

## INTERVENTIONAL CARDIOLOGY AND SURGERY

## Early experience with a helical coronary thrombectomy device in patients with acute coronary thrombosis.

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Heart 2002;87:455-460

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Accepted  
25 January 2002

**Objective:** To report our experience with a new thrombectomy device (X-SIZER™) in patients with angiographically visible thrombus or total coronary occlusion in the setting of acute coronary syndromes.

**Design:** A safety and feasibility study in the use of the X-SIZER during intervention in patients with acute coronary syndromes.

**Patients:** 35 patients, age range 31 to 83 years (mean 60).

**Setting:** University Hospitals of Coventry and Warwickshire NHS Trust (tertiary referral centre).

**Interventions:** The indication for intervention was primary or salvage percutaneous coronary intervention for acute myocardial infarction in 17 of the 35 patients; unstable angina or non-ST-elevation myocardial infarction in 10; and unstable postinfarct angina in eight. Abciximab was given in 11 patients.

**Main outcome measures:** Device success (successful deployment of the device at the site of the lesion with resultant improvement in TIMI flow); clinical success (no residual stenosis at the end of the procedure with no in-hospital major adverse coronary events).

**Results:** Successful use of the device was achieved in 26 of the 35 cases. It failed to cross the lesion in five and failed to improve TIMI flow despite crossing the lesion in four. Clinical success was achieved in 30 of the 35 cases. Device related complications occurred in two cases (vessel perforation) and there was one intraprocedural death (acute myocardial infarction with cardiogenic shock).

**Conclusions:** Thrombectomy with the X-SIZER catheter system appears promising in percutaneous coronary intervention where thrombus extraction is considered necessary before stent implantation.

Thrombosis in the background of plaque rupture or fissure is increasingly recognised as the pivotal event in the pathogenesis of acute coronary syndromes, not only in acute myocardial infarction but also in the syndrome of unstable angina/non-ST-elevation myocardial infarction.<sup>1,2</sup> There is now general understanding that in all acute ischaemic syndromes it is the extent and duration of the thrombotic occlusion that largely determines the clinical course of the episode, and surrogate markers of such events are 12 lead ECG and measurement of cardiac troponin T.<sup>3</sup> In this context, thrombus extraction may play a significant role, as early angiography and percutaneous coronary interventions are increasingly performed in the acute or postacute phase of acute coronary syndromes. In this setting, intraluminal thrombus (fig 1)—whether angiographically apparent or not—is known to have an adverse effect on the outcome of the procedure.

In this paper, we present our early experience with the X-SIZER™ catheter thrombectomy device (EndiCOR Medical, San Clemente, California, USA) in the treatment of patients undergoing percutaneous coronary interventions for acute coronary syndromes. We assessed the safety and efficacy of the device in extracting atherothrombotic tissue and restoring TIMI (thrombolysis in myocardial infarction trial) grade 3 flow in the target vessel.

## METHODS

### Patients

The X-SIZER device was used in 35 patients, all of whom were emergency admissions to our institution with an acute coronary syndrome between December 1999 and June 2001. Indications for use of the device were based on a combination of clinical and angiographic findings. Its use was advocated mostly where intracoronary thrombus was suspected from the initial diagnostic coronary angiogram. Thrombus was suspected when an intracoronary filling defect with contrast

staining was observed (fig 1) or when total coronary occlusion was seen with a clinical background of acute coronary syndromes (fig 2).

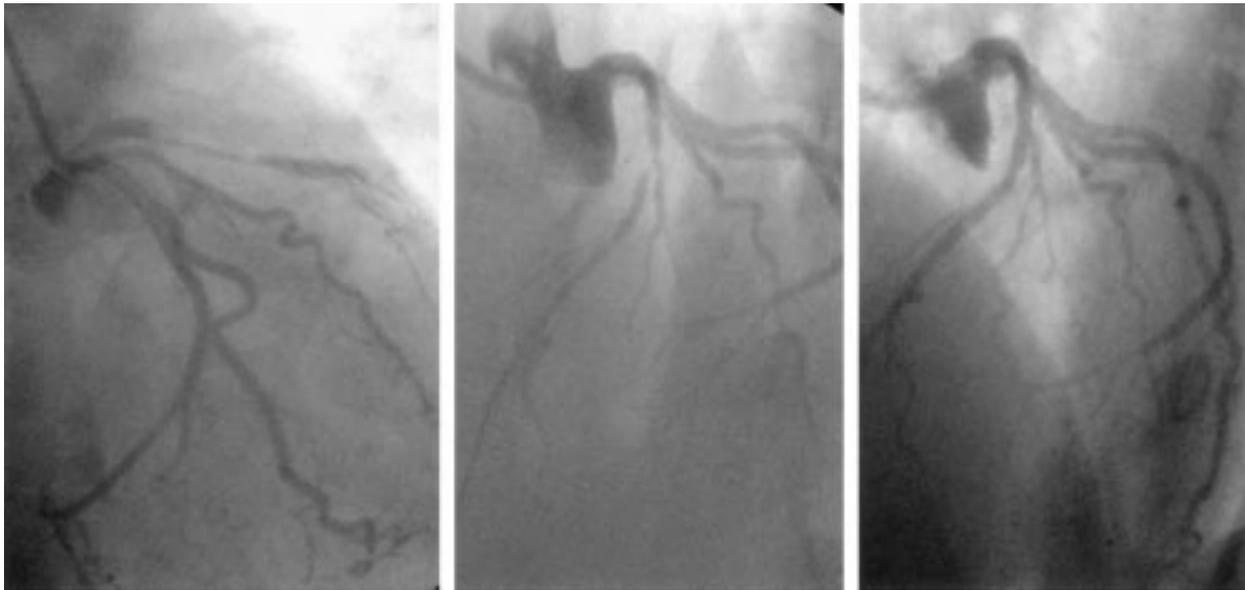
The characteristics of the patients are summarised in table 1. The indication for coronary angiography and intervention was salvage percutaneous coronary intervention (failed thrombolysis) for acute myocardial infarction in 14 cases, and primary percutaneous coronary intervention for acute myocardial infarction (no previous thrombolysis) in three. Unstable angina or non-ST-elevation myocardial infarction was present in 10 cases, and unstable postinfarct angina was the indication in the remaining eight. All the procedures were performed within eight days of the index admission, with the majority being done on the day of admission or within the first two days.

