PERSPECTIVE

Macrophages stimulate neutrophils to stop an electrical storm after myocardial infarction

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ABSTRACT

In patients with coronary heart disease, sudden cardiac death, caused by aberrant electrical conduction, commonly happens. Arrhythmia and significant myocardial leukocyte alterations are brought on by myocardial ischemia at the same time. In this study, we improved a mouse model in which myocardial infarction and hypokalemia caused ambulatory animals to spontaneously develop ventricular tachycardia, and we demonstrated that major leukocyte subsets have opposing effects on cardiac conduction. In mice, neutrophils promoted ventricular tachycardia through lipocalin-2, but in patients, neutrophilia was linked to ventricular tachycardia. Macrophages, on the other hand, provide protection from arrhythmia. When Csf1 receptor blockade was used to reduce recruited macrophages in Ccr2/ mice or all macrophage subsets, it enhanced ventricular tachycardia and fibrillation. When evaluated in conjunction with decreased mitochondrial integrity and accelerated cardiomyocyte death in the absence of macrophages, higher arrhythmia burden and mortality in Cd36/+ and Mertk/+ mice suggested that receptor-mediated phagocytosis protects against deadly electrical storm. Leukocyte function modification thus offers a potential therapeutic route for lowering the risk of sudden cardiac mortality.

Key Words: *Myocardial infarction; Hypokalemia; Cardiomyocyte; Macrophages*

INTRODUCTION

When the myocardium's regular rhythmic depolarization is disrupted, it results in sudden cardiac death because the flow of oxygen-rich blood is stopped. The annual survival rate for this ailment, which affects more than 200,000 Americans and more than 5 million people worldwide, is less than 10%. Myocardial ischemia, which causes Ventricular Tachycardia (VT) or ventricular fibrillation, is the most common underlying disease. Death results if these arrhythmias are not addressed right away. Despite its incidence and lethality, defibrillation, which returns normal myocyte depolarization, is the primary kind of treatment now available. Secondary prevention relies on increasing blood flow and implanting a defibrillator if a patient survives. Implantable defibrillators can lower cardiac mortality in the future, but they can also lower quality of life because they cannot stop recurrent arrhythmias. One-third of patients with a defibrillator never receive an appropriate therapy since it is challenging to predict arrhythmia risk. Numerous studies have been done on the basic electrophysiological processes that cause ventricular arrhythmias. Following Myocardial Infarction (MI), regions of regional heterogeneity act as the substrate for re-entry in place of the myocardium's usual homogeneous depolarization. Re-entry can be spread by a number of diseases, such as defective ion channel function, structural alterations in ion channels and gap junctions brought on by oxidation, and hereditary abnormalities. Conduction may also be slowed by myocardial fibrosis and dead or dying cells, which would add to the arrhythmogenic substrate. The potential that leukocytes may be involved in rhythm problems or aid in the prevention of arrhythmias is raised by the growing significance of innate immune cells in the healthy and ischemic heart. With a frequency of 6%-8% in the mouse and human heart, cardiac resident macrophages are crucial for myocyte energy metabolism and sustain normal electrical conduction. Massive alterations in myocardial leukocyte numbers and morphologies are linked to conditions that enhance the risk of cardiac arrhythmia, such as acute MI or myocarditis. The lack of appropriate animal models is a significant barrier for such studies. Despite the ease with which large animals can suffer spontaneous arrhythmia, the instruments available to research their immune systems are scarce.

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The mouse, in comparison, offers a wide range of sophisticated techniques, although spontaneous VT and Vfib are infrequent. There have been discussions on the lack of spontaneous VT as being caused by the fast heart rate, tiny stature, and unique action potential. By using a clinically applicable and surprisingly straightforward intervention—diet-induced hypokalemia before ischemia, which resulted in recurrent ventricular arrhythmias in awake, ambulatory mice—we were able to overcome this obstacle.

