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Left Ventricular Diastolic Function in Athletes

Linksventrikuläre diastolische Funktion beim Athleten

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ZUSAMMENFASSUNG

Die diastolische Funktion des linken Ventrikels ist ein komplexes physiologisches Phänomen, bestehend aus intrinsischer Relaxation, Vorhofsystole und Compliance. Die Messung der Funktion des linken Ventrikels ist schwierig aufgrund multipler intrinsischer Eigenschaften sowie extrinsischen Faktoren, die für die Ventrikelfüllung verantwortlich sind. Trotzdem tragen neue Erkenntnisse über die Funktion des linken Ventrikels zu einem besseren Verständnis der kardiovaskulären Gesundheit bei. Die Funktion des linken Ventrikels spielt eine wichtige Rolle für die Pumpfunktion des Herzens und ist deshalb entscheidend für ein hohes Maß an kardiovaskulärer Fitness und Ausdauerleistungsfähigkeit. Dieser Übersichtsartikel beschäftigt sich zunächst mit der Definition der Diastole, der zugrunde liegenden mechanischen Prozesse sowie der quantitativen Erfassung der diastolischen Funktion, einschließlich neuer echokardiologischer Bildgebungsverfahren. Im Hauptteil des Artikels werden die Studienergebnisse vorgestellt, die mittels Doppler, Gewebe-Doppler und anderer relevanter Methoden die linke ventrikuläre Funktion darstellen. Zusammengefasst gibt es eindeutige Hinweise dafür, dass Ausdauerathleten eine erhöhte diastolische Funktion aufweisen. Dies bezieht sich auf eine erhöhte frühe Relaxation, Füllung und Compliance. Kontroverse Ergebnisse und Limitationen der aktuellen Studien werden präsentiert und Forschungsdefizite werden aufgezeigt.

Schlüsselwörter: Echokardiographie, Übungen, kardiovasulär, Training.

SUMMARY

Left ventricular (LV) diastolic function is a complex physiological phenomenon involving intrinsic relaxation, atrial systole and compliance. Likewise, LV diastolic function is difficult to assess because of multiple intrinsic components as well as external factors that mediate LV filling. Despite these issues knowledge of LV diastolic function is vital to our understanding of overall cardiac health and performance. LV diastolic function plays a key role in the enhancement of overall cardiac pumping capacity that underpins high levels of cardio-respiratory fitness and endurance performance. This brief review presentation will initially address the definition of diastole and the mechanical processes that occur during the diastolic period as well as the quantitative assessment of diastolic function, including recent developments in echocardiographic imaging modes. In the main section, we will document evidence for enhancement of LV diastolic function in athletes using Doppler, tissue-Doppler, strain and other relevant methods. Cross-sectional athlete-control data will be critiqued as will a smaller database from longitudinal training studies. Overall, there is some evidence of enhanced diastolic function in endurance athletes. This pertains to augmented early relaxation and filling as well as increased compliance. However, contradictory evidence is noted and a number of limitations will be discussed. Finally, we will provide conclusions and directions for on-going study.

Key Words: Echocardiography, exercise, cardiovascular, training.

INTRODUCTION

Diastole, in relation to the left ventricle (LV), is defined as the period from aortic valve closure (AVC) to mitral valve closure (MVC). The complex physiological, mechanical, electrical components of diastole actually begin during the latter stages of systole, through isovolumic relaxation, early filling, diastasis and atrial contraction. Diastolic function of the LV comprises early relaxation and compliance that serve to facilitate an atrial to ventricle pressure gradient which allows blood to fill the LV. The processes of relaxation and compliance are themselves complex. Early relaxation begins in systole even before AVC and continues through isovolumic relaxation and early filling. Compliance overlaps with early relaxation as blood moves into the LV and is also important in relation to atrial systole that later in diastole "tops-up" LV volume prior to MVC. It is, of course, also important to note that as well as intrinsic LV tissue properties there are a number of extrinsic factors that exert some influence over LV diastolic function.

