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REVIEW ARTICLE

The Type 2 Diabetic Heart: Its Role in Exercise Intolerance and the Challenge to Find Effective Exercise Interventions

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Abstract The metabolic and microvascular benefits of regular exercise for people with diabetes are unequivocal. However, cardiovascular disease, which disproportionately affects people with diabetes, is not reduced by regular exercise, and heart disease remains the leading cause of death for people with type 2 diabetes. 'Subclinical' changes in the function of the diabetic left ventricle are common and reduce cardiac reserve and exercise capacity. This review describes the changes in resting and exercising left ventricular function, and the possible causes of these changes, and introduces the possibility that more vigorous exercise may be needed to improve left ventricular function and reduce rates of cardiovascular disease in people with type 2 diabetes.

Key Points

Diastolic and systolic dysfunction limit cardiac reserve in the diabetic heart.

Autonomic dysregulation appears to limit heart rate reserve and exercising left ventricular contractility.

Cardiac dysfunction begins in early, uncomplicated diabetes and may worsen with diabetes duration and poor metabolic control.

People with diabetes respond to exercise training similarly to non-diabetic subjects but may need more vigorous activity to improve cardiac function.

1 Introduction

People with type 2 diabetes often have lower aerobic capacity ($\dot{V}O_2max$) than their non-diabetic counterparts (reviewed by Green et al. [1]). $\dot{V}O_2max$ is the product of the rate of blood flow through the body, called 'cardiac output' ($\dot{Q}$), and the amount of oxygen extracted by the tissues as blood flows from arteries to veins ($a-\bar{V}o_2$). Therefore, a reduction in $\dot{Q}$, $a-\bar{V}o_2$ or a combination of both must occur to explain the effect of diabetes on $\dot{V}O_2max$. There have been few comparisons of $a-\bar{V}o_2$ in diabetic and non-diabetic subjects during exercise, and their results have been contradictory [2–4]. In contrast, reduced exercising $\dot{Q}$ is a common finding in people with diabetes [2, 5–8].

Resting cardiac output, the product of heart rate and stroke volume, appears normal in people with type 2

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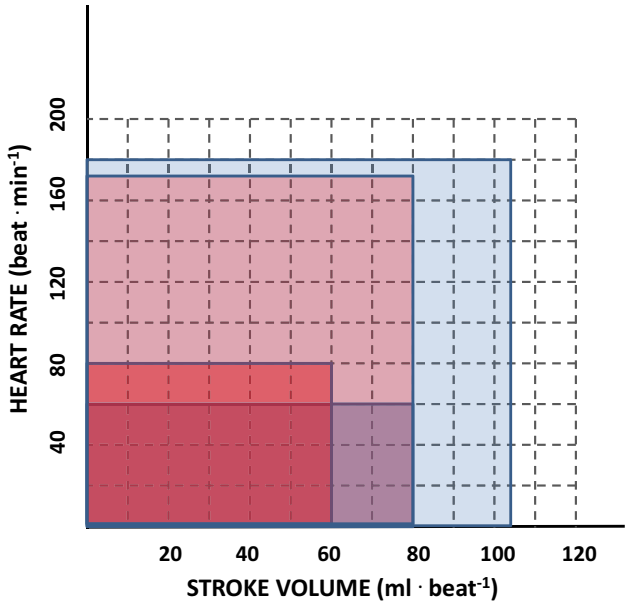

Fig. 1 Effects of type 2 diabetes on left ventricular stroke volume (*horizontal axis*) and heart rate (*vertical axis*) and their contributions to cardiac output ($\dot{Q}$) during rest and peak exercise. *Red:* people with type 2 diabetes; *blue:* non-diabetic controls; *dark shading:* resting; *light shading:* peak exercise. The area resulting from the intersection of the *horizontal* and *vertical* axes = $\dot{Q}$. In this schematic, the area of each dashed square = 200 ml·min^{-1} because it is the product of 10 ml·beat^{-1} (*horizontal axis*) × 20 beats·min^{-1} (*vertical axis*). Note that the resting $\dot{Q}$ (*dark-shaded squares*) is the same in both groups (24 *squares*; 4.8 l·min^{-1}) because a smaller stroke volume is balanced by a higher resting heart rate in the diabetes group. However, during peak exercise, smaller increases in heart rate and stroke volume cause a smaller peak $\dot{Q}$ (*light-shaded squares*) in people with diabetes (~14 l·min^{-1}) than in non-diabetic controls (~18 l·min^{-1})

diabetes. However, people with type 2 diabetes achieve this with a higher heart rate [1] and lower resting left ventricular stroke volume [2, 3, 9, 10] than their non-diabetic, body composition–matched peers. During exercise, heart rate reserve (peak−resting heart rate) is reduced [3, 9, 11–13] and left ventricular stroke volume increases less [3, 9, 14] or does not increase at all [2] in people with diabetes. By attenuating cardiac output during exercise, these changes affect oxygen-carrying capacity and ultimately $\dot{V}O_2$max in people with type 2 diabetes. Figure 1 provides a graphic representation of the contributions of smaller stroke volume and reduced heart rate reserve to decreased cardiac reserve in people with type 2 diabetes.

