Coronary Collateral Circulation

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31.1 Introduction

Coronary collateral circulation is the small vessel connections formed between one epicardial coronary artery and another. Coronary collaterals can exist in the presence or absence of coronary artery disease (CAD) [1–3]. They can be recruited when a territory is jeopardized by the occlusion of an epicardial coronary artery, potentially providing an alternative source of blood supply to the myocardium. The presence of coronary collaterals is associated with preservation of left ventricular function and improved prognosis [4–10]. Beyond their protective role, recent interest has focused on the utility of collaterals during chronic total occlusion (CTO) percutaneous coronary intervention (PCI). In addition to providing visualization of the distal bed of an occluded coronary artery, collaterals can potentially be crossed retrogradely via their donor vessel, allowing access to the occluded artery and facilitating recanalization of the occlusive segment.

31.2 Historical Knowledge of Coronary Collateral Circulation

The debate around the possible existence of human coronary collateral circulation began in the mid-seventeenth century. Anastomoses between the right and left coronary arteries were first documented by Richard Lower in Amsterdam using postmortem imaging [11]. Two centuries later, Cohnheim conducted canine studies and pronounced that coronary arteries were in fact end arteries. It was not until 1963 in Glasgow that William Fulton unequivocally demonstrated the existence of coronary anastomoses using a pathoanatomical imaging technique developed to differentiate between vascular overlay and true connections between adjacent parts of the circulation [1] (Fig. 31.1). Fulton discovered the presence of coronary collaterals in human hearts, even in the absence of CAD. These coronary anastomoses, which can be identified in autopsy specimens, are usually too small to be visible angiographically in the absence of significant CAD and impaired coronary perfusion. The collateral vessels identified ranged in size from <200 μm in the absence of CAD to 800 μm in the presence of CAD [1].

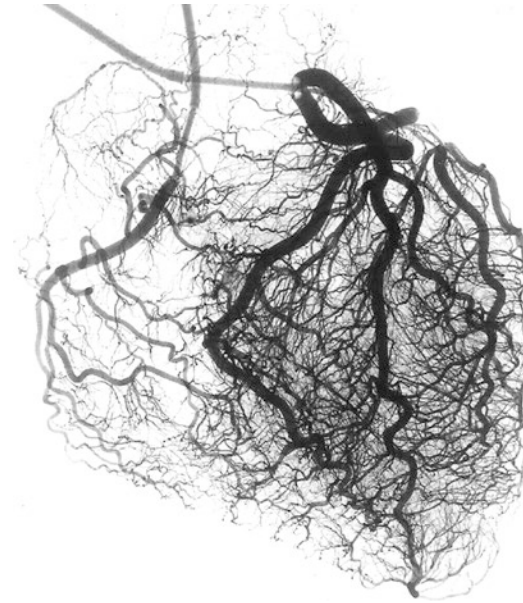

Fig. 31.1 Filling of coronary collaterals in a normal postmortem human heart by immersion radiography (Reprinted from Fulton [46], with permission)

In his landmark paper in 1974, Levin described the anatomical distribution of coronary collaterals in a small number of subjects with both stenotic and occluded vessels [12] (Fig. 31.2a–c). In 1985 Rentrop devised his collateral score as an index of collateral function [13]. This assessment of the extent of retrograde filling was originally performed using balloon occlusion of the contralateral coronary artery. While the balloon occlusion method is now rarely employed, the Rentrop score is commonly used in research and the clinical setting to grade collateral perfusion from the donor vessel to the occluded vessel (Table 31.1).

31.3 Development of Coronary Collateral Circulation

The development of functional coronary collateral circulation is driven by the process of arteriogenesis. This involves recruitment and remodeling of pre-existing collateral vessels [14, 15]. While angiogenesis (development of new vessels) is driven by recurrent and severe myocardial ischemia [16], arteriogenesis does not require an ischemic stimulus but instead is induced by the pressure gradient created by a hemodynamically significant obstruction of a major coronary artery and the resulting increase in shear stress [17, 18].

