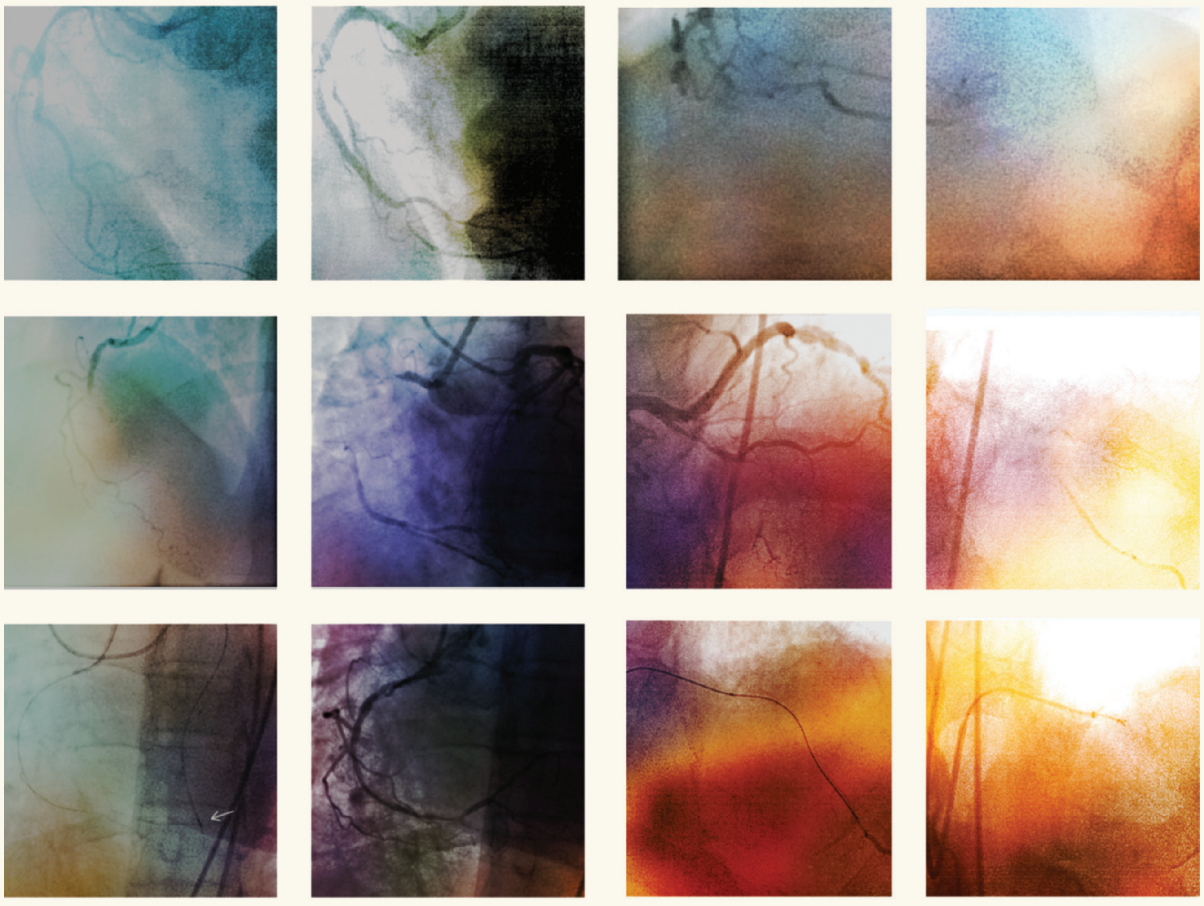
chronic total occlusions

A GUIDE TO RECANALIZATION

second edition



Edited by Ron Waksman and Shigeru Saito

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Chronic Total Occlusions

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A Guide to Recanalization

Second Edition

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Foreword

Many years ago I was chairing a symposium at the American Heart Association annual Scientific Sessions during which a paper on chronic total occlusions was presented by colleagues from Japan, some of whom are authors of this book. The audience was stunned by the report that 90% of attempted chronic total occlusions were actually recanalized by this group. The reaction could be best described as incredulous. I confess that my reaction must not have been very different since my colleague, John Douglas, and I had been working alongside our partner, Andreas Gruentzig – who was a pretty competent interventionalist – and our success rate was just over two-thirds of CTOs attempted. Perhaps in response to the perceived reaction of the audience, these Japanese colleagues invited me to a small live case demonstration course in Japan. As I recall, 10 cases of chronic total occlusion were attempted and nine were successful, convincing me that a 90% success rate was not unattainable. Since then, chronic total occlusion revascularization has developed into what borders on a specialty unto itself. Some operators have taken on these cases as a special interest, even while many interventionalists around the world continue to avoid dealing with this difficult subset. The debate over the clinical relevance of chronic total occlusions has evolved from an attitude of indifference to one of recognition that many of these patients are highly ischemic and restoration of perfusion is beneficial. Indeed chronic total occlusion is the main feature that results in incomplete revascularization with percutaneous coronary intervention and is a primary reason for surgical referral of these patients.

The first edition of *Chronic Total Occlusion: A Guide to Recanalization* brought together an impressive group of "thinkers and tinkerers" from around the world to address this challenging condition. Now, four years later, Drs. Waksman and Saito, and the highly experienced authors they have recruited, have brought the knowledge base of this technology up to date. The advances have necessitated a significant increase in the number of chapters to now include the radial artery approach and several novel techniques.

As the limitations of percutaneous coronary intervention using current technology become clear from the SYNTAX trial and other observations, it is even more interesting to contemplate the future of the less invasive approach. The solutions to chronic total occlusion, not only in the hands of expert operators, but widely applied will be pivotal in charting the direction of coronary intervention in the years to come. This second edition will be of great value to those who strive to influence that course.

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Preface

On behalf of our expert contributors, we are proud to present the second edition of *Chronic Total Occlusions*.

Over the past decade we have been privy to tremendous progress in technology and technique when treating chronic total occlusion (CTO) lesions. Namely, the Japanese and experts worldwide have pioneered new tools and strategies to increase success rates and to minimize complication rates for what is considered the most challenging and complex intervention. Due to their complex anatomy, CTOs have been referred to as the final frontier in interventional cardiology. CTO treatment remains quite resource intensive – it requires great knowledge, operator expertise, and patience.

Due to perceived difficulties in recanalization, percutaneous coronary intervention is often not the treatment of choice when a CTO is present, with operators instead choosing medical treatment or coronary artery bypass surgery. In recent years, however, with advances in specialized equipment and techniques, expert operators have significantly improved recanalization rates.

Our goal with the second edition of *Chronic Total Occlusions* is to provide interventionalists with an in-depth view into the latest advancements in the field. In this edition you will find introductory chapters describing CTO pathology and physiology; indications and case selection; and a review of current clinical trials.

