Is Postextrasystolic Potentiation Dependent on Starling’s Law?

Biplane Angiographic Studies in Normal Subjects

CHUNG-SHIN SUNG, M.D., VIRENDR A. MATHUR, M.D., EFRAIN GARCIA, M.D., CARLOS M. DE CASTRO, M.D., AND ROBERT J. HALL, M.D.

SUMMARY  The cineangiograms of 26 normal subjects were analyzed to study the effect of Starling’s mechanism on postextrasystolic potentiation. The end-diastolic volumes (single plane and biplane) of the left ventricle were similar in the regular sinus beat before an extrasystole and sequential sinus beats after an extrasystole. However, the ejection fraction, mean normalized systolic ejection rate, mean velocity of fiber shortening and long-axis shortening were consistently larger in the first sinus beat after an extrasystole. We conclude that postextrasystolic potentiation is independent of left ventricular end-diastolic volume in normal human hearts and the compensatory pause after an extrasystole does not result in increased end-diastolic volume.

SINCE its first description by Langendorff,1, 2 postextrasystolic potentiation has become a well recognized phenomenon. Many investigations3-12 based on papillary muscle or heart-lung preparations have shown that postextrasystolic potentiation results in increased cardiac contractility regardless of changes in preload and afterload.

In the intact human heart, however, the nature of postextrasystolic potentiation is unclear. Cranefield,13 in a historical review, commented, “Starling’s law of the heart had come into the picture, and its widespread acceptance led many people more or less casually to attribute the increased force of the postextrasystolic beat to increased filling.” Braunwald,14 in reference to the intact ventricle, stated that it is independent of variations in diastolic filling of the ventricle; it has been demonstrated in the isovolumetrically contracting heart and in isometrically contracting cardiac muscle. But he also stated, “In the ejecting ventricle, when the premature beat is followed by a compensatory pause, the ventricular end-diastolic volume is augmented, and this increased preload contributes to the enhanced performance which characterizes the postextrasystolic contraction.” Results of several recent reports15-18 support this concept. However, this view is not shared uniformly. Other investigators19, 20 found that the left ventricular end-diastolic volume was not augmented after extrasystolic beats. To clarify this issue, we studied the relationship between the postextrasystolic potentiation and the left ventricular end-diastolic volume in normal subjects.

Materials and Methods

From 1974-1977, 2089 cardiac catheterizations were performed in the Clayton Foundation for Research Laboratory. Among these, the hemodynamics and coronary arteries were normal in 125 patients (6%). The cineangiograms of these patients were reviewed carefully. Only those with left ventriculograms of good quality that included an isolated premature ventricular contraction were selected for analysis. Twenty-six patients satisfied the criteria. All were premedicated with oral administration of 5 mg of diazepam, 25-50 mg of meperidine hydrochloride i.m. and 25 mg of promethazine hydrochloride.

At cardiac catheterization, the left ventricle was entered retrogradely from the brachial artery. Left ventricular images were recorded at 60 frames/sec simultaneously in the right anterior oblique (RAO) 30° and left anterior oblique 60° positions by injecting 50 ml of Renovist II (28.5% diatrizoate meglumine, 29.1% diatrizoate sodium and 31% bound iodine) into the left ventricle over 3-4 seconds. The peak of the R
wave for each QRS complex was indicated electronically on the cineangiographic films, and the time of each frame of cineangiogram was recorded on paper with the ECG. The center of the left ventricle was located by simultaneous biplane fluoroscopy. A centimeter grid was filmed for both planes at the level of the center of the left ventricle to derive magnification factor. In both projections, the end-diastolic volume was identified as the largest area of the ventricular silhouette. As the time of each cine frame was recorded on paper at 100 mm/sec, the interval between onset of QRS and the end-diastolic frame could be measured in each subject; it averaged 40 msec. The end-systolic frame was defined as the smallest area of the ventricular silhouette without further inward motion of any segment of the perimeter. The left ventricular silhouettes were manually traced, and biplane left ventricular volumes were calculated with the aid of computer analysis based on Dodge’s method. The regression equation used for the area-length method was as follows: \( V_{\text{actual}} = 0.938 \times \text{volume calculated} + 3.8 \text{ ml} \). The single-plane (RAO) left ventricular volume was calculated by the method described by Sandler. Ejection fraction and mean normalized systolic ejection rate were based on the calculated volumes. Mean velocity of fiber shortening and long-axis shortening were calculated by the method of Karliner et al.