The decrease in pressure distal to the obstruction causes redistribution of blood flow through preexisting collateral vessels which, as a consequence, now connect a high-pressure system to a low-pressure system. The increased flow velocity leads to increased shear stress, which activates expression of endothelial chemokines, adhesion molecules, and growth factors. This process causes proliferation of endothelial and smooth muscle cells in the collateral vessels, resulting in vascular remodeling and development of angiographically visible collateral vessels within weeks following a coronary artery occlusion [19–21]. As collateral vessels grow in size, their numbers decrease, reflecting a reduction in vascular resistance. This process, called «pruning,» efficiently improves collateral flow through a smaller number of larger vessels [22].

Several clinical and angiographic variables correlate with the degree of collateralization. Variables that are associated with more extensive collateralization in patients without CAD include hypertension and a lower resting heart rate [23], while in patients with CAD they include severity of coronary stenosis (for angiographically visible collaterals to develop, severe narrowing (>90%) or complete obstruction is necessary), longer duration of angina, longer duration of vessel occlusion, and proximal lesion location [24–27].

31.4 Physiological Function of Coronary Collateral Circulation

While collateral function can be assessed using the Rentrop score, which angiographically grades the degree of perfusion from the donor vessel to the recipient vessel, this method is semiquantita-

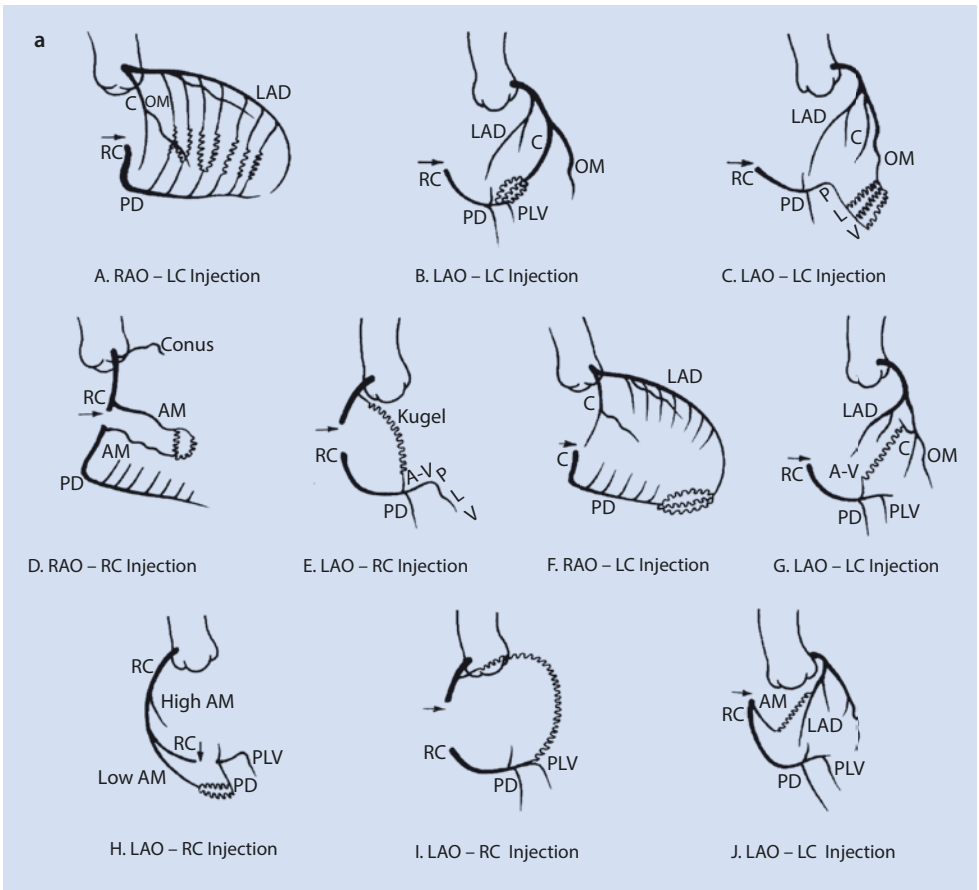

Fig. 31.2 Collateral pathways in **a** right coronary artery (RCA) obstruction, **b** left anterior descending artery (LAD) obstruction, and **c** circumflex artery (Cx) obstruction (Reprinted from Levin [12], with permission)

