
Anxious	33 (9)	41(8)	14 (7)
Fearful	31 (8)	30 (9)	3 (2)
Relaxed/ Calm*	-46 (3)	-31 (7)	-9 (6)
Happy	-35 (5)	-13 (5)	-2 (6)

Bristol study used 'relaxed', Woods et al used calm.

Effect of 7.5% CO₂ on Subjective Anxiety



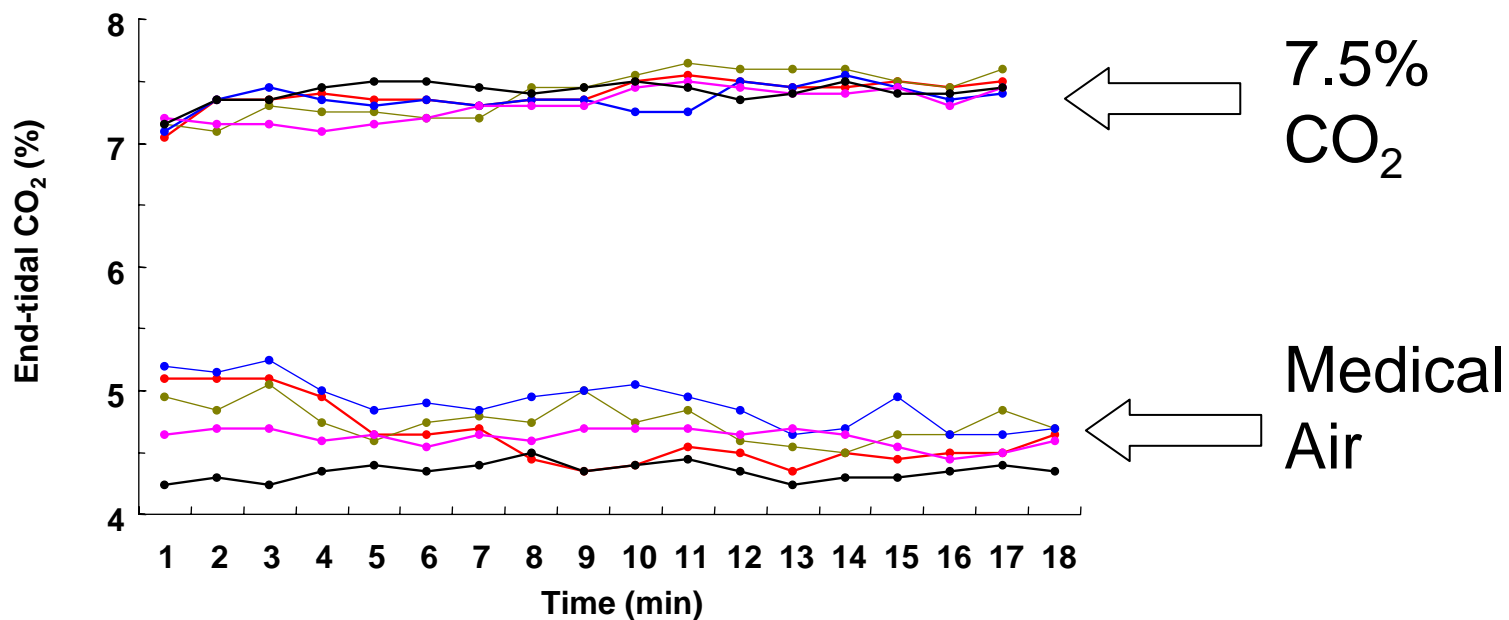
Peak effects of CO₂ or air inhaled for 20 minutes by 20 healthy volunteers



Effect of 7.5% CO₂ on Respiration



End Tidal CO₂ for 5 subjects:



Effect of 7.5% CO₂ on Blood Pressure and Heart Rate

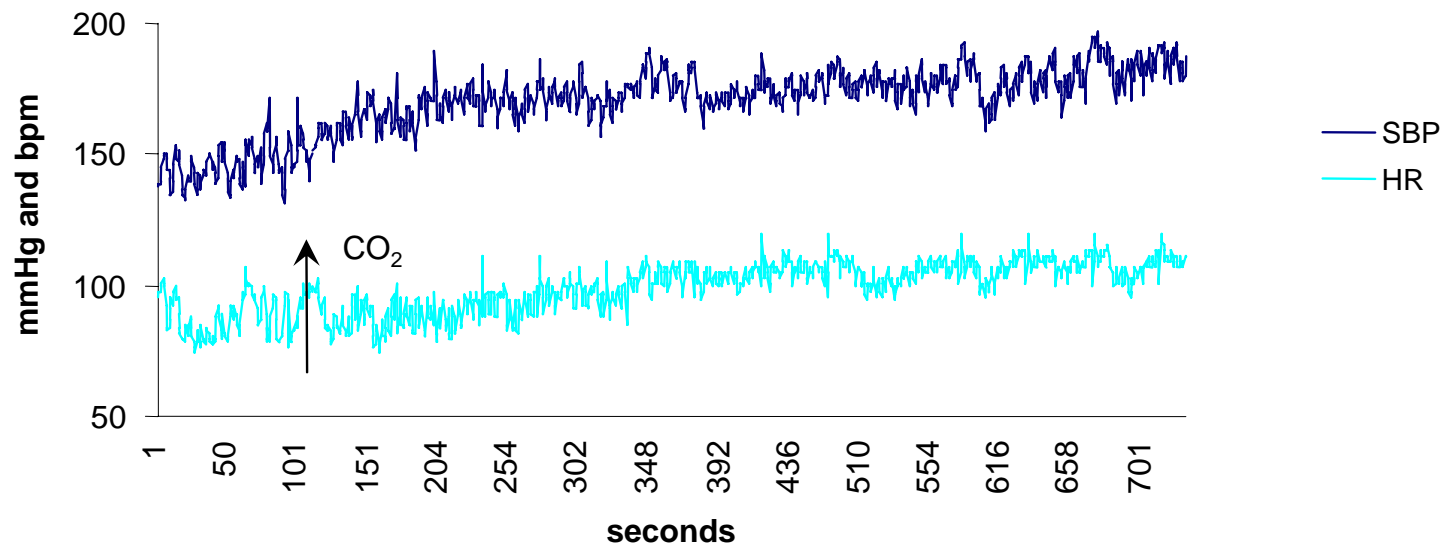


Mean heart rate and blood pressure values during 20 min inhalation of air or 7.5% CO₂

Value	Air	CO ₂	
SBP	154 (17.7)	172 (16.7)	p=<0.001
DBP	91 (18.2)	94 (14.8)	ns
HR	76 (9.3)	84 (14.7)	p=<0.001

Data are mean ± sd, n=20.

Inhalation of 7.5% CO₂ in one subject



Subjective Effects of 7.5% CO₂



Rating	Peak Air	Peak CO₂
Anxious	2 (2.1)	25 (5.8)*
Fear	1 (2.9)	24 (4.5)*
Feel like leaving	3 (2.5)	23 (5.8)*
Happy	-10 (2.9)	-27 (4.0)*
Relaxed	-13 (5.5)	-35 (4.9)*
Tense	4 (2.9)	29 (5.1)*

VAS data are change from baseline values for peak effects of gas

*Data are mean ± sem, n=20; Wilcoxon test: *= $P < 0.01$*

A Model of Anxiety not Panic?



