Thermoplastic Elastomers for Small Diameter Compliant Grafts

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Abstract: The development of satisfactory replacement prostheses for small diameter natural vessels (less than 7 mm) still appears to be an unsolved problem. It has been suggested that mismatch in compliance between the graft and the natural vessel is one of the most important causes of the occlusion of the graft itself. The authors' approach was to synthesize potentially hemocompatible thermoplastic elastomers whose elastic properties could be deliberately varied by modifying their chemical structure. For this purpose, polyurethanes were synthesized with both traditional polyether or polyester blocks of different lengths and with new soft and hard blocks such as polyisobutylene and poly 7-oxabicyclo [221] heptane. The authors have also synthesized new comb-like thermoplastic elastomers obtained by reacting styrene-butadiene two-block living polymeric chains with ethylene-maleic anhydride copolymer (EMAC). With such materials, grafts with diameters ranging from 2.5–5 mm were produced using traditional techniques described in the literature. The mechanical properties of these vascular grafts were compared with those of the natural vessels, using various techniques. Prostheses that possessed mechanical properties most similar to those of the natural vessels were implanted in the femoral artery of dogs. Patency was checked daily by means of Doppler measurements of the distal femoral pulses. Some of the implanted grafts remained patent until the autopsy of the animal (45 days) and others are still in place. **Key Words:** Artificial vascular graft—Polyurethane—Thermoplastic elastomer—Vascular implant—Vascular prosthesis.

During the last 25 years, the problem of substituting damaged natural vessels of large diameter (>7 mm) has been satisfactorily solved by the use of vascular prostheses made of woven or knitted Teflon or Dacron fabrics. These grafts were specifically designed to prevent kinking by a technological process of circumferential heat crimping. The reasons for the success of such prostheses have already been discussed in the relevant literature (1) and appear mainly due to the formation of a tissue that is structurally very similar to that of the natural artery inside the grafts. These artificial grafts, however, usually fail when used for the replacement of arteries smaller than 7 mm in internal diameter. The reasons for this failure have also been discussed and appear to be related mainly to the crimped inner surface of the fabric graft, which may cause turbulence of the blood and cause thrombosis.

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One of the major advances in the construction of artificial arterial grafts has been the development of expanded polytetrafluorethylene (PTFE) that needs no crimping and exhibits a grossly smooth internal line. These grafts have serious limitations, however, when used for the replacement of arteries smaller than 7 mm in internal diameter. Quite recently, it has been suggested (1,2) that the failure of small diameter inelastic prostheses may be due to a mismatch in the mechanical properties between the synthetic artery and the natural artery to which the graft is attached.

It has been suggested that such problems may be solved by using elastomeric materials, such as polyurethane, that are specifically designed to possess mechanical properties similar to those of natural vessels (1–3). The relevance of a certain degree of biodegradability of the grafts has already been demonstrated (3). This feature should facilitate tissue ingrowth and decrease the chance of aneurysm formation.

The use of elastomeric materials for the produc-

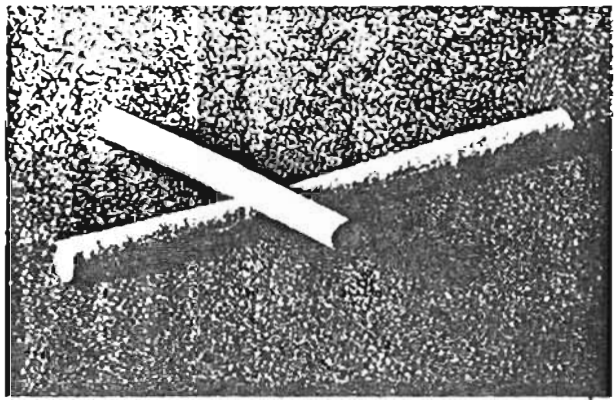


FIG. 1. Two prototype small diameter compliant grafts fabricated using polyurethanes.

tion of artificial grafts has not yet been carried out on an industrial basis although very interesting results have been obtained in animal experiments. In brief, the ideal vascular prosthesis should be compliant, microporous, nonthrombogenic, and preferably biodegradable. To attain these objectives, the authors' research work was organized as follows: (a) the synthesis and characterization of new, potentially hemocompatible, segmented, thermoplastic elastomers; and (b) the use of these materials for the fabrication of prototype vascular grafts with mechanical properties similar to those of the natural vessels which were obtained either by varying the hard to soft segment length ratio or by using special technologies.