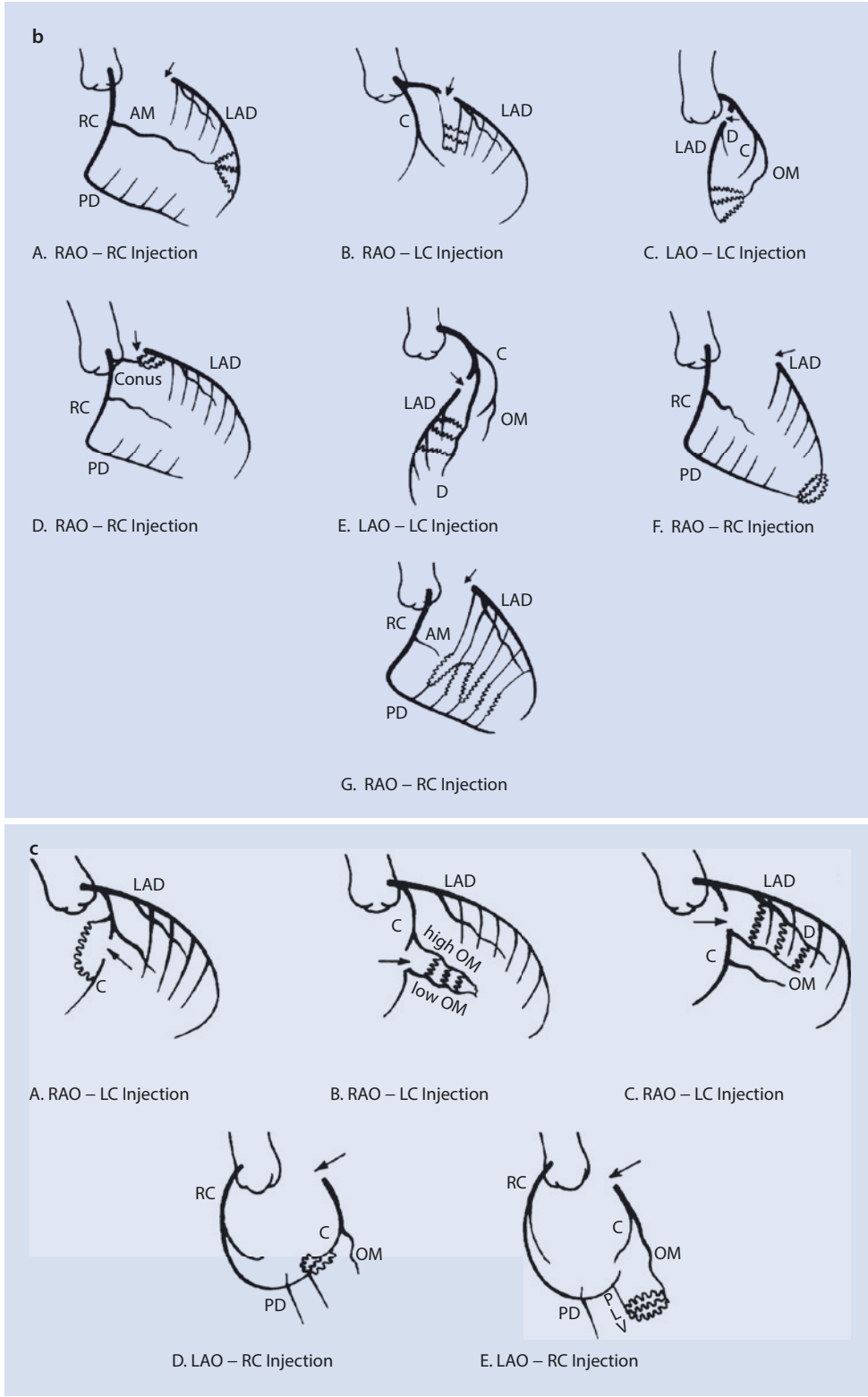

Fig. 31.2 (continued)

