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Short Review

Animal chronic total occlusion models: A review of the current literature and future goals

Usaid K. Allahwala[a,b,*], James Weaver[c], Ravinay Bhindi[a,b]

[a] Department of Cardiology, Royal North Shore Hospital, Sydney, Australia
[b] The University of Sydney, Sydney, Australia
[c] Cardiology Department, St George Hospital, Sydney, Australia

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ABSTRACT

Coronary chronic total occlusions (CTOs) are commonly found in patients undergoing coronary angiography and is associated with poorer prognosis than in those patients with other forms of stable coronary artery disease. As such, with an increasing appreciation of this clinical entity, there is a need to identify, firstly the pathophysiological process driving its formation, as well as new percutaneous strategies for revascularisation with long term durability and improved outcomes. An appropriate, reliable and reproducible animal model is vital for both of these objectives.

We review the prevalence of spontaneous collaterals in different species, as well as review the current literature with respect to animal models of CTOs, and compare and contrast the advantages and disadvantages of these differing models. Whilst both extrinsic compression models and endoluminal procedures may create situations analogous to a CTO in a human, the ideal animal model of a CTO will include an occluded artery, functional collaterals and a viable myocardium. This would allow study of the process driving collateral formation and arteriogenesis as well as percutaneous intervention strategies for both acute and long term benefits.

1. Introduction

A coronary chronic total occlusion (CTO) is characterised by significant atherosclerotic plaque burden within an artery resulting in complete (or near complete) occlusion of the vessel present for at least 3 months [1]. The incidence of a CTO has been shown to be almost 20% in patients presenting for non-urgent coronary angiography [2] and 6.6% of those presenting with an ST elevation myocardial infarction [3]. The presence of a CTO is independently associated with greater mortality and poorer prognosis [4]. Current success rates of CTO percutaneous coronary intervention in the setting of experienced operators is 91% [5], with rates of restenosis or re-occlusion 20% at 1 year, depending on stent type and PCI strategy [6]. Consequently, this remains one of the most challenging management dilemmas in modern interventional cardiology.

Animal models have been pivotal in the advancement of interventional cardiology over the past 40 years, particularly since the advent of catheter based technologies. Initial research into drug eluting stents [7,8], bifurcation stenting strategies [9], mechanisms of in stent restenosis [10], bioresorbable scaffolds [11] as well as the first transcatheter heart valves [12] (precursor to transcatheter aortic valve implantation) were all conducted in animal models. As such, a reliable and reproducible animal model of a coronary CTO is vital to appreciate not only the underlying pathophysiological processes of CTO and collateral formation, but also to trial potential therapeutic modalities and approaches to revascularisation.

In this paper, we will review the existing animal CTO models in both coronary and peripheral circulations and how these may be utilised to gain a better understanding of the disease process and formulate novel interventional approaches.

2. Human CTO histopathology

The histopathological process of CTO progression in human coronary arteries, whilst incompletely understood, is dependent on the duration of the CTO. The vast majority of data pertaining to the pathophysiology of human CTO formation is based on post-mortem data, rather than consecutive in-vivo assessment. The most commonly accepted process involves an acute occlusive thrombus, rather than gradual luminal obliteration by atheromatous progression [13]. The acute thrombus subsequently develops into an organised thrombus, which is more rigid than fresh thrombus, with a dense concentration of collagen

* Corresponding author at: Department of Cardiology, Royal North Shore Hospital, Reserve Rd, St. Leonards, Sydney 2065, Australia.
E-mail address: usaid.allahwala@sydney.edu.au (U.K. Allahwala).

