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Mechanism of harm from left bundle branch block☆

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ABSTRACT

The impact of left bundle branch block (LBBB) on cardiac mechanical function ranges from minimal effect in some patients to marked reduction in left ventricular (LV) systolic function in others. It appears that this variability in part reflects differences in anatomical location of the bundle block. In most patients with LBBB and congestive heart failure, however, there is associated cardiac disease such as cardiomyopathies or coronary artery disease which contributes to LV dysfunction. The mechanism of harmful effect of LBBB on cardiac function is in-coordinated ventricular contractions which result in LV contractile inefficiency. Septal contribution to LV systolic function is lost or attenuated and an excessive workload is placed on the LV free wall which responds with remodeling and in some cases it decompensates. The magnitude of the contractile inefficiency depends on the extent of electrical conduction delay and degree of associated heart disease. Another mechanism, which in many patients contributes to cardiac dysfunction in LBBB, is mitral regurgitation due to in-coordinated contractions of the papillary muscles and altered mitral valve function due to LV remodeling. Potentially, reduced LV filling time due to prolonged LV systole may contribute to cardiac dysfunction, but there is limited knowledge about the clinical importance of this mechanism. In LBBB there is typically reduced septal perfusion, probably not as a sign of ischemia, but reflecting physiologic autoregulation of coronary flow in response to reduced septal work that reduces metabolic demand. Future studies should explore how current insights into mechanisms of cardiac mechanical effects of LBBB can be incorporated into decision algorithms for selection of patients for cardiac resynchronization therapy, as well as how to manage patients with LBBB and preserved LV function.

Introduction

Normal electrical activation of the left ventricle occurs by impulses that enter the base of the ventricle at the Bundle of His. The impulses then follow the left and right bundle branches along the interventricular septum and the bundle branches divide into an extensive system of Purkinje fibers, which conduct electrical impulses at high velocity and secures synchronized activation of both ventricles. In left bundle branch block (LBBB), the left ventricle is activated via the right bundle branch and the septum is activated from right-to-left, which is opposite to direction of septal activation in the normal heart. Furthermore, activation of the septum and the left ventricular (LV) free wall occurs via myocardial tissue, which conducts much slower than the specialized Purkinje fibres [1]. Fig. 1 shows the typical ECG features of LBBB.

An electrographic pattern somewhat similar to LBBB may be seen in patients with intact bundle branches and fascicles and is named diffuse intraventricular conduction delay. In most cases, the ECG morphology in patients with diffuse intraventricular conduction delay can be differentiated from classical LBBB [1]. Furthermore, patients with right ventricular (RV) pacing may have an electrical activation pattern of the left ventricle that resembles LBBB. Both of these conditions imply abnormal electrical activation of the ventricles and may also have harmful effects on ventricular function. The present review will be limited to patients with LBBB.

☆ Conflicts of interest: Otto A. Smiseth is co-inventor, but no longer has ownership of the patent "Method for myocardial segment work analysis", which is described in the article. John M. Aalen reports no conflicts.

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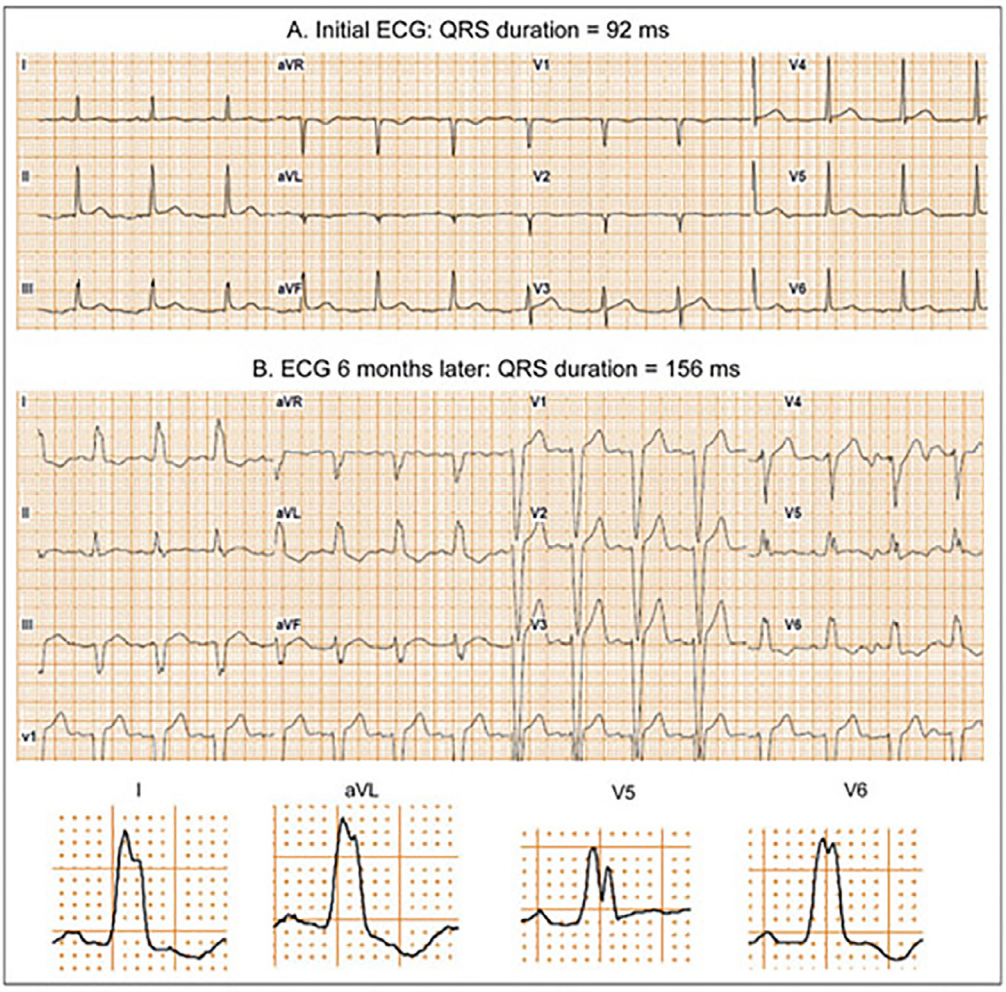