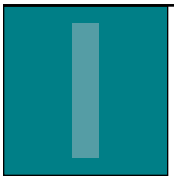
As we aim to improve CTO procedure safety and efficacy while reducing procedure time, several invasive and noninvasive imaging techniques have helped facilitate improved image guidance during this time. Discussed modalities include computed tomography angiography and magnetic navigation wires, as well as intravascular ultrasound and optical coherence tomography.

In the last few years, the advent of new and dedicated CTO crossing wires, re-entry devices, and crossing catheters, combined with new and innovative techniques, has led to a significant improvement in success rates. Our Japanese colleagues have once again shared with us their knowledge and expertise on the innovative tips and tricks they've developed, including chapters on the latest family of wires, wire control handling, and the parallel wire technique.

We would like to thank our highly regarded, respected contributors for their expertise on this specialized subject matter, our managing editors, and the publisher for bringing this edition to press.

It is our hope that the second edition of *Chronic Total Occlusions* serves as an instructional tool and comprehensive guide to help understand the multiple complexities of treating CTOs.

Ron Waksman
Shigeru Saito



PART I

Pathology, Indications, and Review of Clinical Trials

CHAPTER 1

The pathobiology of CTO

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Introduction

Chronic total occlusion (CTO) is defined as occlusion age of at least one month, with angiographic thrombolysis in myocardial infarction (TIMI) flow grade 0 or 1 [1]. CTOs are classified as "early chronic" and "late chronic" if their age is 1–3 months old and >3 months old respectively. The current understanding of CTO development is based on animal CTO models as well as on autopsy and imaging studies in humans. Recent progress in elucidating CTO pathobiology has led our group to identify several novel biological targets to facilitate guidewire crossing during percutaneous coronary intervention (PCI).

Current paradigm of CTO evolution

The development of CTOs includes several specific stages with unique histologic characteristics present at each stage. The initial acute event leading to the development of a CTO is in many cases a ruptured atherosclerotic plaque with bidirectional thrombus formation [2]. Clinically the arterial occlusion may develop insidiously with minimal symptoms or may present as an acute coronary syndrome. In patients with minimal or no symptoms, the timing of the occlusive event cannot be clearly identified. In fact, the age of approximately 60% of CTO cases cannot be reliably dated by symptoms [3]. In patients with ST segment elevation myocardial infarction (STEMI) not treated with reperfusion therapy, an occluded infarct related artery has been found in 87% of patients within 4 hours, in 65% within 12–24 hours, and in 45% at 1 month [4, 5]. Up to 30% of patients treated with thrombolytic therapy alone have a chronically occluded artery 3–6 months after MI [6]. In patients treated with percutaneous coronary intervention (PCI) during evolving acute myocardial infarction (AMI), approximately 6–11% will have chronic occlusion of an infarct related artery at 6 months, due to either initial treatment failure or late re-occlusion [7].

Characterization of CTO development in human studies is problematic since CTOs are often diagnosed at a very late stage, and data regarding initial stages in their evolution is lacking. Several animal models have been developed to systematically define the development stages of a CTO; however these models have certain characteristics that could potentially limit their relevance to humans, such as the lack of underlying atherosclerotic substrate or significant calcification. In this chapter we shall review the current understanding of CTO pathobiology.

Development of CTOs

Acute arterial occlusion due to atherosclerotic plaque rupture with thrombus formation seems to be a common initiating event, which then triggers an inflammatory reaction. The freshly formed thrombus contains platelets and erythrocytes within a fibrin mesh, which is followed by an invasion of acute inflammatory cells. Jaffe *et al.* [8] have recently shown that an acute inflammatory response during the first 2 weeks after the initial event is accompanied by patchy formation of a proteolycan-enriched extracellular matrix and myofibroblast infiltration into the thrombotic occlusion. At the initial part of the intermediate stage (6 weeks), there is marked negative arterial remodeling and disruption of the internal elastic lamina accompanied by intense intraluminal

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neovascularization and increased CTO perfusion. Total microvessel cross-sectional area increases 2-fold along with a nearly 3-fold increase in the size of individual intraluminal vessels. However, the latter intermediate stage (12 weeks) is characterized by decreasing microvessel formation and CTO perfusion which further declines at the advanced stage (18–24 weeks). A progressive decrease in the CTO perfusion coincides with gradual replacement of proteoglycans by collagen in the extracellular matrix. Accumulation of collagen and calcium characterize the later stages of CTO maturation (Figures 1.1 and 1.2). The density of the fibrocalcific tissue is highest at the proximal and distal ends of the lesion compared to the body. Thus, the composition of the CTO evolves over time with remarkable spatial variability along the length of the CTO. From a pathobiology standpoint, three specific regions of the CTO have been identified:

(1) The proximal fibrous cap is a thickened structure at the entrance (the proximal end) of the CTO containing particularly densely packed collagen. It usually contains types I, III, V, and VI of collagen. Type IV collagen has also been observed in calcified tissues [9]. This region represents a distinct physical barrier to accessing the CTO.

(2) The distal fibrous cap also contains densely packed collagen, but is commonly regarded (although not proven in studies) as a thinner and softer structure compared to the proximal cap. This has been part of the rationale for developing the retrograde approach to cross the CTO.

(3) The main body of CTO.

Human coronary artery autopsy studies [10] have shown that the lumen of the CTO in some cases contains organized thrombus. Recanalization channels were observed in nearly 60% of lesions. Unlike the preclinical rabbit femoral artery model, the frequency of lumen recanalization and sizes of the channels were similar in different CTO ages. The intimal plaques within the CTO contained collagen, calcium, elastin, cholesterol clefts, foam cells, giant cell atherophagocytes, mononuclear cells (lymphocytes, monocytes), and red blood cells. "Soft" or cholesterol-laden lesions were more prevalent in younger CTOs age (< 1 year); however the amount of cholesterol-laden and foam cells declined with advancing CTO age. Older age CTOs typically contained hard fibrocalcific lesions ("hard plaque"). Iron and hemosiderin depositions could be observed at sites of previous intimal plaque hemorrhage. Extensive recanalization of the intimal plaques by neovascular channels was frequently evident particularly within and adjacent to the sites infiltrated by inflammatory cells (lymphocytes and macrophages). In some cases, intimal neovascular channels directly communicate with adventitial vasa vasorum, while their communication with lumen recanalization channels was rarely observed. Neovascular channels were also observed in the vascular medial layer; the extent of medial neovascularization was proportional to the cellular inflammation in the intimal plaque. The adventitia of the vessel is usually extensively revascularized in CTOs of all ages.

