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Review

Myocardial ischemia/reperfusion: Translational pathophysiology of ischemic heart disease

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SUMMARY

Ischemic heart disease is the greatest health burden and most frequent cause of death worldwide. Myocardial ischemia/reperfusion is the pathophysiological substrate of ischemic heart disease. Improvements in prevention and treatment of ischemic heart disease have reduced mortality in developed countries over the last decades, but further progress is now stagnant, and morbidity and mortality from ischemic heart disease in developing countries are increasing. Significant problems remain to be resolved and require a better pathophysiological understanding. The present review attempts to briefly summarize the state of the art in myocardial ischemia/reperfusion research, with a view on both its coronary vascular and myocardial aspects, and to define the cutting edges where further mechanistic knowledge is needed to facilitate translation to clinical practice.

BACKGROUND AND RATIONALE

Myocardial ischemia/reperfusion is the pathophysiological substrate of ischemic heart disease (IHD). There has been enormous progress in the prevention, diagnosis, and treatment of IHD in the last decades. Better prevention by reduced smoking, increased statin use, and better blood pressure control has reduced the mortality from IHD. However, this progress is now stagnant, and IHD still ranks #1 worldwide in causes for global deaths.[1] The profile of risk factors that facilitate the pathogenesis of myocardial ischemia is shifting. There is a temporal trend with a reduction in smoking and cholesterol but an increase in obesity and diabetes; reductions in smoking and cholesterol are less in women than in men, and the prevalence of obesity increases more in women than in men.[2]

Chronic coronary syndromes are a relatively benign manifestation of IHD. However, after decades of increasing use of percutaneous coronary interventions (PCIs), including angioplasty and stenting, we are back to square one, and the jury is still out on whether PCI or conservative therapy is preferable, as PCI—except for left main stem coronary stenosis, which threatens the perfusion of the entire left ventricle—does not improve prognosis[3,4] and does not relieve symptoms in 20%–40% cases.[5] The absence of manifest epicardial atherosclerosis in many patients with angina points toward a significant role for coronary microvascular dysfunction in IHD.[6] On the other hand, angina is a frequent symptom in the general population and only loosely associates with obstructive and non-obstructive coronary atherosclerosis.[7] In women, the manifestation of myocardial ischemia is less frequently characterized by typical angina but is more often characterized by diffuse discomfort extending into the abdomen, neck, shoulder, and head[8,9]; this difference in

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https://doi.org/10.1016/j.medj.2023.12.007

manifestation of myocardial ischemia may relate to different mechanisms of pain perception.[10]

The clinical manifestation of acute myocardial infarction (AMI) is changing, with a decrease in ST segment elevation and an increase in non-ST segment elevation myocardial infarction (STEMI vs. NSTEMI)[11]—suggesting a change in underlying pathophysiology.[12] Mortality from AMI has decreased substantially in the last decades as a result of the success and increased availability of rapid reperfusion by PCI, but 1-year mortality is still between 15% and 21% in large European registries, and there is currently no further decrease in mortality in a population of increasing age.[13,14] Hospitalization for heart failure in survivors of AMI is at 20%–30% at 1 year after hospital discharge.[15] In developing countries, access to PCI is limited, making mortality from AMI worse and even increasing.[16] Even in developed countries, mortality from AMI is higher and access to PCI is limited in low-income vs. high-income patients.[17] Whereas premenopausal women appear to be protected against myocardial infarction and women suffer from myocardial infarction at older age than men,[8,9] women experience significant delays in diagnosis and treatment.[18] Obviously, there is a need for further cardioprotection beyond that provided by rapid reperfusion.[19] Furthermore, the processes of healing,[20] repair,[21–24] and remodeling[25] following myocardial infarction need more attention.

There has been enormous progress in the pathophysiological understanding of IHD, but the translation of preclinical research to clinical benefits for patients has been difficult.[26–29] Therefore, the present article attempts to review and update[26] the state of the art in myocardial ischemia/reperfusion pathophysiology and to identify topics in need of greater translational efforts.

THE CORONARY CIRCULATION AS THE CULPRIT OF IHD

IHD is a result of coronary atherosclerosis[30] and is a manifestation of reduced coronary blood flow.[31] Coronary atherosclerosis affects the entire coronary vascular tree, not only the angiographically visible epicardial coronary arteries but also the coronary microcirculation,[6] and it involves the entire vascular wall, including the endothelium, smooth muscle cells, and adventitial tissue. Atherosclerosis is a chronic systemic vascular disease that develops in response to injurious stimuli, notably hypercholesterolemia and hypertension, which are driven by genetic factors. The disease progresses from endothelial dysfunction to lipid deposition, inflammatory reaction, fibrosis, and calcification of the inner and mid-vascular walls and progressively obstructs the luminal diameter; the lesion can also break up acutely with plaque rupture or erosion.[30] The coronary circulation is a predilection site for atherosclerosis, most probably because of enhanced shear stress from pulsatile coronary blood flow.[32,33] Recent studies, mostly in murine aortae but also in human coronary arteries, have identified afferent and efferent nerves and a neuro-immune interface in the adventitia overlying the plaque, that contribute to atherosclerosis progression but may also contribute to acute events and pain sensation.[34]

Stable plaque: Not so stable?

Traditionally, the coronary circulation has been considered a passive conduit, and active vasomotion was neglected. An angiographically visible epicardial coronary obstruction was considered fixed and the poststenotic coronary vascular bed maximally dilated in compensation for the stenosis. In fact, however, active coronary vasoconstriction plays a major role in the initiation and aggravation of myocardial ischemia. Severe focal vasoconstriction in the absence of visible epicardial coronary obstruction can occur in epicardial and coronary microvascular segments and precipitate myocardial ischemia; such