The culprit vessel was the right coronary artery in 20 of the 35 cases, the left anterior descending coronary artery in nine, the circumflex coronary artery in two, and a saphenous vein graft in four. Total coronary occlusion was present in 27 cases. Angiographically visible thrombus was suspected in 33 of the 35 cases.

### Procedures

The X-SIZER™ consists of a helical rotational cutter (1.5 or 2.0 mm in diameter) housed within the distal tip of the catheter. It is activated by a hand held battery driven motor module. The catheter has two lumens, one for over-the-wire use and the other for aspiration of extracted debris. It comes as an independent, single use, disposable unit and is compatible with standard coronary guidewires and 6 F or 8 F guide catheters (fig 3).

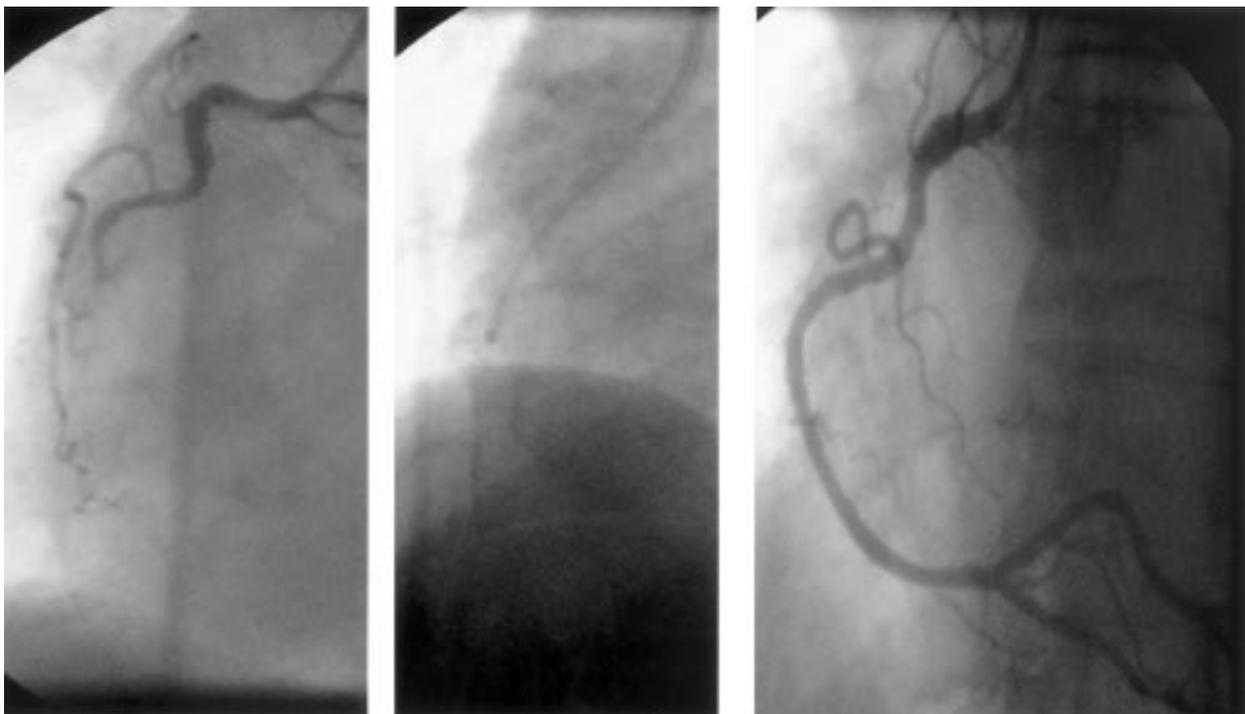
Coronary angiograms were performed through a 6 F or 8 F sheath inserted under a local anaesthetic in the right femoral artery in all but one case. In the latter it was done using the right radial artery. A 10 000 unit bolus of heparin was given at the start of the procedure (or 5000 units if the patient was



