A novel balloon angioplasty catheter impregnated with beta-particle emitting radioisotopes for vascular brachytherapy to prevent restenosis

First in vivo results

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Background According to early clinical trials, vascular brachytherapy performed prior to or shortly after angioplasty is very effective in reducing restenosis rates. The purpose of this study was to investigate the effects of a novel radioactive catheter that allows simultaneous balloon angioplasty and beta-particle irradiation in the prevention of restenosis.

Material and Methods The balloon surface of an angioplasty catheter was impregnated with the radioisotope ³²P. Dosimetry calculations using a Monte Carlo method were performed at a radial distance of 0·2 mm from the balloon surface. Rabbit iliac arteries were dilated and simultaneously irradiated with a dose of 20 Gy delivered to the adventitia. Control arteries were only dilated and not irradiated. Neointimal areas, cell numbers and the perimeter of the arteries were measured by histomorphometry after 6 weeks.

Results Neointima formation was reduced after balloon dilatation and simultaneous beta-particle irradiation using the ³²P impregnated angioplasty catheter as compared to balloon dilatation alone with a non-impregnated catheter (0·09 ± 0·06 vs 0·27 ± 0·09 mm² neointimal area and 168 ± 45 vs 360 ± 133 cells/0·05 mm² neointima, P<0·001 vs control, respectively). In addition, balloon dilatation with the ³²P impregnated angioplasty catheter increased the vessel perimeter as compared to balloon dilatation with a non-impregnated catheter (4·7 ± 0·2 vs 3·9 ± 0·3 mm, P<0·001 vs control).

Conclusions Simultaneous balloon dilatation and vascular brachytherapy with a novel ³²P impregnated angioplasty catheter markedly reduces restenosis in vivo by preventing neointimal hyperplasia and constrictive vascular remodelling.

Key Words: Balloon angioplasty, constrictive remodelling, neointimal hyperplasia, radioisotopes, radiotherapy, restenosis.

See page 1994 for the Editorial comment on this article

Introduction

Restenosis is a major problem after initially successful angioplasty procedures¹–³. Recently, vascular brachytherapy with gamma- and beta-radiation sources has been shown to markedly reduce restenosis rates in animal models and in preliminary clinical trials⁴–⁶. Beta-radiation offers the advantage of shorter irradiation periods and fewer radiation protection measures in the catheterization laboratory compared with gamma-radiation⁷. However, radiation therapy prior to or after the angioplasty procedure may still be too time-consuming to be easily implemented on a routine basis in busy interventional catheterization laboratories. In this study, we introduce the concept of simultaneous vascular brachytherapy during angioplasty for restenosis prevention using a novel balloon angioplasty catheter impregnated with the radioisotope phosphorus-32. The purpose of this study was to...
investigate the effects of this device on neointimal hyperplasia and vascular remodelling in a rabbit restenosis model.

Materials and Methods

Ex vivo bench testing of the $^{32}$P impregnated angioplasty catheter

An impregnation process was developed resulting in thin films containing $^{32}$P which tightly adhere to the surface of the balloon of a Scimed© angioplasty catheter (Boston Scientific, U.S.A.)[8]. In brief, $^{32}$P in solution was mixed with a polymer carrier which was attached homogeneously to the balloon surface. The $^{32}$P impregnation process of the balloon was performed with and without the protective coating of the radioisotope film. The protective film was applied to seal off the radioisotope layer. The loss of $^{32}$P from the catheter with and without the protective film was measured after multiple balloon inflations and deflations at the German Cancer Research Center in Heidelberg using a beta-scintillation counter (TRICARB Analyzer 2500 TR, Canberra Packard). For these tests, the balloons were impregnated with a total of 0·05 mCi $^{32}$P. After balloon inflations to 8 atm and deflations × 15, the activity was measured in a vial filled with 10 ml of whole blood. The loss of $^{32}$P from the balloon of the catheter was then calculated from the activity of the blood.

Dosimetry

Radiation doses were calculated using a Monte Carlo simulation model. At a given mean wall thickness (0·2 mm) of the rabbit iliac artery, the radiation dose penetrating to the adventitia was calculated for different balloon surface activities and periods of balloon expansion, i.e. balloon surface contact with the arterial wall. The experiments were planned to deliver a minimum dose of 20 Gy to the adventitia. The appropriate period of balloon inflation was chosen from the calculated dose charts according to the actual surface activity of the catheter. In the dosimetric calculation, it was assumed that the balloon is shaped like a cylinder and that the $^{32}$P isotope is distributed uniformly on the curved surface of the balloon. Assuming that the total activity of $^{32}$P is $A$, the radius and the length of the cylinder are $R$ and $L$, respectively, then the dose rate at a point $r$ is

$$D(r) = \frac{A}{2\pi RL} k(r - \bar{r}) \frac{ds}{d}$$  \hspace{1cm} (1)

where $k(r - \bar{r})$ is the point dose rate kernel of $^{32}$P per unit activity in water and the integration is over the curved surface of the cylindrical balloon. In the calculation, a first order approximation was made to overlook the self-absorption by the $^{32}$P isotope itself. The point dose rate kernel of $^{32}$P in water was obtained with Monte Carlo simulation. Integrated TIGER Series (ITS) of Coupled Electron/Photon Monte Carlo Code System (Version 2.1) was used for kernel calculation. The ITS system was run on a DEC AlphaStation 200/66. The cutoff energy was 1 keV. The number of histories was 100 000. The energy spectrum of a beta particle emitted by the $^{32}$P source was computed based on the work by Prestwich et al.[9]. The maximum beta energy used was 1·708 MeV. The ITS calculated dose corresponds to that deposited by a single beta particle emitted by a $^{32}$P point source. The point dose rate kernel per unit $^{32}$P activity (mCi) is obtained by multiplying the dose with a constant $3·7 \times 10^7$ s$^{-1}$.

