Review

Integrative Cardiac Reserve

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Key Words

Integrative cardiac reserve · Coronary flow reserve · Myocardial reserve · Energy reserve ·
Heart rate reserve

Abstract

Recent progress suggests that integrative cardiac reserve is important in coronary artery disease, chronic heart failure, cardiomyopathy, and other cardiovascular diseases. Integrative cardiac reserve includes coronary flow reserve, myocardial reserve, energy reserve, and heart rate reserve. In the case of stress reaction, coronary flow reserve can provide excessive blood and energy supply and increase the heart rate. Thus, the dysfunctional myocardium can recover its contractile characteristics. In this study, we review the current knowledge on integrative cardiac reserve in order to provide an additional cure and strategy for the treatment of heart diseases.

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Background

The heart is not only our most vital but also our most complex organ. It is precisely controlled by the interplay of electrical and mechanical fields and consists of 4 chambers and 4 valves, which act in concert to regulate its filling, ejection, and overall pump function [1]. In normal circumstances, the heart supplies blood to satisfy the needs of the entire body, but in cases of stress reactions, the heart needs to increase its contractile force and heart rate and exhaust excessive energy to satisfy the needs of the body; thus, it is extremely important for the heart to reserve sufficient energy, flow, and heart rate. This reserve ability needed in the case of stress reactions is usually called ‘integrative cardiac reserve’, including flow reserve, myocardial reserve, energy reserve, and heart rate reserve. In a healthy heart, integrative cardiac reserve can satisfy the needs of the body, also in cases of stress reaction; however, in

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patients with coronary heart disease, chronic heart failure, or cardiomyopathy, integrative cardiac reserves are decreased or injured. The condition of the patient will deteriorate. What are the properties of integrative cardiac reserve and how does it work? Understanding its processes is important in the diagnosis and treatment of heart diseases.

Coronary Flow Reserve

Coronary flow reserve (CFR) is the most important type of the integrative cardiac reserves. The coronary circulation is unique in that it is responsible for generating the arterial pressure that is required to perfuse the systemic circulation and yet, at the same time, it has its own perfusion impeded during the systolic portion of the cardiac cycle. Because myocardial contraction is closely connected to coronary flow and oxygen delivery, the balance between oxygen supply and demand is a critical determinant of the normal beat-to-beat function of the heart. When this relationship is acutely disrupted by diseases affecting the coronary blood flow, the resulting imbalance can immediately precipitate a vicious cycle, whereby ischemia-induced contractile dysfunction precipitates hypotension and further myocardial ischemia [2]. Thus, knowledge of the coronary blood flow regulation, the determinants of myocardial oxygen consumption, and the relationship between ischemia and contraction is essential for the understanding of the pathophysiological basis and management of many cardiovascular disorders [3].

The coronary arterial circulation consists of large epicardial arteries and a microvascular system [4]. Epicardial coronary arteries can be visualized by coronary angiography, and their diameters range from a few millimeters to 400–500 μm . The microvascular system cannot be clearly delineated by coronary angiography, and it is responsible for most of the coronary vascular resistance. The vascular tone and resistance of these vessels can be modulated under various physiological and pharmacological conditions in order to control the myocardial blood flow. Because the microvessels are too small to be revascularized by either percutaneous or surgical intervention and are difficult to assess, the main focus of clinical cardiology has been on the large epicardial arteries [5]. However, it is well known that patients with microvascular dysfunction have worse outcomes than those without [6]. Furthermore, recent technical advances have enabled easy and reliable assessment of the microvascular system in a catheterization laboratory [7, 8]. CFR has been used to assess the microvascular function in patients without significant epicardial lesions [9]. Coronary resistance arteries and arterioles also regulate their diameter in response to changes in local shear stress, which is endothelium dependent and mediated by nitric oxide, because it could be abolished with an L-arginine analogue. Nitric oxide-mediated vasodilatation plays a role in determining the physiological vascular tone in some segments of the coronary resistance vasculature [10].