**Figure 1** Angiographic views during percutaneous coronary intervention in a 70 year old woman presenting with unstable angina pectoris and deep ECG T wave inversion. Left panel: Right anterior oblique view showing thrombus as a filling defect in the left anterior descending coronary artery. Middle panel: Left anterior oblique view showing the thrombus. Right panel: Left anterior oblique view showing marked angiographic improvement following thrombectomy.

already receiving a heparin infusion). All patients had been given aspirin before the procedure. Either a 6 F or an 8 F guiding catheter was used, and a long exchange guide wire was inserted to cross the lesion or the occlusion site. The thrombectomy device was then placed over the wire at the site of the lesion and slowly advanced under fluoroscopic guidance, while being activated by the hand held motor unit.

Adjuvant treatment with glycoprotein IIb/IIIa inhibitor (abciximab) was given according to the operator's discretion. An angioplasty balloon was used to dilate the target lesion following thrombus extraction if there was a significant residual stenosis after thrombectomy. Intracoronary stents were deployed to complete the procedure, unless there was a specific contraindication. A daily dose of clopidogrel (Plavix), 75 mg orally, was given for two weeks following stent implantation.



**Figure 2** Angiographic views during percutaneous coronary intervention in a 61 year old man with unstable angina after an inferior myocardial infarct, at seven days after the index event. Left panel: Left anterior oblique view of a total right coronary artery occlusion. Middle panel: Left anterior oblique view showing the radiopaque tip of the X-SIZER advancing over the guide wire in the occluded right coronary artery. Right panel: Angiographic appearance in the left anterior oblique view of the recanalised right coronary artery following thrombectomy and stent implantation.

**Table 1** Patient characteristics

Number of patients		35
Age (years)	Range	31 to 83
	Mean	60
Sex	Male	22
	Female	13
Diabetes		4
Diagnosis	AMI (failed thrombolysis)	14
	AMI (primary)	3
	Unstable angina	10
	Postinfarct angina	8

AMI, acute myocardial infarction.



**Figure 3** The X-SIZER catheter system consisting of the drive unit, catheter shaft, aspiration tubing with in-line filter and vacuum bottle (not shown). *Insert:* Schematic representation of the helical cutting tip.

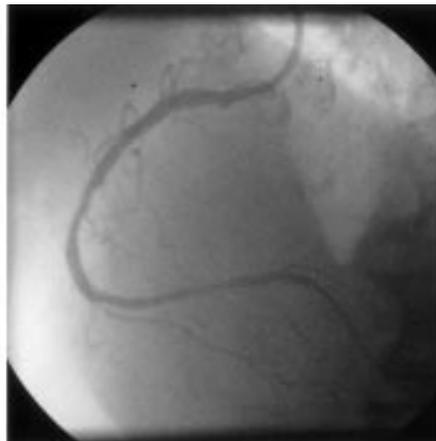
### Definitions

#### X-SIZER success

The X-SIZER successfully reached the lesion, giving rise to an improvement in TIMI flow by at least one grade, as well as the presence of extracted atherothrombotic material in the in-line filter.

#### Clinical success

Clinical success was defined as the achievement of a patent target vessel with no residual stenosis and no major adverse cardiac events during the hospital stay, irrespective of the X-SIZER result.



**Figure 4** Angiographic views in a 54 year old man presenting with unstable postinfarct angina and previous coronary artery bypass graft 10 years earlier. Right panel: Recent right coronary artery saphenous vein graft occlusion despite guide wire crossing (left anterior oblique projection). Middle panel: Following thrombectomy and balloon angioplasty to distal lesion, TIMI grade 3 flow established with residual thrombus proximally. Right panel: Following repeat thrombectomy and the implantation of intracoronary stents.

## RESULTS

### X-SIZER success

X-SIZER success was achieved in 26 of the 35 cases overall. In the 17 cases of acute myocardial infarction (salvage or primary intervention), the X-SIZER was successful in 13 (fig 2). In the 10 cases of unstable angina pectoris/non-ST-elevation myocardial infarction, it was successful in six. In the eight cases of unstable postinfarct angina, it was successful in seven (fig 1).

There was a predominance of right coronary artery lesions in this series, with only two circumflex lesions. The X-SIZER appeared to be equally effective in the different coronary vessels. It was successful in 14 of the 20 right coronary arteries treated, seven of the nine left anterior descending coronary arteries, in both the circumflex artery lesions, and in three of the four saphenous vein grafts (fig 4).

In the presence of angiographically suspected thrombus X-SIZER success was achieved in 26 of 33 cases. In total coronary occlusion, the X-SIZER was successful in 23 of the 27 cases in which it was used.

