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Modified Contrast Microinjection Technique to Facilitate Chronic Total Occlusion Recanalization

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Objectives: To assess the efficacy and safety of the modified contrast microinjection technique to facilitate chronic total occlusion recanalization. Background: The success rate of chronic total occlusion percutaneous coronary intervention (CTO-PCI) does not exceed 90% even in the most experienced centres. We have previously demonstrated that a large volume of contrast injected into the subintimal space can facilitate recanalization but is limited by a risk of serious complication. The aim of this study was to assess the application, efficacy and safety of a modified contrast microinjection technique that utilizes the injection of a much smaller volume of contrast in CTO-PCI. Methods: A retrospective analysis of patients in whom the modified microinjection technique was utilised in patients undergoing CTO-PCI at five tertiary centres was conducted. Results: Of 1,192 patients who underwent CTO-PCI, the microinjection technique was used in 59 patients (4.7%). The majority of CTOs treated were in the right coronary artery (79.7%), were of high complexity and 35.6% of lesions had a least one previously failed PCI attempt. The modified microinjection technique was used for more than one indication in 7 (11.9%) of patients. The success rate was 81.4%. There were no procedural complications related to the use of the reported modified microinjection. Conclusion: Initial experience with the modified microinjection demonstrates that it can be performed safely, is reproducible, and is broadly applicable. Whilst not required for all CTO procedures it can be a helpful adjunctive tool to increase the likelihood of success especially in complex, or refractory cases, without compromising the safety of the procedure.

Key words: mircoinjection; chronic total occlusion; subintimal space; fibrous cap modification

INTRODUCTION

Successful chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is associated with improved outcomes and patient symptoms [1–3]. The Subintimal Tracking and Re-entry (STAR) technique [4] first demonstrated the efficacy and safety of subintimal strategies confirming that blunt dissection through the subintimal space could be performed rapidly and safely even in long, tortuous and calcified occlusions where it was otherwise highly challenging by wire-based techniques to negotiate in-CTO tortuosity whilst staying within the boundaries of the external elastic membrane (EEM). This technique encouraged the development of the more controlled contemporary subintimal techniques including the retrograde "Controlled Antegrade and Retrograde subintimal Tracking technique (CART) [5] and a

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dedicated antegrade subintimal dissection/re-entry system [6] which have become established into clinical practice.

The appreciation that contrast injection into the intra-occlusional space, initially in the setting of the STAR technique, further improved procedural success was a significant advancement of this revascularisation strategy [7]. Our initial description involved the injection of a relatively large volume of contrast (up to 5 mL) with the aim of providing a 'road map' of the occluded segment, which was particularly useful for long and tortuous segments facilitating the safe advancement of a "knuckled" wire in the subintimal space, increasing operator confidence in tackling difficult CTOs. Occasionally injection of this large volume also facilitated re-entry into the true lumen. The technique was limited however by a high rate of re-stenosis, unpredictability of the re-entry site [8] and the potential for coronary perforation [7].

We have modified this technique with the appreciation that the injection of smaller contrast volumes (<1 mL) appeared to be equally effective. We have expanded the use of this manoeuvre to resolving fibrous cap ambiguity and modifying plaque characteristics (e.g., in extensive calcification).

Advances in technique and increased operator experience have significantly improved success rates [9] in contemporary CTO PCI. However, even in the most expert centres, success rates rarely exceed 90% [10]. Therefore, further adjunctive techniques to improve the likelihood of procedural success are still required.

We describe our experience using this modified microinjection manoeuvre in the setting of CTO PCI reporting its efficacy, reproducibility and safety.

MATERIALS AND METHODS

All patients who underwent CTO PCI at five tertiary CTO expert centres (San Raffaele Scientific Institute, Milan, Italy; Edinburgh Royal Infirmary, Scotland, United Kingdom; Belfast Trust Hospital, Belfast, Northern Ireland, United Kingdom; Central Arkansas Veterans Health System, Little Rock, AR; and University of Texas Southwestern Medical Center, Texas) between January 2013 and December 2014 were reviewed. The subgroup of patients in whom intra-occlusional microinjection was performed is reported in the analysis.

