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Relationship between tensile stress and plaque growth after balloon angioplasty treated with and without intracoronary beta-brachytherapy

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Aims We investigated the influence of tensile stress on plaque growth after balloon angioplasty with and without beta-radiation therapy.

Methods and Results Thirty-one consecutive patients successfully treated with balloon angioplasty were analysed qualitatively and quantitatively by means of an ECG-gated three-dimensional intravascular ultrasound post-procedure and at follow-up. Eighteen patients were irradiated with catheter-based beta-radiation ($^{90}Sr/^{90}Y$ source) and 13 were not (control). Studied segments were divided into 2 mm subsegments. Thus 184 irradiated and 111 non-irradiated subsegments were included. Tensile stress was calculated according to Laplace's law. The radiation dose was calculated by means of dose–volume histograms. Plaque growth was positively correlated to tensile stress in both the radiation and control groups ($r=0{\cdot}374$, $P=0{\cdot}0001$ and $r=0{\cdot}305$, $P=0{\cdot}001$). Low-dose subsegments (<6 Gy) had a significant correlation ($r=0{\cdot}410$, $P=0{\cdot}0001$) whereas no correlation was observed in the effective-dose subsegments (≥ 6 Gy). Multivariate analysis identified tensile stress as the only independent predictor of plaque increase in non-irradiated subsegments, whereas actual dose and plaque morphology were stronger predictors in irradiated subsegments.

Conclusion The results of this study suggest that plaque growth is related to tensile stress after balloon angioplasty. Intracoronary brachytherapy may alter the biophysical process on plaque growth when the prescribed dose is effectively delivered.
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Key Words: Tensile stress, balloon angioplasty, intracoronary radiation, intravascular ultrasound, plaque growth, dose–volume histogram.

See page 1994 for the Editorial comment on this article

Introduction

Intracoronary brachytherapy is a novel technique to prevent restenosis after percutaneous coronary intervention. A significant reduction in re-restenosis after intravascular radiation therapy of in-stent restenosis has been reported recently[1]. In addition, this mode of therapy has been applied in the treatment of de novo coronary lesions[2–4], since experimental and clinical work has shown that radiation favourably affects both vascular remodelling and neointimal proliferation after angioplasty[5–9].

Mechanical stimuli, such as the force exerted by blood pressure on the vessel wall, may evoke various signal transductions (i.e. calcium/natrium ion channels, renin–angiotensin systems, integrins) in vascular smooth muscle cells and to stimulate extracellular matrix formation[10,11]. Accordingly, tensile stress, together with shear stress, may contribute to atherosclerosis[12,13]. The clinical confirmation of these hypotheses requires laborious and sophisticated methodology[14] and has yet to be investigated. Furthermore, whether these biophysical factors still influence neointimal formation after balloon injury when coronary vessels are treated with

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intracoronary radiation, a therapy suggested to inhibit neointimal formation in a dose-dependent manner[15,16], remains to be determined.

We endeavoured to investigate the influence of tensile stress on plaque growth after balloon angioplasty in a population treated with beta-radiation therapy using 3-D intravascular ultrasound volumetric analysis.

Method

Population

Thirty-one consecutive patients successfully treated with balloon angioplasty were enrolled in this study. Eighteen patients underwent catheter-based intracoronary beta-radiation therapy using the Beta-Cath System™ (Novoste Corp), 13 patients (the control group) were treated with conventional balloon angioplasty without radiation during the same period. The irradiated patients were randomly assigned to three different prescribed doses (12, 14 and 16 Gy) 2 mm from the axis of the source. The radiation source train consists of a series of 12 independent 2·5 mm long cylindrical seeds, which contain the radioisotope $^{90}Sr/^{90}Y$ sources, and are bordered by two gold radioopaque markers, distal and proximal, separated by 30 mm.

Inclusion criteria were age 18 to 80 years; evidence of ischaemia; reference diameter of 2·5 to 3·5 mm; lesion length <20 mm; single vessel disease; de novo lesion. Patients treated with any other percutaneous device (i.e. cutting balloon, directional coronary atherectomy, rotational atherectomy, laser ablation, or stents) or those taking any specific medication under investigation were not included. Only patients with scheduled or completed 6-month angiographic and intravascular ultrasound follow-up were included in the analysis.