Fig. 1. ECG during LBBB.
75-year old woman with normal looking ECG (upper panel) undergoing sudden increase in QRS-duration with development of LBBB (lower panel). During LBBB there is typical mid-QRS notching in lead I, aVL, V5 and V6. Modified from Strauss et al. [1].

LBBB and cardiovascular risk

LBBB is usually associated with organic heart disease, but in some cases it is an incidental finding in subjects with no symptoms and apparently normal hearts. In a random-sampled population of 855 men who were followed for 30 years, the prevalence of bundle-branch block increased from 1% at age 50 to 17% at age 80 (Fig. 2). In another randomly selected population, the prevalence of LBBB was 0.43% for men and 0.28% for women of middle age [2]. LBBB, however, is seen more frequently in cardiology practice both acutely in myocardial infarction and myocarditis, and in chronic cardiac diseases and conditions, which includes coronary artery disease, hypertension and cardiomyopathies. In chronic disorders, the precise mechanisms of the conduction block are usually unknown, but presumably microscopic remodelling with myocardial fibrosis plays a role.

It has been discussed if LBBB is just a bystander or represents an independent risk factor. When LBBB occurs in otherwise healthy individuals, it is associated with mildly increased cardiovascular risk, but the current literature is not conclusive with regard to mechanisms of the increased risk, if it is underlying heart disease or LBBB as such. Similarly, in patients with acute myocardial infarction, it is debated if LBBB is an independent contributor to risk and mortality [3,4]. In a study of Stenestrand et al. [3] it was concluded that LBBB did not represent an independent risk factor. Importantly, in their study, outcome data in terms of 1-year mortality were adjusted for a number of variables that included LV ejection fraction (EF). Since reduction in LV systolic function is a key feature of LBBB, one may question if the analysis eliminated the most important hemodynamic effect of LBBB.

LBBB is found in 20–30% of all patients with congestive heart failure and is associated with increased mortality [5]. A number of studies have discussed the cause-and-effect relationship between LBBB and mortality in heart failure [5,6]. In one of the studies where the role of LBBB as an independent predictor of mortality was questioned, the analysis was done to test if effects of LBBB were independent of LVEF [7]. As discussed above, LBBB acts directly on LVEF, and the conclusion in the latter study may not be justified. In a study from the Swedish Heart Failure Registry, which included nearly 15.000 heart failure patients and about 25% with LBBB, it was concluded that LBBB was an independent predictor of mortality at all ages [8]. Furthermore, the large number of studies of cardiac resynchronization therapy (CRT) that have shown improvement of prognosis along with improved systolic function is consistent with the notion that LBBB has direct negative effects on prognosis in congestive heart failure.

The negative effects of LBBB on cardiac function are seen acutely, but are enhanced due to associated remodeling in the chronic phase. The effects include not only myocardial dysfunction, but also mitral regurgitation. Furthermore, LBBB has effects on the

