

Supplementary Materials:

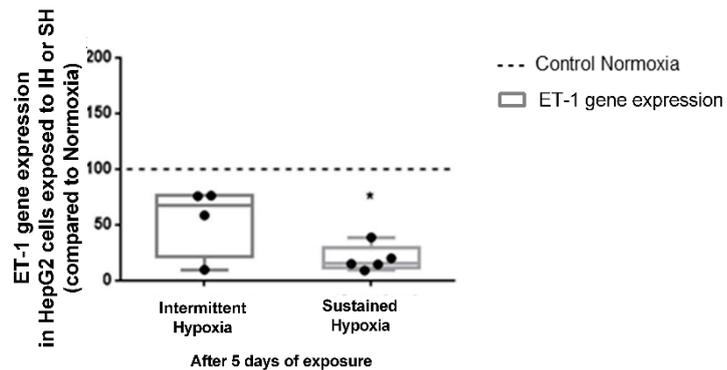
- Supplementary data

QPCR Primers

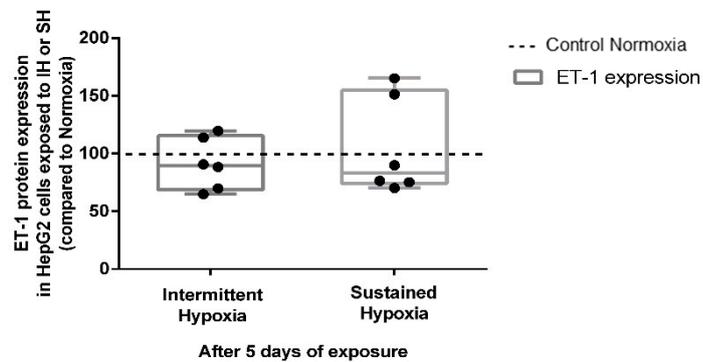
Gene expression was normalized to HPRT1 and RPLP0 rRNA content as internal controls and expressed as fold change compared with control. The primers sequences associated with the 3 genes tested are summarized were as follows:,with the following qPCR program: 1 cycle: 15min, 95°C, 40 cycles: 15sec-94°C, 30sec-60°C, 30sec-72°C, 1 cycle: 1min-95°C, 30sec-60°C, 30sec-95°C.

Gene expression was quantified using the comparative threshold cycle (Ct) method<sup>14</sup> with a normalization against HPRT1 (F- TCTTTGCTGACCTGCTGGATTACAT, R- CCAGGGAAAGCAAAGTTTGCATT) and RPLP0 (F- CCCTGCACCTCTCGCTTCTGGA, R- AGGGGCAGCAGCCGCAAATG). HIF-1 $\alpha$  (Hif1a F- CGGCGACATGGTTTACATTTCTG, R- CTTTTCTACTGGCCATTCTGT), endothelin-1 (Edn1, F- CGTACCGTATGGACTGGGAG, R- GAGCGCACTGACATCTAACTG), VEGF-A (Vegfa F- CTCAAGCCATCCTGTGTGC, R- TTGCTCTATCTTTCTTGGTCTGC).

- Supplementary Figures



(a)

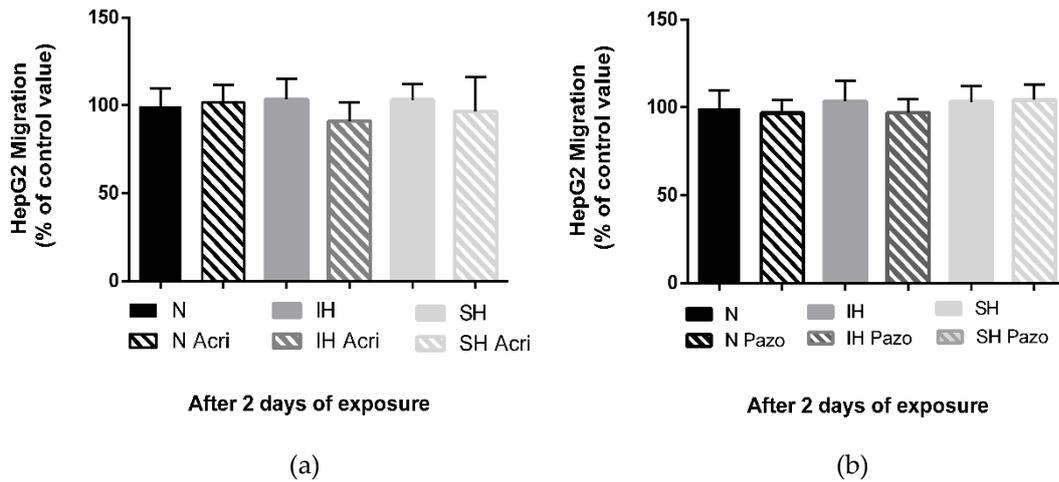


(b)

