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Nitinol urethral stents: long-term results in dogs

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Abstract No information has been available to date on the long-term behavior of nitinol (nickel-titanium alloy) urethral stents. In the present study, prostheses of this type were implanted in 18 German shepherd dogs in order to evaluate the reaction of the mucosa, muscles and periurethral tissue. Follow-up examinations performed after 1 week, and 1, 3, 6, 12 and 18 months included urine, macroscopic, radiologic, histologic and scanning electron microscopic analyses. Despite the excellent biocompatibility of the material, with no evidence of foreign body reactions or corrosion, there were no complete incorporations of the stent by epithelialization. Clinical application therefore appears to be problematic.

Key words Nitinol · Urethral stents · Animal experiments · Long-term results

Urethral stents have been used for the treatment of urethral strictures since 1989 [18] as an alternative to open surgical and endoscopic procedures. They are applied as temporarily implanted stents, which are removed after a suitable period, or as permanently implanted stents, intended to epithelialize and become completely incorporated into the urethra.

The materials used for temporarily implanted stents placed in the region of the prostatic urethra are metal [8] or polyurethane [19]. In the remaining urethral segments, some of the stents applied are removable [30], whereas others are placed for permanent diversion and are therefore designed to allow ingrowth of the urothelium [17, 18, 23, 27].

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Complete epithelialization prevents encrustation and thus ensures that any endoscopic measures or transurethral resections that may be necessary at a later date will not be a problem. However, there is disagreement as to the extent of urethral stent incorporation. Whereas Lymberopoulos [15], Parra [23], Saramon [25], Milroy [18] and Gottfried [9] reported complete epithelialization, Ashken [11] and Pansadoro [22] demonstrated this effect for only 70–90% of the stent surface after 6 months of placement.

The immediate clinical results with prostheses of this type appear satisfactory, but long-term results are not yet available. Apart from epithelialization, primary concerns with permanently implanted foreign bodies are biocompatibility, maximum expansion power at body temperature, and flexibility of the material.

In a multicenter study by Pansadoro [22], who used a superalloy tubular mesh, coverage of more than 85% of the stent area with urothelium was observed in only 70% of patients, 8% of whom exhibited stone formation at the free ends of the stents. Issues that remain undecided are reactions of, or damage to, the urethral wall or the periurethral tissue, alterations of the mucosal relief and the urethral lumen, whether prolonged implantation results in complete epithelialization or dislocation of the stent, and how well the foreign body is tolerated. All these points are crucial for selecting the material.

The present, experimental long-term study in dogs, covering an observation period of 18 month, relied on nitinol stents, because of the excellent biocompatibility of intravasally applied nickel-titanium alloy [3–5, 13, 14, 24, 31] which has been demonstrated.

Materials and methods

The urethra was measured in 18 male German shepherd dogs (body wt. 33–40 kg) under general anesthesia (thiopental i.v. 25 mg/kg body wt., atropine i.v. 5 mg/kg, intubation N_2O+O_2+halothane) from the meatus using a 15-Ch. catheter. The position chosen for stent implantation was such that the proximal end of the stent was

