

Release of endothelin-1 from human endocardium after radiofrequency catheter ablation and coronary angioplasty: comparative results

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Abstract

Background: Plasma levels of endothelin-1 (ET-1) increase after coronary angioplasty (PTCA) due to endothelial injury during the procedure. ET-1 has been found in human endocardial and myocardial cells. It is not known whether ET-1 increases after thermal injury induced by radiofrequency catheter ablation (RFA).

Methods: We determined plasma ET-1 levels at baseline, immediately after, and at 2 and 6 h post-procedure in 31 patients undergoing PTCA and 16 patients undergoing RFA. Patients subjected to diagnostic coronary angiography ($n=15$) or electrophysiology study ($n=13$) served as controls.

Results: Compared to baseline, ET-1 levels increased significantly immediately post-PTCA (55.1 ± 20.1 vs. 42.7 ± 14.9 pg/ml, $p < 0.01$) and at 2 h post-RFA (98.0 ± 11.7 vs. 53.0 ± 17.4 pg/ml, $p < 0.01$) and returned to baseline measurements at 2 h post-PTCA and 6 h post-RFA. There was no change of ET-1 levels in the control groups. ET-1 kinetics curve was significantly higher post-RFA compared to post-PTCA ($p < 0.001$). ET-1 immediately post-PTCA correlated with total pressure–time product applied for balloon inflation during the procedure ($r = 0.56$, $p < 0.01$). There was no correlation between ET-1 levels and the number of RFA applications. No patient developed ischemia post-PTCA. There were no complications or arrhythmia recurrences post-RFA.

Conclusion: Endocardial thermal injury incurred during RFA is another mechanism of endothelin increase apart from mechanical injury of the coronary endothelium during PTCA and represents further evidence for the existence of the peptide in human endocardial endothelial and myocardial cells. ET-1 increase is delayed and more pronounced post-RFA compared to post-PTCA. Despite that, it does not seem to have any clinical impact in the immediate post-RFA period.

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1. Introduction

Endothelins constitute a family of four peptides with a wide spectrum of paracrine regulatory functions [1,2]. Initially, endothelins 1, 2, and 3 were isolated [3], and lately endothelin 4 (vasoactive intestinal contracting peptide) [4]. Endothelins are produced by a variety of tissues where they act locally as modulators of the vascular tone,

cellular proliferation, and other hormone production. Perhaps the most important action is regulation of vascular physiology and participation in the pathophysiology of vascular disease [1,2]. Endothelin-1 (ET-1) is the predominant peptide in the cardiovascular system. It has potent vasoconstrictor actions and is mainly produced by vascular endothelial cells [1,2]. In vitro studies have shown that among other stimuli, various physical factors acting on vascular endothelium, like shear stress [5,6], mechanical stretching [7], or mechanical pressure [8,9], modify ET-1 gene expression and also lead to ET-1 secretion from endothelial cells. The corresponding clinical model is

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percutaneous transluminal coronary angioplasty (PTCA), during which ET-1 has been shown to increase, and this has been attributed to mechanical trauma of the coronary endothelial cells [10–22]. Most studies to date have examined the effect of single-vessel, single-lesion PTCA on ET-1 plasma levels. It is not known whether PTCA of more than one lesion and/or vessel is associated with higher ET-1 plasma levels.

Radiofrequency catheter ablation (RFA) constitutes a very efficient and safe procedure for treating a variety of tachyarrhythmias, both supraventricular and ventricular in origin [23–32]. However, RFA induces thermal injury of the endocardium and underlying myocardium with resultant increase in CK-MB and cardiac troponin activity [33–36]. ET-1 has been found in human endocardial endothelial and myocardial cells [37]. Also, ET-1 may possess direct arrhythmogenic actions [38]. It is not known whether thermal injury during RFA could induce ET-1 formation and/or release from the heart, and if this could be related to arrhythmic events in the immediate post-RFA period.

