Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation

Dominik Linz, MD,* Ulrich Schotten, MD, PhD,† Hans-Ruprecht Neuberger, MD, PhD,* Michael Böhm, MD,* Klaus Wirth, PhD‡

*From the *Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Homburg/Saar, Germany, †Cardiovascular Research Institute Maastricht (CARIM), The Netherlands, and ‡Sanofi-Aventis Deutschland GmbH, R&D, Aging/Disability of CVC Origin, Frankfurt, Germany.*

BACKGROUND Obstructive sleep apnea (OSA) causes negative tracheal pressure (NTP) and is associated with atrial fibrillation (AF).

OBJECTIVE This study aimed to determine the mechanism of atrial electrophysiological changes during tracheal occlusion with or without applied NTP and to evaluate the role of vagal activation, Na^+/H^+exchanger (NHE), and ATP-dependent potassium channels (K_{ATP}).

METHODS Seventeen closed-chest pigs were anesthetized with urethane, and an endotracheal tube was placed to apply NTP (up to −100 mbar), comparable to clinically observed OSA in patients by a negative pressure device for a time period of 2 minutes. Right atrial refractory periods (AERP) and AF inducibility were measured transvenously by a monophasic action potential recording and stimulation catheter.

RESULTS All tracheal occlusions with and without applied NTP resulted in comparable increases in blood pressure and hypoxemia. NTP shortened AERP (157.0 ± 2.8 to 102.1 ± 6.2 ms; $P < .0001$) and enhanced AF inducibility during AERP measurements from 0% at baseline to 90% ($P < .00001$) during NTP. Release of NTP resulted in a prompt restoration of sinus rhythm, and AERP returned to normal. NTP-induced AERP shortening and AF inducibility were prevented by atropine or vagotomy. Neither the NHE blocker cariporide nor the K_{ATP} channel blocker glibenclamide abolished NTP-induced AERP shortening. By contrast, tracheal occlusion without applied NTP caused comparable changes in blood gases but did not induce AERP shortening or AF inducibility.

CONCLUSION NTP during obstructive events is a strong trigger for AF compared with changes in blood gases alone. NTP caused AERP shortening and increased susceptibility to AF mainly by enhanced vagal activation. AERP shortening was not prevented by K_{ATP} channel blockade or NHE blockade.

KEYWORDS Obstructive sleep apnea; Atrial fibrillation; Atrial electrophysiology parasympathetic activity; Cariporide; Glibenclamide

ABBREVIATIONS **AERP** = atrial effective refractory period; **AF** = atrial fibrillation; **BCL** = basic cycle length; **K_{ATP}** = ATP-dependent potassium channel; **MAP** = monophasic action potential; **NHE** = Na+/H+ exchanger subtype 1; **NTP** = negative tracheal pressure; **OSA** = obstructive sleep apnea

(Heart Rhythm 2011;8:1436–1443)

Introduction

Patients with obstructive sleep apnea (OSA) show a high prevalence of atrial fibrillation (AF) ranging from 32% to 49%.[1–3] OSA was the strongest predictor of recurrent AF after catheter ablation,[4] and patients with untreated OSA have a higher risk of recurrence of AF after successful cardioversion.[5] The finding that appropriate treatment of OSA with continuous positive airway pressure is associated with lower recurrence of AF suggests a causal association of OSA inducing AF.[6] Several mechanisms causing AF in OSA have been discussed, including hypoxemia and acidosis. These changes in blood gases might influence the parasympathetic and sympathetic tone leading to a substrate for AF. While enhanced vagal tone is known to induce atrial effective refractory period (AERP) shortening, increased sympathetic tone and autonomic dysbalance may enhance spontaneous triggered activity that could induce AF.[7] Severe bradycardia and atrioventricular block are frequently seen in OSA and suggest vagal activation.[8] However, other mediators beyond hypoxemia might be relevant in humans. Obstructive apneas are caused by collapse of the upper airway during sleep resulting in repetitive forced inspiration against the obstructed upper airway. Correspondingly substantial negative changes in intratracheal pressure down to −100 mbar were observed in OSA patients.[3,9,10] The resulting intrathoracic pressure changes might stretch heart chambers and lead to changes in transmural pressure gradients, particularly in the thinly walled atria. The influence of negative tracheal pressure (NTP) on atrial electrophysiology has not been investigated yet. We hypothesized that the NTP during obstructive events and not changes in blood

Address reprint requests and correspondence: Dominik Linz, M.D., Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, 66421 Homburg/Saar, Germany. E-mail address: Dominik.Linz@uniklinikum-saarland.de.
(Received February 13, 2011; accepted March 23, 2011.)

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.03.053

gases is responsible for increased AF susceptibility in OSA. Therefore, we investigated electrophysiological changes in the pig right atrium during airway obstructions with or without NTP generated by a negative pressure device. Atropine followed by vagotomy was used to study the role of vagal activation. Additionally, we characterized the role of hypoxia and stretch-activated Na^+/H^+ exchanger subtype 1 (NHE) and ATP-dependent potassium channel (K_{ATP})[11–13] by cariporide and glibenclamide.