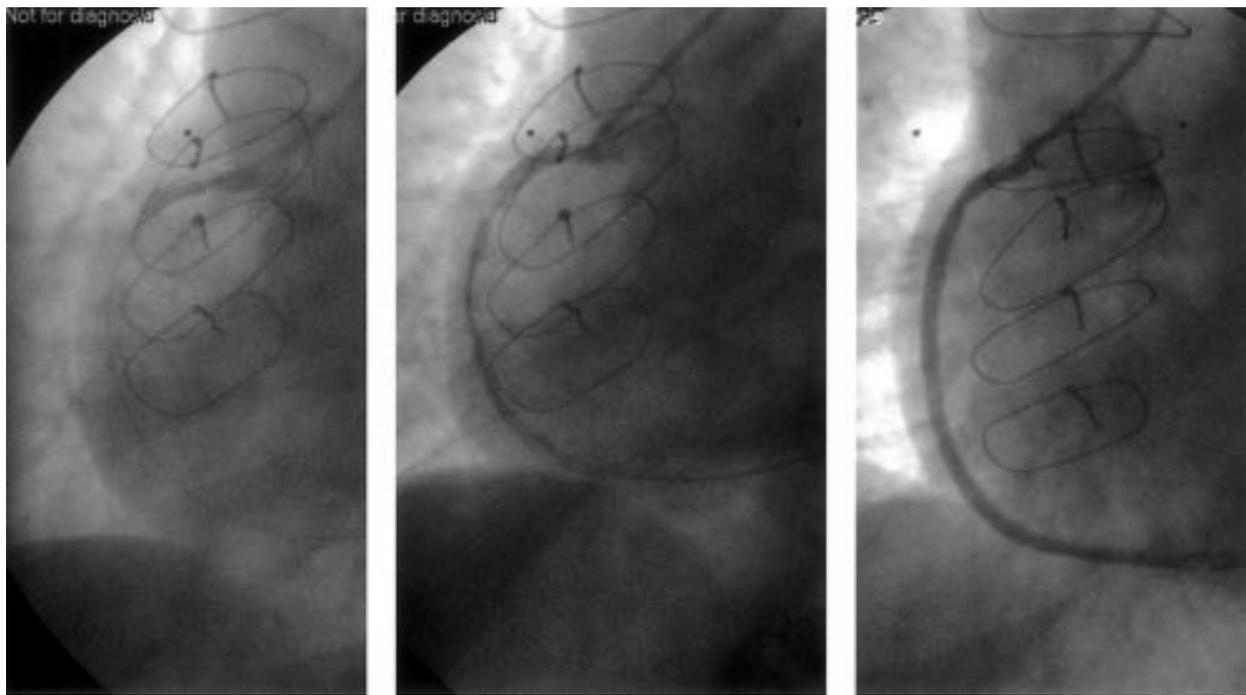
Overall, the device failed to cross or reach the lesion for effective thrombus aspiration in five of the 35 cases. The lesions that the device failed to cross were in the left anterior descending coronary artery ( $n = 2$ ), the right coronary artery ( $n = 2$ ), and in a saphenous vein graft ( $n = 1$ ). Three of those five vessels were totally occluded on initial coronary angiography. In all cases the wire successfully crossed the occlusion and they were treated by conventional balloon angioplasty and stents.

In four of the 35 cases there was no improvement in TIMI flow, even though the atherothrombectomy device reached or crossed the lesion. Two of these cases involved right coronary arteries with a large amount of thrombus in the setting of salvage percutaneous coronary intervention for acute myocardial infarction; the other two were also right coronary arteries with total occlusion at the start of the procedure.

### Clinical success

In 30 of the 35 cases, the procedure resulted in restoration of TIMI-3 flow with less than 20% residual stenosis and no in-hospital major adverse coronary events (death, new ST elevation myocardial infarction, need for target vessel revascularisation). In five of the nine cases where X-SIZER success was not achieved, clinical success was achieved using standard percutaneous coronary intervention equipment. Of the five cases where clinical success was not achieved, four were also X-SIZER failures (failure to reach the lesion in three; no improvement in TIMI flow despite reaching the lesion in one).

Clinical success was achieved in 27 of the 33 cases where thrombus was suspected on the diagnostic angiogram. The procedure was successfully completed in 25 of the 27 cases with total coronary occlusion.



**Figure 5** Angiographic views during percutaneous coronary intervention in a 74 year old woman with failed thrombolysis following an acute inferior myocardial infarct. Left panel: Left anterior oblique view of the totally occluded right coronary artery on initial diagnostic angiogram. Right panel: After thrombectomy with the X-SIZER catheter, no significant lesion was observed. No stent was implanted. Follow up angiogram at four months showed no significant stenosis.