exaggerated focal coronary vasoconstriction is often elicited by acetylcholine for diagnostic purposes in humans with angina in the absence of epicardial coronary obstruction.[35] With an increasing atherosclerotic obstruction of the epicardial coronary lumen, the poststenotic coronary dilator reserve is progressively recruited by autoregulation to compensate for the stenosis and maintain coronary blood flow. At a poststenotic coronary perfusion pressure of 40–50 mmHg in dogs, autoregulation is eventually exhausted, and coronary blood flow is decreased.[36] In patients, assessment of coronary dilator reserve, as elicited by adenosine, provides better information on the functional severity of a coronary stenosis than luminal obstruction.[37] The stenotic segment itself can retain contractile smooth muscle cells, and further active narrowing of the stenotic segment can be provoked by exercise.[38] In pigs, in the presence of epicardial coronary obstruction, the poststenotic circulation remodels with atrophy of larger (diameter > 75 μm) and hypertrophy of smaller (diameter < 75 μm) vessels,[39,40] and the microcirculation has enhanced vasoconstrictor responses to endothelin.[40] α-Adrenergic coronary vasoconstriction by sympathetic activation during stress, exercise, excitement, and pain is of major importance in reducing coronary blood flow and precipitating myocardial ischemia distal to an otherwise compensated epicardial coronary obstruction, as initially demonstrated in dogs[41,42] and subsequently in patients with coronary atherosclerosis.[43,44] The ischemic coronary microcirculation is not only subject to passive extravascular compression by the contracting ventricle but has significant active vasoconstrictor tone, which in dogs can be attenuated by vasodilator agents such that coronary blood flow and consequently contractile function are improved.[45,46] The structural remodeling of the coronary microcirculation and the active microvascular constriction distal to a severe coronary stenosis probably contribute to the persistence of angina and lack of improved prognosis[3,4] after interventional vs. conservative treatment. As such, the individual choice of treatment must take the frequency and severity of symptoms, coronary anatomy, left ventricular function, and comorbidities into account. Whether or not interventional revascularization provides a symptomatic benefit (exercise duration, angina frequency) may depend on the presence[47] or absence[48] of optimal medical therapy.

Unstable plaque: Rupture vs. erosion

Apart from low-density lipoprotein (LDL) deposition and oxidation in the intima, endothelial activation and recruitment of leukocytes to the endothelium is an early event in atherosclerosis, and inflammatory processes are key to the further progress of plaque development and instability.[30] A fully developed plaque becomes vulnerable to rupture when inflammation induces thinning of the fibrous cap over the necrotic lipid core by decreasing collagen synthesis and increasing its degradation. When the plaque eventually ruptures upon hemodynamic stress, the plaque debris is exposed to the blood and induces immediate thrombosis, which, together with the released particulate plaque material, causes complete obstruction of the epicardial coronary artery and subsequent transmural AMI presenting as STEMI.[49] More recently, however, there has been a temporal shift in the presentation of acute coronary syndromes from such typical plaque rupture to plaque erosion where a leak in the endothelial lining, neutrophil activation, and the formation of neutrophil extracellular traps (NETs) induce further inflammation and thrombosis.[50–52] Plaque rupture and plaque erosion can be distinguished by intravascular imaging. Notably, optical coherence tomography (OCT) in patients with acute coronary syndromes has revealed that those with plaque erosion have a lower systemic inflammatory response and better clinical outcome.[30,53,54] The temporal shift from plaque rupture to plaque erosion is related to more widespread use of intense lipid lowering by statins and goes along with a shift from STEMI to NSTEMI presentation.[53,55] This suggests a role for embolization of plaque debris and thrombotic material into the microcirculation as an underlying mechanism of NSTEMI.[12] In fact, coronary

microembolization is also associated with the release of vasoconstrictor, pro-thrombotic, and pro-inflammatory soluble factors into the coronary microcirculation.[56] Coronary microembolization is also a typical complication of PCI, notably in saphenous vein grafts.[12] The key role of inflammation in coronary atherosclerosis and its sequelae was evidenced by the reduction of cardiovascular mortality and myocardial infarction by treatment with a monoclonal antibody against interleukin-1β in patients with prior myocardial infarction and elevated C-reactive protein.[57]

Underestimated: Ischemia/myocardial infarction with non-obstructive coronary arteries

As compared to an angiographically visible epicardial coronary obstruction, active coronary vasomotion has long been neglected. However, there is now an increasing awareness that myocardial ischemia and even myocardial infarction can occur in the absence of major epicardial coronary obstruction (<50% diameter reduction), i.e., an obstruction that poses no indication for PCI.[58] In fact, angina may occur in up to 50% patients without obstructive coronary disease.[59] Ischemia with non-obstructive coronary arteries (INOCA) is more frequent in women than in men. These patients have invariably some atherosclerosis on intravascular imaging and a decrease in coronary reserve. Endothelial dysfunction is an early and generalized manifestation of coronary atherosclerosis that results in attenuated vasodilator and enhanced vasoconstrictor responses. Enhanced vasoconstrictor responses can be more generalized or more focal, and they can occur in the epicardial coronary artery and the microcirculation. Coronary spasm involves both endothelial dysfunction and local vascular smooth muscle hyper-responsiveness and adventitial tissue inflammation.[60] The decrease in coronary reserve in the absence of significant epicardial coronary obstruction suggests coronary microvascular dysfunction. Coronary microvascular dysfunction has been suggested as a common ground for INOCA and heart failure with preserved ejection fraction,[59,61] and coronary microvascular dysfunction may also underlie takotsubo cardiomyopathy.[62] Myocardial infarction with NOCAs (MINOCA) accounts for 6%–15% all AMI, is also more frequent in women than in men, and is characterized by less pronounced hyperlipidemia than classical AMI.[63,64] Plaque rupture but also spasm, dissection, embolization, and—again—microvascular dysfunction can cause MINOCA, and its diagnosis is particularly challenging. Using multi-modal imaging, causes for MINOCA can be identified in >80% patients and are 75% ischemic in nature.[63]

THE MYOCARDIUM AS THE TARGET OF ISCHEMIA/REPERFUSION

Sequence of metabolic and functional events: Rapid ischemic dysfunction

Upon a sudden coronary occlusion and lack of further delivery of arterial blood to the myocardium, the remaining hemoglobin-bound O_2 and the cardiomyocyte myoglobin-bound O_2 suffice only for a few cardiac cycles/seconds before mitochondrial respiration and oxidative phosphorylation cease. The available energy-rich phosphate stores and the free energy change of ATP hydrolysis, which is used to drive the energy-consuming processes of ionic pumps and contractile function, quickly decrease.[31,42] Phosphorus nuclear magnetic resonance (P-NMR) spectroscopy can reflect such changes in energy-rich phosphates.[65,66,67] Lactate production indicating anaerobic glycolysis develops quickly, but its assessment requires sophisticated techniques before it eventually becomes manifest in the coronary sinus blood.[68]