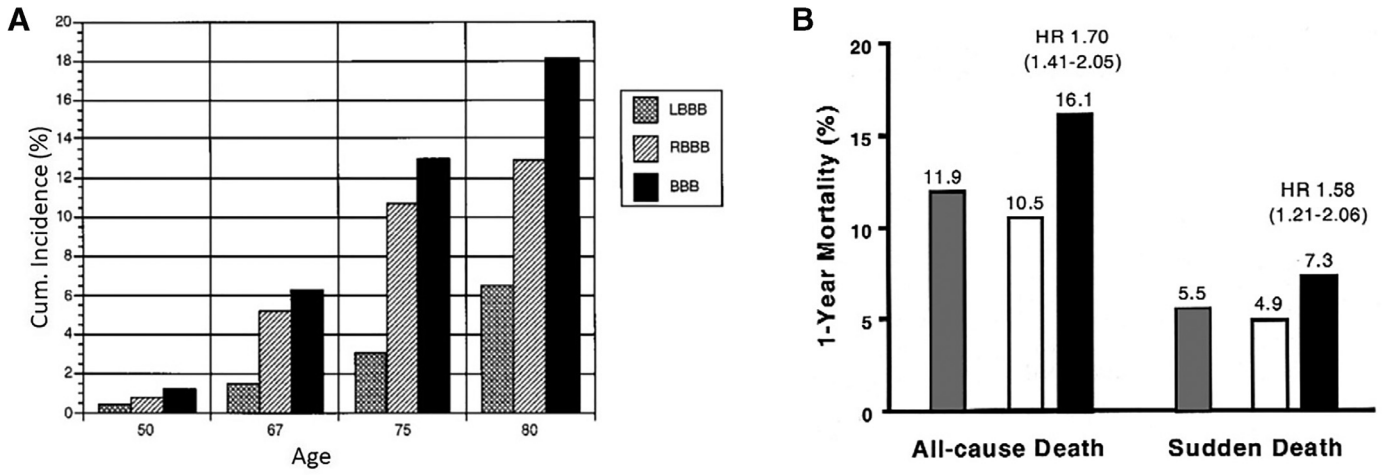

Fig. 2. Incidence and mortality risk.
A: Cumulative incidence of bundle branch block (BBB; L, left; R, right) in men from 50 to 80 years old. Modified from Eriksson et al. [50].
B: One-year mortality rate for all-cause death and sudden death in a study population of 5517 patients with congestive heart failure (gray bars) and in subgroups with complete LBBB (black bars) or without complete LBBB (white bars). Unadjusted hazard ratio (HR) with 95% confidence interval is indicated. Modified from Baldasseroni et al. [5].

right ventricle, although the most important clinical effects are the result of left heart dysfunction. Whereas most attention has been given to effects on systolic function, LBBB also modifies LV diastolic function. Due to progression of underlying disease, patients with LBBB may develop complete atrioventricular block. More recently, there has been interest in the effects of acute LBBB as a complication in patients undergoing transcatheter aortic valve replacement (TAVR). It has been debated to what extent LBBB worsens prognosis after TAVR and mortality data have been conflicting [9,10]. A meta-analysis, however, showed association between new-onset LBBB and increased risk of cardiac death at 1-year follow-up [11].

Effects of LBBB on LV systolic function

In patients with isolated LBBB who appear to be otherwise healthy, LVEF usually is either normal or just mildly reduced [12,13]. When there is LBBB in patients with congestive heart failure, however, LVEF is usually markedly reduced. The variability in degree of systolic dysfunction in patients with LBBB may in part reflect individual differences in anatomic location of the conduction block, which may vary substantially despite a similar LBBB pattern in the ECG [14]. Furthermore, associated cardiac disease, most often coronary artery disease and cardiomyopathies, contributes to systolic dysfunction to a variable degree.

A causal relationship between LBBB and systolic heart failure has been established in experimental studies where induction of LBBB leads to immediate reduction in systolic function [15–17]. As shown in patients with systolic heart failure, the direct contribution of LBBB to LV dysfunction is often substantial, as indicated by reverse remodeling and improvement in LVEF in most patients who receive CRT [18,19].

The mechanism of systolic dysfunction in LBBB is incoordinated ventricular contractions, where contractions in different parts of the left ventricle are out of phase. This is illustrated in Fig. 3. In LBBB, the early activated septum contracts when the LV lateral wall is fully relaxed, and rather than contributing to LV ejection, septal contraction displaces blood towards the lateral wall that is stretched to abnormally high preload. When the lateral wall is activated, it contracts vigorously according to the Starling mechanism, and displaces blood back towards the septum that is stretched and displaced towards the right ventricle. When the septum is stretched and displaced, it absorbs energy from work performed by the LV lateral wall, which can be assessed as wasted work in the septum [20]. Contraction of the LV free wall ultimately causes ejection of blood into the aorta. Since the septum represents approximately 1/3 of the LV mass, loss of a large portion of septal contribution to LV function adds substantial workload on the LV lateral wall, and this is a major stimulus to adverse remodeling in patients with heart failure and LBBB. Hence, during LBBB there is often hypertrophy of the LV lateral wall and thinning of the septum, which can be reversed by CRT [21]. In accordance with this, Spragg et al. [22] showed protein dysregulation concentrated to the LV lateral wall in animals after induction of dyssynchronous heart failure.

A number of imaging based indices have been introduced to assess the abnormal contraction patterns in LBBB. Using M-mode echocardiography, the early activated septum shows rapid leftward and then rightward motion during the LV pre-ejection phase and this contraction pattern is named septal flash or septal beaking [23,24] (Fig. 3C, right panel). When using strain imaging this contraction pattern is seen as septal pre-ejection shortening immediately followed by re-lengthening (rebound stretch) and is often associated with substantial reduction in net septal systolic shortening (Fig. 3C, left panel). Due to the early septal activation, there is also premature termination of septal shortening, followed by late-systolic lengthening. Furthermore, the early septal shortening, followed by vigorous LV lateral wall contraction, pulls the apex back (rightward) and forth (leftward), creating a characteristic transverse motion named apical rocking (Fig. 3D) [25]. Coexisting cardiac disease that affects regional contractility in the septum and LV lateral wall can modify these patterns to a large extent [26,27].

Calculation of myocardial work using a non-invasive LV pressure estimate in combination with strain by speckle tracking echocardiography was recently introduced and offers direct and quantitative insight into myocardial energetics [28] (Figs. 3A and 4). Therefore, it provides a better representation of LV dysfunction in LBBB than just measuring velocity or deformation indices. Indices such as septal flash and apical rocking, however, may provide similar information as myocardial work, but are essentially only qualitative. The reported prevalence of septal flash among LBBB patients varies substantially [29,30], and may be absent in spite of typical LBBB [27].

