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Brachytherapy: Potential Therapy for Refractory Coronary Spasm

Paul Erne, MD,* Peiman Jamshidi, MD,* Peter Juelke, MD,† Hans-Peter Hafner, PHD,† Peter Thum, MD,† Therese Resink, PHD‡

Luzern and Basel, Switzerland

OBJECTIVES We sought to demonstrate that brachytherapy reduces coronary spasm in refractory and highly symptomatic variant angina.

BACKGROUND In some patients with variant angina due to extensive vasoconstriction, intensive drug therapy fails to sufficiently relieve symptoms.

METHODS In 18 patients with frequent angina episodes despite triple anti-anginal therapy, coronary spasm was induced by intracoronary acetylcholine (ACh) infusion. Five patients had spasm in a second vessel. Intracoronary radiation (20 Gy) was applied to vasospastic segments using a beta-emitting (^{32}P) wire source centered within a Galileo balloon. Parameters of vessel function before and after brachytherapy were investigated.

RESULTS Before brachytherapy, artery diameters decreased ($p < 0.0001$) from 2.8 ± 0.4 mm to 1.0 ± 0.4 mm for the first vessels and from 3.1 ± 0.3 mm to 1.0 ± 0.2 mm for the second vessels. After brachytherapy (143 ± 106 and 80 ± 52 days for first and second vessels, respectively), ACh-induced vasoconstriction was significantly reduced. The ACh-induced changes in artery diameter before and after brachytherapy were −1.5 ± 0.5 mm and −0.5 ± 0.3 mm ($p < 0.0001$) for the first vessels and −1.4 ± 0.3 mm and −0.4 ± 0.2 mm ($p < 0.01$) for the second vessels, respectively. In non-irradiated spastic vessels, ACh-induced vasoconstriction remained unchanged (e.g., −1.7 ± 0.6 mm, −1.6 ± 0.3 mm, and −1.5 ± 0.5 mm for second vessels, at first investigation, first follow-up, and immediately before brachytherapy, respectively). Angina frequency decreased from 15.6 ± 6.0 to 2.2 ± 2.4 angina episodes/week ($p < 0.001$) in treated patients.

CONCLUSIONS Brachytherapy is a potential therapy in patients with highly symptomatic variant angina. (J Am Coll Cardiol 2004;44:1415–9) © 2004 by the American College of Cardiology Foundation

In most patients with variant angina, spasm occurs at the site of atheromatous plaque, although the degree of stenosis due to plaque is moderate and commonly <30% of the normal segment diameter (1). To document variant angina, a provocative test by infusion of acetylcholine (ACh) into coronary arteries is sometimes necessary (2). Most patients can be medically treated with vasodilating drugs. However, some are highly symptomatic and drug-resistant, and stenting has been used (3).

Although application of brachytherapy produces an immediate increase of vasoconstriction and spasms (4,5), a loss of vasomotion some weeks after brachytherapy occurs (6). This effect renders brachytherapy as a potential therapeutic modality for patients with highly symptomatic variant angina. We reported an index case of a post-brachytherapy reduction of angina in a patient with coronary vasospasm (7). This patient died subsequently, and autopsy revealed coronary thrombosis of the irradiated left anterior descending (LAD) coronary artery and untreated intermediate artery. Nevertheless, given the significant effect of brachytherapy in relieving angina, we cautiously further investigated the potential of brachytherapy in refractory coronary spasm.

From the Divisions of *Cardiology and †Radiotherapy, Kantonsspital Luzern, Luzern; and the ‡Department of Research, Kantonsspital Basel, Basel, Switzerland.

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METHODS

Patients. Eighteen patients with frequent angina and refractoriness to intensive anti-ischemic therapy were included. Seven and four patients had ST-segment elevations and depressions, respectively, on the electrocardiogram during chest pain at rest. Patients underwent initial diagnostic work-up to exclude coronary artery disease and document vasoconstrictive responsiveness to ACh. If similar ACh-responsiveness was documented within eight weeks (inclusion criteria), investigation was repeated and brachytherapy applied to the dominant vasospastic vessel. The local ethical committee approved the protocol. Patients gave written, informed consent. Three months before brachytherapy and for the study duration, patients reported weekly anginal episode occurrence and nitrate use. Relevant patient characteristics, risk factors, and drug therapies are presented in Table 1.

