Phantom Systole: A Failed Ejection Phenomenon between Pulsus Alternans and Systolic Aortic Regurgitation

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INTRODUCTION

Among clinical signs of left ventricular (LV) systolic dysfunction, "pulsus alternans" (PA) has been well described and analyzed in terms of its pathophysiology, representing beat-to-beat variation of ejected volume, despite a similar electrical activation sequence and diastolic times, constituting a phenomenon of chaotic and impaired ejection. It involves the entire cardiac cycle, as demonstrated by echocardiography. A dramatic sign of systolic dysfunction could be called failed ejection (FE) and represents the inability of the left ventricle to generate pressure that exceeds that of the ascending aorta, failing to open the aortic valve and to generate an effective (ejected) systolic volume. This can be observed in patients with advanced heart failure connected to LV assist devices and in the presence of systolic aortic regurgitation (SAR), being preceded by a premature ventricular complex (PVC). These findings are associated with heart failure, and its prognostic contribution, except for PA, has not been convincingly demonstrated to date. In this article we report a patient who presented FE not related to the triggers previously described (i.e., not an extrasystolic phenomenon), with electrically normal systolic activation, which we refer to as "phantom systole."

CASE PRESENTATION

A 52-year-old man with nonischemic dilated cardiomyopathy presented for follow-up transthoracic echocardiography. Electrocardiography showed the presence of a left bundle branch block. Cardiac magnetic resonance imaging showed an ejection fraction of 15% and no myocardial delayed gadolinium enhancement. As he remained symptomatic in New York Heart Association functional class III with optimal medical therapy, cardiac resynchronization therapy was indicated, although the device had not yet been implanted.

Transthoracic echocardiography was performed, showing a severely dilated left ventricle (end-diastolic volume 190 mL/m^2), with severe diffuse hypokinesia (Video 1; ejection fraction by the Simpson' biplane method was 15%); indexed stroke volume of 25 mL/m^2 and cardiac index of 1.1 L/min/m^2; a moderately dilated left atrium (indexed volume 46 mL/m^2); diastolic dysfunction, with a mean E/e' ratio of 16; systolic apical tethering of both mitral valve leaflets, with mild regurgitation as assessed by Doppler; and mild aortic regurgitation (AR).

At the start of examination, the patient was in sinus rhythm. With pulsed-wave Doppler analysis over the LV outflow tract, we observed velocity-time integrals of different (chaotic) magnitudes (Figure 1), compatible with "PA" on physical examination. Within a few minutes, the electrocardiogram began to show isolated PVCs, and post-extrasystolic FE due to nonopening of the aortic valve was observed in several of the following cycles, producing the immediate appearance of SAR. However, the next cycle, which was generated by normal electrical activation (sinus rhythm), showed FE as observed both by pulsed-wave Doppler (Figure 2) and by continuous-wave Doppler. This finding was remarkable, because it was an FE phenomenon not immediately preceded by a PVC (not post-extrasystolic), and despite not being able to open the aortic valve, it interrupted the AR of the previous cycle; thus, this "phantom systole" immediately caused SAR not preceded by a PVC (Figure 3).

DISCUSSION

In this section we analyze the findings according to their temporal occurrence in this case.

PA

The existence of "PA" was initially described by Traube[1] and is observed in patients with severe LV systolic dysfunction, representing beat-to-beat variation of ejected volumes, despite a similar electrical activation sequence and diastolic times. This significant finding is not just systolic but involves the entire cardiac cycle, and it has been demonstrated on echocardiography.[2]

Regarding its pathophysiology, it was initially believed that PA was a consequence of hemodynamic changes that influenced the filling volume of each cardiac cycle. However, Adler *et al.*[3] demonstrated, in a mathematical experimental model with comparative data of filling and systolic volumes obtained from canine hearts, that the mechanisms responsible for generating PA or sustained mechanical alternans could be classified into two main categories, myocardial and hemodynamic.

Myocardial PA involves the occurrence of alternating changes in myocardial contractility, as a consequence of variations in intracellular calcium availability during excitation-contraction coupling. Experimental studies have shown that it is possible to define a critical cycle length (threshold) for the induction of sustained mechanical alternans. Transient alternans may also be observed after a single premature systole.

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VIDEO HIGHLIGHTS

Video 1: Four-chamber apical view. Left ventricle with severe dilatation and systolic dysfunction.

