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Research Article

To examine the mechanism of mitral flow deceleration in diastole and its potential influence on the genesis of third (S3) and fourth (S4) heart sounds, we simultaneously recorded left atrial and left ventricular pressures (micromanometers), mitral flow velocity (electromagnetic catheter-tip flow velocity meter), and internal and external phonocardiograms in 25 open-chest dogs. Diastolic time intervals, transmitral pressure gradients (planimetry), maximum mitral flow velocity, and acceleration and deceleration of flow were measured under different loading conditions. It was found that deceleration of mitral flow in early and late diastole is always caused by a negative transmitral pressure gradient. After volume loading, diastolic pressures, positive (forward) and negative (backward) transmitral pressure gradients, and acceleration and deceleration of flow increased, and an S3 or S4 appeared (20:25 dogs). These sounds occurred during the phase of flow deceleration and could be recorded from the chest wall, inside the left ventricle, and directly from the epicardial surface of the freely exposed left ventricular wall. After balloon occlusion of the inferior vena cava (17:25 dogs), the opposite changes were observed and gallop sounds disappeared. The results indicate that the left ventricular pressure rise in response to filling reverses the transmitral pressure gradient and decelerates flow. Deceleration of inflow by the left ventricular wall in early and late diastole may represent a key mechanism in the genesis [...]

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The Genesis of the Third and Fourth Heart Sounds

A Pressure-Flow Study in Dogs

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Abstract. To examine the mechanism of mitral flow deceleration in diastole and its potential influence on the genesis of third (S_3) and fourth (S_4) heart sounds, we simultaneously recorded left atrial and left ventricular pressures (micromanometers), mitral flow velocity (electromagnetic catheter-tip flow velocity meter), and internal and external phonocardiograms in 25 open-chest dogs. Diastolic time intervals, transmitral pressure gradients (planimetry), maximum mitral flow velocity, and acceleration and deceleration of flow were measured under different loading conditions. It was found that deceleration of mitral flow in early and late diastole is always caused by a negative transmitral pressure gradient. After volume loading, diastolic pressures, positive (forward) and negative (backward) transmitral pressure gradients, and acceleration and deceleration of flow increased, and an S_3 or S_4 appeared (20:25 dogs). These sounds occurred during the phase of flow deceleration and could be recorded from the chest wall, inside the left ventricle, and directly from the epicardial surface of the freely exposed left ventricular wall. After balloon occlusion of the inferior vena cava (17:25 dogs), the opposite changes were observed and gallop sounds disappeared. The results indicate that the left ventricular pressure rise in response to filling reverses the transmitral pressure gradient and decelerates flow. Deceleration of inflow by the left ventricular wall in early and late diastole may represent a key mechanism in the genesis of S_3 and S_4 .

Introduction

The third (S_3)¹ and fourth (S_4) heart sounds, also called gallop sounds, are low-frequency sounds occurring in early and late

diastole under highly variable physiological and pathological conditions. Though various theories have been advanced regarding the genesis of these sounds, the fundamental mechanism of production is still unknown (1-7). According to Rushmer (4), heart sounds should be considered as vibrations of the cardiohemic system due to acceleration or deceleration of flow. Within this general concept of sound generation, we postulated that deceleration of mitral flow in early and late diastole is involved in the genesis of S_3 and S_4 .

Transmitral pressure-flow relationship, mitral valve function, and ventricular inflow have been extensively studied by different techniques (8-12). Factors contributing to the generation of a positive forward pressure gradient and to left ventricular filling are well known and have been discussed recently (13-15). A positive gradient is accomplished mainly by active relaxation of the ventricle. Other factors which may influence the early filling process are the level of left atrial pressure (LAP) at the time of mitral valve opening and mitral valve function. Under conditions of a low to moderate heart rate, the driving pressure becomes zero in middiastole (diastasis). During left atrial contraction, a positive transmitral pressure gradient is reestablished and is responsible for a second acceleration of flow.

In contrast to the process of relaxation, flow acceleration, and filling, few experimental data are available describing the mechanism of flow deceleration. Recent studies (16, 17) have concluded that viscous dissipation is not important in the dynamics of left ventricular ejection. However, it is thought that in normal conditions deceleration of mitral flow during ventricular filling is produced by viscous dissipation of the inertial energy in the absence of an inverse pressure gradient (12, 13). Occasionally, in cases of rapid inflow into a large ventricle or under conditions of an early atrial contraction and/or rapid atrial relaxation, a reversal of the pressures in early and late diastole, respectively, has been reported (12, 13).