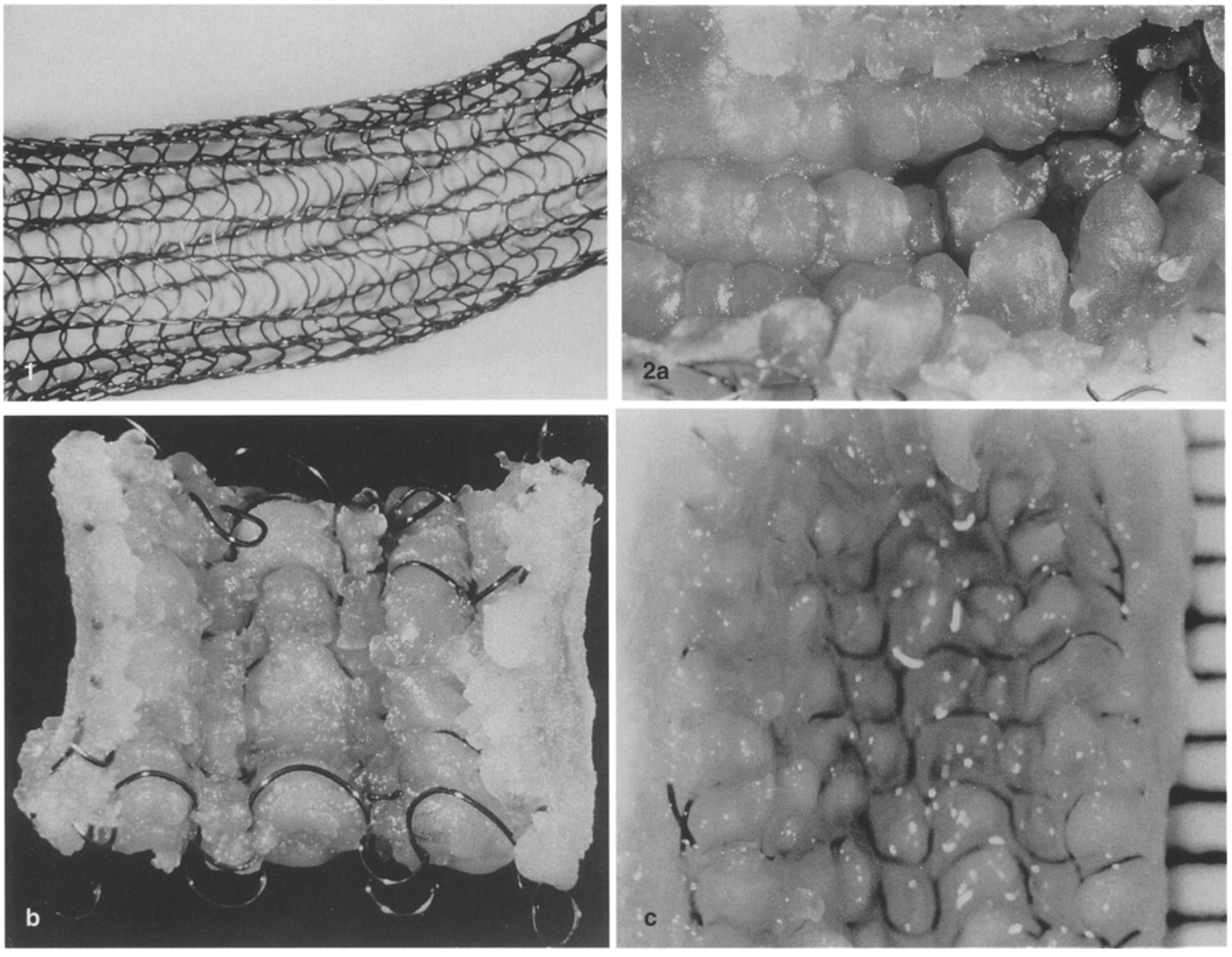


Fig. 1 Nitinol stent (macroscopic)

Fig. 2 a–c Mucosal hyperplasia after **a** 6, **b** 12 and **c** 18 months (macroscopic)

in the bulbar urethra with the ischium radiologically superimposed. The self-expanding stents (Boston Scientific, Watertown, Mass., USA) were constructed specifically for the canine urethra. They were knitted from a single strand of nickel-titanium wire (0.1 mm in diameter). The stents were mounted of a catheter telescope delivery system, giving an outer diameter in this state of 3 mm. After inserting the device into the urethra, the stent was released in the predefined area and its position monitored using a plain film and retrograde urethrography. Once expanded the stent had an outer diameter of 8 mm and a length of 4 cm (Fig. 1). Extrapolated to human conditions, the size of these "canine" stents corresponded to the size of stents used in the human urethra.

