Editorial Comment

Upward Shift and Outward Bulge
Divergent Myocardial Effects of Pacing Angina and Brief Coronary Occlusion

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Research into the myocardial effects of pacing angina and brief coronary artery occlusion evolved in opposite directions. Decreased left ventricular diastolic distensibility during pacing angina was first reported clinically1-3 and later reproduced in an animal model.4,5 Segmental dyskinesis of ischemic myocardium during a brief coronary artery occlusion was first reported in an animal model6-8 and later clinically reappraised during the balloon inflations of coronary angioplasty.9-13 Studies14-16 that directly compared pacing angina with brief coronary artery occlusion in the same anesthetized open-chest, open-pericardium dog preparation stood at the crossroads of this evolution. From these studies, divergent myocardial effects of pacing angina and brief coronary occlusion emerged. Three minutes of pacing tachycardia in the presence of two-vessel critical coronary stenoses resulted in an upward shift of the diastolic left ventricular (LV) pressure-segment length relation of the ischemic myocardium. At the time of this upward shift, systolic segmental shortening was only slightly reduced (±25%). In the same experimental preparation, 3 minutes of coronary occlusion caused an outward bulge of the ischemic segment during systole, accompanied by a rightward shift of the diastolic LV pressure-segment length relation. From these observations, it was concluded that decreased diastolic distensibility with minor reduction of systolic shortening characterized ischemic myocardium during pacing angina and that increased diastolic distensibility and substitution of systolic shortening by passive outward bulging were the hallmarks of ischemic myocardium during brief coronary occlusion.14,15

The meticulous study of Applegate et al.17 reported in this issue of Circulation, and recent work on myocardial function during the balloon occlusions of coronary angioplasty10 seem to be at odds with the concept that upward shift and outward bulge characterize ischemic myocardium respectively during pacing angina and brief coronary occlusion. In contrast to previous studies on pacing angina, Applegate et al.17 observed a rightward shift of the diastolic LV pressure-dimension relation after 3 minutes of pacing tachycardia in the presence of two-vessel critical coronary stenoses in an anesthetized open-pericardium dog preparation. In contrast to previous experimental work on brief coronary occlusions, an upward shift of the diastolic LV pressure-radial length relation was reported in patients with coronary artery disease after a ±30-second balloon occlusion of coronary angioplasty.10 Because of these new experimental and clinical findings, the concept of upward shift and outward bulge, as specific markers of pacing angina and brief coronary occlusion, needs reassessment.

Clinical Observations
Regional Left Ventricular Diastolic Distensibility

When patients with three-vessel coronary disease were paced to angina, a reversible decrease in regional diastolic distensibility of the ischemic myocardium was deduced from an upward shift of the diastolic LV pressure-wall thickness relation of the ischemic segment.18 At the time of this reversible decrease in regional diastolic distensibility during pacing angina, systolic performance of the ischemic segment was well preserved, as evident from a decrease of only 14% in systolic wall thickening. Recent studies19,20 reported on a small subset of patients who, during pacing angina, showed no shift of the diastolic LV pressure-radial length relation of the ischemic myocardium. In this subset of patients whose regional diastolic distensibility remained unaltered, systolic performance of the ischemic segment was severely depressed, as evident from a more than 50% decrease in systolic shortening. A severe reduction of segmental shortening, therefore, seems to preclude the decrease in regional diastolic distensibility usually observed during pacing angina.

An upward shift of the diastolic LV pressure-radial length relation of the ischemic segment and a small decrease (20%) in systolic segmental shortening was observed during short (±30 seconds) balloon occlusions of coronary angioplasty.10 In recent studies on myocardial function during balloon occlusions...
of coronary angioplasty, the balloon inflation time was doubled to ±60 seconds.\textsuperscript{11,20} These studies reported no significant changes of regional diastolic distensibility\textsuperscript{20} and, because of longer duration of myocardial ischemia, a severe depression of systolic performance of the ischemic segment. This was evident from a 75\% decrease in systolic shortening\textsuperscript{20} and from the development of midsystolic and holosystolic bulging.\textsuperscript{12,20} Hence, in both pacing angina and balloon occlusion of coronary angioplasty, the relation between systolic performance of the ischemic segment and its diastolic distensibility seems to be similar. A severe reduction in systolic performance of the ischemic segment precludes a decrease in regional diastolic distensibility or, inversely, preserved systolic shortening of the ischemic segment is a prerequisite for an upward shift of the diastolic LV pressure–segment length relation because, for an ischemic myocardial segment, upward shift and outward bulge do not seem to coexist! 