Diastolic function, in a closed loop system, will largely determine LV output. Indeed, when LV output is maximised during intense physical effort we now know that an enhanced diastolic function is crucial and several reports have suggested that high levels of cardio-respiratory fitness are supported by augmented diastolic filling (22). Conversely, when cardiac function is depressed, as in various disease states we know that diastolic dysfunction is often an important and early marker of disease progression (13). With impaired relaxation, LV filling shifts to late diastole and becomes more dependent on left atrial systolic function. This accounts for the marked clinical deterioration that is often seen in cardiac patients with diastolic dysfunction.

Whilst we understand the broad importance of diastolic function, the relative complexity (compared to systole) of the physiology and mechanics of LV motion before and during filling has meant diastolic function has been difficult to comprehensively measure or characterise. Whilst previous research and reviews (9,24) have aided our understanding, on-going developments in the ability to non-invasively image the heart (14,18) continue to provide new insight. These imaging modalities in turn have been used to interrogate the impact of exercise training on LV diastolic function, which provides the major focus of this short review.

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DIASTOLIC FUNCTION: ASSESSMENT

Given that the interaction of myocyte relaxation, compliance and atrial systole are important events during diastole a comprehensive assessment is challenging. A clear understanding of the mechanics of LV relaxation is a useful starting point in the mission to assess diastolic function. In LV systole, myocytes contract in numerous layers of fibres that lie in an oblique double helical pattern (12). Contraction produces LV rotation/twist, radial thickening and longitudinal shortening that stores energy within the collagen matrix (59) and titin (11). Before AVC the stored pressure is released and the LV untwists. Untwisting continues through the isovolumic period and into early diastole. This is a sentinel event in reducing LV pressure that allows the LV to fill at low left atrial pressures (LAP) as well as developing an intra-ventricular pressure gradient (Fig. 1). This process produces a "suction" effect and underpins peak early filling blood flow velocity as well as preceding radial and longitudinal expansion (33,35). After early filling a period of diastasis occurs when little blood flow occurs across the mitral valve. Diastasis is followed by atrial contraction, consequent to the ECG P-wave. This produces a small rise in left atrial pressure and results in late, or atrial, flow and serves to top-up LV volume. At rest in young healthy adults about 2/3 of blood flow across the mitral valve occurs in early diastole and the ratio of peak blood flow velocities in early (E) and atrial (A) filling is c.1.5 - 2.5 (48).

The ability to accurately reflect LV diastolic function non-invasively has largely fallen upon echocardiography, especially since the development of Doppler imaging tools in the 1980's. Doppler echocardiography visualises blood flow velocity and has been widely used to evaluate LV diastolic function non-invasively (34,48). As well as quantitatively assessing peak flow velocities in E and A phases, and calculating the E/A ratio, this technique is also used to assess timing events such as the duration of isovolumetric relaxation and the decay or deceleration time of the E wave. Other uses of Doppler imaging include the visualisation of pulmonary venous blood flow into the left atria which can also inform the global picture of LV diastolic function. The E/A ratio is relatively easy to measure and is useful in giving an overview of diastolic function. Indeed if the E/A ratio is normal and the left atrial volume is normal ($<34\,ml/m^2$), then this usually indicates normal LV diastolic function (Fig. 2a). If the E/A ratio is <0.8, this may indicate LV diastolic dysfunction (Fig. 2b), although care must be taken over interpretation of the E/A ratio that declines with age. Even when the E/A ratio is ≥0.7 pseudonormalisation should be ruled out as a consequence of elevated LAP (5,28,48).

In the last 15 years the Doppler principle has also been applied to the assessment of the LV walls to determine the velocity of tissue movement in diastole. By placing the Doppler sample volume in different areas of the LV wall this technique allows the assessment of regional diastolic function and is believed to be indicative of regional relaxation (39). Myocardial velocities corresponding to early diastole (E') and late diastole (A') are measured and can be used to grade diastolic function. Septal wall E' ≥ $8\,cm.s^{-1}$ and lateral wall E' ≥ $10\,cm.s^{-1}$ and an LA volume $<34\,ml/m^2$ indicates normal diastolic function (Fig. 3a). Septal E' < $8\,cm.s^{-1}$ and a lateral wall E' < $10\,cm.s^{-1}$ and an LA volume ≥ $34\,ml/m^2$ indicates diastolic dysfunction (Fig. 3b; 5,28,48). A combination of E and E' (E/E') has been shown to correlate with capillary wedge pressure and hence LAP in cardiac patients (27,53). This is useful in that E/E' ≤ 8 indicates normal LAP and hence normal LV diastolic function (Fig. 3a), whereas an E/E' of 9 - 14 with an enlarged LA may indicate diastolic dysfunction. A septal E/E' ≥ 15 or lateral E/E' ≥ 12 indicates raised LAP and abnormal LV diastolic function (Fig. 3b). E/E' aids in the differentiation between normal and pseudo-normal diastolic function (5,28,48).