MATERIALS AND METHODS

Synthesis and characterization of segmented thermoplastic elastomers

The synthesis of new polyurethanes was carried out following the usual procedure described in the relevant literature (4). α, ω polyisobutylene diols were obtained by the polymerization of isobutylene

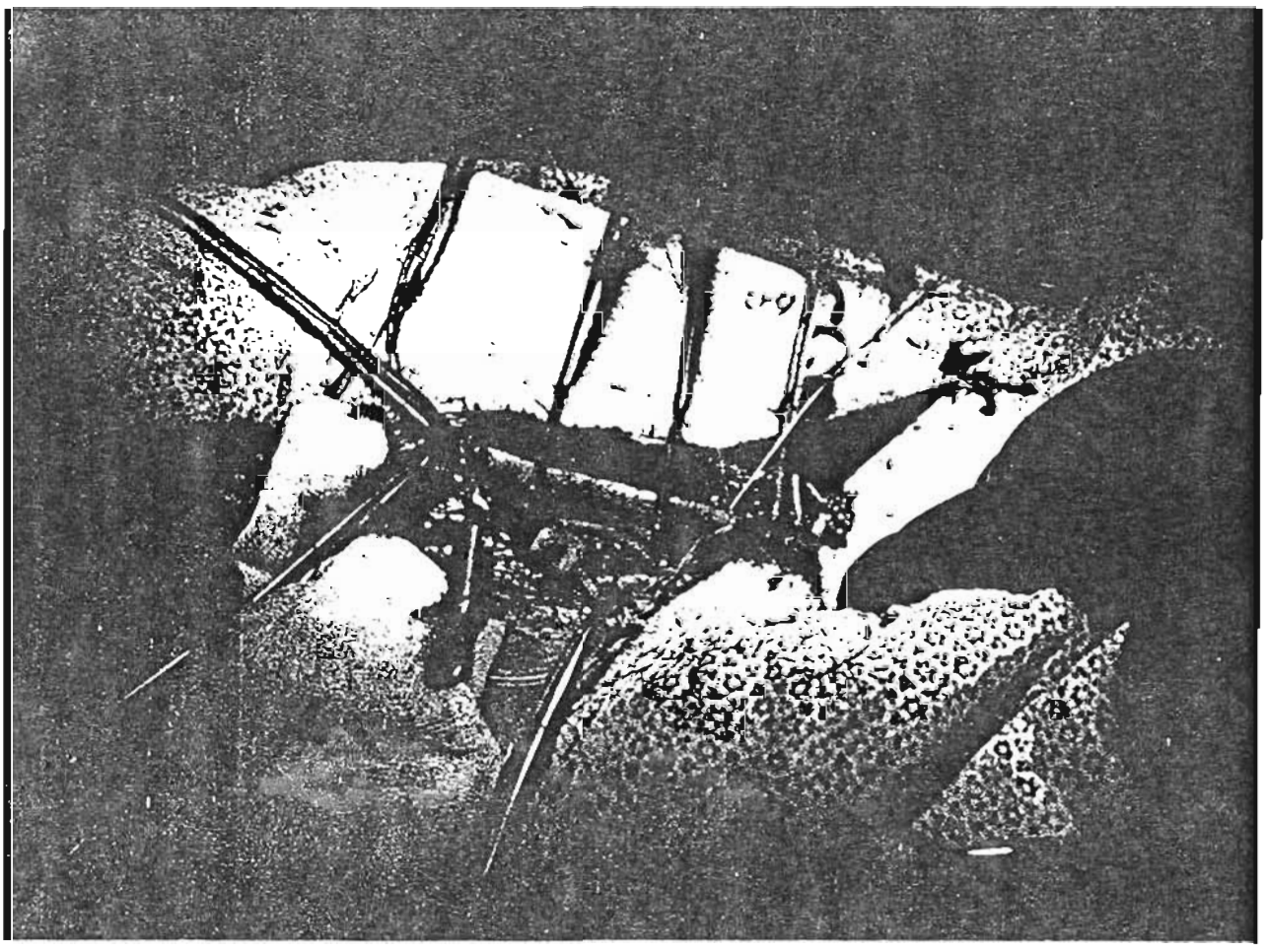


FIG. 2. Immediately after the implantation of an artificial graft in a dog, two pressure transducers and an electromagnetic flowmeter are used to record the pressure drop created by the prosthesis, the waveforms of the pressure and of the flow rate.

using Kennedy's Inifer technique (5). α, ω poly 7-oxabicyclo [221] heptane diols were obtained by cationic polymerization of 7-oxabicyclo [221] heptane carried out under vacuum with $AlEt_3$ and H_2O as the catalytic system. Graft copolymers were synthesized by nucleophilic reaction between maleic anhydride copolymers and living polyanions as previously described (6). For the physicochemical and biological characterization of the materials described above, the authors used some of the tests recommended in a recent publication of the U.S. National Institutes of Health (7) in which guidelines for the characterization of biomaterials are given. To determine bulk properties, the following tests were conducted: IR and NMR spectra, solvent response molecular weight and distribution, extractability, thermal characterization (DSC), and stress-strain measurements. To determine surface properties, light microscope morphology and internal reflection infrared spectroscopy were performed. Finally, the following biological tests were performed: agar overlay tissue culture test on the material and agar overlay on material extracts.

Blood-polymer interactions were determined by some of the tests described in another publication of the U.S. National Institutes of Health (8), in which guidelines for blood-material interactions are given. These tests included determination of whole blood clotting time in tubes, sheets or films of testing materials (the modified Lee-White clotting test), thrombin time, and platelet aggregation.

