



## Review

# The Canadian Contribution to Science, Techniques, Technology, and Education in Chronic Total Occlusion Percutaneous Coronary Intervention

Luiz F. Ybarra, MD, PhD, MBA,<sup>a</sup> Christopher E. Buller, MD,<sup>b</sup> and Stéphane Rinfret, MD, SM<sup>c</sup>

<sup>a</sup>London Health Sciences Centre, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

<sup>b</sup>Medical Director, Teleflex Inc, Wayne, Pennsylvania, USA

<sup>c</sup>Division of Cardiology, Department of Medicine, McGill University Health Centre, McGill University, Montreal, Quebec, Canada

### ABSTRACT

Chronic total occlusions are considered the most complex coronary lesions in interventional cardiology. This article reviews the Canadian clinical and academic contributions to this field, including innovative procedural techniques, teaching and proctoring, clinical research, and the development of novel tools and therapies.

### RÉSUMÉ

L'occlusion totale chronique est considérée comme étant la lésion coronarienne la plus complexe dans le domaine de la cardiologie interventionnelle. Nous passons ici en revue les contributions des cliniciens et des universitaires canadiens dans ce domaine, notamment en matière de techniques d'intervention novatrices, d'enseignement et d'encadrement, de recherche clinique et de mise au point de nouveaux outils et traitements.

Chronic total occlusions (CTOs) have long been considered a barrier to percutaneous revascularization. Nevertheless, early Canadian pioneers, with very limited tools, were active in this field as early as the 1980s. In their steps, subsequent Canadian interventional cardiologists came to occupy an internationally prominent role in the development of techniques and equipment, in CTO percutaneous coronary intervention (PCI) research, and in impactful knowledge translation to a broad audience of learners.

As early as the late 1980s, several centers across the country had already gained substantial experience with balloon angioplasty once Simpson's over-the-wire (OTW) balloon systems became available. With this catheter system, one could easily remove and replace a workhorse guidewire with one with a stiffer tip. At this time, procedures were performed with only antegrade coronary access. Dual access to visualize the distal bed, the current standard approach, started much later. Operators, once they believed they had successfully crossed the occlusion, would use the OTW balloon lumen to

inject diluted dye to confirm true lumen position and give additional branching detail not available otherwise. However, this technique often precipitated termination of the procedure when, due to a non-luminal position, contrast was injected into the vessel wall causing hydraulic dissection, or worse, outside the vessel. In spite of this issue, use of monorail systems was considered best practice and thus their use increased, with only minimal improvement in OTW technology.

Although the Canadian success and complication rates were not reported in this era, major limitations were recognized, including the sobering restenosis and re-occlusion rates of the vessel after long successful attempts. Work presented at the 1992 Canadian Cardiovascular Society scientific sessions demonstrated severe recoil and frequent re-occlusion within 24 hours of plain old balloon angioplasty for CTOs. This, and other observational studies, led to the Total Occlusion Study of Canada (TOSCA) trial. The trial assembled experienced PCI operators from across the country and randomized 410 patients after successful crossing of the occlusion to either angioplasty alone or stenting.<sup>1,2</sup> Only patients with native coronary stenoses accompanied by thrombolysis in myocardial infarction (TIMI) grade 0 or 1 flow in  $\geq 3.0$  mm-diameter vessels could be recruited. It is important to mention that vessels with TIMI 1 flow would not be considered CTOs according to current definitions. Of 1118 patients screened, only 101 were excluded for inability to cross with a guidewire, which corresponds to quite a high success rate despite the paucity of dedicated equipment at that time. Such good crossing success was likely explained by the experience of the

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Corresponding author: Dr Stéphane Rinfret, Associate professor of Medicine, McGill University, Director, Interventional Cardiology, McGill University Health Centre, Glen site, 1001 Boulevard Décarie, Montréal, Quebec, H4A 3J1, Canada. Tel.: +1-514-843-1502; fax: +1-514-843-1694.

E-mail: [stephane.rinfret@mcgill.ca](mailto:stephane.rinfret@mcgill.ca)

See page 24 for disclosure information.

operators in the trial but also by the fact that 36% of the lesions had TIMI 1 flow, with a relatively short median length of 30.5 mm. Stenting (generally requiring multiple Palmaz-Shatz 15-mm-length devices) reduced the re-occlusion rate from 20% to 11% and target vessel revascularisation from 15.4% to 8.4%. The binary restenosis rate was reduced from 70% to 55%. Although the results using multiple first-generation bare-metal stents were better than with balloon angioplasty alone, 1 in 10 stented vessels developed re-occlusion, and half of the segments had re-stenosis, proportions that were much higher than bare-metal stenting of non-occluded vessels.<sup>3,4</sup> TOSCA was also the first study to link improvement in ejection fraction to sustained coronary patency.