Table 31.1 Rentrop classification of coronary collateral circulation [13]

Rentrop score	Definition
Grade 0	No visible filling of any collateral channel
Grade 1	Filling of the side branches of the occluded artery, with no dye reaching the epicardial segment
Grade 2	Partial filling of the epicardial vessel
Grade 3	Complete filling of the epicardial vessel by collaterals

Table 31.2 Werner collateral connection (CC) classification of coronary collateral circulation [36]

Collateral connection grade	Definition
CC0	No continuous connection
CC1	Threadlike continuous connection
CC2	Side branch–like connection (≥0.4 mm)
CC3	>1 mm diameter of direct connection (not included in the original description by Werner)

tive and can be influenced by the blood pressure, force of contrast injection, and duration of angiographic acquisition. In 2003, on demonstrating a poor correlation between the Rentrop score and invasive measures of collateral function, Werner proposed a visual grading of the size of collateral connections [28] (Table 31.2). With the collateral connection (CC) classification he was able to discriminate collaterals with different functional capacity and predict collateral adequacy to preserve left ventricular (LV) function [28].

The gold standard assessment of collateral function is the invasively measured collateral flow index (CFI) [29, 30]. The CFI utilizes simultaneous coronary pressure measurements to quantify coronary flow through the collateral circulation. The amount of flow via collaterals to the vascular region of interest is expressed as a fraction of the flow via a patent vessel. Taking into account the central venous pressure (CVP), and assuming that coronary pressure directly reflects coronary flow, the CFI is the ratio between the pressure proximal to and distal to the occlusion. The resulting equation is $CFI = (P_{occl} - CVP)/(P_{ao} - CVP)$, where P_{occl} is the distal coronary occlusive or wedge pressure and P_{ao} is the aortic pressure.

Severe stenoses are associated with increased collateral function and a higher CFI [2]. Patients with a CTO have a higher CFI in the occluded vascular territory than patients with nonocclusive CAD [31]. Collateral function can therefore be considered both an adverse marker (as a direct indicator of CAD severity) and a favorable marker (of the degree of protection provided to the jeopardized myocardium). The net effect is determined by the balance between CAD severity and the presence and extent of coronary collateral circulation [32].

31.5 Clinical Significance of Coronary Collateral Circulation

The benefit of well-developed coronary collateral circulation is the potential to preserve myocardial function, with associated improved survival. This is evident in patients with preserved LV function without regional wall motion abnormalities, despite the presence of a totally occluded coronary artery [33]. While this preservation of function is frequently seen in patients with CTO, with an acute coronary occlusion the collateral circulation is usually inadequate to prevent myocardial ischemia and injury without emergency recanalization and reperfusion [34]. In fact, only a quarter of patients with normal coronary arteries, and a third of those with CAD, have sufficient recruitable collaterals to prevent ischemia during an acute occlusion [3, 10, 35, 36]. In patients with an acute myocardial infarction without detectable collaterals on presentation, several weeks or months are required to develop collaterals to a functional capacity similar to that seen in patients with pre-existing

collateral circulation [19–21]. In patients with pre-existing collaterals at the time of an acute occlusion, the presence of collaterals has been shown to preserve myocardial function, limit infarct size, and reduce postinfarct ventricular dilatation, aneurysm formation, and the risk of cardiogenic shock [6, 10, 37, 38].

However, despite this protective role, there is no evidence that the extent of collateral supply is an indicator of myocardial viability [39, 40]. Well-developed collaterals can be present in the absence of viable myocardium, as the development of collaterals is the result of a pressure gradient across the circulation and is independent of ischemia [40].

