REVIEW | Heart Failure: Novel Therapeutic Pathways Emerging from Basic Science

Cardioprotection during ischemia by coronary collateral growth

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Jamaiyar A, Juguilon C, Dong F, Cumpston D, Enrick M, Chilian WM, Yin L. Cardioprotection during ischemia by coronary collateral growth. Am J Physiol Heart Circ Physiol 316: H1–H9, 2019. First published October 31, 2018; doi: 10.1152/ajpheart.00145.2018.—Ischemic heart diseases (IHD) cause millions of deaths around the world annually. While surgical and pharmacological interventions are commonly used to treat patients with IHD, their efficacy varies from patient to patient and is limited by the severity of the disease. One promising, at least theoretically, approach for treating IHD is induction of coronary collateral growth (CCG). Coronary collaterals are arteriole-to-arteriole anastomoses that can undergo expansion and remodeling in the setting of coronary disease when the disease elicits myocardial ischemia and creates a pressure difference across the collateral vessel that creates unidirectional flow. Well-developed collaterals can restore blood flow in the ischemic area of the myocardium and protect the myocardium at risk. Moreover, such collaterals are correlated to reduced mortality and infarct size and better cardiac function during occlusion of coronary arteries. Therefore, understanding the process of CCG is highly important as a potentially viable treatment of IHD. While there are several excellent review articles on this topic, this review will provide a unified overview of the various aspects related to CCG as well as an update of the advancements in the field. We also call for more detailed studies with an interdisciplinary approach to advance our knowledge of CCG. In this review, we will describe growth of coronary collaterals, the various factors that contribute to CCG, animal models used to study CCG, and the cardioprotective effects of coronary collaterals during ischemia. We will also discuss the impairment of CCG in metabolic syndrome and the therapeutic potentials of CCG in IHD.

INTRODUCTION

Cardiovascular disease remains the top underlying cause of death worldwide, with 17.3 of 54 million deaths attributed to it in 2013 (3). It is further estimated that 16.5 million Americans over the age of 20 yr old have coronary heart disease (CHD) and ~790,000 individuals suffer myocardial infarctions (MIs) each year (3). The consequences of such can be severe: in 2014, 114,019 deaths were attributed to MI, and ~36% of the people who experienced a coronary event perished (3). Even aside from possible mortality, acute coronary syndrome events (i.e., MI) caused by heart disease and atherosclerotic plaque ruptures can lead to tissue ischemia and successive tissue damage. A sobering statistic of these acute coronary events is that they are often the first indicator that a patient has ischemic heart disease (IHD). Accordingly, preserving the viability and contractility of the myocardium after MI are two of the objectives of treating patients with IHD. The conundrum of this treatment lies in the timely restoration of blood flow to the area at risk, but even timely reperfusion can induce further damage to the tissue, a phenomenon known as reperfusion injury (26). Common procedures to reestablish blood flow in the setting of severe coronary disease, such as stent implantation and angioplasty, can lead to complications including reperfusion injury as well as restenosis or rupture followed by additional episodes of coronary ischemia, MI, stroke, and death, especially in the elderly (3, 13).

Because reperfusion injury plays a significant role in a patient’s outcome, a great deal of focus has been directed toward cardioprotection by ischemic pre-, per-, and postconditioning, yielding disparate results in terms of potential therapies. Although pharmacological approaches have not translated into therapies (26) and most postconditioning trials have not produced positive outcomes (12, 32), some recent trials using perconditioning strategies have shown promise (44).

The coronary collateral circulation is a network of arterial-arterial anastomotic connections present in the heart between
vascular branches from different regions (16). In their native state, these vessels cannot offer much protection against ischemia due to their small caliber, which renders high resistance and poor ability to conduct flow. In ideal circumstances, when a major coronary artery is obstructed, native coronary collaterals will undergo arteriogenesis or abluminal expansion into natural bypasses to compensate for the deficient blood supply to the myocardial regions distal to stenotic lesion. Stimulation of CCG is therefore a potential therapy for patients with severe angina pectoris who have contraindications for coronary artery bypass grafting or percutaneous coronary intervention (17, 53, 69). Furthermore, when patients with IHD with preexisting coronary collaterals suffer a MI, the well-developed collaterals can provide sufficient blood flow to limit the extent of ischemic injury to the myocardium (22).