RESULTS

A mouse model of electrical storm

Due to the use of diuretics or sympathetic nervous system stimulation during treatment for acute MI, patients may experience hypokalemia, which is defined as serum potassium levels below 3.5 mM. We proposed that hypokalemic mice have spontaneous arrhythmias after MI because the occurrence of life-threatening tachyarrhythmias is inversely associated to serum potassium levels. By providing C57BL/6J wild-type mice with a diet lacking in potassium, we put this theory to the test. After inducing an infarct, we were able to keep an eye on waking mice thanks to the implant of a telemetric device. A diet low in potassium for three weeks caused moderate hypokalemia and the associated electrolyte abnormalities. The QTc time was longer in hypokalemia, which indicated a slower rate of ventricular repolarization and decreased resting heart rate. The echocardiography-measured diastolic and systolic functions remained unaffected. Neutrophil and monocyte recruitment after MI, the removal of resident cardiac macrophages from the ischemic myocardium, or the extent of the infarct 24 hours following permanent coronary artery ligation were not impacted by hypokalemia.

Neutrophils incite ventricular arrhythmia

Although neutrophils play a variety of roles following MI, it is yet unknown if they are a factor in ventricular arrhythmias. Therefore, we used injections of antibodies against neutrophil surface markers to reduce the number of circulating neutrophils. We chose permanent coronary artery closure without re-perfusion to rule out the role of neutrophil depletion on infarct size, which affects the occurrence of arrhythmia. Neutrophil numbers in STORM animals were sufficiently reduced by antibody treatment, but blood troponin, the extent of 24-hour infarcts, the weight of the heart, monocyte and macrophage populations, and other variables were unaltered.

Neutrophil-derived lipocalin-2 is pro-arrhythmic

We first investigated whether neutrophil depletion decreases ischemic cell death, but at the time when arrhythmia was most common, we discovered comparable amounts of TUNEL+ myocytes and caspase-3 activity in the infarcts of STORM mice with reduced and normal neutrophil counts. We then investigated whether neutrophils encourage post-MI arrhythmia via ROS (ROS). A fluorescent ROS imaging sensor, which we verified for the particular experiment, was enriched in the infarct five hours after coronary ligation, though to a lower extent if neutrophils were depleted. This protective response, meanwhile, has the potential to backfire and harm ischemic cardiomyocytes. In patients with MI and heart failure, serum LCN2, also known as Neutrophil Gelatinase-associated Lipocalin (NGAL), rises and is a predictor of infarct mortality and unfavourable outcomes. We proposed that neutrophils may cause post-MI VT via Lcn2-related pathways in response to these clinical data and earlier research associating ROS to arrhythmia.

Macrophages protect against ventricular arrhythmias

Cardiac macrophage numbers and morphologies significantly alter concurrently with post-MI arrhythmias, as local macrophage death and monocyte recruitment start soon after ischemia onset. We investigated the effects of monocytes and macrophages on post-MI arrhythmias using two distinct depletion methods. The colony-stimulating factor 1 receptor was first blocked (Csf1R). This receptor encourages myeloid cell growth and resident macrophage survival. Even before MI, ten days of Csf1R suppression effectively reduced cardiac macrophage numbers, although left ventricular function, serum potassium levels, and the expression of genes linked to cell death were unchanged. The second depletion method was genetically eliminating the Ccr2 chemokine receptor. Mice deficient in Ccr2 are unable to mobilise bone marrow-derived monocytes or attract macrophages to the infarcted heart. Rapid pacing generated comparable VT in controls, Csf1R inhibitor-treated mice, and Ccr2/ animals in mice without MI. Macrophage depletion did not cause spontaneous VT or Vfib in hypokalemic mice without MI. Next, we merged the STORM method with macrophage depletion. While neutrophil and monocyte numbers, infarct size at 24 hours after coronary artery ligation, and heart weight were unaltered by Csf1R inhibition, macrophages were decreased after MI. Similar to wild-type STORM controls, neutrophils, infarct size, and heart weight were observed. The post-MI VT and Vfib burden was higher in Ccr2/ STORM mice. Since the QTc time was unaffected, repolarization was unaffected by macrophage reduction. Macrophage depletion did not affect survival in the first day following MI in STORM mice. These findings collectively imply that macrophages—regardless of cell subset—play a protective role in MI-induced ventricular arrhythmias. This realisation inspired us to investigate how macrophages perform this role in acute MI.