The principal purpose of this study is to explore the process of flow deceleration in diastole and to establish its potential

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1. Abbreviations used in this paper: a, top of atrial a-wave; C, enddiastole; F, end of rapid left ventricular pressure rise in early diastole; LAP, left atrial pressure; LVP, left ventricular pressure; MFV, mitral flow velocity; O, minimum LVP in early diastole; S_2 , S_3 , S_4 , second, third, or fourth heart sound; v, top of atrial v-wave; X_1 , X_2 , X_3 , first, second, or third LAP-LVP pressure crossover.

influence on the production of gallop sounds. We therefore evaluated the pressure-flow relationship in a quantitative way by measuring transmitral pressure gradients (planimetry) during different phases of diastolic filling in the anesthetized dog. Gallop sounds were generated by rapid fluid administration and the exact temporal relationship with the simultaneously occurring dynamic pressure and flow changes was examined.

Methods

Preparation

25 mongrel dogs, ranging in weight from 16 to 29 kg, were premedicated with 0.4 ml/kg Hypnorm (Duphar, Amsterdam, Holland) and anesthetized by intravenous injection of 10–15 mg/kg sodium pentobarbital (Nembutal, Abbott Laboratories, North Chicago, IL). Hypnorm, containing 10 mg fluanisone (neuroleptic drug) and 0.2 mg fentanyl (synthetic opioid)/ml, was used because of the cholinergic actions of fentanyl in order to keep heart rate relatively slow throughout the experiment. Artificial respiration was instituted through a tracheal cannula by means of a respirator (Bird Corp., Palm Springs, CA). During the experimental procedure, several arterial blood gas analyses were performed using a semiautomatic pH/blood gas analyzer (Croning Limited, Halstead, United Kingdom). Ventilation conditions were adjusted as required. All dogs underwent a left fifth interspace thoracotomy. Without opening the pericardium a 7 F tip micromanometer with a fluid-filled side lumen (Gaeltec, Isle of Skye, United Kingdom) was introduced into the left atrium via a pulmonary vein. An 8 F fluid-filled Sones catheter (United States Catheter and Instrument Corporation, Billerica, MA) was introduced in the left ventricle via the left carotid artery. The electrical signal from the micromanometer was amplified and used both for pressure and internal phono registrations. The “pressure part” (frequency range, 0–2000 Hz) was further filtered using a two-pole active low-pass filter. The whole system had a flat frequency response up to 300 Hz. The “phono part” of the signal (frequency range, 0–2000 Hz) was filtered using Mannheim filters: octave phonocardiographic filters with a nominal frequency of 25 and 50 Hz and a logarithmic filter. Reference tracings for measuring zero pressure were obtained from the fluid-filled catheter in the left ventricle and the fluid-filled side lumen of the micromanometer in the left atrium. External pressure transducers (Siemens-Elema, Solna, Sweden) were put at midthoracic level and the pressure signals were further amplified and filtered (Electromanometer 863, Siemens-Elema). For the measurement of mitral flow velocity (MFV), a special combined pressure/electromagnetic flow velocity catheter was designed (Medelad, Antwerp, Belgium). The catheter, which had no side lumen, consisted of a pressure transducer at the tip and an electromagnetic flow velocity sensor placed 2 cm above the pressure transducer. The pressure transducer had the same characteristics as the other micromanometers (see above). The flow velocity probe had a sensitivity of 0.2 μ V root mean square (at 10 μ V = 25 cm/s) and a resistance of \pm 8 Ohm (600 Hz). The technical specifications of the electromagnetic pulsed wave constant current flowmeter are as follows: carrier frequency: 600 Hz; excitation current: 0.1–0.5 A; frequency response: DC–100 Hz. The catheter was positioned via a pulmonary vein in such a way that the flow sensor measured MFV at the level of the annulus while the tip of the catheter measured left ventricular pressure (LVP). An appropriate catheter position was maintained by suturing the catheter to the pulmonary vein. The external phonocardiogram was recorded using an acceleration-type microphone (Siemens-Elema) attached to the skin at the place of maximum apical impulse on the right side of the thorax. The same filters were used as for the internal phonocardiogram. The

electrocardiogram, the internal and external phonocardiogram, LAP (micromanometer and fluid-filled system), LVP (micromanometer and fluid-filled system), and MFV were recorded simultaneously on an 8-channel ink-jet recorder (Siemens-Elema) at a paperspeed of 50, 100, and 250 mm/s.