Follow-up examinations were performed after 1 week and 1, 3, 6, 12, and 18 months (three dogs in each group), including urinalyses, plain radiographs and retrograde urethrograms with the dogs under general anesthesia. Subsequently the dogs were put to death and the urinary bladder together with the entire urethra excised. Part of the stented urethra was opened and examined macroscopically. A segment of stented urethra approximately 2 cm long and adjacent to normal urethra was fixed in 4% formaldehyde (buffered to pH 7.2).

Because the inserted stent did not enable the tissue to be sectioned with conventional histologic techniques, analysis was performed using a modified version [6] of the "sawing-and-grinding" technique described by Donath et al. [7]. First the specimens were embedded in glucolmethacrylate. After polymerization, the plastic block containing the tissue was placed in the vacuum holder of an EXAKT microgrinding unit (EXAKT-Apparatebau, Norderstedt, FRG) and the areas to be analyzed were ground into plane, parallel slices. This technique yielded thin grindings (5–10 μm) which were then stained with hematoxylin-eosin or toluidine blue. A second, identical native specimen was kept in 2.5% glutaraldehyde (in cacodylate buffer), dried to the critical point, sputtered with gold and subsequently analyzed by scanning electron microscopy.

Results

Both transurethral stent implantation and radiologic follow-up examinations in anesthesia were tolerated well by all 18 dogs. The postoperative state of the animals was excellent. Two of the 18 animals died prematurely after 1 month of babesiosis and of protozoa infection, respectively, but both dogs were autopsied in time.

Urinalyses gave no evidence of infections. No dislocation of the stents or foreign body reactions were observed

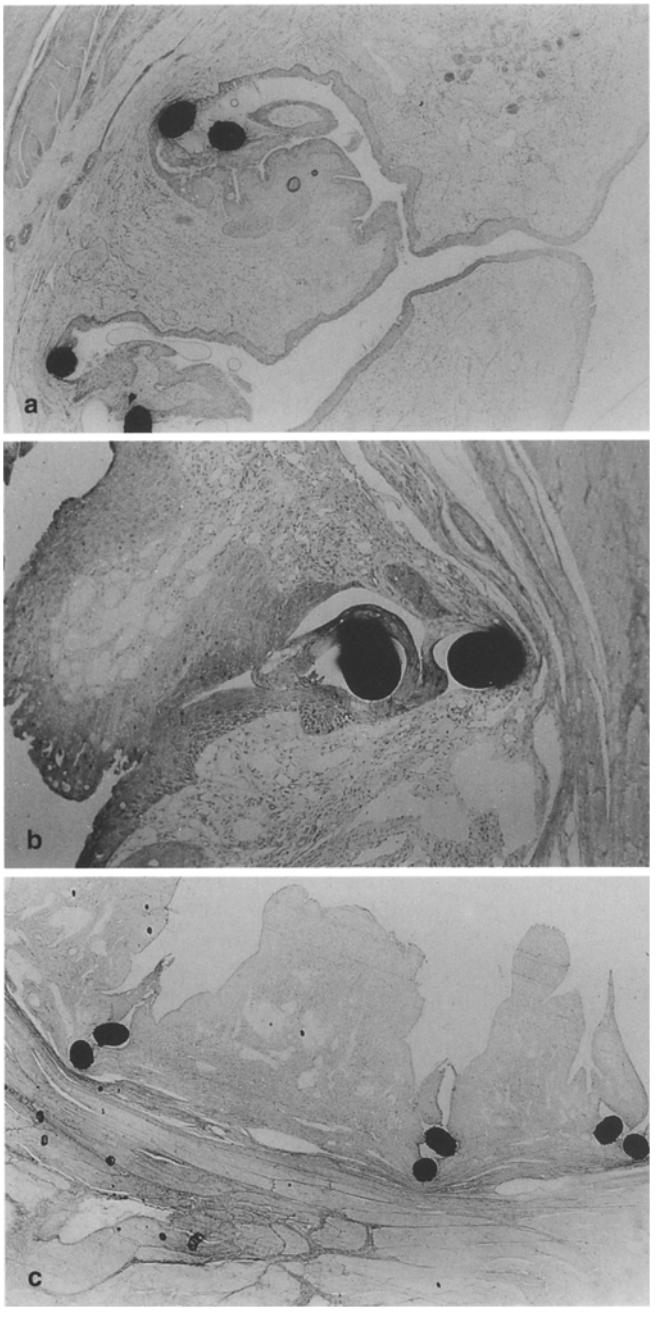
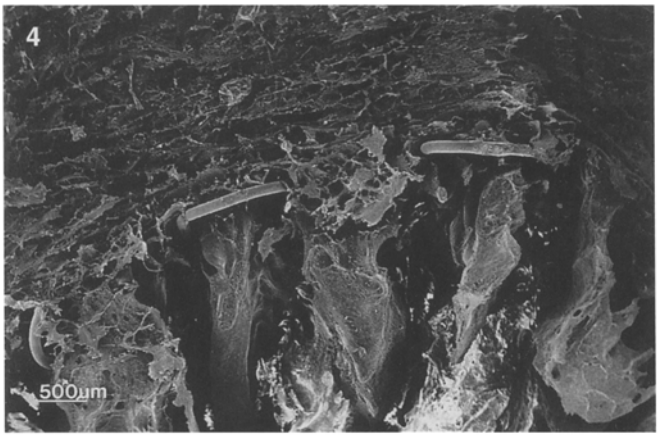


