Vasectomy and vasectomy reversal : development of newly designed nonabsorbable polymeric stent for reconstructing the vas deferens

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Introduction and aims of the study

How it all started!

A microscopical vasovasostomy is of course a time consuming operation, but those who have done a reversal procedure with a microscope will never revert to a macroscopical procedure again. Operating times vary between 2 –4 hours depending on the use of a one- or two-layer technique and the technical difficulties to encounter. Next to the difficult technical performance, it is frequently annoying that initial good sperm results can decline several months later. The cause of this decline is probably due to secondary stricturing because you initially start with semen samples of satisfying quality. Those patients undergoing a re-vasovasostomy have even a greater chance of developing partial or complete stricturing of the new anastomosis area. That's were our search for an alternative reversal method began.

A permanently present hollow stent in the vas could be the solution. The literature reported on the use of stents especially in the 70's, intravasal suture materials were used and polyglycolic acid as a bioabsorbable material became very popular in this decade. The results were promising but no further reports on this subject were seen in the years to follow. A possible explanation could be that supplementary studies in men were disappointing?

At the end of the 1980's, Berger et.al. restarted the use of a stent and published data from a study in men. His results were promising but not what he expected it to be. It appeared from the literature that nobody ever used a non-absorbable polymeric stent. After contacting several firms in the U.S., a couple of prototypes were realized. The big problem was to create a hollow stent that had small measurements and could also satisfy the condition of allowing sperm passage. We started to look for a suitable animal to test these prototypes and ended up with rabbits. They have an easy accessible vas deferens and the diameter of the vas equals that of men. Next to that, semen is easily obtained from these animals using an artificial vagina system

to collect sperm for an adequate follow-up. The biomaterial prototypes from the US were not successful and so we proceeded our search for a new stent that suited the purpose. We contacted the Technical University of Eindhoven, Eindhoven, The Netherlands and made an appointment at the biomaterials department. After explaining our ideas we were referred to the Center for Biomaterials in Maastricht, The Netherlands. We started to develop this stent using a non-biodegradable material.

Development of a polymeric stent for vasovasostomy

Development of a stent to rejoin two loose ends of the vas deferens requires a biomaterial that must meet several stringent requirements in terms of mechanical strength and biocompatibility. In situ, the stent has to withstand radial compression forces (especially those associated with peristaltic contractions of the vas deferens), to prevent narrowing or even closure of the stent lumen. With respect to the biocompatibility, two requirements can be formulated: (i) the presence of the stent should not evoke incompatibility effects, such as (chronic) inflammation, etc., and (ii) sperm cells should not be injured or damaged upon contacting the inner surface of the stent: epithelialization of the stents luminal surface should occur preferably.

At the onset of this study, it was believed that these requirements could be met with a special type of hydrophilic-hydrophobic copolymers, i.e. those derived from the reactive monomer N-vinylpyrrollidinone (NVP) as the hydrophilic building block, and the reactive monomer n-butyl methacrylate (BMA) as the hydrophobic building block (see fig.1).

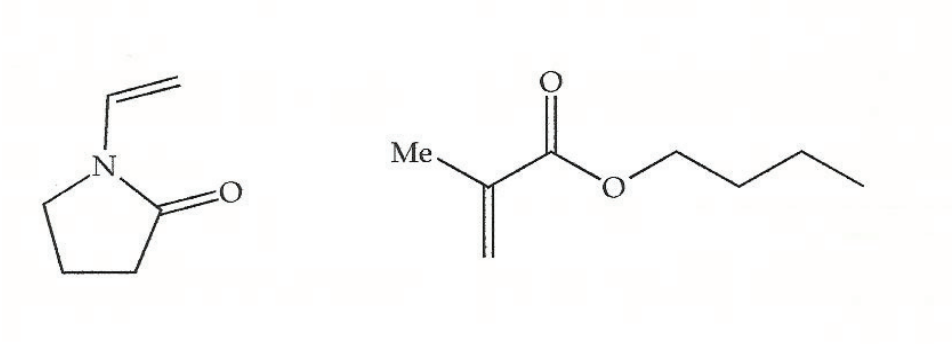

Fig 1. *Structural formulas of the NVP (left) and BMA (right) reactive monomers.*

Previous research has revealed the excellent biocompatibility (passivity) of such biomaterials, e.g., in contact with blood. Moreover, there is a wide range of NVP-based polymers and copolymers that find use in contact with human tissue (either in the clinic, or in cosmetic products). In our case, the ratio NVP:BMA provides a convenient handle to control the hydrophilicity, as well as the degree of swelling upon immersion in an aqueous environment, of the resulting copolymer. Furthermore, it was clear that the mechanical properties can be fine-tuned by means of physical cross linking of the polymer chains, through introduction of a bifunctional reactive monomer during copolymer synthesis. For clarity: these mechanical properties refer to the swollen (wet) state, in which the stent biomaterial is saturated with water. In the dry state, the NVP-BMA-type copolymers are all hard and glassy materials, which can be machined with high accuracy and reproducibility. Upon absorption of water, however, the materials become more or less flexible and rubbery.