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As premature systoles may also be followed by post-extrasystolic potentiation, the critical factor that seems to predict the occurrence of post-extrasystolic alternans is heart rate. Post-extrasystolic potentiation disappears and is replaced by post-extrasystolic alternans as heart rate increases. It is evident that in our patient, the presence of frequent PVCs and the use of β-blockers resulted in suppression of sustained mechanical alternans.[4] This myocardial mechanism appears to be the strongest explanation for the appearance of PA.

In hemodynamic (Frank-Starling) PA, in the presence of diastolic dysfunction, the increase in LV end-diastolic pressure could lead to greater end-diastolic length of individual muscle fibers, favoring greater muscle shortening and thus greater systolic emptying. This would decrease the LV end-diastolic pressure of the next cardiac cycle, generating an opposite effect (i.e., a weaker contraction). Thus, the variation between the stroke volumes of beats is maintained, independent of filling periods.[5] However, the contribution of this mechanism is much less compared with the "myocardial" factor.

In summary, the main mechanism that explains the appearance of PA involves variation in the basic inotropic state of the myocardium, with alternation in the number of cardiac fibers contributing to each systole.

SAR

The presence of SAR was initially described by Unger and Vanderbossche,[6] and its prevalence has been calculated at about 2% of hospital echocardiograms and up to 5.9% of patients with heart failure.[7] However, it is not clear if its occurrence is associated with a worse prognosis. SAR is an FE phenomenon, but with known triggers: there are associations with various clinical conditions, mainly ventricular arrhythmias and the use of LV assist devices in patients with preexisting AR, being a consequence of artificial suction by the device from the LV apex rather than a spontaneous finding. Spontaneous SAR (not related to an LV assist device) requires the existence of an immediately preceding PVC for its appearance (it is a post-extrasystolic phenomenon) and develops when, in the presence of diastolic AR, a PVC interrupts the rapid filling phase. Decreased preload due to its prematurity and altered ventricular contractility due to an abnormal electrical activation sequence results in a reduced pressure gradient, which is not high enough to open the aortic valve. Therefore, the resulting AR would have diastolic–systolic (due to PVC)–diastolic components.[8] An interesting question is whether the described mechanism alone is sufficient to explain the nonejection phenomenon derived from PVCs in these patients.

Phantom Systole

The previous two notable findings highlighted in this case, although not common, have already been described. In fact, SAR originates from a nonejection phenomenon related to a preceding PVC (post-extrasystolic) and is a consequence of abnormal cardiac electrical activation. Here, we report a systole generated by normal electrical activation (sinus rhythm) and not immediately preceded by a PVC (not