Methods

All animal studies were performed in accordance with the German law for the protection of animals. Furthermore, the investigation conforms with the guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Experimental model for OSA

In 17 chest-closed male castrated pigs (25–30 kg) of the German Landrace (anesthetized with 20% urethane [0.8 mL/kg intravenous load, 0.4 mL/kg/hour maintenance] and 4% alpha-chloralose [0.4 mL/kg intravenous load, 0.1 mL/kg/hour maintenance]), a tracheotomy was performed to place an endotracheal tube. This tube was used for tracheal occlusion and to apply different levels of NTPs by a negative pressure device. The negative pressure device consisted of a negative pressure container (50 L) and a vacuum pump controlled by a manometer. The tracheal tube was connected to the vacuum container, and a solenoid valve was opened and the tracheal tube and the vacuum container created a closed system. In pilot experiments, spontaneous breathing attempts during tracheal occlusion without NTP just created fluctuating tracheal pressures down to −40 mbar without causing electrophysiological changes. The Mueller maneuver (forced inspiration against airway obstruction) is used in the clinical setting to simulate conditions, particularly negative thoracic pressure, during OSA.[14] As a modification of this maneuver, we applied NTP at −100 mbar during tracheal occlusion corresponding to NTPs found in patients with OSA.[3,9,10]

Right atrial pressure changes were investigated by a catheter that was advanced via the femoral vein (Gould, P23 series pressure transducer, Hato Rey, Puerto Rico). Blood pressure was measured by a TIP-catheter (Millar PC 350; Millar Instruments, Houston, TX) in the femoral artery. Temperature was measured via a rectal probe and maintained around 37.0°C by a heating lamp. Blood gas analysis (pO_2, pCO_2, pH, O_2 saturation) was performed before, at the end, and 15 minutes after release of tracheal occlusion without or with applied NTP in seven pigs. In all pigs of group 1, the cervical vagi were dissected and bilateral vagotomy was performed.

Experimental design

In Figure 1, the electrophysiological protocol (Figure 1A) and the experimental design (Figure 1B) are shown. AERP measurements and monophasic action potential (MAP) recordings were performed, and AF inducibility was investigated during normal breathing and every 30 seconds during 2 minutes of either tracheal occlusion without applied NTP

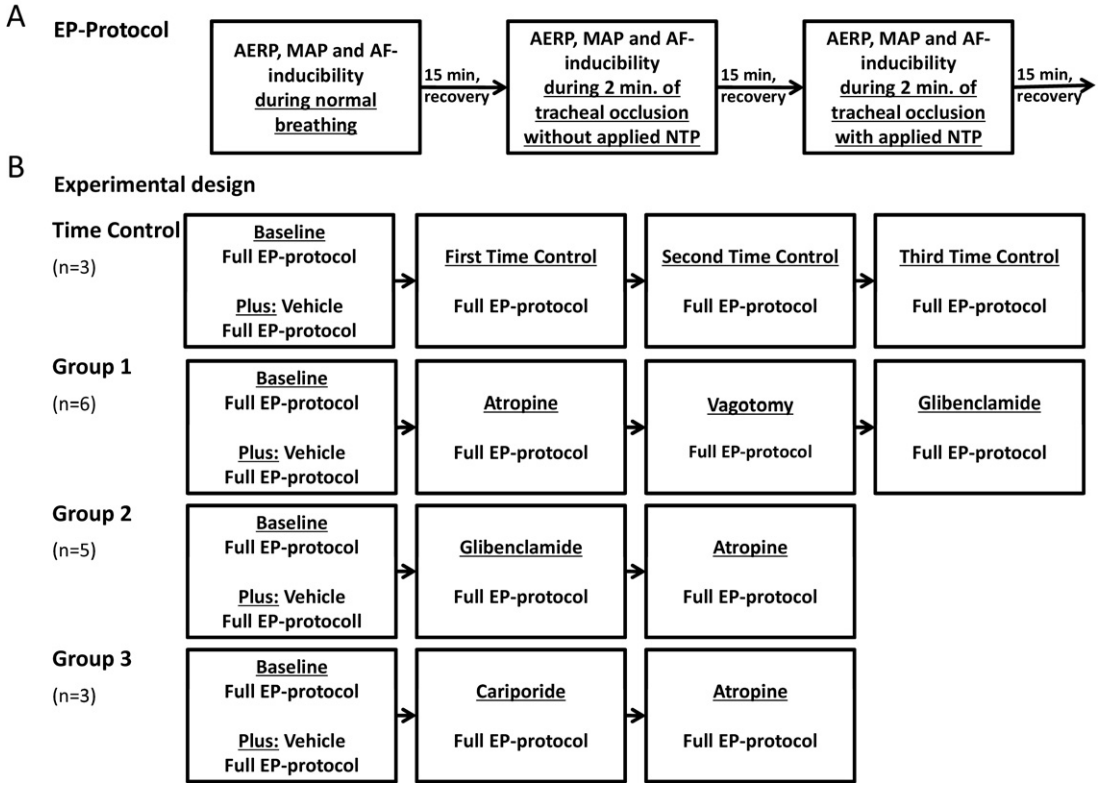

Figure 1 Flow chart of the electrophysiological protocol (EP protocol; Figure 1A). A complete EP protocol included AERP measurement, MAP recording, and AF inducibility during normal breathing and every 30 seconds during 2 minutes of tracheal occlusion without and with applied NTP at −100 mbar with a recovery period of 15 minutes between the different NTP maneuvers. In panel **B**, the experimental design is shown.