Myocardial ischemia caused by coronary artery stenosis induces angina pectoris, which is associated with poor clinical outcome in patients with coronary artery disease (CAD). Various factors other than the degree of epicardial stenosis influence the physiological significance of coronary artery stenosis; however, the gold standard diagnosis of CAD is coronary artery angiography, which can provide valuable information on the ischemic condition. Revascularization of stenotic coronary lesions, inducing myocardial ischemia, can improve the patient's functional status and outcome [11]. On the other hand, if stenotic lesions do not induce ischemia, the benefit of revascularization is limited [12]. The present edition of the 2013 European Society of Cardiology (ESC) guidelines on the management of stable CAD has not only considered evident atherosclerotic narrowing, but also microvascular dysfunction and coronary vasospasm in the diagnostic and prognostic algorithms. Further, this guideline distinguishes diagnostic testing from prognostic assessment, gives increased importance to the pretest probability of the disease strongly influencing the diagnostic algorithms and takes into account recent advances in tech-

nology, the importance of physiological assessment of CAD in the catheterization laboratory, and the increasing evidence that the prognostic benefit of revascularization may be less than has been traditionally expected [13]. Investigations have shown that angina is more prevalent in middle-aged women than in men, probably due to the higher prevalence of functional CAD, and this may be because the integrative cardiac reserve is deficient in middle-aged women compared to men [14]. Therefore, in these patients, we should focus on integrative cardiac reserve, including myocardial flow reserve (MFR), myocardial energy reserve, and heart rate reserve.

MFR consists of two types: MFR in nonstenotic territory and MFR in stenotic territory. The latter one is the reserve for the areas of myocardial ischemia, which is monitored by the hyperemic flow in the myocardial territory through the stenotic artery and nonstenotic vessel to detect perfusion defects [15].

Myocardial fractional flow reserve (FFR), namely the ratio of maximal blood flow in a stenotic artery to normal maximal flow [16], is a type of MFR. FFR provides a direct estimate of coronary blood supply independent of heart rate, blood pressure, or contractility changes [17]. FFR may be a cost-effective method for the assessment of MFR in functionally significant CAD [18] to identify physiologically significant stenosis inducing reversible ischemia and is indispensable in the catheterization laboratory [19]. The FFR value not only depends on the epicardial conduit resistance but also on the coronary blood flow volume through the stenosis. As the coronary flow increases, the pressure gradient also increases [20]. The amount of coronary blood flow correlates with the volume of the regional myocardial mass supplied by the coronary artery [21]. Incorporation of FFR measurements in clinical practice may affect patient outcomes. A randomized trial of 70 patients found that using FFR instead of noninvasive imaging in patients after unstable angina or non-ST-elevated myocardial infarction may be cost effective and shorten hospitalization [14]. Clinical follow-up over 1 year showed no differences in clinical outcome. FFR, alone or with some other diagnostic test, can help identify patients in whom percutaneous intervention may be indicated. Why does FFR-guided percutaneous coronary intervention (PCI) decrease the rate of death and myocardial infarction? Stenting a functionally significant stenosis improves patient outcome, whereas stenting a functionally insignificant stenosis worsens the outcome; FFR-guided PCI can identify patients with excellent integrative cardiac reserve, is superior to angiography-guided PCI, and the excellent integrative cardiac reserve is the key to patient prognosis [22].

Myocardial perfusion imaging with single-photon emission computerized tomography (SPECT) not only allows the accurate detection of CAD but also reliably discriminates between patients at low versus high risk of major adverse cardiovascular events, including cardiac death [23]. A normal SPECT myocardial perfusion imaging may reliably exclude an adverse outcome, even in the presence of coronary lesions. CFR has been proposed as an index to evaluate the coronary circulation in the epicardial coronary arteries and in the microcirculation. However, each method for assessing myocardial ischemia has technical limitations. Quantitative coronary angiography does not include information on stenosis length and may underestimate or overestimate stenosis severity. Perfusion imaging can be analyzed by more or less reliable quantitative methods, whereas dobutamine stress echocardiography still relies on the visual assessment of wall motion abnormalities. FFR depends on the presence of microvascular disease and the different protocols of adenosine administration.

Myocardial Reserve

In myocardial ischemia patients, especially after acute myocardial infarction, a part of the myocardium, for example stunned myocardium, no reflow myocardium, or hibernating myocardium, becomes inactive and then, after revascularization or drug administration,

endothelial cell (EC) function improves and the contractile function recovers, which is related to myocardial reserve.

