Hemodynamic Variables Affecting the Relation Between Mean Left Atrial and Left Ventricular End-Diastolic Pressures

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Changes of pressure in the atrium have two direct and important circulatory consequences. The first is that a change of mean atrial pressure alters the central pressure level which must be exceeded by blood returning from the venous system. The second is that a change of atrial pressure will influence the rate of ventricular filling and ventricular end-diastolic pressure. The significance of the latter is that this value is known to exert important effects on the stroke work and stroke power of the ventricle and thus influence the forward propulsion of blood. Those factors which determine the level of mean atrial pressure for any given level of ventricular end-diastolic pressure achieved are, therefore, of importance for an increased understanding of total circulatory integration.

Previous studies have shown that autonomic nerve stimulation can change substantially the relation between mean left atrial pressure (MLAP) and left ventricular end-diastolic pressure (LVEDP). The objectives of this communication are first to present data from experiments in which this relation (MLAP—LVEDP) was examined while aortic pressure, stroke volume, and heart rate were each varied independently. Second, experiments will also be described to make clear the importance of sympathetic nerve activity in keeping this relation within narrow limits when tachycardia occurs. A preliminary report of these observations has appeared elsewhere.

Methods

Mongrel dogs weighing 16 to 25 kg were anesthetized with a warmed mixture of chlordiazepoxide (60 mg/kg) and urethane (600 mg/kg) given intravenously. Congestion was prevented by an initial intravenous dose of 75 mg of heparin followed by doses of 10 mg given hourly. Respiration was maintained by a Starling pump.

Two preparations were used. The first is illustrated in figure 1. Total aortic flow (cardiac output minus coronary flow) was led through a bypass placed in the descending thoracic aorta and measured with a Potter electroturbinometer (Pet.). After cannulation of the carotid arteries the brachiocephalic artery was ligated and the head was perfused from the bypass, distal to the flow meter. Aortic flow could be controlled or varied by means of a pump-operated arteriovenous shunt (AVS) between the aortic bypass and the inferior vena cava (IVC). Aortic pressure was measured through a large bore metal sound introduced into the left subclavian artery and mean aortic pressure was controlled by connecting a large reservoir (Pressure bottle) to the aortic line and keeping a constant air pressure, equal to the desired mean aortic pressure, over the blood. The heart was paced from the right atrium (RA) with a Grass impulse generator. Left atrial (LA) and left ventricular (LV) pressures were measured through wide-bore sounds introduced through the atrial appendage and apical dimple, respectively, and connected to Statham strain gauge transducers (Tr.). The right stellate ganglion was resected; the left stellate was isolated by cutting all central rami and placed in a bipolar stimulating electrode. Bilateral cervical vagotomy was performed in all animals. In all studies other than those concerning the effects of stellate ganglion stimulation, reflex activity was diminished by a dose of mecamylamine (Inversine), 10 to 20 mg/kg, sufficient to abolish the pressor response to bilateral carotid artery occlusion.

The second preparation has been described in detail elsewhere. It consisted of a right heart bypass in which all venous blood was led from the right heart to a reservoir and then pumped through...
FIGURE 1
Schema for arteriovenous fistula preparation in which cardiac output, mean aortic pressure, and heart rate could be varied independently. Abbreviations defined in text.

A) EFFECT OF CHANGING AORTIC PRESSURE
Ten experiments were performed on six animals in which the effect of changing mean aortic pressure on the MLAP—LVEDP relation was observed. In these experiments mean aortic pressure was varied over a maximal range of 50 to 160 mm Hg while stroke volume and heart rate were maintained constant. Increasing or decreasing mean aortic pressure did not modify the MLAP—LVEDP relation in any of these animals. The experiments are summarized in table 1 and one such study is graphed in figure 2A.

B) EFFECT OF CHANGING STROKE VOLUME
The influence of changing stroke volume on the MLAP—LVEDP relation was investigated in eight animals. Heart rate and mean aortic pressure were each held constant while cardiac output was augmented. Stroke volume was changed over a maximal range of 5 to 46 ml with no consistent effect on the MLAP—LVEDP relation. One such study is graphed in figure 2B and data from 10 experiments are summarized in table 1.

