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New Multifunctional Percutaneous Transluminal Coronary Angioplasty Catheter Device Capable of Balloon Inflation, Local Drug Delivery and Coronary Perfusion

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Abstract

A new percutaneous transluminal coronary angioplasty catheter with multiple functions of balloon inflation, local drug delivery and coronary perfusion has been devised. The device consists of an inflatable lumen, a drug delivery lumen, and a perfusion (or guide wire) lumen. A drug can be infused from the port located distal to the inflated balloon during continuous blood perfusion via the perfusion lumen. Fluorescence-labeled heparin and peroxidase administered using the device permeated into denuded vessel tissues during ongoing perfusion and remained there for over 24 hr. This prototype device indicates the potential therapeutic implications of the concepts of the device.

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Key Words

■ Angioplasty ■ Coronary artery disease ■ Restenosis ■ Tech assessment

INTRODUCTION

Restenosis develops within 3 to 6 months after treatment in 30–50% of patients treated with percutaneous transluminal coronary angioplasty despite extensive treatment, including adjunctive therapies and mechanical techniques[1]. A major cause of restenosis is neointimal hyperplasia triggered by thrombus formation[2]. Numerous pharmacological agents that can prevent thrombosis or neointimal proliferation have been tested[3]. However, clinical studies with these agents have demonstrated disappointing results, which may be related to the systemic side effects of the doses required to achieve local beneficial effects at the site of arterial injury.

Recently, local administration of such agents directly to the injured site has attracted increasing interest as a potential therapeutic method for the prevention of restenosis[4]. Local drug delivery may

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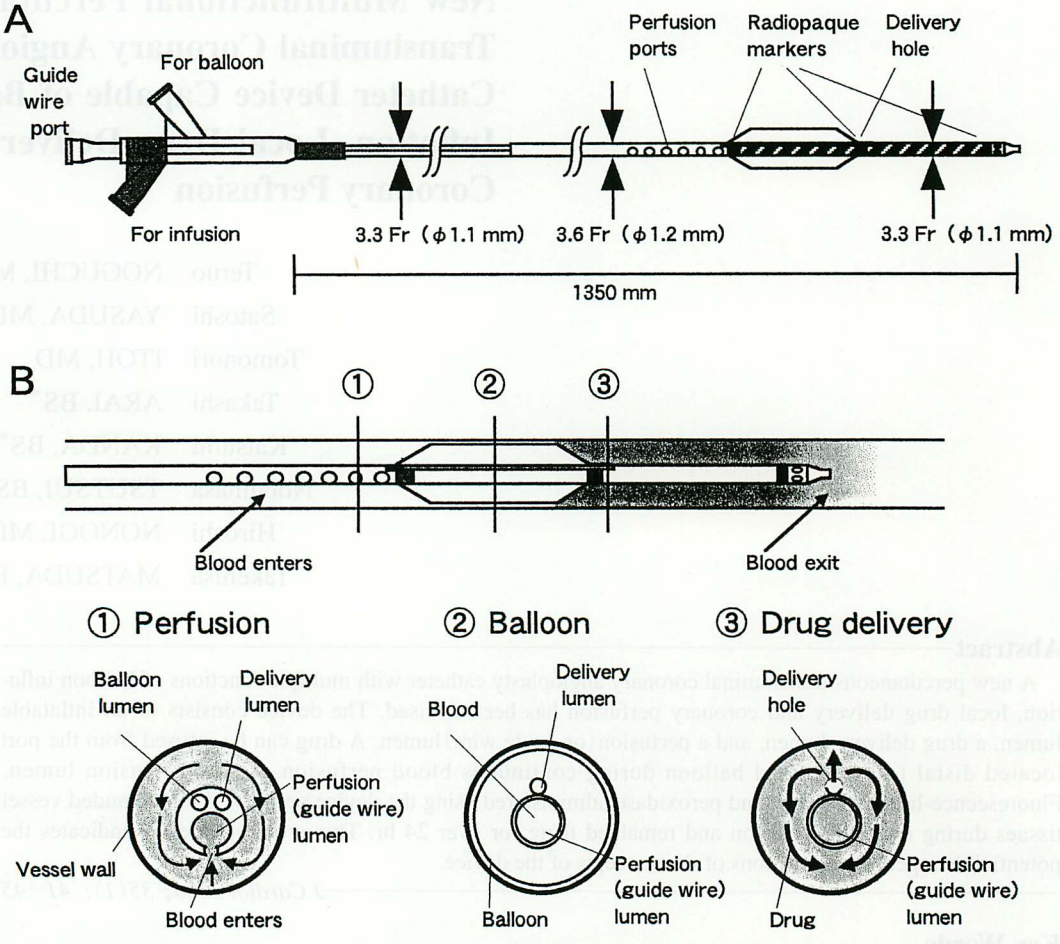

Fig. 1 Schema of the balloon catheter (*A*) and cross section of the catheter with 3 lumens (*B*)

allow a sufficient concentration of the drug to be achieved at the tissue, while minimizing systemic adverse effects. Therefore, we have devised a catheter, which allows simultaneous balloon angioplasty coronary perfusion, and drug delivery. This paper describes the design concept of our catheter and discusses the possible uses.