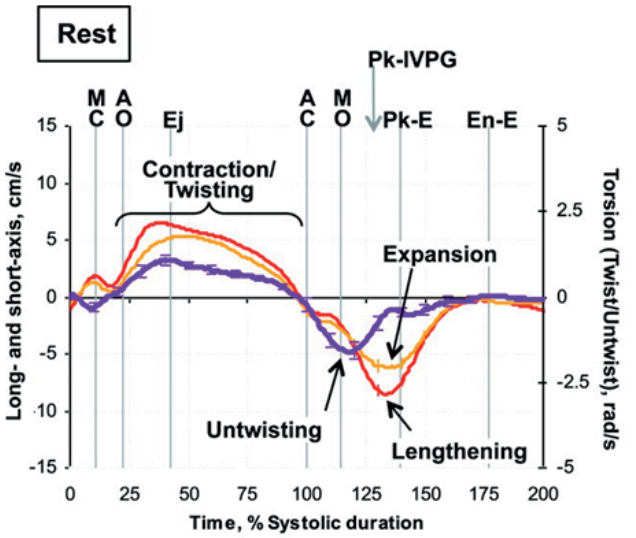

Figure 1: Schema of LV rotation at the base, mid-wall and apex that produces LV twist that begins before isovolumetric relaxation and precedes radial and longitudinal expansion (adapted and reproduced from Notomi et al. 35 permission granted).

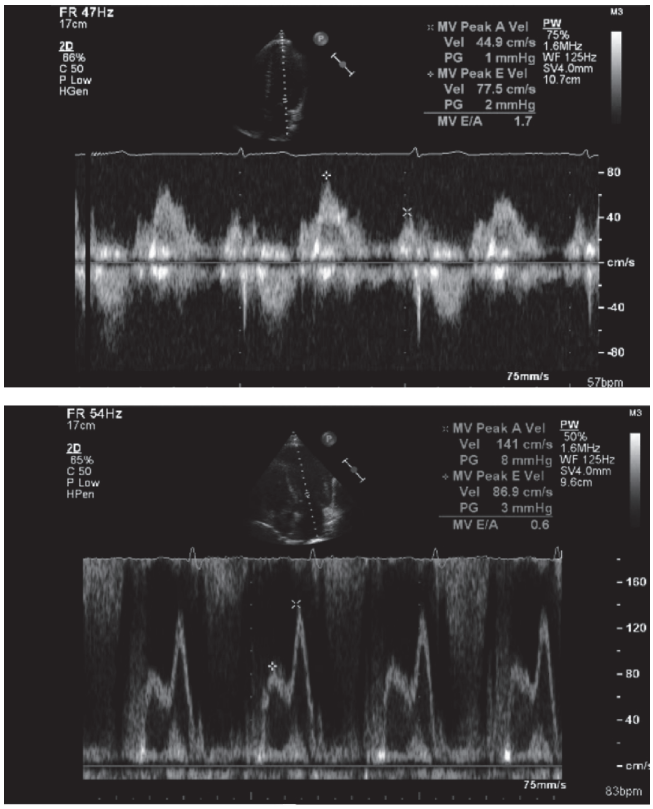

Figure 2: Exemplar Doppler transmitral flow images taken from an athlete. (a), note the E/A ratio of 1.7, and a patient with hypertrophic cardiomyopathy (b), note the reversed E/A ratio of 0.6.

