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RESEARCH LETTER

Ultrasound-guided catheter implantation improves conscious radiotelemetric blood pressure measurement in mice

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1. Introduction

Animal models of arterial hypertension are invaluable for unravelling pathophysiological molecular mechanisms and for developing new therapeutic strategies. Radiotelemetric measurement of blood pressure (BP) by implants of pressure catheters is an established gold-standard,[1] yet suffering pitfalls like the complex surgical approach, the low control on the catheter positioning,[2] and the vascular tree variability.[3] Aim of this work was to find an optimization protocol for implanting radiotelemetric catheters through an ultrasound-guided approach. By this way, we show that this optimized procedure for catheter placement requires a significantly lower number of animals to reach a predetermined sample size of experimental subjects with accurate BP measurement.

2. Methods

Experimental procedures were carried out according to the EC Council Directive 2010/63 and Italian legislation on animal experimentation (Decreto Legislativo D.Lgs 26/2014). All procedures were designed and performed to minimize animal suffering while respecting the ARRIVE principles. Male mice of different transgenic and non-transgenic strains, on a C57Bl/6J background, aged 8–12 weeks, were used in all the procedures, housed under controlled temperature (21 ± 1°C) and relative humidity (60 ± 10%), with a 12–12 h dark-light cycle, sawdust as bedding, pellet food, and water ad libitum.

Mice were anaesthetized with 5% isoflurane and maintained with 1.5–2% with 1 L/min of oxygen to perform the surgery to implant HD-X11 (DSI) pressure catheter device.[4] During the surgery optimal catheter positioning was assessed by aortic arch echography,[5] performed with a 40 MHz transducer on Vevo2100 and analysed on VevoLab (VisualSonics, Fujifilm). One week after the surgery, the signals were acquired by the Physiotel RPC-1 receiver in a dedicated recording room and analysed with Ponemah 6.33. After the BP recordings (lasting 3–4 weeks), we extracted the percentage of Bad Data Marks (BDM) represents a parameter that summarizes the quality of recordings by estimating the number of beats in which the blood pressure does not display an adequate waveform or present one of the following issues: signal noise, signal dropout, negative pressure values, inadequate pressure values (BP < -50 mmHg, BP > 500 mmHg), inadequate bpm (HR < 200 bpm, HR > 1000 bpm). We evaluated the overall success of the US-guided implant compared to a similar number of standard implants with matched genetic background mice. We compared the ratio between valid quality-checked recordings and the number of procedures needed to achieve adequate cardinality for each experiment. Mice were euthanized by an overdose of isoflurane (5%). Statistical analysis has been carried out by PRISM 5 (GraphPad Software). Linear regression was used to assess the predictability of BDM from ultrasound derived parameters. Chi-square test was used to assess the difference between US-guided and standard procedure success rates.

3. Results and discussion

From ultrasound intraoperative imaging, we extracted two parameters: (i) distance from the centre of the aortic arch, expressed as a percentage and denominated Tip Distance from the Center (TDC); (ii) angle between the catheter and the lower wall of the aortic arch, denominated Tip Angle of Incidence (TAI) (*Figure 1A*). TDC and BDMs are linearly correlated ($n = 38$, $r^2 = 0.2475$, $P = 0.0015$) with better recordings obtained near the centre of the aortic arch. TAI correlated as well with the BDMs ($n = 38$, $r^2 = 0.1038$, $P = 0.0485$). We obtained the best recordings in case of TAI and TDC near 0, with worse more than 10% displacement from the centre or more than 10° from the optimal direction. Considering the overall success ratio of the procedure, the US-guided procedure has 88% success rate, with 38 successful procedures on 43 performed. Our methodology improves the success rate over the standard procedure, needing 68 implants to achieve 30 successful recordings (44%, $P < 0.0001$).