No patient had angiographically visible plaque. Acetylcholine was infused (10 μmol/l, constant) into coronary arteries, and vasospasms were quantitated by quantitative coronary angiography if vasoconstriction >50% diameter stenosis occurred (8). Vasospastic vessel locations were identified anatomically in a predefined projection, which was repeated at follow-up investigations. A prophylactic temporary pacing lead was placed into the right ventricular apex at a backup rate of 40 beats/min. Nitroglycerin was

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Abbreviations and Acronyms

ACh = acetylcholine
CFR = coronary flow reserve
+dv/dt = flow acceleration rate
−dv/dt = flow deceleration rate
LAD = left anterior descending

injected (100 to 200 μg bolus) into the coronary artery to relieve spasm. Coronary flow and its response to intracoronary injection of adenosine (30 μg bolus) and nitroglycerin (200 μg bolus) were assessed. Average peak velocities, coronary flow reserve (CFR), flow acceleration rate (+dv/dt), and flow deceleration rate (−dv/dt) were determined with a Cardiometrics Doppler guidewire (9). To assess functional vessel distensibility, adenosine-induced changes in acceleration and deceleration rate of flow velocities (Δdv/dt and Δ−dv/dt, respectively) were determined.

Vessel response to ACh by length was inhomogeneous. Vessel areas with the greatest spasm (>50% diameter stenosis) were selected for radiation. The entire length of this region was irradiated. We applied a 32- or 52-mm-long centering balloon if the length of spasm was <25 mm or >25 mm, respectively. Irradiated vessels included the LAD, circumflex artery, and right coronary artery. Brachytherapy (20 Gy, based on non-constricted vessel diameter) was applied through a beta-emitting (^{32}P) wire source centered within Galileo balloons (Guidant Corp., Santa Clara, California) (10). Radiation was targeted 1 mm beyond the vessel wall (11) and over the entire length (38 ± 12 mm) of the affected segment. In three patients in whom the affected area was longer than 52 mm, a second more proximal part of the vessel was treated after pullback of the centering balloon.

Patients were re-investigated 143 ± 106 days after the first brachytherapy. To assess putative changes over time, follow-up after intracoronary irradiation was carried out between weeks 5 to 8, 10 to 3, 7 to 20, 35 to 38, and 80 to 83 (3, 4, 5, 3, and 3 patients, respectively). Vessel function was documented by intracoronary administration of ACh and flow measurements repeated. Five patients had insufficient improvement of symptoms because of vasospasms in a second artery. Vasospasm in these arteries was identified during pre-diagnostic work-up, but a decision not to irradiate these arteries at the first brachytherapy session was made on the basis of: 1) uncertainty of clinical outcome of the first brachytherapy; and 2) risk of late thrombosis. In these, brachytherapy was staged. These patients served as an important control group, as parameters for the second spastic vessels in the non-irradiated state were assessed on three occasions: initial diagnostic work-up, first brachytherapy, and first follow-up (136 ± 39 days) after irradiation of the first vessel. Invasive follow-up of the second vessels was carried out after 80 ± 52 days (between weeks 4 to 7, 9 to 12, and 16 to 19 in 1, 2, and 2 patients, respectively).

After brachytherapy, patients were treated with clopidogrel (75 mg/day) for one year and acetylsalicylic acid (100 mg/day) life-long to prevent thrombosis. Patients were followed clinically each month for one year, and drug therapies were individually reduced according to symptoms.

Statistical analysis. Results are expressed as the mean value ± SD. The Student *t* test (two-tailed, paired) was applied for statistical evaluation.

Table 1. Patient Description

Gender (M/F)	15/3
Age (yrs)	60 ± 9.4 (43–72)
Height (cm)	171 ± 8 (151–181)
Weight (kg)	78 ± 11 (60–104)
Cardiovascular risk factors	
Hypertension	11
Dyslipidemia	15
Diabetes	2
Current/former smokers	5/5
Previous myocardial infarction	4
Indication for coronary angiography	
ST-segment changes on exercise	5
Angina at rest	6
Vasospastic infarction	3
Unstable angina	4

	Before Brachytherapy	At Final Follow-Up
Episodes and pharmacotherapies		
Anginal episodes/week	15.6 ± 6.0	2.2 ± 2.4
Amlodipine (mg/day)	7.7 ± 4.3	1.8 ± 2.0
Nebivolol (mg/day)	6.4 ± 3.2	1.9 ± 1.6
Molsidomine (mg/day)	12.0 ± 7.5	0
Nitrate use/week	8.5 ± 3.6	1.3 ± 1.4

Data are presented as the mean value ± SD (range) or number of patients.