MATERIALS AND RESULTS

A schema of the balloon catheter device developed is illustrated in **Fig. 1**. The device is an over-the-wire (0.014″) system and consists of 2 parts: a conventional balloon and a drug delivery tube. The device has a shaft diameter of 3.6 F, and length of 1,350 mm, and has 3 lumens: a central lumen for the angioplasty guide wire access or perfusion, and 2 eccentric lumens for balloon inflation and drug delivery, respectively. The balloon is a 20-mm-long compliant balloon (quarter size increase at 10 atm)

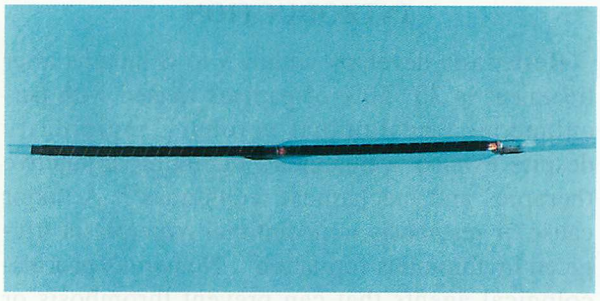

Fig. 2 An inflated 3.0-mm balloon catheter

with 2 radiopaque markers (**Fig. 2**). The nominal pressure is 6 atm, and the rated pressure is 12 atm. The balloon is available in diameters varying from 2.0−3.5 mm in 0.5 mm increments. The proximal end of the balloon has 12 perfusion ports of 0.4 mm diameter at intervals of 1 mm. A 0.3-mm-diameter port for drug delivery is located 0.5 mm distal to the