Recordings were made in the control state (at least 30 min after the last dose of anesthetics) and after rapid administration of either Ringer's lactate (16:25 dogs) or a plasma expander (9:25 dogs). Over a 3–8-min period, either 250–500 ml Ringer's lactate or 300–500 ml Macrodex (Povite, Boxtel, Holland) were infused until an enddiastolic pressure of \sim 10–12 mmHg was reached. In 17 dogs, acute volume loading was followed by a brief inflation of a balloon (35 ml) in the inferior vena cava in order to reduce ventricular filling abruptly. For this purpose, a commercially available aortic balloon catheter (Vygon, Aachen, West Germany) was introduced via a femoral vein and was advanced 20 cm in the inferior vena cava. During these balloon occlusions, pressures, flow, and phonocardiogram were continuously monitored.

Calibration, measurements, and calculations

Pressure tracing. The same calibration technique was used for the four pressure recordings. Mechanical calibration was performed using a sphygmomanometer filled with distilled water (H_2O) instead of mercury. The pressure of a column of 135.5 mm H_2O (= 10 mmHg) was applied to the transducers and recorded at great sensitivity: 10 mmHg = 135.5 mm H_2O = 40 mm deflection on the recording paper. After mechanical calibration, the electrical calibration was adjusted very carefully. During the experimental recordings, the four transducers and the gain of the channels of the ink-jet recorder were made equisensitive: 1 mm on the paper equals 0.25 mmHg. Because of eventual base-line shifts of the micromanometer, conventional pressures from the fluid-filled system were recorded throughout the whole experiment. The level of zero pressure was obtained from the strain gauge put at midthoracic level. Before each recording, the micromanometer pressure was zeroed in accordance with its corresponding fluid-filled pressure. High-gain LAP and LVP recordings from the fluid-filled system and from the micromanometer, respectively, were superimposed on the paper. As both micromanometer pressures were adjusted to the same zero level, the transmitral pressure gradient could be measured directly and very accurately from micromanometer pressures at any time of diastole. The following time intervals (milliseconds) were measured on the high fidelity pressure tracings (Fig. 1): from the first LAP-LVP crossover (X_1) to minimum LVP (O): $X_1 - O$; from X_1 to a second LAP-LVP crossover (X_2): $X_1 - X_2$; from X_2 to a third LAP-LVP crossover (X_3): $X_2 - X_3$. X_3 represents the point after which LAP and LVP equilibrate.

Maximum systolic LVP was measured on the low-gain tracings. Pressures of following points in diastole were measured on the high-grain tracings (Fig. 1): top of atrial v-wave (v), X_1 , minimum LVP in early diastole (O), X_2 , end of rapid left ventricular pressure rise in early diastole (F), X_3 , top of atrial a-wave (a), and enddiastole (C). The pressure difference between O and F represents the height of the so-called rapid filling wave. The pressure difference between O and C represents total developed diastolic pressure. After X_1 , a small positive atrioventricular pressure gradient was observed which is responsible for the rapidly increasing mitral flow (Fig. 1). This gradient declines to zero at the time of X_2 . After X_2 , an inverse transmitral gradient was always present. The pressure-time product of these gradients was measured by planimetry. For this purpose, an X – Y digitizing table connected to an HP 9810 A desk calculator (Hewlett Packard Co., Fort Collins, CO) was used. Each area of the same beat was measured 5 times and was expressed as mmHg \times millisecond. The mean speed of pressure rise was measured between O and F (ΔOF) and between O and C (ΔOC). Therefore, the

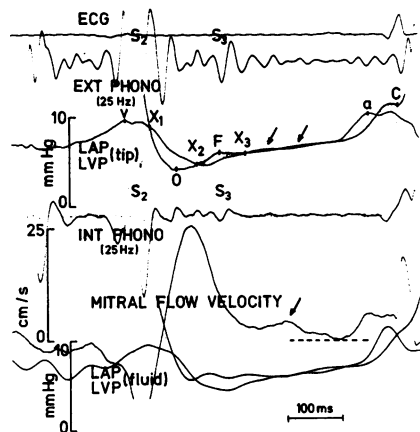


Figure 1. Simultaneous recording of MFV, LAP and LVP (tip: micromanometer; fluid-filled system), and internal and external phonocardiogram (int phono, ext phono) in a dog after volume loading. After minimum diastolic LVP (O), a negative (backward) transmittal pressure gradient is observed which is responsible for rapid deceleration of flow. The vibrations of the S_3 occur during the phase of rapid LVP rise and flow deceleration. During diastasis, small transmittal pressure oscillations and concomitant changes in mitral flow are observed (arrows). Dotted line indicates zero flow.

pressure differences between O and F and between O and C were divided by the time intervals between these points. Similarly, the mean speed of LVP fall after X_1 ($\Delta X_1 \bar{O}$) was measured by dividing the pressure difference between X_1 and O by the time interval $X_1 - O$. These parameters were expressed in mmHg per second (Fig. 1).