In this review, we will discuss the cardioprotective effect of a well-developed coronary collateral circulation as well as underlying mechanisms for this adaptive process and how to stimulate the CCG in IHD.

CORONARY COLLATERALS AND CCG

Native Coronary Collaterals

The term “collaterals” encompasses both collateral arteries and microvascular collaterals. Microvascular collaterals are arteriole-to-arteriole anastomoses found in the crowns of adjacent arterial trees (16). Microvascular collaterals are distinguished from collateral arteries, which are artery-to-artery anastomoses and present in other systemic arterial territories such as the superior ulnar collateral artery, palmar and plantar arch collaterals, etc. These microvascular collateral vessels connect an extremely small percentage of arterioles. In the absence of occlusion (and therefore a pressure gradient), these native collaterals experience almost no net flow between the adjacent trees, although there appears to be both anterograde and retrograde flow, which keeps the vessel patent and prevents any clots from forming (66). In their native, unstimulated state, the diameter of these vessels is small as they have not yet undergone remodeling and expansion. Intratree anastomoses, such as those within left anterior descending coronary artery (LAD), also function similar to collaterals but cover a much smaller area.

Native collaterals are typically microvascular arterial-to-arterial anastomoses that are present in healthy tissues without any arterial obstructions. Native coronary collaterals can be present at birth but show wide variation in their functional capacity. In most species, microvascular collateral vessels are present in healthy organs under normal physiological conditions (no occlusion of arteries). However, the presence of native collaterals can be difficult to identify by conventional angiography or even more advanced techniques, such as laser speckle contrast, until obstruction is induced (16). Studies to better image the coronary collaterals will help to address the presence and extent of native collaterals. It is important to mention that there is a species to species variation in native coronary collaterals. It is well documented that humans have native coronary collaterals (80), although there may be substantial variations in the extent of this native circulation. Guinea pigs have the most abundant native coronary collaterals. Maxwell et al. (33) reported that the coronary collaterals in guinea pigs could compensate blood flow in the whole heart during occlusion of a major coronary artery. Also, canines and felines have well-developed coronary collaterals. In contrast, the native coronary collateral circulation of rats, ferrets, baboons, rabbits, and pigs appears to be less developed than the dog and cat. Interestingly, we (unpublished observations) have shown that in murine hearts, native collaterals are absent by microcomputed tomography scanning with high resolution (4 μm), which is consistent with a report by Zhang and Faber (77).

CGG (Arteriogenesis)

The native coronary collateral circuit exists as artery-artery anastomotic connections that can function as an alternative source of blood flow supply during upstream coronary occlusion. Upon stimulation by coronary occlusion, these vessels can undergo remodeling to a larger caliber with diameters expanding 5- to 10-fold in humans, which greatly reduces their resistance to blood flow and can alleviate ischemia (11, 50, 70). Fulton (18) demonstrated that the diameter of the anastomoses in the absence of coronary artery disease (CAD) ranges from 10 to 200 μm compared with 100–800 μm in the presence of CAD. The process of abluminal expansion of collateral vessels is known as CCG or coronary arteriogenesis. CCG has been shown to reduce infarct size and prevent sudden death during coronary occlusions (4, 10).

During arteriogenesis, collaterals undergo abluminal expansion and wall thickening so as to transform into wider, cork-screw-like vessels. Collaterals exhibit significant tortuosity, which distinguishes them from other vessels of similar diameter. Unlike arteries, collaterals also grow lengthwise during their remodeling, reducing axial tension, which explains the tortuous path they take to connect one arteriole to another through the myocardium (54). However, one or more collaterals could regress after remodeling as part of their pruning process, whereas other collaterals become dominant and persist.

