One of the primary mechanisms by which a heart can increase its pump performance is beating more frequently. Elevating heart rate enhances net cardiac output by the simple algebra of having more stroke volumes ejected per minute but also by an intrinsic effect of stimulation frequency on contractility. The latter, known as the force-frequency relation (FFR), relates to rate-dependent increases in calcium entry into a myocyte (more action potentials and thus Ca\(^{2+}\) channel openings per minute) coupled with greater Ca\(^{2+}\) uptake into the sarcoplasmatic reticulum. The net effect is an increase in calcium released to the myofilaments with each stimulation, resulting in a “positive staircase” as heart rate rises from normal basal levels to fast physiological rates (≈180 bpm in normal humans). This process has a limit, as calcium becomes effectively trapped within the sarcoplasmic reticulum when heart rate is faster than the kinetics of Ca\(^{2+}\) cycling can accommodate, leading to a “negative staircase” at more rapid rates.

The FFR plays an important role in normal contractile reserve under stress, yielding a near 100% rise in cardiac chamber contractility in healthy adults when heart rate is varied from 60 to 150 bpm. As with many features of contractile regulation, however, the FFR becomes abnormal in the failing heart, characterized by both blunting of the peak response and a shift to a lower heart rate at which the maximal response is observed. In a patient with heart failure, this could result in a flat or even negative response, as calcium becomes effectively trapped within the sarcoplasmic reticulum when heart rate is faster than the kinetics of Ca\(^{2+}\) cycling can accommodate, leading to a “negative staircase” at more rapid rates.

Although optimal resynchronization might seem to require stimulation from both the right and left sides, studies have repeatedly found that LV free wall pacing itself yields nearly identical (if not greater) benefits on resting mechanoenergetics in patients with heart failure with left bundle–type conduction delay. Although electrical delay remains with LV-only pacing, mechanical synchrony is improved, although perhaps not quite as much as with BiV stimulation. Fusion of supraventricular stimulation through a patent right bundle with LV stimulation achieved by biventricular (BiV) stimulation, combining a right ventricular (RV) apical or septal stimulation site with one in the left ventricular (LV) free wall. In patients with heart failure with intrinsic or iatrogenic left bundle delay (eg, RV pacing), BiV stimulation improves resting systolic heart function and mechanoenergetics.

The impact of CRT on heart function has been largely examined under resting conditions; thus, little is known as to whether CRT-induced changes decline, remain the same, or are even enhanced under different conditions. In the current issue of Circulation, Vollmann et al. provide new evidence that CRT effects on cardiac function are enhanced at faster heart rates, but that this benefit depends on how CRT is implemented. They studied 22 patients with dilated heart failure and a wide QRS complex (that is, CRT eligible), examining acute cardiac pressure responses to varying heart rates (80 to 140 bpm) while also altering the cardiac activation mode between RV, LV, or BiV pacing. The primary measure of contractile function was the maximal rate of pressure rise (dP/dt\(_{max}\)), that increased with heart rate (positive FFR) only when BiV stimulation was used. FFR obtained with RV- or LV-only pacing were essentially flat. At the
fastest rates, BiV stimulation also increased systolic while reducing diastolic pressures.

These findings support prior data of Hay et al., who studied patients with atrial fibrillation and AV block and found that increased cardiac output with LV or BiV versus RV pacing at 80 bpm was even more disparate at 120 bpm. In the study by Vollmann et al., heart rate had to be raised to the highest level (140 bpm) to observe significant differences in $dP/dt_{max}$ between pacing modes—particularly differences between LV and BiV modes. LV-only pacing was also consistently better than RV-only stimulation.

Why is the FFR steeper with BiV versus RV- or LV-only stimulation? It seems unlikely that acute changes in pacing mode altered intrinsic myocyte calcium handling or the state of various related proteins. Rather, different pacing modes may affect synchrony and/or cardiac loading differently at different heart rates, leading to disparities in the FFR. One possibility is that the extent of mechanical dyssynchrony or resynchronization is sensitive to heart rate, particularly with single-site pacing. One might imagine that contractile synchrony with LV-only pacing is less effective at faster rates because of differences in myocardial versus His-Purkinje conduction, whereas BiV stimulation is less influenced. Because neither the Vollmann study nor the prior study determined mechanical dyssynchrony at the different heart rates, this remains speculation. Net chamber filling was also not determined by Vollmann et al., although prior data suggest that this may indeed be compromised at faster rates with LV (and RV) pacing as the result of shortening of the diastolic filling period. Such diastolic effects have been revealed by several groups, and, although the exact mechanism remains unclear, it could limit net filling and thus $dP/dt_{max}$ increase, as the latter can be preload dependent. From the perspective of CRT treatment, the current data lend further support to use of BiV mode pacing as the better mode for enhancing both rest and exercise-stress cardiac function.

The presence of a positive $dP/dt_{max}$ FFR with BiV-CRT in this study contrasts to prior in vivo human investigations with atrial pacing that found the relation to be quite flat in subjects with heart failure, even those with less severe disease. Although subjects in the earlier studies might have developed rate-dependent conduction delay, this seems unlikely, given that few had delay at rest. However, acute CRT in susceptible subjects improves both myocardial function and energetic efficiency at rest. The latter might enhance energy reserve when heart rate is increased acutely, perhaps assisting the $dP/dt_{max}$ response. It should be noted that the FFR responses observed by Vollmann et al. were still quite blunted compared with normal subjects.

There are a number of caveats to the data presented by Vollmann et al. worth noting. First, the primary contraction index, $dP/dt_{max}$, is not load-independent and in particular is sensitive to changes in chamber filling that can decline at faster heart rates. Concluding that such preload change does not occur on the basis of diastolic pressures may not be justified, as these do not always correlate at fast heart rates. Second, the authors used dual chamber stimulation (DDD mode), which introduces a delay time between atrial excitation and contraction that itself may vary between pacing modes and at different heart rates. Recent data suggest that LV function is better with VDD (atrial sensing and ventricular preexcitation) than with DDD stimulation, even at resting heart rates. In part, this stems from a compromise that must be made between optimizing atrial-ventricular systole (booster pump function) and maintaining preexcitation (resynchronization)—all with the same net AV delay time, ultimately compromising net filing time. At faster heart rates, optimal atrial delay and AV delay itself may vary differently with each pacing mode.

The introduction of CRT as a heart failure therapy has opened a novel chapter in the treatment of this disorder. It was among the first therapies to be selectively targeted to a subgroup of patients thought to have dyssynchrony, it involved wider use of an implantable device in subjects who were not necessarily moribund (that is, in contrast to LV assist devices), and it appeared to improve systolic function while reducing overall mortality rates. The new evidence provided by Vollmann et al. improves our understanding of why this might be the case. It again raises questions about the use of standard RV-apical rate response pacing in patients with LV dysfunction and highlights how BiV-CRT effects at rest maybe even more pronounced under stress. Further studies that reveal the mechanism for this effect may help guide our use of this treatment more effectively in the appropriate patients.

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