A CTO lesion was defined as the obstruction of a native coronary artery with a thrombolysis in myocardial infarction (TIMI) flow grade 0 with an estimated duration of longer than 3 months [11].

Indications for CTO PCI, procedural approaches, use of adjunctive tools (e.g., intravascular imaging) and choice of the stents implanted were left at the operator's discretion. Successful angiographic recanalization was defined as a restoration of TIMI flow grade 3 and residual stenosis <30% in the occluded artery [11].

Experienced interventional cardiologists at each centre reviewed all angiograms. Each CTO was scored using the J-CTO (Japanese Chronic Total Occlusion) score [12].

MODIFIED MICROINJECTION MANOEUVRE

In comparison to the original description of the contrast-guided STAR technique [4], the modified microinjection manoeuvre involves the injection of a small volume of contrast (<1 mL) through a microcatheter or an over-the-wire (OTW) balloon. However a microcatheter is preferable due to the radiopaque marker at the catheter tip (as opposed to in the middle of most currently available OTW balloons) and its lower profile. The original technique where the contrast administration was performed via a forceful injection of contrast with the aim of using the hydraulic pressure to facilitate subintimal passage of a "knuckled" wire. The microinjection technique, on the other hand, involves a more gentle injection of a small volume of contrast. The rationale behind the minimal amount of contrast and reduced injection force relates to the generation of hydraulic forces in a forward direction along the longitudinal axis of the involved vessel. If hydraulic forces are applied through a solid occlusion by a selective injection of a small volume of contrast, the contrast will follow the path of least resistance, represented by the loose tissue segments within the occlusion. If the amount of contrast or the injection pressure used is increased, the presence of high-resistance intra-occlusional areas (fibro-calcific plaques) will divert hydraulic forces in a radial direction to the subintimal space, which is usually softer than the intraluminal obstructing material. In fact, excessive force may lead to extravascular contrast extravasation. The purpose of the microinjection is to modify the compliance of the plaque by softening the loose tissue of the occluded segment through an injection of viscous liquid (in this case contrast). This technique may facilitate CTO crossing with a dedicated coronary guide wire or enable access to the subintima thereby facilitating a dedicated re-entry procedure.

An additional application of this manoeuvre is to identify the exact position of the distal tip of the guidewire/microcatheter and its relationship to the target vessel architecture. An injection in the subintimal space resulting in a tubular dissection (Fig. 1) would indicate a location within the architecture of the main vessel and provide a road map to aid in further wire

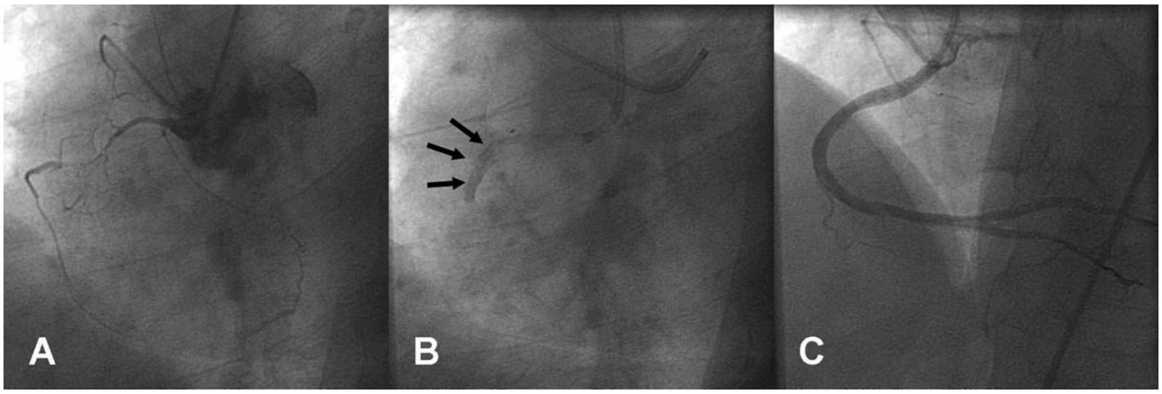

Fig. 1. **Appearance of tubular dissection. Initial appearance of proximal right coronary artery chronic total occlusion (A). Following microinjection through tip of OTW balloon, appearance of tubular dissection (black arrows, (B) indicating position within architecture of vessel. Final angiographic appearance following revascularization (C).**