2. Patients and methods

2.1. Patients

We determined peripheral vein plasma ET-1 levels in 31 consecutive patients undergoing PTCA for stable coronary artery disease and 16 patients undergoing RFA for various cardiac arrhythmias. Fifteen patients subjected to diagnostic coronary angiography and 13 patients subjected to diagnostic electrophysiology study (EPS) served as controls. Patients with acute or recent myocardial infarction or unstable angina were excluded. All patients subjected to PTCA or RFA were hospitalized for at least 24 h in the coronary care unit of our hospital.

2.2. Measurements of endothelin

Blood samples were collected before each procedure (baseline), immediately after coronary angiography and PTCA, 30 min after the last RFA energy application or 30 min after EPS, and at 2 and 6 h post-procedure. Syringes and EDTA tubes for blood sample collection and storage were pre-frozen at $-24\text{ }^{\circ}\text{C}$. Blood was collected in all patients from the left antecubital veins after arm constriction was released for about 1 min. The EDTA tubes were centrifuged and the plasma extracted was stored at $-70\text{ }^{\circ}\text{C}$ until assayed. Endothelin plasma levels were determined using Amersham's RPA 555 RIA kit after extraction from C2 Amprep columns RPN 1913 [39]. The measurement of ET-1 was based on the competition between unlabelled ET-1 and a fixed quantity of ^{125}I -labelled ET-3 for a limited number of binding sites on an ET-1-specific antibody. The above antibody has a 100% cross-reactivity with ET-1, 144% with ET-2, 52% with ET-3, and 0.4% with big ET-1.

A sample of known ET-1 content was measured in triplicate. The average recovery was $65\pm 5\%$. All measurements for ET-1 were adjusted to 100%. It should be clarified that the measurements of ET-1 obtained in this study are contingent upon the specific method employed and the specific groups studied, all having undergone vessel puncture and catheter insertion before blood samples were collected. The hospital's local ethics committee approved the study, and all patients gave informed written consent for blood sampling.

2.3. Statistics

Values of ET-1 are presented as mean \pm standard deviation (SD). One-way analysis of variance (ANOVA) was used for comparison of ET-1 plasma levels among the four patient groups at baseline. Repetitive measures ANOVA was used for comparison of ET-1 levels within the same group of patients at different time points (baseline, immediately post-procedure and 2 and 6 h post-procedure). Bonferroni correction was applied for post hoc comparisons. A doubly multivariate repeated-measures analysis of variance (ANOVA) model was employed for comparison of ET-1 kinetics curves among different patient groups. Statistical significance for type-I error was set at $p\leq 0.05$. Time was considered as the within-subjects factor and type of procedure as the between-subjects factor. Spearman's correlation was used to explore relationship between ET-1 plasma levels and various parameters of PTCA and RFA. All analyses were carried out with the statistical package SPSS for Windows, Version-10 (Chicago, IL).

3. Results

Sixteen patients, 9 men and 7 women, aged 49.5 ± 16.1 years, were subjected to RFA for various arrhythmias. These included atrioventricular tachycardia with conduction over an accessory pathway in seven patients, atrioventricular nodal reentry tachycardia in six patients, right ventricular outflow tract tachycardia in two patients, and atrial flutter in one patient. Radiofrequency energy (30–50 W) was applied for 30 s each time. The mean number of RF applications was 12 ± 8 (range 2–30).

Thirty-one patients, 28 men and 3 women, aged 55.6 ± 8.7 years, were subjected to PTCA for symptomatic coronary artery disease. Twenty-four patients had one-vessel disease; 1 lesion was dilated in 19 patients and 2 lesions in 5 patients. Seven patients had two-vessel disease and one lesion in each vessel was dilated. The total number of lesions dilated were 43. Six patients were subjected to plain old balloon angioplasty alone, all of them for one-vessel disease; two patients had two lesions dilated. The remaining patients were subjected to balloon angioplasty and stenting. A total of 25 stents were used; 19 patients received 1 stent, 5 patients 2 stents, and 1 patient 3 stents.