C) EFFECT OF CHANGING HEART RATE
The influence of changing heart rate on the MLAP—LVEDP relation was examined in seven animals at constant mean aortic pressure and stroke volume. As seen in table 1 heart rate could be changed over a wide range with little or no effect on this relation. In nearly all animals, however, MLAP increased in relation to LVEDP at the higher rates studied. One such experiment is graphed in figure 3. Heart rate was increased from 120 to 150 beats/min with essentially no change in the MLAP—LVEDP relation, but as the rate was increased further MLAP—LVEDP rose. The increase of the MLAP—LVEDP relation at rapid rates was always the result of an elevation of MLAP with little change of LVEDP.

In all animals in which the MLAP—LVEDP relation increased, the heart rate at which this was observed coincided with the rate at which part or all of the atrial "A" wave occurred within the preceding ventricular beat. Figure 4 shows the effect of increasing heart rate on left atrial pressure and left ventricular diastolic pressure. Aortic pressure and stroke volume were constant. Ventricular end-diastolic pressure was only...
1 cm H₂O higher at the rate of 222 than at 115. Mean atrial pressure, however, was 10 cm H₂O higher at the rate of 222 than at 115. Diastolic time between ventricular beats was reduced markedly at the rapid rate and the interval between atrial systole and ventricular systole (A₁-V₁ interval) was prolonged from 58 msec at the rate of 115 to 120 msec at the rate of 222. Similar prolongation of the A₁-V₁ interval was noted in all animals at the higher heart rates. The abbreviated ventricular diastole and the prolonged A₁-V₁ interval both contributed to placing atrial systole largely within the period of the previous ventricular beat at the rapid rate.

D) EFFECT OF STELLATE GANGLION STIMULATION

The influence of stimulating the left stellate ganglion on the MLAP—LVEDP relation was investigated 29 times in 10 animals at constant mean aortic pressure and heart rate. In each experiment the effect was observed over a wide range of stroke volumes. In all animals, regardless of heart rate or stroke

### TABLE 1

<table>
<thead>
<tr>
<th>Stroke volume: ml (8)*</th>
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<tbody>
<tr>
<td>6-10</td>
<td>11-15</td>
</tr>
<tr>
<td>t</td>
<td>-0.2</td>
</tr>
<tr>
<td>t</td>
<td>±0.6</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart rate: beats/min (7)*</th>
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<tbody>
<tr>
<td>101-110</td>
<td>111-120</td>
</tr>
<tr>
<td>t</td>
<td>0.7</td>
</tr>
<tr>
<td>t</td>
<td>±0.7</td>
</tr>
</tbody>
</table>

*Number of animals studied.
†MLAP—LVEDP relation in cm H₂O; data are grouped under each variable, mean for group.
‡SE of the mean in cm H₂O.

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volume, stellate ganglion stimulation decreased the MLAP—LVEDP relation. In any given animal stellate stimulation always produced a greater fall of the MLAP—LVEDP relation at rapid heart rates than at slow heart rates. In certain instances the effect of stellate stimulation was somewhat more prominent at high stroke volumes than at low stroke volumes, but this was not a consistent finding. The experiments illustrated in figure 5 are representative of the data. They show that as heart rate was increased from 131 to 221, stellate ganglion stimulation produced a greater fall of MLAP in relation to LVEDP.

In figure 6 the data from figure 5 are re-plotted by placing all the observations without stellate stimulation in the left panel (A) and all the observations during stellate stimulation in the right panel (B). Data obtained at a heart rate of 175 are also included. On the left, heart rate was increased from 131 to 175 with little effect on the MLAP—LVEDP relation. At rates of 206 and 221, however, MLAP was substantially higher for any given LVEDP. During stellate stimulation, heart rate was increased over the entire range from 131 to 221 with essentially no change in the MLAP—LVEDP relation.

Figure 7 shows tracings from an experiment which illustrates further the effects of stellate stimulation. In this experiment heart rate was held constant at 221 beats/min and mean aortic pressure at 70 mm Hg. In panel A, during the control period, LVEDP was 10 cm H₂O, MLAP was 12.5 cm H₂O, and cardiac output was 1850 ml/min. During stellate stimulation, panel B, cardiac output was 3350 ml/min, LVEDP was 10 cm H₂O and despite the markedly augmented cardiac output MLAP was only 5 cm H₂O. With stellate ganglion stimulation the duration of ventricular systole shortened from 195 msec to 160 msec and the Δs-Vs interval shortened from 90 msec to 60 msec. Both the longer diastolic interval and the shorter Δs-Vs interval enabled the atrium to contract after the mitral valve opened; before sympathetic stimulation the atrium clearly contracted prior to opening of the mitral valve.