This review describes the structural and functional changes that alter the performance of the diabetic heart, the role of the autonomic nervous system in causing or compensating for these changes, and how these changes affect exercise performance. Finally, the potential for exercise therapy to affect changes in the diabetic left ventricle is considered.

2 The Diabetic Heart

Impaired left ventricular function in type 2 diabetes has been well described. Using cardiac catheterization, the pioneering work of Regan et al. [10] showed that the resting left ventricular pressure–volume relationship is shifted up and to the left in people with diabetes, and that this occurs independently of ischaemic disease. Regan et al. [10] also found that left ventricular biopsies from patients with diabetes had increased staining for glycoprotein, which we have subsequently learned is a chemically modified advanced glycation end-product, or 'AGE' [15, 16], as has been reviewed elsewhere [17]. These authors and others [18] have shown that increased deposition of AGE increases left ventricular stiffness. Others [19] have shown that increased left ventricular filling pressure and delayed relaxation are evident without AGE accumulation in diabetic and pre-diabetic heart tissue, and more recent studies have suggested that diabetes hyperphosphorylates the trans-sarcomere protein titin, which increases cardiomyocyte stiffness [20]. Because of these morphological changes in the extracellular and intracellular components of the myocardium, increases in left ventricular filling are associated with exaggerated intraventricular pressure development. Consequently, the diabetic heart (1) develops elevated intraventricular pressure to achieve a 'normal' end-diastolic volume; (2) achieves a smaller end-diastolic volume at 'normal' intraventricular pressures; or (3) undergoes some combination of the above. Most studies have shown that resting supine end-diastolic and stroke volumes are smaller in people with type 2 diabetes than in non-diabetic controls [9, 10, 21], and one study has shown that in middle-aged women with type 2 diabetes, resting end-diastolic pressure is comparable to or slightly higher than that in age- and weight-matched non-diabetic women [22]. This suggests that resting left ventricular filling pressures are kept normal, or slightly elevated, at the expense of left ventricular volume.

However, during increased venous return (rapid saline infusion), the canine diabetic left ventricle experiences a significant elevation in pressure without a corresponding increase in end-diastolic volume [23]. Regensteiner et al. [22] showed that pulmonary capillary wedge pressure (indirect left ventricular end-diastolic pressure) rose 40 % more during incremental cycling exercise (increased venous return) in healthy 40- to 60-year-old women with recently diagnosed type 2 diabetes than it did in matched non-diabetic controls. These findings clearly indicated that increased venous return to the heart causes a steeper increase in end-diastolic pressure and smaller end-diastolic volume in the diabetic ventricle than in the non-diabetic ventricle. As a consequence, stroke volume must also be

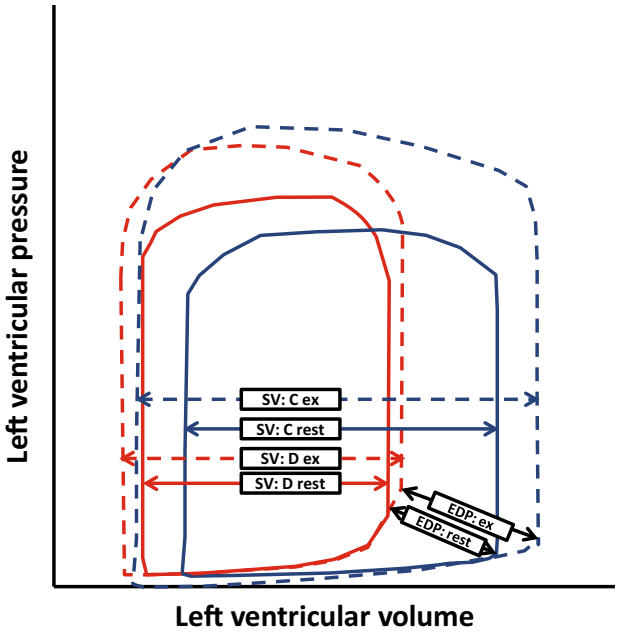

Fig. 2 Resting (rest; *solid lines*) and exercising (ex; *dashed lines*) left ventricular pressure–volume relationships in people with type 2 diabetes (D; *red*) and non-diabetic controls (C; *blue*). These relationships were developed using left ventricular volumes measured with magnetic resonance imaging at rest and during a 36W pedalling exercise [9] and using pulmonary capillary wedge pressures at rest and during a 50W pedalling exercise [22] to generate representative pressure–volume relationships in diabetic and non-diabetic individuals. Note (1) the up- and leftward shift of the resting diabetic curve; (2) the smaller rest-to-exercise increment in stroke volume (SV) and end-diastolic volume in the diabetic curves; and (3) the increase in end-diastolic pressure (EDP) in people with diabetes

smaller during exercise unless contractility increases, causing a comparable reduction in end-systolic volume (Fig. 2).

