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Resetting the baroreflex during snoring: Role of resistive loading and intra-thoracic pressure

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ABSTRACT

Baroreflex sensitivity (BRS) is reduced during snoring in humans and animal models. We utilised our rabbit model to examine the contribution of increased upper airway resistance to baroreflex resetting during snoring, by comparing BRS and baroreflex operating point (OP) values during IS to those obtained during tracheostomised breathing through an external resistive load (RL) titrated to match IS levels of peak inspiratory pleural pressure (Ppl). During both IS and RL, BRS decreased by 45% and 49%. There was a linear relationship between the change in Ppl and the decrease in BRS, which was similar for IS and RL. During both RL and IS, there was a shift in OP driven by ~16% increase in HR and no change in arterial pressure. Snoring related depression of BRS is likely mediated via a HR driven change in OP, which itself may be the outcome of negative intra-thoracic pressure mediated effects on right atrial wall stretch reflex control of heart rate.

1. Introduction

The arterial baroreflex is a pressure sensing, negative feedback control system that modulates short-term beat-to-beat regulation of arterial blood pressure. The sensitivity of this homeostatic control system is defined in terms of the slope of the relationship between arterial blood pressure and heart rate. Sleep-wake state influences BRS such that, in healthy subjects, values measured during sleep tend to be higher than those recorded during wakefulness (Conway et al., 1983; Legramante et al., 2003; Lombardi and Parati, 2000; Vaile et al., 1996; Van de Borne et al., 1994). However, the opposite is the case when subjects experience sleep disordered breathing (SDB), with a number of studies documenting lower BRS values during sleep in patients with obstructive sleep apnoea (OSA) (Carlson et al., 1996; Gates et al., 2004; Mateika et al., 1999; Parati et al., 1997; Ryan et al., 2007).

OSA is characterised by snoring with recurrent apnoeas and hypopnoeas, frequently accompanied by episodes of hypoxaemia (Dempsey et al., 2010; White, 2006). The mechanistic linkage between these nocturnal SDB events and reduced BRS remains unclear, but sympathetic surges commonly associated with apnoeic events (Carlson et al., 1993, 1996; Levinson and Millman, 1991; Somers et al., 1995) and/or chemoreceptor activation, particularly in response to hypoxaemia (Dunai et al., 1999; Levinson and Millman, 1991; Polo et al., 1991; Prabhakar et al., 2005, 2007; Shahar et al., 2001; Somers et al., 1989) are most commonly proposed.

Reduced BRS values during sleep, however, are also known to occur during periods of non-hypoxic snoring (Mateika et al., 1999), suggesting linkages between SDB and BRS that do not depend on the presence of hypoxaemia or occurrence of the sympathetic activation associated with apneic events. Recently, we described a non-hypoxic, non-apneic, anaesthetised rabbit model in which external compression of the pharyngeal airway is used to increase upper airway resistance and induce snoring (Narayan et al., 2012). In this model, induced snoring led to ~40% fall in BRS and a change in BRS operating point (prevailing heart rate and blood pressure) characterised by an increase in heart rate but no significant change in blood pressure. In the present study we examine the contribution of increased upper airway resistance to baroreflex resetting during snoring by comparing BRS and operating point values obtained during induced snoring in anaesthetised rabbits (intact upper airway) with those obtained during tracheostomised breathing through an external resistive load titrated to match induced snoring levels of peak inspiratory intra-pleural pressure (Ppl).

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2. Methods

2.1. Animals

Studies were conducted in six anaesthetised, spontaneously breathing, adult, male, New Zealand white rabbits (weight: 3.2–4.0 kg). Anaesthesia was induced with intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg) and maintained via continuous intravenous infusion (ear vein) of ketamine (15 mg/kg/h) and xylazine (4.5 mg/kg/h). On study completion animals were euthanised with an overdose of intravenous sodium pentobarbitone. The experimental protocol was approved by the Western Sydney Area Health Service Animal Ethics Committee, and complied with the regulations of the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Surgical preparation

The experimental set-up was similar to that previously described (Narayan et al., 2012). All rabbits were studied supine, with head elevated 50° to the horizontal in a U-shaped head-rest. A skin incision was performed on the ventral surface of the neck and blunt dissection was used to expose the trachea, and right and left common carotid arteries. Another skin incision on the left inner mid-thigh allowed access to the femoral artery for arterial blood pressure monitoring purposes. In all rabbits, following acquisition of tidal breathing and induced snoring data, the exposed trachea was severed (tracheostomy), thus allowing breathing to bypass the upper airway.