Myocardial ischemia and reperfusion (I/R) injury was first discovered in 1960 by Jennings et al. [24], who described the histological features of reperfused ischemic canine myocardium. Damage to the myocardial reserve can aggravate myocardial I/R injury. In this condition, the process of restoring blood flow to the ischemic myocardium can induce myocardial injury and produce a spectrum of reperfusion-associated pathologies. This process is defined as myocardial I/R injury, which is characterized by an acute inflammatory process in which activated leukocytes and ECs are primarily involved [25]. Myocardial I/R injury occurs in some conditions of cardiovascular diseases (e.g., arteriosclerosis, coronary artery spasm, and thrombosis) [26, 27], and the therapeutic strategies include PCI, coronary artery bypass grafting, and cardiopulmonary bypass in cardiac operations and cardiac transplantations [28, 29]. A series of postoperative complications occur in patients who undergo coronary artery bypass grafting, including prolonged contractile dysfunction, low output syndrome, perioperative myocardial infarction, and heart failure. Restoration of blood flow achieved with PCI can result in an acute cardiac local inflammatory response and myocardial cell and EC damage [30–32].

I/R injury causes severe clinical symptoms, including cardiac contractile dysfunction, arrhythmias, cell death mediating heart failure, and sudden death. In myocardial stunning after short episodes of myocardial I/R, prolonged mechanical dysfunction persists, although no prominent histological features of irreversible myocardial injury exist. This phenomenon was called ‘myocardial stunning’ [33–35]. Myocardial stunning is characterized by reversible myocardial contractile dysfunction, within a prolonged period after reperfusion of ischemic myocardial tissue. The myocytes are capable of recovering from this reversible form of injury after several days or weeks. The clinical symptoms of stunned myocardium range from cardiac arrest in open cardiac surgery and PCI to thrombolysis and unstable and stable angina [36, 37].

The no-reflow phenomenon was originally defined as the ‘inability to reperfuse a previously ischemic region’ [38]. It refers to myocardial I/R injury which obviously impairs EC function, disturbing the restoration of blood flow in the microvasculature. This phenomenon is secondary to vasoconstriction, platelet and leukocyte activation, increased oxidant production, and increased fluid and protein extravasation [39, 40]. The no-reflow phenomenon usually occurs after more prolonged episodes of myocardial ischemia [28].

Hibernating myocardium is normally defined as viable and dysfunctional myocardium that improves in function with the restoration of adequate blood flow following revascularization [41]. This reversible state should be clearly distinguished from irreversibly injured or infarcted myocardium, in which case the restoration of coronary blood flow would not be justified. However, significant improvement in global left ventricular (LV) function after revascularization requires a substantial amount of viable myocardium. Methods to monitor this part of the myocardium and its recovery of function are needed. Cardiovascular magnetic resonance (CMR) with its high spatial resolution could provide qualitative and quantitative, global and regional information on myocardial anatomy and function [42]. In combination with a gadolinium-based contrast agent, CMR allows an accurate quantification of the myocardial scar [43] and predicts the likelihood of functional recovery after revascularization [44, 45]. How long does it take for hibernating myocardium to change into functional myocardium? In most studies [46, 47], functional outcome is assessed 3–6 months after revascularization, whereas a longer follow-up interval would be more appropriate, taking into account that functional recovery may be considerably delayed in hibernating myocardium having more advanced structural damage [48]. Our study shows that in patients with chronic ischemic LV, improvement in dysfunctional but viable myocardium can be considerably

delayed. Both the likelihood and the time course of functional improvement are related to the late gadolinium enhancement, CMR, and the degree of contractile dysfunction at baseline. At 35 ± 6 months after revascularization, patients with $\geq 55\%$ of viable segments from all dysfunctional and revascularized segments had significantly improved LV ejection fraction and experienced reverse LV remodeling. A combination of low-dose dobutamine CMR and late gadolinium enhancement CMR is a simple and powerful tool for identifying which patients with impaired LV function will benefit from revascularization [49].

It is important for chronic heart failure patients to monitor their cardiac reserve. For example, although cardiac resynchronization therapy (CRT) is an established treatment option for patients with heart failure, depressed LV ejection fraction and left bundle branch block, or prolonged duration of the QRS complex [50, 51], a significant proportion of treated patients still lack functional, clinical, and structural improvement. The identification of nonresponders to CRT has been a matter of intensive investigation over the last several years. The absence of myocardial contractile reserve, as assessed by dobutamine stress echocardiography, could detect patients who are less likely to respond beneficially to CRT [52].