RESULTS

The indications for coronary angiography are shown in Table 1. Spasm in response to ACh infusion was documented at the initial diagnostic work-up ("reference vessel diameters") (Table 2). Parameters of the second vessels in their non-irradiated state, repeatedly measured, remained constant (Tables 2 and 3, Figs. 1 and 2). The effects of brachytherapy were consistent for all patients and for both spastic vessels and independent of the follow-up period.

Table 2 summarizes invasive parameters. Before brachytherapy, affected vessels exhibited vasoconstriction to ACh. Enhanced acute vasoconstriction occurred immediately after brachytherapy, and nitroglycerin (mean of 400 μg [range 200 to 1,200 μg]) was required to resolve spasms. At follow-up after brachytherapy, ACh-induced vasoconstriction at the brachytherapy location was abrogated, while vasospastic vessels in the non-irradiated state maintained the constrictor response to ACh (Table 2, Fig. 1). Ejection fraction, left ventricular end-diastolic pressure, and responsiveness to nitrate were unaffected (Table 2).

Table 2. Effects of Brachytherapy on Invasively Determined Parameters of Vessel Function

	Reference Diameters (Initial Diagnostic Work-Up)		Pre-Therapy Investigation		First Follow-Up		Second Follow-Up
	First Vessel (n = 18)	Second Vessel (n = 5)	First Vessel (n = 18)	Second Vessel (n = 5)	First Vessel After Brachytherapy (n = 18)	Nonirradiated Second Vessel (n = 5)	Second Vessel After Brachytherapy (n = 5)
Follow-up (days)					143 ± 106	136 ± 39	80 ± 52
Ejection fraction (%)			61 ± 11	66 ± 4	61 ± 12	68 ± 6	ND
LVEDP			18 ± 6	15 ± 2.2	13 ± 2	13 ± 3	ND
Vessels irradiated							
LAD					10		1
Cx					4		3
RCA					4		1
Diameter of vessels (mm)							
Baseline	2.9 ± 0.4	2.3 ± 0.4	2.8 ± 0.4	3.1 ± 0.3	2.9 ± 0.4	3.0 ± 0.2	2.8 ± 0.3
Acetylcholine	1.2 ± 0.3	1.2 ± 0.2	1.0 ± 0.4	1.0 ± 0.2	2.5 ± 0.4*	1.1 ± 0.2	2.3 ± 0.3*
Nitrate	3.0 ± 0.4	2.8 ± 0.4	3.0 ± 0.5	3.2 ± 0.3	3.0 ± 0.4	3.3 ± 0.2	2.8 ± 0.3

Vessel diameters after acetylcholine administration differ before and after brachytherapy (*$p < 0.0001$). Data are presented as the mean value ± SD.
Cx = circumflex artery; LAD = left anterior descending coronary artery; LVEDP = left ventricular end-diastolic pressure; RCA = right coronary artery.

Table 3 summarizes flow parameters. The CFR was not affected. After brachytherapy, baseline +dv/dt and −dv/dt were increased, whereas +dv/dt and −dv/dt responses to adenosine tended to decrease. Evaluation of the difference in flow measurements before and after brachytherapy revealed an alteration in the adenosine-induced change in both Δ+dv/dt and Δ−dv/dt (Fig. 2). Vasospastic vessels in their non-irradiated state retain their vasomotor response to adenosine (Table 3, Fig. 2).

Molsidomine was stopped at hospital discharge after the first brachytherapy in all patients, and other anti-anginal drugs were reduced at follow-up (Table 1). By the 12-month final follow-up, patients were experiencing less anginal episodes per week (Table 1, Fig. 3).

Two adverse events were associated with the protocols. One patient suffered a hematoma at the puncture site on the occasion of invasive follow-up and required blood transfusion. A second patient developed a significant stenosis of the left main artery between first brachytherapy of the LAD and invasive follow-up.