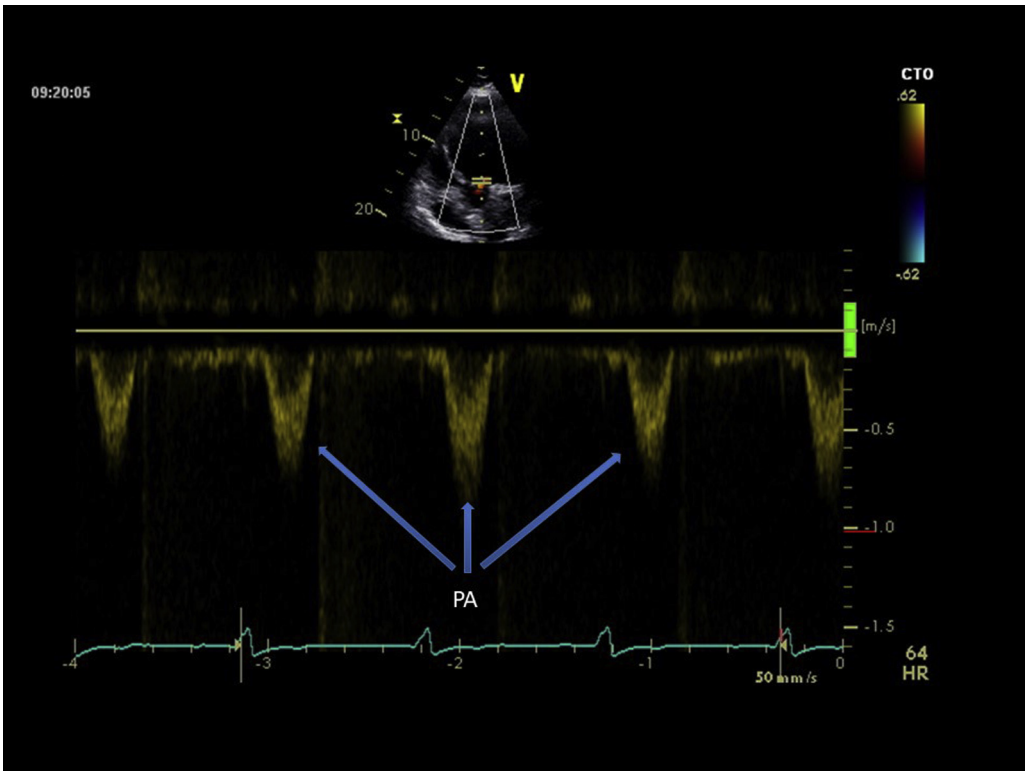

Figure 1 Five-chamber apical view. Pulsed-wave Doppler over LV outflow tract: PA. Several velocity-time integrals achieved different distances (*blue arrows*), despite similar filling times. *HR*, Heart rate.

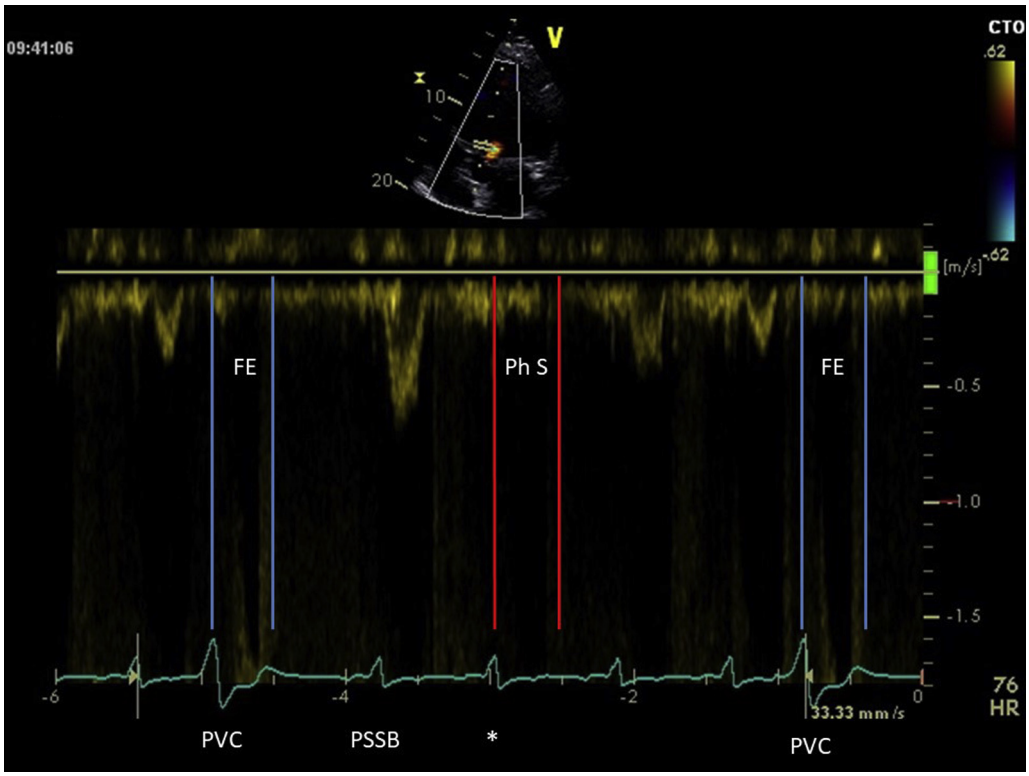

Figure 2 Five-chamber apical view. Pulsed-wave Doppler over LV outflow tract. An isolated PVC produces an FE phenomenon (between *blue lines*). A post-extrasystolic sinus beat (PSSB) opens the aortic valve and generates effective systolic volume (ejection). However, with the following QRS complex (*asterisk*), also with sinus activation, LV contraction fails to open the aortic valve. This is what we call "phantom systole" (Ph S) (between *red lines*). *HR*, Heart rate.

post-extrasystolic), which generates a pressure gradient that is not strong enough to produce an effective ejection but is sufficiently strong to generate a large notch in the SAR spectral Doppler. With a little imagination, one could compare it with a ghostly presence, and thus we have called it "phantom systole". To elucidate the factors that could determine this FE phenomenon, careful observation of Figure 3 is helpful.