Contractile function decreases within a few cardiac cycles, i.e., within 10 s following abrupt coronary artery occlusion.[69] In dogs with exercise-induced myocardial ischemia, reduced regional contractile function precedes ST segment elevation in

the local electrocardiogram (ECG), reflecting the higher energy required for contractile function than for ionic homeostasis and indicating that regional dysfunction may be a more sensitive sign of ischemia than ECG changes.[70] Within 2–5 min, a steady state develops, and contractile function is decreased to a level that the available remaining myocardial blood to flow through collaterals from adjacent non-ischemic myocardium permits.[31] During partial coronary occlusion (stenosis), baseline contractile function of the dependent myocardium is maintained as long as autoregulation can compensate for the stenosis and maintain coronary blood flow by a vasodilation of the coronary microcirculation. Such autoregulation operates down to a perfusion pressure of 40–50 mmHg; with further decrease in perfusion pressure, coronary blood flow decreases in linear proportion to perfusion pressure. Contractile function then decreases in linear proportion to coronary blood flow when both are normalized to their baseline values. Such perfusion-contraction matching[71] also holds with exercise, when heart rate and blood pressure are markedly increased, in that contractile function and coronary blood flow for each cardiac cycle remain matched.[31] The alterations in blood flow, contractile function, and electrical function remain reversible for 20–40 min after complete coronary occlusion, depending on the available collateral blood flow and the hemodynamic situation; eventual full recovery ensues but can be prolonged for contractile function (stunning).[72,73] With partial coronary obstruction, a reduction of coronary blood flow by 50% can be sustained for 5 h, with perfusion-contraction matching at a reduced level but without overt necrosis.[74] It is currently not clear whether the observed minor increases in troponin in otherwise fully reversible ischemic myocardial dysfunction reflect cell death of individual cardiomyocytes by apoptosis or reversible injury to the sarcolemmal membrane by stretch.[75]

Novel modes of regulated and non-regulated cardiomyocyte death

Traditionally, necrosis was considered the cause of cardiomyocyte cell death that occurred when coronary occlusion was longer than 20–40 min. Necrosis is characterized by rupture of mitochondria and sarcolemma and elicits an inflammatory reaction (Figure 1).[76,77] Necrotic cell death follows a decrease in free energy change of ATP hydrolysis and the failure of ionic pumps, which increase the systolic Na^+ concentration (after failure of sarcolemmal Na^+/K^+-ATPase) and a subsequent increase in cytosolic Ca^{2+} concentration (by Na^+/Ca^{2+} exchange operating in reverse mode).[78,79] The increased cytosolic Ca^{2+} concentration activates phospholipases and proteases such as calpain.[80] Fluctuations in sarcoplasmic uptake and release of cytosolic Ca^{2+}, with a decrease in activity of the sarcoplasmic reticulum calcium ATPase, induce Ca^{2+} cycling and excessive, uncoordinated contractions. These become morphologically apparent as contraction bands and contribute to membrane rupture and cell death.[81] Upon reperfusion, oxygen is re-introduced, and increased formation of reactive oxygen species (ROS), from mitochondria and NADPH oxidases, damages proteins, lipids, and DNA by oxidative modification.[82,83] The relief of acidosis by washout of protons and activation of the Na^+/H^+ exchanger intensifies calcium overload and removes inhibition of contractile function by acidosis.[26] Necrosis, evident from contraction bands and the inflammatory reaction, probably makes up for the core and the majority of an infarcted myocardial region. However, more recently, several more regulated modes of cell death have been recognized to contribute to myocardial infarction (Figure 1).[26,84] Apoptosis is a form of cell death, which results from activation of an intrinsic pathway involving calcium overload and increased ROS formation and an extrinsic pathway by activation of sarcolemmal death receptors. Apoptosis is characterized by an intact sarcolemma and therefore lacks an inflammatory reaction and by typical DNA fragmentation. The opening of the mitochondrial permeability transition pore is largely

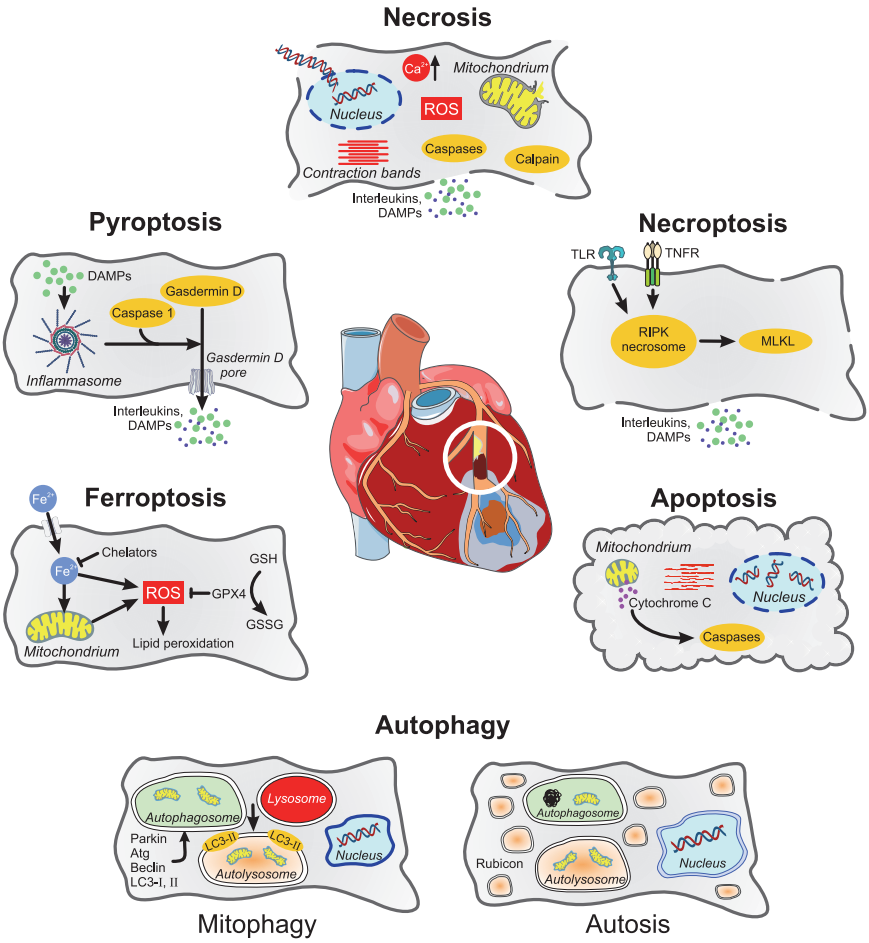

Figure 1. Modes of cardiomyocyte death during myocardial ischemia/reperfusion with their most characteristic features

Atg, autophagy-related gene protein; DAMPs, danger-associated molecular patterns; GPX, glutathione peroxidase; GSH, glutathione; GSSG, glutathione disulfate; LC3, microtubule-associated protein light chain 3; MLKL, mixed-lineage kinase domain-like kinase; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species; TLR, Toll-like receptor; TNFR, tumor necrosis factor receptor. Modified from Heusch and Gersh[19] and Heusch[26] with permission.