Growth of collateral vessels (also termed arteriogenesis) and angiogenesis are frequently used as synonyms; however, they are different processes. Angiogenesis is defined as new capillaries that stem from the budding of preexisting capillary vessels (16). Arteriogenesis, as previously defined, pertains to the remodeling of preexisting arterial vessels through the “anatomic increase in lumen area and wall thickness.” CCG in adult animals is thought to develop by expansion of a preexisting collateral network. However, there are not systemic studies to exclude the growth of new vessels. Zhang and Faber (77) reported that new collaterals formed in response to a very distal occlusion of coronary artery in the apex in murine hearts. In the same study, new anastomoses were found to connect the branches of LAD to the right coronary artery and the septal artery. However, it is not clear that whether these connections occurred from preexisting vessels or the formation of new vessels. More detailed studies such as lineage tracing would be beneficial in addressing where these connections are coming from.

The mechanisms of CCG are also incompletely understood. The factors causing arteriogenesis are likely a combination of mechanical (shear stress) and chemical factors (related to ischemia and genes activated by ischemia), whereas angiogenesis is thought to be related to tissue hypoxia and the chemical...
The incidence of interarterial coronary anastomoses was 95% in nonhypertrophic hearts with coronary artery occlusion. Seventeen percent of hearts with a slight narrowing of a coronary artery had interarterial anastomoses, whereas, those with moderate and marked narrowing of a coronary artery, this percentage rose to 25% and 63%, respectively. Anastomoses were present in 25% of hypertrophic hearts without any coronary or valvular disease. The factor of relative cardiac hypoxia in all these conditions appears to be a common underlying stimulus for the development of interarterial coronary anastomoses (80). The collaterals protect the “at-risk” myocardium, and the extent of CCG is associated with improved outcomes in patients with IHD (79).

**CLINICAL STUDIES IN THE CORONARY COLLATERAL CIRCULATION**

There are three prevalent clinical methods used to measure the extent of coronary collaterals: the Rentrop score, collateral flow index (CFI), and intracoronary electrocardiogram. The Rentrop score is assessed during coronary angiography as a visual assessment, with the score ranging from grade 0 to 3, where 0 indicates no visible filling of collaterals and 3 signifies complete collateral filling of the vessel being dilated (48). One limitation is that the scores can be influenced by systemic and coronary hemodynamics (24). Currently, the most well-accepted method is CFI, which was first calculated by Seiler et al. (56). The procedure for measuring CFI involves the occlusion of the stenosis by an angioplasty catheter and measurement of aortic pressure, distal coronary artery pressure, central venous pressure, and flow velocity (Fig. 1A). By measurement of the intracoronary occlusive pressure distal to the stenosis, collateral flow can be expressed relative to the normal flow through the same vessel. CFI can be calculated as follows:

\[
CFI_p = \frac{(P_{ocea} - CVP)}{(P_{ao} - CVP)}
\]

where CFI\(_p\) is pressure-derived CFI, P\(_{ocea}\) is distal intracoronary occlusive pressure, \(P_{ao}\) is mean aortic pressure, and CVP