#### Adjuvant treatments

Adjuvant treatment with a glycoprotein IIb/IIIa inhibitor (abciximab) was given in 11 of the 35 patients. An angioplasty balloon was used to dilate the target lesion following thrombus extraction in 22 cases. Direct stenting without previous balloon inflation was possible following thrombectomy in 11. One or more stents were deployed in 32 of the 35 procedures. In two cases the X-SIZER was used as a stand alone procedure: one was an acute early in-stent thrombosis where thrombus was successfully retrieved; the other was a case of failed thrombolysis for an acute inferior myocardial infarct (thrombectomy of a totally occluded right coronary artery revealed a minimal lesion that did not require the implantation of a stent (fig 5)).

#### Histology of extracted material

The histology of particular material collected in the in-line filter showed largely fibrinous thrombus with little evidence of cellular structures and occasionally atheromatous plaque material.

#### Complications

One intraprocedural death occurred. The patient was a 68 year old woman with late presentation of extensive anterior myocardial infarction. She was in cardiogenic shock on arrival at the cardiac catheterisation laboratory and died during the procedure despite successful recanalisation of the occluded left anterior descending coronary artery with the X-SIZER.

There were two procedure related coronary artery perforations. One was a total thrombotic occlusion of an old saphenous vein graft presenting as an acute myocardial infarct with angiographic evidence of failed thrombolysis. There was vessel perforation after successful thrombectomy and restoration of TIMI-2 from TIMI-0 flow. The complication was treated by deployment of a covered stent with no immediate sequelae. The second perforation occurred in an occluded left anterior descending coronary artery, also in the setting of failed thrombolysis for acute anterior myocardial infarction. There

was vessel tortuosity in the pre-occlusion section of the artery. In trying to cross the lesion with the X-SIZER at the point of total occlusion, vessel perforation occurred with haemodynamic compromise. This was treated with the insertion of a pericardial drain followed by implantation of a covered stent. The stented segment occluded within a week. Attempts to recanalise the artery were unsuccessful. The patient suffered no further myocardial infarction and was discharged home well.

#### DISCUSSION

Percutaneous coronary intervention procedures are increasingly undertaken in the setting of acute coronary syndromes (acute myocardial infarction or unstable angina/non-ST-elevation myocardial infarction). There is now a general view that in all acute ischaemic syndromes, while the initiating event may be plaque rupture or fissure, it is the extent and duration of thrombotic occlusion that influences the clinical course. Thus thrombus extraction can be expected to play an important role in management, as many patients are likely to have thrombus in the target vessel near the culprit lesion.

With current evidence supporting early intervention in the acute ischaemic syndromes and the use of primary intervention instead of thrombolysis for acute myocardial infarction, efforts to deal with thrombus can be expected to increase.<sup>3</sup> Intervention in this setting is known to be associated with a higher risk of death, myocardial infarction, or recurrent ischaemia. For example, primary balloon angioplasty for acute myocardial infarction is associated with a 5–15% rate of ischaemia related complications before discharge from hospital, and the need for repeat revascularisation has been reported in as many as 35% of cases.<sup>4–11</sup> In addition, the presence of angiographically identifiable thrombus at the time of angioplasty has been shown to be associated with a higher restenosis rate.<sup>12–14</sup>

There are various reasons why the presence of thrombus during coronary intervention may be associated with a higher

complication rate. Distal embolisation of thrombotic fragments occurs following balloon dilatation, causing branch occlusion or the no reflow phenomenon. While balloon and stent expansion is possible in the presence of thrombus, the entrapped thrombus can act as a nidus for further thrombosis (thrombus begets thrombus). Furthermore, it can obscure the geometry of the underlying lesion, resulting in imperfect stent choice, positioning, and deployment.

In the presence of angiographically obvious thrombus, an alternative approach is to delay intervention until some time after the use of a platelet membrane glycoprotein IIb/IIIa receptor inhibitor. However, even with the use of agents such as abciximab, the speed with which thrombus is cleared is unpredictable. In general, abciximab has been shown to improve outcomes during coronary interventions for both unstable angina and acute myocardial infarction.<sup>15-17</sup> It is suggested that thromboembolic events occur in high risk percutaneous coronary interventions, and abciximab acts to reduce ischaemic complications.

The relatively low use of abciximab in our series reflected the fact that nearly half the patients had received full dose thrombolytic treatment just before the procedure. The operators were reluctant to use abciximab in conjunction with full dose thrombolysis owing to the lack of safety data and the potential risk of bleeding complications. In the latter part of the study, and following publication of the NICE (National Institute for Clinical Excellence) guidelines for the use of glycoprotein IIb/IIIa inhibitors, abciximab was used in every case in which the X-SIZER was used provided that no thrombolytic treatment had been given within the previous 24 hours.

The mechanical extraction of thrombus present in the target vessel during percutaneous intervention is an attractive alternative to thrombolysis. It has the advantage of establishing prompt restoration of antegrade flow and unmasking the underlying lesion. Using the X-SIZER we saw little angiographic evidence of distal embolisation of clot fragments. Given the current evidence for direct percutaneous coronary intervention for acute myocardial infarction without previous thrombolysis, the X-SIZER appears to be a useful tool for thrombectomy before stent implantation.