Graft fabrication

Grafts were fabricated following the method described by Lyman (9), which produced a polymer tube with a controlled void structure, thus rendering a white, opaque, spongy material with considerably more compliance than the typical oven-dried product (Fig. 1). Prostheses were sterilized with ethylene oxide.

Animal experiments

The grafts were implanted in medium-size dogs (about 20 kg) of both sexes. The surgical operation was performed under general anesthesia with endotracheal intubation and controlled ventilation. The entire length of the femoral artery was exposed from the inguinal ligament to its intersection with the semimembraneous muscle. At this point, a 5-cm tract of the artery was replaced with a 3–4 mm diameter tubular graft. A termino-terminal anastomosis was performed using Ethibond 5-0 single stitches (Ethicon, Pomezia, Italy) (Fig. 2). No anticoagulants or platelet drugs were used either locally or systemically, even at the time of intervention. A flowmeter was positioned at the distal end of the graft to measure the relative flow rate. At the same time, two pressure transducers were inserted 2 cm above the proximal anastomosis and on the largest distal branch of the femoral artery. It was thus possible to continuously record the pressure above and below the prostheses, as shown in Fig. 3. After removing the flowmeter and pressure transducers, the surgical field was washed with an antibiotic solution, and the wound was sutured. Antibiotic therapy was continued by parenteral injection for 5 days. The patency of the graft was checked daily by means of Doppler examination of the distal section of the artery. An arteriographic examination by means of a catheter introduced into