Collateral function, quantified by the CFI, is an independent predictor of prognosis [41]. A meta-analysis assessing the impact of coronary collateral circulation on mortality in patients with stable or acute CAD found that a high degree compared with a low degree of collateralization was associated with improved survival, with the association being stronger in patients with stable CAD [9].

31.6 Coronary Collateral Pathways

Coronary collateral pathways, first described by Levin in 1974, were recently comprehensively described and illustrated in a large cohort of patients with CTOs [12, 42]. CTOs most commonly occur in the right coronary artery (RCA), followed by the left anterior descending artery (LAD), and least frequently the circumflex artery (Cx) [42]. The most prevalent collateral pathways to an RCA CTO are LAD septal collaterals to the right posterior descending artery (RPDA), followed by collaterals from the Cx to the right postero-lateral ventricular branch (RPLV). The commonest collateral pathways to an LAD CTO are RPDA septal collaterals to LAD, followed by right atrial (RA) or right ventricular (RV) collaterals to LAD. The collateral pathways to Cx CTOs are less prevalent with the most common, diagonal (D) to obtuse marginal (OM) collaterals, followed by RPLV to Cx collaterals (Fig. 31.3a–c).

31.7 Role of Coronary Collateral Circulation in Percutaneous Coronary Intervention

CTO PCI can be performed antegradely, working forward through the target vessel, or retrogradely, working backward via a donor artery and collateral that connect with the distal vessel beyond the occlusive segment. The approach is determined by the specific anatomy and characteristics of the occlusion and the potential utility of the collaterals. Therefore, collateral circulation has two key roles in CTO PCI: to provide visualization of the distal coronary bed beyond an occlusion; and to provide retrograde access to the occluded vessel to facilitate crossing and recanalization of the occlusive segment.

A collateral channel is defined as «interventional» if it is considered suitable to deliver equipment from the donor vessel to the target vessel beyond the occlusion [42]. The specific collateral pathways available have implications for the feasibility and safety of obtaining retrograde access to the target artery [42] (Table 31.3). In RCA CTOs, while the LAD septal collaterals, when present, are considered to be «interventional» in over 75% of patients, the Cx to RPLV collaterals can be used in fewer than 20% of cases. In LAD CTOs, when RPDA septal collaterals are present they can be used in 80% of patients, and while LAD septal to septal autocollaterals are infrequent, when present they can be used in over 60% of cases. In Cx CTOs, when a posterolateral ventricular branch (PLV) to Cx or OM collateral is present it can be used in 50% of cases. In a left-dominant Cx, LAD septal to left posterior descending artery (LPDA) collaterals, when present, can be used in two thirds of cases.

The most common reason for failed retrograde CTO PCI is an inability to cross the collateral connections. It is therefore important to identify for each individual case which of the available collaterals are anatomically suitable for retrograde access. The collateral characteristics that should be considered are listed in Table 31.4 [42]. By simplifying these criteria to the four