The X-SIZER can be used by experienced interventionists without special training. It takes less than two minutes to assemble and prepare for use. The larger (2 mm) device is less flexible and requires firmer back up from the guiding catheter. The problems with its use in moderately tortuous vessels of smaller calibre has been overcome to some extent by the development of the more flexible 1.5 mm catheter. In this series, all the device failures occurred with the 2 mm catheter, largely because of inability to reach the lesion.

The 1.5 mm catheter only became available in the latter half of the study period. It is compatible with 6 F guiding catheters and therefore can be used from alternative vascular entry points such as the radial artery. It has the advantage of being able to reach more distal and moderately tortuous smaller calibre sites, but at the cost of a slower extraction rate. It may not be effective in larger vessels.

There were some cases where TIMI flow did not improve despite successful deployment at the site of the lesion. In these instances there may have been a high grade hard lesion associated with only a small amount of thrombus. Intracoronary thrombus is usually seen as a filling defect and is assumed to be present in significant amount in acute total coronary occlusions. However, high grade coronary lesions or complex eccentric atheromatous lesions can often mimic the appearance of intracoronary thrombus, in which case thrombectomy would be inappropriate. The current device is considered suitable for cutting soft plaque only, and its use in chronic severe stenoses would be inappropriate.

The device is most useful in the presence of angiographically evident intracoronary thrombus. This is most often seen

in the setting of acute coronary syndromes such as unstable angina or acute myocardial infarction.<sup>18,19</sup> When there is a totally occluded coronary vessel in the context of an acute infarct, it can be assumed that there will be sufficient thrombotic material to warrant the use of the X-SIZER. The higher success rate in our series during total coronary occlusion suggests the higher prevalence and larger quantity of intracoronary thrombus in those clinical settings.

While the device can be used in moderately tortuous vessels, it should not be deployed in highly tortuous vessels because of the risk of vessel perforation. Use of the device is not recommended in newly deployed intracoronary stents until they have adequately endothelialised (up to four weeks after deployment). This is to prevent the possibility of stent strut disruption by the cutting head.

### Complications

In the 35 patients reported in this study there were three serious complications (death or vessel perforation). One intraprocedural death occurred in a patient with late presentation of acute anterior myocardial infarction in cardiogenic shock, despite successful thrombectomy and transient restoration of TIMI-2 from TIMI-0 flow. We believe that the use of the thrombectomy device did not contribute to death in that case. Two vessel perforations occurred, which were obviously related to the use of the X-SIZER and probably reflect the limitations of the use of the device in very tortuous diseased vessels, as described above.

### Study limitations

This study is an observational account for the safety, feasibility, and efficacy of the X-SIZER device in the treatment of patients with acute coronary syndromes undergoing percutaneous coronary intervention, and in whom the presence of intracoronary thrombus was strongly suspected. It therefore represents a highly selective yet heterogeneous group of patients presenting with a variety of clinical syndromes and coronary anatomical features. The decision on the use of the X-SIZER took account of the clinical background, the operator's assessment of the presence of intracoronary thrombus, and the suitability of the coronary anatomy. No analysis was made of the additional benefit of using the X-SIZER in comparison with standard balloon angioplasty and stenting. This will be the subject of randomised clinical trials in Europe and the USA, which will be directed at comparing the X-SIZER with standard percutaneous coronary intervention equipment in the treatment of acute myocardial infarction and in other clinical settings, such as the treatment of saphenous vein grafts and in-stent restenosis.

We have not looked at any medium or long term outcome data as we aimed to focus on the immediate safety and efficacy of the device. It is most likely, as has been shown in published interventional studies, that it is the initial angiographic result (luminal gain, TIMI flow) that largely dictates the long term outcome.

Finally, we have not looked at cardiac enzyme release data following the procedure, as the majority of our cases already had acute myocardial infarction, which would make interpretation of postprocedural enzyme release very difficult.

### Alternative devices

Various other thrombectomy devices are available or are in the process of being developed. These include a transluminal extraction catheter (TEC) (Interventional Technologies, San Diego, California, USA), the Cordis endovascular hydrolyser thrombectomy system (Johnson and Johnson, Warren, New Jersey, USA), and the Angiojet (POSSIS Medical, Minneapolis, Minnesota, USA). The TEC device is another rotational cutting device with debris retrieval by suction, which has been used

for vein grafts. Unlike the X-SIZER, it has an unprotected cutting blade which greatly limits its use in native coronary vessels. The other two devices remove thrombi by the venturi effect from backwardly directed fluid jets.<sup>20-22</sup> The Angiojet is the more effective device as it employs several high velocity jets, while the Hydrolyser uses a single fluid channel. Compared with the X-SIZER, the Angiojet is a more complex system, requiring a separate power console to generate some 26 atmospheres of pressure in the fluid jets.