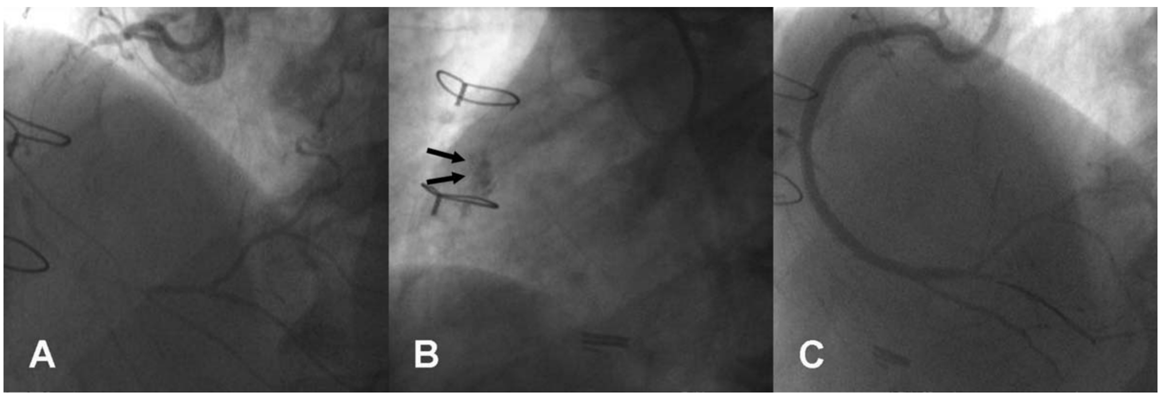

Fig. 2. **Storm cloud appearance. Initial appearance of proximal right coronary artery chronic total occlusion (A). Following microinjection, appearance of storm cloud (black arrows, (B) indicating position of tip in small branch. Final angiographic appearance following revascularization (C).**

manipulation. A storm cloud appearance [7] (Fig. 2), on the other hand would indicate the catheter tip in a small branch. This appearance will thus guide wire re-direction and correct placement of the wire in the architecture of the main vessel, allowing the safe continuation of the procedure.

From the technical point of view, the injection should be performed very gently with a very small amount of contrast in order to delineate a vague localized "blush" of contrast with a "patchy" distribution inside the occluded segment. This "patchy" distribution of the contrast could indicate the presence of islands of fibrotic tissue and/or loose fibrous tissue in the context of a very high calcific occlusion (Fig. 3). In order to prevent uncontrolled propagation of the dissection, the microinjection must be performed in a gentle manner, under fluoroscopic guidance. This approach enables tailoring the amount of contrast administered along with the force of injection in each individual case, as these parameters depend on the anatomic characteristics of the occlusive plaque.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation (SD). Normality of each continuous variable was tested with the Kolmogorov-Smirnov test. Differences in continuous variables between groups were compared using the Student *t*-test. Categorical variables are presented as numerical values and percentages and were compared using the Fisher's exact test. All report P values are 2-sided and values of $P < 0.05$ were regarded as statistically significant. Analyses were performed with SPP version 21.0 (SPSS, Chicago, IL).

RESULTS

During the study period, 59 patients were identified, in whom the microinjection technique was used (representing 4.7% of 1,192 patients treated with CTO PCI in the period under examination). Patient characteristics are summarized in Table I.