As a general framework, it is necessary to mention that sinus rhythm is predominant (five of seven QRS complexes), with a heart rate of 58 beats/min (β-blocker-induced bradycardia) and blood pressure of 100/62 mm Hg. The recording was obtained with continuous Doppler interrogating the aortic valve.

Maximum antegrade flow velocities (from the left ventricle to the aorta, i.e., ejection volume) range from 0.8 m/sec up to almost 2 m/sec, which according to the simplified Bernoulli equation would generate pressure gradients between 2.56 and 16 mm Hg.

The first QRS complex recorded in the figure is the consequence of normal electrical activation and generates the highest systolic volume in this sequence. This QRS complex comes after a PVC (not shown in the figure). When diastolic phase begins, the appearance of AR is observed.

In the following cycle, the appearance of a polymorphic PV couple (comprising two PVCs) occurs: neither of them achieves an effective systole (there is no ejection), but spectral Doppler of the AR provides interesting information:

The first PVC (PVC 1), whose morphology suggests an electrical location below the bundle of His, generates a small notch (N1) that does not exceed 1 m/sec velocity (without even considering the gradient's own decrease due to the advancement of AR toward the left ventricle). That is, it causes a small pressure gradient (<4 mm Hg).

The second PVC (PVC 2) has an activation sequence that looks similar to the morphology of the patient with left bundle branch block. Although it does not generate an ejection volume, it almost completely interrupts AR, evidenced by a large notch (N2) in AR continuous Doppler, which suggests the generation of a much higher pressure gradient (practically 3 m/sec, nearly 36 mm Hg) compared with PVC 1. We could say that it looks like an intense isovolumic contraction.

After a postsystolic pause, the patient's normal electrical activation reappears, generating an effective systole and an ejection gradient close to 10 mm Hg, which is less (despite prolonged diastolic times after the PVC couple) than the first ejection gradient in the figure, which was preceded by an isolated PVC.

The QRS complex (asterisk) that follows the postsystolic beat, despite being generated by sinus electrical activation, fails to open the aortic valve (ejection failure: phantom systole) but generates a pressure gradient very similar to that produced by PVC 2.

If we try to analyze the peculiarities of this sequence, we reach the following realizations:

- Despite the large diastolic and nonejection time generated by the PVC couple, the postsystolic beat does not generate the highest ejection gradient in the sequence, suggesting that the Frank-Starling mechanism and increased preload are not sufficient to ensure, by themselves, greater contractile capacity. The absence of "phantom systoles" in patients with severe LV systolic dysfunction and atrial fibrillation (great variability in beat-to-beat filling times) supports this observation.
- In the presence of sinus electrical activation, phantom systole was observed only preceded by one sinus activation beat, and that one preceded by a PVC couple (Figure 3) or an isolated PVC (Figure 2). This abnormal activation