Initially, a small number of prototype stents was manufactured out of a cross-linked version of the NVP-BMA copolymer. A number of preliminary experiments were performed, using the prototype stents and pieces of explanted vas deferens from an animal source. These preliminary experiments revealed two important points:

First, it became clear that joining of the two vas deferens ends by means of a simple intraluminal tube was inadequate. Most likely, such a tube can move along the intraluminal channel, especially as a result of the peristaltic movements of the vas during ejaculation. The stent was designed in such a way that longitudinal movements are prevented. This was realised by a ridge in the middle part of the stent (see fig. 2)

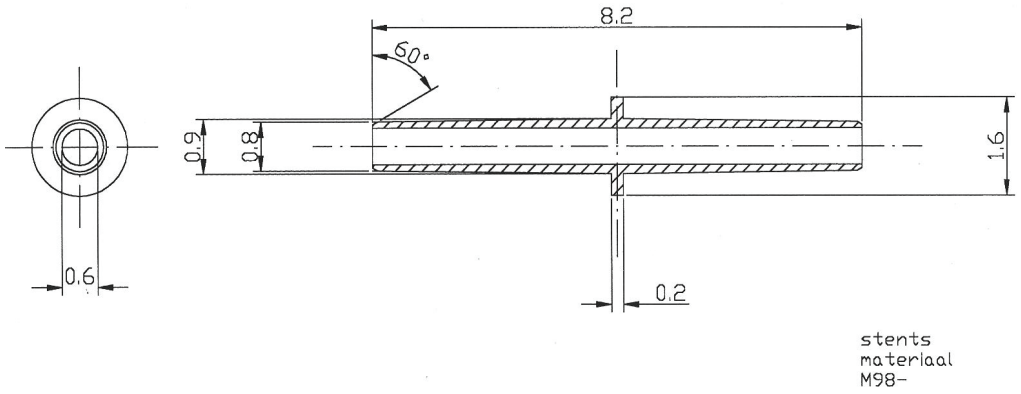

Fig 2. *Schematic drawing of the stent for vasovasostomy, as designed and tested during this project.*

The two vas deferens ends are joined on each side of the ridge, and connected through three stitches. This principle was used in all animal experiments with the stent for vasovasostomy, as described in this thesis.

Secondly, it became clear that the implantation of the vasovasostomy stent is essentially a three-step procedure, i.e. (i), insertion of the first stent half into the lumen of one of the vas deferens ends, (ii), insertion of the other stent half in the other lumen; (iii), fixation of the vas ends over the stent ridge, by three stitches. It was found that steps (i) and (ii) are difficult to perform when the stent is already equilibrated with water, since the material is to soft and

rubbery. The implantation proceeds conveniently if the stent is implanted in its dry (rather stiff) state, and allowed to absorb water in situ. The implantation must be executed quickly, and dry gloves must be used. This implies that the hydrophilic swelling nature of the biomaterial can be used advantageously during the implantation of the stent. The implantation technique proved to be straightforward; the technique can be taught to the skilled professional surgeon within approximately 1 day.

The experiment

The prototype looked very promising and we started with the set-up of our animal experiment. Collection of semen was of outmost importance to prove that our stent would function adequately. In the middle of the province of Limburg in the Netherlands, we found a rabbit farm specialized in artificial insemination of rabbits. An artificial vagina semen collection system was demonstrated to us. A male and female rabbit were placed just above each other in a small cage but were initially separated from each other. The sexual arousal of these animals was impressing and within a few minutes the male and female rabbits were brought together. They started to cohabitate immediately and it was the experience of the owner of the insemination station at what exact time he had to put the artificial vagina system between the rear legs of the female rabbit. Within seconds the male rabbit ejaculated in the artificial vagina and the semen was collected in a tube that was connected to the artificial vagina. Average volume of the ejaculate varied between 1-1.5 cc. We decided to buy this system and after some practicing we became experts in collecting semen from rabbits. The prototype of the new stent fitted perfectly in the vas deferens of the rabbits and we used 2 rabbits for a pilot. Both produced sperm even after 2 months. What we didn't know was how long it would take a vasectomized rabbit to become azoospermic. This was of importance because when a reversal

procedure would fail, due to complete obstruction, we would know the average time it would take for the animal to become azoospermic. Four rabbits were used for this experiment and after 6 weeks they all became azoospermic. Now it was time to start a randomized comparative study between rabbits that received bilateral stents and rabbits undergoing the conventional microscopic procedure. Together with the animal laboratory, we performed 28 vasovasostomy procedures and collected 142 semen samples. The animals were kept in cages, they were well nourished and postoperative care was taken care off. The animals were sacrificed 4-11 months after the initial operation and vas anastomoses, testes and epididymi were histologically analyzed. The results of our experiments are presented in this book.