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**Fig. 1. Clinical aspect of coronary collaterals. A: schematic showing calculation of the collateral flow index (CFI). \(P_{ao}\), mean aortic pressure; \(P_{ocea}\), distal intracoronary occlusive pressure. CFI can be calculated as follows: \((P_{ocea} - CVP)/(P_{ao} - CVP)\), where CVP is central venous pressure. B: CFI as calculated by Stoller et al. in different systemic arterial territories. CA, coronary artery; left SCA, left subclavian artery; RA, renal artery; left SFA, left superficial femoral artery. C: schematic showing the orientation of the right and left internal thoracic (mammary) arteries with respect to the heart. The internal thoracic arteries give rise to the pericardiacophrenic arteries, which supply blood to the heart. Stoller et al. (63) reported increased CFI (in the right CA) in patients whose distal right internal thoracic arteries had been closed permanently. This figure was created by modifying graphic elements freely available from Servier Medical Art (https://smart.servier.com/) under a Creative Commons Attribution 3.0 Unported License.
is central venous pressure (40, 72). Although this index has untested assumptions, such as the assumption that the vascular resistances distal to the occlusion are equivalent, it is a reasonable estimate of collateral growth. Stoller and Steiler (63) measured CFI in different arterial regions within the same individual (Fig. 1B) and found that in the human heart, the left and right internal thoracic arteries [formerly referred to as the internal mammary arteries (IMAs)] form anastomoses with the LCAs and RCAs, respectively. Occlusion of the distal left IMA and LCA simultaneously resulted in an increase in CFI (61). Simultaneous occlusion of the right IMA (RIMA) and RCA also increased CFI. They also showed that permanent closure of the RIMA helps to improve blood flow to the respective myocardial region via ipsilateral connections between the RIMA and RCA resulting in anti-ischemic benefits (Fig. 1C) (62). CFI also increases with prevalence of atherosclerotic lesions, given that the lesions are in hemodynamically appropriate regions (59). Patients with chronic complete coronary occlusion also have higher CFI values than those lacking it (39). It would appear that collateral growth is directly stimulated in the setting of occlusive coronary disease. It is well known that coronary collaterals occur in patients with overt CAD (59), suggesting some degree of compensation for the developing coronary lesions. Another interesting feature of patients with IHD with increased CFI is the increased prevalence of larger diameter anastomoses, whereas smaller anastomoses are “pruned” and tend to regress (39).

Because reperfusion of the ischemic myocardium is critical to minimize ischemic injury (26) and collaterals can restore the blood flow, increasing CFI has been targeted as a potential therapy for patients with IHD. In the “EXCITE” study (exercise induced the formation of collaterals), CFI increased in patients with chronic stable CAD (40). While the coronary collateral circulation is related to poor outcomes in patients with CAD, the collateral circulation itself contributes beneficially by promoting reperfusion post-MI (59). The coronary microvasculature is perfused mostly during diastole, so increasing the diastolic duration by exercise improves the coronary blood flow. Therefore, a pharmacological agent capable of reducing heart rate without any adverse effects could be used to improve coronary blood flow and collateral function. Gloekler et al. (19) reported that CFI of patients with chronic stable CAD increased after 6 mo of treatment with ivabradine, whereas CFI of patients in the placebo-treated group decreased. Patients treated with ivabradine also exhibited a significant decrease in heart rate. This study corroborated the results of a previous study in a canine model of CAD (31), where bradycardia during gradual coronary occlusion stimulated arteriolar and collateral growth, improved myocardial perfusion, and upregulated VEGF and Tie-2, which are involved in angiogenesis. Another beneficial effect of ivabradine-induced diastolic prolongation is an improvement in coronary flow reserve (60, 64), which is the ratio of coronary blood flow that can be achieved under maximum vasodilation to the blood flow at baseline under normal physiological conditions. Diastolic prolongation has also been associated with improved collateral growth. Patel et al. (43) have shown that a significantly larger proportion (97%) of patients with obstructive CAD with a heart rate of 50 beats/min or lower had developed collaterals compared with patients with a heart rate of 60 beats/min or higher (55%).

**CARDIOPROTECTIVE EFFECTS OF MICROVASCULAR CORONARY COLLATERALS**

Development of collaterals in response to occlusion of the coronary artery is a compensatory mechanism to restore blood flow in the ischemic areas. A case was reported where the patient had complete occlusion of the main LCA and 80–90% stenosis in the RCA. Interestingly, the patient had no angina symptoms and only mild symptoms with exertion. Collaterals provided the entire blood supply to the heart, bypassing the lesion to supply the RCA area and also the LAD and left circumflex areas (34). This patient benefited from coronary collaterals. However, this line of thinking has not always been the consensus. The presence of a highly developed coronary collateral network in patients with CAD has also been shown to be positively correlated to adverse cardiovascular outcomes (52). As previously mentioned, the growth of collaterals is likely a response to the progression of coronary disease; thus, the collateral circulation should not be viewed as causative, rather as a consequence of IHD. Hence, CAD is responsible for both collateral growth as well as an unfavorable prognosis for the patient.

