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Hemodynamic Correlates of the Third Heart Sound During the Evolution of Chronic Heart Failure

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Objectives. The purpose of this study was to examine the temporal relation between the development of a third heart sound during the course of evolving heart failure and associated hemodynamic abnormalities.

Background. Although various theories have been proposed to explain the origin of the third heart sound, the exact origin of this sound remains unknown.

Methods. Studies were performed in seven dogs in which heart failure was produced by multiple sequential intracoronary microembolizations. Hemodynamic studies including ventriculography, pulsed wave Doppler echocardiography and intracardiac phonocardiography were performed at baseline, at the time a third heart sound was first heard and at 6 and 24 weeks after onset of the third heart sound.

Results. All dogs developed a third heart sound at 9 ± 2 weeks after the initial embolization. The onset of the sound was accompanied by an increase in left ventricular chamber stiffness relative to the baseline value (0.25 ± 0.03 vs. 0.14 ± 0.01 mm Hg/ml) ($p < 0.05$) and mean deceleration of early mitral inflow velocity (1,040 ± 90 vs. 590 ± 40 cm/s per s) ($p < 0.05$).

Conclusions. These data indicate that the onset of a third heart sound during the course of evolving heart failure occurs coincident with the development of increased left ventricular chamber stiffness and the manifestation of rapid deceleration of early mitral inflow velocity. These findings are consistent with a myocardial vibratory origin of this sound.

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Although various theories have been advanced to explain the genesis of the third heart sound (1–9), the exact origin of both the physiologic and the pathologic third heart sound remains unknown. Most investigators (1–6) attribute this sound to vibrations of the left ventricular wall. Other less accepted theories attribute it to valvular events (7,8) or to the impact of the heart against the chest wall (9). Recent studies (5) have demonstrated that the third heart sound invariably occurs during the deceleration phase of early mitral inflow velocity at a time when the rapidly expanding left ventricle reaches the point where the fibroelastic nature of the myocardium limits ventricular distension. The resulting resistance to further chamber expansion promotes rapid deceleration of mitral inflow and seems to generate a vibratory wave that is detectable on the chest wall as a low frequency third heart sound. This interpretation clearly places myocardial fibroelasticity as a key component in the genesis of the third heart sound. Accordingly, factors that decrease myocardial distensibility, such as increased chamber stiffness, or factors that reflect decreased distensibility, such as prolongation of isovolumetric relaxation, have been shown to be closely associated with the presence of a third heart sound (5,10,11). The present study was designed to test the hypothesis that the development of a third heart sound during the course of evolving heart failure coincides with the development of increased left ventricular chamber stiffness and rapid deceleration of early mitral inflow velocity.

Methods

The canine model of chronic heart failure used in the present study has been previously described in detail (12). In this experimental preparation, heart failure is produced by multiple sequential intracoronary embolizations with polystyrene latex microspheres (70- to 102-μm diameter), which lead to the loss of viable myocardium. The model manifests many of the sequelae of heart failure observed in patients, including marked and sustained depression of left ventricular systolic and diastolic function, left ventricular hypertrophy and dilation, reduced cardiac output, increased systemic vascular resistance and enhanced activity of the sympathetic nervous system as evidenced by a marked elevation of plasma norepinephrine concentration (12).

In the present study, seven healthy mongrel dogs, weighing between 23 and 35 kg, underwent a series of cardiac catheterization and coronary embolization procedures to produce heart failure. The protocol was approved by the Henry Ford Hospital Care of Experimental Animals Committee. All cardiac catheterization procedures were per-

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formed under general anesthesia and sterile conditions with the chest closed. Dogs were anesthetized with an intravenous injection of 0.1 mg/kg of Innovar-Vet (droperidol, 2 mg/kg, and fentanyl citrate, 0.04 mg/kg), followed by an intravenous injection of 7.5 mg/kg of sodium pentobarbital. Each dog underwent five to nine embolizations 1 to 3 weeks apart. Embolizations were discontinued when left ventricular ejection fraction, determined angiographically, was ≤35%.

Hemodynamic, phonocardiographic and angiographic assessments. Hemodynamic, phonocardiographic and angiographic evaluations were made in anesthetized dogs during cardiac catheterization. Aortic and left ventricular pressures and a left ventricular intracavitary phonocardiogram were obtained using a 5F catheter-tip micromanometer (Millar Instruments). The intracardiac phonocardiogram was derived from the ventricular pressure waveform, using an analog filter (Krohn-Hite, model 3100) with a frequency window of 30 to 1 kHz. The first onset of the third heart sound was documented by auscultation and confirmed by intracardiac phonocardiography. Auscultation and phonocardiography were performed, respectively, at baseline and every 1 to 3 weeks thereafter until the final day of the study. Auscultation was performed by two independent observers who had no knowledge of the phonocardiographic findings but were aware of the length of time from the onset of coronary microembolization. The amplitude of the third sound was quantified by using the intracardiac phonocardiogram. Because of possible variations in sound amplitude within the left ventricular cavity, the tip of the catheter was always positioned near the midventricular level with the aid of fluoroscopic guidance. The amplitude at the time of the first observation of the sound was defined as 100%. The sound amplitude during subsequent observations was expressed as a percent of this initial amplitude. The gain of the sound amplifiers and that of left ventricular pressure was kept unchanged throughout the study.