2.3. Instrumentation

An electric blanket (Riveria, AEM Co Pty. Ltd, Sydney, Australia) and rectal thermometer (YSI 400, Yellow Springs Instrument Co., Ohio, USA) were used to maintain and monitor core body temperature, respectively. Heart rate (RR interval) was determined via a three-lead electrocardiogram (ECG). A conical shaped mask (GaleMed VM-2 size 2, GaleMed, Taiwan) was positioned over the snout of the rabbit and attached to a heated pneumotachograph (Fleisch 8300A, Hans Rudolph Inc., MO, USA), with differential pressure transducer (Validyne DP45-32 [$\pm$5.6 cmH_2O], Engineering Corp., CA, USA) for measurement of airflow ($\dot{V}$). Mask pressure (P_{mask}) was monitored with a separate pressure transducer (Celesco LCVR [$\pm$100 cmH_2O], Celesco Transducer Products, CA, USA).

Arterial oxygen saturation (O_2sat%) was monitored using a pulse oximeter probe (Ohmeda Biox 3700e, BOC Healthcare, USA) taped onto the shaved skin of the rabbit's right leg, while expired gas was sampled at the inlet port on the mask or at the site of the tracheostomy allowing carbon dioxide concentration (CO_2%) to be monitored continuously using a carbon dioxide analyser (ESW 0.91, Exerstress, Australia). Supplemental oxygen (open circuit; 0.5–1.0 l/min) was also provided throughout the study at the inlet of the breathing port on the mask or at the tracheostomy site as required to prevent hypoxaemia.

Peri-carotid tissue pressure (P_{CT}) was measured via a transducer-tipped catheter (SPR-524, Millar Instruments, TX, USA) advanced into the tissues adjacent to the right carotid artery at the level of the carotid sinus (region of carotid baroreceptors). A second catheter was advanced via the femoral artery into the aorta for measurement of continuous beat-to-beat systolic and diastolic blood pressure (SBP and DBP, respectively). Catheter positions were verified post mortem.

Pleural pressure (Ppl) was measured continuously via a separate transducer-tipped catheter (SPR-524, Millar Instruments, TX, USA) introduced through a small incision in the cervical oesophageal wall and then positioned with its tip in the lumen of the intra-thoracic oesophagus.

2.4. Measurement of BRS

BRS was quantified from beat-to-beat measurements of systolic blood pressure (SBP) and RR interval (ECG) using the spontaneous sequence technique (Bertinieri et al., 1988). This well-validated methodology (Bertinieri et al., 1988; Blaber et al., 1995; Laude et al., 2004; Oka et al., 2003; Persson et al., 2001; Stauss et al., 2006) is based on identification of spontaneous beat-to-beat sequences in SBP and corresponding RR intervals. A specifically developed software program (BSA, University of Melbourne) identified sequences of 3 or more beats, where the increases or decreases in SBP by 0.3 mmHg, were accompanied by lengthening or shortening of the RR interval by at least 0.6 ms (Legramante et al., 1999; Tank et al., 2004). The BRS was then determined as the average slope of the individual SBP versus RR relationships detected across the time period of interest. Baroreflex operating point was defined by the mean systolic pressure and corresponding mean heart rate for each 5-min period of tidal breathing, induced snoring, IS and resistive loading.

2.5. Induced snoring

Snoring was induced via external compression of the upper airway, using lead-filled latex bags (weight: 8.3–19.1 g) as described previously (Amatoury et al., 2006). Weights were placed ventrally onto the pharyngeal airway wall, at the level of the hypopharynx. Bag weight was progressively increased until sufficient airway narrowing occurred to produce induced snoring, which occurred predominantly during inspiration, and was defined as an audible sound perceived as snoring, accompanied by high frequency oscillations on the airflow signal, together with evidence of inspiratory airflow limitation. Snores were induced on every breath during each induced snoring period.

2.6. Determination of peak inspiratory Ppl from oesophageal pressure signal

For each 5-min induced snoring period, the average peak inspiratory Ppl was determined using the cyclic variables function of the signal processing software (Chart 4.2.3, ADInstruments, Sydney, Australia). These data were then subsequently used to set the within rabbit target levels for peak inspiratory Ppl during resistive loading.

2.7. Resistive loading – tracheostomy breathing

External resistive loads were applied to the lower airways via a tracheostomy. A pneumotachograph was connected to the caudal tracheal segment using an L-shaped connector and a polyethylene tube with an adjustable clamp attached to the pneumotachograph. Adjusting the clamp allowed the level of resistive loading to be adjusted and the inspiratory Ppl level titrated to match that generated in the same animal during induced snoring. Thus, the resistive loading imposed reflected the external compression used to generate induced snoring in that it was fixed in nature and was present during both inspiration and expiration.

2.8. Peripharyngeal tissue loading – tracheostomy breathing

In five of the rabbits, in order to assess the direct effect of increasing P_{CT}, without inducing snoring, lead-filled latex bags were placed ventrally onto the pharyngeal airway wall (as described during induced snoring above), breathing via a tracheostomy. Bag weight