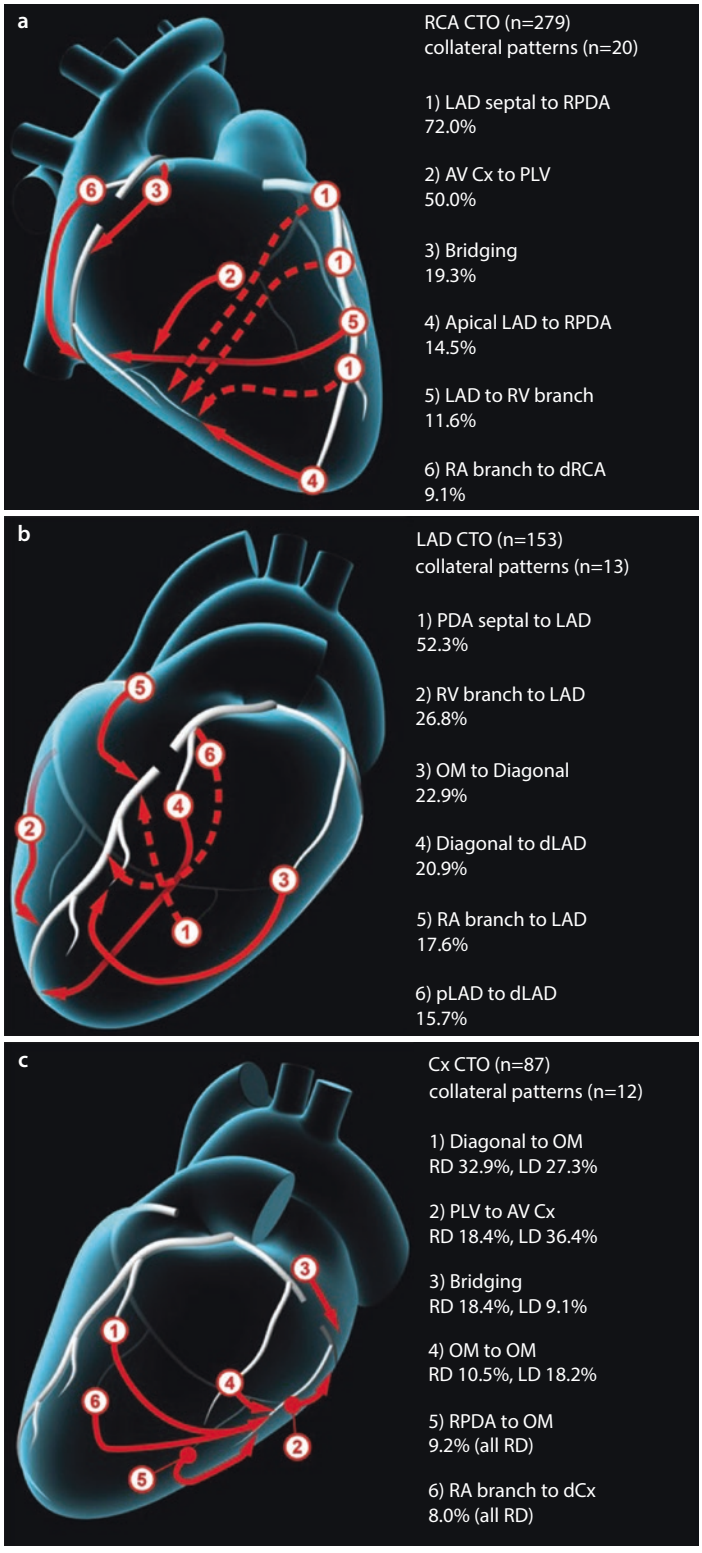

Fig. 31.3 Common collateral patterns in **a** right coronary artery (RCA) chronic total occlusions (CTOs), **b** left anterior descending artery (LAD) CTOs, and **c** circumflex artery (Cx) CTOs (Reprinted from McEntegart et al. [42], with permission)

Table 31.3 Common chronic total occlusion (CTO) collateral pathways and interventional suitability for the right coronary artery (RCA), left anterior descending artery (LAD), and circumflex artery (Cx) (Reprinted from McEntegart et al. [42], with permission)

