Editorial

In search of the ideal animal model for urethral strictures for therapeutic purposes

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The search for the ideal animal model of urethral strictures (US) is not new. This translational research topic aims to investigate different novel US therapies in animal studies as a prerequisite for successful clinical application in humans. Therefore, the histology of the US of these animals should be comparable to that of the most common human US. To develop a valid animal model for strictures, a holistic understanding of the pathogenesis and the histopathology of the stricture process is required.

Currently, many studies in both human and animal specimens specifically address the histopathology of US (1-6). In humans, various pathologies lead to US, including iatrogenic, traumatic, and inflammatory causes, each resulting in an individual degree of spongiofibrosis depending on the type of damage to the urothelium and paraurethral spongy tissue. These characteristics have a critical impact on current and future treatment choice in humans; thus, these different scenarios should be implemented in different animal models.

In addition, it is crucial to understand how the urethra typically heals in response to different damaging interventions and how different manipulations may alter the healing response to a different extent. For example, thermal injury by coagulation might be expected to produce a stricture with different histologic features and severity than a stricture following incision and subsequent suturing of the urethra. Thus, since different levels of spongiofibrosis and residual lumen integrity in humans require different therapeutic procedures, different animal models with varying damage to the urethra and corpus spongiosum should also be established.

There are already numerous efforts by various scientific groups to determine the best method to provoke a US that resembles the human strictures using different animal species. Singh & Blandy published 1976 the first animal study using rats subjected to various types of iatrogenic urethral lesions, including crushing with forceps, excision of a urothelial window and complete urethral transection. In each group, one rat had a vesicostomy, and a further rat had no urinary diversion. The results demonstrated that urinary extravasation after surgical disruption of urothelium by window creation or complete transection triggered a severe inflammatory process leading to successive replacement of the vascular structures by collagenous connective tissue, known as spongiofibrosis. In contrast, tissue crushing did not result in severe reactions or strictures (7).

Scherz *et al.* used 95 New Zealand white rabbits and attempted to create a stricture model by making an open longitudinal incision in the bulbar urethra (8). The authors wondered whether the presence and type of urinary diversion, closure or non-closure of the urethrotomy, and suture composition could contribute to stricture formation. The subgroup in which the urethrotomy was left open and just the overlying skin was closed showed

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increased rates of inflammation and fistula in the urethra. Polyglactin compared with chromic sutures showed no significant histological difference. Urinary diversion via indwelling urethral catheters resulted in decreased urethral inflammation in rabbits with closed urethrotomy, confirming the findings of Singh & Blandy. Vesicostomy resulted in even less inflammation. Surprisingly, skin incision and closure in the sham group resulted also in periurethral inflammation, suggesting that skin incisions should be avoided in an ideal sham group because they may alter periurethral histology (8).

The recent study of Yao *et al.* describes and compares three different surgical procedures for establishing US animal models in New Zealand rabbits opposing them to a control group (9). All procedures used the principles of open surgery with urethra dissection and suturing after the intervention; however, the stricture formation was based on the electrocoagulation effect. This was applied on the ventral side of the urethra in the first group, the dorsal side in the second, and circumferentially in the third one, however no information about the power of the current used was included. In the sham group, the urethra got dissected but primarily closed without electrocoagulation. Interestingly, the bladder was drained for one single day. Operative time in the ventral group was significantly shorter since no urethral opening was needed so that a surgical step could be skipped. On a follow-up of 4 weeks, US was successfully created in 75% of the ventral semi-circumferential electrocoagulation group, 41.6% of the dorsal semi-circumferential group, and 91.7% of the circumferential group, as verified by urethroscopy and urethrography. However, one rabbit in the third group died due to urethral obliteration four days postoperatively. Histologically, inflammatory reaction with a decrease in smooth muscle fibers and blood vessels were observed, just like in most previous animal studies investigating stricture histology.

The main obvious advantage of these procedures is the wide availability of the necessary surgical instruments in each hospital, including scalpels or scissors, forceps, needle holders, and monopolar electrocautery devices. On the other hand, pediatric endoscopic instruments, which are expensive, difficult to handle precisely and only available in institutions with pediatric urology departments, are not needed. Additionally, these procedures do not require a microscope or even optical magnification, as described in studies of urethral tissue resection (10). Finally, blood loss should be significantly less with electrocoagulation rather than resection of a urethral segment. However, the impact of transient urethral hemorrhage on model outcomes or animal morbidity is questionable. To our knowledge, there are no reports in the literature of animals that died during such an experimental study due to excessive hematuria.

