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Prevention of Coronary Microvascular Obstruction by Addressing the Individual Susceptibility

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Introduction

Another pathogenetic component of coronary microvascular obstruction (CMVO) is represented by the individual susceptibility to microvascular dysfunction, maybe related to the function, as well as to the structure and the density of the microcirculation [1]. Previous studies indicated that abnormal nonendothelium-dependent microvascular dilatation appears to be involved in functional and structural alterations that lead to impaired coronary flow reserve (CFR) with aging, hypertension, diabetes, dyslipidemia, insulin resistance, and chronic inflammatory diseases [2]. Moreover, a pre-existing transient or permanent microvascular dysfunction may contribute to the development and prognosis of acute coronary syndrome (ACS) via reduction of coronary blood flow, leading to an alteration of shear stress which aggravates endothelial dysfunction in epicardial arteries and might enhance thrombus formation [3]. Indeed, a pre-existing impairment of the myocardial microcirculation has been shown to yield greater vulnerability to percutaneous coronary intervention (PCI)-related myocardial injury as well as a poorer long-term outcome [4,5]. On the other hand, genetic factors may enhance the individual susceptibility of CMVO, affecting polymorphism of genes responsible of the onset, trigger and/or modulation of coronary microvascular dysfunction, as well as the resistance to the lysis. Another factor conditioning the individual susceptibility to CMVO is the presence of ischemic pre-conditioning (IPC), which seems to protect both the myocardium and the coronary microcirculation. Accordingly, pre-infarction angina (PIA) might help preventing CMVO, by inducing IPC. Importantly, beneficial effect of PIA may be blunted in humans due to risk factors or drugs therapy affecting unfavorably IPC [6]. In this chapter, we will review the mechanisms and the effects of the single causes of individual susceptibility of CMVO (Fig. 13−1), also addressing the prevention and treatment.
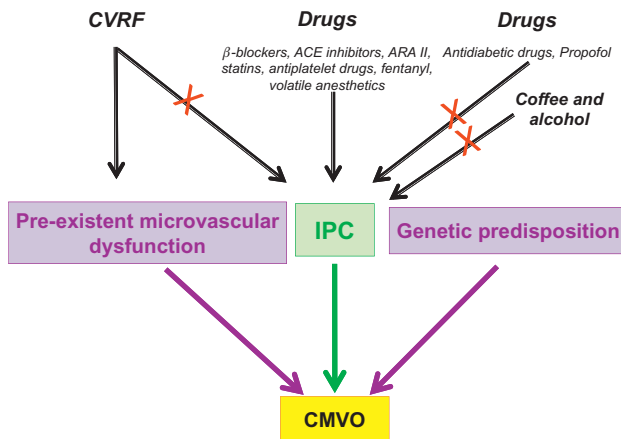
FIGURE 13–1 Main causes of the individual susceptibility for CMVO.
Causes of the individual susceptibility for coronay microvascular obtrsuction (CMVO) are represented by several factors that can promote (purple color) or prevent (green color) the CMVO: the pre-existent microvascular dysfunction, presence of ischemic pre-conditioning (IPC) and genetic predisposition. Common and uncommon cardiovascular risk factors (CVRF) may be the cause of pre-existent microvascular dysfunction but also reduce (red-cross) the beneficial effect of IPC on the CMVO. Other elements may modulate IPC inducing a protective effect (e.g., β-blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, statins, antiplatelet drugs, fentanyl, and volatile anesthetics) or, conversely, blunting (red cross) the beneficial effect (e.g., propofol, sulfonylurea, and antidiabetic drugs). Finally, coffee and alcohol intake may nullify (red-cross) the IPC-mediated reduction in the CMVO-rate.

Pre-Existent Microvascular Dysfunction

Pre-existent microvascular dysfunction can represent an important pathogenetic component of CMVO. The coronary blood flow is reduced by 50% in the nonculprit coronary arteries in acute myocardial infarction (AMI) before and after coronary intervention, thus confirming a global rather than a regional myocardial microcirculatory impairment [7]. Furthermore, in patients without obstructive coronary artery disease (CAD) and/or evidence of coronary epicardial and microvascular endothelial dysfunction during invasive cardiac evaluation, future cardiovascular (CV) events, including 38% that could be attributed to ACS, occurred in those with a reduction of coronary blood flow response to intracoronary infusion of acetyl-choline [8]. These data are in agreement with data from Britten et al. who studied patients with angiographically normal or minimally diseased coronary arteries and pointed out a more than threefold higher CV event rate in patients in the lowest compared with the highest tertile of CFR with 36% of all events related to ACS [9]. Moreover CFR, an indicator of the myocardial microcirculation, was an independent predictor of prognosis. Again, Marks et al. followed patients with chest pain/ischemic cardiac disease and normal coronary angiograms and reported a nearly threefold higher mortality for those patients with an abnormal CFR over a long-term follow-up [10]. Hence, the presence of myocardial microcirculatory

dysfunction has been confirmed a strong predictor of future acute coronary events, even in the absence of hemodynamically significant epicardial disease [4].

In this context, PCI can be considered as an iatrogenic form of plaque rupture and allows the evaluation of the significance of the myocardial microcirculation in a more specific setting. Of note, it has to be remarked that clinical studies of PCI showed that patients with pre-procedural CFR impairment were more likely to have post-procedural CFR impairment and procedure-related myocardial injury as well as worse long-term outcome [4,5]. These data demonstrate that pre-existing impairment of the myocardial microcirculation yields greater vulnerability to myocardial injury, thus implying a primary role of the myocardial microcirculation, at least in CMVO. A more general applicability of this concept is supported by the higher risk of acute coronary events as well as the injurious consequences of ischemia and reperfusion in patients with myocardial microcirculatory dysfunction due to CV risk factor profile [5]. Hence, traditional and nontraditional risk factors play a role in epicardial and microvascular endothelial-dependent dysfunction, specifically in the high-risk subset with ST elevation myocardial infarction (STEMI) [11−16].