Flow velocity tracing. The flow velocity probe was factory calibrated. An electrical calibration signal corresponding to a velocity of 25 cm/s was generated and the gain of the channel of the ink-jet recorder was put in such a way that 1 mm on the paper equals a velocity of 0.5 cm/s.

Mechanical calibration and determination of zero flow during the experiment was impossible. Indeed, the heart, unlike an artery, cannot be occluded to give "mechanical" zero. Therefore, mechanical zero was determined from the decay of MFV toward zero at the end of diastasis just before left atrial contraction. As heart rates were kept relatively low by the administration of fentanyl, this method of zero determination could be used in each experiment. The maximum value of MFV in early diastole (expressed in centimeters per second) and its time relation to minimum LVP (O) were measured (Fig. 1). The mean rate of change of increasing MFV, or mean acceleration, was calculated as the increase of MFV from zero to its maximum value divided by the corresponding time interval (from X_1 to maximum MFV).

Similarly, the mean rate of change of decreasing MFV, or mean deceleration, was calculated as the decrease of MFV from its maximum to nearly zero, at the onset of diastasis, divided by the corresponding time interval (from maximum MFV to X_3) (Fig. 1). Both parameters were expressed in centimeters per square second.

Phonocardiogram. An S_3 or S_4 was considered to be present whenever characteristic proto- or enddiastolic vibrations of $>10\%$ of the height of the second or first heart sound, respectively, were recorded in the 25-Hz filter band, either on the internal or on the external phonocardiogram. The 10% value was chosen arbitrarily in order to eliminate

noise. The same definition was already used in a previous noninvasive study from our laboratory (18).

In 9 dogs where an S_3 or S_4 was present on the external phonocardiogram, the microphone was placed in direct contact with the epicardial surface of the left ventricular free wall. Contact with the thoracic wall or other structures was carefully avoided.

Statistical methods

All measurements were done on at least 5 consecutive beats, in the control state (c) and immediately after rapid fluid administration (f). Paired *t* tests were used to evaluate the changes after volume loading. Results are reported as mean \pm SE.

Results

Time relationships. Table I shows the different time intervals in the control state (c) and after rapid fluid administration (f). Heart rates were nearly identical in the control state (58.5 ± 2.7 beats/min) and after fluid administration (58.1 ± 2.5 beats/min). During isovolumic relaxation, LVP fell to the level of LAP: first pressure crossover (X_1). After X_1 , MFV increased rapidly while LVP was still decreasing. Minimum LVP (O) was reached 62.9 (c) and 65.9 ms (f) after X_1 and preceded peak flow by 25–30 ms on average. After the O point, LVP increased (the so-called rapid filling wave) while LAP continued to decrease. As a consequence, a second pressure crossover (X_2) occurred, 100.7 (c) and 99.8 ms (f) after the first (Fig. 1). A second crossover point with an inversion of the pressure gradient was a consistent finding in each dog experiment in both the control state and after volume loading. Moreover, an inversion of the pressure gradient also occurred at the time of atrial contraction as Fig. 2 illustrates.

After X_2 , LAP increased and reached the level of LVP in X_3 , 120.5 (c) and 108.0 ms (f) after X_2 . When heart rate was slow, LVP and LAP equalized during a period starting at X_3 to the beginning of the left atrial contraction (diastasis). After fluid administration, most diastolic time intervals remained constant. Only the time interval $X_2 - X_3$ shortened (± 10 ms), but this just did not reach the level of statistical significance (Table I).

Pressures and pressure-time relations. Fluid administration increased maximum systolic LVP from 83.3 ± 2.6 to 97.6 ± 3.8

Table I. Time Intervals in Early Diastole Before and After Rapid Fluid Administration*

	$X_1 - O$	$X_1 - X_2$	$X_2 - X_3$
Control state	62.9 ± 5.0	100.7 ± 3.6	120.5 ± 7.3
Volume loading	65.9 ± 3.2	99.8 ± 2.9	108.0 ± 5.2
<i>t</i>	0.66‡	0.28‡	2.04‡
<i>n</i>	23	24	23

* The data are expressed in milliseconds and are the mean \pm SE.

‡ Not significant.