Whilst providing substantial insights into LV diastolic function, Doppler imaging has well known limitations. Preload-dependence of Doppler and tissue-Doppler parameters has been well documented (47) as has an association with heart rate (HR) (10). Angle-dependence of Doppler signals is also clear as are problems with tethering and translation (9). Consequently, imaging developments have continued to search for the ability to assess the complex 3D motion of the LV during diastole. Interest has recently been focused on strain and strain rate analysis (26). Speckle-tracking analysis of 2-D images (Fig. 4) provides strain and strain rate data with the benefit of angle-independence (26). This technique can generate longitudinal, radial and circumferential strain across the cardiac cycle and provide data for diastolic strain rate in early and atrial phases. Generation of rotational strain and strain rate at the base and apical levels of the LV has further precipitated the assessment of twist (torsion) and untwist data (15).

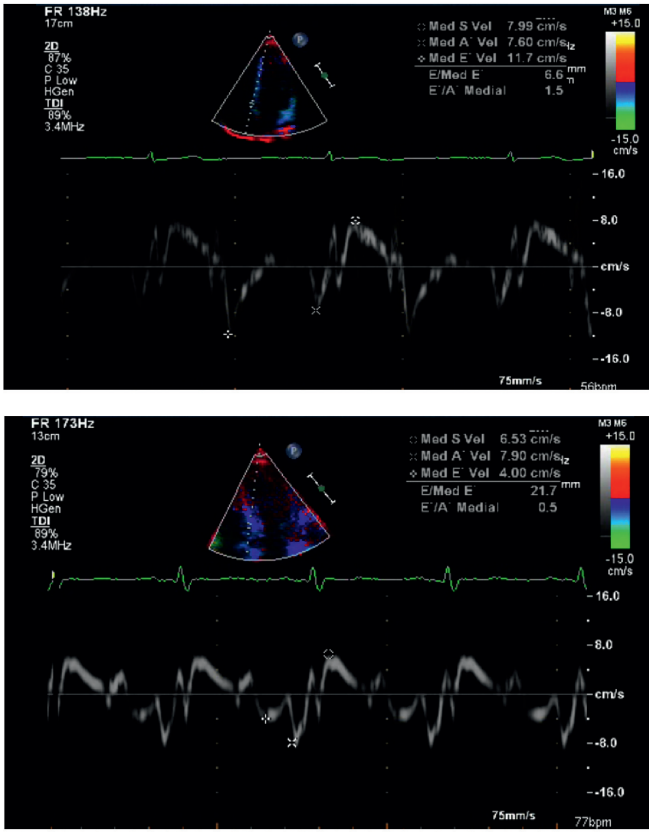

Figure 3: Exemplar tissue-Doppler images taken at the septal wall in an athlete (a), note the positive E'/A' ratio of 1.5 and the E/E' ratio of 6.6, and a patient with hypertrophic cardiomyopathy (b), note the reversed E'/A' ratio of 0.5 and the elevated E/E' of 21.7.

DIASTOLIC FUNCTION IN ATHLETES

Acute exercise is a strong stimulus for muscular adaptation and there is substantial evidence that cardiac morphology and output are altered by exercise training (10). In a closed circulation, when cardiac output increases with acute exercise and is matched by enhanced LV diastolic filling (24), there is a strong rationale that LV diastolic function may change with repeated exercise exposures. Since the advent of Doppler technology the study of diastolic function in the athletic heart has advanced significantly with most evidence coming from cross-sectional athlete-control studies using non-invasive imaging at rest. This data will be reviewed first followed by a smaller number of studies that have used invasive tools or longitudinal research designs.

Cross-sectional data

Most initial cross-sectional studies to address athlete-control differences in LV diastolic function have interrogated trans-mitral Doppler flow patterns. A number of these studies were summarised in a large meta-analysis (44) that also assessed cardiac morphology and ejection fraction data. In groups of endurance-, resistance- and mixed-training athletes and healthy controls, Pluim et al. (44) reported that the E/A ratio was either normal or slightly, but not significantly, enhanced in athletes compared to controls. Any potential change in the E/A ratio in athletes could be the result of an increase in peak E wave velocities in athletes (16) or a decrease in peak A filling velocities. Further, whether changes in E and A velocities reflect augmented intrinsic function or alterations in loading or heart rate is also difficult to determine. Even when MRI has been employed to compare diastolic filling in athletes and controls contrasting data has been reported in terms of statistical significance (42,43). A more recent systematic review (20) suggested that an enhanced E/A in athletes is largely due to a reduced resting HR. A HR-independent augmentation of diastolic flow data may only be apparent in older athletes (20).

