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Workman, A.J. and Rankine, A.C. (2010) *Do hypoxemia or hypercapnia predispose to atrial fibrillation in breathing disorders, and, if so, how?* Heart Rhythm, 7 (9). pp. 1271-1272. ISSN 1547-5271

<http://eprints.gla.ac.uk/35852/>

Deposited on: 31 August 2010

Do hypoxaemia or hypercapnoea predispose to atrial fibrillation in breathing disorders, and if so, how?

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There are no conflicts of interest

Emerging risk factors for the development of atrial fibrillation (AF) include a variety of breathing disorders. For example, reduced lung function,¹ and sleep-disordered breathing (SDB),² have each been independently associated with increased risk of AF. Obstructive sleep apnea (OSA) was the strongest predictor of recurrent AF following catheter ablation.³ The severity of nocturnal hypoxaemia in patients with OSA independently predicted new-onset AF.⁴ However, transient arterial hypoxaemia, and hypercapnoea, such as occur during SDB may be associated with over-compensatory fluctuations in autonomic tone, intrathoracic pressures and cardiac haemodynamics, with possible atrial stretch and remodelling, each of which could predispose to AF. It is unclear whether hypoxaemia or hypercapnoea *per se*, i.e., in the absence of pathophysiological confounders or autonomic fluctuations, could cause atrial electrophysiological changes that could predispose to AF.

This question is addressed in the present issue of *Heart Rhythm*, in a study by Stevenson *et al.*⁵ They used an anaesthetised sheep model of hypoxaemia and of hypercapnoea, permitting the required control over physiological and pathophysiological variables, and the measurement of detailed invasive atrial electrophysiological parameters relating to reentry, a prominent electrophysiological mechanism of AF.⁶ The effective refractory period (ERP), conduction velocity (θ), and their temporal and spatial heterogeneity were examined in both atria. Acute hypoxaemia was induced by replacing O₂ with N₂ while maintaining normal CO₂, which reduced arterial O₂ saturation (SaO₂) to 80%. Neither this intervention, nor its acute reversal, significantly affected any of the electrophysiological measurements. By contrast, acute hypercapnoea, and its subsequent reversal, produced some intriguing changes in atrial electrophysiology. Hypercapnoea was induced with a re-breathing circuit while maintaining physiological SaO₂ (>98%) which elevated arterial CO₂ pressure (PaCO₂) to 97 mmHg. This resulted

in a progressive increase in atrial ERP which peaked, at steady-state hypercapnoea, with a 52% prolongation over the normocapnoeic value. Atrial conduction delay was also increased by hypercapnoea, slowing θ by up to 27%. Hypercapnoea had no effect on the temporal or spatial heterogeneity of ERP or θ . Since the minimum pathlength for reentry, i.e., wavelength (λ), equals ERP x θ ,⁶ these changes in ERP and θ should produce an overall lengthening of λ and thus potentially inhibit reentry. The vulnerability to extrastimulus-induced AF was assessed at that point, and AF could not be induced.⁵ However, strikingly, well after full reversal of hypercapnoea, while the ERP had recovered to pre-hypercapnoeic levels, θ remained slowed by up to 22%, thus potentially shortening λ at that time. This coincided with an increased vulnerability to inducible AF.

A consideration of the potential underlying mechanisms and clinical implications of these findings raises some intriguing questions and possibilities for future study. For example, how did elevated PaCO₂ increase ERP and slow θ , and why did the θ -slowing persist after the reversal of hypercapnoea while the ERP-increase did not? The mechanisms underlying the changes in ERP and θ were not specifically investigated.⁵ ERP is determined by Na⁺ current (I_{Na}) reactivation, which depends largely on action potential duration (APD). APD is determined by the relative magnitude of ion currents flowing during repolarisation.⁶ Hypercapnoea caused a significant decrease in serum pH, which reversed when PCO₂ was returned to normal,⁵ and since the ERP changes were co-incident with these pH changes, one might suspect a causal link between them. However, this seems unlikely, since acidosis may actually shorten APD and ERP, by increasing a steady-state outward current.⁷ θ is determined by action potential maximum upstroke velocity (V_{max}), which depends mainly on I_{Na} , and also by gap junction current (I_{gap}), which reflects the degree of intercellular electrical coupling. Hypercapnoea caused a small increase in serum [K⁺].⁵ This likely resulted from the associated fall in pH, since CO₂ forms carbonic acid thereby liberating H⁺, with consequent re-compartmentalisation of K⁺ and H⁺. It is unclear, therefore, why [K⁺] increased further when hypercapnoea and acidosis were reversed. Nevertheless, hyperkalaemia would shift the K⁺ electrochemical diffusion potential positively, partially depolarising the resting potential (V_m), thereby potentially slowing θ by reducing I_{Na} availability and V_{max} . However, a study in guinea-pig atria⁸ suggests that the degree of [K⁺] increase observed,⁵ either during hypercapnoea or following its reversal, may have been insufficient to account for the observed θ -slowing; depolarising V_m by a maximum of only approximately 3 mV. Alternative explanations for the hypercapnoea-induced θ -slowing could include a reduction in I_{gap} since, in canine ventricle, hypercapnoeic-acidosis slowed θ preferentially in the transverse direction, which may be determined by I_{gap} rather than I_{Na} .⁹ However, such an effect on I_{gap} would need to persist for ≥ 2 hours after the hypercapnoea-reversal to explain the