Fig. 3 a–c Urethral wall after **a** 6, **b** 12 and **c** 18 months: epithelialization is incomplete. H & E, ×40



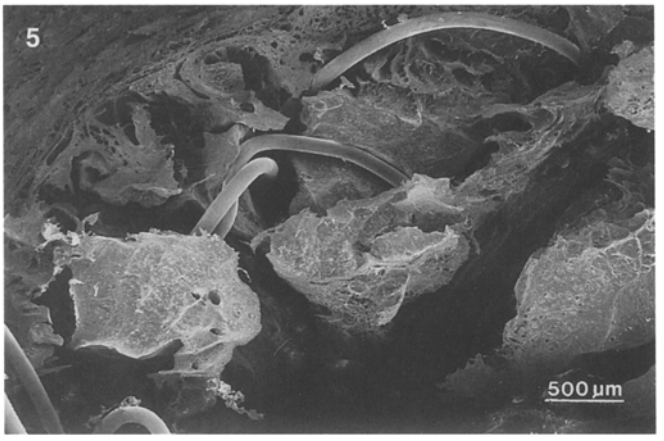


Fig. 4 Urethral wall after 12 months: representation of mucosal hyperplasia by scanning electron microscopy. ×20.3

Fig. 5 Urethral wall after 12 months: representation of mucosal hyperplasia by scanning electron microscopy. ×29.3

at any point of time. Gradually, however, pseudopolypous hyperplasia of the mucosa developed, measuring 0.8 mm (±0.1) after 3 months, 2 mm (±0.8) after 6 months, and 1.1 mm (±0.5) after both 12 and 18 months as determined microscopically.

The distance between the wire meshes and the muscularis propria was a consistent 0.4 mm. Muscles and periurethral tissue showed no reactions. After 6 months, the intended coverage of the mesh with urothelium was only partial, and was still not complete after 12 and 18 months (Figs. 2, 3). This was confirmed by scanning electron microscopy. The above-mentioned mucosal hyperplasia became apparent at the 12-month follow-up (Fig. 2). Only occasionally were the meshes of the stents covered by mucosa; otherwise they lay bare in the urethral lumen (Figs. 4, 5). This lack of epithelialization was demonstrable in all dogs.

The urethral lumina after 6, 12 and 18 months were evaluated using retrograde urethrograms. They were measured on the X-rays (30×40 cm) before and after stent implantation. The postoperative measurements were taken at five sites, three of which were in the stent area. The lumina were found to be markedly narrowed by a maximum of 2.5 mm (±0.5) and the 6-month follow-up, by a maximum of 2 mm (±0.4) at 12 months and, with slight improvement, by a maximum of 1.2 mm (±0.2) at 18 months (Fig. 6).