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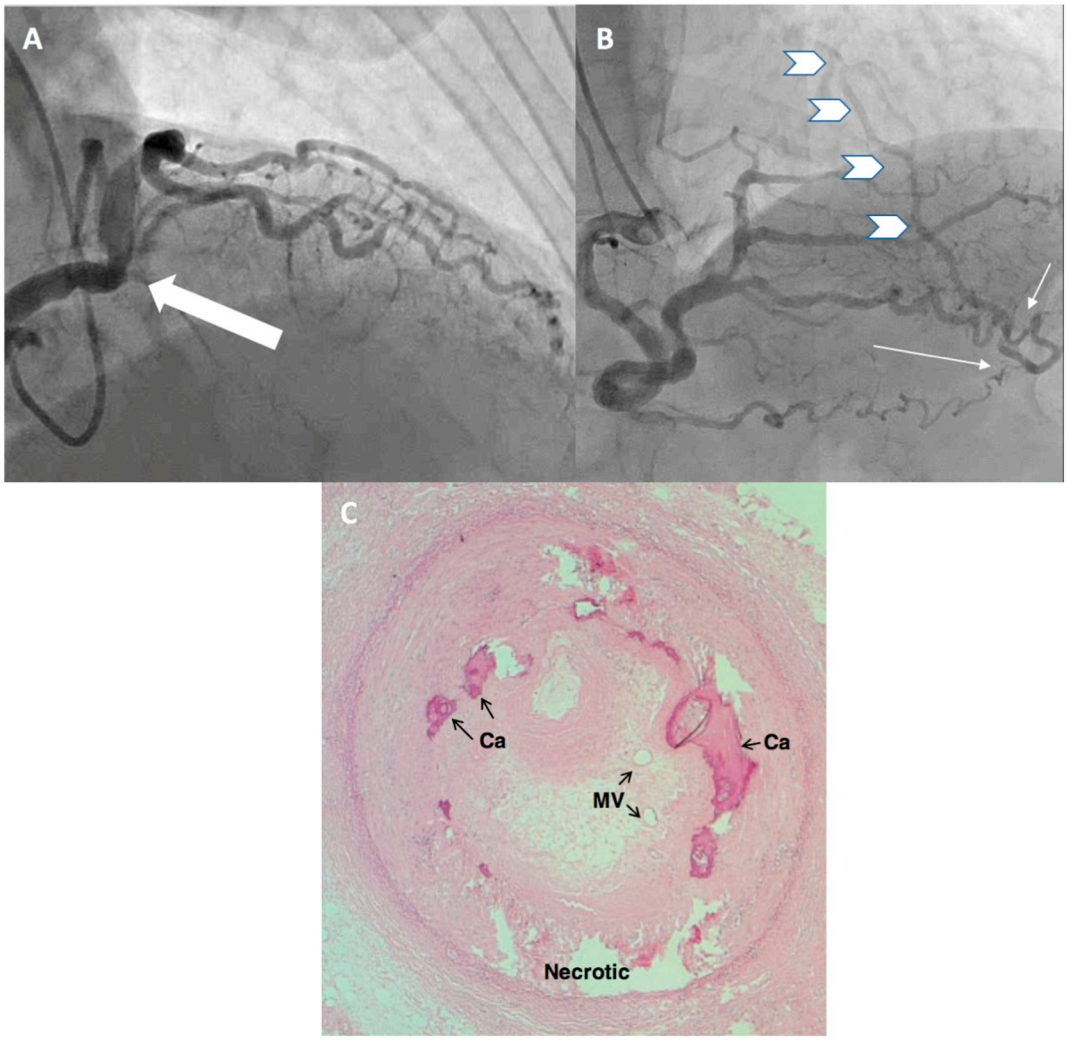

Fig. 1. Angiographic and histological images of a CTO
A & B: Angiographic images of a patient with a CTO of the proximal left anterior descending artery (LAD). (A) The occluded LAD proximal stump is seen when injecting radio-opaque contrast into the left coronary system. (B) Retrograde filling of the occluded LAD (thick arrows) via collaterals (thin arrows) is seen with injection of radio-opaque dye in the right coronary artery. C. Hematoxylin-eosin stained human CTO, demonstrating extensive collagen-rich fibrous tissue, several patches of calcification (Ca), small microvessels (MV), and a large necrotic area.
Adapted from [49].

rich fibrous tissue at the proximal and distal ends of the lesion, referred to as proximal and distal fibrous caps [14]. Early occlusions consist of microchannels within the organised thrombus, whilst CTOs of shorter duration consist of organised thrombus with necrotic core, extracellular matrix, smooth muscle cells and lipid deposits with fewer calcified lesions [15,16]. As the CTO gets older, the intimal plaque gets harder and more dense calcium formations occur without microchannels and severe negative remodelling [17] (Fig. 1). Similarly, in native vessel CTOs which have undergone coronary artery bypass grafting (CABG), there is severe calcification and moderate negative remodelling [18], whilst the presence of the bypass graft itself may accelerate CTO formation, with 43.6% of patients developing a new CTO following CABG at 1 year [19]. Whilst there is some understanding of the mechanism of the occlusion of the culprit vessel, the recruitment of collaterals, which prevent an early myocardial infarction and hence maintain a viable myocardium, and their subsequent development and maturation, is an area of ongoing research.

3. Rationale for an animal model & characteristics

Given the incidence and prognostic effects of the presence of a CTO, an appropriate animal model is indicated for a number of reasons. Broadly, these may be divided into 5 aspects;

(i) The natural history of a CTO
(ii) Pathophysiology of the CTO plaque formation
(iii) Pathophysiology of collateral formation, function and recruitability
(iv) Assess efficacy of treatment strategies – percutaneous coronary intervention (PCI) and pharmacological agents to increase collateral formation and function.
(v) Long term assessment and outcomes of a CTO and its intervention on both coronary arteries as well as the territory of myocardium supplied.