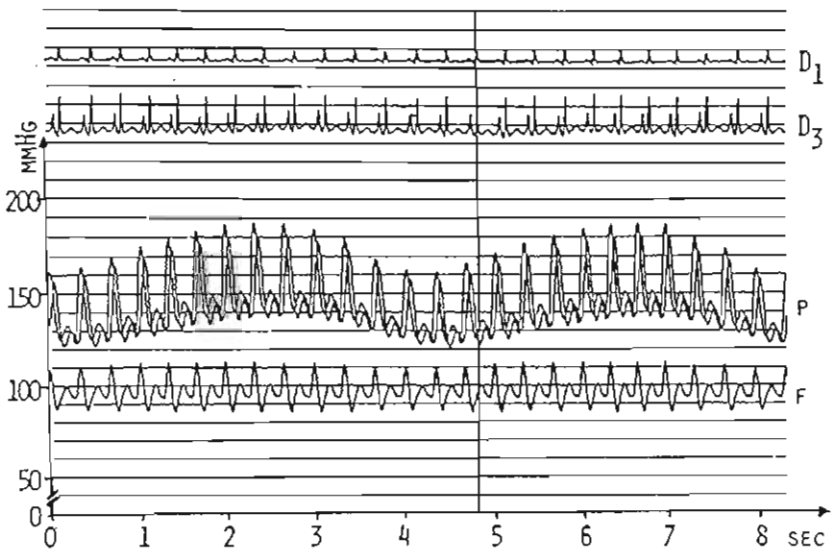


FIG. 3. Postoperative simultaneous recorded trace: D_1: ECG (D_1); D_3: ECG (D_3); p: pressure waveforms upstream and downstream of the prosthetic graft; f: qualitative flow rate diagram through the prosthetic graft. The figure scale is related to the pressure waveforms.

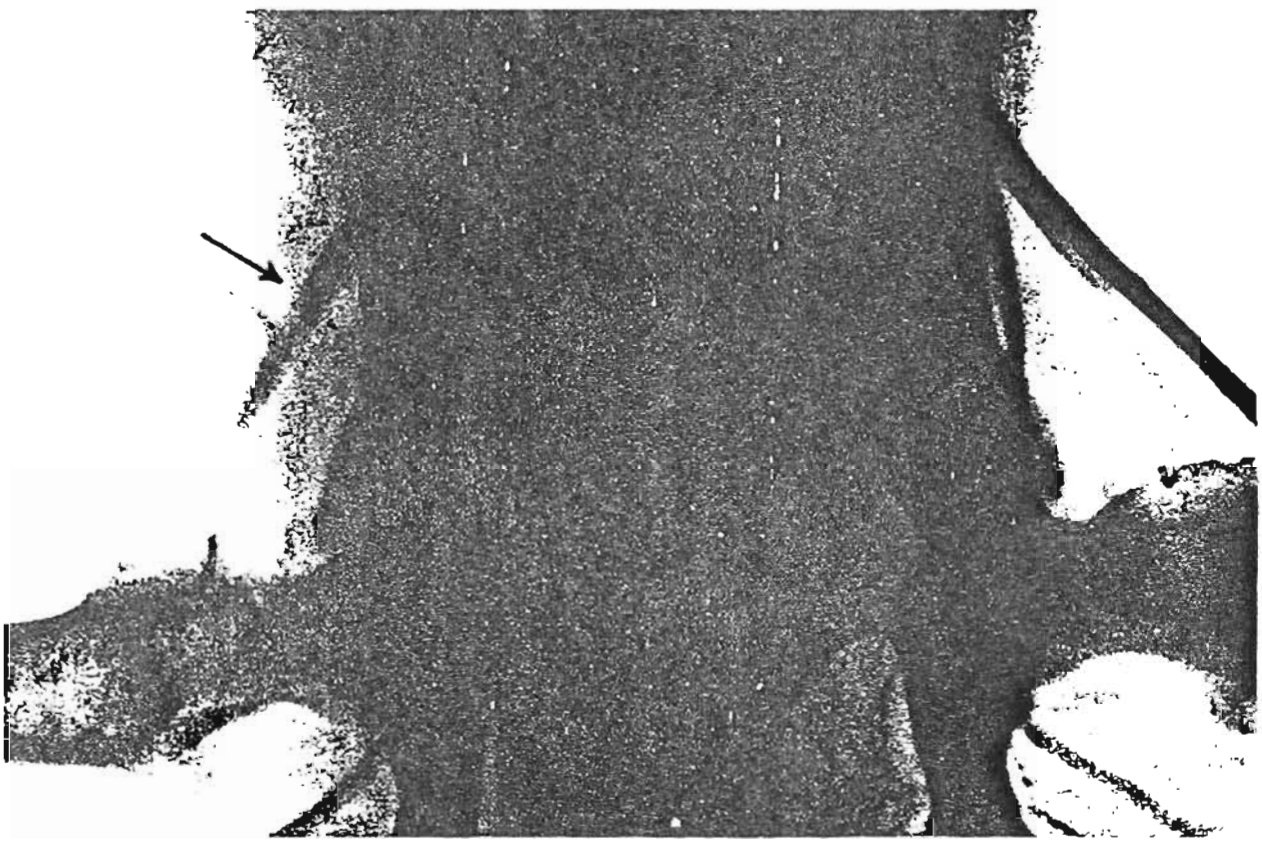


FIG. 4. Postoperative arteriogram showing the patency of the artificial graft implanted on the dog's right femoral artery. First day after implantation.