Major Cardiovascular Risk Factors

Hyperglycemia

Diabetes mellitus (DM) is a well-established risk factor for death and cardiac complications such as cardiogenic shock in patients with STEMI [17,18]. Although the introduction of reperfusion therapy in the treatment of STEMI has considerably improved the survival, DM still remains an important predictor of mortality [19,20]. Of note, the Diabetes Association guidelines introduced a new category of impaired fasting glucose (IFG) for glucose levels ranging from 6.1 to 7 mmol/L (110 to 126 mg/dL), below the threshold for DM [21]. In this context, patients with abnormal fasting glycemia represent a large proportion of MI population and the effects of such abnormal glucose metabolism during AMI are deleterious with regard to short-term clinical outcomes [18,22,23]. Several studies have demonstrated an association between acute hyperglycemia and CMVO, which was independent of previous glycemic control evaluated by glycosylated hemoglobin A1c levels, therefore suggesting a direct detrimental effect of acute hyperglycemia on reperfusion injury [24,25]. Underlying endothelial dysfunction [26], diminished CFR [27] and structural microvasculature abnormalities in myocardial tissue [28] may be the causes of the decreased microvascular perfusion and subsequent poorer outcomes observed in patients with DM. Disturbances in glucose metabolism *per se* may also have a negative impact effect on myocardial reperfusion. Elevated levels of free fatty acids during hyperglycemia reduce endothelium-derived vasodilation of the myocardial vasculature [29] and hyperglycemia causes the plugging of leukocytes in the microvasculature of the myocardium and increases pro-coagulable properties of platelets [30,31]. These deleterious consequences of abnormal glucose metabolism on microvascular perfusion have been documented using different modalities to quantify myocardial reperfusion in patients treated with primary stent PCI [24,32]. In this context, optimal and prompt treatment of hyperglycemia is likely to be an important target in the prevention of

CMVO. Accordingly, the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study demonstrated that a peri-procedural reduction in blood glucose was associated with a reduction in infarct size (IS) [33]. Moreover, data from Emerald trial showed that patients with DM exhibit an impaired myocardial perfusion after PCI, lower rates of complete 30 minute ST resolution (STR), and a greater IS and 30-day mortality compared with patients without DM. Again, use of distal protection devices did not improve outcomes in diabetic or nondiabetic patients. At multivariate logistic regression analysis, DM was independent predictor of lack of complete STR and mortality at 6 months. Of note, it was associated with decreased myocardial reperfusion, larger infarct, development of congestive heart failure, and decreased survival [34].

Hypercolesterolemia

Cholesterol levels are considered to be a major independent risk factor for development of peripheral vascular disease and CAD [35−37]. Cholesterol has been demonstrated to interrupt and alter vascular structure and function as it builds within the lining of the vascular wall, and can interfere with endothelial function leading to lesions, plaques, occlusion, and emboli; along with a reduction in healing, recovery, and appropriate management of ischemia/reperfusion (I/R) injury [38−42]. With specific relevance to the microcirculation, it has been clearly shown that the evolution of hypercholesterolemia is associated with the endothelial cell dysfunction [38,43−47]. Moreover, reports have demonstrated a near-complete abrogation in vascular nitric oxide (NO) bioavailability, elevated oxidant stress, and the creation of a strongly pro-inflammatory condition; which can cause impairments to vascular reactivity [35,38,41−48]. Although a substantial risk factor for CV disease, hypercholesterolemia demonstrated to be manageable with pharmaceutical interventions that reduced the cholesterol levels and the CV event incidence. Of note, ongoing statin therapy at the time of STEMI was associated to a lower rate of CMVO, and better functional recovery of myocardial function after 6 months of follow-up as compared to patients not on statin [48]. Recently, the administration of high doses of statins prior to primary PCI has been demonstrated to improve CMVO as compared to that of low doses [49].

Arterial Hypertension

The propensity of the hypertensive heart to ischemic events is multifactorial including epicardial coronary stenosis (e.g., due to atherosclerosis), cardiac microvascular disease, and endothelial dysfunction, accompanied with ultra-structural remodeling of cardiac microvessels, that can cause a progressive impairment of flow-mediated vasodilation. Other features are represented by arterial stiffness with long standing hypertension and increased left ventricular (LV) afterload and central pulse pressure; the concomitant fall in central diastolic pressure reduces coronary perfusion, thus exacerbating myocardial ischemia [50−55]. Of note, changes in energy metabolism of the hypertensive heart also increase susceptibility to ischemia [56]. An approximately 30% reduction in CFR can be found by dipyridamole positron emission tomography (PET) studies in the asymptomatic early stages of systemic arterial hypertension [14,15].

The role of chronic treatment of angiotensin-converting-enzyme (ACE) inhibitors or nitrates, both associated with better reperfusion in small retrospective studies, should be tested on a large scale [57–60].

Smoking

Tobacco smoking is a well-established preventable risk factor for the development and progression of CAD and is strongly related to CV causes of morbidity and mortality [61].

Extensive data have been provided about the influence of cigarette smoke and its constituents on early atherogenesis, particularly on endothelial cells [62]. Specifically, endothelial dysfunction induced by smoking is initiated by reduced NO bioavailability and further by the increased expression of adhesion molecules, as well as macrophages and platelets recruitment [63,64]. The reduction of NO levels within the cells is responsible of the loss of function of smooth muscle cells (SMCs) in the vessel media [65]. Again, in response to smoke exposure, endothelial cells release inflammatory and pro-atherogenic cytokines [66]. Direct physical effects of smoke are represented by the production of reactive oxygen species (ROS) [67], and endothelial cell loss by apoptosis or necrosis [68]. After adhesion and trans-endothelial migration, macrophages take up oxidized lipids produced by oxidative modification through smoke-increased ROS production [69]. Scavenger receptor-mediated uptake of lipids induces the formation of so-called foam cells within the aortic wall, and subsequent death of foam cells induces the release of these lipids and the formation of lipid-rich aortic plaques [69]. Moreover, it is postulated that smoking induces an increase in SMC proliferation and migration provoking intimal thickening and plaque formation [70]. Destruction of extracellular matrix proteins is further enhanced by increased expression of matrix metalloproteinases (MMPs) and reduced expression of tissue inhibitors of MMPs (TIMPs) [71].