As spontaneous formation of atherosclerosis is rare in animals [20], and spontaneous CTO formation has not previously been described, interventions are required to create such a model. This results in confounders based on the intervention, however does allow study of the effects of such an occlusion. Furthermore, once a model is created, therapeutic interventions may be trialled. This would include pharmacological agents to either improve collateral formation, function and

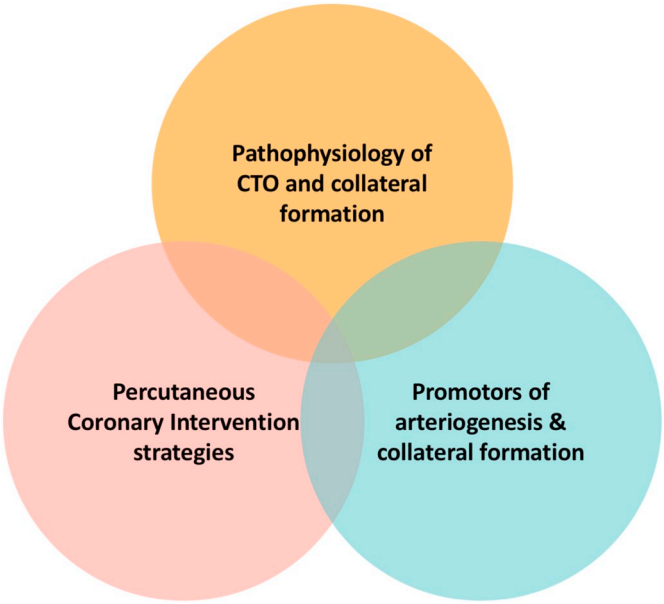

Fig. 2. Inter-species differences in collateral flow.
Adapted from [24].

recruitability or else different strategies for coronary intervention with angioplasty. Hence, an ideal animal model should include an occluded artery, functional collaterals and a viable myocardium, which would allow study of the process driving collateral formation and arteriogenesis as well as percutaneous intervention strategies for both acute and long term benefits (Fig. 3).

4. The coronary collateral circulation in animals

In humans, spontaneous coronary collaterals with sufficient collateral flow to prevent ischaemia following coronary occlusion are found in 20–25% of patients with normal coronary arteries, and 28% of those with coronary artery disease [21]. The prevalence of spontaneous coronary collaterals in animals, varies greatly amongst different species. In pigs, there are few spontaneous collaterals, and those that exist are located endomurally and subendocardially [22,23]. In contrast, in canines, there are extensive vascular communications between epicardial branches [22]. This protective occurrence, manifests as a lower mortality rate in acute myocardial infarction models compared with pigs. Maxwell et al. [24] utilised radiolabelled microspheres to

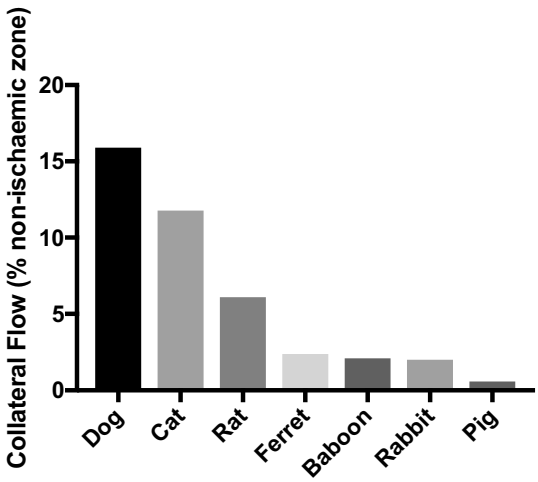

Fig. 3. Components of an ideal animal model of CTO.

determine the pre-existing collateral circulation in 8 different animals following occlusion of a major epicardial vessel to determine the relative blood flow to the non-ischaemic area of the myocardium. They found that in Guinea pigs, there was no zone of relevant underperfusion (i.e. a complete collateral circulation). The relative flow, as a percentage of normal, non-ischaemic flow was 15.9 ± 1.8% in dogs, 11.8 ± 1.1% in cats, 6.1 ± 0.7% in rats, 2.4 ± 0.6% in ferrets, 2.1 ± 0.3% in baboons, 2.0 ± 0.5% in rabbits and 0.6 ± 0.2% in pigs (Fig. 2).