Collaterals show beneficial effects on cardiovascular outcomes in chronic as well as acute ischemia. Collaterals start to restore blood flow in cases of chronic total occlusion after ~12 wk postocclusion (71). A slower progression of CAD allows more time for the collaterals to remodel and develop. In cases of progressive coronary disease leading to total occlusion, normal left ventricular function has been observed as a result of collaterals restoring blood flow to the myocardium at risk. There is also evidence that left ventricular function correlates with collateral flow in acute ischemia. Siefer et al. (57) observed that patients’ CFI correlated significantly with systolic and diastolic ventricular function during myocardial ischemia. Similarly, Werner et al. (71) showed that in patients with chronic total coronary occlusion and normal regional function, collateral flow was better compared with those with impaired regional function. Moreover, Habib et al. (22) showed that in humans the presence of coronary collaterals before MI occurs leads to a smaller sized infarct as well as better left ventricular ejection fraction. On the other hand, in patients with a poor collateral network, acute MI may lead to cardiogenic shock, if the infarct is large. A well-developed coronary collateral circulation has been shown to have a beneficial effect on QT prolongation caused by ischemia, again suggesting a salubrious effect of collaterals in the setting of ischemia (36).

The presence of coronary collaterals might be also a predictor of prognosis in patients of CAD. Meier et al. (38) conducted a meta-analysis of 12 separate studies of over 6,000 patients with stable or acute CAD. Most of the studies included in this meta-analysis used Rentrop scoring to estimate coronary collateral conductance, although one used CFI (37). Subjects were grouped into two categories: high or low collateralization based on either Rentrop scores or CFI. The results indicated that patients with a higher degree of collateralization had significantly lower risk of mortality (42). Regieli et al. (47) also reported that 2-yr event-free survival was 84% and 92% in patients without and with coronary collaterals, respectively. The beneficial effect of coronary collaterals was not modified by the extent of vascular disease. The authors concluded that
angiographically visible coronary collaterals are predictive of a good prognosis in patients with CHD (9, 47).

IMPAIRED CCG IN METABOLIC SYNDROME

As important as it is to fully understand the process of CCG under normal metabolic conditions, it is also important to study CCG within the context of disorders of metabolism. CCG is impaired in type II diabetes and metabolic syndrome, and patients with metabolism disorders are likely to have more severe CAD or mortality (70). The hostile environment of diabetes and metabolic syndrome affects factors that stimulate CCG, including proangiogenic growth factors, endothelial cell and smooth muscle cell function, signaling pathways, inflammatory cells and stem cells, and the redox state of the coronary circulation (70).

There is also growing appreciation of CCG in the prognosis of CHD in patients with metabolic syndrome, a condition characterized by abnormal obesity, hypertiglyceridemia, insulin resistance, and hyperinsulinemia (14, 45). Metabolic syndrome confers a two- to fourfold increased risk for cardiovascular disease (30). Overall, patients with metabolic syndrome have a higher risk of IHDs, and nearly 30–40% of these patients have little to no growth of the coronary collateral circulation (1, 49, 74). In contrast, patients with well-defined coronary collaterals show better outcomes from a MI than those with a poorly developed collateral circulation (45). We and others have shown that CCG is impaired in preclinical models of metabolic syndrome (15, 21, 28, 29, 46). There are some reports suggesting the possible causes. In an animal model of metabolic syndrome, elevations in 20-hydroxyecosatetraenoic acid are linked to impaired CCG via excessive infiltration of neutrophils (29). Oxidative stress in metabolic syndrome could also cause progenitor cell dysfunction and impair CCG (23, 45, 46). MicroRNAs like miR-21 and miR-145 were shown to be involved in the impaired CCG in rats with metabolic syndrome (27). Increased generation of endostatin and angiostatin via metalloproteinase activation inhibited late-stage collateral remodeling (15). Overall, the underlying mechanisms that impede collateral growth in these models of disease are not well understood, due in part to the lack of a well-developed mouse model that allows for genetic modification. Further studies using genetically modified rodents will lead to better understanding of the mechanisms underlying the inhibitory influences on collateral growth.

