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CLINICAL RESEARCH

Cutting balloon combined with paclitaxel-eluting balloon for treatment of in-stent restenosis

Cutting balloon combiné à un ballon paclitaxel pour le traitement de la resténose intra-stent

Junying Kong[a,1], Jingbo Hou[a,1], Lijia Ma[a], Lei Xing[a], Haibo Jia[a], Huimin Liu[a], Shaosong Zhang[b,c], Bo Yu[a,*], Ik-Kyung Jang[d]

[a] *Department of Cardiology, Second Affiliated Hospital of Harbin Medical University, Key Laboratories of Education, Ministry for Myocardial Ischaemia Mechanism and Treatment, 150086 Harbin, Heilongjiang, China*
[b] *LightLab Imaging, St. Jude Medical, Westford, MA, USA*
[c] *Harbin Medical University, Harbin, Heilongjiang, China*
[d] *Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

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KEYWORDS
In-stent restenosis;
Angioplasty;
Animal model;
Apoptosis

Summary
Background. — The optimal therapy for in-stent restenosis (ISR) is controversial. We evaluated three different strategies for the treatment of in-stent restenosis: cutting balloon angioplasty (CBA), paclitaxel-eluting balloon angioplasty (PEBA) and cutting balloon followed by paclitaxel-eluting balloon angioplasty (CB + PEBA).
Methods. — Forty-five coronary arteries in 45 mini-pigs underwent oversized bare-metal stent (stent-to-artery ratio, 1.2:1) implantation to induce in-stent restenosis. After 28 days, vessels with in-stent restenosis (≥ 50% diameter stenosis) were randomly divided into three groups: CBA, PEBA and CB + PEBA. In vivo angiography was performed before intervention, immediately after intervention and at 28-day follow-up. Stented arteries were harvested for pathological

Abbreviations: AS%, percentage of lumen area stenosis; BMS, bare-metal stent; CBA, cutting balloon angioplasty; CB+PEBA, cutting balloon followed by paclitaxel-eluting balloon angioplasty; EELA, elastic lamina area; IELA, internal elastic lamina area; ISR, in-stent restenosis; LA, lumen area; LD, lumen diameter; NA, neointimal area; PCNA, proliferating cell nuclear antigen; PEBA, paclitaxel-eluting balloon angioplasty; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling; VSMCs, vascular smooth muscle cells.

* Corresponding author. Fax: +86 45186605180.
E-mail address: yuboteacher@163.com (B. Yu).

[1] Junying Kong and Jingbo Hou contributed equally to this work.

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analyses. The proliferation and apoptosis of vascular smooth muscle cells were evaluated by immunohistochemical staining and the terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) assay, respectively.
Results. — Acute lumen gain was not different between the three groups. Late lumen loss and neointimal area at follow-up were lower for CB + PEBA compared with CBA but similar for CB + PEBA compared with PEBA. There were no significant differences in proliferating cell nuclear antigen-positive vascular smooth muscle cells and TUNEL-positive vascular smooth muscle cells between the CB + PEBA and PEBA groups.
Conclusions. — PEBA with or without cutting balloon was superior to CBA alone for in-stent restenosis. The underlying mechanism was probably related to inhibition of smooth muscle cell proliferation and increased apoptosis. In this porcine coronary artery restenosis model, PEBA with or without cutting balloon was superior.

MOTS CLÉS
Resténose intra-stent ;
Angioplastie ;
Modèle animal ;
Apoptose (mort cellulaire)

Résumé
Justification. — Le traitement optimal de la resténose intra-stent reste controversé. Nous avons évalué trois stratégies différentes pour le traitement de la resténose intra-stent : angioplastie avec *cutting balloon*, angioplastie avec ballon au paclitaxel et *cutting balloon* suivi d'une angioplastie avec ballon au paclitaxel.
Méthode. — Quarante-cinq artères coronaires chez 45 cochons ont bénéficié d'une angioplastie par un stent métallique surdimensionné (ratio stent/artère : 2.1) afin d'induire une resténose intra-stent. Après 28 jours, une resténose intra-stent définie comme un diamètre de sténose supérieur ou égal à 50 % de l'artère coronaire ont été randomisés dans trois groupes : angioplastie avec *cutting balloon*, angioplastie avec ballon au paclitaxel et *cutting balloon* suivi d'une angioplastie par ballon au paclitaxel. L'angiographie in vivo a été réalisée avant l'intervention, immédiatement au décours et à 28 jours. Les artères stentées ont été prélevées pour analyse anatomopathologique. La prolifération et l'apoptose des cellules musculaires lisses vasculaires ont été évaluées par immuno-histochimie et par un marquage terminal deoxynucléotidyle transferase d'UTD (marquage TUNEL), respectivement.
Résultats. — La réduction immédiate de calibre coronaire n'était pas différente dans les trois groupes. La réduction tardive du diamètre luminal et la surface néo-intimale au suivi était moindre dans le groupe *cutting balloon* suivi d'une angioplastie avec ballon au paclitaxel, comparativement au groupe angioplastie par *cutting balloon* mais similaire au groupe angioplastie par ballon au paclitaxel. Il n'y avait pas de différence significative dans la détection de prolifération de cellules musculaires lisses vasculaires par reconnaissance antigénique ou par le test TUNEL, entre le groupe *cutting balloon* suivi d'une angioplastie par ballon au paclitaxel et le groupe angioplastie par ballon au paclitaxel.
Conclusion. — L'angioplastie par ballon au paclitaxel avec ou sans *cutting balloon* s'avère supérieure à l'angioplastie par *cutting balloon* seule pour la prévention de la resténose intra-stent. Le mécanisme est probablement lié à l'inhibition de la prolifération des cellules musculaires lisses vasculaires, et une augmentation de l'apoptose. Dans ce modèle porcin de resténose coronaire, l'angioplastie par ballon au paclitaxel avec ou sans *cutting balloon* s'avère supérieure aux autres méthodes testées.

Introduction

Treatment of in-stent restenosis (ISR) remains challenging. Several studies have shown variable results using balloon angioplasty alone [1], repeat stenting [2—4], cutting balloon angioplasty (CBA) [5,6], intracoronary irradiation (brachytherapy) [7,8] or excimer laser angioplasty [9]. Other studies have compared these different techniques and it is still unclear which one, if any, will provide the most favourable outcomes [10—15].

Recently, paclitaxel-eluting balloon angioplasty (PEBA) has been developed as a novel approach, which combines the features of conventional balloon angioplasty with paclitaxel eluting for the treatment of ISR. Preclinical trials have demonstrated that the efficacy of PEBA in the treatment of ISR is superior to that of conventional balloon angioplasty and not inferior to that of a paclitaxel-eluting stent [16,17]. However, given the structure of the paclitaxel-eluting balloon, it must have some of the shortcomings of conventional balloon angioplasty, such as balloon slippage and edge dissections post procedure. All these shortcomings have been associated with cumbersome procedures, suboptimal results and adverse clinical and angiographical outcomes [18]. The use of CBA could potentially reduce the occurrence of these complications. However, the outcome of cutting balloon predilatation followed by PEBA for the treatment of ISR compared with PEBA or CBA alone is unknown.