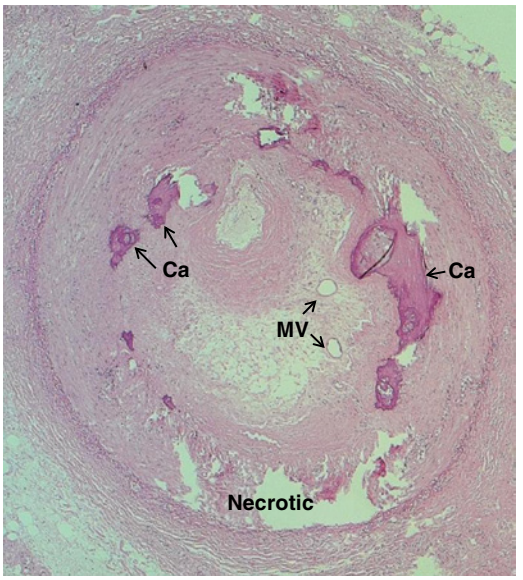

Figure 1.1 Hematoxylin-eosin stained human coronary CTO, demonstrating extensive collagen-rich fibrous tissue, several patches of calcification (Ca), two small microvessels (MV), and a large necrotic area (necrotic). (Courtesy of Dr. Jagdish Butany, University Health Network, Toronto, ON, Canada.)

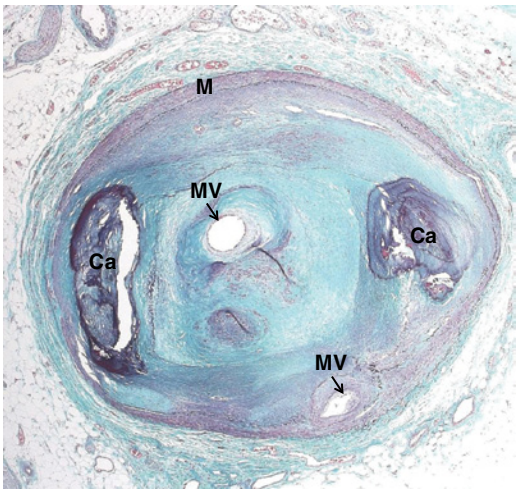

Figure 1.2 Elastin-trichrome stained human coronary CTO, demonstrating fibrous tissue (lighter staining material inside the lumen), with two distinct areas of calcification (Ca) and two microvessels (MV). M = media. (Courtesy of Dr. Jagdish Butany, University Health Network, Toronto, ON, Canada.)

Again, the extent of adventitial neovascularization is correlated to adventitial cellular inflammation. Munce *et al.* have shown in a rabbit peripheral artery CTO model that a large rise in extravascular vessels surrounding the occluded artery occurred at early time points, which was followed by a significant increase in intravascular vessels within the central body of the occlusion. The temporal and geographic pattern of microvessel formation and the presence of connecting microvessels support the thesis that the extravascular vessels may indeed initiate formation of the intravascular channels within the center of the occlusion. However, as the CTO matures beyond 6 weeks, a reduction in the size and number of central intravascular microchannels was demonstrated, suggesting that many of the vessels in this region become nonfunctional [11].

Neovascularization and angiogenesis

There are three types of microvessel formation in arteries with advanced atherosclerotic lesions. The first pattern occurs in the vasa vasorum, which is the fine network of microvessels in the adventitia and outer media. These vessels proliferate in atherosclerosis and in response to vascular injury such as angioplasty and stenting [10, 12, 13]. Hypoxia in the outer layers of the vessel wall appears to act as an important stimulus [13]. Occasionally in CTOs these adventitial blood vessels are well developed and can be recognized as "bridging collaterals." Such microchannels, which can recanalize the distal lumen, may result from thrombus derived from angiogenic stimuli [14], and can be recognized on an angiogram by the appearance of a well defined stump leading into the CTO. Second, neovascularization can develop within occlusive atherosclerotic intimal plaques, predominantly in response to chronic inflammation [15]. The localization of plaque vessels in so-called "hot spots" in the shoulders of atheromas may predispose these plaques to rupture and acute coronary events [16, 17]. The third type is the pattern of intraluminal microvessel formation or "recanalization channels." These microvessels generally range in size from 100 to 200 μm, but can be as large as 500 μm [10]. In contrast to the vasa vasorum which run in radial direction, these intimal microvessels run within and parallel to the thrombosed parent vessel [16], and therefore have particular relevance for crossing of CTOs as a pathway for guidewire crossing.

Angiogenesis within the CTO is a complex process which starts with recanalization of the thrombus through a mechanism that is dependent on the proteolytic activity of circulating mononuclear cells and engraftment of endothelial progenitor cells [17]. Angiogenesis within the arterial thrombi is modulated by pro-angiogenic molecules in the extracellular matrix, including perlecan [18], hyaluronan [19], and anti-angiogenic agents such as collagen type I [20] and decorin [21]. The process of angiogenesis is initiated by vasodilation and increased permeability of the existing microvessels. This is followed by coordinated proteolysis, resulting in the destabilization of the vessel wall and endothelial cell migration and proliferation with subsequent formation of primitive endothelial tubes [22, 23]. Maturation of these tubes includes recruitment of pericytes or smooth muscle cells and deposition of extracellular matrix [24, 25]. Various aspects of angiogenesis are regulated by multiple growth factors including vascular endothelial growth factor (VEGF) and its receptor VEGFR2; platelet derived growth factor (PDGF) and its receptor PDGFR-β [25, 26] , angiopoietin-1, angiopoetin -2, and TIE-2 receptor [21, 22, 24, 27], fibroblast growth factor-2 (FGF-2) [28], TGFβ [29], and endothelium derived nitric oxide [30].

Calcification

For non-CTO atherosclerotic plaques; calcification is correlated with chronic kidney disease, diabetes mellitus, and is a consequence of aging. Our understanding of the balance between promotion and inhibition of calcification in the CTO is much more limited.

Most CTOs contain calcification that ranges from minor to extensive, depending on several factors including the age of the occlusion [31]. Intimal plaque calcification is seen in 54% of CTOs aged 3 months or less, and reaches 100% in CTOs aged above 5 years. In contrast, insulin-dependent diabetes mellitus was more frequently observed in patients with predominantly cholesterol laden or mixed CTOs than in those with fibrocalcific CTOs [9]. The extent of the CTO calcification has repeatedly been identified as a negative predictor of PCI success due to failure to cross with guidewires [32, 33, 34].

The process of the CTO calcification is usually simplified into two mechanisms [35, 36]:

(1) Passive process: It was initially considered that calcium precipitation occurred when apoptotic cell fragments and cholesterol crystals served as a crystallization nidus and the calcium and phosphate concentration approached the salt solubility product in the presence of a lower concentration of local calcium-chelating molecules. The formation of hydroxyapatite crystals in this way is now regarded as a semi-regulated process, and the high phosphate levels might induce vascular smooth muscle cells to differentiate into an osteoblastic phenotype resulting in bone formation.