Intravascular ultrasound image acquisition

The coronary segment subject to 3-D reconstruction was examined with a mechanical intravascular ultrasound system (CVIS, Boston Scientific Corporation, Maple Grove, MN, U.S.A.) with a sheath-based intravascular ultrasound catheter, incorporating a 30 MHz single-element transducer rotating at 1800 rpm. ECG-gated image acquisition and digitization was performed by a workstation designed for the 3-D reconstruction of echocardiographic images (EchoScan, Tomtec, Munich, Germany). A description of this system has been reported in detail elsewhere[17–19]. In brief, the steering logic of the workstation was heart rate variability and acquired images from cycles meeting a pre-determined range of periods and coinciding with the peak of the R wave.

The methodology to define the segment of interest to be analysed has also been described previously[8,22,23]. An angiogram was performed with contrast injection after positioning the radiation delivery catheter and a deflated balloon at the site of the procedure. By the use of the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands), each angiographic sequence showing the radiation delivery catheter or the deflated balloon during contrast injection were displayed on the screen with simultaneous ECG tracing. By selecting frames at the same part of the cardiac cycle, we were able to define the location of the radiation source train, balloon inflations and their relationship with anatomical landmarks. Typically, the aorto-ostial junction and/or side-branches were used as landmarks. The anatomical landmark closest to either of the balloon markers was used as a reference point. During the subsequent intravascular ultrasound imaging, this reference point was recognized and used for selecting the area of interest: a 30 mm long segment irradiated by the radioactive source train or the balloon injured segment. At follow-up, correct matching of the region of interest was assured by both the use of the same intravascular ultrasound motorized pull-back system and comparison of longitudinal image reconstruction with that post-procedure. In the radiation group, a 26 mm segment was selected by excluding both 2 mm ends of the 30 mm whole segments between the two gold markers; this radiation source had undergone an acute dose fall-off. In the control group, segments up to 26 mm long were selected in the same manner and treated by balloon.

Intravascular ultrasound quantitative analysis

A Microsoft Windows™-based contour detection program, developed at the Thoraxcenter, was used for off-line volumetric quantification[20]. Briefly, this program constructed longitudinal sections from the data set and identified the contours corresponding to the lumen and media boundaries. Volumetric data were calculated by the formula: $V=\Sigma^{n}_{i=1} A_i * H$, where V=volume, A=area of external elastic membrane, lumen, or plaque in a given cross-sectional ultrasound image, H=thickness of the coronary artery slice reported in this digitized cross-section, and n=the number of digitized cross-sectional images encompassing the volume to be measured. Checking and editing of the contours of the planar images were performed by two independent experienced analysts. Intra-observer variability assessed by analysing intravascular ultrasound volumetric studies at least 3 months apart has been reported: $-0{\cdot}4 \pm 1{\cdot}1\%$ in lumen volume, $-0{\cdot}4 \pm 0{\cdot}6\%$ in external elastic membrane volume and $-0{\cdot}3 \pm 1{\cdot}0\%$ in plaque volumes using motorized ECG-gated pullback[19]. The application of this system has been reported in clinical studies[8,9,21,22].

Coronary segments were divided into 2 mm long subsegments (each of them presenting 10 cross-sections — 0·2 mm/slice)[9]. The independence of each subsegment is assured by the use of an ECG-gated pullback device (0·2 mm/step)[18,24].

Lumen, plaque and total vessel (external elastic membrane) volumes were quantified in each subsegment. Change (deltas) in plaque volume was calculated as follow-up minus post-procedure plaque volume.

Intravascular ultrasound qualitative analysis

All individual cross-sections were analysed qualitatively by two independent investigators blinded to the volumetric results. Thus, the type of plaque was defined in every cross-section, as intimal thickening, soft, fibrous, mixed (soft–fibrous, soft–calcific and fibrous–calcific) and diffuse calcified as proposed by Di Mario *et al.*[25]. Each subsegment was categorized as normal (<0·3 mm intimal thickening), soft, hard (fibrous and mixed) or diffuse calcified, when at least 80% of the cross-sections within the subsegments were of the same type, as described previously[9]. In those cross-sections, which contained a calcium arc up to 90°, the contour of the external elastic membrane was interpolated from the contours of the slice immediately proximal and distal to the cross-section in question. Subsegments with side-branches involving >90° of the circumferential arc in more than 50% of the cross-sections or those categorized as diffuse calcified were excluded from the quantitative analysis. Dissection was defined as a tear parallel to the vessel wall in the intravascular ultrasound images[25]; a plaque-free vessel wall was characterized by local wall thickness <0·5 mm[26] occupying <180° of the cross-section. These qualitative data should also meet the 80% criteria which characterize a subsegment.