Animal care and surgical procedure

All experiments were performed in accordance with the guidelines for animal research established by the American Heart Association. Twelve female New Zealand White rabbits weighing between 2·3 to 2·6 kg were used for the study. Anaesthesia was performed with ketamine (35 mg . kg$^{-1}$) and xylazine (5 mg . kg$^{-1}$). Both femoral arteries were exposed and a 4F paediatric sheath was inserted into each artery. Five hundred units of heparin were given intra-arterially via the sheath. Retrograde angiograms were performed to determine the diameters in the iliac arteries. A $^{32}$P impregnated balloon with a total surface activity of 2 mCi was used for the study. In six rabbits, a $^{32}$P impregnated angioplasty balloon catheter (3·0 diameter, length 20 mm) was advanced into the iliac artery. The balloon was inflated with physiological saline solution to 6 atm and remained inflated for a period of 20 min. The mean diameter of the iliac artery as determined by angiography was 2·5 mm, and thus the mean balloon to artery ratio was 1·2 inducing overstretch injury at the time of vessel irradiation. It was calculated to deliver a dose of 20 Gy to the adventitia of the rabbit arteries.
The contra-lateral iliac artery of the rabbit was then dilated for another 20 min with a non-impregnated conventional balloon angioplasty catheter (control). The rabbits were killed after 6 weeks for histological analysis. Six rabbits underwent sham-operation in order to compare the vessel perimeter of the uninjured iliac arteries with the vessel perimeter of the treated iliac arteries.

**Tissue collection and fixation**

The rabbits were killed by a lethal dose of sodium pentobarbital (120 mg . kg$^{-1}$). The abdominal aorta was canulated and the iliac arteries were flushed with physiological saline solution for 3 min. For in situ pressure fixation, the iliac arteries were infused with 4%
paraformaldehyde at 100 mmHg for 10 min. The iliac arteries were then removed and immersed in 1·5% paraformaldehyde and 1·5% glutaraldehyde overnight. The arterial specimens were dehydrated using graded alcohol solutions and then embedded in paraffin. The specimens were cut into serial 4–6 μm thick cross-sections at a rate of 20 cross-sections per artery.

Histomorphometry and cell counting

After staining the sections with Hematoxylin-Eosin, the neointimal cross-sectional areas were measured (computer-assisted) using a light microscope (Olympus) connected to a video camera (Sony) and a high-resolution digitizing image analyser (Pavlov Inc., Heidelberg), as described previously[10]. Vessel perimeter, delineated by the length of the external elastic lamina, and the neointimal area were measured from each cross-section. Total cell numbers of the neointima in an area 0·05 mm² were counted and compared between the study groups by two independent observers.

Statistics

The histomorphometric data are expressed as mean ± SD. The data were compared with the StatView software package. ANOVA followed by Scheffe’s F test was applied for comparisons of multiple group means.

Results

Ex vivo bench testing

The radioisotope loss from the impregnated catheter without a protective coating was 1% of the total activity. The loss was <0·1% with a protective film covering the impregnated balloon surface of the catheter (Fig. 1). Multiple balloon inflations and deflations of the ‘sealed source’ produced no detectable beta activity in the test medium blood, i.e. the activity of the blood was below the detection limit of the scintillation counter.

Dosimetry calculations

Three-dimensional dosimetric distributions were calculated for 32P impregnated balloons, 20 mm long and with diameters of 2·5, 3·0, and 3·5 mm, respectively. Figure 2 shows the dose rate distribution along the longitudinal axis of balloons inflated to diameters of 2·5–3·5 mm at a radial distance of 0·2 mm from the radioactive balloon surface (2 mCi). As shown in the figure, the dose is uniform across most of the balloon along the longitudinal axis, and drops off rapidly at both ends of the balloon. Figure 3 shows the dose–time relationships for the same three balloons, and the dose referred to is that 0·2 mm from the balloon surface. The dose increases with a decrease in balloon diameter. Figure 4 depicts the dose delivered by a 32P impregnated balloon inflated to a diameter of 3 mm increasing with source activity and inflation time. High source activities, i.e. 10 mCi, require only a brief inflation period of 5 min to deliver a dose of 30 Gy to a target of 0·2 mm in the arterial wall.