5. Animal models of chronic total occlusions

To study the pathophysiological basis of CTOs, both coronary as well as peripheral animal models have been developed. To summarise these existing models, we performed a PubMed and Medline search including the terms “animal” “coronary” and “chronic total occlusion” to review existing and relevant papers. Whilst generalised percutaneous treatment strategies may be tested in either coronary or peripheral CTOs, the pathophysiological factors driving coronary CTO formations are likely to be varied, and hence would require a coronary model. Broadly, the methods of achieving this, irrespective of species studied, may be categorised as either progressive extrinsic compression, or else endoluminal intervention (Table 1).

5.1. Coronary CTO models

5.1.1. Extrinsic compression

In the method of extrinsic compression, the aim is to create progressive occlusion of a vessel, so as to reduce anterograde myocardial blood flow and allow recruitment of collateral vessels before complete coronary occlusion, thereby preventing (or limiting) myocardial infarction. The process of decrease in anterograde blood flow in the vessel results in increased blood flow and shear stress on the collateral circulation from the donor vessel, activating the process of arteriogenesis [25] and hence maturing the collateral circulation to become functional. Operschall et al. [26] utilised an ameroid constrictor in the coronary circulation of the rabbit to create a CTO model. An ameroid constrictor is a cylindrical device made up of an inner ring of casein (a hygroscopic substance that slowly expands as it absorbs fluid) surrounded by a metallic sheath. As the casein layer expands, it causes progressive external compression, until there is obliteration of the vessel lumen (Fig. 4). An ameroid constrictor was applied to the left circumflex (LCx) artery, with animal euthanasia at day 21. There was a 21.6% rate of early death, whilst in those that survived, 88% had coronary occlusion. Of these, corrosive casts showed that 4 out of 7 had vascular connections suggesting retrograde collateral flow. In the 3 others, either there was selective collateral recruitment or issues with the casting process. Radiolabelled microspheres illustrated an increase in coronary blood flow back to baseline flow (prior to occlusion) in the epicardium, but remained 50% of baseline in the endocardium, illustrating collateral maturation is greater in the epicardium compared to the endocardium.

Toyota et al. [27] utilised a method of repetitive extrinsic compression to promote and recruit coronary collaterals in the rat. In the model, rats had implantation of a mini-pneumatic snare occluder to the left anterior descending artery (LAD), following which a protocol of repetitive brief inflations were carried over 10 days. Following the end of the protocol, the rats were euthanised and coronary blood flow was measured using radiolabelled microspheres, as well as micro CT to image vascular connections. They demonstrated that repetitive myocardial ischaemia created a 6 fold increase in collateral flow from baseline and a 3 fold increase in the number of arterial-arterial anastomoses compared to baseline. This method has successfully been repeated by Hattan et al. [28], Rocic et al. [29] and Reed et al. [30]. Whilst this process recruited collaterals during brief occlusion of the LAD, a CTO was not created per se, as the ability of these collaterals to

Table 1
Published animal CTO models.

Reference	Method of occlusion	Early death	Animal Sacrifice	Method of confirmation	Vessel	Successful CTO	Histology
Rabbit							
Operschall et al. [26]	Ameroid constrictor	11/51 (21.6%)	21 days	Angiography, corrosion plastic cast, myocardial blood flow by radiolabelled microspheres, histology	LCx	7/8 (88%) by angiography 7/8 (88%) by cast	Mean infarct size 9%
Pig							
Suzuki et al. [35]	Bioabsorbable polymer sponger	3/6 (50%)	4 weeks	Angiography and histology	LAD	3/3 (100%)	Microcalcifications, microvascular channels and elastic tissue in occluded segment.
Sim et al. [34]	Copper Stent & bioabsorbable polymer	13/20 (65%) 4/20 (20%)	5 weeks and 4 weeks	Angiography and histology	LAD	7/7 (100%) and 16/16 (100%)	Fibrosis, necrosis, organised thrombus and inflammation, particularly in close proximity to the copper wire; gradual absorption of the $_{L}$-PLA polymer and formation of thrombus and fibrotic tissue
Song et al. [32]	Copper plated stent	1/18 (6%)	1 week, 4 weeks and 8 weeks	Angiography and histology	LCx	14/17 (82%)	Early group: Red thrombus and intimal fibrin with prominent inflammation; Intermediate group: organised thrombus with vascularised intima and calcification around the stent struts; Late group: Collagenous stroma and more organised calcification
Prosser et al. [36]	Oxygen enhanced bioabsorbable polymer	2/14 (14%)	Day 10 and 28	Angiography and histology	Various	12/12 (100%)	PLA completely reabsorbed with the occlusion consisting of fibrothrombotic lesions with microchannels and prominent adventitial arterioles.
Suzuki et al. [38]	Bone chips & absorbable gelatin sponge	8/20 (40%)	28 days	Angiography, histology and intravascular ultrasound (IVUS).	LAD, RCA & LCx	10/12 (83%)	Inflammatory cells and microvessel channels with moderate disruption of the internal elastic lamina, external elastic lamina and medial wall
Fefer et al. [37]	Collagen plug (angioseal)	9/26 (34.6%)	6 weeks and 12 weeks	Angiography, MRI, 3D spin CT, micro-CT imaging, histological analysis	LAD	15/17 (88.2%)	Early: Intense inflammatory reaction with prominent macrophage infiltration and a proteoglycan and collagen rich matrix Late; Less inflammation with a densely packed collagen and elastin rich matrix
Rat							
Toyota et al. [27]	Repetitive ischaemia via extrinsic compression	Nil	10 days	Myocardial blood flow radiolabelled microspheres, functional assessment, micro-CT	LAD	100% increase in collateral blood flow	N/A