responsible for both necrotic and apoptotic cell death.[85,86] Necroptosis is a cell death response to activation of sarcolemmal tumor necrosis factor- or Toll-like receptors, which specifically involves a receptor-interacting serine/threonine protein kinase and induces pores in the sarcolemma—this cell death mode can be specifically reduced by necrostatin.[87] Pyroptosis is a form of cell death that occurs in response to damage-associated molecular patterns (DAMPs), such as mitochondrial DNA and interleukins acting on the sarcolemma, and results in a characteristic intracellular inflammasome multi-protein complex. In turn, the inflammasome activates caspase-1 and induces the polymerization of gasdermin to form membrane pores of 10- to 20-nm diameter, through which further DAMPs and interleukins are released, thus propagating cell death into neighboring cardiomyocytes.[88–90] Recently, ferroptosis has been recognized as a novel form of cell death. It was initially attributed to iron overload that caused excessive ROS formation but is now considered to be mainly characterized by abnormalities in glutathione metabolism secondary to inactivation of glutathione peroxidase 4, which protects from iron-dependent lipid peroxidation. Morphologically, mitochondrial destruction predominates over

changes in the nucleus.[91] A peculiar form of cell death is driven by autophagy, which is important for cellular homeostasis physiologically and serves to degrade, dispose, and re-circulate material of damaged intracellular organelles, notably mitochondria (mitophagy).[92] Macro-autophagy is characterized by upregulation of specific proteins such as beclin-1 and parkin and involves the formation of double-membraned organelles (autophagosomes), which merge with lysosomes to autolysosomes for digestion of the debris, whereas chaperone-mediated autophagy degrades soluble proteins.[93] In myocardial ischemia/reperfusion, there is selective autophagy of damaged mitochondria, i.e., mitophagy, which can be dependent on parkin and ubiquitin or be mediated by receptors such as BCL interacting protein 3 (BNIP3). Mitophagy serves a cardioprotective function.[94] Mitophagy leaves the sarcolemma intact and therefore does not cause an inflammatory reaction.[86,95] Activation of autophagy by chloramphenicol reduced infarct size in a pig model of myocardial ischemia/reperfusion.[96] However, a particular form of excessive autophagy (autosis) is mediated by upregulation of Rubicon and dysregulation of autophagic flux, and it contributes to infarct size progression after several hours of reperfusion in mice.[97] The role of autophagy in the human heart is still unclear; autophagy marker proteins were increased in right atrial samples,[98] but not left ventricular samples,[99] from patients undergoing cardiovascular surgery with ischemic cardioplegic arrest.

Traditionally, all myocardial infarctions have been considered the result of cardiomyocyte and coronary microvascular necrosis,[100] whereas the more regulated modes of cell death have only been identified more recently. The contribution of each to aggregate infarct size is difficult to determine, as most studies that quantify infarct size used methods (triphenyl tetrazolium chloride staining, gadolinium contrast retention) that do not distinguish the modes of cell death.[101] Other studies have attempted to manipulate one single mode of cell death in order to estimate its contribution to infarct size; however, different cell death modes may interact.[86,102] The contribution of cell death modes to aggregate infarct size may vary between cardiomyocytes and non-cardiomyocytes (apoptosis affects mostly non-cardiomyocytes[86]) and may reflect the severity and spatial development of myocardial injury (necrosis and hemorrhage in the center, pyroptosis and inflammatory conditions at the border) and the timing (protective mitophagy early on, injurious autosis at later reperfusion[97]).

Reversible injury: Perfusion-contraction matching

Patients with coronary spasm or chronic stable angina typically have reversible ischemia. Epicardial or microvascular coronary spasm in the presence of non-obstructive coronary atherosclerosis occurs spontaneously or is elicited by individually variable, often specific triggers but then resolves either spontaneously or upon use of a calcium antagonist.[35] Chronic stable angina with obstructive coronary atherosclerosis is typically elicited in situations of sympathetic activation such as exercise, excitement, and stress and is relieved by termination of the initiating trigger or use of nitroglycerine. In both coronary spasm and chronic stable angina, the coronary vasculature has impaired endothelial function and hyper-responsiveness to contractile stimuli. In coronary spasm, therefore, acetylcholine is used for diagnostic provocation tests.[35] In chronic stable angina, a vasoconstrictor response of the poststenotic coronary vascular bed to α-adrenoceptor activation by catecholamines is predominant in the precipitation of angina.[44] Traditionally, chronic stable angina has been considered as a manifestation of supply-demand mismatch, induced by β-adrenoceptor-mediated increases in heart rate, contractile function, and oxygen demand that could not be supported by the limited coronary blood flow response. This view is not correct, as the contractile function and thus the oxygen consumption of the ischemic poststenotic myocardium are in fact decreased and not increased. Perfusion-contraction matching is a hallmark of poststenotic myocardial

ischemia when contractile function and coronary blood flow each are normalized for a single cardiac cycle.[31] It is the increase in heart rate during sympathetic activation that reduces diastolic duration and the time for coronary blood flow. The α-adrenergic coronary vasoconstriction reduces coronary blood flow, and contractile function follows down to the level that the reduced blood flow permits. This causality is best evidenced by the fact that β-blockade, with consequently reduced heart rate, increases, rather than decreases, contractile function of the poststenotic myocardium.[103] In the absence of reduced heart rate, β-blockade reduces blood flow and contractile function by enhanced α-adrenergic coronary vasoconstriction.[42,104] If anything, increased oxygen demand due to increased heart rate and contractile function in the non-ischemic adjacent myocardium will cause metabolic coronary vasodilation, thus decreasing collateral perfusion pressure and inducing a redistribution of blood flow away from the ischemic myocardium through collaterals.[31] Depending on the severity of blood flow reduction, perfusion-contraction in previously healthy dogs and pigs can be maintained over several hours with recovery of ischemic metabolism (creatine phosphate, lactate) and maintenance of viability.[73,74,105,106] In patients with AMI, who have probably experienced prior episodes of myocardial ischemia that stimulated collateral growth and myocardial adaptive mechanisms, such short-term hibernation retains viability even after 24 h from symptom onset, and interventional reperfusion still salvages significant amounts of myocardium and improves clinical outcome.[107,108]

Whereas perfusion-contraction matching prevails during myocardial ischemia, coronary blood flow and contractile function are dissociated during reperfusion following ischemia, as coronary blood flow displays reactive hyperemia. The contractile function of the previously ischemic myocardium remains depressed (stunned) and recovers only over several hours.[72,73] Stunning is a manifestation of contractile dysfunction in response to calcium overload and increased ROS formation, which decrease the calcium responsiveness of the contractile machinery by oxidation and proteolysis of contractile proteins.[73] Stunning provided the first evidence that reperfusion is not entirely beneficial but inflicts additional injury on top of ischemia. Stunned myocardium recovers spontaneously and remains responsive to inotropic stimulation. Stunning after a single episode of myocardial ischemia is probably more of paradigmatic than of clinical importance, except maybe for recovery after ischemic cardioplegic arrest in cardiac surgery. However, in a pig model, upon repetitive stunning episodes, a state of chronic dysfunction develops. It is again characterized by perfusion-contraction matching[109,110] but also displays more profound molecular and morphological alterations, such as downregulation of mitochondrial and sarcoplasmic reticulum calcium handling proteins, upregulation of survival proteins, loss of myofibrils, degeneration of mitochondria, and increased fibrosis. Such chronic hibernation retains viability with eventual recovery after revascularization.[111] Hibernating myocardium in humans also displays perfusion-contraction matching,[112] recovery of contractile function upon revascularization,[113] signs of cardiomyocyte dedifferentiation/degeneration and fibrosis,[114] and upregulation of survival proteins.[115] Chronic hibernation in patients with obstructive coronary artery disease and left ventricular (LV) dysfunction is diagnosed by retained viability (preserved metabolism, inotropic reserve) on imaging by positron emission tomography and magnetic resonance imaging (MRI). However, the interaction of viability,[116] recovery of contractile function, and surgical[117] or interventional[118] revascularization with respect to long-term clinical outcomes, including quality of life, is still equivocal in patients with chronic ischemic LV dysfunction.[119]