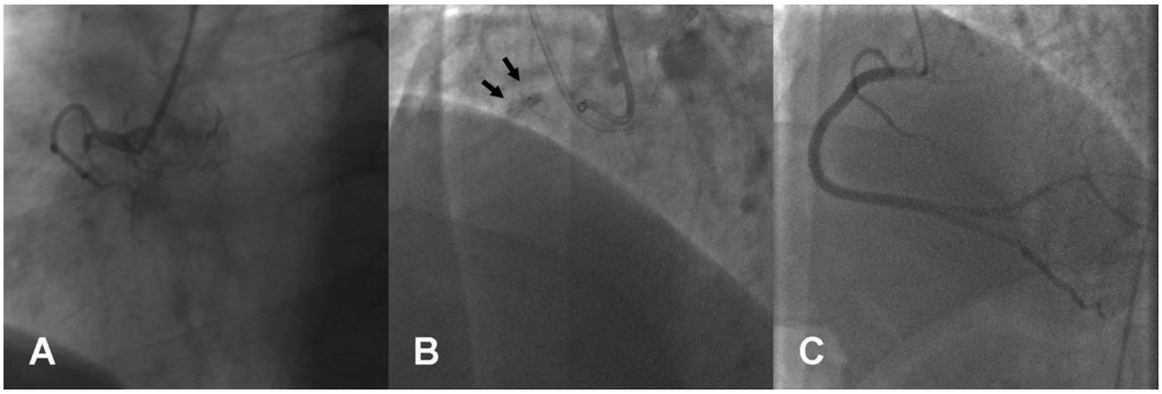

Fig. 3. Patchy appearance. Initial appearance of proximal right coronary artery chronic total occlusion (A). Following intralesional microinjection, patchy appearance (black arrows, (B) within occluded segment. Final angiographic appearance following revascularization (C).

TABLE I. Patient Characteristics

	Modified microinjection ($n = 59$)
Age, mean (± SD) (year)	65.6 ± 10.1
Male, *n* (%)	55 (93.2)
Hypertension, *n* (%)	46 (80)
Hyperlipidaemia, *n* (%)	34 (57.6)
Smoking, *n* (%)	25 (42.4)
Diabetes mellitus, *n* (%)	18 (30.5)
Family history, *n* (%)	29 49.2)
Previous CABG, *n* (%)	15 (25.4)
Renal failure, *n* (%)	7 (11.9)

n: number; SD: standard deviation; CABG: coronary artery bypass grafting.

TABLE II. Lesion Characteristics

	Modified microinjection ($n = 59$)
Target vessel	
LAD, *n* (%)	4 (6.8)
LCx, *n* (%)	8 (13.6)
RCA, *n* (%)	47 (79.7)
De novo lesion, *n* (%)	56 (94.9)
In-stent restenosis, *n* (%)	3 (5.1)
Bifurcation involvement, *n* (%)	25 (42.4)
J-CTO score	3.9 ± 0.7
Previous attempt, *n* (%)	21 (35.6)

n: number; LAD: left anterior descending artery, LCx: left circumflex artery; RCA: right coronary artery; J-CTO: Japanese chronic total occlusion score; SD: standard deviation.

Lesion characteristics are summarised in Table II. The majority of CTOs treated were in the right coronary artery (79.7%) and as expected were of high complexity with a mean J-CTO score of 3.9. 35.6% of lesions had a least one previously failed PCI attempt.

Indications for microinjection are summarised in Table III. 7 (11.9%) patients had the modified microinjection technique performed for more than one indication within the course of the same procedure.

TABLE III. Indications for Modified Microinjection Technique

	Modified microinjection ($n = 59$)
Plaque modification (proximal fibrous cap)	21 (35.6%)
Plaque modification (vessel course)	24 (40.7%)
Resolution of proximal cap ambiguity	7 (11.9%)
Resolution of vessel course	14 (23.7%)

Procedural characteristics and outcomes are summarised in Table IV. In spite of the high overall lesion complexity, the success rate in this patient cohort was 81.4% (left anterior descending artery: 75%, left circumflex artery: 87.5% and right coronary artery: 80.9%). A final anterograde approach was utilised in 45.8% of cases with the use of subintimal track/re-entry techniques in 76.3% of patients. Strikingly, there were no procedural complications related to the use of the reported modified microinjection.