Changes in left ventricular isovolumetric relaxation were quantified by using the time constant τ, calculated as described by Craig et al. (13). Because instantaneous left ventricular pressure-volume loops were not obtained in this study, left ventricular end-diastolic chamber stiffness was estimated from the ratio of end-diastolic pressure to end-diastolic volume. This approach, however, is limited in that an increase in this single point ratio can result from either a true increase in chamber stiffness or an upward parallel shift in the pressure-volume loop caused by extrinsic factors such as pericardial restraint (14). To determine whether the observed changes in this ratio reflect changes in left ventricular chamber stiffness, the slope of the diastolic pressure-volume relation was estimated as: [LVEDP − LVmin]/[EDV − ESV], where LVEDP is left ventricular end-diastolic pressure, LVmin is minimal left ventricular pressure during early diastole, EDV is end-diastolic volume and ESV is end-systolic volume (15). An increase in the end-diastolic pressure-volume ratio coincident with an increase in the slope was used as evidence of increased chamber stiffness. Conversely, an increased ratio without a change in the slope was considered a reflection of an upward parallel shift in the pressure-volume loop.

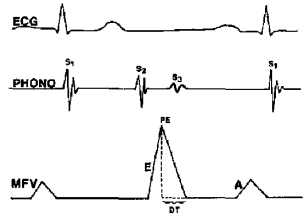


Figure 1. Diagrammatic representation of the temporal association between the electrocardiogram (ECG), intracardiac phonocardiogram (PHONO) and phasic mitral inflow velocity (MFV) measured by pulsed wave Doppler echocardiography. S_1 = first heart sound; S_2 = second heart sound; S_3 = third heart sound. The letter E on the mitral inflow velocity recording denotes the early component of left ventricular filling; the letter A denotes the atrial component. DT = deceleration time; PE = peak velocity during early filling.

Left ventriculograms were performed with the dog placed on its right side and were recorded on 35-mm cine film at 30 frames/s during the injection of 20 ml of contrast material (Reno M-60, Squibb Diagnostics). Correction for image magnification was made with a radiopaque calibrated grid placed at the level of the left ventricle. Left ventricular chamber volumes at end-systole and end-diastole were calculated with the area-length method (16) and were used to determine ejection fraction. Premature and postextrasystolic beats were excluded from the analysis.

Pulsed wave Doppler echocardiography. Phasic mitral inflow velocity was measured with pulsed wave Doppler echocardiography (Hewlett-Packard, model 77020A ultrasound system with a 2.5-MHz transducer) with the dog placed in the right lateral decubitus position. Doppler measurements were performed from the cardiac apex, with the beam aligned parallel to the transmitral flow. The sample volume was placed between the tips of the mitral leaflets to obtain maximal inflow velocity during early diastole (17). Doppler echocardiograms were recorded on a Panasonic 6300 VHS recorder for subsequent analysis. A hard copy of selected records was made on a strip-chart recorder (Hewlett-Packard model 77500A) at a paper speed of 100 mm/s. The following characteristics of phasic mitral inflow velocity (Fig. 1) were measured: 1) peak mitral flow velocity during early diastole, 2) deceleration time of mitral inflow velocity during early diastole, and 3) average deceleration rate of mitral flow velocity during early diastole. Deceleration time was defined as the time interval between peak velocity and the zero intercept of the deceleration slope (18) (Fig. 1). For each transmitral flow measurement, five con-

Table 1. Hemodynamic, Phonocardiographic, Angiographic and Mitral Inflow Velocity Measurements During the Course of Evolving Heart Failure

	Baseline	Onset of S_3	6 Weeks After the Onset of S_3	24 Weeks After the Onset of S_3
S_3 (%)	0	100	154 ± 34	60 ± 25
HR	76 ± 4	76 ± 4	96 ± 3*	72 ± 3
LV EF (%)	56 ± 2	44 ± 4*	31 ± 2*	22 ± 1*
LV EDV (ml)	59 ± 3	63 ± 3	65 ± 3	91 ± 6*
LV EDP (mm Hg)	8 ± 1	17 ± 1*	26 ± 2*	19 ± 1*
EDP/EDV (mm Hg/ml)	0.14 ± 0.01	0.25 ± 0.03†	0.41 ± 0.03*	0.21 ± 0.02†
Slope (mm Hg/ml)	0.22 ± 0.02	0.39 ± 0.05†	1.04 ± 0.09*	0.50 ± 0.05†
τ (ms)	36 ± 4	41 ± 4	51 ± 4†	58 ± 3*
PE (cm/s)	71 ± 4	74 ± 4	78 ± 3	56 ± 3†
DT (ms)	122 ± 7	73 ± 3*	61 ± 3*	81 ± 6*
PE/DT (cm/s per s)	590 ± 40	1,040 ± 90†	1,300 ± 100*	740 ± 110