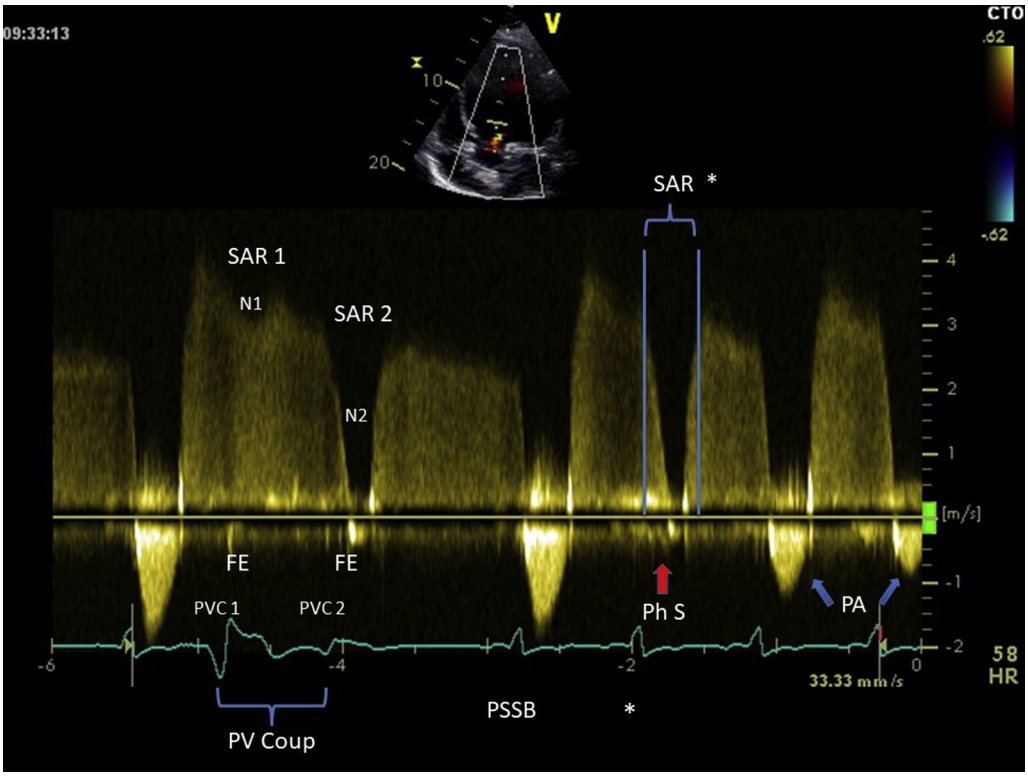

Figure 3 Five-chamber apical view. Continuous-wave Doppler over aortic valve. PVC couple (PVC Coup; PVC 1 and PVC 2). Notch 1 (N1) and notch 2 (N2) on spectral continuous-wave Doppler of SAR. *Red arrow* indicates phantom systole (Ph S). *Asterisk* denotes SAR generated by phantom systole. PSSB, Post-extrasystolic sinus beat.

could have produced an alteration in the availability of intracellular calcium, which, although it did not prevent an effective systole in the activation immediately after the arrhythmia (probably aided by greater preload and greater length of fibers at the end of this prolonged diastolic phase), was indeed a critical point in the next cycle, as it had a lower volume and filling time than sinus activation immediate after the PVC couple. We believe that this issue is especially relevant because of the known effect of increased sensitization of cardiomyocytes to the effect of calcium derived from a greater end-diastolic length.[9] Furthermore, although anecdotal, there are some reports of nonejection conditions and transient electromechanical dissociation (one ejection every two QRS complexes) in a pediatric patient with severe LV systolic dysfunction and presence of hypocalcemia, whose condition recovered with intravenously calcium replacement and inotropic drugs administration.[10]

- The existence of PVCs during this study is relevant not only for the appearance of SAR but in playing a key role in explaining of our finding of phantom systole. Studies in animal models (canine cardiomyocytes) have shown that the existence of maintained (for weeks) PVC's is related to disturbances and decreasing of several ionic currents that affect not only the duration of the action potential (due to lower current density) but also in variability of repolarization time, with a higher risk for malignant arrhythmias and sudden cardiac death. Furthermore, this study demonstrated a lower current density of calcium, which is the main force that preserves the duration of the plateau phase of the action potential and triggers the release of calcium from the sarcoplasmic reticulum during the coupling of contractile proteins, to then replace its storage in the same organelle.[11] This alteration of different currents derived from the prolonged effect of abnormal electrical activation by PVCs could not only explain the existence of phantom systole but may also play an important role in our understanding of the pathophysiology of arrythmia-related cardiomyopathy. In our patient, both coronary angiography and cardiac magnetic resonance imaging showed no solid etiology to explain this degree of systolic dysfunction, so this hypothesis is not yet ruled out.

CONCLUSION

There are several clinical and echocardiographic findings in systolic heart failure. Those related to impaired LV or chaotic ejection are the most representative and provide clear evidence of antegrade ventricular failure.

Phantom systole is a finding that could be the most dramatic sign of LV systolic failure, a remarkable proof of an FE phenomenon, but with triggering events and (probably) a pathophysiology different from that of SAR and PA, because phantom systole is not a post-extrasystolic event.

Recent studies have revealed the increasing importance (and perhaps a key role) of cardiac electrical activation sequence not only in overall cardiac synchrony but also in maintenance of action potential stability and calcium currents directly involved in contractile performance.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2020.08.010.

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