Differential Effects of Diethyl Ether Anesthesia Upon Right and Left Myocardial Function

Shiro Shimosato, M.D., Ph.D., Charles Gamble, B.S., Benjamin E. Etsten, M.D.†*

Effects of diethyl ether anesthesia upon the mechanical performance of the left and right ventricles were determined in 10 dogs. Deep ether anesthesia resulted in reductions of left ventricular stroke work, stroke power, stroke velocity and tension-time index per beat at any given left ventricular end-diastolic pressure. In contrast, right ventricular function curves were unchanged. The slope of the left ventricular function curve, the ratio of external ventricular stroke work in gram-meters to a unit of ventricular end-diastolic pressure in centimeters of water, decreased proportionately with increasing inspiratory concentration of diethyl ether. The difference in the effect of ether upon left and right ventricular stroke work was found to be due to a decrease in mean aortic pressure and an unchanged mean pulmonary arterial pressure. We conclude that the difference between the left and right "work and power-performances" was not related to the difference in inotropic state of ventricles but to the differential effects of ether upon afterload, namely, mean aortic and pulmonary arterial pressures.

THE concept that diethyl ether evokes a negative inotropic action upon the heart is supported by studies on the isolated dog ventricle and the heart-lung preparation.[1-4] In anesthetized intact subjects there is evidence that the sympathetic nervous system plays an important role in maintaining circulatory homeostasis.[5-7] However, the effects of ether upon the heart with an intact neurohormonal system have not been thoroughly examined. The purpose of this study, therefore, was to determine the influence of diethyl ether specifically upon the performance of the right and left ventricles in intact dogs, not subjected to the stress of surgery[8]: this was evaluated in terms of right and left ventricular stroke work, power-velocity-performances.

Method

Studies were performed on 10 dogs (average weight, 18.6 kg.), each serving as its own control. Each dog was anesthetized with 50 per cent nitrous oxide in oxygen. One per cent procaine was infiltrated in the cut-down areas to be sure that the dog had no pain. The trachea was intubated with a cuffed endotracheal tube after the administration of succinylcholine chloride, 0.1 per cent in 5 per cent dextrose in water. Respiration was controlled by means of a volume limited ventilator[9] with a Frumin valve. The tidal volume and respiratory frequency were kept constant to maintain arterial blood gases within a normal range (*p*H, 7.35–7.40; P_{CO_2} 35–40 mm. of mercury).[8]

Under fluoroscopic control, three cardiac catheters were positioned: A double-lumen Cournand cardiac catheter (7F) was inserted through the left femoral vein into the pulmonary artery and right ventricle; A second double-lumen catheter was inserted through the left femoral artery into the left atrium and left ventricle. A specially constructed catheter (7F, 40 cm. long) was placed in the ascending aorta through the right carotid artery. Intrapleural pressure was estimated by measurement of pressure in a rubber balloon attached to a polyethylene tube, introduced into the mid-esophagus. Pressure transducers were used to obtain pulmonary arterial, left ventricular and right ventricular pressures (Statham P23Db), aortic pressure (Statham P23Gb), and esophageal pressure (Statham Pm131TC).

* Assistant Professor of Anesthesiology.
† Professor of Anesthesiology.
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To permit rapid bleeding and infusion of blood, cannulae were placed in the right femoral artery and vein and connected to a reservoir of the animal's own blood which had been collected in ACD solution 10 to 14 days prior to the study. The blood in the reservoir was kept at 37° C. and mixed continuously by a magnetic stirrer. The animal's body temperature was maintained at 37 ± 0.5° C. by means of a thermal blanket.

Measurements. Thirty to 60 minutes after catheterization, nitrous oxide was discontinued and the dog was allowed to emerge fully from anesthesia. Control measurements of left and right ventricular function curves, left ventricular stroke power and stroke velocity were made. The methods used to obtain ventricular function curves were similar to those reported in previous publications.[8] Blood from the reservoir was then infused, in 50- to 100-ml. increments every 60 to 90 seconds, to alter the ventricular end-diastolic pressures. Thirty to 60 seconds after each infusion, cardiac output was determined by the dye dilution technique, using indocyanine dye mixed with plasma.[8] Femoral arterial blood was drawn into a cuvette densitometer (Colson Model 103-IR) at the rate of 0.9 ml. per second to provide a timed dye concentration curve.* Blood withdrawn for each determination of cardiac output was re-infused as soon as the dye concentration was recorded.