Of note, Nakamura et al. demonstrated that smoking habit abolishes IPC-induced increase of endothelium-dependent vasodilation [72]. Possible mechanisms explaining this result might involve down regulation of vascular endothelial growth factor (VEGF) receptor-2 expression, endothelial nitric oxide synthase (eNOS) protein levels, and VEGF-induced VEGF receptor-2 phosphorylation, leading to impaired VEGF-induced cell migration and angiogenesis [72]. Clinically, culprit lesions of smokers with AMI have a greater thrombotic component with relatively less atherosclerotic plaque, in comparison with those of no-smokers [73]. Regarding CMVO, several previous reports have suggested that smokers have a more effective reperfusion. Albertal et al. demonstrated that post-procedural thrombolysis in myocardial infarction (TIMI) flow grade and TIMI frame were better in smokers, and percentage of complete STR was higher in active smokers than nonsmokers. Multivariate logistic regression analysis identified active smoking as an independent predictor of complete STR [74]. Similarly, Ndrepepa et al. showed that among 1140 patients with STEMI undergoing primary PCI, smokers had less CMVO [75].

This phenomenon, called "paradoxical effect of active smoking" could be explained by less extensive atherosclerotic disease and hence, smaller plaque burden in smokers rather than non smokers. Finally, Shemirani showed that CMVO or short-term complications are not significantly different between current smokers and nonsmokers in patients with STEMI who undergone primary PCI [76].

Aging

Advancing age is the major risk factor for the development of CAD. This can be considered attributable to the development of vascular endothelial dysfunction, as indicated by reduced peripheral artery endothelium-dependent dilation in response to chemical typically acetylcholine or mechanical stimuli. Reduced bioavailability of the endothelium-synthesized dilating molecule NO as a result of oxidative stress is the crucial mechanism mediating reduced endothelium-dependent dilation with aging. Vascular oxidative stress increases with age as a consequence of greater production of ROS (e.g., superoxide) without a compensatory increase in antioxidant defenses. Sources of increased superoxide production include up-regulation of the oxidant enzyme NADPH oxidase, uncoupling of the normally NO-producing enzyme, eNOS, due to reduced availability of the cofactor tetrahydrobiopterin and increased mitochondrial synthesis during oxidative phosphorylation. Increased bioactivity of the potent endothelial-derived constricting factor endothelin-1, reduced endothelial production of/responsiveness to dilatory prostaglandins, the development of vascular inflammation, formation of advanced glycation end-products, and increased rate of endothelial apoptosis and reduced expression of estrogen receptor α (in postmenopausal females) also probably contribute to impaired endothelium-dependent dilation with aging [77]. Clinically, during AMI, older age is associated with adverse outcomes, abnormalities of LV diastolic function [78,79] and, decrease in systemic vascular compliance [80], increase in LV mass index [81] and altered neurohormonal and autonomic influences [82]. Moreover, advanced age has been shown to be an independent predictor of CMVO [83,84]. How this association can influence the outcome of this group of patients it has to be tested in large scale trials.

Gender

There are substantial sex/gender differences in the prevalence and burden of different CV disease [85]. Regarding cardioprotection, gender differences are observed in some animal studies suggesting that, compared to males, intact pre-menopausal females have reduced I/R injury [86,87]. In particular, this happened under conditions where calcium is elevated or contractility is increased just prior to ischemia [88]. This protection has been shown to involve an increase in NO signaling leading to S-nitrosylation of the L-type calcium channel, which reduces calcium loading during ischemia and early reperfusion thereby reducing I/R injury [89]. Again, estrogen binding to nuclear estrogen receptors results in altered expression of a number of cardioprotective genes such as NOS and heat shock proteins [90−92]. Estrogens also alter a number of genes involved in metabolism such as lipoprotein lipase, prostaglandin D2 synthase, and peroxisome proliferator activated receptor gamma coactivator 1 alpha [93]. The effects of these alterations in gene expression may

depend on other hormonal or physiological stimuli. Furthermore, addition of estrogen has acute nongenomic responses that involve activation of the phosphatidylinositol 3-kinase (PI 3-kinase) pathway, which has been shown to be protective, at least when activated for short durations [92,93]. Moreover, estradiol decreases phosphorylation of connexin 43 [94], that has been shown to be associated with cardioprotection. However, despite these experimental results, a large clinical trial, the Women's Health Initiative, found an increase in CV incidents in women on hormone replacement therapy [95]. Several clinical studies demonstrated gender differences in the clinical manifestation of CAD [85,96]. Compared to the men, the female patients with AMI followed in the clinical trials were older, presented more co-morbidites and less often received reperfusion therapy [96,97]. Of note, most recent studies are in agreement that women's older age is largely contributory to the adverse outcomes of women with AMI [98,99].

In this context, Ishiara showed that, the in-hospital mortality rate after AMI was significantly greater in women >70 years old age than in men >70 years old but was comparable between women and men in patients <70 years old [100].

