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Normoxic recovery reverses intermittent hypoxia-induced systemic and vascular inflammation

Comments on: Intermittent hypoxia-induced cardiovascular remodeling is reversed by normoxia in a mouse model of sleep apnea, by Castro-Grattoni et al[1].

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Castro-Grattoni et al[1] should be congratulated for demonstrating in a mouse model of sleep apnea (OSA) that intermittent hypoxia (IH)-induced cardiovascular remodeling is reversed after removal of IH exposure (mimicking OSA treatment by continuous positive airway pressure). We would like to contribute to this important topic by providing additional data and comments.

First, in Castro-Grattoni study[1], animals were exposed to a 6 weeks IH exposure, followed by 6 weeks of normoxia. We previously demonstrated that only 14 days IH are enough to induce the same vascular remodeling, with increased intima-media thickness, elastin fiber network disorganization and mucoid deposition[2]. Therefore, more than the duration of IH exposure, we believe that the kinetics of hypoxia/re-oxygenation cycles, as well as the severity of hypoxia represents the main triggers explaining IH-induced deleterious effects.

Second, the authors mentioned that aortic wall remodeling is "*the result of multiple interactions between intermediary mechanisms, including oxidative stress, systemic and tissue inflammation"*, but they do not investigate the impact of IH removal on these parameters. In previous studies, we indeed demonstrated that inflammation plays a major role in the IH-induced vascular remodeling and atherosclerosis[2-7]. IH-induced inflammation has been evidenced by increased splenocyte migration capacities, expression of chemokines and increased leucocyte rolling at the systemic level and by an elevated expression of the pro-inflammatory transcription factor NF-kB, chemokine expression and increased infiltration of lymphocytes in the arterial wall (i.e. aorta) (Arnaud et al[2] and Figure 1). In accordance with the study of Castro-Grattoni et al[1], we have also observed a beneficial effect of IH exposure cessation on these inflammatory markers. After only few days of return to a normoxic situation, proliferative capacities of splenocytes, splenic chemokine expressions and aortic expression of NF-kB were indeed normalized (Figure 1).

These experiments in rodents are reflecting the effects of relatively short exposure to IH before irreversible lesions of the vasculature. Taken together, the study of Castro-Grattoni et al[1], and our additional results strongly support the high interest to early diagnose and alleviate IH in OSA patients, in order to limit cardiovascular complications.

Figure legend

Splenic chemokine mRNA expressions (A); splenocyte proliferative capacities in response to increasing doses of concanavalin A (Con-A) (B) and aortic NF-kB protein expression (C). All these experiments were realized on tissues from mice exposed to either 14 days intermittent hypoxia (IH) or normoxia and 14 days IH or N, followed by 7 days normoxic recovery. (n=5-10 per group; **P*<0.05 versus N). ▨ Data already published in *AJRCCM* by Arnaud et al[2].