On the other hand, due to the limited number of cases, the study was not sufficiently powered to establish a clear superiority between ventral and circumferential electrocoagulation. Since the SR did not reach a significant difference between the two groups, the authors concluded that ventral semi-circumferential coagulation should be the first recommendation for a stable US model without the risk of complete urethral obliteration and death of the animal. However, a proposed explanation for the lower SR of the dorsal semi-circumferential electrocoagulation was lacking. Mainly because all operations were performed in the pendulous urethra, where the corpus spongiosum surrounds both sides of the urethral mucosa (ventral and dorsal) to the same extent, there should be no differences in the abundant blood supply of the injured area. Therefore, adding a ventral suture line to the dorsal coagulation would be expected to result in more extensive spongiofibrosis on both sides of the urethra and provoke a US.

Starting from the ideal animal, every clinical institution has access to different laboratory animals. Most of the current experimental US studies, though, have used rabbits due to their availability and the anatomical characteristics of their urethra, which resemble the human one and have a sufficient length of 5–7 cm for surgery and the approximate lumen diameter as a 1-year-old boy, making it suitable for manipulation using existing pediatric instruments. Moreover, the urethra consists of a thin epithelium surrounded by a corpus spongiosum with rich vascularity laterally and an almost avascular plane in the midline, which allows dissection avoiding excessive bleeding (11). The good lateral blood supply of the spongy tissue, however, provides a supporting layer for urethral healing (12).

Model efficacy is the primary concern in experimental animal studies. Different procedures have different risks of not forming strictures following injury. Such failures relate most likely to the mechanism of injury, which should be severe; otherwise, the abundant blood supply of the corpus spongiosum may lead to proper healing preventing hyperplastic scar formation. Both endoscopic electroresection of urethral tissues (13,14) and open excision of urethral segments (10,15) have demonstrated high SR approaching 100%. These surgical techniques construct a model of urethral defect, but not a genuine US, possibly not reflect the actual process of the human US, also lacking some typical histologic features of it, such as the presence of urothelium. Moreover, the open surgical excision might cause fistulas since the urethral wall was opened, a complication that could be expected to impact the model significance negatively.

Sievert *et al.* noticed that strictures created through thermocoagulation have the best histologic resemblance to human strictures (16). Thermal injury caused by an endoscopic holmium:YAG laser with 20 W power showed excellent efficacy of 100% in a single study (17). On the other hand, endoscopic circumferential electrocoagulation has demonstrated controversial results, including low efficacy in causing strictures with SR of 0–50% in some studies, when the procedure involved short urethral segments of 3 to 5 mm (11,14). Other studies, however, reported an excellent SR of 100% (18,19), especially when the current was applied over a 15-mm urethral segment, leading to the assumption, that the size of the thermal injury significantly affects stricture formation. The current intensity, on the other hand, does not seem to play a significant role, as Nagler *et al.* obtained excellent SR when using a lower current intensity (10 *vs.* 40 W) than the other groups (20). Regarding the coagulation time, in most studies the current was applied until "bleaching and ulceration of the mucosa occurred (14)". Although endoscopic electrocoagulation was applied circumferentially in all studies, Yao *et al.* compared the optimal site of application for open surgical electrocoagulation. As expected, the highest SR was observed in the circumferential electrocoagulation group, but at the cost of a higher risk for the occurrence of urethral obliteration resulting in the death of some animals. As an alternative, ventral semi-circumferential electrocoagulation has been proposed as an effective and safe US model (9).

The next research milestones in order to determine the ideal animal US model by using open electrocoagulation would be (I) to apply this current to even longer urethral lengths than 1 cm to determine the ideal length that would result in definite stricture formation; and (II) to investigate the electrocoagulation effect in different urethral segments since the surrounding tissue and blood supply of the pendulous urethra differ from the bulbar urethra, a fact which may contribute to different healing properties and, consequently, different efficacy of each US model.

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Footnote

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