Drug-eluting stents changed *post*-PCI results dramatically,<sup>5,6</sup> typically yielding single-digit re-occlusion rates among vessels with initial treatment success. Nevertheless, CTOs remained challenging to cross such that CTO PCI remained unpredictable for years after widespread use of drug-eluting stents. Strauss and collaborators assembled the first Canadian CTO registry, which collected data from close to 15,000 all-comers undergoing coronary angiography from 3 Canadian centers.<sup>7</sup> His seminal work aimed to document how many of those patients had a CTO present, and how they were managed. In this registry, 18% of patients had a CTO present, and in the majority of cases, it was managed medically despite the presence of angina in the majority of patients. Of those patients with multivessel disease who were managed with PCI, most CTO segments were not revascularized. When CTO PCI was attempted, the success rate was only 70% in this highly selected subgroup. As a comparison, the surgeons were able to revascularize 89% of the CTO vessels.<sup>7</sup> This Canadian study is among the most commonly cited publications in the CTO field, with over 500 citations. Subanalysis from a large surgical trial showed that a coronary artery bypass graft (CABG) causes new CTOs in 20% of patients,<sup>8</sup> confirming earlier findings by Bourassa and collaborators.<sup>9</sup> This phenomenon is likely attributable to competitive flow from the graft and is more common in vessels that had more than 90% stenoses.<sup>8</sup> Such a process is not benign, as new CTOs had an adverse impact on outcomes.<sup>10</sup> The Canadian CTO registry also confirmed a lower CTO prevalence and lower revascularization rates of CTOs by CABG in female compared with male patients.<sup>11</sup> Animal models for CTOs were also developed,<sup>12,13</sup> including a calcified preclinical model of CTO,<sup>14</sup> as well as other alternative treatments (collagenase) with promising effect.<sup>15-18</sup>

Although clinical benefits of CTO PCI were often debated in the 2000s, and frequently used to justify lack of attempts by many operators, Joyal et al.<sup>19</sup> published the first meta-analysis assessing clinical outcomes of patients with successful vs failed CTO PCI. This work demonstrated a strong and independent association between successful PCI and lower long-term mortality, with similar observations with respect to lower rates of angina and CABG.<sup>19</sup> This paper has been cited over 400 times in the literature. At the same time, operators were focusing on newer techniques to achieve higher success in a broader spectrum of CTO anatomies. With a focus in facilitating CTO crossing, collagenase was tested in a first-in-man pilot study, with good initial results.<sup>20</sup> Subsequently, the TOSCA-5 trial tested the impact of collagenase in softening

**Table 1. Studies published by Canadian training centers**

Topic	Finding
Complexity scores	First validation of the Japanese-CTO score in large series <sup>76</sup>
Peri-procedural myocardial infarction	Troponin elevation was quite frequent and had however no adverse prognostic significance in the Quebec cohort. <sup>77</sup>
Quality of life	Patients with angina derived the same benefit irrespective of the complexity of their CTO, which showed the importance of being able to master all techniques for a variety of patients who benefit from the procedure irrespective of their anatomy. <sup>78</sup>
CTO revascularization	Infrequent in a large single-center experience <sup>79</sup>
Outcomes in different subgroups	In-stent CTOs, <sup>80</sup> post-CABG CTOs, <sup>81</sup> sub-stent revascularisation, <sup>82</sup> post-rotational atherectomy, <sup>83</sup> and using newer dissection-reentry techniques <sup>84,85</sup>
Techniques and approaches	Use diseased or occluded saphenous vein graft instead of collaterals to perform a retrograde approach in post-CABG patients <sup>86</sup> ; effectiveness of the surfing technique to cross septal collaterals <sup>87</sup> ; use of sheathless 8F guide catheters through the radial approach <sup>88</sup> ; use of drug-eluting balloon to optimize midterm result after failed CTO PCI and to help a subsequent reattempt <sup>89</sup>
Definition standardization / ARC	Need for standardized definitions in the CTO field, leading to the creation of the international collaboration CTO-ARC. <sup>90</sup>