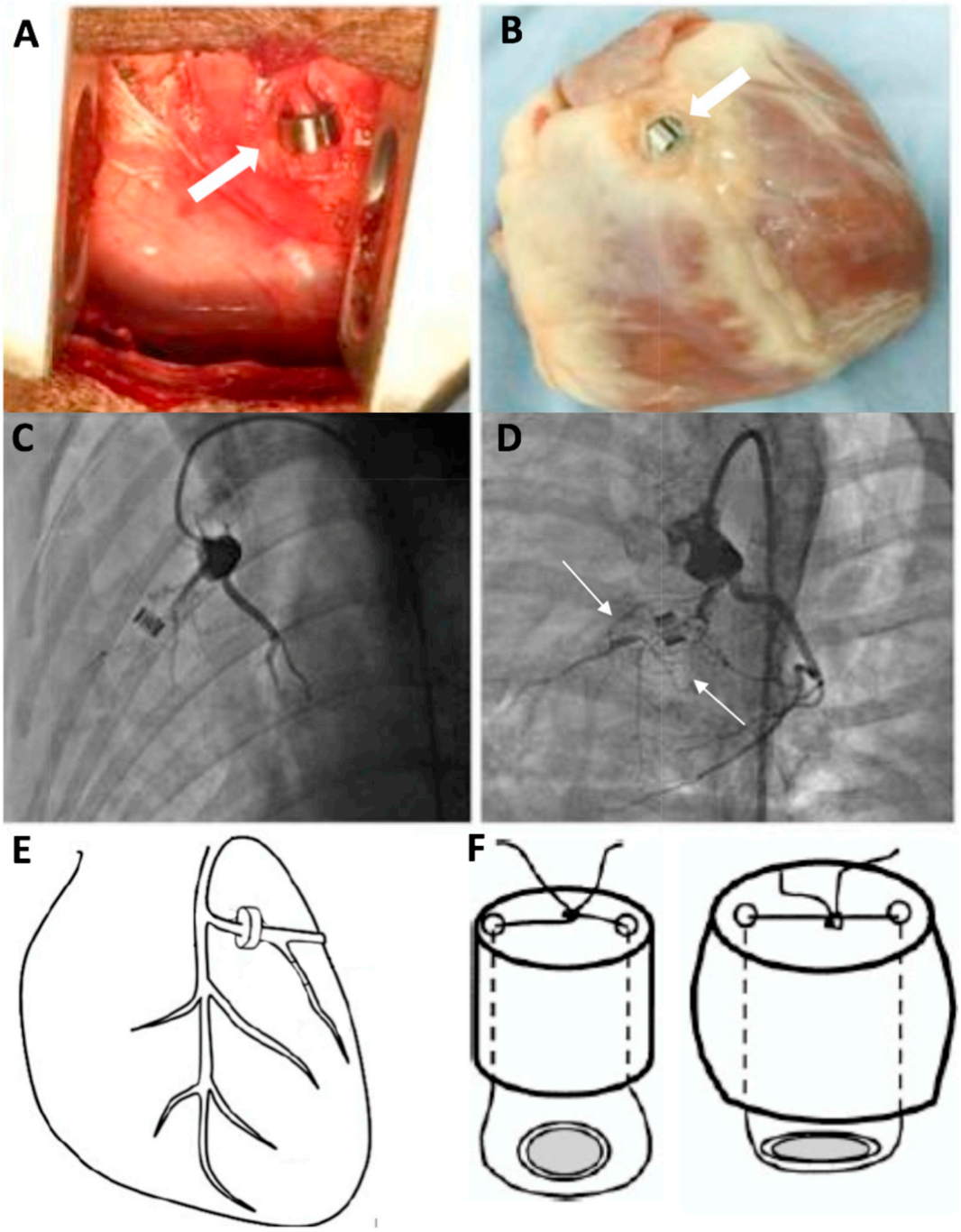

Fig. 4. Extrinsic compression model of a coronary CTO using an ameroid constrictor.
Implantation of the hydroscopic ameroid constrictor on a coronary artery within the chest cavity (A) and after explantation of the heart (B). Angiographic image of the ameroid constrictor showing occlusion of the coronary artery (C) with development of collaterals (thin arrows) filling the distal vessel beyond the ameroid constrictor (D). (E) Schematic of the ameroid constrictor implantation with (F) schematic of implantation illustrating after the suture is passed deep to the intramyocardial coronary artery and tied to the ameroid constrictor, with progressive swelling of the constrictor, the coronary artery is progressively obstructed. Adapted from [26,50].

prevent infarction with prolonged occlusion was not assessed.

Interestingly, Cohen et al. [31] attempted a similar process of repetitive myocardial ischemia with a protocol of intermittent inflation of a balloon encircling a superficial branch of the left coronary artery in the rabbit. However, in this model, there was no appreciable increase in collateral coronary blood flow, suggesting this process may either be species dependent or else highly operator dependent.

5.1.2. Endoluminal approach

Given the use of extrinsic compression renders the model unsuitable for studying revascularisation techniques, endoluminal approaches of creating a CTO have also been studied.

Song et al. [32] utilised copper stent implantation to induce a coronary CTO in a pig model. Copper stents have been shown to produce an intense inflammatory reaction and gradual obstruction of porcine arteries [33] and hence have been investigated in this setting. Stents were modified so that the copper coating was only present on the

abluminal surface, to minimise acute stent thrombosis, and implantation only into the left circumflex artery was chosen, resulting in a low early mortality rate of 5.6%. Animals were euthanised at differing time points. Animals euthanised after 1 week showed 100% occlusion, with 12 out of 14 vessels showing bridging collaterals. Histological assessment in those > 1 week showed organised thrombus with vascularised intima and calcification around the stent struts. In the late group (8 weeks) the inflammatory changes and intimal smooth muscle