After the completion of function curve determinations, the total amount of infused blood minus the blood withdrawn for arterial gas analysis was withdrawn into the reservoir. After pressures returned to control levels, an EMO † vaporizer was inserted into the nonrebreathing ventilation system, and a constant inspiratory concentration of diethyl ether was administered for at least 30 minutes. Infusions of blood were then repeated, and cardiac output and ventricular function curves were determined. Additional determinations were made in three dogs after they had fully recovered from diethyl ether anesthesia. Total time of experiments ranged from 6 to 8 hours. In three dogs, the concentration of ether in the systemic arterial blood was determined.[10] Arterial blood samples, taken immediately before the measurements of ventricular function, were analyzed for *p*H and

TABLE 1. Slopes of Left and Right VFC Before, During and After Ether Anesthesia in 10 Dogs

Dog	Insp. Conc. (vol. %)	Slope (G.M./cm. H_2O)	
		Lt. VFC	Rt. VFC
1	C_1	4.5	0.7
	5	4.3	0.7
	C_2	5.4	0.7
2	C_1	14.6	0.8
	4	12.0	0.8
	20	0.9	0.6
	C_2	13.0	1.0
3	C_1	13.3	1.1
	4	16.6	1.7
	8	11.6	—*
	15	6.3	1.5
4	C_1	3.7	1.1
	4	4.0	1.0
	4	3.2	1.3
	C_2	5.6	1.5
5	C_1	4.9	1.2
	4	5.7	1.3
	15	2.3	1.3
6	C_1	5.3	0.9
	10	2.9	0.9
7	C_1	4.8	1.2
	4	6.1	1.4
	4	5.9	1.2
8	C_1	3.2	0.7
	15	2.4	0.9
9	C_1	3.2	0.9
	8	4.0	1.0
10	C_1	4.8	2.3
	6	5.1	2.1

C_1: Control observation before anesthesia.
C_2: Control observation after anesthesia.
* No VFC determination was made.

* The area under the curve was integrated by an on-line analog computer (Sanborn Model 130). Electronic and manual computed values were highly correlated ($r = +0.999$) for 119 cardiac outputs ranging from 0.5 to 8.0 liters per minute in four subjects.

† Calibration of the EMO vaporizer by a gas chromatographic technique[9] revealed that it delivered 20, 15, and 9 volume per cent of ether in oxygen at dialsets of 20, 15 and 10 volume per cent, respectively.

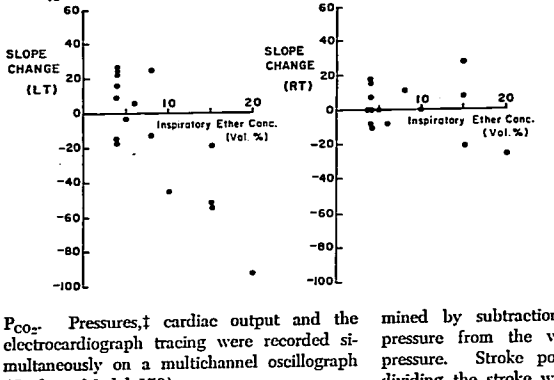

FIG. 1. Percentage changes in slopes of the left and right VFC's plotted against the inspiratory concentration of ether (volume per cent).

P_{CO_2}. Pressures,‡ cardiac output and the electrocardiograph tracing were recorded simultaneously on a multichannel oscillograph (Sanborn Model 150).

Calculations. Ventricular stroke work, VSW (in grammeters) was calculated from the following formula[11]:

$$\frac{(MAP - EVFP) \times (SV)}{100}$$

where, MAP = mean arterial blood pressure (in cm. H_2O), EVFP = effective ventricular filling pressure (in cm. H_2O), and SV = stroke volume (in ml). The effective ventricular filling pressure (in cm. H_2O) was determined by subtraction of the intrathoracic pressure from the ventricular end-diastolic pressure. Stroke power was obtained by dividing the stroke work by the duration of ejection and expressed in watts (1 watt = 10 180 g. cm./sec.). Mean stroke velocity, ml./sec. was calculated by dividing stroke volume by the duration of ejection. The tension-time index (TTI) mm. of mercury-second was calculated as the product of the mean systolic aortic pressure and the duration of ejection.[12] The mean systolic aortic pressure was measured by planimetric integration of the aortic pulse during systole.