Minor Cardiovascular Risk Factors

Inflammation

Inflammation may be a common link between epicardial macrovascular and myocardial microvascular disease. Indeed, an acute inflammatory process has been shown to involve the coronary microvessels but not the cardiomyocytes in unstable angina patients [101]. In this setting, inflammation of the myocardial microcirculation could not represent the consequence of myocardial necrosis or even myocardial ischemia but rather it could be due to an immunological process, possibly by downstream spread of immunogenic material from ruptured plaques. Intriguingly, several studies highlighted the presence of multiple and not just one plaque rupture in all three and not just one coronary artery in patients with ACS [102,103]. Moreover, widespread activation of neutrophils across the coronary vascular bed has been reported in patients with unstable angina, regardless of the location of the culprit stenosis [104]. Again, high levels of C-reactive protein (CRP) serum concentration has been widely demonstrated to be an independent predictor of a blunted coronary blood flow response to adenosine and substance P in patients undergoing elective PCI [105], and an indicator of presence of macrophages in the culprit plaque of patients with ACS [106]. Finally, in patients with normal coronary angiograms, a significant inverse correlation was noted between CRP serum concentrations and myocardial blood flow responses to cold pressor testing by 13 N-ammonia and PET imaging [107]. These latter findings seem to suggest that the inflammatory mechanisms linked to plaque rupture also cause microvascular dysfunction. However, there is no definitive agreement regarding the predictive value of inflammation on CMVO. In this context, a similar prevalence of final TIMI flow < 3 and Myocardial blush grade (MBG) < 3 was observed in patients with AMI with high and low CRP serum levels [108], suggesting that the basal inflammation would not predict CMVO. In contrast, the combination of peak concentrations of CRP, fibrinogen and white blood cell count, have

been recently shown to be significantly higher in patients with compared to those without CMVO [109]. In conclusion, the predictive role of inflammation on CMVO deserves to be investigated in future larger studies.

Hyperhomocystinemia

Extensive experimental evidence, both in vitro and in vivo, indicates that hyperhomocystine-mia impairs endothelial function [110−112]. Indeed, it changes vascular tone by regulating endothelium-dependent vasodilator and constrictor substances, including decreasing NO bioavailability, increasing contractile prostanoids as well as interfering myoendothelial communication. Oxidative stress and eNOS uncoupling have been suggested to play a critical role in hyperhomocystinemiy-induced endothelial dysfunction [110]. Results of randomized controlled trials of antioxidant vitamin supplements in large numbers of participants have been ambiguous or contradictory [113]. This discrepancy remains to be investigated in future experimental and clinical studies.

Renal Dysfunction

Many clinical studies have shown that patients with baseline renal dysfunction have increased CV risk and correlate with a major decrease in life expectancy after the procedure [114]. Baseline renal dysfunction, analyzed according to MDRD equation, was an independent predictor of in-hospital mortality in STEMI patients undergoing successful primary PCI [115]. Indeed, renal impairment is associated with hypercoagulable states. Therefore, reflecting the severity of the hypercoagulable state, admission glomerular filtration rate (eGFR) lower than 60 mL/min/1.73 m^2 might be valuable as a predictor of distal embolization and/or CMVO in patients with STEMI.

In this context, several studies showed that lower initial eGFR values have been associated with CMVO, and these poor perfusion criteria are indicators of a worsening of hospital outcome [116].

Genetic Factors

Recent studies seem to support a role for genetic variation in the heterogeneity of CFR that can lead to myocardial ischemia [117]. In this context, Yoshino identified sex-specific single nucleotide polymorphisms (SNP) associated with coronary microvascular dysfunction, measured as CFR < 2.5 Genes with at least one SNP which is associated with increased risk of abnormal CFR are myosin heavy chain 15 (MYH15), vascular endothelial growth factor A (VEGFA), and Ecto-5-prime-nucleotidase (NT5E). In particular, they include one signal within the gene VEGFA represented by one SNP [118] and one signal within the gene **Cyclin-dependent kinase 4 inhibitor B** (CDKN2B) antisense RNA1 (CDKN2B-AS1) represented by five correlated SNPs. Regarding the gender differences, SNPs within MYH15, VEGFA, and NT5E are associated with abnormal CFR in men. No SNPs were associated with abnormal CFR in women [118].

Genetic factors may also modulate adenosine-induced vasodilation. In this context, 1976T.C polymorphism of the adenosine 2A receptors gene was suspected to be related with a higher prevalence of CMVO [1]. Furthermore, patients with the homozygous TT genotype mutation in eNOS Glu298AspeNOS have been shown present a greater risk to develop CMVO in the setting of STEMI [119].

Again, patients with CMVO show a more compact fibrin network, possibly suggesting a genetic mediated resistance to lysis [120,121]. Significant associations between unfavorable fibrin clot properties and the CMVO phenomenon have been observed in STEMI patients after primary PCI.

Moreover, angiopoietin 2 plays a crucial role in the inflammatory remodeling of the blood vasculature. Changes between pre-discharge and basal values of angiopoietin 2 have been proved to be greater in patients with sustained CMVO or lack of STR, as compared with those with reversible CMVO [122]. These results seem to suggest that the reversibility of this phenomenon can be also regulated by genetic factors.

Finally, a recent study showed that the Rs1333040 variants of the 9p21 locus, a genetic marker of atherosclerosis development and progression [123] and hypoxic neovessel maturation [124], is able to predict CMVO in patients with STEMI [125].

The study of genetic factors and the identification of surrogate genetic markers represent an intriguing future matter of investigation, useful to understand the pathogenesis of CMVO, identify subjects at increased risk of such a complication, and to develop new lines of therapy.