cells were less but more collagenous stroma and more organised calcification. Sim et al. [34] also utilised copper stents in their pig CTO model, inserting stents into the LAD rather than the circumflex, which may explain the higher early mortality rate of 65% with 7 animals euthanised at 5 weeks. All animals had an occluded LAD with evidence of a collateral circulation with histological assessment yielding fibrosis, necrosis, organised thrombus and inflammation, particularly close to the copper wire.

Bioabsorbable polymers have also been used in endoluminal models of CTO formation. Sim et al. [34] used a preparation of levo-polyactic acid polymer ($_L$-PLA) and inserted it into the distal LAD of pigs. 20% of pigs died as a result of ventricular fibrillation (VF) during the procedure, whilst the remaining 16 pigs all demonstrated total occlusion of the distal LAD with collateral circulation. Histopathological assessment showed gradual absorption of the ($_L$-PLA) polymer by 4 weeks. Suzuki et al. [35] created bioabsorbable sponges made of poly($_L$-lactide) (PLA), polyglycolide (PGA) or poly(DL-lactide-co-glycolide) coated in an apatite layer. These bioabsorbable sponges were implanted into the LAD of pigs, with 50% dying within 24 h. Of the remaining 3 pigs, after 4 weeks, all developed rich collaterals, however histological assessment demonstrated that the PLA and PGA sponges had not completely reabsorbed. Prosser et al. [36] treated PLA sponges in an oxygen environment before coronary implantation. 12% died during the procedure of VF with all of the remaining 12 developing a CTO with complete PLA reabsorption. Fefer et al. [37] used a commercially available collagen plug (Angio-Seal® Terumo IS Somerset, NJ, USA) in the LAD. 34.6% had an early death, with 15 of the remaining 17 (88%) pigs developing a successful CTO. Histological assessment revealed at 12 weeks, the occluded segment was composed of densely packed collagen and elastin rich with an inflammatory reaction. Suzuki et al. [38] attempted to create increased calcification within a CTO by injecting bone chips (harvested from the ribs of previously euthanised pigs) and a reabsorbable gelatine sponge in the coronary arteries. 40% died early with 10 of the remaining 12 (83%) developing an occluded artery with either contralateral or bridging collaterals.