Several promising studies have looked at myocardial work as a predictor of CRT response [20,31,32], but there is need for fur-

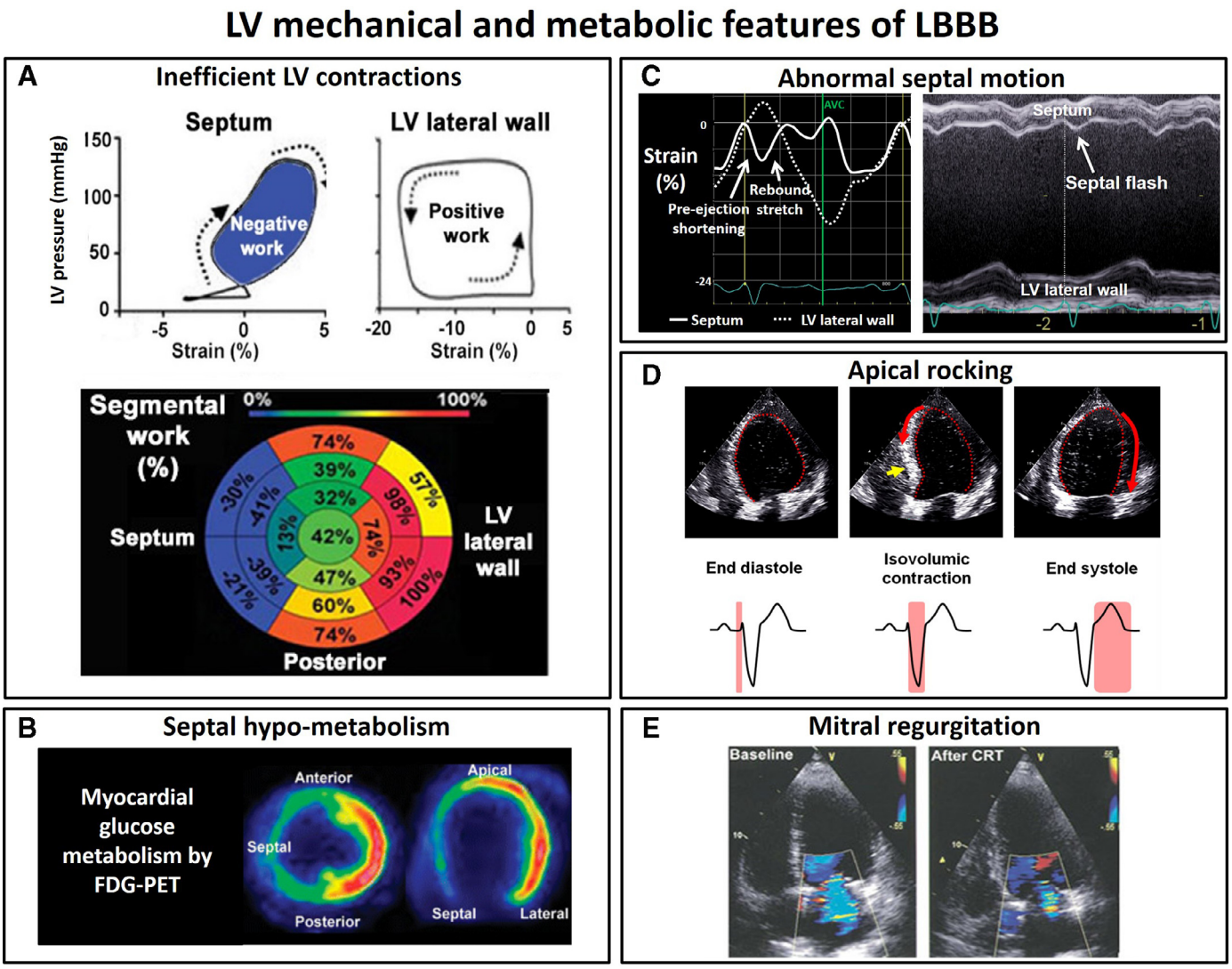

Fig. 3. Pathophysiology of LBBB.
A: Contractile inefficiency: Upper panels display pressure-strain loops from the septum and LV lateral wall in a patient with LBBB and non-ischemic cardiomyopathy. Loop area reflects segmental work. The lateral wall shows normal counter-clockwise rotation of the pressure-strain coordinates with shortening in systole. The septal pressure-strain loop, however, rotates clockwise, which means lengthening in systole and the result is negative (wasted) work as indicated by the blue-colored (dark) loop area. The lower panel displays segmental work distribution in the entire ventricle. Values are given as percentages of the segment with the highest work value. Modified from Russell et al. [28].
B: Septal hypo-metabolism: Fluorodeoxyglucose-positron emission tomographic (FDG-PET) LV short- and long-axis images from a representative patient with LBBB and non-ischemic cardiomyopathy. The point with the highest FDG uptake was used as reference (100%), and segmental values are reported in percent of this value. Green (low intensity) color in septum indicates low metabolism relative to the lateral wall. The reduced septal work illustrated in panel A, explains reduced septal metabolism. Red (high intensity) color in the LV lateral wall indicates high rate of glucose metabolism. Modified from Russell et al. [28].
C: Abnormal septal motion: Left panel: Septal and LV lateral wall strain traces from a representative LBBB patient with non-ischemic cardiomyopathy. There is septal pre-ejection shortening with corresponding LV lateral wall stretch. As the LV lateral wall starts to shorten, there is rebound stretch of the septum and septal shortening at end-systole is reduced. Right panel: Parasternal M-mode image from the same patient. Please note how pre-ejection shortening and rebound stretch are visualized as septal flash.
