STUDY PROTOCOL

VIA MEDICA

The role of superficial wall stress and mechanical factors in scaffold failure: Protocol of the RANSOMED study

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Background

Bioresorbable scaffolds (BRS) were once heralded as the fourth revolution in interventional cardiology [1] (after percutaneous coronary intervention [PCI], bare-metal stents [BMS], and drug-eluting stents [DES]). They were theoretically supposed to prevent restenosis as efficiently as DES, whilst dissipating the threat of late and very late stent thrombosis (VLST), because all intracoronary foreign bodies and potentially pro-inflammatory material completely disappeared from the coronary artery. Nonetheless, after initially promising results in pilot studies [2–6], BRS started to be questioned, as several observational studies and clinical trials consistently reported higher rates of scaffold thrombosis and device-oriented composite endpoint (cardiac death, target vessel myocardial infarction, and target vessel revascularization) than those observed in second generation DES [7–10]. Moreover, approximately two-thirds of the cases of scaffold thrombosis occurred at very late stages [9, 10], thus blasting the appealing hypothesis of transient scaffolding, whose risk of thrombosis vanishes in parallel with the bioresorption of the foreign body. Not even vasomotion was restored as initially expected [9], notwithstanding the encouraging results in the pilot studies [2, 11].

The reasons for the poor clinical performance of BRS are not fully elucidated, but they are most likely multifactorial. Procedural factors at the time of implantation play an important role, as suggested in the Coronary Slow-flow and Microvascular Disease Registry (MICAT), wherein the incidence of scaffold thrombosis was significantly reduced from 3.3% to 1.0% at 12 months after implementation of an angiographically guided BVS-dedicated implantation protocol [12]. A small series of 54 patients has reported 0% scaffold thrombosis at 12 months after an optical coherence tomography-guided implantation protocol, with tailored plaque preparation depending on the tissue characterization of the stenosis, and targeted optimization if needed [13]. Nonetheless the procedural factors do not fully explain the higher incidence of scaffold thrombosis: an excessively broad and non-selective indication to implant the
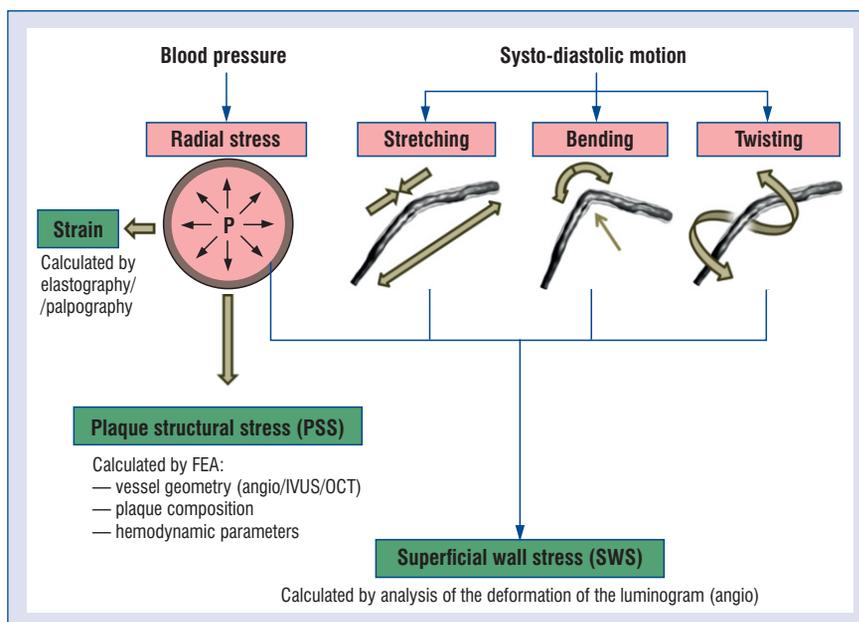
Figure 1. The four vectors of dynamic superficial wall stress and their relationship with other mechanical forces; FEA — finite element analysis; IVUS — intravascular ultrasound; OCT — optical coherence tomography.

device, disregarding the plaque characteristics, the eagerness of the operators to pioneer off-label indications, or an overly prolonged resorption process [14], protracted beyond the time slots defined in preclinical studies [15], might have played a relevant role in the failure of this promising technology.