Our methodology, by combining a sonographer equipped with a 40 MHz transducer to the surgical station, optimizes the implant of radiotelemetric devices in mice and improves the efficiency of accurate BP measurement that can be maintained for several weeks of recordings (*Figure 1B*). Moreover, our approach maximizes the number of

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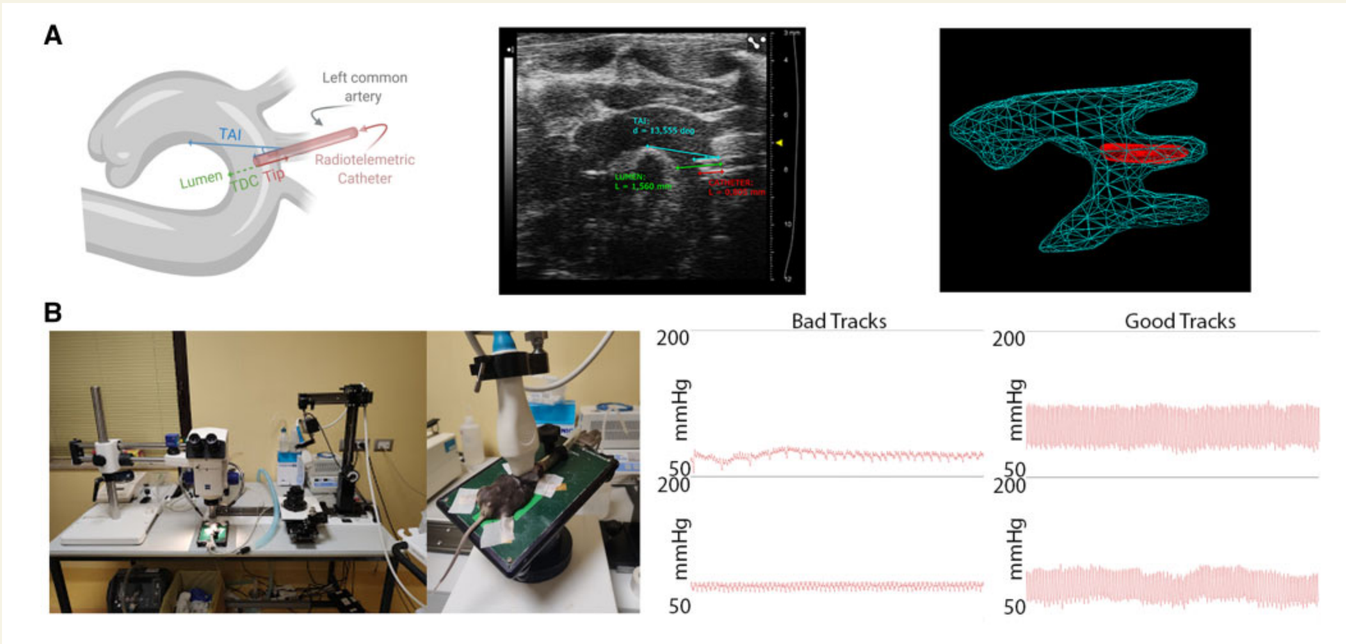

Figure 1 (*A*) Representative image and abstract schematics annotations (created with Biorender.com) of US-guided implant in the aortic arch and a 3D reconstruction of vessel walls (blue) and catheter (red). (*B*) Setup of the surgical-imaging station, with a detail of the optimal probe positioning for aortic arch imaging and representative segments of bad tracks obtained with unsupervised catheter implant and good tracks obtained after ultrasound catheter positioning check and kept stable across 1 week of recording.

successful procedures lowering the impact of animal usage in respect of the ARRIVE principles. These advantages could be especially important in those experimental settings where a specific genetic background might make mice more susceptible to the procedure or where neurovascular-related phenotypes are object of investigation. In fact, in this latter case, while a mispositioning of the catheter might have no overt effect on cardiovascular variables and give good blood pressure data, subtle effects on the cerebral circulation may be induced, affecting neurovascular phenotypes. An imaging-guided procedure appears as an innovative solutions for overcoming challenging experimental situations.

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