2.1 Left Ventricular Relaxation and Filling

Left ventricular filling is also influenced by the rate of early diastolic relaxation and the magnitude of left ventricular expansion during diastole. Early left ventricular relaxation is reduced (decelerated) by diabetes [21, 24–27], though the effect of diabetes on diastolic filling capacity (volume) is less clear. At rest, diastole lasts for approximately two thirds of the cardiac cycle [21]. Therefore, during each diastolic period, 70–100 ml of blood (normal resting stroke volume) flows from the left atrium to the left ventricle in 0.66 s (106–152 ml·s^{-1}) in an average human with a heart rate of 60 beats·min^{-1}. However, during exercise at a heart rate of 190 beats·min^{-1}, increased venous return and a preferential reduction in the diastolic filling time (reduced to ~0.10 to 0.15 s) necessitates peak filling rates ranging from 1100 to 1880 ml·s^{-1} in order to produce stroke volumes of 100–200 ml [28]. To achieve this, a large pressure gradient must be quickly established between the atria and the ventricle by rapid relaxation of the ventricle after systole.

At a clinical level, magnetic resonance imaging (MRI) studies of the left ventricle have provided evidence that the relaxation rate is reduced by diabetes in a way that reduces left ventricular filling. Resting supine end-diastolic volume is smaller in patients with diabetes [3, 9, 10, 21], which, as discussed above, may reflect reduced left ventricular compliance [10]. However, during supine exercise at a heart rate of 110 beats·min^{-1}, end-diastolic volume is further reduced in people with diabetes but is maintained in non-diabetic participants [3, 9], suggesting that the diabetic left ventricle cannot increase the rate of relaxation enough to maintain filling in a shortened diastolic filling period. This reduction in end-diastolic volume is associated with a smaller stroke volume at rest and during exercise in uncomplicated diabetes [9, 21]. Lalande et al. [21] found that diastolic duration was shortened in people with diabetes, providing an even greater challenge to ventricular filling in people with type 2 diabetes.

In the cardiomyocyte, systole requires large transient increases in intracellular Ca^{2+}, which allow thick- and thin-filament binding and force generation in the sarcomere. Consequently, left ventricular relaxation requires rapid removal of residual intracellular Ca^{2+} from the previous systolic period to 'disengage' thick and thin myofilaments and provide time for 'recoil' of myocardial tissues. Diabetes appears to slow down the intracellular processes that remove intracellular Ca^{2+}; however, the role of specific Ca^{2+}-handling proteins governing these events is equivocal. Figure 3 summarizes the mechanisms by which intracellular [Ca^{2+}] is reduced by (1) co-transport across the cell membrane through the Na^{+}/Ca^{2+} exchanger (NCX); or (2) being sequestered into the sarcoplasmic reticulum by sarcoplasmic reticular Ca^{2+} ATPase (SERCA). SERCA, in turn, is inhibited by phospholamban (PLB). Animal studies have shown that reduced rates of intracellular Ca^{2+} decay are accompanied by reductions in the SERCA/PLB ratio but not NCX [25, 29], suggesting that impaired cardiac relaxation (diastolic dysfunction) in diabetes originates with a poorly functioning SERCA/PLB system. However, recent studies of the human right atrium have reported an increase [30] or no change [31] in the SERCA/PLB ratio in people with type 2 diabetes, even when the maximum rate of pressure reduction ($-dP/dt$) and the relaxation time constant (τ) are reduced [26]. Therefore, while a reduced rate of cytoplasmic Ca^{2+} decay is well established in the diabetic myocardium, the proteins and cytosolic processes involved, particularly in human tissue, are unclear.