Tensile stress

Tensile stress was calculated from the law of Laplace: TS=P * r/d, where P was the distending pressure (mean blood pressure), r the lumen radius and d the wall thickness as described previously[27]. Blood pressure was obtained from the arterial line after the introduction of the sheath and before administration of any vasodilating agent. Lumen radius was automatically calculated from cross-sectional areas[21] using the formula, $\text{radius}_{\text{mean}}=\sqrt{area/\pi}$ in each cross-section, assuming a circular model. Mean wall thickness was calculated from the difference in the local radius between the total vessel and the lumen.

Dose calculation

The actual dose received by each subsegment of the target vessel was calculated by means of dose–volume histograms[28]. This method is based on volumetric quantitative three-dimensional intravascular ultrasound. The distances between the centre of the catheter and both the lumen–intima and media–adventitia interfaces were calculated in 24 pie-slices (15°) in all cross-sections corresponding to the irradiated area (30 mm length of the source train). The prescribed dose and the accurate geometric data obtained from three-dimensional intravascular ultrasound with ECG-gated motorized pullback, enabled the cumulative curve of the dose–volume histogram for a pre-defined volume (i.e. adventitia) to be obtained. From this curve, the minimum dose received by 90% of the adventitia volume (DV_{90}Adv) was calculated. The methodology and feasibility of this dosimetry approach to vascular brachytherapy has been reported previously[29].

In order to investigate the influence of radiation dose on plaque growth and its interaction with tensile stress, we categorized irradiated subsegments into a low dose group (DV_{90}Adv <6 Gy) and an effective dose group (DV_{90}Adv ≥6 Gy). This cut-off point was based on previous observations from our group and others[9,30], that have shown that plaque growth was inhibited when at least 6–8 Gy was delivered at the adventitia.

Table 1 Baseline characteristics. Values were non-significant

Variable	Radiation group (n=18)	Control group (n=13)
Age, years	57·3 ± 9·9	59·7 ± 8·7
Gender, male	14 (78%)	13 (100%)
Hypertension	8 (44%)	4 (31%)
Diabetes	2 (11%)	2 (15%)
Dyslipidaemia	11 (61%)	7 (54%)
Family history	9 (50%)	7 (54%)
Smoking history	12 (67%)	8 (62%)
Previous MI	1 (6%)	5 (39%)
Angina status, CCS 3/4	10 (56%)	10 (77%)
Target lesion site		
LAD	8 (44%)	5 (48%)
RCA	4 (22%)	4 (31%)
LCX	6 (33%)	4 (31%)

MI=myocardial infarction; CCS=Canadian Cardiovascular Society angina class; LAD=left anterior descending coronary artery; RCA=right coronary artery; LCX=left circumflex coronary artery.

Table 2 Intravascular ultrasound quantitative and qualitative data

Variables	Radiation group	Control group	*P* value
No. of subsegments	184	111	
Baseline TVV (mm^3)	32·0 ± 9·1	30·3 ± 11·9	ns
Baseline PV (mm^3)	15·0 ± 6·1	14·1 ± 6·3	ns
Plaque morphology			
Intimal thickening	22 (12%)	26 (23%)	
Soft	49 (27%)	39 (35%)	0·002
Hard	113 (61%)	46 (41%)	
Dissection	55 (29%)	35 (32%)	ns
Plaque-free wall site	121 (66%)	58 (52%)	0·027
DV_{90}adv	5·37 ± 2·48	0	

TVV=total vessel volume; PV=plaque volume; DV_{90}adv=the minimum dose received by 90% of the adventitia volume.