The first regular sinus beat after the extrasystole and a compensatory pause was called the postextrasystolic potentiated (P) beat. It was compared with the sinus or control beat (C) preceding the extrasystole in 10 subjects and with the sinus beat (C) immediately after the potentiated beat in 22 subjects. All data were analyzed using the standard deviation and the paired \( t \) test.

**Results**

The results of calculated ventricular volumes and functional measurements, based on both single-plane and biplane methods, are summarized in tables 1–3. Values obtained using the single-plane method were in agreement with the results of biplane method. By using the paired \( t \) test, we found no statistically significant difference in the left ventricular end-diastolic volume among sinus beat preceding the potentiated beat, the potentiated beat and the subsequent sinus beat. Although the end-diastolic size was unchanged,

| Table 2. Comparison of End-diastolic Volume Index Between the Potentiated Beat and the Second Sinus Beat After the Extrasystole, Using the Single-plane and Biplane Method |
|-----------------|----------------|----------------|----------------|
|                 | Compensatory pause* | EDVI (ml/m²)  |
|                 | P | C₁ | P | C₁ |
| Case           |
| 1              | 112% | 58 | 56 | 60 | 4 | 71 | 5 | 70 | 5 |
| 2              | 141% | 50 | 54 | 60 | 4 | 71 | 5 | 70 | 5 |
| 3              | 105% | 37 | 38 | 60 | 4 | 71 | 5 | 70 | 5 |
| 4              | 150% | 63 | 63 | 68 | 67 | 67 | 67 | 67 | 67 |
| 5              | 114% | 47 | 47 | 49 | 48 | 48 | 48 | 48 | 48 |
| 6              | 101% | 76 | 82 | 79 | 81 | 81 | 81 | 81 | 81 |
| 7              | 134% | 50 | 49 | 63 | 59 | 59 | 59 | 59 | 59 |
| 8              | 137% | 85 | 78 | 90 | 80 | 80 | 80 | 80 | 80 |
| 9              | 113% | 68 | 69 | 79 | 79 | 79 | 79 | 79 | 79 |
| 10             | 139% | 61 | 68 | 72 | 77 | 77 | 77 | 77 | 77 |
| Mean = \( p \) | 112% | 60 | 60 | 71 | 5 | 70 | 5 | 70 | 5 |
| SEM            |

*Compensatory pause was measured as the interval between the extrasystole and the subsequent potentiated beat and is reported as a percentage of normal RR interval for each subject.

**Abbreviations:** EDVI = end-diastolic volume index; P = potentiated beat; C₁ = sinus beat.

The results of calculated ventricular volumes and functional measurements, based on both single-plane and biplane methods, are summarized in tables 1–3.
the indexes of left ventricular function indicated enhanced performance in the potentiated beat. The ejection fraction, mean normalized systolic ejection rate, mean velocity of fiber shortening and long-axis shortening were consistently larger and statistically significant for the potentiated beat.

**Discussion**

In the 9 decades since the discovery of postextrasystolic potentiation, several investigations have been published and Cranefield has summarized the early experience with this phenomenon. Despite results of several studies done most often in mammalian myocardial strips or isolated hearts, our knowledge of postextrasystolic potentiation is incomplete. Meijler et al. found that in the isolated heart of the rat, the Frank-Starling mechanism did not participate in the increase of the contraction after a premature beat and a compensatory pause. Other experiments, conducted in the isometrically contracting canine ventricle, produced similar results as shown by Siebens et al. and Lendrum et al.