Ischemic Pre-Conditioning and Its Modulation

Another factor modulating the individual susceptibility to CMVO is the presence of IPC, which seems to protect both the myocardium and the coronary microcirculation [126]. Accordingly, PIA, angina episodes preceding the onset of definite AMI, might help preventing CMVO, by inducing IPC. Other mechanisms underlying this association range from an improvement of collateral circulation to an increased sensitivity to thrombolysis [127−129]. IPC, in its early and delayed forms, is currently the most important paradigm for experimental studies aiming at minimizing IS and reducing the incidence of other adverse events related to I/R damage [130]. Heusch et al. demonstrated that early IPC appears quickly (within a few minutes) and lasts almost 2, up to 3 hours; conversely, delayed IPC appears from 12 up to 24 hours later and lasts from 3 to 4 days [131]. The time frame of PIA onset was widely various in previous studies focused on PIA, and, therefore it was not possible to attribute the protective effects of PIA to either early or delayed IPC. Animal models showed that the beneficial effect against the reperfusion damage is related to improvement of endothelial dysfunction, to prevention of neutrophil activation caused by I/R, and to the activation of adenosine triphosphate-sensitive K(+) [K(ATP)] channels [132−135]. On the other hand, experimental studies reported that IPC is able to reduce IS preventing morphological alternations induced by ischemia, including myofilament, cell membrane,

cell matrix, nucleus, mitochondria, and sarcoplasmic reticulum damage in skeletal muscle cells [136]. Other studies pointed out as IPC may play its cardioprotective role acting on toll-like receptor 4 (TLR4), an immunosurveillance receptor known to enhance tissue injury during I/R by enhancing the inflammatory response [137]. Finally, other evidences reported that sodium/glucose cotransporter-1 (SGLT1) is responsible of the IPC-induced cardioprotection [138]. Clinically, PIA is also associated with preservation of myocardial microvasculature as assessed by echocontrastography in STEMI patients [139]. Furthermore, Jesel et al. have shown that the absence of PIA is the only independent predictor of magnetic resonance imaging-detected CMVO [140]. Despite these encouraging results, several studies have emphasized the hypothesis that the use of at least some drugs and the presence of CV risk factors may modulate these protective effects of PIA [141].

Of course, a major confounder could be use of specific drugs. Indeed, some drugs could themselves induce a protective effect (e.g., β-blockers, angiotensin- converting enzyme inhibitors and angiotensin II receptor antagonists, statins, antiplatelet drugs, fentanyl, and volatile anesthetics); conversely, other drugs (e.g., propofol) could specifically blunt the protective effect of PIA-IPC or disrupt cardioprotection through inhibition of ATP-dependent potassium channels (e.g., sulfonylurea antidiabetic drugs) [142]. Niccoli et al. showed as CV risk factors may modulate the PIA-mediated reduction in the CMVO rate [6] (Figs. 13−2 and 13−3). In particular, this modulation was detected for hypertension, smoking habit, dyslipidemia, and familiar history of CV disease.
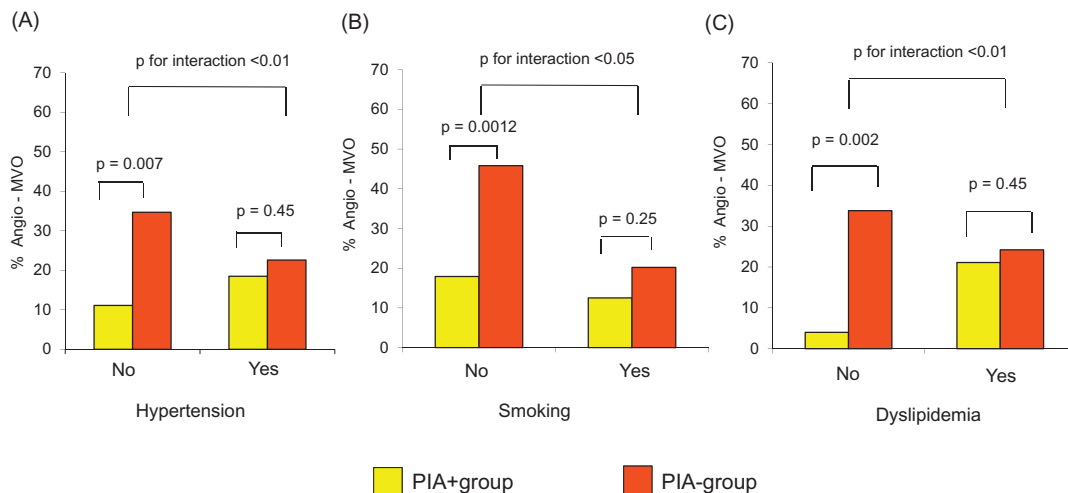

FIGURE 13–2 Rate of angiographic microvascular obstruction (MCVO) according to the presence of absence of pre-infarction angina (PIA) among patients with and without (A) hypertension, (B) smoking habit, and (C) dyslipidemia. *From G. Niccoli, G. Scalone, N. Cosentino, A. Fabretti, A.M. Mirizzi, M. Gramegna, et al., Protective effect of pre-infarction angina on microvascular obstruction after primary percutaneous coronary intervention is blunted in humans by cardiovascular risk factors, Circ J 78 (8), 2014, 1935−1941.*