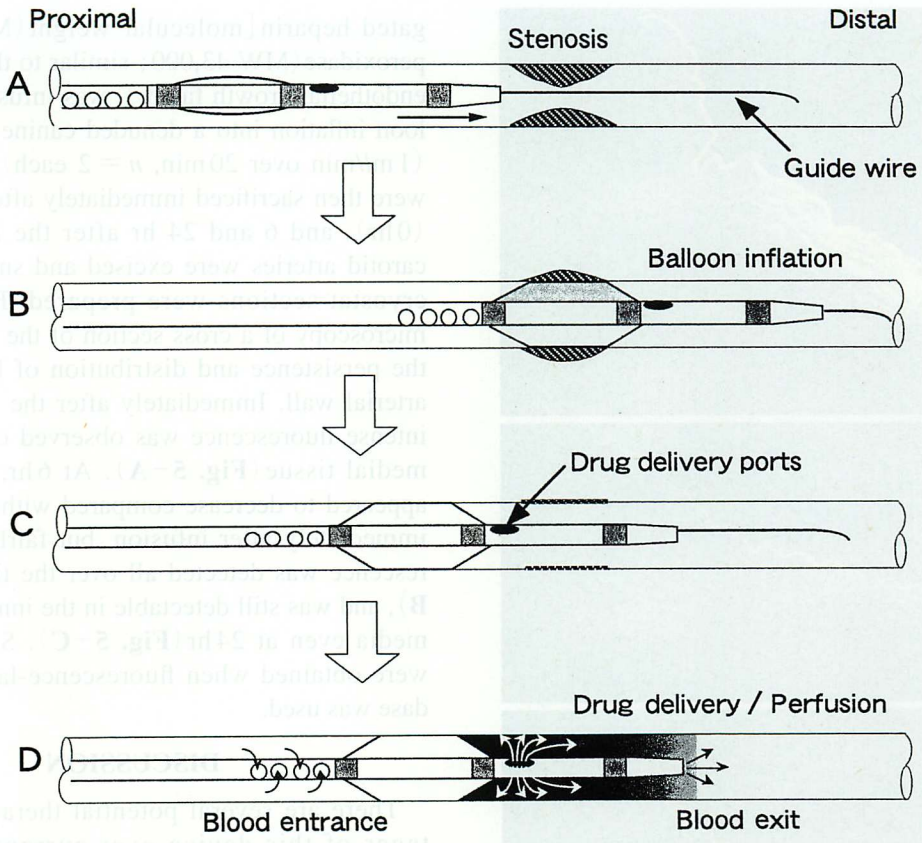

Fig. 3 Three functions of the balloon catheter

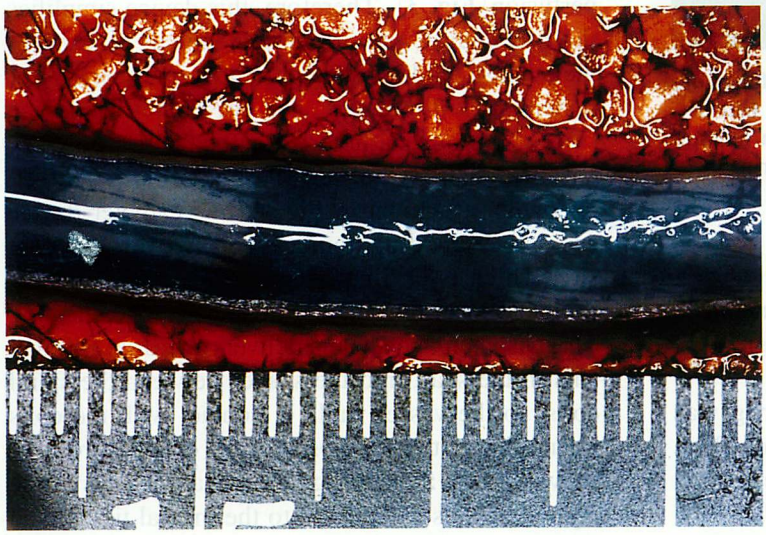

Fig. 4 Photomicrograph of the vessel wall in the canine carotid artery after the local administration of Evans Blue using the multifunctional balloon catheter
Magnification × 100.

balloon. At the top of the 20-mm-long drug delivery tube, there is a radiopaque marker.

Various simultaneous therapeutic procedures are possible. After the balloon is inflated at the site of stenosis (**Figs. 3−A, B**), the drug delivery port is re-positioned at the target lesion and the balloon is inflated to a low pressure (2 atm) to allow drug accumulation (**Fig. 3−C**). Then the guide wire is removed to a site proximal to the perfusion ports, which then allows for distal coronary perfusion (**Fig. 3−D**). In the canine model ($n = 2$), this device was found to maintain 34 ± 7 ml/min of dis-

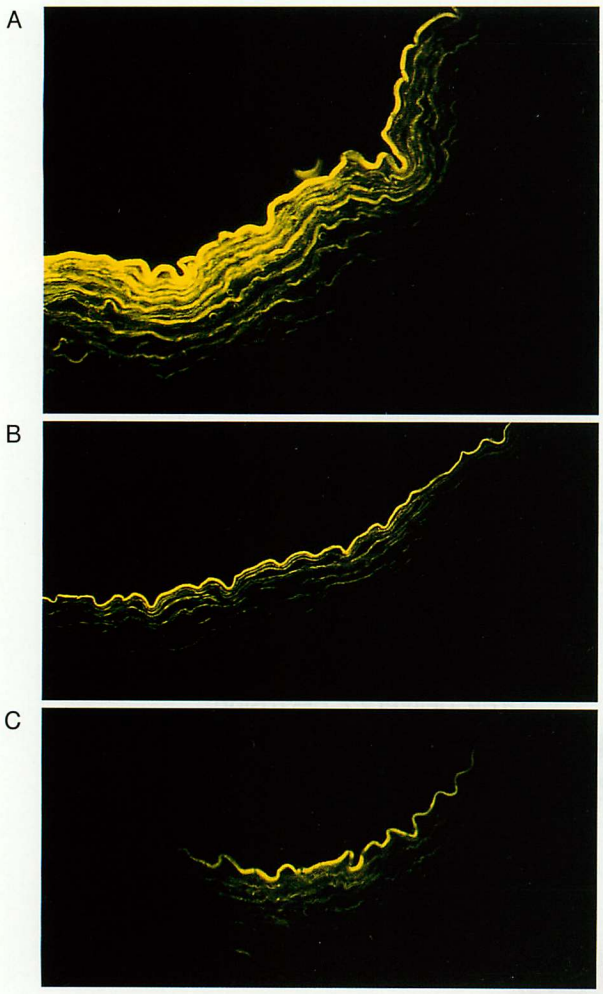

Fig. 5 Fluorescence photomicrographs of canine carotid arteries immediately (0 hr, *A*), 6 hr (*B*), and 24 hr (*C*) after local administration of fluorescein isothiocyanate-conjugated heparin
Magnification × 100.

tal blood flow during drug administration into a carotid artery at a mean aortic pressure of 100 mmHg.

