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EDITORIAL COMMENT

LBBB and High Afterload

A Dangerous Liaison?*

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Left bundle branch block (LBBB) is rare in the general population (~0.5%); however, LBBB is fairly common in patients with chronic heart failure (~25%) (1). These numbers indicate an association between LBBB and cardiovascular disease, including hypertension and heart failure (2). These associations have raised the question of what is cause and what is consequence. Half a century ago, it was commonly believed that newly acquired LBBB was a hallmark of advanced hypertensive or ischemic heart disease. On the other hand, Breithardt and Breithardt reviewed literature evidencing that LBBB could promote development of heart failure (3). The latter observations were substantiated 2 decades later in animal experiments, in which induction of LBBB in otherwise normal dogs led to ventricular dilatation, asymmetrical hypertrophy, and a reduction in left ventricular ejection fraction (LVEF) (4). More recently, studies in patients who developed LBBB after valve replacement procedures confirmed a causal relation between LBBB and mortality (5). Obviously, the success of cardiac resynchronization therapy, which acutely improves pump function by correction of (most of) the electrical disturbances, also strongly supports the negative functional consequences of LBBB (6).

In this issue of *iJACC*, Aalen et al. (7) present a very elegant study in patients and dogs that demonstrates that hearts with LBBB are more sensitive to increased left ventricular (LV) afterload than normal hearts. In asymptomatic patients with LBBB, afterload was increased by handgrip exercise and arm-cuff inflation, whereas in dogs, afterload was increased in a more controlled way by aortic constriction. Although in normal subjects, increased afterload reduced LVEF only mildly (7%), this reduction was more pronounced in LBBB patients (14%). The dog experiments showed that in particular, septal stretch during the ejection phase deteriorated at high afterload. Both in humans and in dogs, increased afterload in the LBBB heart created a clockwise rotation of the septal pressure-length loop, which indicates negative ("wasted") work generated by the septum.

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Therefore, this study adds important information to the above-mentioned discussion as to whether LBBB is the chicken or the egg in relation to heart failure and hypertension: maybe it is both! After all, if LBBB develops in hypertensive patients (whether caused by hypertension or not), it creates a disproportionately negative effect on pump function.

The strain measurements reported by Aalen et al. (7) provide insight into the mechanism by which LBBB and high afterload synergistically cause deterioration in LV pump function. We can speculate about the mechanism as to why the reduction in function is seen especially in the septum. After discovery of abnormal strain patterns in asynchronous hearts, it was noted that the explanation for worsening of pump function could be sought largely in the inherent property of myocardial cells called *length-dependent activation* (also known as the Frank-Starling mechanism) (8). The earliest-activated region (the septum in LBBB) starts to contract and shorten early, thereby stretching the later-activated LV lateral wall. After electrical activation of the LV lateral wall, its contraction is strong because of its pre-stretch, and this augmented contraction forces the septal myocardium to be stretched, even though it is still

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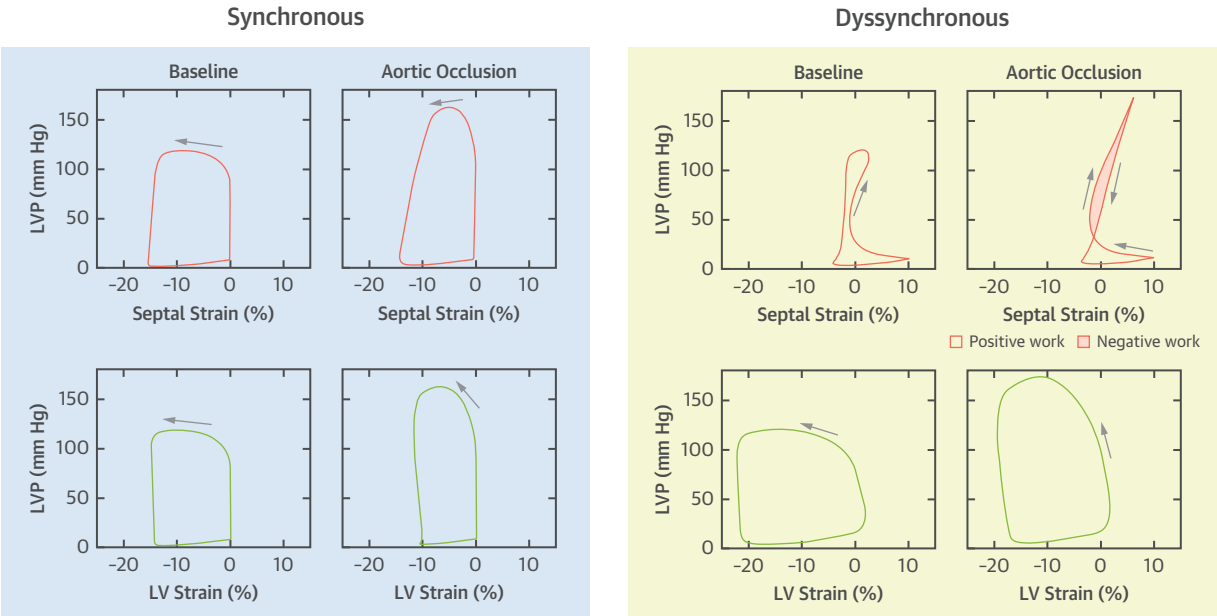
FIGURE 1 Pressure-Strain Diagrams From CircAdapt Simulations of Synchronously and Dyssynchronously Activated Heart Before and After Increasing Afterload Through Partial Aortic Valve Occlusion