5.2. Peripheral CTO models

Given the relative size of the coronary arteries, particularly in smaller animals, the peripheral circulation has been suggested as an alternative model to assess the pathophysiological process of CTO formation. As with the coronary circulation, both extrinsic compression, as well as endoluminal approaches have been described in the formation of a CTO.

Suzuki et al. [35] created a peripheral CTO model in pigs with implantation of bioabsorbable sponges into the femoral arteries. All 7 pigs had successful formation of a CTO with rich collaterals. Kim et al. [39], addressing the high rates of acute stent thrombosis with copper stents, coated these stents with a thin layer of PGA, aiming to facilitate gradual contact of copper to the vascular endothelium, achieved through progressive reabsorption of the PGA. Six stents were inserted into the femoral arteries of 3 pigs followed by euthanasia at 5 weeks. Five out of the 6 arteries developed a successful CTO, with most developing bridging collaterals. Zhu et al. [40] utilised a novel technique of inducing calcification within the occluded CTO, whereby polycaprolactone (PCL) scaffolds (a biodegradable polymer) coated with the growth factor TGFB1 and seeded with primary human osteoblasts (HOB) were inserted into New Zealand white rabbit femoral arteries. 17 out of 18 rabbits developed a successful CTO, with animals euthanised at 10 days showing the greatest extent of calcification, whilst those at 28 days had less calcification. The inflammatory milieu within the CTO also changed with early findings of lymphocytes and leukocytes near the stent struts, maturing to leukocytes within the adventitia and fibroblasts. At 28 days, leukocytes seen close to the stent struts became mixed with fibroblasts and infiltrated into the occlusion sites with microvessels from the adventitia migrating into the lumen.

Murphy et al. [41], in one of the earlier successful animal CTO models used varying combinations of multiple injury processes to induce occlusion. The femoral arteries of New Zealand white rabbits were subjected to gas drying with carbon dioxide following temporary proximal vessel occlusion, injection of bovine thrombi or injury by serial transverse clamp injury using a needle holder. Seventeen of 34 arteries demonstrated CTO formation with bridging collaterals, with the highest success rates with gas drying, thrombin injection and mechanical injury (78%), followed by gas drying and thrombin injection (60%). Histological assessment demonstrated atherosclerotic plaque with lipid laden cells and thrombus, although fibromuscular cells were also noted. Of note, there was no microcalcifications or evidence of neovascularisation within the occluded segment. Strauss et al. [42] used a similar method of thrombin injection to create a successful CTO model.

Nikol et al. utilised 3 different endoluminal approaches to create a femoral artery CTO; implantation of detachable angioplasty balloons supported by platinum coils, implantation of coils alone and specifically manufactured blind ended grafts. At 6 months, 100% of those implanted with blind ended stents remained occluded, whilst 33% of the detachable angioplasty balloons were occluded whilst all of the coil only group spontaneously recanalised.

5.3. Murine models

The mouse has become the most important, and widely used laboratory species for research, particularly in cardiovascular and metabolic disease research, owing to the availability of numerous transgenic strains, low cost, ease of housing and care as well as growing researcher familiarity. However, there are numerous physiological differences between the hearts of mice and humans, including differences in the action potential of cardiomyocytes, whereby mice cardiomyocyte action potentials have a short duration without a plateau phase as seen in humans, a five-fold higher resting heart rate than humans, and differences in active ion channel transporters [43,44].

Despite these differences, there is increasing work to create a reliable, and reproducible coronary CTO model in the mouse, although this is in its relative infancy and requires further investigation. There has been some initial success with the extrinsic compression models described above in rat models, with implantation of a mini pneumatic snare on a coronary artery during an open chest procedure, with intermittent repetitive occlusive ischaemia [45]. Other models of acute coronary ligation have demonstrated that whilst neo-collateral formation does occur, with size and numbers depending on different genetic strains, a large myocardial infarction still occurs, which precludes this method for studying human CTOs, although may have merit for investigating recruitment of acute collaterals [46].

5.4. Quantifying collaterals and CTOs

Once a potential CTO model is created, quantification of the collateral supply, both qualitatively and quantitatively may be done in a number of ways, to determine its success. These include direct visualisation using angiographic assessment or CT angiography, perfusion imaging, histological assessment and plastic mouldings; each with inherent advantages and disadvantages. In general, quantitative assessment requires explantation of the heart model, obviating the ability to test therapeutic interventions, whilst qualitative assessment allows

Table 2
Comparison between extrinsic compression and endovascular approaches to CTO formation.

	Extrinsic compression	Endovascular
Formation	Progressive occlusion	Acute occlusion
Technical difficulty	+	+ +
Rodent model	Yes	No
Early mortality	Low	High
Histopathology	Unable to assess	Organised thrombus with microchannels
Identify systemic markers/promotors of collaterals	Yes	Yes
Trial therapeutic revascularisation strategies (i.e. stent)	No	Yes

testing of such therapeutic options, although does not allow detailed analysis of the form and function of collaterals.