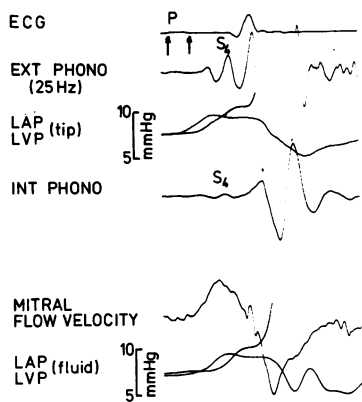


Figure 2. Recording of the pressure-flow sound relationship at time of left atrial contraction. The vibrations of the S_4 occur during deceleration of left ventricular inflow following atrial contraction. Arrows indicate the P wave of the electrocardiogram (ECG). Same abbreviations as in Fig. 1.

mmHg on average ($t = 4.19$; $P < 0.001$). Table II presents LVP and LAP in diastole before and after rapid fluid administration. After volume expansion, there was a significant increase of all diastolic pressures (X_1 , O, X_2 , F, X_3 , C, v, a). The amplitude and the mean rate of change of LVP fall after mitral valve opening and LVP rise during early and total diastole were significantly greater after volume loading (Fig. 3). The pressure gradient present from X_1 to X_2 and responsible for the rapidly increasing flow described an area of 131.4 ± 10.4 mmHg \times ms in the control state. This area increased significantly to 182.2 ± 11.2 mmHg \times ms after volume expansion (Table III). As the $X_1 - X_2$ interval remained constant (Table I), this increase of area must be due to an increased transmitral pressure difference. The inverse pressure gradient present from X_2 to X_3 and responsible for deceleration of flow described an area of 85.3 ± 9.1 mmHg \times ms in the control state. After fluid administration, there was a (statistically insignificant) increase to 101.4 ± 12.1 mmHg \times ms. As the time interval $X_2 - X_3$ decreased after fluid administration (Table I), a greater pressure difference should also be responsible for this increase in area. Both in the control state and after fluid administration, the pressure gradient (area) responsible for increasing flow was greater than the pressure gradient (area) responsible for decreasing flow: $t:3.93$, $P < 0.001$, (c); $t:5.29$, $P < 0.001$, (f).

Flow velocity. In the total group, maximum MFV in early diastole in the control condition was on average 11.9 ± 0.7 cm/s. After fluid administration, maximum MFV increased significantly to 15.3 ± 0.9 cm/s (Table III). The mean rate of increase of MFV, or acceleration, and the mean rate of decrease of MFV, or deceleration, were significantly greater after volume loading (Table III). Changes in acceleration and deceleration after volume loading were significantly correlated ($r:0.65$, $P < 0.001$). Both in control conditions and after volume expansion, acceleration exceeded deceleration: $t:5.3$, $P < 0.001$ (c), $t:5.2$, $P < 0.001$ (f).

Phonocardiogram. An S_4 was present in the control state in 1 dog and after fluid administration in 11 dogs. An S_3 was found in 2 dogs before and in 19 dogs after fluid administration. In 11 dogs both an S_4 and S_3 were recorded after volume loading. In 20 dogs an S_4 or an S_3 were present after volume expansion. When gallop sounds were present on the external phonocardiogram, comparable low-frequency vibrations could always be recorded directly from the left ventricular wall (nine experiments). Figs. 4 and 5 give an example of an S_3 recorded from the chest wall and from the epicardial surface of the left ventricle in the same dog.

Balloon occlusions. In 17 dogs, a balloon was inflated in the inferior vena cava in order to reduce left ventricular filling abruptly. During these acute interventions, heart rate, pressures, flow, and phono were continuously changing.

Therefore, no quantitative measurements and statistical analyses were performed on these tracings. However, the hemodynamic effects of the balloon occlusions were self-evident and are illustrated in Figs. 6 and 7. By reducing left ventricular filling, diastolic pressures suddenly decreased, positive and negative transmitral pressure gradients and maximum MFV declined, acceleration and deceleration of flow were much slower, and gallop sounds disappeared.

Discussion

This study was especially designed to explore the process of flow deceleration in diastole and to establish its potential influence on the genesis of S_3 and S_4 .

Methodology. Transmitral flow was measured directly by means of an electromagnetic flow velocity meter. When com-

Table II. Diastolic Pressures Before and After Rapid Fluid Administration*

	X_1	O	X_2	F	X_3	C	v	a
Control state	4.97 ± 0.46	1.14 ± 0.36	1.59 ± 0.35	2.75 ± 0.38	2.65 ± 0.35	4.24 ± 0.44	5.05 ± 0.46	4.98 ± 0.41
Volume loading	10.01 ± 0.66	4.38 ± 0.50	5.25 ± 0.48	7.38 ± 0.54	7.25 ± 0.53	11.35 ± 0.65	10.34 ± 0.64	12.02 ± 0.56
<i>t</i>	12.65‡	11.20‡	13.56‡	13.33‡	13.55‡	16.05‡	13.51‡	19.05‡
<i>n</i>	24	24	21	23	25	25	25	25

* The data are expressed in mmHg and are the mean \pm SE. ‡ $P < 0.001$.