The MultiPatch version (10) was used for these simulations, with segments for the right ventricular, septal, and left ventricular (LV) wall. During synchronous activation, all segments were activated simultaneously, whereas for dyssynchrony, activation of the septum and LV wall was delayed by 15 and 60 ms, respectively, with respect to the right ventricle. LVP = left ventricular pressure.

actively generating force itself. There is evidence that the reduced systolic septal shortening (or even stretching) directly relates to the loss in pump function in dyssynchronous hearts (9).

A next step is to try to explain the further worsening of septal systolic function at high afterload. This could relate to the muscle property that contraction lasts longer when afterload is high. As a consequence, systolic stress in the LV lateral wall might remain elevated and could thereby stretch the septum more than when afterload is normal, thus amplifying mechanical dyscoordination.

Support for this idea comes from simulations we conducted in the CircAdapt computer program to simulate mechanics of the heart and circulation (10). **Figure 1** illustrates pressure-strain loops that are comparable to the pressure-segment length loops in the paper by Aalen et al. (7). Increasing afterload hardly affects the loops in the synchronous heart, where simulating a mechanical activation delay in the LV free wall leads to a small pressure-strain loop that starts to turn clockwise when afterload is increased (simulated by partial aortic occlusion). Importantly, the CircAdapt model contains only a few elementary muscle properties, of which length-dependent activation is an important one. Therefore, it seems highly likely that the afterload hypersensitivity of LBBB hearts can be (largely) explained by a combination of basic muscle properties, interaction between ventricular walls, and the arterial afterload (**Figure 1**).

This likely explanation has at least 3 important clinical ramifications. First, quantification of mechanical dyssynchrony and discoordination is sensitive to afterload. This has also been shown to some extent by Park et al. (11), who used pneumatic leg compression and nitroglycerin administration to alter loading conditions. This implies that afterload is an important additional variable that should be known for proper interpretation of mechanical dyssynchrony data.

Second, because LVEF also shows afterload hypersensitivity in patients with LBBB, blood pressure should be taken into account when interpreting LVEF measurements. This seems especially important when decisions are made based on a cutoff value, such as 35% for device implantation.

Third, lowering the afterload in patients with LBBB might be even more favorable than in patients with narrow QRS complex and thus could be even more important for their proper treatment.

Of course, extrapolation of the results of this study to clinical care should be done with care. The study by

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Aalen et al. (7) only investigated patients with LBBB without heart failure symptoms. Further studies are required to determine whether the afterload hypersensitivity also occurs in failing LBBB hearts. It would be equally interesting to investigate whether application of cardiac resynchronization therapy in such patients would reduce the afterload hypersensitivity. If this were to happen acutely, it would provide strong support for the mechanism of afterload hypersensitivity proposed above.

Besides the small numbers of patients, a limitation of the study by Aalen et al. (7) is its acute design. There is no information on the potential long-term effects. However, the "natural" adaptation of the myocardium under these conditions is usually counterproductive: long-term dyssynchrony and pump failure induce dilatation and asymmetrical hypertrophy, complicated by adverse molecular changes (4,12) and, through the cardiorenal axis, increased fluid maintenance. These all lead to further worsening of the condition of the patient. Therefore, the acute adverse effects of afterload could be amplified in the longer term. It is clearly of utmost importance to investigate this question in more detail.

In conclusion, the article by Aalen et al. (7) could be an important piece of the puzzle of understanding dyssynchronous heart failure, a piece that indicates that LBBB and LV pressure overload form a dangerous liaison, becoming hazardous at a much earlier stage than dangerous liaisons in fictional stories usually do.

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