HYPOXIA AS A REVERSIBLE CAUSE OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE II DIABETES AND IMPAIRED RENAL FUNCTION.

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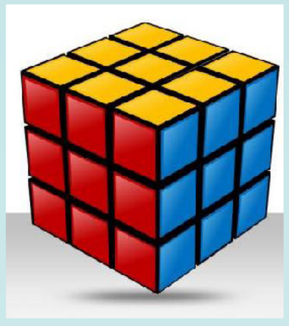
Objectives:

Cardiovascular autonomic neuropathy (CAN) is common in patients with diabetes mellitus.
It is characterized by an imbalance between sympathetic and parasympathetic activities, as demonstrated by elevated plasma norepinephrine levels and impaired arterial baroreflex sensitivity (BRS).

Although CAN is conventionally considered to be an organic, irreversible disorder, it has already been demonstrated in patients with type 1 diabetes that BRS could be corrected by deep breathing, thus suggesting a functional component to the disorder.
In this study we tested this hypothesis in the clinical setting of type 2 diabetic patients with or without renal impairment.

Methods:

26 patients affected by type 2 diabetes were enrolled. Exclusion criteria were age > 65 years, BMI > 35 kg/m2 and treatment with beta-blockers. Mean (±SE) age was 61±0.8 years; diabetic duration was 10.5±2years and BMI 29.4±3.5 kg/m2. GFR, estimated by CKD-EPI formula was 68.1±5.5 ml/min (range 36-116 ml/min), 6 patients presented macroalbuminuria and 6 microalbuminuria.
24 healthy sex and age-matched subjects were enrolled as controls.
Autonomic system function was assessed in basal conditions by blood pressure (BP) and heart rate (HR), while BRS was obtained from recording fluctuations in the RR interval and BP during: a) spontaneous breathing, b) normal (15 breaths per min) and c) slow, deep (6 breaths per min) controlled breathing. To test the potential influence of hypoxia on CAN, the participants repeated the entire protocol in condition of hyperoxia, breathing 5 L/min oxygen.



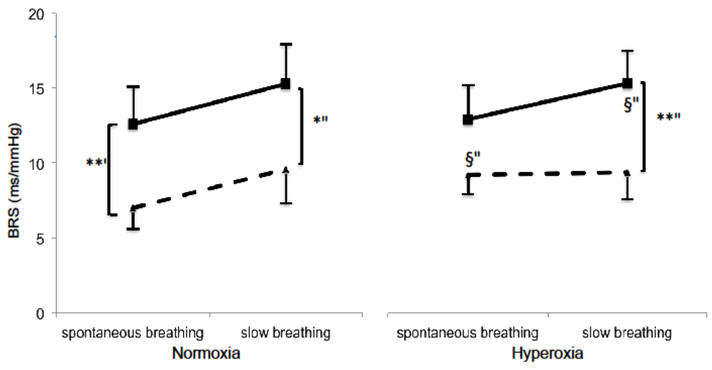


Figure 1

Figure 1. Effect of oxygen and slow breathing on BRS.

Data are expressed as means+SEM. Continuous lines represent healthy subjects, broken lines represent diabetic patients.
In ambient conditions (normoxia) BRS was depressed in individuals with type 2 diabetes, while slow breathing increased BRS in both the groups of subjects.
In hyperoxia diabetic patients presented an improved BRS, that was unaffected by slow breathing, indicating that the two effects are probably related.
On the contrary, in healthy subjects hyperoxia induced a further increase in BRS during slow breathing

* p<0.05, p <0.005, § p<0.05 vs spontaneous breathing

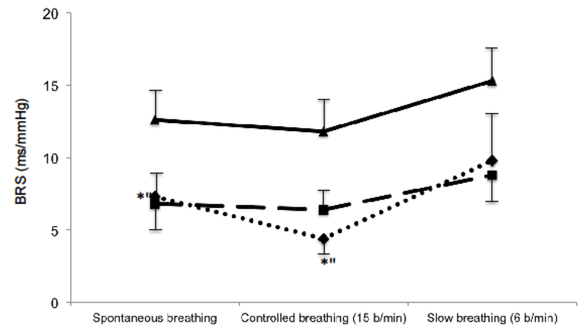


Figure 2

Figure 2. Effect of respiratory manoeuvres on BRS in diabetic subject with or without renal impairment.

Data are expressed as means+SEM. Continuous line represents healthy subjects, broken line represents diabetic patients without renal impairment, dotted line represents diabetic patients with chronic kidney disease (CKD). During spontaneous breathing in ambient conditions (normoxia) BRS was depressed in all the diabetic subjects. However, CKD patients presented a further decrease in BRS during controlled breathing. On the contrary, during slow breathing CKD patients, such as non-CKD diabetic subjects, increased BRS more than controls, and the difference found at rest disappeared.

* p<0.05 vs control.

Results:

During spontaneous and normal controlled breathing, diabetic patients presented higher heart rate (HR) and lower BRS compared with the control participants (5.5±0.6 vs 11.8±2.0 ms/mmHg, p<0.005). Slow breathing and oxygen administration, compared with normal controlled breathing, significantly reduced HR and increased BRS in both diabetic patients and the control group (9.6±1.9 and 15.3±2.3 ms/mmHg, respectively, p<0.05). FIGURE 1
Moreover, among diabetic subjects 12 patients (48%) resulted affected by chronic kidney disease (CKD), defined on the basis of the presence of proteinuria and/or a reduced GFR. CKD patients compared with non-CKD subjects showed a longer duration of diabetes and a poorer glycaemic control. Indeed, there was a significant inverse correlation between diabetes duration and eGFR values (r2 0.20, p=0.02). Interestingly, also this group of patients presented a significant improvement of BRS during deep breathing and hyperoxia (9.8±3.7 and 10.7±3.4 ms/mmHg, respectively, p<0.05 vs spontaneous breathing). FIGURE 2

Conclusions:

CAN present in type 2 diabetic patients can be partially reversed by increasing oxygen supply, suggesting a possible role of hypoxia as a treatable cause of diabetic complications, including renal damage.
Therefore, interventions addressed to reduce hypoxia by physical activity and respiratory training may be effective in reducing sympathetic overdrive in diabetic patients with or without CKD.
Further studies are needed to assess if the improvement of BRS and the amelioration of CAN do translate into better clinical and prognostic outcomes.

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