DISCUSSION

This is the first clinical study on brachytherapy in drug-resistant vasospastic angina and ACh-induced coronary spasms. Clinical follow-up demonstrated major symptom relief. A brachytherapy-associated reduction of angina was accompanied by a loss of vasoconstriction to ACh. Brachytherapy reduced vasomotor response to adenosine, which may be due to increased baseline dv/dt and −dv/dt and reflective of decreased vessel distensibility. Anti-anginal therapy can be reduced after brachytherapy.

Follow-up periods varied (21 to 463 days), but the results were consistent, suggesting that vessel wall response to brachytherapy takes place early and is persistent. This is

Table 3. Effects of Brachytherapy on Flow Parameters

	Pre-Therapy Investigation		First Follow-Up		Second Follow-Up
	First Vessel (n = 18)	Second Vessel (n = 5)	First Vessel After Brachytherapy (n = 18)	Nonirradiated Second Vessel (n = 5)	Second Vessel After Brachytherapy (n = 5)
CFR	2.7 ± 0.9	2.9 ± 0.6	2.5 ± 0.8	2.9 ± 0.6	2.2 ± 0.3
Baseline					
Acceleration (+dv/dt)	238.6 ± 91.9	312.3 ± 69.4	283.0 ± 74.3†	305.1 ± 61.4	280 ± 139.4
Deceleration (−dv/dt)	104.0 ± 36.0	104.4 ± 27.2	203.3 ± 67.6‡	105.3 ± 25.3	230.0 ± 28.1†
Adenosine					
Acceleration (+dv/dt)	369.7 ± 116.4	459.6 ± 96.5	295.5 ± 73.6	460.5 ± 76.5	278.0 ± 116.7
Deceleration (−dv/dt)	262.2 ± 70.8	262.2 ± 57.4	214.0 ± 69.7*	252.1 ± 48.2	225.6 ± 30.2

*$p < 0.05$, †$p < 0.01$, and ‡$p < 0.001$ indicate the difference before and after brachytherapy. Data are presented as the mean value ± SD.
CFR = coronary flow reserve; +dv/dt = flow acceleration rate; −dv/dt = flow deceleration rate.

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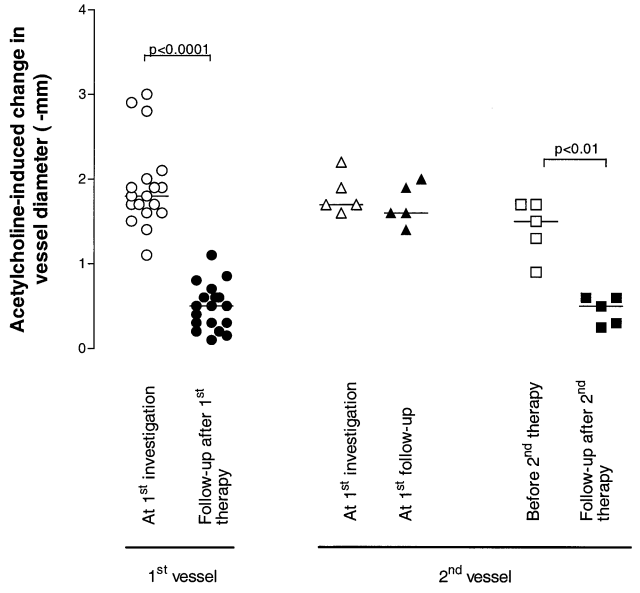

Figure 1. Brachytherapy reduces acetylcholine (ACh)-induced vasoconstriction. Individual vessel diameter changes (with median values) after infusion with ACh before and after brachytherapy. **Circles** = first vessel and **squares** = second vessel before **(open circles and open squares)** and at follow-up after brachytherapy **(solid circles and solid squares)**; second vessel in non-irradiated states at first investigation **(open triangles)** and follow-up after brachytherapy of first vessel **(solid triangles)**. p indicates effect of brachytherapy.