ARC, Academic Research Consortium; CABG, coronary artery bypass graft; CTO, coronary chronic total occlusion; PCI, percutaneous coronary intervention

the proximal cap of CTOs in suitable lesions. Although collagenase did not improve the success rate, lesions were crossed using softer wires.<sup>21</sup>

Following soon after seminal work by Japanese and American pioneers,<sup>22</sup> the first successful retrograde CTO PCI was performed in Canada in 2010.<sup>23</sup> With increased interest across Canada in learning new techniques and especially incorporating the trans-radial approach in CTO PCI, several operators started contributing to the early experience through exchange and collegiality. During these years, we witnessed a progressive move from the traditional bifemoral approach to liberal use of the radial-femoral approach, and ultimately biradial access, largely attributable to Canadian advocates.<sup>23,24</sup> In 2011, the first Canadian antegrade dissection re-entry case using the CrossBoss and StingRay system was performed in Quebec City. This early era gave birth to the so-called hybrid approach, developed in collaboration with US peers, which became the standard of care until now.<sup>25,26</sup> This approach advocates for a rapid switching between 3 techniques (antegrade wiring, retrograde, and antegrade dissection-re-entry) in order to maximize the success rate of one single procedure, a rate that is now higher than 90%. The long-term safety of subintimal stenting in CTO PCI reassured the community regarding the value of the hybrid approach.<sup>27</sup>

New CTO PCI techniques were then developed, such as the balloon-assisted microdissection technique for balloon-undilatable lesions,<sup>28</sup> and move-the-cap techniques for ambiguous proximal CTO cap.<sup>29</sup> Wijeyesundera et al. reported in a cohort of 387 patients from the Canadian CTO registry that CTO territory revascularisation was associated with substantial quality-of-life improvements, one of the few early studies on this important health status metric.<sup>30</sup> Another study showed that CTO revascularisation (with either CABG or PCI) was associated with improved outcomes in a population-based analysis of 7864 patients in Ontario. In the overall cohort, 29% of the patients had a CTO, and only 41% of the CTO patients were revascularized with PCI, highlighting the need for further expansion of the CTO PCI techniques and training.<sup>31</sup> Combining the experiences from multiple centers, the Canadian CTO PCI registry, which gathered data on CTO PCI short- and long-term outcomes across Canada since 2012, has recently been completed with over 1000 patients. This study answers important questions, especially those related to the sustainability of treatment benefits.

Many Canadian centres also started to offer dedicated CTO PCI training programs, which led to multiple high-quality research efforts in different aspects of the CTO PCI field (Table 1).

Furthermore, it is important to mention the Canadian contributions to innovation in tools for CTO PCI. The Progress CTO Guidewire family (Abbott, Santa Clara, CA), as well as the TrapLiner (Teleflex, Wayne, PA), a guide extension catheter with a balloon attached to facilitate equipment exchange, were some of the creations. The Newton system is a technology that suspends the lead apron to reduce musculoskeletal burden on CTO operators. Finally, a new guidewire technology developed by SoundBite Medical, a company from Montreal, which uses “jackhammer-like” energy to ease crossing of CTOs, was first used in a human coronary occlusion in Canada and is now being tested in a large international study.

The CTO PCI field remains dynamic. From an era of dabbling with poorly selected guidewires bent with large radius curves, without contra-lateral guidance, and poor expected (and observed) results, we have successfully moved to an era where up-to-date standardized techniques and approaches are taught, encouraged, and available in most hospitals across the country. Canadian authors have contributed to the rapid expansion of information sources available to learn the hybrid approach, from consensus statements,<sup>32,33</sup> international research collaborations,<sup>34-42</sup> review articles,<sup>43-55</sup> editorial comments,<sup>26,56-65</sup> case series or reports,<sup>66-74</sup> dedicated textbooks,<sup>75</sup> and as faculty in large dedicated CTO PCI conferences across the world. All sources of information converge to the same message: mastering all steps of the hybrid approach is key to providing the best results with the lowest complications in patients considered for CTO PCI.

Mirroring specialized practices such as transcatheter aortic valve implantation, CTO PCI has evolved into an interventional cardiology subspecialty of its own. Increasingly, Canadian clinical cardiologists now recognize the role of state-of-the-art CTO PCI in management of symptomatic chronic ischemic heart disease. CTO PCI now offers a predictable, effective, and durable treatment option for patients. The

emphasis on collaborative teaching and proctoring that has accompanied technical progress has resulted in CTO PCI availability at most major Canadian interventional programs.

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