D: Apical rocking: During isovolumetric contraction the apex is pulled rightwards by early septal and RV free wall contraction (middle panel), whereas later in systole it is pulled back by the forceful contraction in the late-activated LV lateral wall. Modified from Stankovic et al. [29].
E. Mitral regurgitation: Echocardiographic recordings from a patient with congestive heart failure and LBBB. The left panel shows severe mitral regurgitation as indicated by large color Doppler jet area. The right panel shows marked reduction of mitral regurgitation with CRT. Modified from Kanzaki et al. [43].

ther validation before it can be recommended as a tool in clinical routine. Importantly, myocardial work is modified by scar and co-existing ischemic dysfunction that need to be taken into account before concluding about the contribution of LBBB to contractile inefficiency [27].

In patients with otherwise normal hearts, LBBB is often well tolerated, and LVEF may remain stable in the lower normal range for decades. As shown recently, normal LVEF in patients with LBBB does not always imply normal systolic function [12]. In this study, global longitudinal strain (GLS), which is a more sensitive measure of systolic function than LVEF, was subnormal in asymptomatic patients with LBBB and normal LVEF. Furthermore, as illustrated in Fig. 5, when these hearts were exposed to acute elevation of blood pressure, they responded with more marked reduction in LVEF than entirely normal subjects, indicating reduced afterload tolerance. This mechanism may explain why LBBB is associated