Recent cross-sectional data using TDI analysis of septal or lateral wall motion in athletes has also produced some evidence of enhanced peak early (E') or reduced atrial (A') tissue velocities compared to controls (3,6,8,17,36,40,45,46,51,58,60). Despite more substantive evidence of augmented diastolic function in athletes using TDI this Doppler technique is still load and rate-dependent and has almost exclusively assessed longitudinal motion only.

Data from strain and strain rate imaging are very limited and are often inconclusive, with respect to comparisons to controls (7). Teske et al. (56) observed no differences in LV strain data in athletes compared to controls, and in a follow-up study noted decreased right ventricular strain data in athletes compared to controls (55). Nottin et al. (37) reported no differences in peak untwisting during early diastole between trained cyclists and controls. It is interesting to note that normal diastolic function was maintained in the athletes despite reduced systolic apical shear strain and torsion. Nottin et al. (37) concluded that athletes may possess an increased shear strain "reserve", capable of being called upon to assist with ejection and diastolic filling during acute bouts of exercise (37). It is likely that as 2D strain imaging becomes more commonplace in research laboratories and clinical practice that new data will be presented to explore LV diastolic function in athletes.

Non-invasive imaging studies of LV diastolic function are relatively common but are limited by their lack of direct measures of LV pressure and compliance. Using a mixture of invasive and non-invasive tools LV compliance was assessed during saline infusion and lower-body negative pressure to modulate ventricular filling pressure (1,23). Both young and old endurance-trained athletes exhibited greater stroke volumes, than controls, at the same pulmonary capillary wedge pressure. This adaptation suggests that that endurance training improved ventricular compliance. Further support was provided by Stickland et al. (54) who observed that LV filling

pressures were lower in athletes versus controls at similar submaximal stroke volumes. Filling pressures remained lower in athletes at maximal exercise, when stroke volume and end-diastolic volume were significantly higher than in controls.

Taken together, the reviews and empirical studies described above suggest that exercise training is associated with enhanced diastolic function probably mediated by a combination of enhanced early relaxation and increased LV compliance.

Longitudinal data

Cross-sectional comparisons of athletes and controls have provided some interesting, but sometimes conflicting, insights into the response of LV diastolic function to exercise training. Cross-sectional research designs are limited in that significant self-selection bias may occur and the ability to separate the influence of training from genetic predisposition is virtually impossible. To address this requires longitudinal training studies. Given the time, expense and complexity of longitudinal designs it is no surprise that there have been relatively few training or detraining studies in either athletes or previously untrained individuals assessing changes in LV diastolic function.

Despite a more powerful research design the available data are still contradictory. Sadaniantz et al. (50) observed no change is Doppler E/A, despite a decrease in resting HR, in 27 sedentary men who underwent 1 year of endurance training. Conversely, Rodrigues et al. (49) reported an increase in septal and lateral wall E' tissue velocities after 6 months of aerobic training in healthy men. Similarly, a recent MRI study reported that 3 months of endurance training in previously sedentary individuals enhanced global and regional diastolic relaxation (19). In paediatric populations, similar study-to-study differences have also been observed (32,38). Recent data from Baggish et al. (2) suggested that training mode may also mediate changes in LV diastolic function. Competitive university endurance athletes (rowers), trained for a period of 3 months, and demonstrated improvements in E' in both the LV and RV, whereas strength trained athletes (American football players) exhibited significant reductions in diastolic tissue velocities over the same time period (2). The authors concluded that endurance exercise induces biventricular dilation accompanied by enhanced diastolic relaxation. The impact of resistance training could diminish diastolic function but further research is required to confirm this isolated finding. Finally, diastolic function may also vary according to the phase of an athletes training cycle. Naylor et al. (30) studied LV flow propagation during diastole in elite rowers following a period of relative inactivity and again after 3 and 6 months of intensive training. After detraining the rowers had significantly decreased LV diastolic flow propagation velocity compared to matched controls. Following resumption of intensive training, flow propagation normalised, suggesting that in athletes, continuation of training is required to maintain normal diastolic function. This finding should also be followed-up with further investigation.