Table 3 Comparison of variables among low dose, effective dose and control groups

Variables	Effective dose	Low dose	Control	*P* value
No. of subsegments	74	110	111	
Baseline				
radius (mm)	1·37 ± 0·4	1·76 ± 0·7	1·55 ± 0·8	0·001
wall thickness (mm)	1·27 ± 0·5	1·25 ± 0·4	1·20 ± 0·5	ns
mean pressure (mmHg)	97·2 ± 17·7	100·2 ± 14·2	92·6 ± 15·2	0·002
Tensile stress (kN/m^2)				
Baseline	18·3 ± 13·4	24·3 ± 18·0	20·3 ± 11·7	0·011
Follow-up	18·4 ± 10·1	17·9 ± 10·9	18·0 ± 10·6	ns

Statistical analysis

Data are presented as mean ± SD. Differences in quantitative intravascular ultrasound data among three groups (non-irradiated, low-dose, effective dose) were assessed by one-way analysis of variance (ANOVA). Comparisons between two groups were performed by the use of unpaired Student's t-test. Univariate and multivariate linear regression analyses were performed to determine the relationship between tensile stress and plaque growth and to examine the influence of other local factors; intravascular ultrasound-derived (types of tissue, presence of dissection and plaque-free wall site, and total vessel volume post-treatment) and dosimetric variables (DV_{90}Adv). Tensile stress was expressed as a logarithm in order to be ranged properly. All tests except the post-hoc test were two-tailed and a *P* value <0·05 was considered statistically significant. The Bonferroni correction was applied for comparison between each group when three groups were compared.

Results

Baseline characteristics

Two hundred and thirty four subsegments were defined in 18 patients in the radiation group and 130 subsegments were analysed in 13 patients in the control group. Fifty subsegments in the radiation group and 19 subsegments in the control group were excluded from the final analysis due to either ostial location (n=8), diffuse calcified plaque which precluded the quantification of the total vessel volume (n=30) or side branches involving >90° of the circumferential arc in more than 50% of the cross-sections (n=31). Therefore, 184 irradiated subsegments and 111 control subsegments were the subject of the study. Baseline characteristics are demonstrated in Table 1. There was no difference between the groups.

Intravascular ultrasound data — volumetric analysis and qualitative data

Baseline intravascular ultrasound data are presented in Tables 2 and 3. Irradiated subsegments have harder plaque and a higher incidence of plaque-free wall sites (Table 2). When the irradiated group is divided into two, those receiving the low-dose and those receiving the effective dose, low-dose subsegments have a higher radius and arterial pressure than effective dose and non-irradiated subsegments. Therefore subsegments receiving low-dose radiation have higher tensile stress at baseline (Table 3).

Plaque increased in both the irradiated and non-irradiated groups (3·1 ± 6·4 mm^3 vs 1·9 ± 4·3 mm^3, *P*=ns, respectively). However, subsegments receiving <6 Gy (n=110) at the adventitia had a significantly higher plaque increase compared to effective dose (≥6 Gy, n=74) and non-irradiated subsegments (n=111) (Fig. 1).

Influence of tensile stress on plaque growth

An example of subsegment analysis with intravascular ultrasound parameters and tensile stress is demonstrated in Fig. 2. In both the radiation and control groups, changes in PV were positively correlated with tensile stress as shown in Fig. 3. When dividing the irradiated group into low and effective doses, a similar correlation between tensile stress and plaque increase was observed in the subsegments receiving a low dose of radiation, but

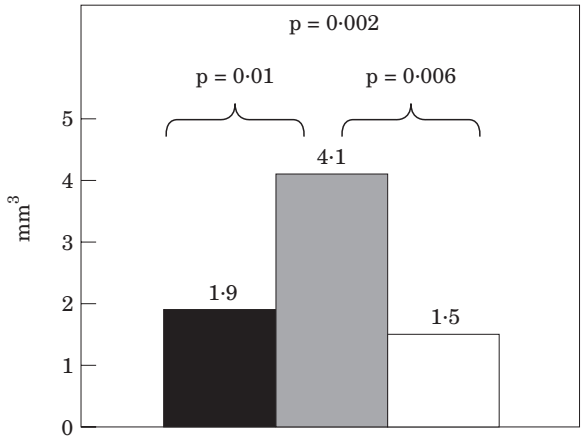

Figure 1 **Changes in plaque volume among non-irradiated (■, n=111), low-dose (▨, <6 Gy, n=110) and effective-dose (□, ≥6 Gy, n=74) subsegments.**