Accumulation of the administered drug was assessed by the administration of Evans Blue (1 ml/min over 20 min *in vivo*) to a canine carotid artery denuded by pullback balloon injury ($n = 2$). The administered dye stained the lesion homogeneously over 80% of the area (**Fig. 4**). This indicates that the dye infused from the drug-delivery port remained in the hydrodynamic stagnation region between the port and exit of blood perfusion of the catheter device.

Intramural drug localization was also assessed using this device. Fluorescein isothiocyanate-conjugated heparin [molecular weight (MW) 6,000] or peroxidase (MW 43,000; similar to that of vascular endothelial growth factor), was infused during balloon inflation into a denuded canine carotid artery (1 ml/min over 20 min, $n = 2$ each). The animals were then sacrificed immediately after the infusion (0 hr), and 6 and 24 hr after the infusion. The carotid arteries were excised and snap-frozen and cryostat sections were prepared. Fluorescence-microscopy of a cross section of the artery showed the persistence and distribution of heparin in the arterial wall. Immediately after the infusion, very intense fluorescence was observed over the entire medial tissue (**Fig. 5-A**). At 6 hr, the intensity appeared to decrease compared with that observed immediately after infusion, but fairly strong fluorescence was detected all over the tissue (**Fig. 5-B**), and was still detectable in the inner layer of the media even at 24 hr (**Fig. 5-C**). Similar results were obtained when fluorescence-labeled peroxidase was used.

DISCUSSION

There are several potential therapeutic advantages of this device over currently available devices. First, this catheter device has 3 functions: balloon inflation, local drug delivery and coronary perfusion (**Fig. 3**). Therefore, this device simplifies the procedures, providing mechanical dilation of the stenosis and subsequent adjunctive therapy for restenosis without the need for changing device from a balloon catheter to a local drug delivery catheter, which has until now been essential. Secondly, as shown in **Fig. 4**, this catheter device can deliver the drug homogeneously over the target site, which is an improvement over the currently available local drug delivery Dispatch™ catheter[5]. The Dispatch™ catheter[5] delivers the drug through slits in the shaft into the spaces between the spiral coils, so the vessel walls in contact with the coils are not likely to be exposed to the drug. Thirdly, as shown in **Fig. 5**, the drug delivery at the sites of the injured vessels extended into the medial tissue, and persisted for at least 24 hr. Intramural drug persistence may modulate the initial processes underlying neointimal proliferation[2]. In fact, recent animal studies have demonstrated that vascular endothelial growth factor reduces in-stent restenosis[6] and heparin prevents initial thrombus formation[5], even with a single and local administration.

This device also has some limitations. The guide

wire should be removed to a site proximal to the perfusion ports during drug delivery to secure antegrade blood flow (**Fig. 3-D**), which may lead to abrupt closure. In addition, a drug delivery tube 20-mm in length is not suitable for tortuous and/or complex lesions.

CONCLUSION

The present prototype multifunctional balloon catheter has potential uses for preventing restenosis after angioplasty by local delivery of pharmacological agents or gene therapy.

要　約

血管拡張，灌流，および薬物送達の機能を有する
新しい経皮的冠動脈形成術用多機能バルーンカテーテルの開発

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狭窄部の血管拡張，遠位部血液灌流，および薬物局所送達の機能を併せ持った新しい経皮的冠動脈形成術用多機能バルーンカテーテルを開発し，その性能について検討した．

カテーテルは3.6Fでシングルバルーンのover-the-wire方式であり，バルーンの0.5mm遠位部には口径0.3mmの注入口を1ヵ所設けた．またバルーン遠位部を20mm延長して薬物停留域を設定した．さらにバルーン近位部に灌流孔として口径0.4mmの側孔を計8ヵ所設けた．イヌ総頸動脈のバルーン傷害部位に送達した色素(Evans Blue)は薬物停留域にほぼ均一に集積した．さらにバルーン傷害部位に蛍光標識したヘパリンおよび蛋白質を送達したところ，蛍光色素は内膜に強く濃縮され，一部は中膜層まで浸透していた．蛍光は送達約24時間後にも内膜側に残存していた．

プロトタイプデバイスの実効機能が確認できた．本研究で得られた基本的技術から，今後の臨床応用が期待される．

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