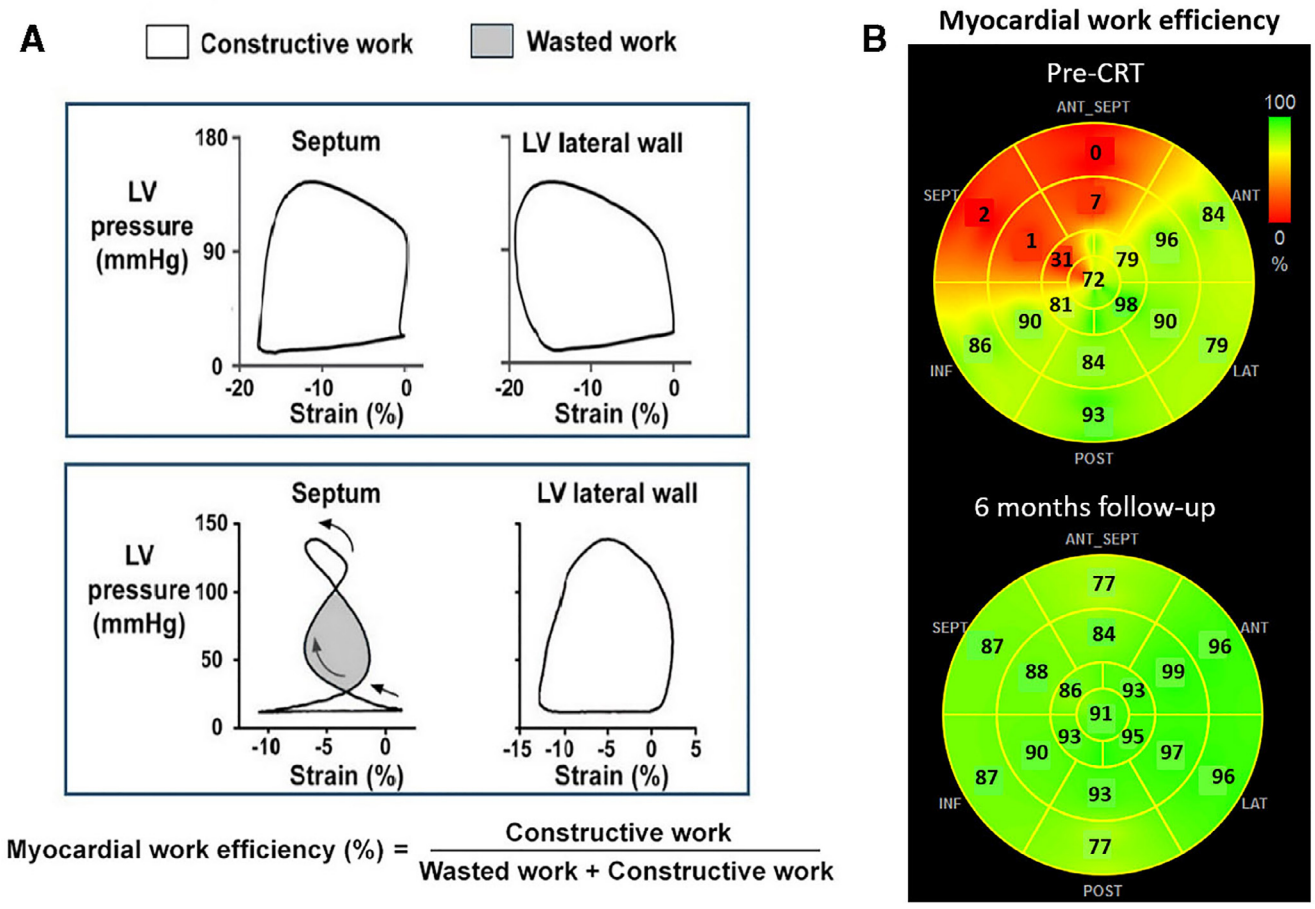

Fig. 4. Myocardial work efficiency.
A: The upper panels show a normal heart where essentially all work is positive (i.e. constructive work). The lower panels is from a patient with LBBB and shows predominantly negative work in the septum (i.e. wasted work). Myocardial work efficiency can be calculated as the percentage ratio between constructive work and the sum of wasted and constructive work. Modified from Aalen et al. [12].
B: Bull's-eye plots displaying myocardial work efficiency immediately before and 6 months after CRT implantation in a LBBB patient with extensive reverse remodeling and marked improvement in systolic function (LVEF increasing from 25 to 61%).

with increased cardiovascular risk in patients with hypertension [33].

In patients with symptomatic heart failure with reduced EF (HFrEF), there is indication for guidelines-directed medical heart failure treatment and often CRT. On the other hand, there is no recommended treatment for patients with LBBB and normal or subnormal LVEF. A retrospective study of almost 100 LBBB patients with normal LVEF showed that 36% developed systolic dysfunction defined as LVEF <45% [34] after an average time of about 4 years. This, however, means that most patients maintained systolic function measured as LVEF. The authors could not identify risk factors for the progression to significant LV dysfunction. Therefore, there is clearly need for further research to understand which patients are at risk for remodeling and progression to heart failure and how this can be prevented. The abovementioned increased afterload sensitivity in these patients suggests that hypertension may play a role and this should be explored in future studies [35]. In a retrospective study of 1436 patients with LBBB and LVEF 36–50%, there was poor outcome, including increased mortality, in the LBBB group compared to a matched control group without intraventricular conduction delay [36]. We believe present knowledge supports close follow-up for patients with LBBB and preserved LVEF. Potentially, CRT should be considered as a first line treatment when signs of dilatation and reduced LVEF become evident [37].

It is well known that many LBBB patients have reduced septal perfusion in the absence of obstructive coronary artery disease [38]. Restricted septal perfusion due to relative prolongation of septal systole during exercise-induced tachycardia has been suggested as a contributor to this finding [39]. Likewise, "painful LBBB syndrome", which was believed to be caused by transient ischemia, could be related to septal hypoperfusion during LBBB. At present, however, there is no clear evidence for ischemia as a cause of such a syndrome [40]. Therefore, the main reason for reduced septal perfusion in LBBB is most likely normal autoregulation of myocardial microcirculation and perfusion, which is reduced due to less metabolic demand because of reduced septal work [15,28] (Fig. 3B).

Mitral regurgitation

Mitral regurgitation is very common in patients with congestive heart failure, usually of mild degree, but about 30% of patients have either moderate or severe regurgitation which is associated with increased mortality [41]. Underlying cardiomyopathy, coronary artery disease or primary valve disease are usually the main reasons for the regurgitation, but LBBB is an independent contributor. This notion is supported by the observation that CRT reduces moderate or severe mitral regurgitation to non-significant regurgitation in about one-third of the patients [42] (Fig. 3E). Left bundle branch block induces and aggravates mitral regurgitation by several mechanisms, which prevent normal coaptation of the valve leaflets.