Collateral pathway	Prevalence, %	Interventional suitability, %
Right coronary artery		
LAD septal–PDA	72.0	76.8
AVCx–PLV	46.9	16.9
Bridging	19.3	0
Apical LAD–PDA	14.5	76.2
LAD–RV	11.6	23.5
RA or SN–distal RCA	9.1	0
OM–PLV	8.4	14.3
OM–RPDA	8.0	35.3
RV–RPDA	5.8	0
LAD septal–PLV	5.1	50
D–PLV	4.0	20
D–RPDA	2.9	14.3
Conus–RV	1.8	16.7
Left anterior descending artery		
PDA–LAD	52.3	80.6
RV–LAD	26.8	14.3
OM–D	22.3	3.8
D–distal LAD	20.9	36.4
RA–LAD	17.6	18.2
Proximal LAD–distal LAD	15.7	62.5
PDA–apical LAD	13.1	7.7
Bridging	11.1	0
Conus–LAD	5.9	28.6
PLV–LAD	3.9	0
Circumflex artery		
D–OM	32.2	20
PLV–AVCx	20.7	50
Bridging	17.2	0
OM–OM	11.5	14.3
PDA–OM	9.2	33.3
RA–distal Cx	8.0	0
Apical LAD–OM	8.0	33.3
Ix–OM	6.9	0
Proximal Cx–distal Cx	6.9	0
LAD septal–OM	5.7	0
LAD septal–LPDA	5.7	66.7
PLV–OM	5.7	50

AVCx atrioventricular groove branch of circumflex artery, *D* diagonal, *Ix* ramus intermedius, *LPDA* left posterior descending artery, *OM* obtuse marginal, *PDA* posterior descending artery, *PLV* posterolateral ventricular branch, *RA* right atrial branch, *RPDA* right posterior descending artery, *RV* right ventricular branch, *SN* sinoatrial nodal artery

Table 31.4 Collateral characteristics that determine favorability for retrograde crossing [42]

Characteristic	
Type of collateral	Septal collaterals are generally safer than epicardial collaterals, as the risk of perforation and cardiac tamponade is lower (Okamura et al. 2016) [47]
Channel size	Channels <1 mm in diameter are generally unlikely to permit passage of a microcatheter without significant risk of damage

Table 31.4 (continued)

Characteristic	
Channel exit	Adverse channel exit angle (<45°), disease, stent, or bifurcation at exit point from donor vessel
Channel tortuosity	Presence of multiple high-frequency (>180° within a segment <3 times the diameter of the collateral) successive curves (within 2 mm) in epicardial collaterals, or a high-frequency curve that fails to uncoil in diastole in septal collaterals, would make utilization of the channel more difficult
Channel entry	Adverse channel entry angle (<45°), disease at channel entry, or channel entry close to/at distal cap or in occlusive segment of target vessel
Channel length	A long collateral channel is more difficult to negotiate
Presence of multiple bifurcations	Particularly at points of marked curvature, or just after collateral channel entry
High risk of damage or ischemia	An epicardial collateral channel less than half the diameter of the microcatheter, or dominant/only collateral supply to territory

characteristics of collateral channel size, collateral exit from the donor vessel, collateral tortuosity, and collateral entry into the target vessel, a collateral score can be devised to identify the most favorable channels for retrograde crossing (Fig. 31.4a–d).

Performing a detailed assessment of the available collateral pathways and their anatomical characteristics during procedural planning can improve CTO PCI procedural efficiency and success.

31.8 Therapeutic Options

Several experimental studies and early clinical studies have demonstrated that it is possible to promote arteriogenesis with the growth factors granulocyte–macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF), or with external counterpulsation [2, 43–45]. However, these studies were too small to evaluate whether these findings would translate into improved clinical outcomes.

31.9 Summary

While coronary collateral circulation can be seen in patients with unobstructed coronary arteries, it is of particular importance in the presence of coronary artery disease. It has an important protective role in acute and chronic ischemia and is associated with preservation of left ventricular function and improved survival. Beyond this physiological function, it plays two key roles in percutaneous coronary intervention for chronic total occlusions: allowing visualization of the distal coronary bed beyond an occlusion; and providing access routes to the distal vessel to facilitate retrograde recanalization of the occlusive segment. Recognizing the protective and interventional importance of collateral circulation, there are ongoing trials of biological therapies aiming to enhance development of coronary collaterals and their capacity for myocardial perfusion.