Energy Reserve

Despite increasing knowledge on the distribution of coronary artery stenosis and microvascular resistance, there is still no consensus regarding specific mediators of metabolic vasodilation. Coronary resistance in any segment of the microcirculation represents the integration of local physical factors (e.g., pressure and flow), vasodilator metabolites (e.g., adenosine, PaO_2 , pH), autacoids, and neural modulation. Each of these mechanisms contributes to net coronary vascular smooth muscle tone, which may ultimately be controlled by opening and closing vascular smooth muscle adenosine triphosphate-sensitive K^+ channels. There is a considerable redundancy in the available local control mechanisms [53]. Because of this, blocking single mechanisms fails to alter coronary autoregulation or metabolic flow regulation at normal coronary pressures. However, this redundancy can be unmasked by stressing the heart and evaluating flow regulation at reduced pressures distal to a coronary stenosis at rest or during exercise [18].

Heart Rate Reserve

The activity of the heart is controlled by the autonomic nervous system (ANS). The sympathetic and vagus nerves control the heart rate, rhythm, myocardial contractility, and energy metabolism. Increased cardiac sympathetic nervous system activity and elevated cardiac synaptic norepinephrine [54] or enhanced myocardial norepinephrine sensitivity may provide a mechanistic explanation for myocardial injury predisposing to the development of impaired LV function and enhanced cardiac risk. In contrast, vagus nerve excitation can slow the heart rate, increase heart rate variability, decrease cardiac contractility, save myocardial energy, and increase myocardial energy reserve.

Determining the heart rate variability is a noninvasive method, reflecting the interaction of the two subsystems of the ANS (sympathetic and parasympathetic), which, besides affecting other organ systems, also affects the cardiovascular system. As to cardiac innervation, there is one heart rate cardio-acceleratory acting sympathetic and one cardio-deceleratory parasympathetic nervous system. At the level of sympathovagal afferentation, there are combined impulses from both vagal mechanoreceptors in the carotid sinus (afferentation by branches of the glossopharyngeal nerve), in the aortic arch, in the pulmonary arteries, subendocar-

dially in the cardiac ventricles and atria (afferent fibers of the vagus nerve) and from sympathetic metabo- and mechanoreceptors in skeletal muscles and carotid and subendocardial cardiac chemoreceptors. The ability to respond to stress stimuli is the basis of the ANS examination using heart rate changes in tests of autonomic cardiovascular function and later established methods of the analysis of heart rate variability. This method evaluates the fluctuations in the intervals between consecutive heart beats (RR intervals) that are related to the influences of the ANS on the sinus node.

As is known, diabetes mellitus, a disease prevalent in the population, often causes autonomic dysfunction. The pathogenesis of autonomic neuropathy in diabetes mellitus is multifactorial, and there is involvement of myelinated and unmyelinated nerve fibers with disorders of autonomic innervation in the cardiovascular, gastrointestinal, and genitourinary systems, and the skin. In the ANS involvement with the cardiovascular system of diabetes mellitus patients, excessive activation of sympathetic fiber and inhibited activation of parasympathetic fibers disappear. This can explain a fixed resting tachycardia due to the dominance of the sympathetic effect and impaired parasympathetic heart rate modulation and baroreflex function. Tachycardia is partially regulated during further progression of cardiac autonomic neuropathy with sympathetic denervation, but the heart rate remains higher than in the healthy population. One aspect of advanced cardiovascular autonomic dysfunction with sympathetic impairment is the tendency to develop orthostatic hypotension. In ischemic heart disease, it has been found that myocardial denervation is caused by interruption of neurotransmission in sympathetic fibers accompanying the affected coronary artery. The areas involved are infarcted as well as noninfarcted areas distal to the infarct. Sympathetic denervation of the heart muscle also occurs in cardiomyopathy of nonischemic origin, such as in dilated cardiomyopathy [55], in the advanced stages of autonomic neuropathy in diabetes mellitus, and generally, in heart failure [56].

In summary, integrative cardiac reserve is critical for the heart, especially in the case of stress reaction. Understanding the pathology and physiology of integrative cardiac reserve can help physicians diagnose and treat many heart diseases.

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The authors declare that there are no conflicts of interest regarding the publication of this article.

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