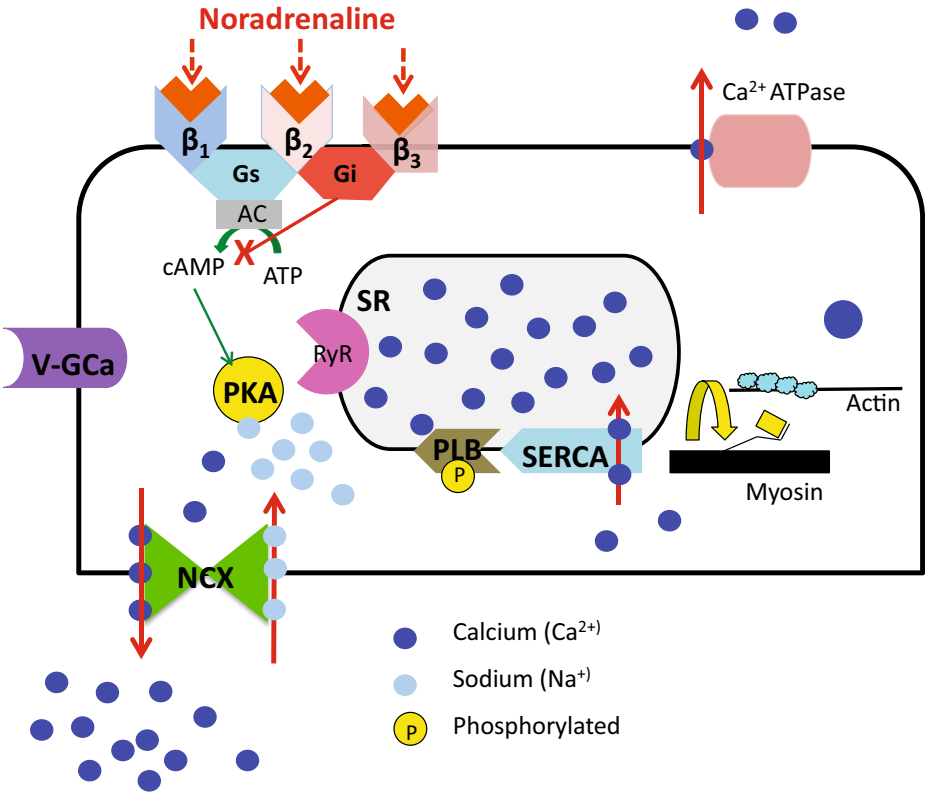

Fig. 3 Cardiomyocyte diastole (relaxation). During diastole, rapid removal of cytoplasmic Ca^{2+} (after the preceding systolic interval) allows cardiomyocyte relaxation. Sarcoplasmic reticular Ca^{2+} ATPase (SERCA) transports cytoplasmic Ca^{2+} into the sarcoplasmic reticulum (SR). The Na^{+}/Ca^{2+} exchanger (NCX) transports Ca^{2+} out of the cell (into the extracellular space), as does Ca^{2+} ATPase, to a smaller degree. Phospholamban (PLB) exists in close proximity to SERCA and inhibits its activity. However, when it is phosphorylated (as shown), the inhibitory action of PLB is abolished. When intracellular Ca^{2+} is reduced in this way, cross-bridge formation is sterically blocked, allowing the cardiomyocyte to return to its resting length and tension (i.e. relaxation). The rate at which these processes occur is increased when noradrenaline binds to β_1-adrenergic receptors (β_1-AR) and β_2-AR linked with stimulatory G proteins (Gs), because Gs activates protein kinase A (PKA), which phosphorylates PLB, increasing the activity of SERCA. In contrast, noradrenaline binding to β_3- and β_2-AR linked with an inhibitory G protein (Gi) slows the transport (flux) of Ca^{2+} because the activity of PKA is reduced. Diabetes reduces the rate of intracellular Ca^{2+} flux; however, it is unclear which Ca^{2+}-handling proteins are involved. *AC* adenylate cyclase, *ATP* adenosine triphosphate, *cAMP* - cyclic adenosine monophosphate, *RyR* ryanodine channel, *V-GCa* voltage-gated Ca^{2+} channel

2.2 Echocardiography of the Diabetic Heart

Intraventricular catheter measurement of pressure decay or end-diastolic filling pressure, which best define the filling characteristics of the left ventricle, are invasive and expensive, and carry some (nominal) risk. Therefore, these measurements are uncommon in uncomplicated diabetes patients. Instead, changes in the ratio of peak early (E) to late (A) mitral inflow velocity (E/A), measured non-invasively with Doppler echocardiography, have been interpreted as 'diastolic dysfunction' in people with diabetes [32]. The rationale for this interpretation is that rapid early diastolic relaxation, by expanding the left ventricle, will quickly generate a large atrioventricular pressure gradient (e.g. suction) through which blood is 'pulled' down to the ventricle (measured as E) during early diastole. Therefore, a high E/A ratio reflects better early relaxation than a low E/A ratio. However, E is also elevated without extensive early relaxation if left atrial volume/pressure is high (ventricular preload). In fact, two patterns of mitral inflow, called 'pseudonormal' and 'restrictive' filling, define poor relaxation with a very high E/A ratio because left atrial pressure is pathologically high [33]. This is particularly important because pseudonormal filling is found in up to 40 % of people with uncomplicated type 2 diabetes [24]. In these examples, the blood is effectively 'pushed' down the atrioventricular pressure gradient by high left atrial pressure, rather than being 'pulled' by rapid ventricular relaxation. Consequently, a high E/A ratio might lead to an interpretation of 'normal' relaxation when, in fact, there is significant diastolic dysfunction.

This 'preload dependency' of mitral inflow velocity has been addressed by measurement of the peak rate of long-axis displacement of the septal and lateral regions of the

mitral annulus during early (E′) and late (A′) diastole. E′ is thought to be a superior and less preload-dependent measurement of early relaxation because it is strongly correlated with $-dP/dt$ and τ in dogs [34], and it is unaffected by preload manipulation (saline and nitroglycerine infusion) in humans [33]. E′ is smaller in people with diabetes [2, 24], which is consistent with slowed ventricular relaxation.

The ratio of E/E′ can also provide information about the diastolic filling pressure of the left ventricle, with strict adherence to important limitations. Ommen et al. [35] found that an E/E′ of >15 was associated with increased mean left ventricular diastolic filling pressure obtained with ventricular catheters, but E/E′ values between 8 and 15 were unrelated to left ventricular pressure [35, 36]. E/E′ is increased in patients with type 2 diabetes [26], but E/E′ values fall between 8 and 15 in studies of patients with uncomplicated diabetes [26, 27]. Therefore, it is unclear whether these changes are associated with differences in left ventricular end-diastolic pressure.