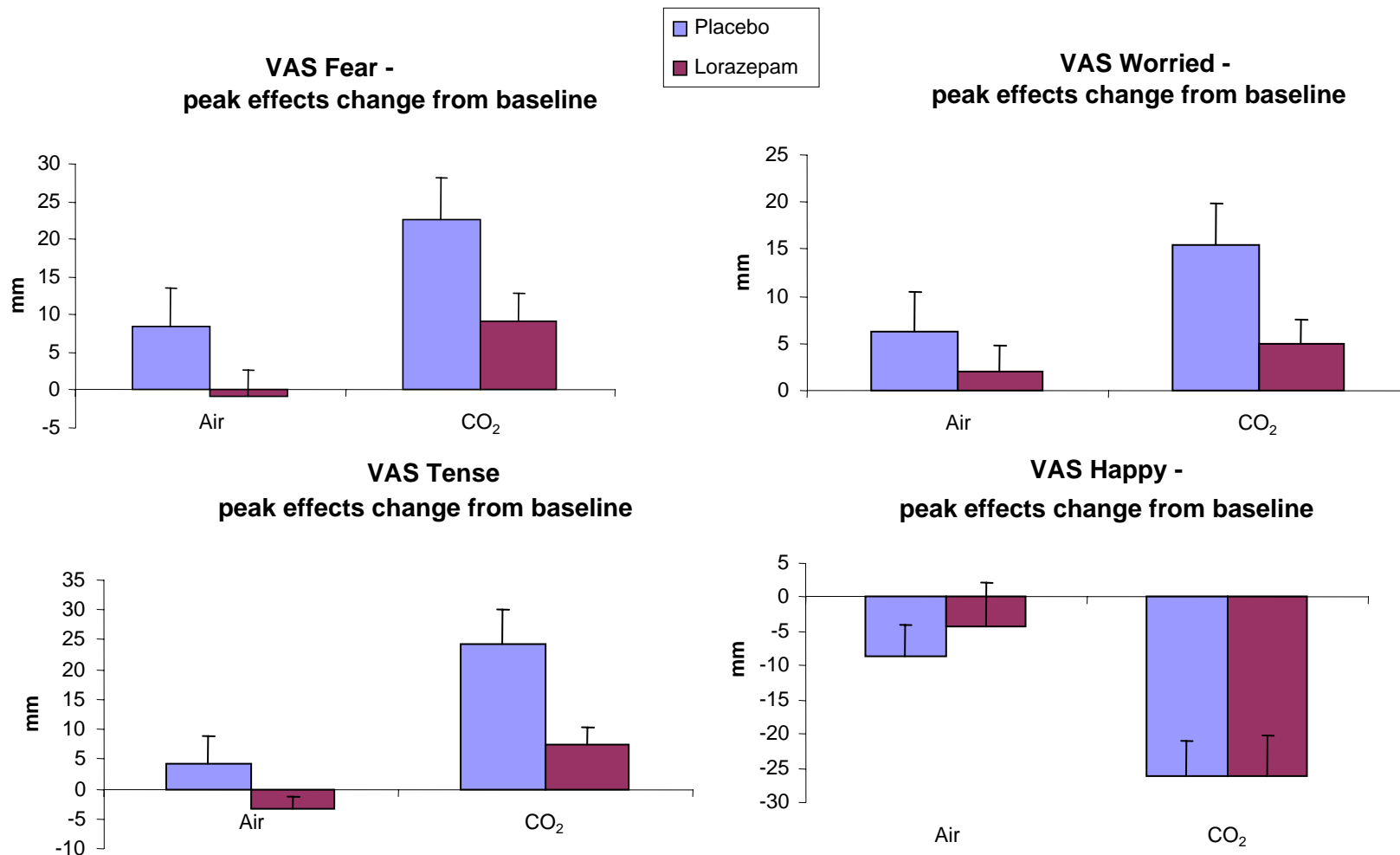
- 7.5% CO₂ produces a different state to that of a single inhalation of 35% CO₂
- Different cardiovascular profile
- No evidence of HPA axis activation?
- Different symptom profile
- More like a patient with GAD than panic?
- Further validation required

Method for Model Validation



- Double-blind, placebo-controlled, randomised study using single dose of standard benzodiazepine anxiolytic
- Effects of 20 minute inhalation of 7.5% CO₂ and air as a control gas
- Baseline measures taken, inhalation 1 – ratings at peak, 20 and 30 minutes, followed by inhalation 2
- CO₂ inhalation given at peak drug effects.
- Psychological (subjective ratings and questionnaires) and physiological measures (Finapres) taken

Effect of Lorazepam on 7.5% CO₂-induced Changes in VAS Scores



N=12, data are values at peak effects of 7.5% CO₂

Cardiovascular Effects of Lorazepam



	Placebo Air	Lorazepam Air	Placebo CO₂	Lorazepam CO₂
SBP	141 (18.9)	140 (17.9)	148 (24.7)	152 (15.4)
DBP	81 (12.8)	81 (10.2)	85 (13.5)	88 (12.8)
HR	69 (10.4)	78 (9.4)*	74 (9.8)	84 (11.1)*

*n=12, mean during 20 min inhalation ± sd, *=p<0.05*

Summary and Further Studies Planned with CO₂ Model



- Single dose of lorazepam significantly reduces CO₂-induced worry, fear and tension measured by VAS
- No effect of lorazepam on VAS measure of happy or CV function
- Further validation studies
 - Double-blind, placebo-controlled lorazepam dose-response
 - Double-blind, placebo-controlled SSRI dose-response