(2) Active osseous process: Recruitment of osteoblasts and osteoblast-like cells, which is triggered by immunomodulating cytokines (including bone morphogenetic proteins, osteogenic transcription factors etc.). Similar to skeletal bone, these bone/cartilage-like structures are subject to resorption by osteoclast-like cells.

Current research in CTO pathobiology

Identification of specific components of the CTO at various stages is critical to understanding CTO pathobiology and improving guidewire crossing success rates. Complementary information is obtained by several approaches:

Human CTO samples

Samples of CTO collected during autopsies, amputations, endarterectomies, and transplants provide an important but very infrequent opportunity to study these highly heterogeneous lesions. Different modalities of *ex vivo* CTO imaging is an important area of present and future studies.

Animal models of CTO

A challenge in developing animal models of CTO is the lack of spontaneous atherosclerosis in animals. Different approaches have included external arterial constriction, thermal injury, gas-drying of the artery, injection of authologous blood above a stenosis, copper stents, stents with occluded outflow, alcohol injection, and insertion of polymer plugs. We have developed a rabbit CTO model in which thrombin is injected into an isolated femoral artery segment [37]. This model was used in investigation of the natural history of CTO [8]. Due to the significant impact of arterial calcification on the success rate of percutaneous CTO revascularization, the creation of a calcified CTO model is important for the future research. Suzuki *et al.* [38] used apatite-coated bioabsorbable polymer sponges to produce calcified CTO lesions in rabbit and pig coronary arteries/peripheral arteries. These lesions were found to have microvascular channels and microcalcification, yet no significant osseous transformation was visible. Recently, we were able to develop a calcified CTO model in a common femoral artery of rabbit (unpublished results), which incorporates both passive and active calcification. The model is unique in that the CTO is heavily calcified and contains islands of bone/cartilage that are very similar to human pathology. Interestingly, we have also noticed that the patterns and time sequences of microvessel formation and underlying inflammatory responses appear to differ between animal models. The rabbit femoral artery had a very predictable pattern of microvessel formation and then regression during the initial 12 weeks of CTO formation [8]. In contrast, pig coronary arteries demonstrated a much more heterogeneous response of neovascularization during the same 12 week period (unpublished observations).

CTO imaging techniques

Coronary angiography remains the primary imaging technique for assessment of the CTO in clinical practice. However, other imaging modalities now provide an opportunity to identify specific components of CTO in patients and experimental models. Proposed imaging techniques for CTOs can be broadly categorized into large field of view and modest resolution (such as cardiac magnetic resonance imaging (MRI) and computed tomography (CT)), and small field of view and high resolution [39]. High-resolution methods include forward-looking adaptations of intravascular ultrasound (IVUS), optical coherence tomography (OCT), and intravascular MRI. Many of these imaging modalities can be coupled with interventional techniques, and thus improve upon the guidance provided by angiography during revascularization. The multi-slice or multi-detector CT coronary angiogram is rapidly gaining in popularity in the assessment of coronary lesions. It is especially useful in the assessment of the amount of CTO calcification, which has a negative predictive value for successful coronary intervention [32, 33, 34]. Three-dimensional micro-CT is a high resolution imaging technique for *ex vivo* samples that provides detailed rendering of complex microscopic vascular structures with a resolution down to 17 μm [11].

Cardiac MRI with contrast agents has a spatial resolution down to 200 μm in plane and about 1 mm through the plane and can determine composition of atherosclerotic plaque components within the CTO. We have used MR contrast agents such as gadolinium and clariscan to assess intraluminal perfusion in experimental CTO [8]. Another application of cardiac MRI that may have relevance to the assessment of CTO is direct thrombus imaging (MRDTI). MRDTI allows for the estimation of the extent and age of thrombi without the use of an exogenous contrast agent and is being refined for use towards coronary lesions.

Intravascular MRI can image soft tissue and may potentially guide therapeutic procedures without ionizing radiation or nephorotoxic agents. Early efforts in intravascular MRI development have been directed toward side-viewing orientations. Currently forward-looking intravascular MRI coils are also available [40]. The recent advent of 3.0 T magnets has

allowed a reduction in exogenous contrast dose without compromising overall imaging quality.

Intravascular ultrasound (IVUS) – both conventional (side-looking) and forward-looking – is a particularly appealing imaging modality for image guidance purposes due to its high resolution and reasonable penetration depth. IVUS based techniques such as elastography, radiofrequency tissue characterization, or virtual histology can be incorporated into the forward-looking IVUS system to identify the mechanical properties and composition of CTOs [11].

Compared to IVUS, optical coherent tomography (OCT) has higher resolution at the cost of poorer penetration. Forward-looking OCT has more than sufficient resolution to clearly depict microchannels and the different layers of the vessel wall.

Summary

In this chapter we have summarized the key components of CTOs and the impact of each on guidewire crossing and balloon compliance. We described innovative imaging modalities, such as forward-looking IVUS and OCT and CMR, which are in various stages of development, including evaluation in animal models. Better understanding of the CTO structure incorporating the above imaging techniques with advances in guidewires and other plaque modification strategies may enable significant improvements in CTO revascularization. The pathophysiology of collagen accumulation and calcification in CTO is now at the frontier of CTO translational to clinical research. These efforts will hopefully lead to a breakthrough in CTO revascularization success rates in the near future.

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CHAPTER 2

Collateral circulation in CTO

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Introduction

Coronary collateral circulation (CCC) is an alternative circuit that conveys blood to the ischemic myocardium perfused by a severely stenosed or occluded coronary artery [1, 2]. The functional role of the coronary collateral circulation has been disputed for a long time. Because a well-developed CCC is usually associated with severe coronary stenosis, some investigators have assumed that the existence of collateral circulation is a marker of coronary artery disease (CAD) [3]. Over the past three decades, accumulating evidence has documented that pre-existing well-developed CCC at the onset of acute myocardial infarction plays an important role in preserving left ventricular function, reducing infarct size, preventing left ventricular aneurysm formation, and survival [1, 4, 5, 6]. Thus a significant functional role of CCC is now well known. The collateral arteries' path can be epicardial or intramyocardial and they can function as contra-lateral or ipsi-lateral conduits [7].