The abovementioned data suggest that increased left ventricular filling pressure [22] and slower early diastolic relaxation [24] may combine to reduce left ventricular end-diastolic and stroke volumes in people with uncomplicated type 2 diabetes. Several studies have suggested that the reduction at rest is sustained or exacerbated [9, 37] during exercise, though some have contradicted this [1]. These findings should be interpreted with the knowledge that exercise echocardiography is often less accurate than resting measures and that MRI measurements require short pauses (of 5–10 cardiac cycles) in exercise in order to acquire measurements of left ventricular volume. In addition, most imaging methods are ineffective in obtaining accurate measurements over a heart rate of 120 beats·min^{-1} [38]. One study used acetylene rebreathing, which acquires cardiac output up to near-maximal exercise intensities in 'real time', to show that elite athletes with poorly controlled type 1 diabetes have reduced stroke volume during peak exercise [8]; however, no such studies have been conducted in people with type 2 diabetes, and this method does not allow researchers to determine the independent effects of end-diastolic and/or end-systolic volume. With these caveats, diabetes-specific impairment in left ventricular relaxation and filling appears to contribute to a reduction in cardiac reserve by reducing stroke volume, but additional studies are needed at higher exercise intensities.

2.3 Systolic Function

Animal models of diabetes have described a stepped deterioration in left ventricular function, beginning with increased left ventricular stiffness and diastolic dysfunction, followed by systolic impairment [39]. This 'duration-dependent' progression may explain equivocal findings regarding the effects of type 2 diabetes on left ventricular systolic function in humans. In early-stage type 2 diabetes, there are numerous reports in humans and animals showing improved resting systolic function [9, 40–42]. However, in people with longer diabetes duration or diabetic comorbidity, diabetes has no effect [21, 43–45] or impairs left ventricular systolic function [37, 44, 46].

A more consistent finding, which appears to be independent of diabetes duration, is that the systolic response to exercise or sympathetic stress (i.e. systolic reserve) is attenuated in people with type 2 diabetes [9, 37, 44, 47–50]. Both early-stage diabetic adolescents with a high resting ejection fraction [9] and older people with more established diabetes [44, 47] are less able to increase the ejection fraction during exercise. The systolic response to controlled β-adrenergic stimulation (dobutamine) is also reduced in people with uncomplicated type 2 diabetes [50, 51]. These data suggest that stress 'unmasks' systolic abnormalities that are not evident in resting echocardiography studies [47, 50]. Moreover, a reduced systolic reserve may compound the effects of diastolic dysfunction in reducing cardiac reserve and aerobic capacity in people with early, uncomplicated type 2 diabetes.

3 A Role for the Autonomic Nervous System

Increased contractility and elevations in heart rate above the intrinsic rate of the cardiac pacemaker (e.g. systolic reserve) are achieved by sympathetic nervous or adrenal medullar release of catecholamines (primarily norepinephrine and epinephrine) in the myocardium; catecholamine binding and stimulation of β-adrenergic receptors (β-AR) on the myocardial cell membrane; and β-AR-mediation of cardiomyocyte function by activation of intracellular signalling pathways [52, 53]. These processes have been reviewed in detail [54] and are summarized in Fig. 4. An interruption or defect in any of these three steps will limit capacity to increase cardiac output during stress unless the other steps in this pathway compensate. In the context of this review, it is necessary to understand the effects of diabetes on (1) central sympathetic signalling to the heart; (2) β-AR responsiveness; and (3) the intracellular events that stimulate/inhibit systolic work, sometimes called 'excitation–contraction coupling'.

3.1 Central Sympathetic Signalling

Cardiac autonomic dysfunction or neuropathy is a well-described clinical consequence of prolonged, poorly controlled diabetes that affects resting heart rate, heart rate