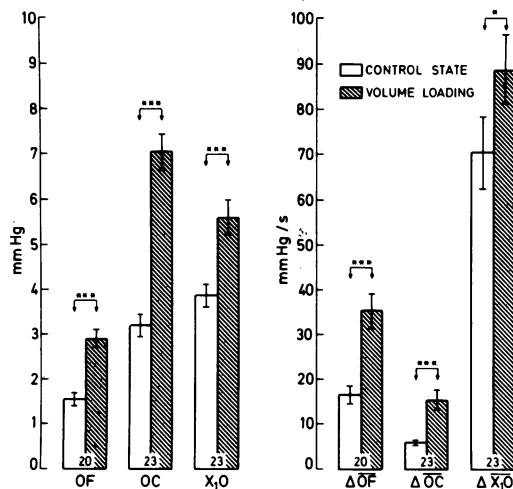


Figure 3. After volume loading, the height and mean rate of LVP rise in early diastole (OF and $\Delta\overline{OF}$) and throughout total diastole (OC and $\Delta\overline{OC}$) were significantly greater. Similarly, the amplitude and the mean rate of LVP fall after X_1 (X_1O and ΔX_1O) increased significantly. Number of dogs indicated at bottom of bar. * $P < 0.05$. *** $P < 0.001$.

pared with circular flow probes, the use of catheter-tip flow velocity meters has several advantages: these flow velocity probes can be placed in the mitral valve annulus via a pulmonary vein within a few minutes; the pericardium, the mitral valve apparatus, and other cardiac structures are left intact; and cardiopulmonary bypass with the potential risk of myocardial damage can be avoided. However, the method also has its limitations: the catheter may disturb transmitral flow; flow velocity is measured only at one point of the mitral ring; and flow velocity and volume flow do not vary linearly because of variations in size of the mitral valve annulus throughout diastole (19). Therefore the absolute values of maximum MFV, acceleration, and deceleration of flow in our study should be interpreted with caution, and they are difficult to compare with the results of circular flow probe measurements. However, because of the

flatness of the velocity profile across the mitral ring (20) and the striking similarity of velocity and volume flow curves, the method is very useful for evaluating time relationships and relative changes within the same animal. Much attention was given to the calibration, zero-setting, and high-gain recordings of LAP and LVP. The recording of conventional (fluid-filled system) pressures for zero-setting throughout the whole experiment and the use of high-gain tracings were considered of the utmost importance.

Transmitral pressure-flow relationship. From our experiments the following consistent transmitral pressure-flow relation can be formulated. After aortic valve closure LVP falls during isovolumic relaxation to the level of LAP. At that time a positive transmitral pressure gradient is established, the mitral valve opens, and early filling starts.

During the initial phase of early filling ventricular relaxation proceeds and pressure continues to decline despite filling. After a certain time filling of the ventricle "exceeds" active relaxation (21) and LVP begins to rise. As LVP is now rapidly increasing and LAP continues to decrease, a second pressure crossover point (X_2) is reached nearly at the time of peak flow.

Hereafter an inverse pressure gradient is present which is responsible for deceleration of flow. Because of the deceleration of inflow atrial emptying declines while atrial filling continues. As a consequence, LAP rises and reaches the level of LVP (X_3). During the subsequent period (diastasis), an equilibrium is obtained and no transmitral pressure gradient is present until atrial contraction begins (Fig. 1). The previous description is valid if the duration of diastole is sufficiently long. At higher heart rates atrial contraction occurs earlier and no period of pressure equalization exists. All these findings are in close agreement with the results of the dog experiments of Yellin and co-workers (9, 10, 12, 13). These authors, however, do not mention an inverse pressure gradient as a normal physiological condition for deceleration of flow. Only in conditions of acute volume distension or increased stiffness was an inverse gradient described which decelerated flow in early diastole more rapidly than normal. Similarly, a negative pressure gradient was described after a trial contraction under conditions of a premature atrial contraction

Table III. Transmitral Pressure Gradients and Flow Changes in Early Diastole Before and After Rapid Fluid Administration

	MFV			Transmitral pressure gradient	
	Peak value* in early diastole	Mean rate‡ of increase	Mean rate‡ of decrease	Forward§	Backward§
Control state	11.9±0.7	131.6±9.1	101.2±6.8	131.4±10.4	85.3±9.1
Volume loading	15.5±0.9	173.2±12.4	133.3±11.0	182.2±11.2	101.4±12.1
<i>t</i>	4.3	4.6	3.6	5.9	1.8 ^{**}
<i>n</i>	22	21	20	24	23

Data are mean±SE. * Expressed in centimeters per second. ‡ Expressed in centimeters per square second. § Expressed in mmHg × millisecond. ^{||} $P < 0.001$ ^{||} $P < 0.005$ ^{**} Not significant.