Coronary collateral arteries in healthy individuals in patients affected by CAD and after acute myocardial infarction

The human coronary circulation is not an end-arterial system as it was previously considered. Indeed, collateral arteries may occur in neonates and in healthy persons without coronary artery disease (CAD) [8, 9, 10]. In these cases collateral circulation may be also unexpectedly visible or recruitable in the absence of coronary occlusion [11]. In a post-mortem study published in 1963, Fulton elegantly resolved this issue using a new radiographic technique and demonstrated that a large number of arterio-arterial anastomoses can be found in all human hearts regardless of the presence or absence of cardiac disease [12]. However, this ubiquity only applied to vessels smaller than 500 μm in luminal diameter and mostly within the range of 40–200 μm [13]. Such small vessels may be considered non-functional because they are too resistant to flow and, therefore, not capable of transmitting sufficient perfusion pressure to the collateral-receiving artery. For adequate blood supply, anastomoses must enlarge and evolve into arteries that show all of the histological features of arterial conductance vessels. This process is referred to as arteriogenesis and includes remodeling of the adventitia and formation of a muscular tunica media, providing the vessel with vasomotor capabilities such as sympathetic and flow-mediated dilation [14, 15].

A recent investigation by de Marchi *et al.* has shown that bradicardia and arterial hypertension are both related to collateral development in patients without CAD. The authors suggest that low rate and hypertension favor shear stress through coronary arteries, thus triggering collateral growth (see below) [16].

The observation of CCC in patients affect by CAD is extremely frequent. In about one third of patients with stable CAD, collaterals are sufficiently developed to prevent myocardial ischemia during brief coronary occlusion [17]. On the other hand, collateral arteries are evident in only a minority of patients with myocardial infarction (10–40%) undergoing primary PCI [18]. The reason being that *de novo* collateral artery formation, after an acute myocardial occlusion, takes at least 24 hours, but the growth of collateral circulation is different in patients and generally becomes angiographically visible within 10 to 14 days after an acute occlusion.

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Stimuli of coronary collateral growth

The growth of coronary collateral vessels is usually believed to depend upon the transformation of pre-existing arteriolar connections with the mature vasculature (arteriogenesis) and occasionally on sprouting new vessels from neighboring blood vessels (angiogenesis) [19]. There has been considerable controversy concerning the stimulus for coronary collateral growth [17]. It is now clear that long standing high-grade coronary stenosis is mainly responsible for collateral vessel growth. Severe coronary narrowing results in myocardial ischemia and a pressure gradient between the providing and receiving coronary arteries across the collateral network, which increases shear stress to collateral conduits. Therefore coronary artery disease is accompanied by two stimuli for the development of CCC, namely myocardial ischemia and shear stress.

Fujita *et al*. demonstrated in a cohort of 248 patients undergoing coronary angiography within 12 hours of the onset of acute myocardial infarction that a history of long-standing pre-infarction angina is the only significant predictor of collateral growth [20]. In a study carried out during elective angioplasty, Rentrop *et al.* demonstrated that the prevalence of increased when the receiving coronary artery presents a stenosis beyond 70% of lumen diameter [21]. Pohl *et al.* nicely showed a positive correlation between the extent of coronary stenosis and collateral flow index in 450 patients [17]. All of these findings indicate that high-grade coronary artery stenosis is responsible for collateral growth. However, in the clinical setting, it seems impossible to discriminate myocardial ischemia from increased shear stress as a stimulus for collateral developments, because severe CAD simultaneously leads to myocardial ischemia and pressure gradient across the collateral network.

Mechanisms of coronary arteriogenesis have been well investigated and signal cascade initiated by increased fluid shear stress at the site of pre-existing collateral vessels has been elucidated in animal models [22]. However, it has not fully clarified whether cytokines and angiogenic growth factors act similarly in humans. More issues, such as angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2) and their receptor Tie-2b, have been identified and they seem to be involved in collateral development [23]. In cardiovascular diseases up-regulation of these factors in patients with acute coronary syndrome (ACS) has been reported [24], and has been related to postnatal neovascularization in experimental models [25]. Mitsuma *et al.* examined Ang-1, Ang-2, and Tie-2 levels in the coronary circulation and their relationship to coronary collateralization in patients affected by coronary artery disease (CAD) with or without coronary collateral vessels. They demonstrated that Tie-2, the receptor for angiopoietins, was significantly elevated within the coronary circulation in CAD patients with coronary collaterals, and that the coronary Tie-2 level related to Ang-2. These results suggest that Tie-2, which is produced within the coronary circulation, may play a role in the development or maintenance of coronary collateral vessels. In CAD patients also Ang-2 has a more important role than Ang-1 in the formation of coronary collaterals [26]. Be aware that some patients with long standing CTO lesions do not show good developed collateral circulation. It is possible to find an explanation for this phenomenon in some patients with advanced CAD which present with high angiogenic inhibitor factor levels. Mitsuma *et al.* dosed levels of endostatin, an anti-angiogenic growth factor, in the coronary circulation of a cohort of patients with advanced CAD and in a cohort of normal subjects with analog characteristics [27]. Their results showed a significant increase in endostatin levels in patients with CAD rather than in normal subjects, and patients who presented incomplete coronary collateral vessel filling showed more production of endostatin within the coronary circulation. Several studies have demonstrated how the renin-angiotensin system (RAS) is involved in cardiovascular disease improvement and the remodeling process. Angiotensin II was reported to induce angiogenesis through the up-regulation of vascular endothelial growth factor (VEGF) [28] and VEGF-induced endothelial progenitor cell proliferation [29]. According to these findings, there were many reports on the beneficial effects of angiotensin II type 1 receptor blockers (ARBs) on the cardiac microvasculature [30]. Angiotensin II was shown to present pro-angiogenic activity mediated by the angiotensin II type 1 receptor (AT1) [31]. On the other hand, angiotensin-converting enzyme inhibitors (ACE-Is) have been reported to increase capillary density in rat limb muscles [32], sciatic nerves [33], and coronary microvasculature [34]. Furthermore, it was reported that in patients with CAD, ACE-I treatment was associated with coronary collateral circulation progression [35]. These effects of ACE-Is may occur through bradykinin (BK) B2 receptor-induced nitric oxide (NO) synthesis [36]. Therefore, the endothelial cells' status, their activation, and the development of collateral circulation are affected by a balance between positive and negative growth factors.

Recently it has been demonstrated, using direct collection of blood from collateral vessels, that plasma levels of pro-arteriogenic growth factors and cytokines such as basic fibroblastic growth factor, transforming growth factor-β, and monocyte chemoattractant protein-1, are increased in patients with less matured CCC, and are

meanwhile decreased in those patients with more developed CCC. These findings suggest that these substances are implicated in arteriogenesis [37].