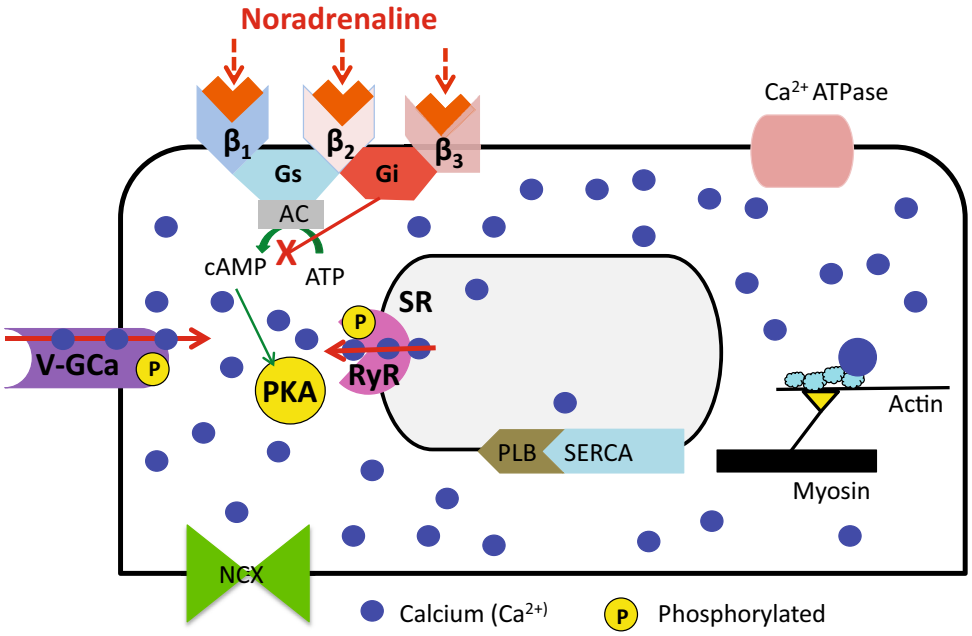

Fig. 4 Cardiomyocyte systole (excitation). During systole, depolarization of the cell membrane activates the voltage-gated Ca^{2+} channel (V-GCa), which transports Ca^{2+} into the cytoplasm from the extracellular space. The resultant increase in Ca^{2+} then activates the ryanodine channel (RyR), which transfers Ca^{2+} from within the sarcoplasmic reticulum (SR) into the cytoplasm (calcium-induced calcium release). These processes are increased when protein kinase A (PKA) phosphorylates these protein channels through β_1-adrenergic receptor (β_1-AR) binding and sometimes β_2-AR binding, but is inhibited by β_3-AR activation. Elevated Ca^{2+} in the cytoplasm binds to, and conformationally alters, the thin filament of cardiac sarcomeres, allowing cross-bridge binding and (if adenosine triphosphate [ATP] is present) contraction. *AC* adenylate cyclase, *cAMP* cyclic adenosine monophosphate, *Gi* inhibitory G protein, *Gs* stimulatory G protein, *NCX* Na^+/Ca^{2+} exchanger, *PLB* phospholamban, *SERCA* sarcoplasmic reticular Ca^{2+} ATPase

reserve, heart rate variability and baro- and metabo-receptor responses [39, 55–57]. However, many of these characteristics may also contribute to impaired cardiac reserve in healthy, non-neuropathic people with type 2 diabetes. Elevated resting heart rate [21, 58], reduced heart rate reserve [2, 3, 9, 21] and reduced heart rate variability [59–61] are commonly described in people with uncomplicated or recently diagnosed type 2 diabetes. In fact, Carnethon et al. [62] found that healthy middle-aged adults with a resting heart rate in the highest quartile or low-frequency heart rate variability in the lowest quartile were up to 60 % more likely to develop diabetes over an 8-year follow-up period. These authors and others [61, 63–65] have suggested that subclinical 'sympathetic hyperactivity' precedes and contributes to insulin resistance/diabetes.

Thaung et al. [66] recently used direct recordings of the left cardiac sympathetic nerve to show that the type 2 diabetic rat ventricle receives 45 % more cardiac sympathetic nerve activity than the non-diabetic rat ventricle at rest. Direct recordings of cardiac nerves are not possible in humans; however, single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging of radio-labelled compounds can describe the pre- and post-synapse activity of cardiac sympathetic nerve endings. Reduced uptake of iodine-123-metaiodobenzylguanidine (^{123}I-MIBG), which results from chronically elevated sympathetic activity in the heart [39, 67, 68], has been reported in patients with type 2 diabetes [68, 69]. Scognamiglio et al. [70] also found that reduced uptake of ^{123}I-MIBG occurred in patients with type 1 diabetes who had a blunted contractile (ejection fraction) response to handgrip exercise and dobutamine stress. These data in animals and humans suggest that sympathetic nervous signalling to the diabetic heart is elevated. The following sections attempt to explain how increased sympathetic excitation of the heart, which acutely increases left ventricular contractility, paradoxically reduces the systolic reserve of the diabetic heart in the longer term.

3.2 β-Adrenergic Receptor Responsiveness

The healthy human heart contains primarily β_1-AR and β_2-AR in a ratio of approximately 70:30 % [71, 72], with a small (<5 %) population of β_3-AR [73]. β_1-AR are linked with a regulatory guanine nucleotide binding 'G' protein, which stimulates (Gs) inotropic, chronotropic and lusitropic functions of the heart through a series of reactions governing Ca^{2+} flux in the cardiomyocyte (Fig. 4) [54]. In

contrast, β_3-AR are linked to an inhibitory G protein (Gi), which inhibits these effects [73], and β_2-AR can be linked to either Gs or Gi. Chronically elevated cardiac sympathetic activation phosphorylates and then downregulates β_1- and sometimes β_2-AR in animals and humans [71, 74]. This attenuates the 'stimulatory' left ventricular responses to β-adrenergic stimulation and has been linked to the development of heart failure [72]. Thaung et al. [66] found that increased sympathetic activity in healthy type 2 diabetic rat hearts was associated with downregulated β_1-AR and Gs but upregulated β_2-AR and Gi. Other studies in animals [75–77] and humans [78] have shown that β_1-AR is downregulated in type 2 diabetes, sometimes with a corresponding increase in β_3-AR [75, 79]. These data suggest that diabetes reduces 'β-AR responsiveness' by a proportional reduction in β_1-AR-mediated 'stimulatory' actions and an increase in β_3-AR-mediated 'inhibitory' actions.