In vivo, however, there is no convincing evidence either to support or negate the Starling’s effect on postextrasystolic potentiation. The most reliable techniques to evaluate left ventricular function in vivo are based upon the angiographic method. Results of extensive reviews have shown close agreement between the calculated volumes of the left ventricle and volumes of the postmortem human heart. Therefore, it is reasonable to use the calculated left ventricular end-diastolic volume as an index of true left ventricular size. By cineangiographically measuring beat-to-beat end-diastolic volume, Karliner et al. established the dependence of left ventricular performance on the Frank-Starling mechanism in patients with atrial fibrillation. Similar measurements to evaluate the Starling’s effect on postextrasystolic potentiation have failed to reach any definite conclusion. Some investigators have shown an increase of left ventricular end-diastolic volume to occur in the first sinust beat after an extrasystole. Others, however, did not find the change of end-diastolic volume to be statistically significant. Most of these studies were concerned with other aspects of postextrasystolic properties.

In our analysis, special care was taken to select only beats with silhouettes that could be easily traced and reproduced. The regular sinus beat before an extrasystole and sequential sinus beats after an extrasystole were analyzed for comparison. Our results clearly show that in regard to the end-diastolic volume (single plane and biplane), not only is the potentiated beat similar to the regular control sinus beat preceding extrasystole, but it is also similar to the subsequent sinus beat. There is no significant statistical difference by paired t test. The indexes of left ventricular performance like ejection fraction, mean normalized systolic ejection rate, mean velocity of fiber shortening and long-axis shortening, however, were consistently larger in the potentiated beat compared with the control beats. A recent report by Boden et al. supports our observations. While studying contractile reserve in acutely ischemic myocardium, these investigators measured the influence of extrasystole on epicardial segment length, and the end-diastolic segment length remained unchanged in control as well as border zones after an extrasystole and compensatory pause although the potentiation was clearly evident in the postextrasystolic beats. In some animals, the postextrasystolic potentiation was accompanied by increased segment length. Similar studies by Diamond et al. revealed significant potentiation of systolic shortening in the postextrasystolic beat without significant change in end-diastolic segment length or pressure in ischemic myocardium.

The enhanced contractility after an extrasystolic beat has been related to the prematurity of the ventricular contraction and subsequent lengthening of the compensatory pause by some investigators. All premature ventricular contractions were uncontrolled in our subjects during performance of the ventriculogram, so the degree of the prematurity was variable. We observed no effect on the degree of the prematurity on the left ventricular end-diastolic volume, provided there were compensatory pauses (tables 1 and 2).

The cause of postextrasystolic potentiation in human hearts, though unproved, has been attributed
to three components: (1) augmented myocardial contractility related to augmented influx of calcium into the myocardium;\(^{31, 32}\) (2) decreased systemic resistance during the compensatory pause;\(^{18}\) and (3) augmented filling during the compensatory pause after the extrasystole.\(^{14-18}\) Our data suggest that augmented filling and consequent Starling’s effect is not a significant contributor, at least in normal persons. The methods used to calculate ventricular volume may not be sufficiently sensitive to detect the differences between regular beats and potentiated beats. While this point cannot be refuted, it cannot be supported unless a better method is found to measure ventricular volume.

The geometrical shape of the left ventricle cannot be refuted, it cannot be supported unless a concomitant increase of volume; but we have not found this to be the case in our subjects. Despite our incomplete understanding of the nature of postextrasystolic potentiation in the human circulatory system, we conclude that the potentiation is the result of improved contractility and Frank-Starling’s mechanism plays no major role in normal subjects. Our observations are in normal subjects and should not be extrapolated for patients with different diseases.

Our results are in agreement with most published reports demonstrating that the postextrasystolic beat is indeed a potentiated beat with increased ejection fraction, mean normalized systolic ejection rate, mean velocity of fiber shortening and long-axis shortening. Our data, however, contradict the widely held belief that the ventricular volume increases during the compensatory pause after an extrasystole and the larger volume and preload contribute towards the enhanced performance via the Frank-Starling mechanism.

### References

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