FIGURE 13–3 Rate of ECG microvascular obstruction (MCVO) according to the presence of absence of pre-infarction angina (PIA) among patients with and without (A) hypertension, (B) smoking habit (C), dyslipidemia, and (D) family history of cardiovascular disease. *From .G. Niccoli, G. Scalone, N. Cosentino, A. Fabretti, A.M. Mirizzi, M. Gramegna, et al., Protective effect of pre-infarction angina on microvascular obstruction after primary percutaneous coronary intervention is blunted in humans by cardiovascular risk factors, Circ J 78 (8), 2014, 1935−1941.*
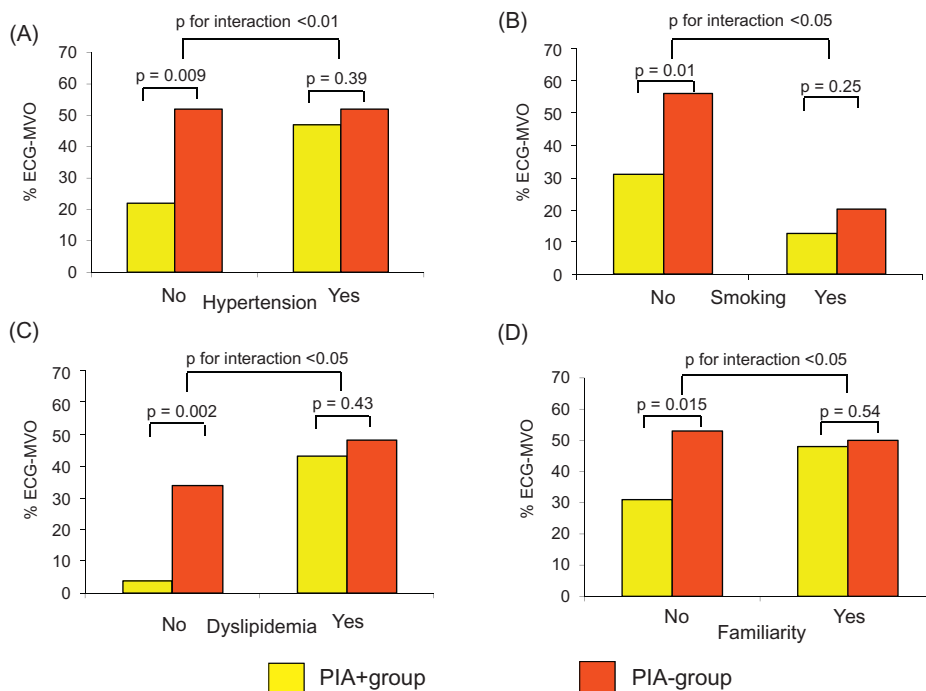
Some experimental studies reported that IPC was able to induce a greater IS-limiting effect in the hypertensive heart, yet other studies suggest that this protective effect is lost in animal models of long-standing hypertension [143−145]. Clinical results seem to be more consistent. Takeuchi et al. demonstrated that LV hypertrophy accompanying hypertension was a crucial determinant of the effects of IPC, for example, significantly less myocardial damage, better LV ejection fraction and greater metaiodobenzylguanidine on dual-isotope (thallium-201/technetium-99 m pyrophosphate) single-PET in normotensive than in hypertensive patients [145]. Impaired coronary endothelial function and vasomotor responsiveness, up to an abnormal balance between the JAK-STAT pathway and its intrinsic inhibitors, might explain these clinical results [146]. If animal studies provide conflicting results concerning the effect of hypercholesterolemia on the protective effects of IPC [135,147], clinical studies consistently demonstrate that hyperlipidemia prevents IPC during repeated balloon inflations [148,149]. In the absence of dyslipidemia, the angiographic and ECG CMVO rates after STEMI have been shown to be lower in patients

with PIA as compared with those without PIA whereas, in presence of dyslipidemia, they were similar between the two groups (Figs. 13−2 and 13−3, panel C) [6]. Similarly, non-smoker patients with STEMI and PIA, presented an angiographic and ECG CMVO rates lower compared with those without PIA, whereas within smokers, there is no difference between the two groups (Figs. 13−2 and 13−3, panel B) [6]. Furthermore, DM has been shown to have a negative impact on PIA, may related to a greater degree of micro-vascular damage in diabetic patients [6]. Finally, among subjects without a family history of CV disease, the ECG CMVO rate has been shown to be lower in patients with PIA as compared with those without PIA, whereas, within patients with a family history of CV disease, it was similar between the two groups (Fig. 13−3, panel D). These findings might support a potential role played by genetic factors in influencing the individual response to IPC/PIA.

Remote ischemic pre-conditioning (RIPC) is a phenomenon where pre-conditioning a tissue distant to the heart confers cardioprotection against index ischemia and reperfusion. It is suggested that the signal from the distant tissue is transmitted to the heart via neural or humoral signaling pathways or an overlap between both [150]. The neural hypothesis proposes that substances (e.g., autacoids, adenosine, and bradykinin) released locally in the remotely ischemic area activate a neural afferent pathway which in turn activates various efferent pathways in the heart that induce cardioprotection [151]. The efferent pathway appears to involve the autonomous nervous system (ANS). Recent evidences suggest that cardioprotection is partially mediated by intrinsic cardiac ganglia in response to increased systemic efferent vagal tone [152]. Moreover, there is also evidence supporting a role for sympathetic adrenergic stimulation in RIPC-induced cardioprotection [153]. Hence, RIPC is associated with changes in ANS activity and mild myocardial ischemic stress that would contribute to cardioprotection. Moreover, RIPC in healthy volunteers attenuated I/R sympathetic activation following I/R limb injury [154]. In this context, exper-imental studies showed as RIPC is able to cause a selective inhibition of intracellular sig-naling pathways, thus increasing the production of intracellular NO and ROS via activation of the JAK-STAT pathway which then inactivated I/R-induced extracellular signal-regulated kinase (ERK) 1/2 signaling pathways, ultimately leading to the suppression of Egr-1 [155]. Clinical studies pointed out that, applying three 5 minutes cycles of brief ischemia and reperfusion of the upper arm by using blood pressure cuff, myocardial salvage was increased in STEMI patients undergoing primary PCI, especially in those with a large area at risk [156].

Of note, previous studies demonstrated that ischemic post-conditioning (PostC), defined as rapid intermittent interruptions of blood flow in the early phase of reperfusion, is also able to reduce IS, myocardial edema and, therefore, the area at risk and to improve coronary microvascular perfusion [157]. Moreover, Mewton et al. showed that the protective effect of ischemic PostC on coronary CMVO is greater than that observed for myocardial infarction

[158]. However, randomized clinical trials pointed out that ischemic PostC during primary PCI in STEMI patients did not improve myocardial salvage or reduce IS [159]. In this context, the DANAMI 3 represents the largest study testing the routine use of ischemic PostC during primary PCI. Over 38 months follow-up, it failed to show in patients treated by PostC a reduction of the composite outcome of death from any cause and hospitalization for heart failure in patients with STEMI and TIMI grade 0-1 flow at arrival [160]. Finally, the LIPSIA conditioning trial pointed out that, combined intra-hospital RIPC + PostC in conjunction with PCI in 696 patients with STEMI, significantly improves myocardial salvage in comparison with control and PostC alone [161].