There are also clinical examples of reduced β-AR responsiveness in type 2 diabetes. Vinereanu et al. [50] found that healthy people with type 2 diabetes had a smaller increase in longitudinal peak systolic velocity during dobutamine (β-AR agonist) infusions than controls. Similarly, dobutamine increased the ejection fraction in non-diabetic controls but not in type 1 diabetic participants [70]. However, when the same participants were exposed to post-extrasystolic potentiation (electrically stimulated myocardial contraction), the control and diabetic groups had a comparable increase in ejection fraction. These studies show that ineffective β-AR stimulation, possibly resulting from downregulation of stimulatory β_1-AR/Gs, reduces the contractile response of the diabetic heart, even when intrinsic contractile capacity is intact.

3.3 Excitation–Contraction Coupling

A final explanation for the reduced systolic reserve in diabetes is that the intrinsic contractile properties of the diabetic cardiomyocyte are reduced. Animal models of type 2 diabetes have consistently shown that total force production and the peak rate of force production are reduced in type 2 diabetic cardiomyocytes [25, 80–82] and that this is explained by attenuated but prolonged intracellular Ca^{2+} flux [25, 31, 82] and reductions in sarcoplasmic reticular Ca^{2+} cycling proteins [25, 82, 83]. In contrast, it has been confirmed in chemically skinned left ventricular cells from coronary bypass patients with and without type 2 diabetes that diabetic cardiomyocytes have reduced Ca^{2+} sensitivity, but these cells produce a maximal Ca^{2+}-saturated force similar to that of non-diabetic cells [84]. The maximum developed force and the maximum rate of force development ($+dP/dt$) are also the same in right atrial trabeculae from cardiac surgery patients with and without type 2 diabetes [26] and right atrial muscle strips from diabetic and non-diabetic patients, despite a prolonged elevation in intracellular Ca^{2+} [31].

It is worth noting that comparisons of human diabetic and non-diabetic cardiomyocytes have been limited to tissue from people with cardiovascular disease, while animal studies have been conducted in left ventricular tissue from animals without cardiovascular disease. Nonetheless, these findings suggest that the contractile potential of the human diabetic myocardium, even in tissues from patients with ischaemic cardiac disease, is normal. Consequently, reductions in systolic reserve appear to result from impaired cardiac sympathetic signalling or reduced β-adrenergic responsiveness, but there are, at present, no data to support a diabetes-specific change in the cardiomyocyte contractile apparatus.

3.4 Parasympathetic Dysregulation of the Diabetic Heart?

An obvious omission in the sympathetic hyperactivity hypothesis is any mention of parasympathetic dysregulation. This likely reflects the fact that our knowledge of the effect of diabetes on the parasympathetic innervation of the heart is poor and is based on indirect measurements. Parasympathetic nervous activity has its greatest effect on heart rate, with only moderating effects on contractility [85]. Ewing et al. [86] suggested that parasympathetic impairment preceded sympathetic impairment in patients with diabetes, on the basis of hemodynamic responses (in heart rate, blood pressure and R–R variability) to a series of tests including the Valsalva manoeuvre, handgrip exercise and controlled breathing [87]. Similarly, heart rate variability, which has been attributed (primarily) to parasympathetic innervation of the heart [88–90], is reduced in diabetes [14, 59–61].

If the assumptions/limitations of heart rate variability measurements [88, 91] are accepted, it seems likely that a relative reduction in parasympathetic activity in the diabetic heart contributes to the increase in resting heart rate, and possibly reduced heart rate recovery [92], commonly seen in diabetes. However, an important role for parasympathetic dysregulation in peak heart rate or systolic reserve in diabetes seems unlikely. For example, parasympathetic nervous input into the heart does not independently affect contractility but attenuates the contractile response to sympathetic stimulation [85]. Therefore, reduced parasympathetic activity would increase contractility during stress. Similarly, attenuated parasympathetic input during stress would, in theory, be associated with an increase in peak heart rate, instead of the lower peak heart rate and contractility reported in patients with diabetes.

4 Exercise Recommendations, Lifestyle Interventions and the Diabetic Heart

Virtually every international health organization recommends diet, exercise and glycaemic control for prevention of diabetes-related morbidity. In the largest prospective trial of type 2 diabetes (the United Kingdom Prospective Diabetes Study [UKPDS]), intensive glycaemic control dramatically reduced microvascular complications for up to 10 years after intervention [93–95]. However, UKPDS [93, 94] and other prospective trials [96–98] showed that glycaemic control did not improve cardiovascular outcomes, and two studies have suggested that intensive glycaemic control causes a small but statistically significant increase in cardiovascular mortality [99, 100]. It is also unclear whether regular exercise improves cardiac function for people with diabetes.

Exercise training, in theory, is an excellent method of preventing or reversing diabetic cardiac dysfunction and morbidity. The Dallas Bed Rest and Training Study demonstrated that regular exercise training increases $\dot{V}O_2$max, stroke volume and cardiac output in deconditioned humans [101]. Moreover, cardiovascular risk is inversely proportional to $\dot{V}O_2$max [102] and exercise training intensity [103]. Type 2 diabetes is characterized by left ventricular dysfunction, reduced cardiac reserve and increased incidence rates of cardiovascular disease and heart failure [104]. Consequently, patients with diabetes are, in theory, an ideal cohort for effective exercise training interventions.