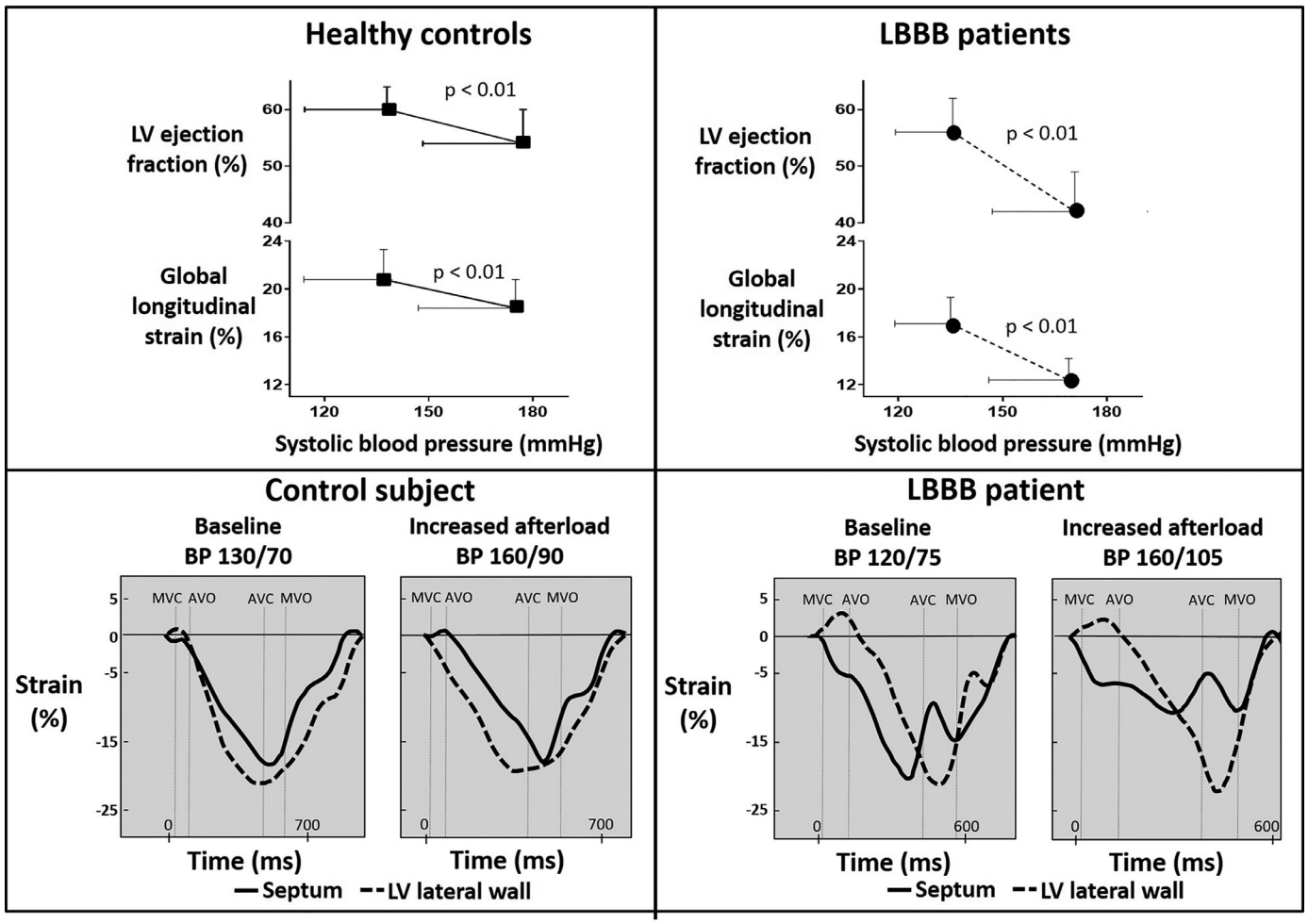

Fig. 5. Afterload hypersensitivity in LBBB.
Upper panels: Systolic function by LVEF and LV global longitudinal strain at baseline and during elevated afterload. Patients with LBBB showed marked reductions in LVEF and strain, which differs significantly from the moderate decline in controls. Lower panels: Representative strain traces. In the control subject, elevation of afterload caused only small reductions in systolic shortening. In the LBBB patient, however, elevation of afterload caused marked reduction in septal shortening. Modified from Aalen et al. [12].

During normal electrical activation of the left ventricle, the impulses travel first to the papillary muscles which are therefore activated prior to the LV walls. This allows the chordae tendineae to tighten up prior LV pressure generation, thereby keeping the mitral leaflets in position and preventing backflow into the left atrium. In LBBB this coordinated activation is disturbed, and is one of the mechanisms of mitral regurgitation [43].

In heart failure patients with dilated ventricles, there is increased tethering forces on the mitral leaflets that may reduce mitral valve competence [44]. During such conditions, proper closure of the mitral valve is more dependent on early systolic LV to left atrial (LA) pressure difference. Since the rate of rise of LV pressure is reduced in LBBB, the closing force is reduced and this appears to be an important contributor to mitral regurgitation in dyssynchrony [44].

In addition to these immediate effects on mitral valve function, LBBB aggravates systolic dysfunction, leading to LV remodelling with apical and lateral displacement of the papillary muscles. The altered valve function is reflected in the phenomenon of tenting, where the mitral leaflet tips are displaced distally during systole, thereby reducing the area for coaptation and ultimately causing regurgitation. The papillary muscles normally arise from the LV wall at its apical and middle thirds, permitting the contracting papillary muscles to exert a desirable vertical force on the chordae tendineae, effectively moving the leaflets together during isovolumetric contraction and restraining them during ventricular ejection [45]. In contrast, when the papillary muscles are not vertically aligned with the annulus (lateral migration due to spherical dilatation of the left ventricle), the systolic forces exerted on the leaflets via the chordae are in a lateral as opposed to a vertical direction. This lateral tension, especially on the anterior leaflet, opposes apposition, and renders the valve incompetent. In systolic heart failure with or without LBBB, the mitral valve itself is usually normal, but the abnormalities in LV structure and function cause tenting of the valve, preventing its closure.