Neointimal area of the arteries

The neointimal area in the arterial cross-sections at 6 weeks after simultaneous dilatation and vessel...
irradiation with the \(^{32}\)P impregnated angioplasty catheter was markedly smaller than after conventional balloon dilatation (0·09 ± 0·06 vs 0·27 ± 0·09 mm\(^2\), \(P<0·001\), irradiation vs control). The significant reduction of neointimal formation in the arteries after using the \(^{32}\)P impregnated catheter is illustrated in Fig. 5.

Neointimal cell numbers in the arteries

The number of cells in the neointima after simultaneous balloon dilatation and vessel irradiation was markedly lower at 6 weeks compared with the cell number in the neointima after conventional vessel dilatation (168 ± 45 vs 360 ± 133 cells/0·05 mm\(^2\) neointima, \(P<0·001\), irradiation vs control).

Remodelling of the arteries

Conventional balloon dilatation caused constrictive vascular remodelling in this rabbit restenosis model. The vessel perimeter was 4·4 ± 0·2 mm in sham-operated uninjured arteries, but only 3·9 ± 0·3 mm in balloon dilated arteries (\(P<0·005\), sham vs control). However, this constrictive remodelling was abolished with irradiation of the arteries at the time of balloon dilatation. The vessel perimeter was significantly greater after simultaneous balloon dilatation and vascular irradiation compared with balloon dilatation alone at 6 weeks (4·7 ± 0·2 vs 3·9 ± 0·3 mm, \(P<0·001\) irradiation vs control).

Discussion

Several studies have indicated that restenosis after angioplasty is due to neointimal hyperplasia and constrictive vascular remodelling\(^{11–13}\). Vascular brachytherapy has been shown to effectively reduce restenosis rates in animal models and early clinical trials\(^{4–6}\). In this study, we report the first results in animals using a novel balloon angioplasty catheter impregnated with the radioisotope \(^{32}\)P. The catheter is designed to perform simultaneously angioplasty and vessel irradiation to...
Radioactive balloon angioplasty catheter prevents restenosis. Radioisotope impregnation of the angioplasty balloon centres the radiation source in the vessel and allows homogeneous irradiation along the natural shape of the lumen during dilatation.

Beta-particle emitters may be preferentially used for impregnation since these radioisotopes have steeper dose fall-off characteristics than gamma emitters. In addition, when a beta-source is in direct contact with the vessel wall instead of being centred in the vessel lumen, a steep dose gradient across the arterial wall is present. Bench tests showed a very tight adherence of $^{32}$P to the balloon even without a protective coating. A protective film which seals off the radioisotope layer prevents radioisotope contamination after multiple balloon inflations and deflations.

Monte Carlo calculations showed that radiation doses delivered to the target area vary with the diameter of balloon inflation, balloon length, balloon activity and contact time at the arterial wall. However, the radiation dose can be easily calculated if these parameters are known. In this study, the balloon was inflated with saline solution because we did not want to alter the dosimetry. However, contrast agents may not significantly change the dose delivered by $^{32}$P impregnated balloons. Further Monte Carlo calculations showed that if an angioplasty balloon is inflated with the contrast agent Hypeaque® (composition 7·88% of C, 7·42% of H, 22·73% of I, 67% of N, 58·92% of O, and 1·38% of Na; density 1·32 g cm$^{-3}$), the overall effect of the contrast agent on the dose is negligible with an uncertainty of ± 5%.

We found a marked decrease in cross-sectional neointimal area after simultaneous balloon dilatation and vessel irradiation. In addition, the vessel perimeter was greater after irradiation, showing that this radioactive instrument prevents constrictive remodelling after angioplasty. The findings of reduced neointimal hyperplasia and an increased vessel perimeter after radiation therapy are consistent with previous observations with other vascular brachytherapy sources in the prevention of restenosis.$^{14,15}$

Sequential cross-sectioning of the entire iliac artery for histological evaluation revealed no increase in neointima formation at the edges of the irradiation zone, i.e. no ‘edge-effect’. It appears from these preliminary experiments that exact coverage of vessel overstretch injury with the irradiation zone using a coated angioplasty balloon prevents edge restenosis.

Long periods of balloon inflations during angioplasty may be used in the treatment of collateralized obstructions of peripheral iliofemoral artery disease, but are certainly not recommended without an autoperfusion system in the coronary arteries. As we have shown with Monte Carlo calculations, higher activities of $^{32}$P impregnated balloon angioplasty catheter as used in this study, i.e. between 5 and 20 mCi, enable the user to deliver a therapeutic dose between 15 and 25 Gy to an intravascular target during a short balloon inflation period. A short balloon inflation and vessel irradiation period using high dose rates eliminates the need for an autoperfusion system even if the catheter is to be used in coronary arteries. In addition, radioactive balloon catheters can be temporarily deflated to allow reperfusion of the coronary artery. However, these conditions still have to be tested in further studies.

The presented experimental results encourage further clinical studies but may not be reproduced in other animal models. Rabbits and porcine restenosis models, for example, treated with vascular balloon overstretch injury have different cell proliferation kinetics, and vary in the intrinsic thrombotic activity associated with the injury. Both models have their limitations, and to date there is no scientific proof that one model is more predictive of human restenosis than another.

References


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