Historically, exercise training has resulted in equal [105–107] or greater [108] relative increases in $\dot{V}O_2$max for people with type 2 diabetes in comparison with non-diabetic controls. Considering the predisposition for cardiovascular disease in patients with diabetes, it is surprising that few studies have examined whether exercise training effectively reduces cardiovascular morbidity or affects left ventricular performance in people with type 2 diabetes. The Look Ahead Trial found that 1 year of intensive diet and moderate-intensity exercise improved body composition and glycaemic control for up to 10 years but had no effect on cardiovascular or all-cause mortality [109]. Other researchers who have combined dietary interventions with moderate-intensity exercise have concluded that physical activity provides 'no additional health benefit' to diet alone [110–112].

4.1 A Need for More Vigorous Exercise?

The abovementioned studies suggested that exercise cannot affect the cardiac consequences of diabetes. Another explanation for the lack of cardiovascular benefit in these studies may be that moderate-intensity exercise, as described in many exercise guidelines [113–115], provides insufficient exercise stimulus to elicit changes in cardiovascular function. In fact, opponents of moderate-intensity exercise recommendations point out that numerous studies, including those used to form the abovementioned guidelines, have shown that vigorous activity (≥6 metabolic equivalents [METs]), but not moderate-intensity activity (<6 METs), reduces the incidence of cardiovascular events [103, 116–120].

Over 30 years ago, we learned that moderate-intensity exercise training induced modest increases in $\dot{V}O_2$max in cardiac patients, which were attributed to peripheral adaptations [121–124]. The interpretation of these findings was that cardiac function could not be improved in these patients. However, Hagberg et al. [125] found that longer interventions using vigorous exercise were safe, induced greater increases in $\dot{V}O_2$max and improved left ventricular stroke volume and stroke work in cardiac patients, confirming earlier findings in healthy adults [126, 127]. More recently, Wisløff et al. [128] showed that high-intensity interval training (HIIT), which incorporates short bursts of very intense activity separated by moderate-intensity 'recovery' intervals, improves left ventricular contractility and reverses left ventricular remodelling in heart failure patients.

No study has conclusively determined whether similarly high-intensity exercise interventions can prevent/reverse cardiac dysfunction in people with type 2 diabetes. Cassidy et al. [129] found that 12 weeks of HIIT increased stroke volume and peak early diastolic filling rates in a small group of patients with type 2 diabetes, suggesting that appropriate forms of exercise training may alter left ventricular function in people with diabetes. As future research examines the efficacy of HIIT, it will be important to establish whether these types of activity will be safe or well adhered to in this population. We are unaware of any data quantifying the safety of high-intensity exercise in patients with diabetes; however, Rognmo et al. [130] evaluated the risk of moderate versus intense aerobic exercise in cardiac patients and found that the rates of cardiac complications were 1 per 129,466 moderate-intensity training hours versus 1 per 23,182 high-intensity training hours. Vigorous exercise may 'protect' against the nocturnal hypoglycaemia reported after moderate-intensity exercise in insulin-dependent diabetes [131]. It is also worth noting that exercise recommendations for cardiac patients have encouraged vigorous exercise for decades, on the basis of the reasoning that a very low risk of adverse events is outweighed by the benefits of regular vigorous activity [132]. Two small studies have suggested that HIIT training is enjoyable [133] and efficacious [134] in obese 'pre-diabetic' individuals. Large, longitudinal evaluations of the

effects of high- versus moderate-intensity exercise training on left ventricular function and long-term cardiovascular morbidity are needed to determine whether high-intensity exercise is well tolerated and safe, and can prevent or reverse the cardiac consequences of type 2 diabetes.

5 Conclusion

Type 2 diabetes reduces the performance of the left ventricle, particularly during exercise. Structural and functional changes in the diabetic heart—such as AGE accumulation, increased left ventricular stiffness and impaired relaxation—appear to play a role in reducing the performance of the diabetic left ventricle. It also appears that reduced systolic function during exercise, caused by altered sympathetic input into the heart and/or reduced responsiveness of β-AR in the diabetic myocardium, may contribute to reduced cardiac reserve. A consistent reduction in heart rate reserve, which may be linked to autonomic dysregulation, also limits capacity to increase cardiac output, and thus aerobic capacity.

Exercise training is the obvious treatment for patients with diabetes. People with type 2 diabetes appear to be capable of increases in relative $\dot{V}O_2$max equal to those seen in their non-diabetic counterparts. Despite this, there is no evidence that exercise training adhering to moderate-intensity exercise guidelines can improve cardiac performance or reduce cardiovascular morbidity. Existing evidence suggests that moderate-intensity exercise, which improves metabolic and microvascular outcomes, provides an insufficient exercise stimulus to affect diabetes-specific changes in left ventricular performance or autonomic balance. HIIT shows promising results in people with diabetes or metabolic syndrome; however, larger controlled trials, accounting for the independent effect of obesity on the heart [2, 27], are needed. It must also be determined whether this type of exercise will be adhered to by patients with type 2 diabetes.

Compliances with Ethical Standards

Conflict of interest J. Chris Baldi, Genevieve A. Wilson, Luke C. Wilson, Gerard T. Wilkins and Regis R. Lamberts declare that they have no conflicts of interest that are directly relevant to the content of this article.

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