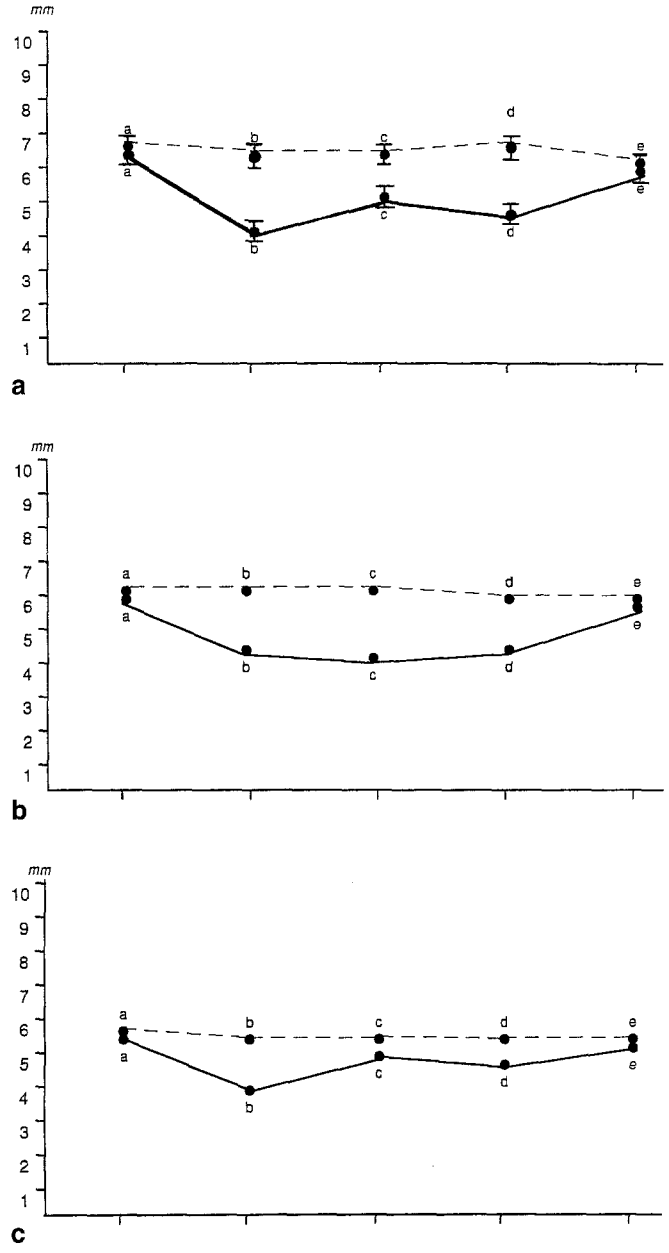


Fig. 6a–c Urethral diameter before (---) and at **a** 6, **b** 12 and **c** 18 months (—) after stent implantation

Discussion

Permanent urethral stents remain fixed at the implantation site by their inherent stress and the resultant outward pressure (expansion power). They are intended to become slowly, but entirely, covered with mucosa. Some reports on urethral prostheses made of stainless steel (wallstent) describe complete epithelialization [15, 16, 18], whereas in others this effect was found to extend to only 70–90% of a given stent [1, 22]. It remains unclear to what degree the position of the stent (prostatic or distal urethra) is relevant in this process. Although permanent stents implanted in the prostatic segment are exposed to urine to the same extent as those in a distal position, the sphincter contractions associated with urinary voiding involve regular movement of the prostatic segment, which increases the chance that the stent is also moved, and complete epithelialization is therefore delayed or prevented. Stents in the bulbar position are not influenced by these movements; yet the results available on epithelialization differ to the same extent. Whereas stone formation was observed at uncovered wire sites in the prostatic position [22, 29], this complication was absent in the bulbar position even when epithelialization was similarly incomplete (observation interval 6–12 months) [1].