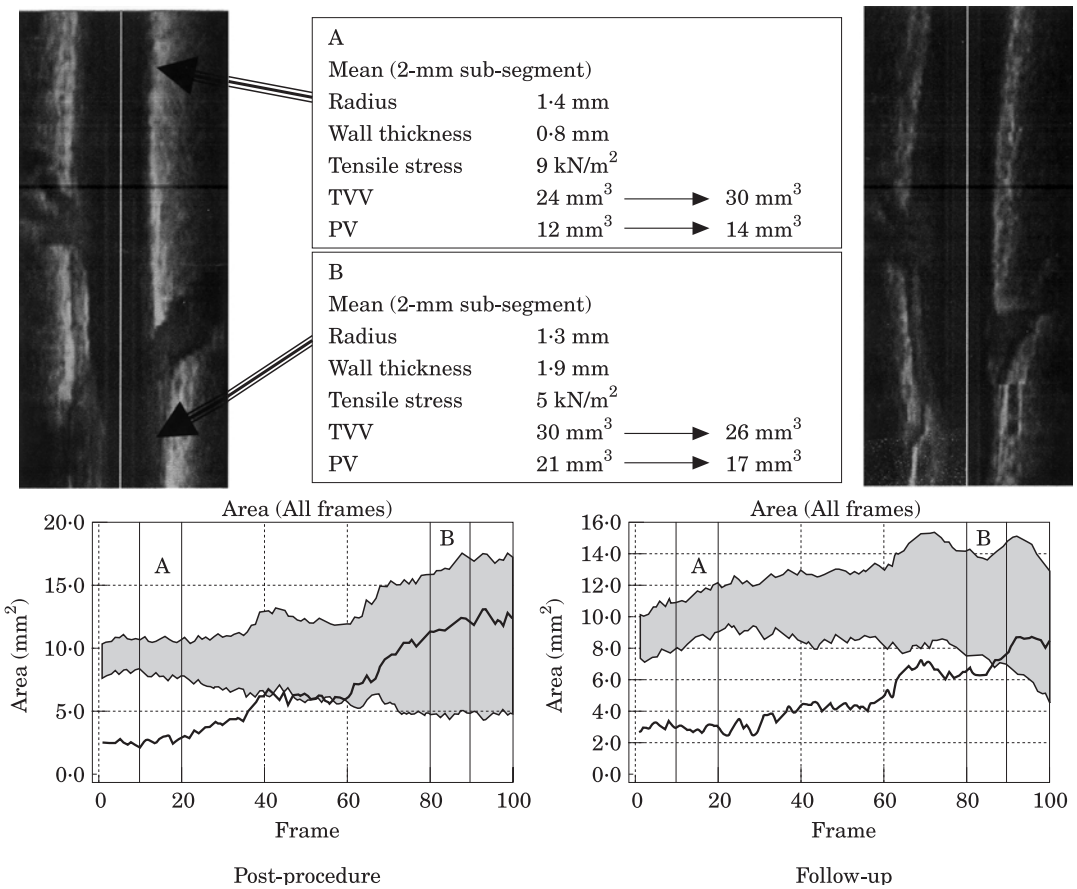

Figure 2 **An example of the results by 3-D longitudinal reconstruction of intravascular ultrasound cross-sectional images using ECG-gated pullback. Upper outside panels: Longitudinal images post-procedure (left) and follow-up (right). Upper inside panels: Parameters used in the present study (A and B). TVV = total vessel volume; PV = plaque volume. Lower panels: Charts display the subsequent volumetric quantification at post-procedure (left) and follow-up (right). The area values of the lumen (lower line) and total vessel (upper line) form the boundaries of the grey zone, which represent the plaque–media complex, and a single line depicts the absolute area value of plaque–media complex. The zones between 2 lines (A and B) correspond to the data shown in the upper inside panels.**

not in the effective dose group (Fig. 4). Although tensile stress values at baseline were different among three groups (low dose, effective dose and control), tensile stress decreased to similar values at follow-up (Table 3).

Predictors of plaque growth

Results of univariate and multivariate linear regression are shown in Table 4. Tensile stress was the only predictor of plaque growth in non-irradiated coronary subsegments in the multivariate model. However, in the irradiated group DV_{90}Adv, and plaque morphology were stronger independent predictors of plaque increase than tensile stress.

Discussion

This study demonstrates for the first time that local plaque growth is related to tensile stress after balloon angioplasty. Tensile stress was positively correlated with an increase in plaque volume in subsegments receiving low or no doses of radiation. Further, this biophysical parameter was the only independent predictor of plaque increase in the non-irradiated subsegments. However, the influence of tensile stress on plaque formation was blunted by the effective dose of radiation (Fig. 4).