Thus, after an acute coronary occlusion, angiogenesis is triggered by shear stress-induced activation of many cytokines. The process of collateral development can happen within a few weeks of occlusion and may explain the possible relation between duration of occlusion and collateral function. In particular the highest levels of this factor are found 2–12 weeks after an acute MI, while after 12 weeks the levels are similar to patients who have no previous MI history. This indicates an increase in endothelial and monocyte activation which leads to secretion of several angiogenetic cytokines [38]. Although acute ischemia leads to increased VEGF levels more than other cytokines, bFGF is superior in enhancing the collateral function [39]. Another important issue is that diabetic patients show lower bFGF and higher MCP-1 levels than nondiabetics but over time they showed no significant differences in collateral function [40].

Coronary collateral arteries classification

The anatomic collaterals' pathway was first categorized by Levine *et al.* into 26 different types and summarized into 4 categories: septal collaterals, intra-arterial (bridging), epicardial collaterals with proximal takeoff (atrial branches), and epicardial collateral with distal take-off [7] (Figure 2.1). In the case of coexisting collateral pathways, the one which first opacified the occluded epicardial segment was defined as the principal collateral.

In time, Rentrop and Cohen proposed another classification that divided the collateral connections into four groups according to the grade of occluded segment opacification. Grade 0 = no filling; grade 1 = side-branch filling of the artery to be dilated using collateral channels without epicardial segment visualization; grade 2 = partial filling of the epicardial segment using the collateral channel; grade 3 = complete filling of the epicardial segment of the artery being dilated using the collateral channel [8].

Recently, Werner *et al.* proposed an evaluation of the size of the collateral connection (CC) diameter measured by three grades: CC0, no continuous connection between donor and recipient artery; CC1, continuous, threadlike connection; and CC2, continuous, small side-branchlike size of the collateral throughout its course (Figure 2.2) [9]. Although coronary angiography is the standard method to visualize collateral arteries, this has a limited resolution. The visible collaterals have a diameter from 0.3 up to 0.5 mm, therefore arterioles smaller than 100 μm are unseen by the human eye. In addition, nitrates and adenosine allow a better visualization of collateral branches exploiting their vasomotor properties.

The prognostic value of collateral circulation

Several studies have emphasized the functional importance of coronary collateral circulation [41, 42, 43]. The presence of collaterals can limit infarct size, prevent infarct expansion, improve perfusion, and preserve myocardial viability in the infarct-related artery territory, and thus would improve recovery of impaired left ventricular function after revascularization, although it will not protect against stress-induced ischemia [41, 44, 45, 46]. Coronary collaterals may well indicate ischemic myocardium that could potentially be salvaged by reperfusion [44]. The presence of well-developed CCC contributes to improving the prognosis of patients affected by CAD. The Osaka Acute Coronary Insufficiency Study (OACIS) group reported that, among 1934 AMI patients with a completely occluded infarct-related artery, angiographic absence of recruitable CCC to the infarct-related artery in patients above 70 years of age is an independent predictor of in-hospital death after adjustment for various other predictors of the end point [47]. The presence of visible CCC on coronary angiography was associated with a favorable effect on a composite end point comprising MI, CAD death, and revascularization at 24-month follow-up in 879 male CAD patients, after adjustment for possible confounding factors [48].

Meier *et al.* evaluated the functional status of recruitable collaterals and their prognostic benefit in 845 patients who were followed up for 10 years [49]. The incidence of cardiac death was 4-fold higher in patients with insufficient CCC (CFI < 0.25) compared to those with sufficient CCC (CFI ≥ 0.25). Multivariate analysis revealed that age, low CFI, and current smoking were independent predictors of cardiac mortality.

There is a paucity of data regarding the pathophysiologic significance of collaterals observed during AMI, and controversy exists regarding their clinical impact. Existing collaterals cannot prevent infarction in the majority of cases; however, they may limit the damage sustained. The prognostic value of collateral arteries in MI survivors after thrombolysis is controversial. Although it is common opinion that early formation of collaterals can reduce the size of necrosis after MI, one angiographic study of 803 survivors of Q-wave anterior MI has showed a worse prognosis in patients with well-developed collaterals compared to those with inadequate collaterals [50]. Habib *et al.* found that patients with an AMI treated by thrombolytics, who failed to reperfuse but had collaterals, sustained a