*$p < 0.01$, †$p < 0.05$ relative to baseline. DT = deceleration time of mitral inflow during rapid filling; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; HR = heart rate; LV = left ventricular; PE = peak mitral flow velocity during rapid filling; Slope = (left ventricular end-diastolic pressure − minimal left ventricular pressure during early diastole)/(end-diastolic volume − end-systolic volume); S_3 = third heart sound; τ = time constant of isovolumetric relaxation.

secutive spectral tracings were evaluated and averaged to obtain a single representative value. Intracardiac phonocardiograms were recorded simultaneously with phasic mitral inflow velocity to examine the timing of the third heart sound during early diastole.

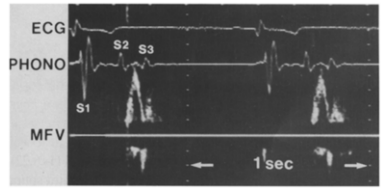
Data analysis. Hemodynamic, phonocardiographic, angiographic and pulsed wave Doppler echocardiographic measurements were obtained at baseline, before any embolization, and were repeated thereafter at intervals of 1 to 3 weeks. In the present study, data are reported at baseline, at the time the third heart sound was first heard, at 6 weeks after the onset of the sound and at 24 weeks after the onset of the sound. Temporal changes in hemodynamic, angiographic, phonocardiographic and pulsed wave echocardiographic measurements were examined by using repeated measures analysis of variance (ANOVA), with the level of significance set at alpha equal to 0.05. If significance was attained by ANOVA, pairwise comparisons between different data acquisition periods were performed by using the Student-Newman-Keuls test (19). For these tests, a p value < 0.05 was considered significant. All data are reported as the mean value ± SEM.

Results

Hemodynamic and angiographic findings at the time of onset of the third heart sound. None of the dogs had a third heart sound at baseline. However, all seven dogs developed an audible third heart sound at a mean of 9 ± 2 weeks after the initial embolization. Once a third heart sound developed, it persisted for the duration of the study. The hemodynamic and angiographic data obtained at all four time periods during the study are shown in Table 1. When a third heart sound was first observed, moderate left ventricular dysfunction was already present and, more important, a significant increase in left ventricular chamber stiffness had developed (Table 1), as evidenced by an increased end-diastolic pressure-volume ratio and increased slope of the diastolic pressure-volume relation (Table 1). The onset of the third heart sound, however, was not associated with an increase in either left ventricular end-diastolic volume or time constant of relaxation (τ) (Table 1).

Changes in mitral inflow velocity pattern at the time of onset of the third heart sound. In all instances, when a third heart sound was first observed and at all observation periods thereafter, the sound occurred simultaneously with the deceleration phase of the early mitral inflow velocity waveform (Fig. 1 and 2). The onset of the third heart sound was associated with the manifestation of rapid deceleration of early mitral inflow velocity and significant shortening of the deceleration time of the early mitral inflow component of ventricular filling. At the time when a third heart sound was first observed, peak mitral inflow velocity during early diastole was unchanged from baseline (74 ± 4 vs. 71 ±

Figure 2. Original electrocardiographic recording (ECG), left ventricular intracavitary phonocardiogram (PHONO) and phasic mitral flow velocity (MFV) in a dog with chronic heart failure. Abbreviations as in Figure 1.



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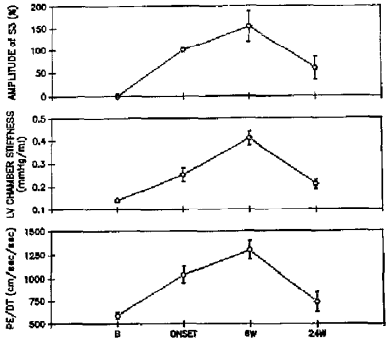

Figure 3. Changes (mean ± SEM) in amplitude of the third heart sound (S3) **(top)**, left ventricular (LV) chamber stiffness **(middle)** and average deceleration (PE/DT) of early mitral inflow velocity **(bottom)** during the course of evolving heart failure. Values are shown at baseline (B), at the time a third heart sound was first observed (ONSET) and 6 (6W) and 24 (24W) weeks after the onset of the third heart sound.