Therapies for the Improvement of Individual Susceptibility

The improvement of individual susceptibility for CMVO starts with the management of editable CV risk factors. In this context, a strict control of serum lipid levels, blood pression values, and glycemia have to be guaranteed. Iwakura demonstrated that chronic therapy with statins was associated to a lower rate of CMVO during STEMI, and better functional recovery of myocardial function after 6 months of follow-up as compared to patients not on statin [48]. Moreover, the administration of high doses of statins prior to primary PCI has been demonstrated to improve CMVO as compared to that of low doses [49].

In a large multinational registry, chronic nitrate use has been associated with a shift away from STEMI in favor of no STEMI and with less release of markers of cardiac necrosis, thus suggesting that in nitrate users, acute coronary events may develop to a smaller extent [59]. At the same time, experimental models and clinical studies demonstrated that pre-treatment with ACE inhibitors and angiotensin receptor blockers significantly improve ventricular function, decrease area of CMVO and reduce necrosis size of MI, in comparison with the control group [57,58]. Observational study showed that pre-treatment with pioglitazone, in diabetic patients with AMI, resulted in better myocardial perfusion with less I/R injury [162]. Moreover, the chronic use of metformin has been associated with the reduction of CMVO in patients with DM after primary PCI [163]. Results of studies with the glucose−insulin−potassium (GIK) in the setting of STEMI have been controversial [164,165]. The CREATE ECLA provided indeed neutral results with no difference in 30 days mortality with GIK as compared to placebo [164]. Conversely, the IMMEDIATE trial showed reduction in IS and lower rate of in-hospital mortality and cardiac arrest in patients randomized GIK than in controls, with trial treatment started in the ambulance by paramedics suggesting to start treatments very early after chest pain onset [165]. In this context, the chronic use of nitrates, ACE-inhibitors and antidiabetics should be tested in a large scale.

The IPC represents the most potent form of endogenous myocardial protection from irreversible ischemic injury [126]. Of note, its beneficial effect can be prevented by several CV risk factors. Hence, careful treatment of CV risk factors is warranted also in order to maintain the cardioprotection of IPC.

Moreover, it have been shown that coffee or alcohol intake, block the IPC in asymptomatic patients at risk of MI [166]. For this reason, the intake of these beverages have to be avoid. Similarly, the use of glibenclamide, a selective ATP-sensitive K^+ channel blocker that prevent IPC, have to be abolished [167]. The potential advantages offered by remote IPC should be offered to all patients without PIA. Botker et al. showed that, applying three 5 minutes cycles of brief ischemia and reperfusion of the upper arm by using blood pressure cuff, myocardial salvage increased in STEMI patients undergoing primary PCI, especially in those with a large area at risk [156]. Of note, adding morphine to remote ischemic conditioning (RIC protocol has been reported further improve the STR [168]. Recently, the LIPSIA trial demonstrated that the combination of intra-hospital RIC and PostC with PCI in STEMI, significantly improves myocardial salvage, evaluated by cardiac magnetic resonance (CMR), in comparison with control and PostC only [161].

Again, studies conducted in humans have demonstrated that infusion of recombinant human CRP can promote the development of CMVO phenomenon by increasing Cyclo-oxygenase 1 (COX-1) and COX-2 expression, which is regulated, in part, via ERK and Jun N-terminal kinase (JNK) activity [169,170]. Starting from these evidences, a new theoretical basis for the clinical application of COX inhibitors in the prevention and treatment of this phenomenon has been recently provided [171].

Among antiplatelet drugs, pre-hospital abciximab administration may be useful [172]. Of note, the FINESSE trial demonstrated that upstream administration of abciximab with half-dose reteplase significantly reduces IS but does not have any overall clinical benefit in primary study end point at 90 days as well as in mortality at 1 year [173]. On the other hand, the Ongoing tirofiban in myocardial infarction evaluation 2 (On-TIME-2) trial showed as a routine pre-hospital initiation of high-bolus dose tirofiban might improve STR and clinical outcome after PCI [174]. Recently, evidences from experimental studies proposed a therapeutic potential role of neutrophil extracellular traps (NET)-targeted intervention in myocardial I/R and CMVO [175,176]. Indeed, DNase I, which targets NETs, in combination with recombinant tissue-type plasminogen activator (rt-PA), which targets fibrin, should be an ideal option to disrupt the NET- and fibrin-provided meshlike backbone structure of thrombus. These treatments should be employed in patients with unfavorable fibrin clot properties and genetic meditated resistance to lysis. New treatments for CMVO, mostly based on the genetic profile of patients, should be developed in the future. Finally, an integrated approach aimed at prevention of CMVO should enhance the effect of single treatments and should be assessed in future larger studies (Table 13−1).

Table 13–1 Main Studies About Management of the Individual Susceptibility for CMVO