A different approach in the prevention of distal fragment embolisation during percutaneous coronary intervention of thrombotic lesions is the distal protection device (PercuSurge, Medtronic, Minneapolis, Minnesota, USA).<sup>23</sup> At present, the use of this device appears to be limited to saphenous vein grafts or non-occluded vessels with a length of normal distal vessel for placement of the capture device.

Finally, entrapment of thrombus in covered stents has also been used, but this seems to have found a place mainly in the treatment of old diseased saphenous vein grafts.

### Conclusions

We used a helical thrombectomy device (X-SIZER) to remove thrombus or atherosclerotic debris from native coronary arteries or saphenous vein grafts in 35 patients who presented with acute coronary syndromes. We experienced two device related complications (vessel perforation). These highlight the importance of case selection and the problems with its use in tortuous vessels and chronic obstructive lesions rather than fresh thrombotic occlusions. No deaths were directly attributable to the use of the X-SIZER. The device is easy to use and allows prompt restoration of TIMI-3 flow before further balloon dilatation and stenting in the majority of cases. It seems likely that the device will play a useful role during intervention for acute ischaemic syndromes, either when there is total thrombotic coronary occlusion or when there is angiographically obvious intracoronary thrombus.

Various full scale clinical trials have been started to evaluate the clinical benefit of this device in different clinical settings, such as acute myocardial infarction and unstable angina pectoris.

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## SCIENTIFIC LETTER

# Evaluation of long term cardiotoxicity after epirubicin containing adjuvant chemotherapy and locoregional radiotherapy for breast cancer using various detection techniques

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Heart 2002;88:81-82

**B**reast cancer patients who present with only locoregional lymphatic metastases have good life expectancy after treatment with surgery and adjuvant anthracycline-containing chemotherapy. Anthracyclines, however, can induce cardiomyopathy, and this may become clinically manifest as chronic heart failure many years after exposure.<sup>1</sup> As the occurrence of this side effect is dependent on the cumulative dose given, breast cancer patients with a favourable prognosis are treated with rather low doses of anthracyclines in order to prevent severe cardiac damage.

## METHODS

We investigated 56 breast cancer patients in a cross sectional design, to determine whether a low cumulative dose of the anthracycline compound epirubicin causes chronic cardiac damage.

The patients were two or more years after treatment with adjuvant chemotherapy, consisting of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC). The chemotherapy had been given after mastectomy or after breast conserving treatment, and was followed by locoregional radiotherapy (40 to 50 Gy). Thirty patients had been treated with five cycles of FEC (total cumulative dose of epirubicin, 450 mg/m<sup>2</sup>). Twenty six patients had received four cycles of FEC (total cumulative dose of epirubicin, 360 mg/m<sup>2</sup>), followed by high dose combination chemotherapy consisting of cyclophosphamide, thiotepa, and carboplatin with haematopoietic stem cell rescue. Their median age at the time of cardiac evaluation was 49 years (range 27 to 58), and the median time after chemotherapy was 37 months (range 24 to 79).

Cardiac evaluation included the following:

- a history and physical examination focusing on signs and symptoms related to cardiac failure
- radionuclide ventriculography for assessment of the left ventricular ejection fraction (LVEF) (normal value > 0.50)
- echocardiography to determine diastolic function by the ratio of early peak flow velocity to atrial peak flow velocity (E/A ratio; normal value > 1), and the early peak flow deceleration time (DT; normal < 220 ms)<sup>2</sup>
- 24 hour Holter monitoring for heart rate variability analysis as a measure of autonomic function, calculating the following time domain parameters: mean of all normal to normal RR intervals (mean NN, ms), standard deviation of all NN intervals in 24 hours (SDNN, ms), standard deviation of the average NN intervals calculated over five minute segments (SDANN, ms), the average of the five minute standard deviation of the NN interval calculated over 24 hours (SDNN index, ms), and the root mean square successive difference of RR intervals (rMSSD, ms).<sup>3</sup>

Heart rate variability in the patients was compared with heart rate variability in a control group consisting of 56 healthy age matched women. Mean values in the two groups were compared using a two tailed Student *t* test. Pearson's correlation coefficient was used to test correlations between variables. Data are expressed as mean (SD).

## RESULTS

Before the start of chemotherapy none of the patients had cardiac disease or cardiac complaints. At the time of cardiac evaluation, 17 (30%) were experiencing exertional dyspnoea (New York Heart Association (NYHA) class II). None of the evaluated patients had NYHA class III or IV symptoms or apparent clinical signs of congestive heart failure on physical examination. The mean LVEF (determined in 54 patients) was 0.57 (range 0.39 to 0.73). A decreased LVEF value (< 0.50) was observed in six patients (11%).