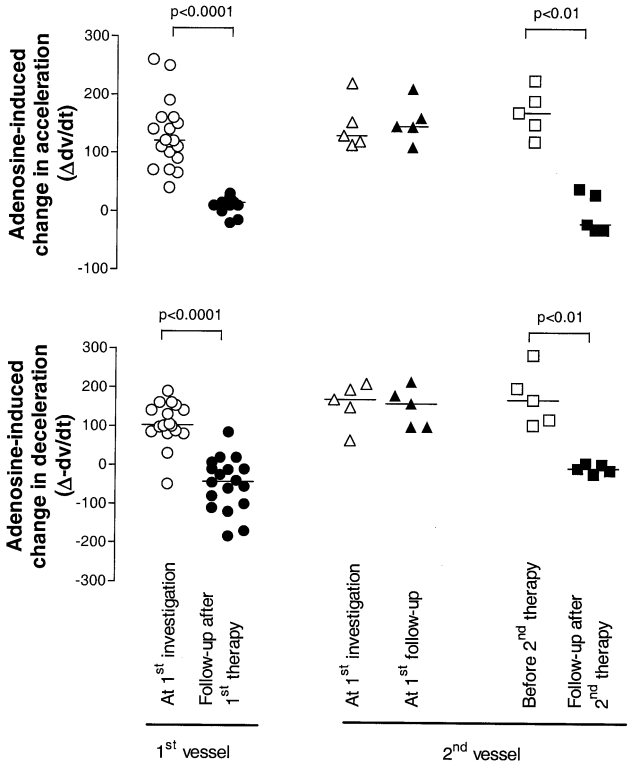

Figure 2. Brachytherapy reduces adenosine-induced changes in acceleration and deceleration time of flow velocities. Individual adenosine-induced changes (with median values) in acceleration (Δ+dv/dt; **upper panel**) and deceleration (Δ−dv/dt; **lower panel**) flow velocities before and after brachytherapy. **Circles** = first vessel and **squares** = second vessel before **(open circles and open squares)** and at follow-up after brachytherapy **(solid circles and solid squares)**. Second vessel in non-irradiated states at both the first investigation **(open triangles)** and follow-up after brachytherapy of first vessel **(solid triangles)**. p indicates effect of brachytherapy.

consistent with the reduction in angina within hours of brachytherapy and the fact that molsidomine administration could be halted at discharge (one day after the procedure).

We caution that brachytherapy can be associated with adverse events. Brachytherapy is known to be associated with a risk of late thrombosis. However, our patients were treated with clopidogrel for 12 months and continuous acetylsalicylic acid. One patient developed progression of a left main plaque narrowing (75%) within 315 days after brachytherapy of the LAD. This could result from progression of native disease or stimulatory effects of irradiation.

Effects of brachytherapy on coronary artery tone and vasomotion are poorly understood. Immediately after brachytherapy, extensive vasoconstriction occurs, as shown in this study and others (4,5), and intracoronary nitroglycerin is necessary. Endothelium-dependent vasomotion of coronary segments treated with balloon angioplasty was reported to normalize at six months after brachytherapy (8). This study investigated patients with coronary artery disease, while herein no patient presented with coronary lesions. Our results suggest additional endothelium-independent effects of brachytherapy.

Study limitations. A larger study of less symptomatic patients is needed to assess the clinical impact of intracoronary irradiation for variant angina. The study did not address the cellular mechanism of action of brachytherapy.

Conclusions. Brachytherapy appears to be a potential therapy in preventing the recurrence of vasospasm in patients with refractory and highly symptomatic variant angina.

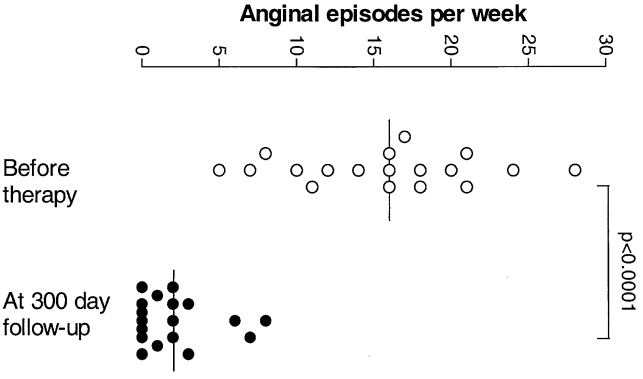

Figure 3. Brachytherapy reduces the frequency of anginal episodes. Weekly frequency of anginal episodes for each patient before brachytherapy **(open circles)** and at follow-up **(solid circles)**.

Reprint requests and correspondence: Dr. Paul Erne, Division of Cardiology, Kantonsspital Luzern, 6006 Luzern 16, Switzerland. E-mail: Paul.Erne@KSL.CH.

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