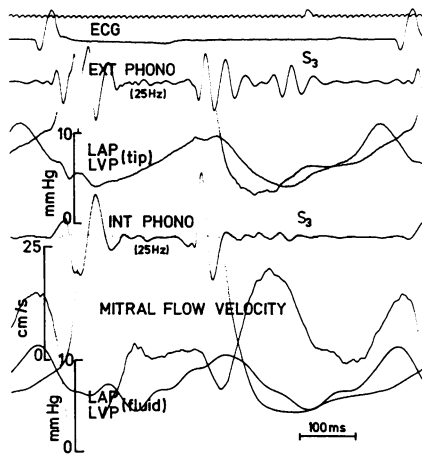


Figure 4. Pressure-flow sound recording in a dog after volume expansion. The S_3 is recordable from the chest wall and inside the left ventricle. Same abbreviations as in Fig. 1.

or a vigorous atrial relaxation. By the use of high-gain tracings (10 mmHg = 40 mm on the paper) and the recording of conventional pressures for zeroing throughout the whole experiment, we were able to detect and to quantitate small transmitral pressure gradients. An inverse pressure gradient after minimum LVP was a constant finding in all our experiments without any exception.

Not only during early diastole but also after atrial contraction, a negative transmitral pressure gradient was observed. This pressure gradient did not close the valve nor did it cause mitral regurgitation because of the forward flow momentum. The generation of an inverse pressure gradient will mainly depend upon

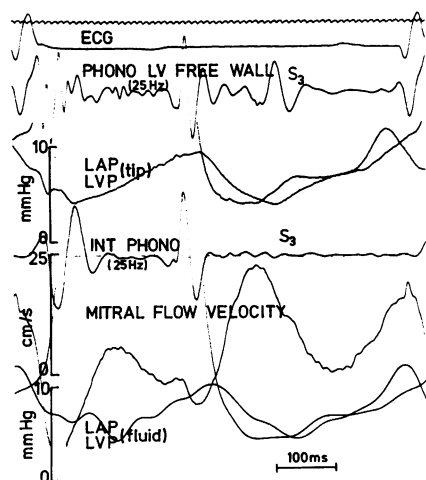


Figure 5. The same dog as in Fig. 4. The microphone is now placed on the epicardial surface of the freely exposed left ventricular (LV) wall. Comparable low-frequency vibrations are recordable directly from the ventricular wall. Same abbreviations as in Fig. 1.

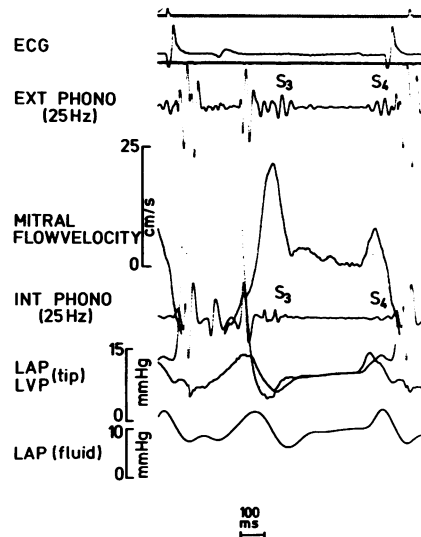


Figure 6. Pressure-flow sound recording in a dog after volume loading. An S_3 and S_4 are present on the internal and external phonocardiogram. Same abbreviations as in Fig. 1.

the speed of pressure rise in response to filling. By these mechanisms, relaxation rate and mechanical properties of the myocardium are able to influence the time course of transmitral pressure and flow: during relaxation, a forward pressure gradient