References

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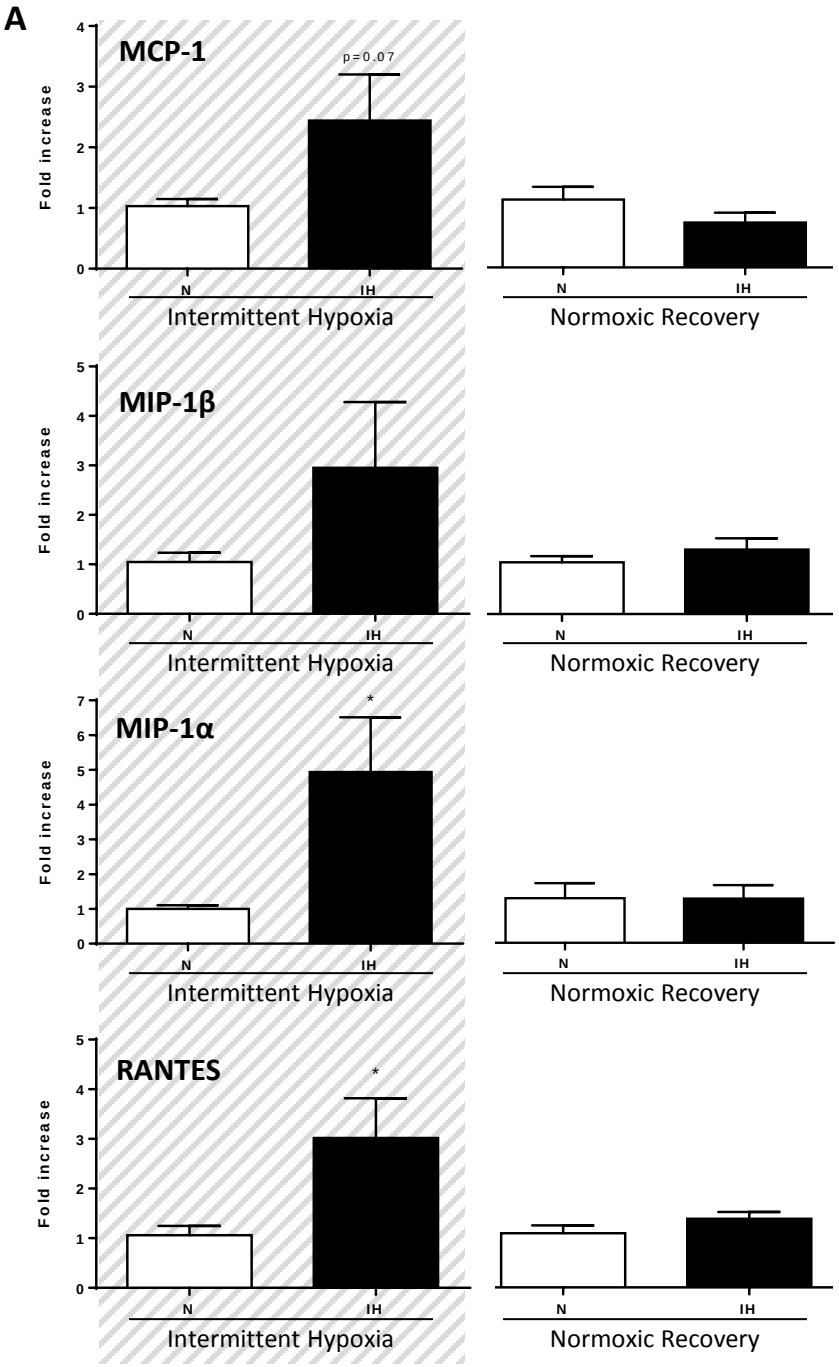
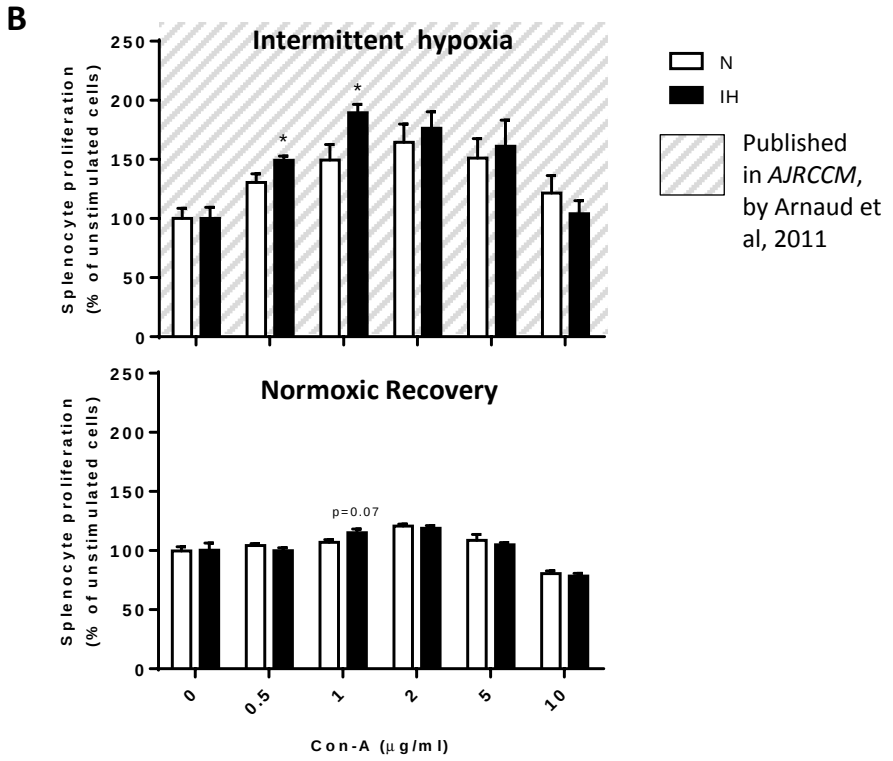
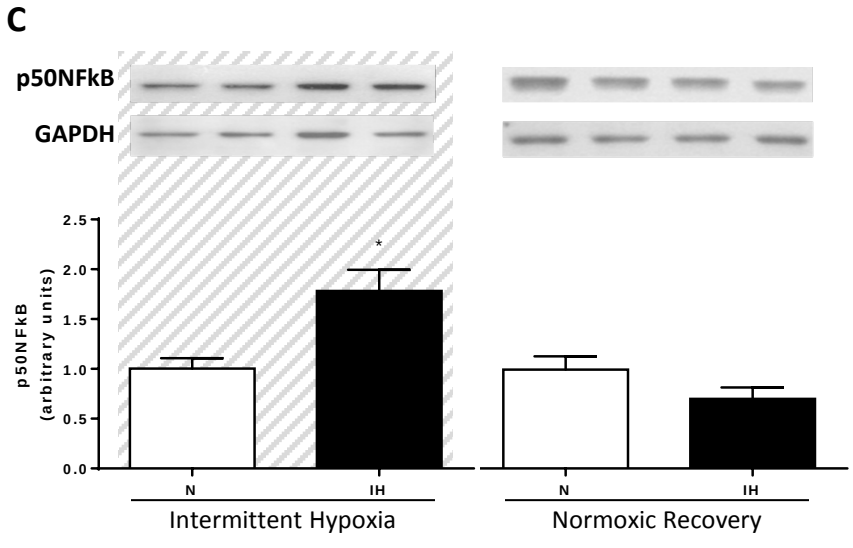
Figure 1


A
MCP-1
p=0.07
Fold increase
N
IH
Intermittent Hypoxia
Normoxic Recovery
MIP-1β
MIP-1α
RANTES
*


B
Intermittent hypoxia
Normoxic Recovery
Splenocyte proliferation (% of unstimulated cells)
N
IH
Published in *AJRCCM*, by Arnaud et al, 2011
p=0.07
*
0
0.5
1
2
5
10
Con-A (μg/ml)


C
p50NFkB
GAPDH
p50NFkB (arbitrary units)
*
N
IH
Intermittent Hypoxia
Normoxic Recovery