Table 1

Changes of plasma endothelin-1 (ET-1) levels observed during procedures of radiofrequency catheter ablation (RFA), coronary angioplasty (PTCA), electrophysiology studies (EPS), and coronary angiography (CATH)

	ET-1 plasma levels (pg/ml)			
	RFA (N=13)	PTCA (N=31)	EPS (N=13)	CATH (N=15)
Baseline	53.0±17.4	42.7±14.9	48.1±20.7	43.8±5.1
Post-procedure	66.2±19.6	55.1±20.1	47.3±20.6	46.0±9.5
Two hours	98.0±15.6*	51.6±23.4*	52.0±24.7*	43.5±10.4*
Six hours	66.1±25.4	43.9±18.4	47.3±15.2	41.3±5.7
ANOVA <i>p</i>	<i>p</i> <0.01	<i>p</i> <0.01	<i>p</i> =0.7	<i>p</i> =0.3

* (*p*<0.01).

Peripheral plasma ET-1 levels for each group of patients at the four time points are presented in Table 1. Baseline plasma ET-1 levels did not differ among the four groups of patients (ANOVA, *p*=0.16). There was no change in plasma ET-1 levels in patients subjected to EPS or coronary angiography (ANOVA *p*=0.7 and *p*=0.3, respectively). There was a significant rise in plasma ET-1 levels in patients subjected to RFA or PTCA (both ANOVA, *p*<0.01). ET-1 was significantly higher than baseline immediately after PTCA (55.1±20.1 vs. 42.7±14.9 pg/ml, Bonferroni *p*<0.01) and returned to baseline levels at 2 h (51.6±23.4 vs. 42.7±14.9 pg/ml, *p*=NS). In patients subjected to RFA, post-procedure ET-1 levels did not differ from baseline (66.2±19.6 vs. 53.0±17.4 pg/ml, *p*=NS). However, ET-1 levels determined at 2 h after RFA were significantly higher compared to baseline (98.0±15.6 vs. 53.0±17.4 pg/ml and 98.0±15.6 vs. 66.2±19.6 pg/ml, respectively, both Bonferroni *p*<0.01). ET-1 levels decreased significantly at 6 h after ablation compared to the 2-h post-procedure levels and were

similar to baseline levels (66.1±25.4 vs. 53.0±17.4 pg/ml, *p*=NS).

Doubly multivariate repetitive measures ANOVA showed that the between-subjects effect (type of procedure) was significant at *a*=0.05 (*p*<0.01). Bonferroni post hoc correction showed that the RFA ET-1 kinetics curve differed significantly from PTCA, EPS, and coronary angiography curve (all *p*<0.01); however, the PTCA ET-1 kinetics curve did not differ from that of EPS and coronary angiography (Fig. 1).

ET-1 levels post-PTCA did not differ between patients subjected to balloon PTCA (*N*=6), compared to the patients (*N*=25) who received stents (46±15.8 vs. 57.3±20.7 pg/ml, *p*=0.1). The number of lesions dilated did not differ between those two groups (1.3±0.5 vs. 1.4±0.5 lesions, respectively, *p*=0.8). Patients who received stents had significantly higher pressure–time product applied during balloon inflation and/or stent deployment compared to plain PTCA patients (1056.6±211.3 vs. 543.1±221.7 atm s, *p*<0.01).