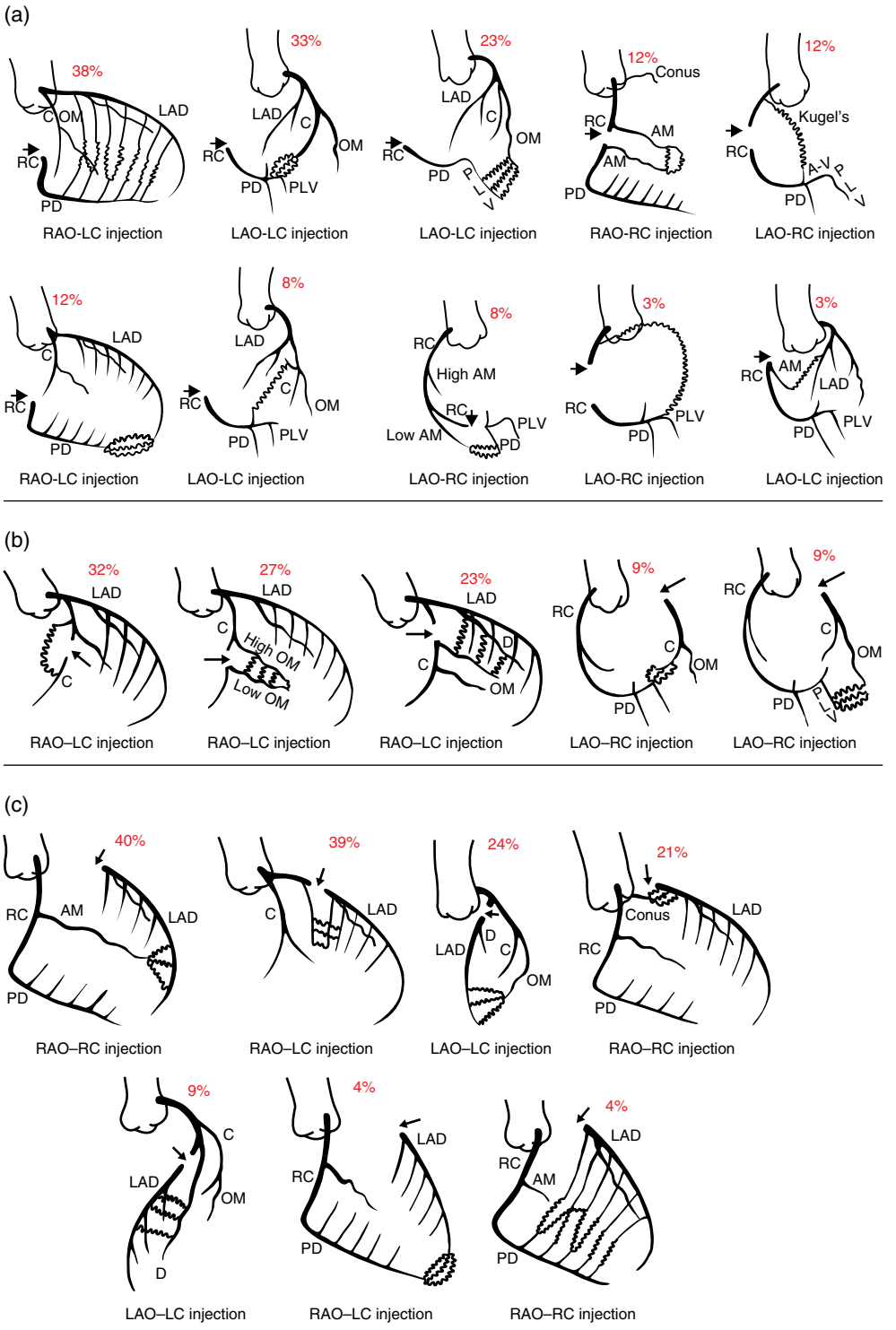

Figure 2.1 Topography of collaterals and collateral function in coronary artery occlusions. (a) Left anterior descending coronary artery (LAD); (b) Circumflex coronary artery (C); (c) Right coronary artery occlusion (RC); AM = acute marginal branch of the right coronary artery; A-V = artery to the atrioventricular node; D = diagonal branch of the left anterior descending; LAO = left anterior oblique; LC = left coronary artery; OM = obtuse marginal branch of the circumflex artery; PD = posterior descending branch of the right coronary artery; PLV = posterior left ventricular branch of the right coronary artery; RAO = right anterior oblique; numbers in parenthesis signify frequency with which the given pathway occurred in this series. (Adapted from Levin DC *et al.* [7].)

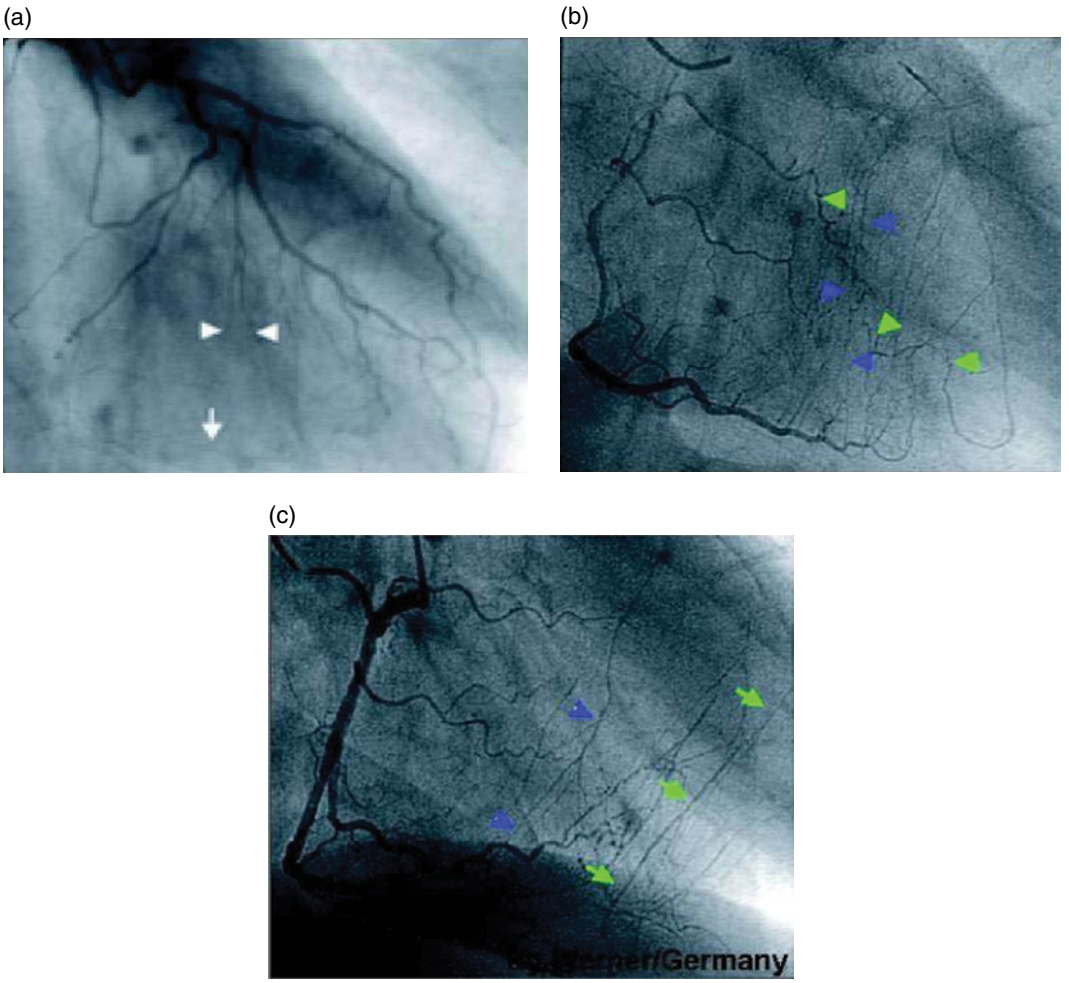

Figure 2.2 Werner classification of collaterals; (a) CC0: no continuous connection between donor and recipient; (b and c) CC1 (blue arrows): continuous, threadlike connection; CC2 (green arrows): continuous, small side-branchlike size of the collateral throughout its course. (Adapted from Werner *et al.* [9].)

smaller infarct – reflected in a lower peak CK – and had a better global ventricular function at discharge than those with no collaterals [51]. Elsman *et al.* have also demonstrated a protective effect of collaterals on enzymatic infarct size in patients with AMI treated by primary intervention [52]. On the other hand, Nicolau *et al.* suggested that collaterals do not reduce infarct size in AMI patients treated by thrombolytics [53]. Similarly, Antoniucci *et al.* found no protective effect of collaterals on infarct size in patients undergoing mechanical intervention within 6 hours of AMI onset [54].

A recent study stated that good collaterals demonstrated by coronary angiography have a high sensitivity and positive predictive value for the prediction of viability as shown by dobutamine stress echocardiography and concluded that one can decide for percutaneous or even surgical revascularization depending solely on the assessment of coronary collateral circulation [44]. Werner *et al.*, assessing the collateral function with an intracoronary doppler, show that the collateral function is more developed in patients with preserved ventricular function than in those with an impaired regional function [55]. On the other hand, the same author reported that recovery of impaired contractility after revascularization of a chronically occluded artery is not directly related to the quality of collateral circulation, since collateral development does not essentially require the presence of viable myocardium [56]. Moreover, another study observed no difference between patients with and without evidence of myocardial viability, concerning the presence of visible collaterals by coronary angiography [57].