the contralateral femoral artery was performed in some cases and always on the day following the operation (Fig. 4).

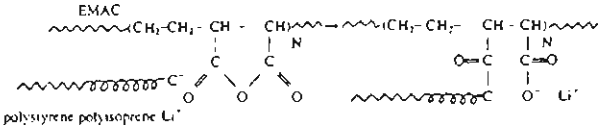
RESULTS AND DISCUSSION

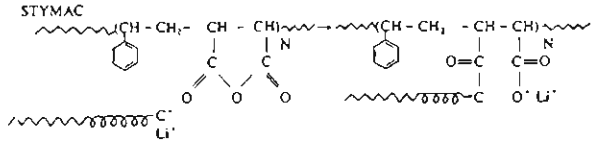
Polymers with elastomeric properties were found to have numerous applications in the cardiocirculatory system for the construction of intraortic balloons, vascular grafts, circulatory assist devices, and artificial hearts. Thermoplastic elastomers are certainly the most promising elastomeric materials for cardiovascular applications because they possess fairly good mechanical properties without the need for vulcanization, which due to complicated compositions introduces many potentially dangerous leachable materials.

In the past, the authors have been active in the synthesis and characterization of elastomeric materials, and quite recently, they have oriented their research program toward the production of new potentially hemocompatible thermoplastic elastomers. Cationic and anionic polymerization systems were used to produce both block copolymers with thermoelastic properties and prepolymers to be used for the synthesis of new polyurethane elastomers. Because polymers used in cardiovascular applications come into contact with the blood directly, the most important problem that remains unsolved is the production of nonthrombogenic materials.

Blood-foreign material interactions have been fairly widely investigated over the last few years, and many reviews on the subject have appeared in the literature (10). Of the different approaches to this problem described in the relevant literature, the authors have chosen the following: (a) to produce, either directly or by successive processes, new thermoplastic elastomers with functional groups that enhance their hemocompatibility and (b) to develop inherently nonthrombogenic materials whose hemocompatibility is achieved through their specific surface molecular structure.

Following the first approach, the authors synthesized new comb-like thermoplastic elastomers by reacting styrene-isoprene two-block living polymeric chains with both ethylene-maleic anhydride copolymer (EMAC) and styrene-maleic anhydride copolymer (STYMAC):

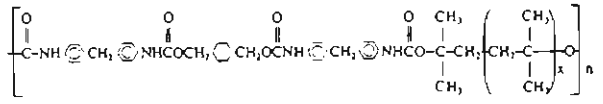




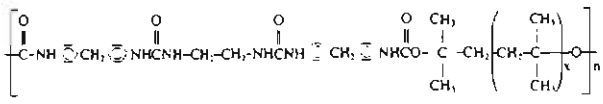
These new copolymers exhibit a very high degree of hemocompatibility, due to the presence of the $-COO^-$ group, as indicated in Table 1. Their elastomeric properties are now being investigated. Following the second approach, new polyurethanes were prepared by reacting α, ω polyisobutylene diols with different diisocyanates and by using various extenders.

The relevant polymer structures are the following:

1) polyisobutylene-based polyurethane



2) polyisobutylene-based polyurethane urea



New polyurethanes were also prepared by the use of the following starting materials:

1) diisocyanates:
   - –diphenylmethane diisocynate (MDI);
   - –1.6-diisocyanate hexane;
   - –toluylene diisocyanate (TDI);

TABLE 1. *Critical response to thrombogenicity*

Materials	Howell test (s)	WBCT (min)	Platelet adhesion (%)
Glass	105	5	4.4
Stymac-g-polyisoprene	220	11	37
Emac-g-(polyisoprene-b-polystyrene)	246	>150	33.7
Stymac-g-(polystyrene)	260	>240	40.4
Polyisobutylene urethane	260	20.6	10
Polyisobutylene urethane urea	153	14	2.3
Cardiothane 51	266	14	4
Poly 7-oxabicyclo [221] heptane urethane	285	22	10

WBCT, whole blood clotting time.