4 cm/s), deceleration time was significantly shorter (73 ± 3 vs. 122 ± 7 ms) ($p < 0.01$) and the consequent deceleration rate was significantly greater than the baseline value (1,040 ± 90 vs. 590 ± 40 cm/s per s) ($p < 0.05$).

Hemodynamic correlates of the amplitude of the third heart sound. At 6 weeks after the onset of a third heart sound, the sound amplitude increased by nearly 54% (Table 1). This increase was accompanied by a significant increase in left ventricular chamber stiffness, early mitral inflow deceleration rate and the time constant of isovolumetric relaxation, without significant alterations of left ventricular end-diastolic volume (Table 1). In contrast, at 24 weeks, the amplitude of the third heart sound decreased significantly to only 60% of its initial level ($p < 0.05$). This decrease in amplitude was associated with a significant decrease in left ventricular chamber stiffness ($p < 0.01$) and deceleration rate of early mitral inflow velocity ($p < 0.01$) (Table 1, Fig. 3). At 24 weeks, left ventricular end-diastolic volume was significantly increased ($p < 0.01$), as was the time constant of isovolumetric relaxation ($p < 0.01$) (Table 1).

Discussion

Origin of the third heart sound. Three principal theories have been advanced to explain the origin of the third heart sound. The sound was attributed to 1) a valvular phenomenon (7,8,20), 2) impact of the heart against the chest wall (9,21), and 3) vibrations of the left ventricular wall (1–6,22). The role of valvular structures in the origin of the third sound has been widely disputed. A third heart sound has been recorded in patients with mitral valve incompetence (23) and was shown to persist even after resection of both atrioventricular valves (24–26). Originally proposed by Boyer (21) in 1942, the theory that early diastolic motion of the heart had an impact on the chest wall and produced a third heart sound has been disputed by recent studies. Craige et al. (27) and Ozawa et al. (4) demonstrated that a third heart sound can be recorded on the epicardial surface of the heart, even when the chest wall has been entirely excluded.

Most investigators (1–6,22,28) attribute the third heart sound to vibrations of the left ventricular wall during rapid filling. According to this theory, the sound is produced as the rapidly expanding ventricle reaches the point where the fibroelastic nature of the myocardium limits further distension. The sudden resistance to further expansion under tension generates a vibratory wave that is detectable on the chest wall as the low frequency third heart sound (22). The results of the present study support this theory. During the evolution of heart failure, a third heart sound was first heard in conjunction with increased left ventricular chamber stiffness and the development of rapid deceleration of early mitral inflow velocity. Increased chamber stiffness was previously shown to be associated with rapid deceleration of early mitral inflow velocity (17) and the presence of a third heart sound (5,10,11,22).

The third heart sound and left ventricular isovolumetric relaxation. The development of a third heart sound has also been linked to prolongation of left ventricular isovolumetric relaxation (5,10), a distinctive feature of the failing heart (15,29). In the present study, there was no significant prolongation of left ventricular isovolumetric relaxation at the time when the third heart sound was first heard. However, isovolumetric relaxation was prolonged in the latter stages of heart failure and was associated with a reduction in the deceleration rate of early mitral inflow velocity. In fact, prolonged isovolumetric relaxation has been shown to be related to a decrease rather than an increase in the deceleration rate of early mitral inflow velocity (17). The absence of prolonged isovolumetric relaxation at the time when the third heart sound was first observed leads us to conclude that this particular diastolic abnormality is not an integral factor in the origin of the third heart sound.

Amplitude of the third heart sound. Few studies (22) have examined the hemodynamic determinants of the amplitude of the third heart sound. To our knowledge, there are no studies that describe the temporal changes in the amplitude of this sound during the course of evolving heart failure. In our study, the amplitude of the third heart sound increased 6 weeks after its onset in association with an increase in both left ventricular stiffness and deceleration rate of early mitral inflow velocity. When both left ventricular chamber stiffness and mitral inflow deceleration rate decreased with the onset of marked left ventricular dilation (24 weeks), the amplitude of the third heart sound decreased significantly. These results are consistent with findings reported by several

investigators (6,22,30). Among patients with a third heart sound, the sound was most prominent in those with increased peak ventricular filling (30). In athletes who manifested a third heart sound and in patients with heart disease and a third heart sound, head-up tilt resulted in a significant decrease in both the deceleration rate of early mitral inflow velocity and the amplitude of the third heart sound (6).

Conclusions. The results of this study indicate that the development of a third heart sound during the course of evolving heart failure is associated with increased left ventricular chamber stiffness and the manifestation of rapid deceleration of early mitral inflow velocity. The amplitude of the third heart sound is dependent on ventricular chamber stiffness and consequently on the deceleration rate of early mitral inflow velocity. These findings are consistent with a myocardial vibration origin of the third heart sound.

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