STIMULATION OF CCG

The association of a high degree of coronary collateralization with better cardiovascular outcomes led to a number of studies in which cytokines, stem cells, or physical means were used to stimulate CCG (see Fig. 3 for a summary; Refs. 8, 11, 51, 65, and 75). VEGF and FGF were two growth factors that were tested on patients with IHD in the VIVA (25) and AGENT (20) trials, respectively. In both studies, the treatment group showed no significant benefits over the control group. To specifically target arteriogenesis to promote collateral growth, Seiler et al. (58) used granulocyte macrophage-colony-stimulating factor on patients with CAD. The results of this small-scale study were promising, as the treatment group was found to have higher CFI compared with the control group. Due to adverse effects of granulocyte monocyte-colony-stimulating factor on some of the patients in a later study (76), the focus shifted to granulocyte colony-stimulating factor (35). Monocyte chemoattractant protein 1 is a proinflammatory cytokine that also showed promise as a therapeutic agent. Monocyte chemoattractant protein-1 administration resulted in the formation of collaterals in a murine model but also resulted in plaque progression at the same time (68), so it is not clear the benefit was entirely from CCG. Overall, attempts to use cytokines to stimulate arteriogenesis have not yielded significant results.

Mechanical phenomena also play a role in arteriogenesis, and fluid shear stress is one likely contributing factor (54). According to Newtonian fluid dynamics, shear stress (\(\tau\)) can be calculated as follows:

\[
\tau = 4\eta Q / \pi a^3
\]

where \(\eta\) is viscosity, \(Q\) is flow rate, and \(a\) is the internal radius of the vessel. It must be noted here, however, that blood is a non-Newtonian fluid. Although it is likely that shear stress contributes to collateral growth, we believe many results have been overinterpreted, especially those implying that fluid shear is the singular cause of collateral growth. For example, augmenting blood flow using physical exercise was found to have a positive impact on collateral growth in clinical studies (41, 73). This was interpreted as an effect of shear stress, but exercise would also exacerbate ischemia in the setting of a coronary stenosis. Our previous data revealed that ischemia initiates CCG (10), but if the effects of shear stress were eliminated, the final growth of collaterals is minimal. We opine that it is an oversimplification to believe CCG is caused by a single factor, and undoubtedly more factors, in addition to shear stress, inflammation, and ischemia, will be discovered as being critical to this adaptive process.

One application of mechanical stimuli for CCG is external counterpulsation, which has been used to facilitate growth of coronary collaterals through increases in flow and shear stress in the coronary circulation. In this method, pressure cuffs are applied to lower limbs and are connected to and triggered by the subjects’ ECG. During systole, these cuffs remain deflated. During diastole, however, the cuffs are inflated with air. When applied with pressures up to 300 mmHg, this procedure is referred to as enhanced external counterpulsation (EECP). Application of this pressure increases coronary driving pressure and coronary blood flow, which causes an increase in shear stress on the endothelial wall of native collaterals. This appears to facilitate the remodeling process. A study by Zhang et al. (78) showed that EECP on high-cholesterol diet-fed pigs significantly increased shear stress on the right brachial artery wall and induced shear stress-responsive gene expression changes that led to vascular remodeling in the treated animals: intimal hyperplasia was inhibited, proliferation of vascular smooth muscle cells into the intima was reduced, and endothelial nitric oxide synthase expression was rescued. In the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP), use of EECP resulted in an increase in the coronary flow reserve (2). Buschmann et al. (6) also showed that external counterpulsation improves fractional flow reserve and CFIp in patients with stable CAD. The researchers calculated a novel parameter to assess blood flow velocity and shear rate, relative pulse slope index, which was significantly higher in arteries than in veins (7). They then used the relative pulse slope index to modify EECP into individual shear rate therapy.
by inflating the cuff with an individualized treatment pressure that achieved optimal peripheral perfusion in patients with peripheral artery disease (5). Flow-mediated dilation in the brachial artery in patients after 30 h of individual shear rate therapy was significantly increased compared with baseline measurements.