CONCLUSION

Cardiac excitation is carried out by myocytes and specialised conduction system cells, and arrhythmias are mostly brought on by the malfunctioning of these cells. Since many years ago, it has been understood that stromal cells' interactions with conducting cells may have an impact on the heart rhythm. For instance, fibroblasts have an impact on conduction both directly and indirectly through electrotonic coupling and matrix deposition. Macrophage involvement in conduction is a fairly recent discovery, as is even the knowledge of local cardiac macrophages. Although the precise role of leukocytes in arrhythmogenesis is yet unknown, it is widely acknowledged that inflammation spreads rhythm abnormalities. This theory is based on the clinical correlation between arrhythmia and blood indicators like C-reactive protein or IL-6 as well as inflammatory diseases like myocarditis or sepsis. Furthermore, inducible atrial arrhythmia in mice is brought on by genetically mandated inflammasome activation in cardiomyocytes. In the current study, we have determined how ischemia-induced ventricular arrhythmias are influenced by the most prevalent cardiac leukocyte populations, namely neutrophils and macrophages. In animals with an acute MI, neutrophil depletion decreased VT burden, identifying these cells as promoters of ventricular arrhythmia. Lcn2, a crucial component of neutrophil defence, raises ROS in cardiomyocytes. Thus, Lcn2 could alter calcium handling and action potential length by oxidising ion channel proteins and their function. The changes that cause VT and Vfib result in variability in conduction velocity, delayed afterdepolarizations, and re-entry. Macrophages offer post-MI arrh-

-ythmia protection in contrast to neutrophils. Increased VT load was caused by either genetically deleting the chemokine receptor Ccr2, which prevents the recruitment of a subset of macrophages thought to be inflammatory, or by blocking the Csf1 receptor, which decreases all macrophages regardless of their source. Phagocytosis of dead cardiomyocytes, a mechanism that aids wound healing after ischemia, is a main activity of macrophages early after MI. Cd36 and Mertk receptors are necessary for monocytes and macrophages to remove dead cells. In mice with acute MI, genetic deletion of these receptors caused deadly arrhythmias. Impaired clearance of injured or dead cells may impede regional conduction and increase electrical heterogeneity in the myocardium, both of which are possible substrates for ventricular and re-entry arrhythmias. Furthermore, our findings imply that macrophages may slow the death of myocytes during ischemia. Although the size of the infarct 24 hours after permanent coronary ligation, which is determined by the location of the coronary artery ligation, was comparable in mice with and without macrophages, TUNEL and caspase assays obtained 5 hours after MI, when VT and Vfib were most prevalent, showed that myocytes perished more gradually if macrophages were present.

It is likely that the absence of macrophages, which in our tests preceded ischemia, accelerated mitochondrial failure since cardiac resident macrophages protect myocytes' metabolic health by scavenging malfunctioning mitochondria. In fact, macrophage depletion hastens the collapse of the mitochondrial membrane potential in ischemic myocytes. Consequently, ATP may have been depleted more quickly, endangering the efficiency of the ion pump and Ca handling. In the absence of macrophages, a buildup of defective mitochondria may result from other processes affecting cardiomyocyte autophagy. In the end, mitochondrial dysfunction results in cell death, a catastrophe that completely eliminates regional conduction. The ensuing local block can increase the electrical heterogeneity of the myocardium. Through gap junction coupling or, in the case of pulmonary hypertension, by secreting amphiregulin, which protects gap junction contact between myocytes, these cells aid conduction. This assistance may be lost to the ischemic myocardium due to macrophage loss during ischemia. We speculate that macrophages' positive functions may also include regulating sympathetic cardiac innervation, cytokine signalling, or scavenging the tissue microenvironment, all of which may have an impact on the survival or activity of myocytes. The contribution of cardiac leukocytes to arrhythmia probably varies depending on the underlying substrate, probably with a lower contribution to VT coming from chronic scarring and greater relevance for conditions with acute inflammatory myocardial injury, including the infarction as tested here and, potentially, also myocarditis, cardiomyopathies, or sarcoidosis. Limiting unfavourable side effects on infarct repair and immunological defence by neutralising particular pro-arrhythmic neutrophil products, including possibly lipocalin-2. Unexpectedly, all macrophage subsets, including monocyte-derived macrophages, which frequently promote harmful inflammation, seem to defend against post-MI arrhythmia, raising the potential that overly aggressive macrophage targeting promotes arrhythmia. Cardiovascular mitochondrial health, myocyte metabolism, and conduction may be compromised by immunotherapeutics that suppress Csf1R and CCR2, as well as other immunotherapeutics that affect the leukocyte reservoir in the heart.