DISCUSSION

There are three major findings with our use of this new contrast microinjection technique:

1. The microinjection is a useful adjunctive manoeuvre to facilitate crossing CTO lesions.
2. The microinjection can be utilized for a number of different indications, applicable to both anterograde and retrograde approaches.
3. The manoeuver appears safe.

Building upon the experiences gained using the STAR [4] and contrast-guided STAR [7] techniques we have further modified the microinjection manoeuver and have developed a completely new adjunctive tool in the treatment of complex CTO lesions. It is

TABLE IV. Procedural Characteristics and Outcomes

	Modified microinjection ($n = 59$)
Procedural success, n (%)	48 (81.4)
LAD, n (%)	3 (75)
LCx, n (%)	7 (87.5)
RCA, n (%)	38 (80.9)
Anterograde, n (%)	27 (45.8)
Subintimal track, n (%)	45 (76.3)
Wire cross time, min	71.9 ± 29.9
Number of stents/patient	3.0 ± 1.1
Total stent length, mm	98.4 ± 32.8
Fluoroscopy time (mins)	56.6 ± 17.2
Radiation dose, Gycm^2	140.8 ± 52.4
Contrast dose, mL	363.6 ± 111.7
Coronary perforation, n (%)	0 (0)
Peri-procedural MI, n (%)	0 (0)
Death, n (%)	0 (0)

n: number; SD: standard deviation; MI: myocardial infarction; LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery.

very important here to highlight the fact that this intervention is not intended to open the artery *per se*, but to facilitate recanalization of a complex lesion irrespective of the chosen technique. We found that the smaller volume (<1 mL) and more gentle contrast injection in many cases resulted in similar outcomes in comparison to the previous techniques but with a significantly lower risk profile. In this study, it is important to emphasize that no complications occurred with the use of this technique. Furthermore, the modified microinjection can be used for different applications including plaque modification and resolving ambiguity, which is particularly helpful when faced with high J-CTO score lesions [13–15].

We do not advocate the use of the contrast microinjection in all cases, but suggest that it can be used safely in instances when initial attempts have failed for example in lesions in the context of tortuosity, calcification or those that are distally located. This may explain the high frequency use of this technique for the treatment of RCA lesions and is also reflected by the fact that fluoroscopy (and therefore procedure) times were high in this patient group. Furthermore its use does not preclude the use of any other strategy or technique. We therefore believe that in the hands of experienced CTO operators, this is very much a simple, safe adjunctive manoeuver to aid in complex cases and to facilitate procedural success in combination with other contemporary techniques.

Anatomical and histopathological analysis of chronic arterial occlusions has demonstrated the presence of patchy fibro-calcific areas intermingled with loose tissue segments [16]. Soft plaque consisting of cholesterol-laden cells with loose fibrous tissue and a network of neovascular channels and is more frequent in younger occlusions (<1 year old). Conversely, hard plaques are more prevalent with increasing CTO age and are characterized by dense fibrous tissue and often contain large fibro-calcific regions without neovascular channels. This age-related increase in calcium and collagen content of CTOs partly explains the progressive difficulty during PCI in crossing older occlusions [16,17]. In refractory cases, the modified microinjection may modify the compliance of the plaque by softening the loose tissue of the occluded segment through an injection of viscous liquid (in this case contrast).

LIMITATIONS

This was a small retrospective study carried out in a small number of high-volume expert CTO centres and so the results may not be applicable to all patients. We do not have long-term data with regards to the influence of this tool on future restenosis rates but do not believe that this would have any impact upon this in view of other more important issues such as complexity of lesion, length of stented segment etc.

CONCLUSIONS

In conclusion, initial experiences with the modified microinjection demonstrate that it can be performed safely, is reproducible by a number of different operators in different centres and is broadly applicable. We describe a completely new approach that is based upon the evolution of the originally described microinjection techniques. Whilst not required for all CTO procedures it can be a helpful adjunctive tool to increase the likelihood of success especially in complex, or refractory cases, without compromising the safety of the procedure.

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