associated persistent θ -slowing⁵ via this mechanism. Why did hypoxaemia have no effect on atrial ERP or θ ? Hypoxaemia may be expected to not affect atrial electrophysiology as long as PCO_2 and pH are controlled, as here,⁵ and consistent with the majority of reports discussed by Stevenson *et al.*⁵ However, this may differ under more physiological conditions, in the presence of a functioning autonomic nervous system. Did the persistent θ -slowing observed after the reversal of hypercapnoea actually cause the associated increased vulnerability to AF? This will require further investigation, since propagation of activation of the beat immediately preceding the onset of AF was not mapped, and non-reentrant activity could also have been involved. Furthermore, this increased susceptibility to AF may have been contributed to by a transient undershoot in λ , since the ERP was observed to transiently shorten by ~ 30 ms at the final stage of hypercapnoea-reversal (see Fig 2 in⁵). A similar undershoot in APD was reported to precede the onset of ventricular tachyarrhythmias resulting from post-ischaemic reperfusion.¹⁰ Future studies might examine the precise temporal relationship between the increased AF vulnerability and changes in ERP and θ .

How do the SaO_2 and PaCO_2 values encountered in the Stevenson *et al* study⁵ compare with those found clinically, in patients with breathing disorders? A review of the literature indicates a wide variation in these values, depending on the type of breathing disorder and whether blood was sampled during wakefulness or sleep. In patients with OSA, episodes of hypoxaemia occur during sleep, with typical mean SaO_2 nadirs in the range of 76-83% saturation. In patients with chronic obstructive pulmonary disease (COPD), the typical waking SaO_2 range is 80-90%. This could fall further during sleep-related hypoxaemic episodes, typically to 65-80%, but in some cases to as low as $<50\%$. Mean PCO_2 in awake patients with COPD is typically in the range 45-53 mmHg. Nocturnal PCO_2 , however, is rarely reported, mainly because continuous measurement of transcutaneous PCO_2 by electrode is unreliable. Post-sleep mean PCO_2 , in patients with OSA, typically is moderately higher than pre-sleep PCO_2 , e.g., 54 *versus* 48 mmHg in one study, and 47 *versus* 45 mmHg in another. However, PCO_2 could well peak momentarily at higher values during sleep. PCO_2 values up to 55-59 mmHg can be attained during breath-holding in healthy adults, and in a single study of patients with severe COPD, in which PCO_2 was measured during sleep via an in-dwelling arterial catheter, a mean maximum PCO_2 of 63 mmHg was detected.¹¹ Therefore, in the Stevenson *et al* study,⁵ the minimum mean SaO_2 produced, of $\sim 80\%$, is representative of typical minimum SaO_2 values in patients with SDB and/or COPD, suggesting that hypoxaemia *per se* might not contribute to the increased propensity to AF in such patients. The maximum mean PaCO_2 produced,⁵ of ~ 97 mmHg, is substantially higher than peak levels expected in patients with SDB and/or COPD. However, intermediate, clinically relevant PCO_2 values, were found to prolong ERP.⁵ Nevertheless, it is unknown whether such intermediate values could also have

slowed atrial θ , since θ was not measured until PaCO₂ had reached ~97 mmHg. Moreover, it is also unknown whether the AF-promoting persistent θ -slowing plus ERP-shortening that was observed⁵ would occur following reversal of PCO₂ from clinically relevant hypercapnoeic levels, rather than from ~97 mmHg. If so, then such a mechanism would be most applicable to SDB, involving cyclical hypercapnoeic episodes, rather than to COPD with chronically maintained hypercapnoea. It should be recognised that obstructive airways diseases cause combined hypoxaemia and hypercapnoea, and also that associated influences of increased adrenergic activity are expected to have wide-ranging and complex effects on atrial electrophysiology, intracellular Ca²⁺-handling, and propensity to AF (see¹² for review).

Stevenson *et al*⁵ have provided provocative data on effects of hypercapnoea, and on a lack of effect of hypoxaemia, on atrial electrophysiology and susceptibility to AF, the mechanisms of which warrant further study. These data should be taken into account when considering the multiple mechanisms linking breathing disorders with the development of AF.

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