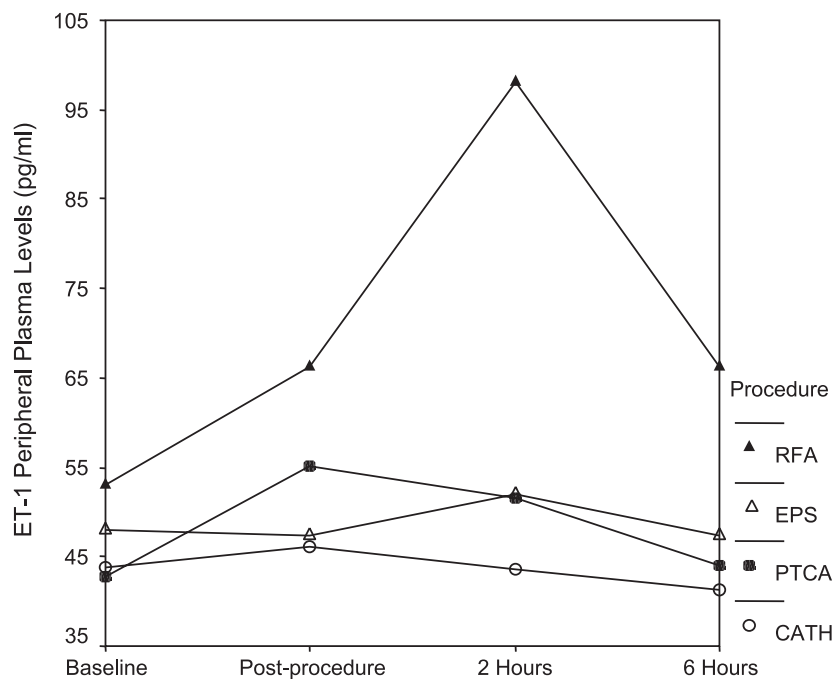


Fig. 1. The increase of ET-1 levels observed during RFA was significantly greater compared to the increase noted during PTCA. ET-1 increased significantly immediately post-PTCA and returned to baseline at 2 h, whereas it increased significantly at 2 h post-RFA and returned to baseline at 6 h. There was no change of ET-1 levels during EPS or during coronary angiography (CATH).

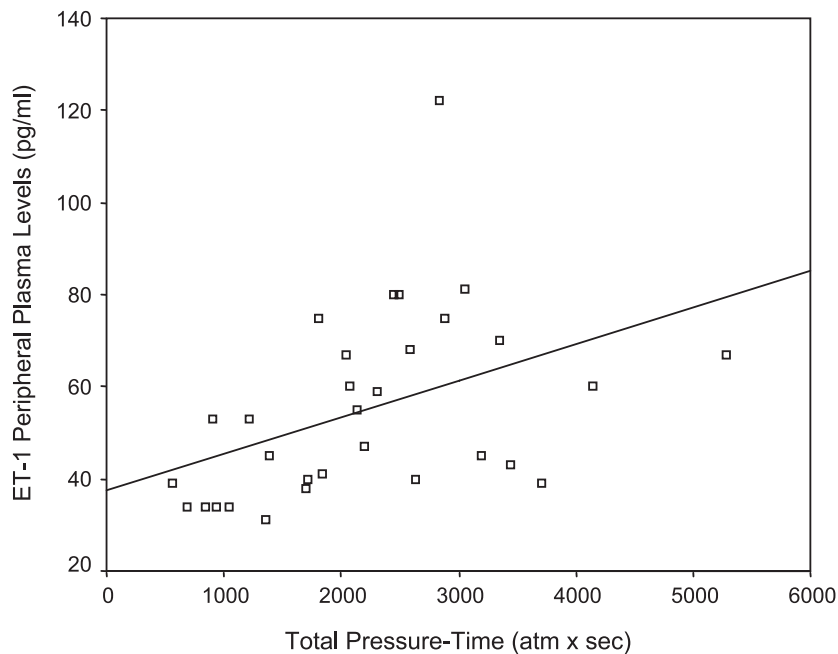


Fig. 2. Correlation of endothelin-1 (ET-1) levels with procedural parameters.

Patients with one lesion subjected to PTCA alone ($n=4$) had similar ET-1 levels post-PTCA with patients subjected to PTCA plus stenting ($n=15$) for one lesion (41.7 ± 8.0 vs. 47.4 ± 12.4 pg/ml, $p=0.3$). The latter were subjected to significantly higher pressure–time products compared to single-vessel PTCA patients (2465.6 ± 1056.6 vs. 1190.0 ± 543.1 atm s, $p=0.01$).