Figure 8 shows tracings from an experiment which illustrates further the effects of stellate stimulation. In this experiment heart rate was held constant at 221 beats/min and mean aortic pressure at 70 mm Hg. In panel A, during the control period, LVEDP was 10 cm H₂O, MLAP was 12.5 cm H₂O, and cardiac output was 1850 ml/min. During stellate stimulation, panel B, cardiac output was 3350 ml/min, LVEDP was 10 cm H₂O and despite the markedly augmented cardiac output MLAP was only 5 cm H₂O. With stellate ganglion stimulation the duration of ventricular systole shortened from 195 msec to 160 msec and the Δs-Vs interval shortened from 90 msec to 60 msec. Both the longer diastolic interval and the shorter Δs-Vs interval enabled the atrium to contract after the mitral valve opened; before sympathetic stimulation the atrium clearly contracted prior to opening of the mitral valve.
valve resistance with a high degree of precision, nevertheless, in neither case did augmentation of mitral valve flow rate measurably influence the difference between mean pressures in the atrium and ventricle during filling. A corollary to this finding is that the elevated mean atrial pressure observed at rapid heart rates resulted from an increase of atrial pressure during ventricular systole, not during the diastolic filling period.

Discussion

The purpose of these experiments was to characterize the influence of several selected hemodynamic variables on the MLAP—LVEDP relation. Two preparations were used, each of which permitted independent control of stroke volume, aortic pressure, and heart rate. The results indicate that the MLAP—LVEDP relation is independent of stroke volume and of aortic pressure. Heart rate can be increased over a substantial range without influencing the MLAP—LVEDP relation. However, a critical rate exists in any given heart above which mean atrial pressure increases in relation to LVEDP. This increase results from an increase of MLAP with little or no change of LVEDP. Stellate ganglion stimulation decreases the MLAP—LVEDP relation at any given heart rate or stroke volume, and this effect is most prominent at rapid heart rates. The following factors were considered to be of importance in influencing the MLAP—LVEDP relation; the vigor of atrial systole, the timing of atrial systole, and the duration of ventricular diastole.

**FIGURE 4**

Effect of increasing heart rate on atrial and ventricular pressures. AP = aortic pressure, LAP = left atrial pressure, LV-D = left ventricular diastolic pressure, HR = heart rate, MLAP = mean left atrial pressure, A-V_t = interval between atrial systole and ventricular systole. Paper speed 100 mm/sec.

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FIGURE 5
Effect of left stellate ganglion stimulation on the relation between LA(mean) and LVEDP at four different heart rates. At each heart rate stroke volume was increased at constant mean aortic pressure before and during stellate ganglion stimulation.

FIGURE 6
Effect of increasing heart rate on the relation between LA(mean) and LVEDP in the absence of stellate stimulation, Panel A, and during stellate stimulation, Panel B. See text for additional description.
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FIGURE 7

Effect of left stellate ganglion stimulation on atrial and ventricular pressures. AP = aortic pressure, LAP = left atrial pressure, LV-D = left ventricular diastolic pressure, MLAP = mean left atrial pressure, DS = duration of systole, A-V_s = interval between atrial and ventricular systole, CO = cardiac output. Paper speed 100 mm/sec.

VIGOR OF ATRIAL SYSTOLE

Recent studies on the transport function of the atrium indicated that when the vigor of atrial systole was increased MLAP was lower for any given LVEDP and vice versa. The data reported in this paper concerning the effect of stellate ganglion stimulation are consistent with those observations and support the view that when atrial contractility is augmented the MLAP—LVEDP relation is reduced. In an investigation of the effect of stellate ganglion stimulation on atrioventricular pressures, Ulmer and Randall stated that mean atrial pressure may increase, decrease, or show no change. In those experiments, however, cardiac output and heart rate were allowed to vary. In this study when heart rate and cardiac output were held constant stellate ganglion stimulation always reduced MLAP.