**Global Left Ventricular Diastolic Distensibility**

Absence of synchronicity between different LV segments slows LV relaxation and abolishes LV suction during LV filling.\textsuperscript{21} A loss of synchronicity thereby raises LV filling pressures and produces an upward shift of the early and middle diastolic LV pressure–volume relation in the absence of any change in regional diastolic distensibility. In humans, synchronicity of diastolic wall motion of normal and ischemic LV segments is drastically affected by brief coronary occlusion and only slightly by pacing angina.

During a 40-second balloon occlusion of a saphenous vein bypass graft, regional wall motion could be continuously monitored by radiopaque epicardial markers that had been implanted in the myocardium perfused by the graft at the time of bypass surgery.\textsuperscript{22} Because of sufficient duration of balloon inflation time and myocardial ischemia, motion of the epicardial markers evolved from diminished systolic shortening to midsystolic bulging and, finally, to holosystolic bulging and early diastolic recoil. Regional diastolic distensibility of the ischemic segment was unaltered, as assessed by the diastolic LV pressure–epicardial length relation. The dysynchronous early diastolic recoil of the ischemic segment caused slower isovolumic LV relaxation and probably a loss of LV suction during LV filling. During balloon occlusion of coronary angioplasty, this slower isovolumic LV pressure decay and the loss of LV suction could explain slower early diastolic LV inflow\textsuperscript{23} and an early to middle diastolic upward shift of the LV pressure-volume relation.\textsuperscript{9,11,12}

A loss of elastic LV recoil at the time of LV filling has recently also been proposed as the mechanism for the upward shift of the diastolic LV pressure–volume relation during pacing angina.\textsuperscript{24} During pacing angina, however, dyssynchrony between normal and ischemic myocardium is much more subtle than during brief coronary occlusion. This is evident from the small (±50 msec) reduction of time to peak posterior wall thickness\textsuperscript{18} and the small (±50 msec) prolongation of time to peak segment lengthening\textsuperscript{25} observed in an ischemic segment during pacing angina. Midsystolic and holosystolic bulging, such as occurs in ischemic myocardium during brief coronary occlusion, has not been reported in humans during pacing angina. Moreover, in patients with coronary disease, a relation was observed during pacing angina between the decrease of global LV diastolic distensibility and the amount of myocardium at risk, as measured by the magnitude of the defect on a simultaneously performed thallium scan.\textsuperscript{26} This relation challenges a significant role of dyssynchrony between normal and ischemic myocardium as the cause of the decreased global LV diastolic distensibility during pacing angina. If the mechanism was dyssynchrony between normal and ischemic myocardium, a maximal effect would occur when the LV myocardium would be equally divided between normal and ischemic zones and not when the LV myocardium became more uniformly ischemic. A similar challenge was provided by the decrease in global LV diastolic distensibility, which was observed when patients with severe aortic stenosis and no coronary disease were paced to angina.\textsuperscript{27} Subendocardial ischemia induced by pacing angina was more evenly distributed over the LV in patients with aortic stenosis than in patients with coronary disease. Despite this different distribution of ischemic myocardium, the effect of pacing angina on global diastolic LV distensibility was similar in patients with aortic stenosis and coronary disease. This indicates that the decreased diastolic LV distensibility during pacing angina results from abnormal diastolic properties of the ischemic myocardium itself and not from dyssynchrony between normal and ischemic segments.