There was no correlation between plasma ET-1 levels at any time point and the number of radiofrequency applications, total energy used, or total time that energy was applied. ET-1 levels immediately post-PTCA correlated with the number of vessels and number of lesions dilated ($r=0.4$, $p=0.027$ and $r=0.56$, $p<0.01$, respectively), total time of balloon inflation for all lesions ($r=0.5$, $p<0.01$), and total pressure–time product ($r=0.56$, $p<0.01$) (Fig. 2).

There were no acute ischemic episodes, such as chest pain, ischemic ECG changes, or CK-MB elevation, in the immediate post-procedure period in any patient in the PTCA group. There were no adverse effects or arrhythmia recurrences in the immediate post-procedure period in any patient in the ablation group.

4. Discussion

This study confirms that plasma ET-1 levels increase slightly, but significantly, immediately post-PTCA and that this increase correlates with the number of lesions and/or vessels dilated, total balloon inflation time and total balloon inflation time \times pressure applied, pointing to the role of mechanical endothelial stress in this phenomenon. To our knowledge, this study also shows for the first time that RFA produces a significant, but more pronounced, albeit delayed

compared with PTCA, increase in plasma ET-1 levels. ET-1 levels do not change during EPS or coronary angiography.

4.1. ET-1 levels during PTCA

A number of studies have shown that ET-1 levels increase after PTCA either locally in the heart [10,14,16,19–21], and/or in the peripheral circulation [11–13,15,17,18,22]. Initial studies supported the idea that this was due to myocardial ischemia. Kyriakides et al. [13] suggested that release of ET-1 during PTCA was linked to myocardial ischemia rather than to mechanical artery injury as ET-1 and cGMP levels did not increase significantly after balloon angioplasty of totally occluded coronary arteries, but did significantly so, after balloon angioplasty of partially occluded arteries. However, the number of totally occluded arteries subjected to PTCA was small ($n=8$) [13]. Most other investigators tend to agree that the increase of ET-1 levels incurred during PTCA is due to endothelial injury rather than ischemia [14,18,21,40]. Franco-Cereceda et al. [14] showed that PTCA is associated with an increase of ET-1 levels in the coronary sinus of humans shortly after the procedure. However, noradrenaline and neuropeptide Y, which is released due to sympathetic activation during ischemia, did not increase after PTCA, implying that ET-1 increases as a result of mechanical injury of the endothelium. Kruger et al. [18] found increased ET-1 levels compared to baseline after PTCA in the coronary sinus and a peripheral vein. No patient developed myocardial ischemia, as detected by monitoring cardiac lactate metabolism and 12-lead electrocardiogram, or a myocardial infarction during the procedure. However, ET-1 levels increased significantly at 1 min after the intervention and

remained elevated for 3 h, with higher coronary sinus than peripheral venous concentrations and decreased gradually to normal values within 6 h. In a control group of patients who underwent diagnostic cardiac catheterization, all parameters remained unchanged, and this is in accord with our results. Similarly, Suzuki et al. [21] reported that plasma levels of ET-1 did not increase in the sinus of Valsalva and the great cardiac vein during right atrial pacing, whereas it increased significantly after PTCA, despite a significant decrease in oxygen saturation of the great cardiac vein during both procedures, further supporting the notion that ET-1 release is related to coronary arterial injury rather than myocardial ischemia.

In our study, ET-1 levels increased slightly, but significantly, immediately post-PTCA, returning to baseline levels at 2 h post-procedure. Avizohar et al. [17] found that 24 h after PTCA, plasma ET-1 levels in venous blood were directly related to the number of balloon inflations, total inflation time, and to the maximal inflation pressure. No such correlation was found in venous blood immediately after PTCA and plasma endothelin levels did not change significantly after balloon angioplasty [17]. However, Hasdai et al. [40], using an assay similar with ours for ET-1 plasma levels determination, showed an immediate doubling of ET-1 plasma levels in the coronary vessels after PTCA. The magnitude of mechanical stress to which the coronary endothelium was subjected in the above study was assessed by the sum of the product of maximal pressure during balloon inflation multiplied by the total inflation time for each coronary lesion. This index correlated with ET-1 levels post-PTCA. This is in accord with our findings. Furthermore, we found a correlation between total time of balloon inflation and ET-1 levels post-PTCA.