It has been shown that the MLAP—LVEDP relation is higher during atrial fibrillation than when an effective atrial systole occurs before each ventricular beat. This finding is consistent with the observation of Braunwald and Frahm who found that MLAP was higher in relation to LVEDP in a patient who developed atrial fibrillation during catheterization. Such findings during experimental and clinical atrial fibrillation support the
view that when the vigor of atrial systole is depressed MLAP is higher for any given LVEDP.²

Wiggers and Katz demonstrated that the atrial contribution to ventricular filling was decreased by vagal stimulation and increased by epinephrine infusion.⁹ It has also been shown that direct cardiac sympathetic nerve stimulation can greatly augment the contribution made by the atrium.¹⁰ In addition, early in vitro studies suggested the possibility that the atrioventricular valve could be closed by atrial systole¹¹,¹² and Little reported convincing experiments in intact animals which demonstrated that the tricuspid valve could be closed solely as the result of atrial activity.¹³ Subsequent studies¹⁴ have shown that the mitral valve can be closed consequent to atrial contraction and relaxation, and that valve closure was dependent upon the vigor of atrial systole. These considerations suggest that atrial contraction can transport significant volumes of blood into the ventricle and close the mitral valve before the onset of ventricular systole.¹⁴ Both of these functions of the atrium provide a booster pump mechanism which tends to maintain a substantially lower mean atrial pressure for any LVEDP.

TIMING OF ATRIAL SYSTOLE

Gesell first noted that the interval between atrial and ventricular systole was of hemodynamic significance.¹⁵ He showed, in dogs with heart block, that when atrial systole occurred at an optimal moment, arterial pressure was highest and venous pressure lowest. Wiggers and Katz⁹ and Jochim¹⁰ confirmed and extended many of the observations of Gesell. In view of the data presented in this report it would appear that a long Aₔ-Vₙ interval may influence the MLAP-LVEDP relation in the following manner. When part or all of atrial systole occurs against a closed mitral valve from the preceding ventricular beat, it contributes to an increase of mean left atrial pressure but fails to propel blood into the ventricle. When heart rate was increased in the absence of concomitant sympathetic nerve stimulation, the A-Vₙ interval²⁰ prolonged atrioventricular transmission time. At rapid heart rates the long Aₔ-Vₙ interval and the short diastolic filling period both contributed to placing atrial systole within the period of the previous ventricular beat (fig. 4). Under these conditions the atrial contraction occurred against a closed mitral valve and increased MLAP. Stellate ganglion stimulation lengthened substantially the diastolic filling period and shortened the Aₔ-Vₙ interval²⁰ (fig. 7). The net effect of sympathetic

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stimulation was to reduce MLAP for any given LVEDP (fig. 5) and to extend markedly the range over which heart rate could be augmented with no change of the MLAP—LVEDP relation (fig. 6).

DURATION OF VENTRICULAR DIASTOLE

The experiments described in this report help to clarify the role of the diastolic filling period in determining the MLAP—LVEDP relation. At rapid heart rates, or at moderate rates with depressed ventricular performance, the duration of diastole may be very short and atrial systole may occur within the preceding ventricular beat. Under these conditions, slowing the heart rate or increasing ventricular contractility at a constant heart rate will lengthen the diastolic interval and permit atrial systole to occur after the mitral valve has opened. This mechanism was clearly an important factor at rapid rates, contributing to the decrease of MLAP—LVEDP by sympathetic stimulation. More rapid ventricular relaxation during sympathetic stimulation also may have contributed importantly to a longer diastolic period. The observation that the mean diastolic pressure difference between atrium and ventricle was not altered by changes of stroke volume or heart rate, suggests strongly that the normal mitral valve offers a negligible resistance to flow and, therefore, that the effect of changes of the diastolic interval on flow rate through the mitral valve is not of itself a critical factor affecting the MLAP—LVEDP relation.

Summary

The observations reported in this paper support the view that a vigorous and properly timed atrial contraction, by transporting blood into the ventricle and by approximating the atrioventricular valve prior to ventricular systole, provides a mechanism by which mean atrial pressure is maintained at a substantially lower level for any ventricular end-diastolic pressure than would be the case if these functions of the atrium were not operative. The central nervous system, by way of efferent sympathetic pathways, can regulate appropriately the vigor and timing of atrial systole as well as the duration of the diastolic filling period. The net effect of such regulation is to decrease mean atrial pressure at any given heart rate and cardiac output, and to permit rapid heart rates which could not otherwise be tolerated without elevations of atrial pressure. The fact that MLAP—LVEDP is independent of aortic pressure and stroke volume, and of heart rate over certain ranges suggests that this hemodynamic measurement is uniquely dependent on, and therefore useful in the analysis of, atrial performance.

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References


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