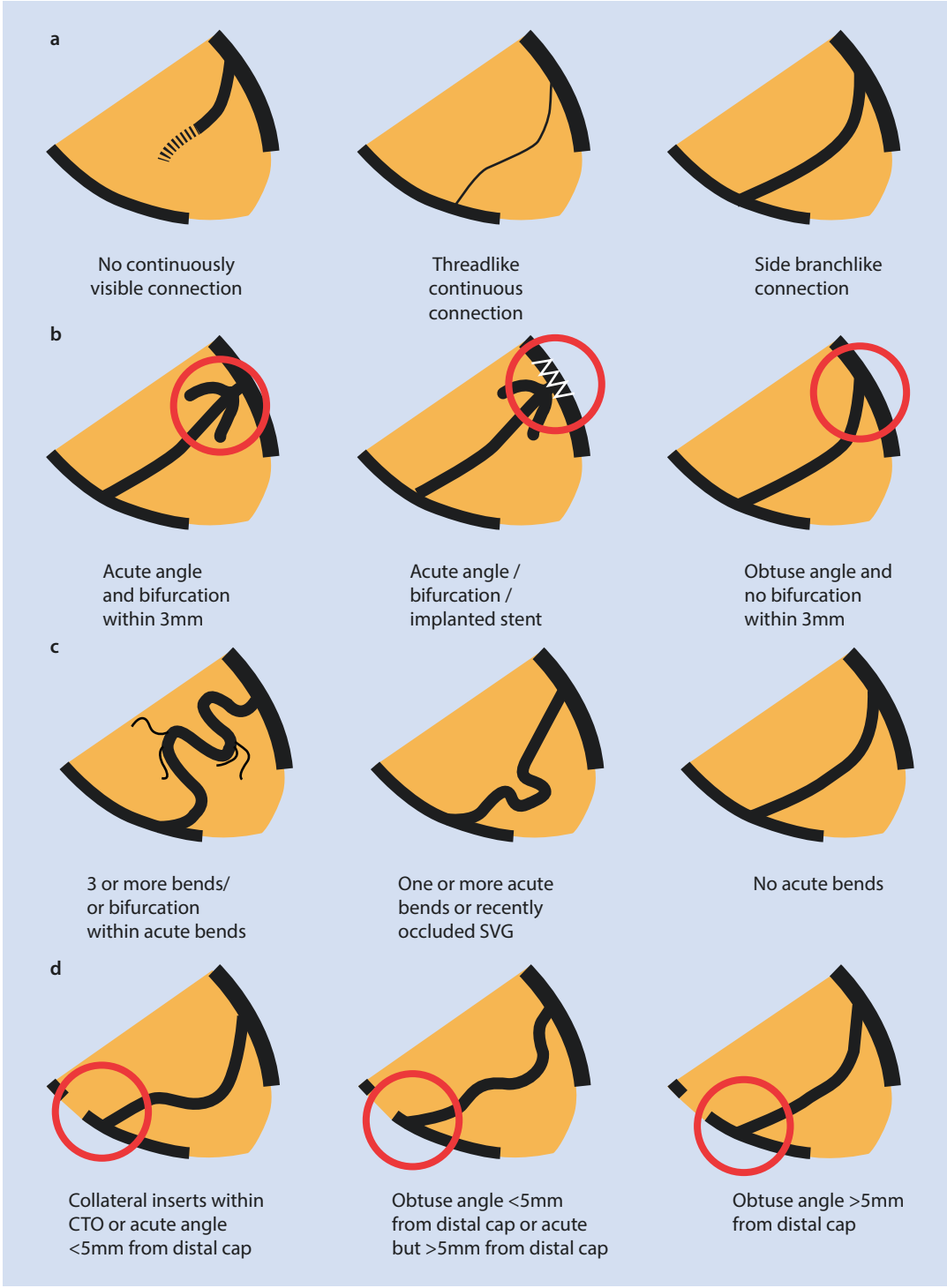

Fig. 31.4 **a** Collateral channel size affecting feasibility of collateral crossing. **b** Collateral exit from donor vessel. **c** Collateral tortuosity. **d** Collateral entry into target vessel

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