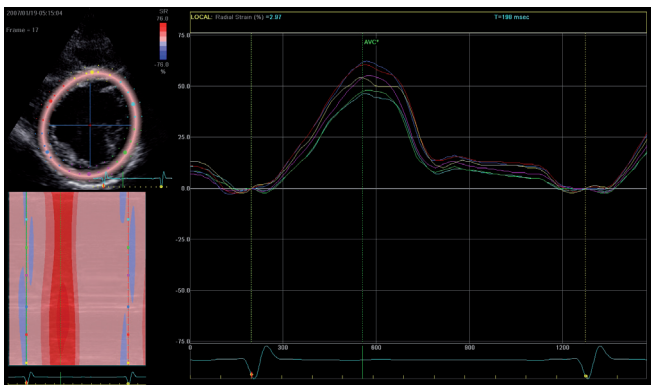

Figure 4: An exemplar scan of myocardial speckle tracking assessment of regional wall strain and strain rate in the para-sternal short-axis view (note the short axis LV view at the level of the papillary muscle and the radial strain traces from six LV wall segments).

Clearly more longitudinal data should be produced, especially in combination with newer techniques of assessment including 2D speckle tracking and/or MRI. The ability to assess regional as well as global LV diastolic functional responses to training is important. It is also important to note that whilst the longitudinal training intervention research design is more powerful in terms of assessing cause and effect, longitudinal studies are not without limitations. Most obvious is that any realistic training study that starts from a sedentary status is unlikely to be able to employ the total volume of exercise training that is undertaken by athletes. Further, athletes often start their training during adolescence (or even early) which may not be directly comparable to shorter-term training studies in adults.

CONCLUSIONS, IMPLICATIONS AND DIRECTIONS FOR FUTURE STUDY

We have provided some clarity related to the basic definition and components of LV diastolic function as well as detailing current assessment techniques. Using this as a backdrop we have attempted to summarise evidence for an effect of exercise training on LV diastolic function. A complex "picture" emerges with some evidence that both earlier diastolic filling and LV compliance is augmented in athletes. This data is far from conclusive and contradictory data exists in most areas, likely related to the nature of the assessment tool, process and research design employed.

Despite a lack of unanimity in the available data newer echocardiographic techniques (tissue Doppler; strain) have been employed in studies comparing physiological vs. pathological LV hypertrophy in an attempt to introduce LV diastolic functional indices into the differential diagnostic procedures used to distinguish the athlete's heart from clinical conditions like hypertrophic cardiomyopathy (HCM) that may predispose to sudden cardiac death. Vinereanu et al. (58) reported that longitudinal diastolic tissue velocities were significantly higher in athletes than patients with HCM. More recently, Nagueh et al. (29) extended the potential value of tissue-Doppler imaging by reporting that early diastolic tissue velocities predicted the development of HCM in subjects initially presenting with subclinical disease. Butz et al. (4) demonstrated that a combination of global strain and tissue-Doppler data had a sensitivity of 100% and specificity of 95% for detection of pathological LV hypertrophy in HCM patients. Whilst there is significant potential in this data and the tools used, clearly on-going research is required before these tools are broadly adopted as a routine part of athlete screening.

As noted in the review there are numerous limitations in the extant literature and on-going study of LV diastolic function is necessary. Future study will continue to develop in line with technical advancements in non-invasive imaging and assessment protocols. For

example, developments in 3D echocardiography (25) have improved the assessment of parameters such as LA volume and function due to the removal of geometric modelling. If 3D echocardiography is to be used in combination with tissue-Doppler, strain and/or stress imaging (52) this could significantly augment our knowledge of LV diastolic function and specifically how it responds to exercise training.

Finally, longitudinal training studies utilising varying levels and modes of exercise stress would seem highly pertinent. This database is still limited and requires further study in a range of different populations.

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