Hasdai et al. [40], using immunochemical methods, found intracellular and extracellular big ET-1 and ET-1 in atheromatous plaques isolated with directional atherectomy and suggested that mechanical endothelial trauma was the main mechanism of plasma ET-1 levels increase. In that study, the mean total balloon inflation time was 10 ± 2 min, which is considerably higher than that in the study by Kruger et al. (1.5 ± 0.5 min) [18], or our study (3.2 ± 1.4 min). It is not known whether ischemia might have played a role in ET-1 levels increase in the study by Hasdai et al. [Hasdai, 1997 #40]. However, in our study, the mean total inflation time was close to that of Kruger et al. [18], who did not implicate ischemia in this increase. Most studies on this topic included patients with one lesion in one coronary vessel. We included patients with one or more lesions in one or more coronary vessels to be able to assess any possible relationship between the number of lesions/vessels dilated and ET-1 levels and indeed such a relationship was confirmed. It appears that mechanical endothelial stress during PTCA is the main mechanism of ET-1 increase post-PTCA [40].

Despite abundant evidence that ET-1 levels increase after PTCA, only a few studies examined the effect of coronary

stenting on ET-1 plasma levels [19,20,22,41]. Hojo et al. did not find any difference in changes of plasma ET-1 levels among 11 patients subjected to balloon angioplasty, 14 patients subjected to percutaneous rotational atherectomy, and 19 patients subjected to stent implantation. Wainstein et al. [22], in a recent study, reported that coronary artery stenting was associated with increased plasma ET-1 levels in the arterial sheath plasma immediately after the procedure. Furthermore, this increase was not associated with the incidence of restenosis at 6 months, putting in dispute the theory that ET-1 released during the procedure might be responsible for restenosis [22]. In our study, ET-1 levels immediately post-PTCA were lower, but not significantly so, in patients who were subjected to plain balloon angioplasty compared to patients who received stents. Similarly, patients with one lesion subjected to angioplasty alone had similar ET-1 levels post-PTCA with patients subjected to angioplasty plus stenting. A significantly higher pressure–time product was the common denominator of patients who received stents compared to patients subjected to plain balloon angioplasty, as a result of further dilatations for stent deployment. Our results are in accord with the study by Hojo et al. [20], and suggest that coronary stenting per se is not an independent factor for ET-1 increase. However, it could theoretically lead to higher ET-1 release if more dilatations are needed for stent deployment. Failure to show higher ET-1 levels in patients who received stents in this study may be due to the small number of patients subjected to plain balloon angioplasty.

4.2. ET-1 levels during RFA

To our knowledge, this is the first study to report an increase of ET-1 levels in peripheral plasma after RFA. Radiofrequency ablation destroys myocardial tissue by delivering electrical energy via electrode catheters placed in contact with the endomyocardium. Resistive heating during ablation is produced by a relatively low voltage (40–70 V), delivered in a continuous unmodulated fashion. Catheter tip temperature usually exceeds 48–50 °C. Myocardial tissue is destroyed by heating; however, current density drops off rapidly as a function of distance from the electrode surface, and thus only a small shell of myocardium adjacent to the distal electrode is directly heated. The major portion of the lesion is produced by conduction of heat away from the electrode-tissue interface into the surrounding tissue. The myocardial injury induced by RFA can be assessed quantitatively by cardiac troponins [33–36] more accurately than with CK-MB.