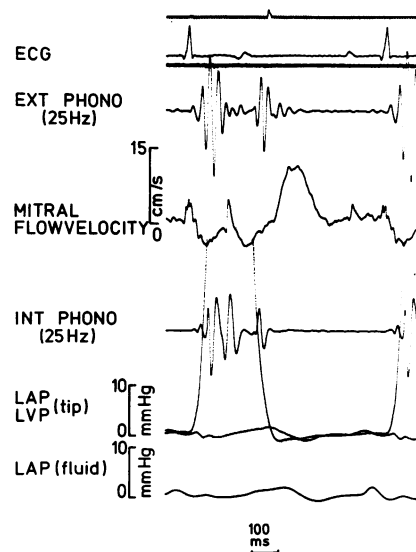


Figure 7. The same dog as in Fig. 6. After volume expansion (Fig. 6), a balloon was inflated in the inferior vena cava in order to reduce ventricular filling abruptly. As a consequence, forward and backward transmitral pressure gradients, peak flow velocity, acceleration and deceleration of flow decline and gallop sounds disappeared. Same abbreviations as in Fig. 1.

is created and flow is accelerated; the pressure rise in response to filling, mainly determined by the completeness of relaxation and by the viscoelastic properties of the myocardium, reverses transmitral pressures and flow is decelerated.

Effects of volume loading. Acute fluid administration increases the filling rate of the ventricle as estimated from the increase of maximum MFV across the mitral valve. Diastolic pressures, forward and backward pressure gradients, and acceleration and deceleration of flow also increased after volume loading. The increased flow acceleration after volume loading may result from an increased relaxation rate of the ventricle (see X_1O and $\Delta\bar{X}_1\bar{O}$ in Fig. 3) and a higher level of LAP at the time of mitral valve opening (see X_1 in Table II). The increased deceleration of flow can be explained by the steeper pressure rise after minimum LVP (see OF and ΔOF in Fig. 3). Thus, by rapid fluid administration, transmitral flow increases and this increased flow must be decelerated by a steeper LVP rise in early diastole. Changes in flow acceleration and deceleration after fluid administration were indeed significantly correlated.

Mechanism of production of gallop sounds. The finding of a reversal of the pressures as a normal physiological hemodynamic event is of importance not only for the understanding of mitral flow but also for the genesis of gallop sounds. After volume loading, a definite S_3 and/or S_4 were recognized in the majority of the dogs. These gallop sounds occurred during a period of rapidly increasing LVP and decreasing mitral flow as illustrated in the figures.

According to Rushmer (4), one may suppose that during deceleration of ventricular inflow the cardiohemic system is set into vibrations which may become audible and recordable from the chest as an S_3 or S_4 if they are transmitted to the thoracic wall with sufficient intensity. The higher the inflow rate (e.g., fluid administration, valvular regurgitation, and high-output states) and/or the steeper the pressure rise in response to filling (altered viscoelastic properties of the myocardium and incomplete relaxation, e.g., dilated cardiomyopathy), the greater the amount of energy imparted to the system. The interrelationship of filling rate, pressure response to filling, and gallop sounds is further stressed by the balloon occlusion experiments. Very recently, Ozawa et al. (22, 23) suggested that the S_3 is due to an intrinsic limitation of longitudinal expansion of the left ventricular wall during early filling. In these studies LVP in diastole were not reported (22) and the time course of filling was estimated indirectly using serial analysis of left ventricular angiograms (23). These observations are in line with our findings. We believe, however, that our results point to a more basic mechanism as it can explain the occurrence of an S_3 in dilated cardiomyopathy where axis changes are small. Moreover, deceleration of flow probably also accounts for the occurrence of an S_4 , which has phonocardiographic characteristics very similar to the S_3 and cannot be explained by a renewed limitation of longitudinal expansion.

In accordance with the findings of others (7, 22, 23), the intensity of gallop sounds was uniformly smaller inside the ven-

tricle compared with either the chest wall or the epicardial surface of the heart. Several possible explanations exist. The relaxation rate and the mechanical properties of the left ventricular wall greatly determine the amount of filling, the pressure changes in response to filling, and as demonstrated in this study, the amount of deceleration of inflow. Therefore, it can be assumed that the left ventricular wall is also the major cardiac structure which is set into vibrations during deceleration of flow. The low frequency of the gallop sounds can then be explained by the great mass of the vibrating structure in proportion to its small elasticity (relaxed walls in diastole) (4). Furthermore, it has been shown that most of the energy contained in cardiovascular sounds travels in the form of transverse vibrations along anatomical surfaces, whereas only a part of the energy is present in the form of compressional waves (24). Since the micromanometer in the ventricle can only record these compression waves, it may be expected that internally recorded gallop sounds are less intense. Finally, the recording of gallop sounds directly from the freely exposed heart, also found by Ozawa et al. (22), makes it highly unlikely that impact of the heart against the chest wall explains the genesis of these sounds as proposed by Reddy et al. (7).

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