Another intriguing phenomenon, named "dismantling", has also been described in some cases of very late scaffold thrombosis. It is defined as the total loss of structural integrity of the scaffold, with the presence of overhanging and floating struts [14], and it could partly explain very late clinical events, because **a persistent scaffold with irregular loss of structural integrity resembles a model of stent fracture**, which is a known risk factor for device failure [16–18]. The analysis of this phenomenon has inspired the so-called mechanical hypothesis of scaffold failure: the **lack of structural integrity (dismantling) will occur at some point with any bioresorbable device, thus becoming a model of stent/scaffold fracture, which under specific mechanical stress conditions might result in increased inflammation, gross structural disarray of both the polymer and the vascular elements, and ultimately very late scaffold thrombosis or other clinical events.**

A novel method to calculate dynamic superficial wall stress (SWS) has been developed recently, based on the dynamic lumen changes assessed in three-dimensional angiography [19–21]. Briefly, SWS summarizes the mechanical forces acting on the vessel wall in four different vectors: radial stress, stretching-compression, bending, and twisting (Fig. 1) [21]. It can be calculated by analysis of the deformation of the luminogram in conventional angiography [19–21]. We hypothesize that BRS implanted in coronary segments with low dynamic SWS will perform clinically better than BRS implanted in segments with high dynamic SWS, in which the repetitive stress can result in material fatigue from the moment of implantation and in mechanical instability once dismantling happens in the resorption process. We also hypothesize that the role played by the vectors depending on the systo-diastolic motion (i.e., stretching, bending, and twisting) on this process is likely to be more relevant than the vector depending on blood pressure (i.e., radial stress). These hypotheses have not been tested to date.

Methods

The aim of the RANSOMED (Resorption Aptness under Nocuous Stress: Outcomes and Mechanics for the Election of Device) study is to test the association between SWS in a coronary segment treated with BRS and very late clinical outcomes: target lesion failure, device failure, scaffold restenosis, and scaffold thrombosis.
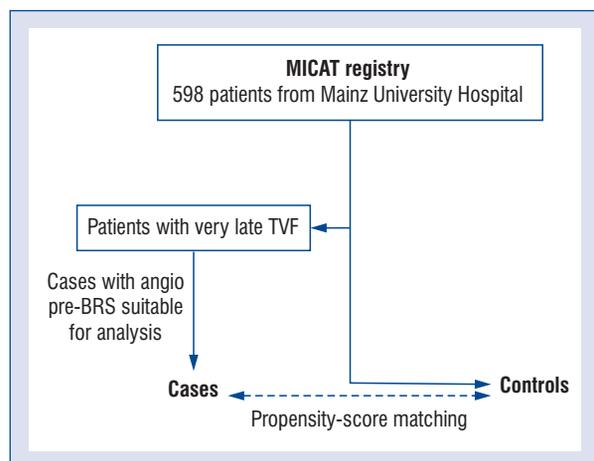
Figure 2. Study flow-chart; BRS— bioresorbable scaffold; TVF — target vessel failure.

Study design and study population

Post-hoc analysis of patients from Mainz enrolled in the MICAT study (NCT02180178) [12], following a case-control design. Patients with very late target vessel failure (TVF) will comprise the cases, while the controls will be selected from event-free BRS patients after propensity score matching (Fig. 2).

The inclusion criteria will be as follows: 1) Patients with one or more BRS implanted and enrolled in the MICAT registry [12]; 2) A TVF event between 12 months and 5 years after BRS implantation (cases) or event-free follow-up for 5 years (controls). TVF will be defined as cardiac death, vessel-related myocardial infarction, and target lesion revascularization. The exclusion criteria for both cases and controls will be as follows: 1) Angiography pre-implantation missing; 2) Documented scaffold rupture at the end of the implantation; 3) Hybrid BRS-DES revascularization in the same coronary segment; 4) Coronary angiography acquisition at < 12.5 frames/s; 5) Coronary angiography deemed of insufficient quality due to vessel overlap, extreme foreshortening, or insufficient opacification of the target artery.

Data management

Anonymized clinical data and angiographies of the patients will be transferred to the online servers of the cardiovascular imaging core lab of Shanghai Jiao Tong University School of Medicine (clinical data) and of Med-X Research Institute (angiographies), in a secured and firewall-protected environment. Investigators responsible for the biomechanical analysis of the angiographies will be blinded to the clinical results and vice versa. The whole process of data handling will warrant patients' data confidentiality. The transferred data will not be used for any purpose other than the one explicitly described in this protocol without formally asking for permission from the MICAT investigators.

Dynamic SWS calculation

Angiography images in DICOM format will be analyzed at the central imaging core lab for conventional quantitative coronary angiography (QCA) analysis and dynamic SWS calculation. SWS at baseline (main target) and after BRS implantation (whenever available, secondary target) will be calculated at the scaffolded segment as previously described [19, 20]. The following parameters will be collected to explore their association with clinical events:
— maximal SWS value in the scaffolded segment before PCI (pre-SWSmax);
— maximal SWS value in the scaffolded segment after BRS implantation (post-SWSmax);
— pre-post difference in maximal SWS (ΔSWSmax);
— mean SWS value in the scaffolded segment before PCI (pre-SWSmean);
— mean SWS value in the scaffolded segment after BRS implantation (post-SWSmean);
— pre-post difference in mean SWS (ΔSWSmean).