Irreversible injury: Infarction

Myocardial infarction results from ischemia per se when it is of too long duration,[120] and it is now clear that reperfusion, although mandatory to terminate ischemic injury,

inflicts additional irreversible injury. The evidence for the long-debated irreversible reperfusion injury is from interventions that, when performed at reperfusion, reduce infarct size, such as gentle reperfusion[121] or ischemic postconditioning.[122] The aggregate size of infarction depends on a number of variables: (1) the site of coronary obstruction and therefore the size of the ischemic area at risk, (2) the magnitude of reduction in blood flow to the area at risk, be that residual antegrade blood flow through the epicardial obstruction or collateral blood flow, (3) the duration of ischemia in interaction with the magnitude of blood flow reduction, and (4) the hemodynamic situation and the potential adaptation of the myocardium to prior ischemia episodes (preconditioning, preinfarction angina).[26] Depending on the species and its heart rate, complete coronary occlusion in healthy, ischemia-naive hearts results in initial infarction after 20–40 min in the inner myocardial layers of the ischemic area at risk. Infarction then spreads with further duration of ischemia transmurally from inner to outer layers as well as laterally toward the borders of the area at risk.[76,77] Such transmural spread of myocardial infarction with the duration of ischemia was recently confirmed by cardiac MRI in patients with STEMI.[123] Morphologically, infarcted cardiomyocytes are characterized by visible glycogen depletion, mitochondrial swelling, sarcolemmal rupture, and contraction bands. The severity of AMI is graded according to the composite of cardiomyocyte and coronary microvascular injury into 4 stages from (1) minor cardiomyocyte necrosis over (2) significant cardiomyocyte necrosis without coronary microvascular injury to (3) cardiomyocyte necrosis with coronary microvascular obstruction and, ultimately, (4) cardiomyocyte necrosis with intramyocardial hemorrhage.[124] Whether or not the development and ultimate size of myocardial infarction depend on sex is still controversial. Female sex is associated with a better risk factor profile, at least before menopause, and female sex has been attributed a protective role against myocardial ischemia/reperfusion injury per se with a subsequent attenuation of further infarct size growth by cardioprotective interventions.[125–127] However, recent studies in rats and pigs did not confirm sex-dependent differences in infarct size, coronary microvascular injury, or cardioprotection by ischemic preconditioning.[128,129] Clearly, sex remains an important variable in experimental animal studies on myocardial infarction,[130] and sex and gender are important variables in the clinical management of IHD.[8,9] In patients with reperfused AMI, infarct size is the major determinant of clinical outcome.[131] The best method to assess infarct size and its features in patients is MRI.[132]

THE CORONARY CIRCULATION AS THE TARGET OF MYOCARDIAL ISCHEMIA/REPERFUSION

Reversibly injured myocardium has impaired endothelial function with reduced responsiveness to acetylcholine.[133] In AMI, however, the coronary circulation exhibits severe signs of injury during reperfusion (Figure 2): edema as a consequence of increased vascular permeability; platelet, leukocyte, and erythrocyte aggregates obstructing the capillary lumen; embolization of particulate atherothrombotic debris; increased microvascular constrictor responses to sympathetic activation[134]; local release of vasoconstrictor substances[56]; pericyte contraction inducing capillary compression[135]; and capillary destruction and intramyocardial hemorrhage.[136–138] These factors cooperate to induce a no-reflow phenomenon/coronary microvascular obstruction in the infarcted myocardium that can be clinically visualized by MRI.[132] Apart from and in addition to infarct size, coronary microvascular obstruction is a major determinant of clinical outcome in patients with reperfused AMI.[139] Recently, intramyocardial hemorrhage has received particular attention[140] because its free iron can be imaged by MRI,[132] it contributes to fatty myocardial degeneration and adverse remodeling,[141] and it provides additional prognostic information.[142]

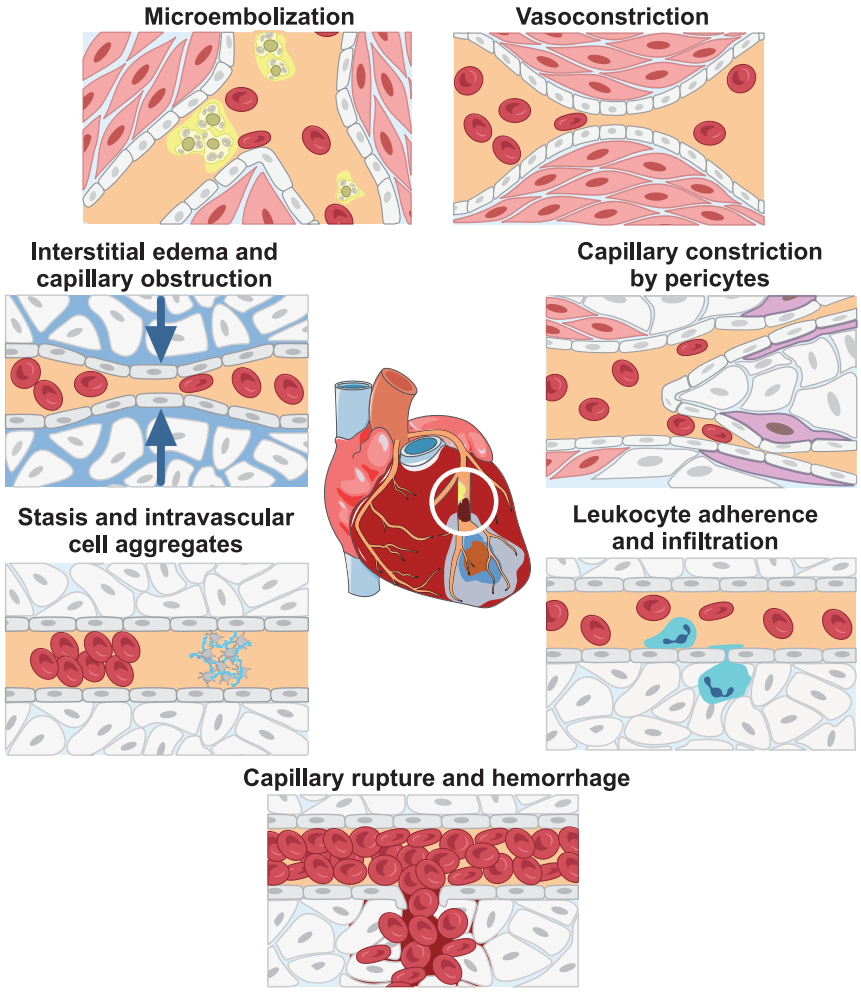

Figure 2. Mechanisms of coronary microvascular obstruction
Modified from Heusch and Gersh[19] and Heusch[26] with permission.