Successful echocardiography in 53 patients showed a mean E/A ratio of 1.1 (range 0.7 to 2.5), and a mean DT of 170 (range 90 to 352) ms. The E/A ratio was < 1 in 20 of the patients (38%). Compared with the age matched healthy women, the patients had a higher mean heart rate (83 (7) v 76 (8) beats/min; *p* < 0.0001) and all heart rate variability indices reflecting short term vagal mediated fluctuations were reduced, including the SDNN index (48 (14) v 59 (16) ms, *p* = 0.001) and the rMSSD (25 (11) v 36 (16) ms; *p* < 0.0001). The SDNN and SDANN, which are more related to sympathetic activity, did not differ from the control group.

Within the patient group age independent correlations were found between the E/A ratio and heart rate variability indices including SDNN (*r* = 0.42; *p* = 0.003), SDANN (*r* = 0.44; *p* = 0.002), and the SDNN index (*r* = 0.33; *p* = 0.026).

A subanalysis of cardiac function data was performed between patients with exertional dyspnoea (*n* = 17 of 56; 30%) and those without exertional dyspnoea (table 1). There was no difference in age or time after chemotherapy between these two groups, and the mean LVEF was comparable. However, patients with exertional dyspnoea had a lower E/A ratio and a longer DT, indicating impaired diastolic function. Furthermore, all heart rate variability indices in these patients were reduced compared with the patients with no exertional dyspnoea. Overall, no differences were found between the two chemotherapy regimens. Left sided thoracic radiotherapy was not associated with a greater degree of cardiac damage.

## COMMENT

Our data show that a low cumulative dose of epirubicin (360-450 mg/m<sup>2</sup>), which is considered safe with respect to cardiotoxicity in the short term,<sup>4</sup> seems to induce chronic mild cardiac damage in a substantial proportion of the patients.

**Table 1** Comparison of patients with and without exertional dyspnoea

Characteristic	With exertional dyspnoea (n=17)	Without exertional dyspnoea (n=39)	Mean difference (95% CI)	p Value
Radionuclide ventriculography				
LVEF	0.57 (0.8)	0.58 (0.7)	0.01 (-0.43 to 0.45)	NS
Echocardiography				
E/A ratio	1.0 (0.3)	1.2 (0.4)	0.2 (0.01 to 0.39)	0.005
DT (ms)	196 (52)	164 (38)	-32 (-59.45 to -4.55)	0.003
Heart rate variability				
Heart rate (beats/min)	85 (7)	82 (8)	-3 (-7.17 to 1.17)	NS
SDNN (ms)	117 (23)	144 (38)	27 (10.82 to 43.18)	0.01
SDANN (ms)	108 (23)	134 (37)	26 (10.05 to 41.95)	0.01
SDNN index (ms)	42 (10)	52 (17)	10 (2.85 to 17.15)	0.02
rMSSD (ms)	20 (8)	28 (12)	8 (2.65 to 13.35)	0.01

Data are mean (SD) or mean and 95% confidence interval (CI).

DT, deceleration time; E/A ratio, ratio of early peak flow velocity to atrial peak flow velocity; LVEF, left ventricular ejection fraction; mean NN, mean of all NN intervals (NN=normal to normal RR interval); rMSSD, root mean square of successive differences of NN intervals; SDANN, standard deviation of the average NN intervals computed over five minute segments; SDNN, standard deviation of all NN intervals; SDNN index, average of all standard deviations of NN intervals computed over five minute segments.

Abnormal systolic function was found in 11% of the patients, while abnormal diastolic function occurred in 38%. Autonomic function as measured by heart rate variability was generally impaired—in particular vagal activity—compared with the healthy age matched controls. Thirty per cent of the patients experienced exertional dyspnoea which was not present before chemotherapy, and this complaint seemed to be related to diastolic and autonomic dysfunction. The positive age independent correlation found between the heart rate variability and diastolic function suggests that the reduction in heart rate variability in these patients may be secondary to diastolic dysfunction.

## CONCLUSIONS

Our findings stress the importance of careful cardiac follow up in patients treated with anthracyclines, including those treated with low cumulative doses. It is evident that normal systolic function does not exclude cardiotoxicity. As previous reported,<sup>5</sup> diastolic and autonomic dysfunction may be earlier signs of chronic anthracycline induced cardiac damage. Whether the affected patients are at increased risk of severe congestive heart failure in the long term needs further follow up.

## ACKNOWLEDGEMENTS

This study was supported by a grant from the University Hospital Groningen. DJvV is an established investigator of the Netherlands Heart Foundation (grant No D97.017).

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Accepted 28 January 2002

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## Cadaveric organ donation: call for papers

The *Journal of Medical Ethics* is planning to publish a series of papers on cadaveric organ donation in the December 2002 issue.

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## CORRECTION

Constantinides S, Lo TSN, Been M, Shiu MF. Early experience with a helical coronary thrombectomy device in patients with acute coronary thrombosis. *Heart* 2002;**87**:455-60

The figures accompanying the captions to figs 4 and 5 were inadvertently transposed. Thus, the figure accompanying fig 4 caption (on page 457) is fig 5, and the figure accompanying fig 5 caption (on page 458) is fig 4. The error is regretted.