Clinical application in patients with strictures showed ingrowth of scar tissue at the site of the stricture, particularly in cases of posttraumatic membranous stricture, through the interstices of the mesh. This leads to renewed narrowing of the lumen and the possibility of restricturing [1, 2, 27].

However, long-term experimental results on tolerance, epithelialization tendency, or the effect of the foreign material on urethral and periurethral tissue have so far not been available. These issues were addressed in the present study by using dog urethras, which resemble the human urethra both in structure and in caliber. Although a number of good clinical results have been achieved with stents of stainless steel, this material nevertheless is potentially corrosive and might give rise to undesired foreign body tissue reactions [11]. In view of these problems, we selected a material that has proved to be highly biocompatible both in animal experiments and clinically [3–5, 13, 14, 23, 31]. Nitinol is highly corrosion resistant [28] and has a good expansion power; yet it is pliable enough to permit easy adaptation to the urethral wall [9, 12].

A clinical trial with a mean observation period of 14 months showed that the biocompatibility of intraurethral titanium stents [23] was good; there was no evidence of infections, encrustations or stone formation. In the present study, stents were used in normal, nonstrictured urethras. Application of these stents is very simple, correct positioning being possible with or without fluoroscopic monitoring. By virtue of its preset expansion pressure, dislocation of the stent is unlikely and indeed was observed in none of the cases. Neither were there any demonstrable infections, encrustations or stone formation.

Although the lamina propria of the urethral mucosa widened in response to the foreign body, the urethral musculature and the periurethral tissue did not react to the permanent pressure from inside. The most striking phenomenon was the pseudopolypous mucosal hyperplasia in the region of the stent, which was readily demonstrable both macroscopically and microscopically. It was particularly marked at 6 months after application, leading to a significant narrowing of the urethral lumen, and was still present after 12 and 18 months, but the narrowing of the lumen was somewhat lessened by the partial onset of re-epithelialization. None of the stents, however, were completely covered with urothelium, i.e.,

in all cases part of the individual meshes lay bare inside the lumen. This phenomenon was demonstrable both histologically and by scanning electron microscopy. While this is in contrast to reports on wallstents [15, 18, 23, 25, 26], these exclusively rest upon radiologic or endoscopic follow-up examinations in humans; hence the assumption of complete epithelialization might well have to be revised on histologic verification following removal of the urethra. Superficial corrosion phenomena were not observed with nitinol; hence this material appears to be well tolerated not only by the vascular system but also by the urinary tract, despite constant contact with urine. Even with good biocompatibility of the material, open contact with urine engenders the risk of stone formation [21, 28]. Whether complete coverage by mucosa is indispensable for preventing stone formation when a nickel-titanium alloy is used remains undecided on the basis of our study, since stone formation was not observed at any stage. Should endoscopic measures become necessary at a later date, they would certainly be less problematic if the stents were completely incorporated.

Permanent urethral stents are currently available in various materials:

1. Stainless steel [8, 17, 20, 21, 30]: Complete re-epithelialization has not been definitely demonstrated and stone formation has been observed.
2. Titanium [23, 25]: Although in a small number of cases, an observation period of 14 months showed complete epithelialization, no evidence of encrustations or stone formation, no infections, and no rejection reactions.
3. Nitinol [9, 10]: This novel alloy has a temperature-dependent shape memory, i.e., the material changes its shape under the influence of temperature. Application of this material in the present study revealed an excellent biocompatibility, but no histologically documented full incorporation into the urethra. A severe pseudopolypous mucosal hyperplasia resulted in a narrowed lumen, although the urethras used had not been manipulated and were normal. If treatment fails and the stent has to be removed, a large wound area will ensue even in cases of incomplete epithelialization.

Despite the good documented biocompatibility and the absence of infections of concrement formation, the final goal of complete epithelialization and, at the same time, preservation of the lumen was not achieved. Further studies including histologic documentation will be needed to obtain experimental long-term results with nitinol stents in strictured urethras. All factors considered, the question of whether to apply a permanent urethral stent should be addressed with caution.

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