MYOCARDIAL HEALING AND REMODELING

Clinical outcome in survivors of AMI is usually assessed by mortality and hospitalization for heart failure after >6 months follow-up and therefore reflects not only the extent of the acute injury of infarct size and coronary microvascular obstruction but also the ensuing processes of infarct healing and remodeling.

Healing-removal of debris, from inflammation to anti-inflammation

The healing process is largely an inflammatory response to injury. This inflammatory response involves cardiac-resident and circulating immune cells as well as their reservoirs in spleen and bone marrow. Healing occurs, in the mouse model, in three distinct temporal phases, in which immune cells exert different, in part opposing, effects.[20,23,143,144] Dying and dead cardiomyocytes release and present cellular debris, notably DAMPs such as mitochondrial DNA and interleukins, which activate pattern recognition receptors, such as Toll-like receptors, on surviving stromal and resident immune cells, which then release cytokines, chemokines, and a variety of inflammatory mediators and activate an innate immune response. The immediate response, which is facilitated by reperfusion, is exerted by neutrophils, which infiltrate the infarcted tissue within 4 h, amplify the secretion of inflammatory mediators,

and form NETs in the coronary microcirculation, but importantly induce a burst of ROS formation to further destruct the dead tissue and initiate its removal. The neutrophil response peaks within 12 h. Different subsets of neutrophils can be identified; whereas neutrophils mostly contribute to further tissue destruction and removal, some subsets may also serve a protective function.[145–147] Following the initial neutrophil response, a second wave of infiltration is carried largely by macrophages, which are recruited within a few hours from the circulating monocytes but also from the spleen. Macrophages can be classified by their molecular signatures into several phenotypes, which differ somewhat between mouse models and humans with myocardial infarction, and serve two almost opposing functions.[148–151] Chemokine receptor 2 CCR2-positive macrophages are pro-inflammatory, secrete cytokines and proteases, increase ROS formation, and contribute to tissue destruction and debris removal by phagocytosis. At 3–4 days post myocardial infarction, anti-inflammatory macrophages predominate; they secrete interleukin-10 and growth factors, contribute to termination of inflammation, and initiate the reparative processes of angiogenesis by endothelial cells[152] and collagen deposition by fibroblasts. Both, B and T lymphocytes also contribute to inflammation by release of cytokines and cytotoxic enzymes, whereas the subset of regulatory T lymphocytes serves an anti-inflammatory and cytoprotective function.[153] While fibroblasts are also involved in the very early response to DAMPs from dying cardiomyocytes, their main function is the secretion of proteins into the extracellular matrix, notably the deposition of collagen, in response to activation by transforming growth factor β from cardiomyocytes and macrophages.[20,154] Pericytes also respond to transforming growth factor β and contribute to scar formation and angiogenesis.[155,156] The process of infarct healing involves a complex and systemic interaction of the local coronary atherosclerosis and infarct environment, the immune system, and the autonomic nervous system. Acute myocardial ischemia induces sympathetic activation,[157] which enhances the release of myeloid progenitor cells from the bone marrow. These cells migrate into the spleen, where they mature into monocytes and, once released, not only infiltrate the infarcted myocardium but also the atherosclerotic coronary culprit lesions, possibly precipitating a recurrent infarction (Figure 3).[148,158] The predominant effect of suppression of inflammation is cardioprotective; however, given the ambivalent actions of all major immune cells types in different temporal phases of the inflammatory process, more complete elimination of each immune cell type may also be detrimental. Detailed information on the healing myocardial infarction is mostly derived from mouse models, but these data are supported at large by the available information from autopsy, blood samples, and imaging by CMR and PET[67,159] in humans. Clinically, treatment with tocilizumab, i.e., antibodies against the interleukin-6 receptor, reduced myocardial and coronary microvascular injury in patients with STEMI.[160] Colchicine did not reduce infarct size when given from admission to day 5 after STEMI[161] but reduced cardiovascular events in patients when administered within 30 days after myocardial infarction.[162]

Remodeling: Scar formation and remote myocardial adaptation

Remodeling starts out with a reparative phase of infarct healing, involves not only the infarcted myocardium but extends also into the remote myocardium, and impacts ventricular geometry and function.[164] Key pathophysiological processes are collagen deposition and its cross-linking, which mature and stabilize the infarct scar, as well as cardiomyocyte hypertrophy and fibrosis in response to the increased wall stress in the remote myocardium.[154] When these processes occur in a controlled fashion, such remodeling acts to preserve ventricular geometry and function. In contrast, adverse remodeling with scar thinning and excessive hypertrophy and fibrosis in remote myocardium eventually ends up in heart failure.[25] In addition to the local control by the reparative healing

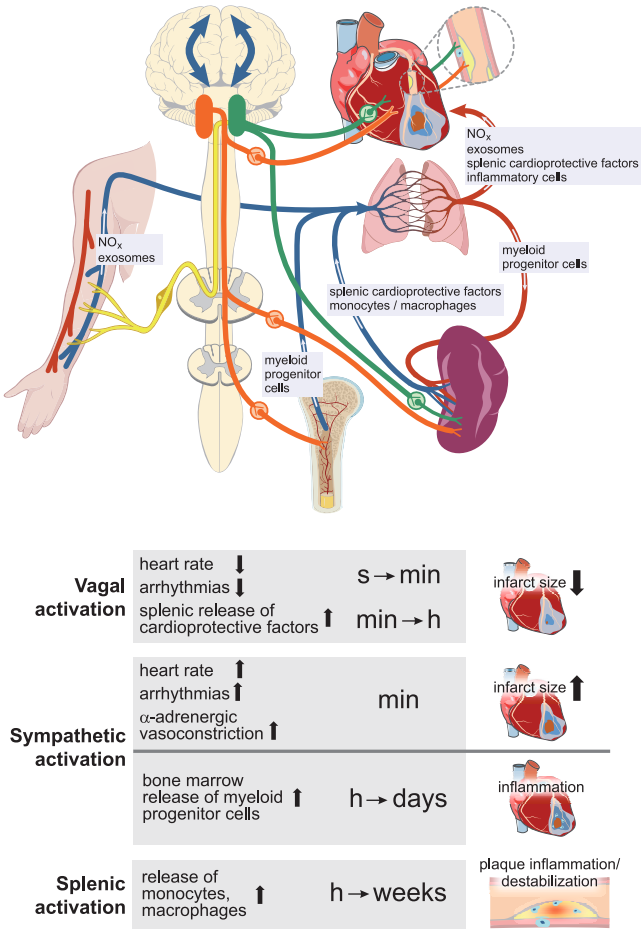

Figure 3. Interaction of vagal and sympathetic nerves with spleen and bone marrow and release of cells and substances that either protect the infarcting heart upon vagal activation during remote ischemic conditioning or damage the infarcting heart upon sympathetic activation, which promotes inflammation