Under physiological conditions and in experimental atherosclerosis, local tensile stress, which is dependent on lumen radius and wall thickness, has been suggested to stimulate atherosclerotic plaque formation[12,13,31,32]. The results of the present investigation suggest that tensile stress represents an adaptive factor in the restoration of wall stress by stimulating plaque growth[12,13,33] after balloon angioplasty, when plaque is disrupted and the balance between lumen size and wall size is lost. This hypothesis may be supported by previous experimental observations showing that: (1) tensile forces induce signal transduction in smooth muscle cells[10], although the mechanoreceptor is still unknown; (2) mechanical strain promotes smooth muscle cell growth, when these

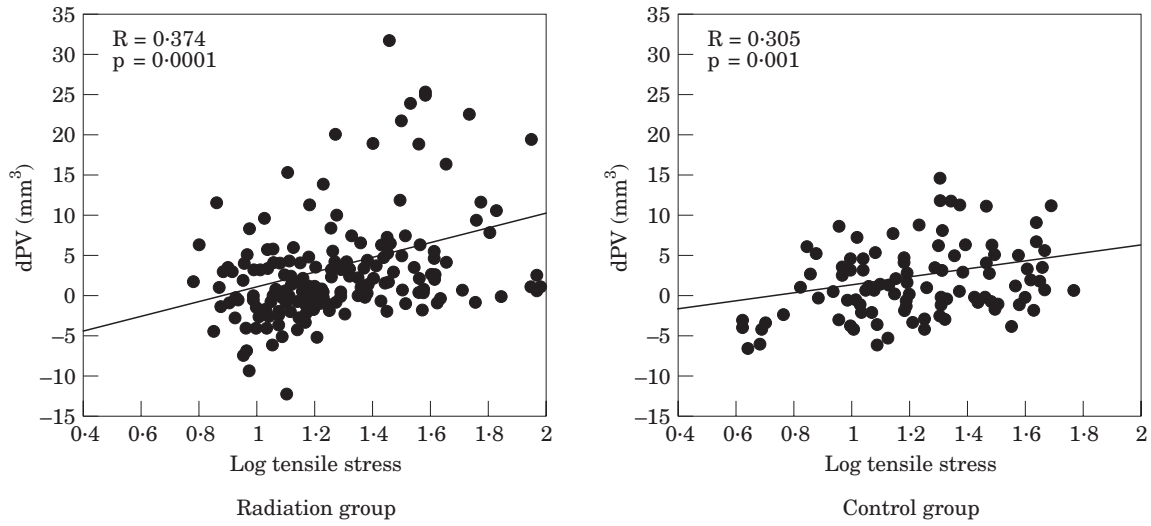

Figure 3 **Correlation between the change in plaque volume and tensile stress in all the subsegments. dPV=change in plaque volume. Tensile stress is expressed as a logarithm. Left: Correlation in all the irradiated subsegments (radiation group, n=184). Right: Correlation in the non-irradiated subsegments (control group, n=111).**

