

## **Individual contributions of isoflurane anaesthesia and surgical incision to haemodynamic regulation in Zucker Diabetic Fatty rats *in vivo***

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Diabetic patients have increased cardiac complications during surgery, possibly due to impaired autonomic regulation of blood pressure. The haemodynamic stress of anaesthesia is well described, however surgery itself can also be a significant cardiovascular stressor. We aimed to determine the unknown interaction between poor diabetic haemodynamic autonomic control, anaesthesia and surgical stress, in particular the role of surgical incision itself.

Male 20-week old Zucker type 2 Diabetic Fatty rats were implanted with a vascular access port for intravenous drug delivery, and a radiotelemeter to measure mean arterial blood pressure (MAP) and heart rate (HR), under inhaled isoflurane anaesthesia. Haemodynamic pharmacological responses were assessed under conscious, isoflurane anaesthetised ( $2.3 \pm 0.1\%$ ) and anaesthesia-surgical conditions; the latter performed as a 3cm full thickness lateral abdominal opening.

Anaesthesia reduced MAP, but this reduction tended to be less in diabetic rats (non-diabetic  $-26 \pm 4$  vs diabetic  $-16 \pm 3$   $\Delta$ mmHg,  $p=0.0571$ ), contrary to previous descriptions. Surgical incision substantially and persistently increased MAP (anaesthetised  $91 \pm 4$  vs surgical  $111 \pm 4$  mmHg,  $p<0.05$ ). Anaesthesia disrupted central baroreflex responses to sympathetic activation ( $10\mu\text{g/kg}$  sodium nitroprusside (SNP); conscious  $83 \pm 13$  vs anaesthetised  $16 \pm 5$   $\Delta$ bpm,  $p<0.05$ ) or sympathetic withdrawal ( $10\mu\text{g/kg}$  phenylephrine (PE); conscious  $-168 \pm 37$  vs anaesthetized  $-20 \pm 6$   $\Delta$ bpm,  $p<0.05$ ) with no additional change by surgical incision. In addition, anaesthesia reduced the primary peripheral vasoreactivity (MAP) to both SNP and PE, while surgical incision encouraged a greater SNP-induced vasodilation. Parasympathetic activity, indicated by atropine-enhanced HR, was virtually abolished by anaesthesia with no additional effect of surgical incision. Anaesthesia uncovered significant atropine-induced peripheral vasodilation, which tended to be greater after surgical incision. No clear interactions between the effects of anaesthesia or surgical incision and diabetes were observed.

Isoflurane anaesthesia markedly impaired autonomic blood pressure regulation, with loss of baroreflex responses and parasympathetic contribution. Additional surgical effects were largely limited to modulation of baseline blood pressure; which are likely locally-mediated, and have limited interaction with the central autonomic dysfunction in diabetes. Whilst minimal, local haemodynamic effects of surgery may be relevant for perioperative management, and more research is needed to assess its long-term clinical consequences.