Ex-vivo 3D spin angiography and CT may be performed on excised hearts with perfusion of a silicon based gel into the coronary vasculature whilst the use of micro-CT allows assessment of the excised heart and vessels to a level of assessment of < 30 μm [37]. Histological assessment of the excised heart allows exquisite assessment of the structure of the collaterals, the presence of calcification, microchannels and thrombus within the CTO as well as the inflammatory response to the method of CTO induction. Corrosion casts [26] of the heart model involves flushing of blood from the microcirculation followed by direct infusion of a plastic mixture into the coronary arteries, before allowing the mixture to harden. The heart tissue is then macerated in sodium hydroxide to reveal the cast. Given the delicate nature of the collaterals, and the fact that they are often dynamic, opening only during significant flow from the contralateral (donor) vessel, meaning that smaller vessels may not be well visualised. Perfusion may be detected using radiolabelled microspheres, whereby during occlusion of a vessel, a radiolabelled microsphere is injected into the coronary circulation, which will not perfuse the tissue subtended by the artery of interest (this will be the so-called “area at risk”). Following formation of a CTO, a different radiolabelled isotope will be infused into the vasculature (during occlusion of the vessel, if not already occluded). After explantation of the tissue, and relative to the concentration of radiolabelled isotopes in the systemic circulation, relative blood flow to the at-risk area may be determined, and hence assess the collateral circulation functionally [26]. Whilst allowing functional assessment, this method does not allow anatomical classification, whilst again, requiring explantation of the heart.

6. Discussion

The ideal animal model for assessment of the pathophysiological basis of CTO and collateral formation and to evaluate the impacts of therapeutic modalities, should have a number of attributes. The model should be in an animal that reflects human biology, easy and reliably reproduced which mimics the histopathological features human CTOs, in a manner that allows intervention to be performed. The process should be such that researchers can quickly learn the skills required to create this model. As animals do not develop coronary artery disease and plaque rupture, both endoluminal and extrinsic methods of creating a CTO model can provide some of these features. The extrinsic compression models have the advantage of being technically less challenging with fewer early deaths. However, as these methods disrupt the natural architecture of the vessel wall, they are not conducive to assessment of percutaneous treatment strategies. Furthermore, they artificially obliterate the vessel lumen which does not mimic local vasomotor changes that occur with endothelial dysfunction and CTO formation.

Endovascular approaches of coronary CTO models have a relatively high early mortality rate, but in those that survive, the CTO mimics the human CTO model more closely, with organised thrombus with fibrous tissue, microcalcifications and microchannels. However, the presence of either a stent, or else other material within the lumen may not be widely applicable to all CTOs with respect to revascularisation. The adjunctive role of anti-arrhythmic therapy whilst forming these models is not standardised, and may minimise early arrhythmia induced mortalities (Table 2).

Peripheral CTO models, whilst easier to perform with less early morbidity and mortality, do not readily correlate with local biochemical and vasomotor changes which are unique to the coronary circulation and cannot reliably be used in the further investigation of coronary CTOs.

The wider implications of these CTO models, as with research in all animal models must however be tempered with caution. In numerous situations, pharmacological research in animals and humans has been discordant, often raising doubt about the wider applicability of animal research in humans [47]. Of note, with the above reviewed animal models, numbers are small, with no specific mention of blinding or independent assessors to determine success of a model, raising the possibility of bias and positive reporting. Furthermore, there are inherent differences and variation in naturally occurring coronary collaterals between species as previously described, and the above models may simply reflect this natural variation, rather than true stimulation of neo-collateralisation.

Nevertheless, the field of interventional cardiology has benefited immensely with the use of animal models, and the early suggestions of these animal models are that whilst a “gold standard” has yet to be found, there are encouraging signs. Already catheter techniques, initially trialled in animals are now available for use for interventional cardiologists for CTO percutaneous coronary intervention [48]. However, a process of rigorous scientific review must be maintained for animal models of CTOs, which will ultimately allow further advancement of disease process understanding and treatment modalities.

7. Conclusion

A reliable and reproducible animal model of a coronary CTO may be created either with extrinsic or endovascular approaches, both of which have inherent limitations. Assessment of the collaterals may either be done quantitatively or qualitatively, but often requires explantation of the heart, obviating its ability to be used for therapeutic trials. With an ever increasing interest in the management of CTOs in humans, newer models, more closely mimicking the human disease process should be continued to be investigated.

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