Remote ischemic conditioning induces release of circulating cardioprotective factors such as nitrite and exosomes from the peripheral site of ischemia/reperfusion and induces vagal activation, which reduces heart rate, activates cardiac cholinergic receptors to induce cardioprotection, and induces release of circulating cardioprotective factors from the spleen. Sympathetic activation increases heart rate and induces α-adrenergic coronary vasoconstriction and the release of myeloid progenitor cells from the bone marrow. These myeloid progenitor cells migrate into the spleen, where they mature into monocytes that, when released, migrate not only into the myocardium but also into atherosclerotic plaques, where they cause destabilization. Modified from Heusch[163] with permission.

processes and local wall stress, remodeling is under systemic neuronal and endocrine control. Activation of the sympathetic nervous system promotes cardiomyocyte hypertrophy, and activation of the renin-angiotensin-aldosterone system promotes cardiomyocyte hypertrophy and fibrosis. The natriuretic peptides counteract these processes by vasodilation, natriuresis, and inhibition of the sympathetic and renin-angiotensin-aldosterone systems. Accordingly, β-blockade, ACE inhibitors/AT_1 antagonists, and, more recently, aldosterone antagonists and neprilysin inhibition to attenuate breakdown of natriuretic peptides are established treatments to prevent postinfarct heart failure development in patients. While remodeling, either beneficial or adverse, typically occurs following AMI, it can also more silently occur with repetitive coronary microembolization and repair on a smaller scale but still eventually result in heart failure. In ischemic cardiomyopathy, the sympathetic innervation also remodels with partial and local denervation,

resulting in inhomogeneity of action potential and conduction responses during sympathetic activation and predisposing to sudden cardiac death.[165]

ARRHYTHMIAS

Whereas any single premature ventricular extrasystole can precipitate ventricular fibrillation when it occurs during the early, spatially heterogeneous ventricular repolarization (R on T-phenomenon in the ECG), myocardial ischemia and reperfusion promote conditions that favor extrasystoles and ventricular fibrillation. Within minutes of myocardial ischemia after coronary occlusion, the ATP-dependent function of cardiomyocyte Na^+/K^+-ATPase[166] and the re-uptake of norepinephrine into sympathetic nerve terminals are impeded.[167] Loss of Na^+/K^+-ATPase function induces a local increase in extracellular K^+, which can depolarize neighboring cardiomyocytes.[166] Loss of norepinephrine re-uptake into sympathetic nerve terminals can elicit action potentials in still-excitable cardiomyocytes.[168] Reflex sympathetic activation during early myocardial ischemia[169] potentiates this arrhythmogenic situation, which is, on the other hand, sensitive to β-blockade.[170] In later myocardial ischemia with progressively spreading cardiomyocyte death, the loss of K^+ ions from cardiomyocytes[166] further promotes both extrasystoles from still-excitable cardiomyocytes and impairment of conduction, which favor re-entry of excitation within the ischemic myocardium and across its border to non-ischemic myocardium and then ventricular fibrillation.[171,172] Reperfusion following myocardial ischemia further promotes ventricular arrhythmias by highly heterogeneous reperfusion on the microvascular level. This consequently results in heterogeneous washout of ions, re-activation of ionic pumps, and normalization of cardiomyocyte excitability and conduction, which create electrical gradients and re-entry mechanisms[173]; the enhanced formation of ROS also contributes to reperfusion arrhythmias.[82,174] The myocardium remains sensitive to serious arrhythmias in the healing phase of myocardial infarction through dispersion of refractoriness, conduction delays, and re-entry mechanisms within the infarcted myocardium and across its borders to non-ischemic myocardium.[175,176] Ventricular fibrillation resulting from myocardial ischemia/infarction remains the predominant cause of sudden cardiac death,[177,178] often out of hospital.[179] Atrial fibrillation is also promoted by an interaction of myocardial ischemia and sympathetic activation.[180]

CARDIOPROTECTION AND REGENERATION

Cardioprotection: Ischemic conditioning, drugs, and physical interventions

Cardioprotection refers to all measures that prevent or attenuate cardiac damage, no matter what the damaging stimulus, but more specifically refers to measures that reduce infarct size and coronary microvascular obstruction.[26] An initial phase of attempted cardioprotection was led by the idea to reduce the oxygen demand of cardiac contraction by manipulation of hemodynamics; as outlined above, the ischemic myocardium does not contract anyway, and therefore not surprisingly, this strategy proved not successful and was abandoned.[29] A second phase of attempted cardioprotection was prompted by the recognition of the ischemic conditioning phenomenon in 1986.[181] Ischemic conditioning is the activation of a complex molecular self-defense program by brief coronary occlusion and reperfusion, which cause no infarction per se but protect from sustained myocardial ischemia with reperfusion that causes infarction.[182] Such ischemic conditioning can be activated before sustained ischemia (preconditioning) and during early reperfusion (postconditioning). Ischemic conditioning with cardioprotection can also be elicited by ischemia/reperfusion in tissues remote from the heart (remote conditioning).[183] The signal transduction of ischemic conditioning involves (1) the activation of sarcolemmal receptors by neurohormones, autacoids, cytokines, and growth factors; (2) the activation of intracellular enzymes, mostly kinases, by activation of these sarcolemmal receptors but also by small molecules such as calcium, nitric oxide, and