Collateral branches characteristic of the CTO artery related territory are influenced by anatomical distribution of the donor vessel, microvascular function, and the duration of occlusion [58, 59].

Many clinical cardiologists believe that collateral circulation is able to preserve ventricular viability

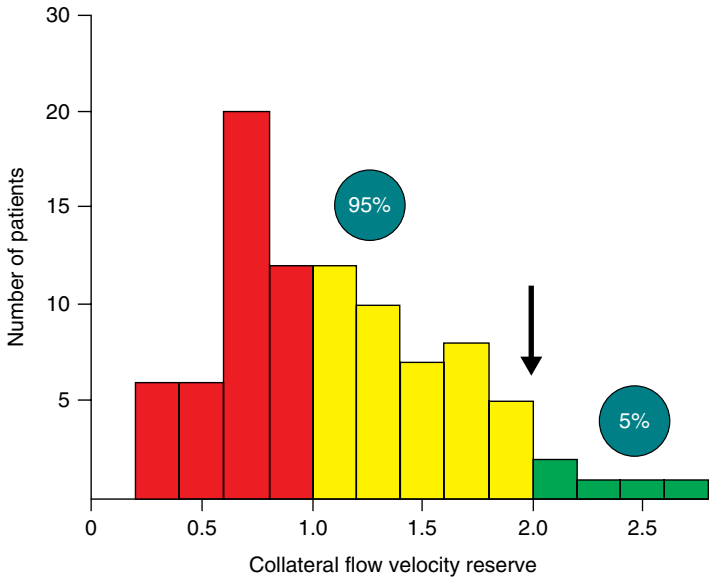

Figure 2.3 Collateral function assessed with collateral flow fraction reserve (FFR) in patients with CTO during adenosine stress. Collateral FFR > 2 was considered sufficient to preserve ventricular function; 95% patients have a FFR < 2.0 while 5% have a FFR > 2.0. (Adapted from Werner *et al*. [62].)

and function at rest and during stress conditions. Therefore they consider the presence of collateral circulation as a sufficient reason to deny interventional procedures and complete revascularization. However, during stress conditions, the so-called "coronary steal" is an important mechanism related to the function of collateral circulation which may cause myocardial ischemia. Coronary steal is a complex phenomenon in which regional myocardial hypoperfusion occurs through the diversion of coronary blood flow to adjacent coronary beds. It is usually mediated by collateral arteries.

Seiler and co-workers [60] defined coronary steal as a decrease in the coronary blood flow in one collateralized vascular region in favor of another one during coronary arteriolar vasodilatation. This mechanism can be "vertical," between different layers of the myocardium, or "lateral," via branches through adjacent vascular areas originating from a common branch bifurcation.

Werner and colleagues analyzed collateral function by adenosine-induced vasodilation in order to study coronary steal phenomenon [15, 61]. In the majority of patients an abnormal coronary flow reserve is more common, especially in those with multivessel epicardial disease. However the impaired vasodilatory reserve of the microcirculation also contributes to coronary steal and might cause coronary steal even without any significant epicardial donor artery stenosis.

Werner's studies showed that, in the majority of patients, the coronary steal phenomenon under pressure will reduce the collateral flow fraction reserve leading to myocardial regional wall motion abnormalities, even if the collateral flow might provide a blood supply sufficient enough to preserve myocardial viability at rest [15] (Figure 2.3).

The relationship between collateral supply and recovery of impaired regional LV function after PCI is complex. A functional myocardial microcirculation associated with viable myocardium is a prerequisite for improvement in LV function after CTO PCI [62]. It has already been shown that collateral size is directly related to myocardial viability, and it is therefore important to preserve good collateral function in case of any interventional approach. However, impaired left ventricular function (LVF) recovery after CTO recanalization is not directly related to the quality of collateral function, as collateral circulation development does not appear to require the presence of viable myocardium. Therefore, revascularization should not be based on the quality of collateral supply [56].

Changes in collateral circulation after CTO recanalization

Collateral blood flow is usually reduced after successful CTO recanalization by re-establishing the antegrade blood flow which leads to an increase in resistance of collateral vessels. Werner *et al*. assessed this change when using intracoronary Doppler flow velocimetry by recording pressure and flow distally to an occluded artery before recanalization. Recruitable circulation was measured during

repeated balloon inflation in the first 24 hours after recanalization [63]. They calculated a collateral flow index (CFI) on the velocity integral during the antegrade flow occlusion/velocity integral. Collateral flow is determined by the resistance from the collateral vessel and the vascular bed, distal to the occlusion. In CTOs they noticed that the collateral flow profile showed two basic patterns: (i) predominantly systolic flow with only minor or no diastolic flow in; (ii) a biphasic systolic and diastolic flow with marked diastolic contribution. After recanalization, the recruitable CFI during reocclusion dropped 50% below its baseline value. There were also qualitative changes in collateral flow with a reduction in diastolic flow contribution. The length of cardiac cycle basal collateral flow was also reduced, indicating a reduction in collateral function. The underlying mechanism in an immediate change in collateral function could be an increase in collateral and/or peripheral resistance. The improved perfusion by antegrade flow may induce these hemodynamic changes, but they are not reversed immediately during balloon reocclusion. It is possible that the collateral function would gradually improve during persistent reocclusion. This information suggests that when an acute reocclusion is present, collateral compromised circulation may be unable to preserve ventricular viability. For this reason an acute thrombosis in a previously occluded artery can lead to acute coronary syndrome. In this study Werner *et al.* also investigated the possible determinants of the collateral flow. The major determinant for CFI appeared to be the extent of regional dysfunction distal in the occluded artery, whereas CFI did not have any interaction with a history of hypertension, diabetes mellitus, prior myocardial infarction, global left ventricular function, or duration of the occlusion [63]. CFI was higher in those lesions which supplied a myocardial area with normal or moderate regional dysfunction, compared to an akinetic myocardial area. This difference was also evident after PTCA, indicating that collateral supply for normokinetic myocardium remains superior to akinetic myocardium. In this cohort, most of the patients with CTOs had a history of infarction despite a high CFI. This indicated that the collaterals were still not fully developed at the infarction time. It is important to underline that preventing myocardial necrosis is strongly related to the connection size, and viability is more likely to be preserved in large collateral networks than in small connections. Therefore, when a retrograde approach is the strategy chosen in the case of simultaneous collateral connection, the smallest suitable circulation should be considered in order to preserve the bigger collateral connection and consequently the myocardial viability.

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