Supplementary Figure S1. In vitro effects of IH and SH on ET-1 gene expression and protein expression

(a). SH but not IH is associated with a significant decrease of ET-1 gene expression in HepG2 cells after 5 days of exposure ( $p < 0.05$ ). The levels of ET-1 gene expression was measured by RT-QPCR;  $n = 3$  independent experiments/group. \* $p < 0.05$ , Mann-Whitney test.

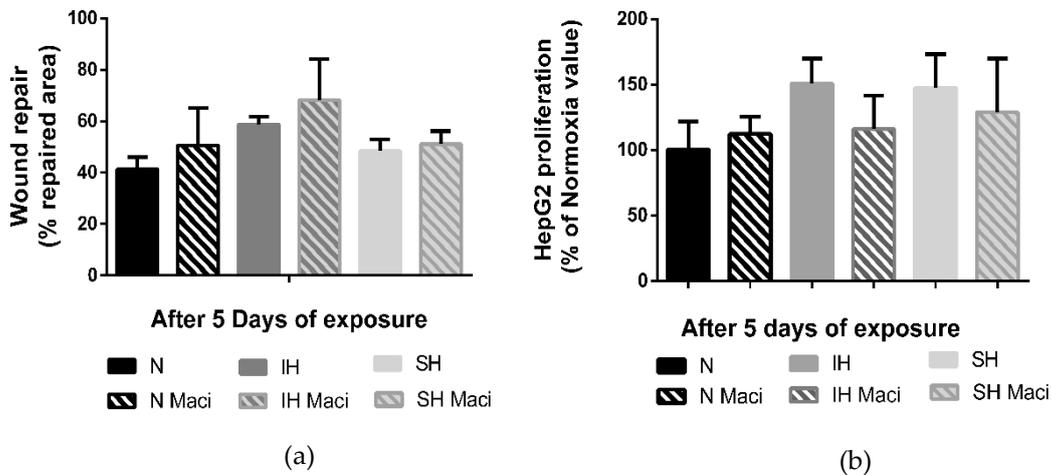
(b). Neither Intermittent Hypoxia nor Sustained Hypoxia modify ET-1 protein secretion by HepG2 cells after 5 days of exposure. The levels of Et-1 protein secreted was measured by Elisa on super natant;  $n = 3$  independent experiments/group, Mann-Whitney test.



Supplementary Figure S2.

(a). Migration, expressed as a % of control values, of viable HepG2 cells after 2 days of Normoxia, Intermittent Hypoxia or Sustained Hypoxia and treated or not by acriflavine (acri);  $n = 3$  independent experiment/group (9 wells/group: 2 transwells/experiments). Mann-Whitney test.  $p$  NS, Mann-Whitney test.

(b). Migration, expressed as a % of control values, of viable HepG2 cells after 2 days of Normoxia, Intermittent Hypoxia or Sustained Hypoxia and treated or not by pazopanib (pazo);  $n = 3$  independent experiment/group (9 wells/group: 2 transwells/experiments). Mann-Whitney test.  $p$  NS, Mann-Whitney test.



Supplementary Figure S3

(a). Wound healing repair, expressed as a % of repaired area, of HepG2 t least 3 wells/experiment after 5 days of Normoxia, Intermittent Hypoxia or Sustained Hypoxia and treated or not by macitentan (maci). p NS, Mann-Whitney test.

(b) Proliferation, expressed as a % of Normoxia, of viable HepG2 cells quantified by MTT staining after 5 days of Normoxia, Intermittent Hypoxia or Sustained Hypoxia and treated or not by macitentan (maci); n=3 independent experiment/group (6 wells/group: 2 transwells/experiments). p NS, Mann-Whitney test.