Stem cells are also promising in their ability to induce CCG, although this is an area of incomplete study. Recently, we used induced vascular progenitor cells partially reprogrammed from vascular endothelial cells to stimulate CCG in a rat model of repetitive ischemia (Fig. 2A). Induced vascular progenitor cells successfully engrafted into blood vessels and improved blood flow during ischemia better than mesenchymal stem cells, pluripotent stem cells, or endothelial cells. It suggested that stem cells might be a novel approach in stimulating CCG (75), but the potential treatment modality for the purpose of increasing collateral flow is in its infancy.

**FUTURE DIRECTIONS**

Despite the clinical importance of coronary collaterals in IHDs, factors that stimulate coronary collateral development and growth in physiological conditions, as well as those that impair CCG under pathological conditions, are still incompletely understood. The growth of coronary collaterals is a conundrum. Their significance is indisputable: a well-developed coronary collateral circulation ameliorates the consequences of CHD, reducing the incidence of sudden death and infarct sizes after coronary occlusion. However, the conundrum is how collateral growth can be stimulated in patients with CHD, as clinical trials directed at stimulating CCG have failed. Although the reasons for these failures are unresolved, one criticism of the preclinical studies (used as a basis for the therapy) was the use of young healthy animals, which does not mimic aged humans with CHD risk factors. The trials also used...
growth factor therapies without even establishing if the growth factors were requisite for CCG. Despite these shortcomings, there is no question that if CCG could be stimulated, it would offer a prophylactic treatment that could ameliorate the consequences of CHD. Although many approaches have been attempted to stimulate CCG, as shown in Fig. 3, to date there have been at best only modest beneficial results. However, with the implementation of new models that can better mimic the risk factors that inhibit collateral growth in patients, there is hope that these approaches could lead to new effective therapeutic strategies (79).

Restoration of CCG in metabolic syndrome is a promising approach for the treatment of IHD. Currently, our understanding of CCG is based on studies in animal models of CCG in pigs, dogs, and rats, in which certain inhibitors are administered to reduce CCG. A limitation of such “loss of function” studies is the cellular “target” of the inhibitor is unknown. The inhibitor could be acting on endothelial cells, smooth muscle cells, cardiac myocytes, inflammatory cells, and/or fibroblasts. There is no way to decipher the cell-based mechanisms of coronary vessel blood growth in the available animal models. Moreover, pharmacological inhibitors suffer from the problem of nonspecificity. To overcome these deficiencies, a murine model of CCG would enable us to use genetically modified mice to investigate many questions regarding the roles of specific genes and cell types involved in the process of CCG. While there are some reports of murine models of CCG, these models previously lacked validation and quantitation of the collateral growth, as detailed in Fig. 2A. In our preliminary study, high-resolution microcomputed topography was used to differentiate CCG from angiogenesis, and vascular tree analysis was able to quantify the CCG (Fig. 2B). We also used contrast echocardiography to measure coronary blood flow in vivo at different time points to maximize CCG (70). Tissue-specific transgenic or knockout mice can help determine the mechanisms and regulators behind CCG, and inducible transgenic mice will help study the temporal and spatial control of CCG. Better understanding of the interaction of cell signaling that regulates CCG will eventually lead to new therapies designed to help patients with IHD, restoring blood flow and providing cardioprotection in ischemic hearts.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.J., C.J., F.D., and L.Y. drafted manuscript; A.J., C.J., F.D., D.C.E., W.M.C., and L.Y. edited and revised manuscript; L.Y. approved final version of manuscript.

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