hydrogen sulfide; and, ultimately, (3) an action of these pathways on mitochondria, where respiration is preserved and ROS formation and opening of the permeability transition pore are reduced such that activation of cell death is inhibited.[184] Remote ischemic conditioning involves a neurohumoral signal transfer from the ischemic/reperfused peripheral tissue to the heart, with the spleen as an important relay organ that releases circulating cardioprotective substances upon vagal activation (Figure 3).[185] A myriad of preclinical studies have demonstrated infarct size reduction by ischemic conditioning interventions and drugs that are related to ischemic conditioning's signal transduction; some of these interventions have also proven successful in smaller clinical proof-of-concept trials in patients with reperfused AMI. However, the translation to clinical practice has been difficult so far.[26] In fact, only a single positive phase 3 trial has reported better clinical outcome in patients undergoing remote ischemic conditioning,[186] whereas a much larger trial was neutral.[187] A number of drugs, many of them with an action on mitochondria,[188] have reduced infarct size in preclinical and smaller clinical proof-of-concept phase 2 trials, but none of them have unequivocally improved clinical outcome of AMI patients in a phase 3 trial.[189] Supplemental oxygen does not improve the clinical outcome of patients with AMI.[190] Hyperoxemic reperfusion reduced infarct size and coronary microvascular injury in preclinical studies and improved outcome in a small cohort of patients with anterior STEMI,[191] but the jury is still out for a prospective phase 3 trial. Mild hypothermia reduced infarct size in preclinical studies[192] but did not improve outcome for patients with AMI.[193] Also, left ventricular unloading by a mechanical assist device before reperfusion reduced infarct size in a pig model,[194] but its clinical use is still under investigation (ClinicalTrials.gov: NCT03947619). The reasons for the poor translation of cardioprotection to clinical practice are multi-fold, including lack of robustness in many preclinical studies[195]; genetically determined non-responsiveness to cardioprotection[28]; confounders such as advanced age, co-morbidities, and co-medications[189]; and recruitment of patients into trials who have a very good outcome anyway, which is difficult to improve further by cardioprotection.[27]

Regeneration

The potential for self-renewal of adult cardiomyocytes is extremely limited, not only in the intact heart but also after injury and loss of viable cardiomyocytes. Cell therapy to regenerate infarcted tissue raised enormous enthusiasm initially[196] but has not fulfilled its promises so far. The original idea that implantation of mesenchymal stem cells or their mobilization from the bone marrow with subsequent migration into infarcted myocardium would result in their transdifferentiation into cardiomyocytes[196] proved equally wrong as that of implantation of more select stem cell populations.[197] Activation of resident cardiomyocytes to form new cardiomyocytes resulted in very limited and functionally insignificant myocardial regeneration.[198] Whereas research into cell therapeutic approaches, cell-cycle induction in cardiomyocytes,[199] and direct reprogramming of fibroblasts into cardiomyocytes[200] has generated an enormous wealth of fundamental knowledge, it has not succeeded in inducing renewal of lost cardiomyocytes in any significant amount so far.[22,201,202] Still, improved ventricular function after cell therapy has been achieved and is mainly attributed to the action of paracrine factors on existing cells, such as stimulation of angiogenesis.[203] Recently, more systematic analysis of such paracrine factors has identified microRNAs,[21,24] peptides,[204,205] and extracellular vesicles[206,207] that mediate cardioprotective and regenerative effects. In mice with permanent coronary ligation, conditional depletion of an acetyltransferase, which activates apoptosis and inhibits the cell cycle, reduced infarct size and improved LV function and survival.[208] In a mouse model of myocardial injury, attention has also been directed to remodeling of the extracellular matrix in response to the protein agrin, which may facilitate regeneration.[209]

Box 1. Research and health policy agenda for ischemic heart disease

BASIC, TRANSLATIONAL, AND CLINICAL RESEARCH AGENDA

Genome-wide analyses for development of risk scores and primordial prevention
Primordial prevention of risk factors and primary prevention of ischemic heart disease
Understanding and targeting the neuro-immune interface at the coronary plaque
Non-invasive imaging for early diagnosis of coronary atherosclerosis
Invasive imaging for understanding of coronary atherosclerosis, plaque erosion/rupture, and treatment control
Personalized medicine approaches for conservative vs. interventional treatment of stable angina
Personalized medicine approaches for conservative vs. interventional treatment of ischemic LV dysfunction
Understanding and treating angina with non-obstructive coronary disease
Understanding and treating coronary microvascular disease
Understanding and treating coronary microvascular obstruction/hemorrhage
Understanding and targeting non-regulated and regulated modes of cell death in cardiomyocytes and non-cardiomyocytes
Development and translation of novel targets for cardioprotection
Understanding the dynamics of immune cell recruitment, their specific role in infarct healing, and potential therapeutic targets
Fundamental understanding and translation of repair/regeneration
Understanding remodeling and preventing postinfarct heart failure

HEALTH POLICY AGENDA

Public awareness, health education
Establishment of chest pain units for rapid triage
Establishment of local primary PCI networks
More research funding (equivalent to that for cancer)

PERSPECTIVES AND AGENDA

Progress in diagnosis and treatment of cardiovascular disease, notably including IHD, has largely contributed to an increasing life expectancy in developed countries.[210,211] However, further efforts in research and in health policy must be directed to better understanding, diagnosis, and treatment of the pathogenesis and manifestation of IHD (Box 1).

Given the pivotal importance to provide timely reperfusion of ischemic myocardium, the awareness of IHD must be improved to achieve better education and prevention already in children.[212] Research using genome-wide analyses will identify further risk factors and facilitate primordial prevention of those risk factors[213] as well as of potential non-responsiveness to cardioprotective interventions.[28]

In patients with stable angina, advances in non-invasive imaging will replace diagnosis by angiography,[214] and personalized medicine approaches will guide decisions for conservative vs. interventional therapy.[215] For patients with persistent angina[5] and angina in the absence of obstructive coronary atherosclerosis, mechanisms of pain perception[10] and of coronary microvascular dysfunction[216,217] must be better understood such that they can be therapeutically targeted.

The availability and logistics of chest pain units for rapid triage and PCI for rapid reperfusion of AMI must be improved[218]; networks for facilitated transport to a PCI center must be established.[219,220] Invasive imaging, notably intravascular ultrasound and OCT,[221] will guide decisions for interventional treatment and improve prognosis.[222] Beyond optimal reperfusion, strategies must be developed to provide

adjunct protection in patients with hemodynamic complications. For that, novel targets in more robust preclinical studies must be identified.[195] Interventions in the healing and early remodeling responses following AMI are currently being explored and may prevent the development of heart failure.[164] With optimism, further advancement in basic science will eventually make the replacement of lost cardiomyocytes by cell therapy, cell-cycle induction in cardiomyocytes, or direct reprogramming of fibroblasts into cardiomyocytes possible.[22]

ACKNOWLEDGMENTS

G.H. was supported by the German Research Foundation (CRC 1116, B8) and the European Union (COST ACTION CARDIOPROTECTION CA 16225).

DECLARATION OF INTERESTS

The author declares no competing interests.

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DOI: 10.1016/j.medj.2023.12.007
URN: urn:nbn:de:hbz:465-20250102-104211-5