Analysis of the four different vectors of SWS

The role of the different components of SWS (radial stress, stretching, bending, and twisting) on the occurrence of very late TVF will be explored, taking the value of each vector provided by the software.

All the SWS vectors except twisting can be indirectly estimated using advanced software for conventional QCA analysis, which requires much lower quality and frame rate during the angiography acquisition than SWS for an accurate assessment. Advanced QCA software (AngioPlus Galley, Pulse Medical, Shanghai, China) can estimate plaque strain as a surrogate for radial stress, and the maximal differences in vessel angulation and segment length between systole and diastole as surrogates for bending and stretching, respectively. Plaque strain depends on blood pressure, whilst bending and stretching depend on systo-diastolic motion; therefore, the different weight of these forces on the process of scaffold structural discontinuity, dismantling, and failure will be indirectly verified.

Study objectives

The comparison of pre-SWSmax between patients with vs. without very late TVF will be the primary objective of the study.

Secondary objectives of the study will be as follows: a comparison of ΔSWSmax, parameters related to the mean dynamic SWS and each of the SWS vectors between patients with vs. without very late TVF, between patients with vs. without definite/probable scaffold thrombosis, and between patients with vs. without TVF at any time. The comparisons of SWS vectors will also include the QCA-derived plaque strain, bending, and stretching, as previously described.

The following exploratory objectives are defined: sensitivity, specificity, + predictive value, – predictive value, diagnostic accuracy, and area under the curve of the receiver-operator characteristics curve of the optimal cut-off value for the primary and secondary objectives, in the case of significant association.

Prespecified subgroup analysis will be performed for the primary and secondary objectives in which a significant association is found: angio- vs. optical coherence tomography-guided scaffold implantation, age groups, and main coronary territory (left anterior descending, left circumflex, and right coronary artery).

Sample size calculation

There are no preliminary data on this topic that enable an accurate sample size for the current study. We believe that the sample size of the MICAT study (n = 1305 patients) and the reported event rate should provide a sufficient sample size to test the hypothesis of this study, which is essentially exploratory of the concept. In the unlikely case that the data from MICAT are not sufficient to provide statistical significance, but a clear trend can be derived from the analysis of the data, the investigators could consider increasing the study sample by the addition of other international BRS registries.

Ethical aspects

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with ICH Good Clinical Practice as well as regulatory requirements. All data management will include anonymity of the participating patients and confidentiality of their clinical data. Access to the central database will be password-protected, and only the authorized investigators will be granted access. The angiography images in DICOM format will be anonymized and sent to the imaging core lab. The analysts of the angiography recordings will be unaware of the identity of the patients included in the study.

Discussion

The mechanical hypothesis explaining cases of very late scaffold failure after a model of stent/scaffold fracture occurring as a natural consequence of the resorption process in BRS has never been clinically tested to date. There are several reasons for this gap in the evidence. First of all, a prospective study with this aim would entail serious logistic challenges due to the low incidence of clinical events and the complex time-consuming evaluation of mechanical forces in the coronary artery. Such a study design would entail evaluation and thousands of angiographies through an expensive, cumbersome, and ponderous process to obtain a significant result. Therefore, the investigators have opted for an observational retrospective study to overcome these currently insurmountable logistic limitations. The study proposed herein follows a classical case-control design, which enables the investigators to focus on the few cases of scaffold failure (cases) and to compare them with matched controls. In this way the mechanical analysis is limited to a few cases (a maximum of 70), which is an affordable sample size and sufficient for a pilot exploratory study. However, this retrospective design entails a potentially severe limitation: the calculation of SWS demands very high quality angiography acquisition and ideally a high frame rate (> 25 frames/s). Neither this unusually high frame rate nor the high-quality requirements can be warranted for most cases in a retrospective study, so the accuracy of the estimation is uncertain, although it might be sufficient to show a meaningful signal. This is also the main reason to have included QCA-derived parameters that can be considered estimators of two of the vectors encompassed in the calculation of SWS: plaque strain — as an estimator of radial stress, and change in systo-diastolic angulation — as an estimator of bending. These two parameters represent vectors that depend on blood pressure and on systo-diastolic motion, respectively, which we hypothesize to play the least and most relevant roles for the occurrence of material fatigue and scaffold failure in BRS from a mechanical point of view, respectively. These QCA-derived parameters are less quality-demanding and therefore might be instrumental to evaluate the mechanical hypothesis if the SWS analysis were unreliable.

Conflict of interest: Juan Luis Gutiérrez-Chico received consultancy fees and speaker honoraria from Abbott, Asahi Intecc, and Boston Scientific. All other authors have nothing to disclose.

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