2) macrodiols:
   - –hydroxyl-terminated polyisobutylene (3,000, 6,000 daltons);
   - –hydroxyl-terminated polyethylene oxide (400, 1,500, 2,000 daltons);
   - –hydroxyl-terminated polypropylene oxide (400, 1,200, 2,000 daltons);
   - –hydroxyl-terminated polycaprolactone (1,250 daltons);
   - –hydroxyl-terminated poly 7-oxabicyclo [221] heptane;

3) chain extenders:
   - –4,4'-diaminocyclohexylmethane;
   - –1,4-cyclohexandiol;
   - –1,4-cyclohexanedimethanol;
   - –ethylenediamine.

All these polymers should be inherently nonthrombogenic materials because their surface molecular structure, composed of a variety of groups, establishes a force field in which plasma proteins can be expected to be in an energetically unstable state that hinders their irreversible attachment. This prevents platelet adhesion, release, and aggregation, as well as the activation of both intrinsic and extrinsic coagulation pathways.

The results of the tests contained in Table 1 appear to confirm the authors' hypothesis because these new polyurethanes behave similarly to other biomedical polyurethanes (Cardiothane 51, for example).

In addition to the above-mentioned characteristics, these polyurethanes possess a wide range of elastic properties. Their elastic behavior may be modified in two ways: to change the ratio of the hard and soft segments and in the selection of chain extenders. Stress-strain tests performed on different polyurethanes show the possibility of endowing the artificial graft with an elastic behavior that is very similar to that of natural arteries.

Using some of these polyurethanes, which have shown the highest degree of hemocompatibility and elasticity, the authors have fabricated a series of artificial compliant grafts with diameters ranging from 2.5–5 mm (Fig. 1). The use of standard techniques previously described made it possible to obtain grafts with the required thickness. Some of these grafts were implanted in dogs with the following results. The sterilization process did not alter the physical properties of the graft; the graft was pliable and tear resistant and did not create any problems in the suturing process. There was no evidence of blood dropping on the anastomotic line or blood filtering along the wall. Finally, the compliance of the graft produced a visible pulsing that

was supported by the shift in the pressure waveforms (Fig. 3). Some of the grafts remained patent until the autopsy of the animal (45 days), and some are still in place.

Among the four failures, two were due to technical surgical complications, the first because of wound suppuration followed by leakage of the anastomosis due to sepsis of the graft. The second was due to the difference in diameter between the original blood vessel and the graft, which caused poor distal anastomosis crimping and, finally, thrombosis. It must be pointed out that the first failure may have been prevented by antibiotic therapy, which the authors now administer routinely, but was not given in this case.

In the third case, the transplanted prosthesis bent irreversibly, thus decreasing the blood flow and favoring a thrombotic process that was discovered at the time of autopsy on the 38th day. The last case of failure was caused by an unexplained thrombosis, which necessitated removal of the graft on the 30th day. This was determined on the basis of the Doppler examination, which showed a marked decrease in the signal the first few days after implantation.

CONCLUSION

The new graft copolymers, poly STYMAC (or EMAC)-g-isoprene-b-styrene, showed a very high degree of hemocompatibility, but their suitability for graft fabrication has not yet been verified. The new polyurethanes, which appear to be of comparable blood compatibility to commercial materials, offer a spectrum of mechanical properties based on segment sequence and the choice of chain extenders. Grafts fabricated with these polymers presented no serious problems from a surgical point of view, but the fabrication of reproducible grafts and long-term mechanical and biocompatible properties must be investigated. Initial results justify further work along these lines.

Acknowledgment: This work was supported by the Italian CNR Progetto Finalizzato "Chimica Fine e Secondaria".

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