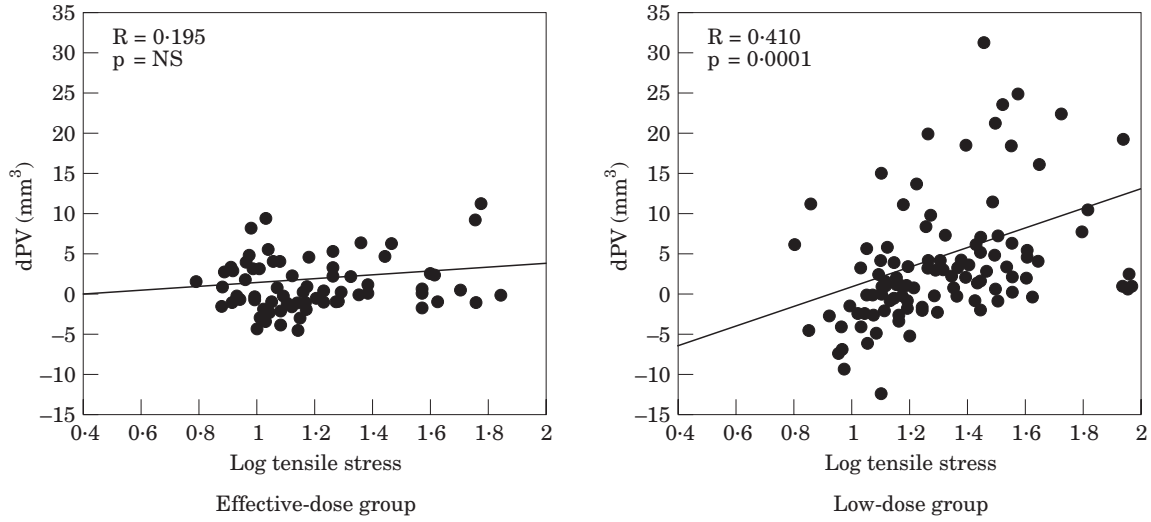

Figure 4 **Correlation between the change in plaque volume and tensile stress in the irradiated subsegments. dPV=change in plaque volume. Tensile stress is expressed as a logarithm. Left: Correlation in the effective-dose (≥6 Gy) subsegments (n=74). Right: Correlation in the low-dose (<6 Gy) subsegments (n=110).**

cells are in the proliferative phenotype (i.e. after balloon injury)[11,34]; (3) wall tension may stimulate mRNA expression of matrix metalloproteinase in human coronary arteries[35,36].

Another observation of the present study was that the influence of tensile stress on plaque volume change was abolished in subsegments receiving effective doses (Dv90 ≥6 Gy) of radiation. Radiation inhibits formation of myofibroblast scar surrounding the injury site and elicits changes in intracellular molecules; DNA is considered the critical target damaged by ionizing radiation by both direct and indirect processes. These molecular changes ultimately prevent negative vascular remodelling and plaque formation in the clinical context[37]. In the multivariate model, one may observe that tensile stress, although still an important predictor of plaque proliferation, lost its power in the irradiated group. It should be taken into account that more than half of the subsegments (n=110) received lower than the effective dose of radiation and that tensile stress was not a predictor of plaque increase when only effectively irradiated subsegments were considered. These findings may be explained by the potential modification of the arterial wall mechanoreceptors responses by radiation. This speculative explanation requires further investigation.

Table 4 Univariate and multivariate analysis for the predictors of plaque growth

Variables	Radiation group				Control group			
	Univariate *P*	Multivariate			Univariate *P*	Multivariate		
		Beta	*P*	95% CI		Beta	*P*	95% CI
Constant		7·43	ns	4·38/10·49		0·05	ns	− 1·51/1·61
Plaque hard	0·0001	− 3·62	0·0001	− 5·46/ − 1·78	ns		ns	
Dissection	0·0001		ns		ns		ns	
Thin wall site	ns				ns			
Total vessel volume	ns				ns			
Tensile stress	0·0001	0·06	0·038	0·003/0·115	0·007	0·09	0·007	0·03/0·16
DV_{90}adv	0·0001	− 0·64	0·0001	− 0·98/ − 0·29	N/A			

The type of plaque characterized by intravascular ultrasound was also negatively correlated with increase in plaque volume (Table 4). Tissue characterization by intravascular ultrasound, as defined in the present study, has been shown to have a high histopathological correlation[38,39]. The diminished lipid contents and lower cellularity characteristics of mature plaques (fibrous or calcified lesions) may explain the diminished proliferative response of hard plaques as characterized by intravascular ultrasound[40].

The findings that subsegments receiving <6 Gy had a higher plaque increase than non-irradiated subsegments are in accordance with recent clinical and experimental reports showing the somewhat paradoxical induction of plaque formation by low-dose radiation[23,41,42]. The higher value of baseline tensile stress in the low-dose subsegments may in itself have impacted on the higher plaque growth. However, it is nevertheless important to note that the dose of radiation was the strongest inhibitory factor of plaque growth (Table 4), which may highlight that radiation inhibits plaque proliferation in a dose-dependent manner[15,16].

Limitations

In the present study, coronary pressure was not obtained by intra-coronary sensor tip wire, but by measuring the aortic pressure through a sheath. Coronary pressure used in the present study may be inaccurate where residual pressure gradient induced by non-significant stenosis exists either proximal to the lesion or in the lesion. Also tensile stress calculation is based on the assumption that the lumen is circular. Further investigation using a finite element model and coronary pressure guide wire will be necessary to confirm the concept.

The contribution of tensile stress to the total plaque growth may be small (approximately 10%). Since restenosis is a multi-factorial process that has not been fully elucidated yet, other local factors (i.e. shear stress and inflammatory markers) may also have considerable impacts in the mechanism of restenosis.

Conclusions

The results of this study suggest that local plaque growth is related to tensile stress after balloon angioplasty. Intracoronary brachytherapy may alter this biophysical process on plaque growth when the prescribed dose is effectively delivered.

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