Expression of ET-1 mRNA and its receptors ET(A) and ET(B) mRNAs have been found in human myocardial and endocardial endothelial cells from the right atrium and left ventricle [37]. It has similar biological activity with ET-1 derived from vascular endothelium [37]. The role of ET-1 produced by endocardial endothelial cells is not known; however, it could play a pivotal role in the regulation of myocardial contractility, or it could further act in other

peripheral target organs [37]. It has also been shown that ET-1 possesses direct arrhythmogenic action as intracoronary infusion of the peptide in anesthetized mongrel dogs can induce sustained ventricular tachycardia and ventricular fibrillation, which can be prevented by bolus injection of the selective endothelin-A-(ETA) receptor antagonist LU 135.252 [42].

In the present study, we showed a significant and sustained increase of ET-1 plasma levels after RFA. We consider this increase as further evidence of the existence of the peptide in human endocardial endothelium and myocardial cells. We presume that it represents the result of thermal injury and necrosis of endocardial and myocardial cells and/or a reaction of neighboring cells to injury. However, it does not seem to correlate with the number of lesions induced and in this regard it differs from classic markers of myocardial injury like troponins. Levels of troponin-I correlate with the number of lesions delivered during RFA [35,36]. However, this correlation is weak and this has been attributed to the fact that not all RFA applications may result in effective lesion formation [36]. This may be due to unstable electrode position, or interruption of RF application within 5–15 s if it is unsuccessful, or if a minimum temperature of 48–50 °C cannot be achieved within this time frame [36]. We speculate that similar mechanisms may be responsible for the lack of correlation between the number of RF applications and peripheral plasma ET-1 levels. Also, due to lack of consistent logging of peak temperature during the procedures, a correlation of greater ET-1 levels with higher achieved temperature cannot be established with accuracy. However, it is tempting to speculate that stimulated peptide synthesis by endocardial, myocardial, or intramyocardial vessel endothelial cells injured during the procedure may also contribute to the observed increase in ET-1 levels after RFA. This could result in an increase not related to the actual magnitude of the damage incurred by RFA. Indeed, ET-1 increase post-RFA is significantly higher than that observed during mechanical trauma of the coronary endothelium during PTCA and peaks at 2 h post-RFA, rather than immediately post-procedure. Therefore, this delayed increase of plasma ET-1 levels 2 h post-ablation may be the result of increased biosynthesis of the peptide from injured but not destroyed endocardial/myocardial cells, rather than the result of immediate release from necrotic tissue.

Peak cardiac troponin I levels correlate with the site of RFA [36]. Lesions created in the ventricular myocardium, albeit numerically fewer, apparently entailed more extensive myocardial injury as reflected by the higher troponin levels when compared with those measured during RF application in the atrial myocardium or in the annuli [36]. This could not be verified for plasma ET-1 levels in our study due to the small number of patients subjected to RFA for ventricular ($n=2$) or atrial ($n=1$) arrhythmias.

The clinical significance of this increase in ET-1 during RFA is unknown, but seems to have no adverse effects at least in the immediate post-procedure period. Further studies

are needed to unravel the pathophysiological mechanism and possible biological role of this phenomenon.

5. Study limitations

The purpose of the study was to explore ET-1 release kinetics from human endocardium during RFA and to compare that with mechanical injury induced on coronary endothelium during PTCA. In this context, the number of patients subjected to plain balloon angioplasty was small and this does not allow definite conclusions to be drawn regarding possible differences between plain balloon angioplasty and stenting in the ET-1 release.

6. Conclusion

Peripheral ET-1 plasma levels increase both after PTCA and RFA compared to baseline values, whereas there is no change after coronary angiography or EPS. Increased ET-1 during PTCA relates to the number of vessels and lesions dilated, total balloon inflation time, and total balloon inflation pressure–time product, implying a role for endothelial mechanical injury in this phenomenon. This increase is small and short lived after PTCA, whereas it is more pronounced and has a later peak after RFA. Apart from mechanical injury of the coronary endothelium during PTCA, thermal injury of the heart during RFA is another mechanism of endothelin increase in peripheral plasma and may represent the reaction to injury of human endocardial endothelial and myocardial cells. The biological role of this increase is unknown. However, it does not seem to be associated with adverse effects in the immediate post-RFA period.

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