Therapeutic Option	Year	Study Design	Patients (n)	Dose	Primary End-Point	Notes	Reference
Pre-Existent Microvascular Dysfunction							
Statins	2006	OS	293	Chronic statin pre-treatment	CMVO (assessed by MCE)	↓ CMVO incidence, ↑ wall motion, ↓ LV dimensions and ↑ LVEF	Iwakura et al. [48]
	2010	RCT	171	Pre PCI: 80 mg vs 10 mg of atorvastatin; 10 mg of atorvastatin before PCI continued for 30 days	Clinical outcome: MACE at 30-days (death, nonfatal MI, and TVR)	↑ MBG and STR, no difference in clinical outcome	Kim et al. [49]
Nitrates	2010	OS	52693	Chronic nitrates pre-treatment	Clinical outcome: incidence of acute ischemic events	Shift away from STEMI to NSTEMI, and ↓ IS (assessed by release of myocardial necrosis markers)	Ambrosio et al. [59]
Ace-inhibitors	2006	OS	259	Chronic ACE-inhibitor pre-treatment	CMVO (assessed as TIMI flow grade <3)	↓ CMVO incidence in chronic ACEI treatment, the absence of ACEI pre-treatment as predictor of the CMVO	Zhao et al. [58]
ARB	2013	OS	276	Chronic-ARB pre-treatment	CMVO (assessed as TIMI flow grade <3)	↓ CMVO incidence in chronic ARB treatment, pre-treatment with ARB as predictor of the CMVO	Hu et al. [57]
Pioglitazone	2011	OS	309	Pioglitazone pre-treatment	CMVO (assessed by MBG and STR) and IS (assessed by myocardial necrosis markers)	↑ MBG ≥ 2 and complete STR	Kataoka et al. [162]
Metformin	2013	OS	154	Metformin chronic pre-treatment	CMVO (assessed as final TIMI flow of ≤2 or final TIMI flow of 3 with a MBG of <2	↓ CMVO incidence in chronic metformin treatment, pre-treatment with metformin as predictor of the CMVO	Zhao et al. [163]

(Continued)

Table 13−1 (Continued)

Therapeutic Option	Year	Study Design	Patients (n)	Dose	Primary End-Point	Notes	Reference
GIK	2005	RCT	20201	IV 1000 mL 25% glucose, 50 UI insulin, 80 mm KCl (1.5 mL/Kg/h during 24 h) vs standard care	Clinical outcome: all cause of mortality at 30 days	No differences in mortality	Mehta et al. [164]
	2012	RCT	871	In ambulance IV 30% glucose, 50 UI/L insulin, 80 mEq of KCl/l (1.5 mL/Kg/h during 12 h)	Clinical outcome: Shift away from ACS to MI within 24 h	↓ Cardiac arrest and in-hospital mortality, and IS at 30 days (assessed by SPECT)	Selker et al. [165]
Ischemic Pre-Conditioning							
Intermittent ischemia	2010	RT	251	Four cycles of 5 min inflation and 5 min deflation of a blood pressure cuff	IS (assessed by myocardial salvage Index through SPECT at 30 days)	↑ Myocardial salvage with a favorable safety profile	Botker et al. [156]
	2010	RT	96	Three-4 min inflations/deflations of arm cuff (RIPC) delivered in ambulance and morphine vs RIPC only	CMVO (assessed by STR)	↑ STR in group RIPC and morphine	Rentoukas et al. [168]
	2015	RT	696	Combined intrahospital RIC + PostC in addition to PCI vs PostC in addition to PCI vs conventional PCI (control)	Salvage index and CMVO and IS (assessed by CMR)	Salvage index was higher in the RIC + PostC in addition to PCI compare to control group	Eitel I et al. [161]
Inflammation							
COX inhibitor	2015	OS	Animal Model	COX inhibitor indomethacin (5 mg/kg) for 120 min	CMVO (assessed by anatomic area)	↓ CMVO	Jiao et al. [171]

(Continued)

Table 13−1 (Continued)

Therapeutic Option	Year	Study Design	Patients (n)	Dose	Primary End-Point	Notes	Reference
Genetic Predisposition							
GpIIB/IIIa	2012	RCT	110	IV bolus of 0.25 mg/Kg Abciximab during transportation vs before PCI	IS (assessed by CMR at 6 months)	↓ IS only in patients with longer transportation time	Petronio et al. [172]
	2009	RCT	2452	IV bolus (2.5 mg/Kg) of Abciximab + 12 h infusion before PCI vs IV bolus Abciximab +12 h infusion after randomization vs IV bolus of Abciximab +12 h infusion + reteplase	Clinical outcome: composite of all-cause mortality or complications of MI at 90 days	↓ IS (assessed by myocardial necrosis markers), no clinical benefit in the primary end-point and in the mortality at 1 year	Ellis [173]
	2008	RCT	936	25 μg/Kg IV bolus of tirofiban and 0.15 μg/Kg/min infusion of tirofiban vs placebo	CMVO (assessed by ST segment deviation >3 mm at 1 h after PCI)	↓ CMVO before and 1 h after PCI	Van't Hof et al. [174]
DNase I and rtPA	2015	OS	Animal model	DNase I, 20 μg/rat) vs rt-PA, 420 μg/rat vs control	CMVO (assessed by anatomic area) and IS (assessed by histopathology)	↓ CMVO and IS	Ge et al. [176]

ACE: angiotensin-converting-enzyme; ACS: acute coronary syndrome; ARB: angiotensin receptor blockers; CMR: cardiac magnetic resonance; CMVO: coronary microvascular obstruction; CV: cardiovascular; EF: ejection fraction; GIK: glucose−insulin−potassium; HF: heart failure; h: hour; IC: intracoronary; IPC: ischemic-pre-conditioiing; IS: infarct size; IU: international unit; IV: intravenous; LV: left ventricular; MACE: major adverse cardiac event; MBG: myocardial blush grade; MCE: myocardial contrast echocardiography; MI: myocardial infarction; min: minutes; NSTEMI: non-ST elevation myocardial infarction; OS: observational study; PCI: percutaneous coronary intervention; PostC: post-conditioning; RCT: randomized controlled trial; RIC: remote ischemic conditioning; RIPC: remote-ischemic pre-conditioning; RT: randomized trial; rt-PA: recombinant tissue-type plasminogen activator; SPECT: single photon emission computed tomography; STEMI: ST-elevation myocardial infarction; STR: ST-resolution; TIMI: thrombolysis in myocardial infarction; TVR: target vessel revascularization.

Conclusions

Individual susceptibility represents an important component of CMVO. It includes pre-existent microvascular dysfunction mostly due to the presence of CV risk factors, IPC and genetic predisposition. The knowledge of the mechanisms of the single causes of individual susceptibility of CMVO may be useful to develop new strategies for prevention and treatment.

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