Effects of LBBB on LV diastolic function

Dyssynchrony in LBBB affects both the contraction and relaxation phases. Experimental studies have shown that LV pressure decay is prolonged [12] and the absolute rate of LV pressure fall is reduced [17]. This leads to prolongation of the isovolumetric relaxation time and thereby less time for LV diastolic filling [13,46]. This is illustrated in Fig. 6, which compares diastolic filling times in the RV and LV. Besides this, there is limited insight into how LBBB modifies LV diastolic function. One study suggest that LV diastolic pressure may be elevated in patients with LBBB, but the study is small and not really conclusive [46]. There is need for insights into

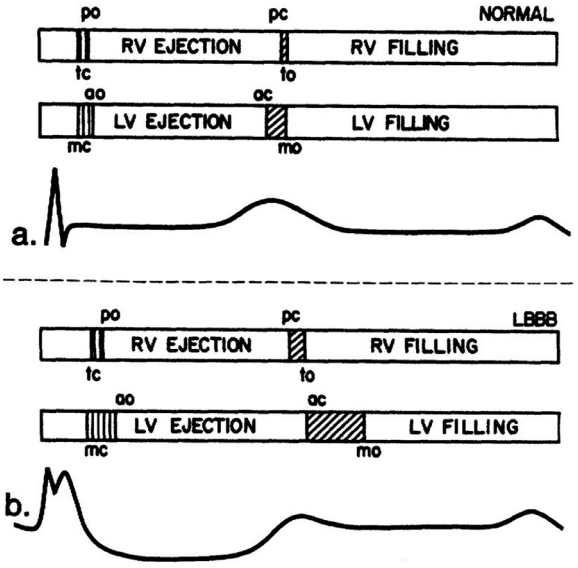

Fig. 6. Abbreviated LV filling time in LBBB.
Upper panel (a) is from a normal subject and the lower panel (b) from a patient with LBBB. The abbreviations po, to, ao and mo refers to pulmonic, tricuspid, aortic and mitral valve openings; pc, tc, ac and mc refer to valve closures. The time interval from mc to ao represents the LV isovolumetric contraction time and the time from ac to mo the LV isovolumetric relaxation time, and both are prolonged in LBBB. Furthermore, there is prolongation of LV ejection time. The result is reduction in diastolic filling time. Modified from Grines et al. [13].

how LBBB modifies LV relaxation and passive elastic stiffness. In a recent experimental study, it was shown that pacing at tachycardic rates caused diastolic stiffening due to incomplete LV relaxation as a result of shortened filling time [47]. It remains to be determined if a similar mechanism is operative in patients during exercise-induced tachycardia.

Similar to other patients with heart failure and reduced LVEF, patients with LBBB have compensatory elevation of LV filling pressure. Besides this general response, there is currently no firm evidence that impaired LV diastolic function contributes to heart failure symptoms in patients with LBBB. It seems likely, however, that the markedly abbreviated LV filling time in LBBB would imply that higher LA pressure is needed to fill the ventricle with similar volumes as with normal electrical conduction, but this remains to be studied.

Effect of LBBB on RV function

LV dysfunction, caused or worsened by LBBB, may indirectly lead to RV dysfunction through increased left-sided filling pressure, causing pulmonary congestion and pulmonary hypertension which increases RV afterload. Furthermore, the interventricular septum is an important contributor to RV systolic function and hence, abnormal septal motion during LBBB may also have a direct mechanical effect on the RV. Computer modeling studies have shown that during LBBB, CRT redistributes myocardial work from the late-activated LV free wall to the early-activated RV free wall [48]. Possibly, additional workload on the RV free wall with CRT may be harmful in the presence of pre-existing RV failure. In support of this concept, it was shown that RV dysfunction is an independent predictor of non-response to CRT [49]. Future studies are needed to determine if there is a causal relationship between CRT and progression of heart failure in patients with RV systolic dysfuction. Possibly, RV failure is just a marker of poor outcome, independent of CRT.

Future perspectives

It is well established that LBBB has negative effect on LV function independent of coexisting heart disease, but there is apparently large individual variability in the magnitude of the cardiodepressive effect of LBBB. Current imaging methods for evaluation of dyssynchrony measure velocity or deformation and can identify indices of LV function that are specific for LBBB. These indices are qualitative and subjective, however, and do not provide quantitative information about the impact of LBBB on global LV function. Myocardial work calculated from non-invasive LV pressure and strain is a novel method that quantifies the effect of LBBB on global LV function and energetics, and its potential as a clinical method is currently being evaluated.

When evaluating LBBB patients as potential candidates for CRT, it is important to determine the impact from the bundle branch block on LV function. This should be done by obtaining a detailed history (onset and duration of LBBB in relation to declining LV function and heart failure symptoms) in addition to assessing the ECG (longer QRS-duration indicates more significant impact of the LBBB) and by cardiac imaging where septal wasted work with reduced myocardial work efficiency suggest negative impact from LBBB. Furthermore, one should estimate if mitral regurgitation can be attributed to LBBB. In patients with a small contribution from LBBB to the heart failure, it is not likely that CRT will have much positive impact. On the other hand, in patients with a large contribution from LBBB, it is more likely that CRT will be of benefit. We also believe that future assessment of patients with LBBB in relation to CRT should include quantification of myocardial macroscopic scarring which may be evaluated by a number of different methods. Future developments in quantification of myocardial interstitial fibrosis by CMR T1 mapping or other methods could also provide important insight into potential for effect of CRT. Use of machine learning and simulation studies based on diagnostic information such as extent and localization of myocardial scar, may be used in individual patients to estimate contribution to LV dysfunction from LBBB and other disease processes. We also suggest applying a similar approach when evaluating patients with LBBB and normal LV function to determine if they are at risk for progression to heart failure.

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