**Experimental Findings in Anesthetized Dogs**

For many years, the upward shift of the diastolic LV pressure–volume relation as observed in humans during pacing angina could not be reproduced in anesthetized or conscious dog animal preparations. The decreased LV diastolic distensibility during pacing angina was, therefore, attributed to pericardial constraints or to ventricular interaction through the shared interventricular septum.\textsuperscript{28,29} The way myocardial blood flow was reduced appeared to be critically important when trying to reproduce, in an experimental model, the abnormal LV function observed in humans during pacing angina. The reduction of myocardial blood flow, both at rest and during the pacing stress test, needed to satisfy the following criteria: 1) Myocardial blood flow was reduced to a large portion of the LV myocardium, 2) myocardial blood flow was reduced without impairment of resting function of the jeopardized myocardium, 3) when myocardial blood flow was reduced by imposing coronary stenoses, the coronary stenoses needed to be sufficiently tight to prevent active hyperemia during pacing, and 4) during pacing, myocardial ischemia remained limited to the subendocardium and
produced the characteristic ST segment depression on the surface electrocardiogram. In an open-chest, open-pericardium anesthetized dog preparation, Serizawa et al.4 satisfied the aforementioned criteria by imposing a coronary stenosis on two vessels (both left anterior descending [LAD] and left circumflex [LCX]) by reducing antegrade coronary blood flow velocity in each vessel to 50% of control value and by imposing a 2–3-minute pacing run at twofold the resting heart rate.4 In this model, the upward shift of the diastolic LV pressure-volume relation during pacing angina could be reproduced in the absence of significant biventricular interaction. By excluding interference of pericardial or right ventricular constraints, these observations attributed the upward shift of the diastolic LV pressure-volume relation during pacing angina to stiffening of the ischemic myocardium, which was subsequently confirmed by an upward shift of the diastolic LV pressure–segment length relation5 and the diastolic LV pressure–wall thickness relation of the ischemic myocardium.14 In the same angina physiology model, microsphere technique15 demonstrated a reduction of myocardial blood flow limited to the subendocardium at the time of the upward shift of the diastolic LV pressure-volume relation. Applegate et al.17 used an anesthetized open-pericardium dog model, which differed only slightly from the previous one. Coronary stenoses were imposed on two vessels (LAD and LCX) and a 3-minute pacing run at twofold the resting heart rate was performed but, in contrast to the previous angina physiology model, antegrade coronary blood flow was reduced in each vessel to a level sufficient to avoid regional LV dysfunction. By using regional LV function as a marker for the severity of the coronary stenoses, myocardial blood flow was more profoundly reduced so that myocardial ischemia was no longer of subendocardial LV distribution during pacing tachycardia but was of transmural LV distribution. Transmural myocardial ischemia during demand angina is a rare clinical event, as evident from the very low incidence of ST segment elevation during stress testing in coronary patients without previous LV scar. Despite the limited clinical relevance of this model, the observed hemodynamic changes during transmural pacing-induced ischemia are valuable because they failed to show a decrease in regional diastolic LV distensibility in the presence of severely impaired systolic performance and of occasional dyskinesis or bulging. This led the authors to the conclusion that low flow–high demand ischemia per se is not sufficient to cause a decrease in regional diastolic distensibility, and that severity of ischemia can offset such changes. By correlating regional diastolic distensibility to regional systolic performance in different experiments and different segments, the same conclusion was reached in the previous angina physiology model14; when systolic performance was severely depressed during pacing ischemia, the upward shift of the diastolic LV pressure–segment length relation was absent or small.

Hence, experimental findings in anesthetized dogs are in accord with clinical observations; during the initial stages of ischemia, upward shift and outward bulge do not coexist in the same myocardial segment!

**Cellular Physiology**

This interaction between systolic performance and diastolic distensibility during the initial stages of ischemia unveils the underlying cellular physiology. When ATP production decreases as a result of ischemia or hypoxia, free myoplasmic calcium will increase. The exact time course and the magnitude of this increase remain debated.30 It definitely occurs during no-flow ischemia and a similar albeit smaller increase has recently been described after 3 minutes of hypoxia.31 During no-flow ischemia, this increase in free myoplasmic calcium is accompanied by a decrease in tissue pH and an increase in inorganic phosphate, both of which have a pronounced inhibitory effect on contractile performance of myofilaments. This inhibition of contractile performance of myofilaments offsets the increased myoplasmic calcium availability, leads to immediate systolic failure, and explains the rapid development of outward bulge during no-flow ischemia of brief coronary occlusion. During hypoxia and also, to a lesser extent, during low flow–high demand ischemia, the increase in free myoplasmic calcium is not accompanied by a buildup of tissue metabolites because of continuous washout. This washout of tissue metabolites avoids an inhibitory effect on contractile performance of myofilaments but, because of higher diastolic free calcium, allows for diastolic cross-bridge cycling, which explains the upward shift during low flow–high demand ischemia of classic pacing angina. During the initial stages of ischemia, the absence or presence of an inhibitory effect on the myofilaments by tissue metabolites explains such divergent myocardial effects as upward shift and outward bulge.

**Conclusions**

The initial myocardial effect of ischemia changes from upward shift to outward bulge if an inadequate washout of metabolites is superimposed on an inadequate supply of oxygen and substrates. Inadequate washout of metabolites is more likely to occur during brief coronary occlusion than during pacing angina. Exceptions exist, however, as shown by Applegate et al.17 who observed depressed systolic performance, occasional bulging, and unaltered diastolic distensibility in severe pacing angina, which elicited transmural rather than the usual subendocardial LV ischemia. Inadequate washout of metabolites during the initial stages of ischemia raises myoplasmic concentrations of H⁺ and inorganic phosphate, both of which inhibit contractile activity of myofilaments. Such inhibition could explain the prompt decline in systolic performance and the unaltered diastolic distensibility despite higher diastolic myoplasmic calcium for the simple reason that myofilaments will not interact in diastole if they do not interact in systole.
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