Ventricular function curves (VFC) were obtained by plotting ventricular stroke work against ventricular end-diastolic pressure.[11] The slope of each VFC was calculated as the change in stroke work per unit of effective filling pressure at the initial linear position of the curve.[8]

In each experiment the slope of the ventricular function curve prior to diethyl ether anesthesia served as the control value and the percentage change in the slope of the curve obtained during the administration of a specific inspiratory concentration of diethyl ether was calculated.

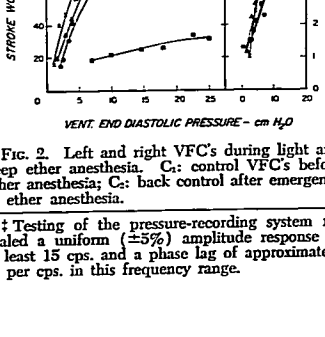

FIG. 2. Left and right VFC's during light and deep ether anesthesia. C_1: control VFC's before ether anesthesia; C_2: back control after emergence of ether anesthesia.

‡ Testing of the pressure-recording system revealed a uniform (±5%) amplitude response to at least 15 cps. and a phase lag of approximately 1° per cps. in this frequency range.

Results

VFC. Pertinent data are summarized in table 1 and figure 1.

Slope Changes. Decreases in the slope of the left VFC were directly proportional to the inspiratory concentrations of diethyl-ether (figure 1: correlation coefficient, r = 0.85).

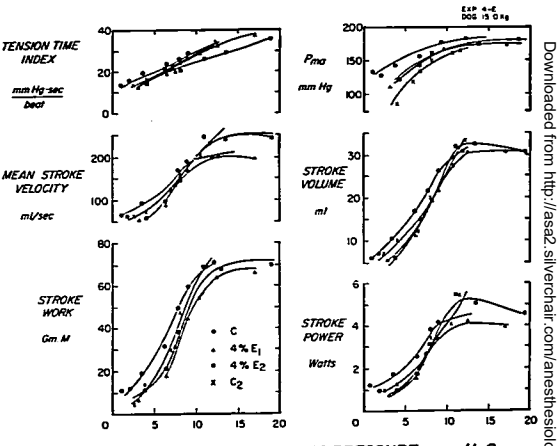

FIG. 3. Characteristics of left ventricular contraction before, during and after light ether anesthesia. Pma: mean aortic pressure. Blood ether concentration: 60 mg./100 ml.

There was no correlation between changes in slope of the right VFC and inspiratory concentration ($r = 0.44$). In general the average net changes of slope of the left and right VFC during light anesthesia (insp. conc. of 4–8 volume per cent) were 0.2 ± 0.14 g/cm. of water ($P > 0.5$), and 0.01 ± 0.01 g./cm. of water ($P > 0.5$), respectively. During deep anesthesia (insp. conc. of 10 to 20 volume per cent), the average net change in slope was -5.3 ± 1.13 g/cm. of water ($0.1 > P > 0.05$) on the left and -0.06 ± 0.05 g/cm. of water ($P < 0.5$) on the right (fig. 2).

Ventricular Stroke Power, Velocity and Tension-Time Index. During light ether anesthesia in all experiments, the left ventricular stroke power, mean stroke velocity, TTI per beat, stroke volume and mean aortic pressure were not altered from the control levels at any given left ventricular end-diastolic pressure. An example of this is shown in figure 3 (blood ether concentration: 60 mg./100 ml.).

During deep anesthesia, the left ventricular stroke power, mean stroke velocity, and TTI per beat were reduced. Figure 4 shows changes in these parameters during deep anesthesia (blood ether concentration: 150 mg/100 ml.) in one dog. Figure 5 shows that the mean aortic pressure decreased concomitantly with left ventricular stroke work at given end-diastolic pressures, in the presence of an unchanged stroke volume during deep anesthesia (blood ether concentration: 105 mg/100 ml.).

Hemodynamic Data. The hemodynamic parameters were obtained before each VFC measurement during control, light and deep ether anesthesia (table 2 and 3). During light ether anesthesia, pulmonary vascular resistance and pulmonary arterial pressure were the only hemodynamic parameters that were significantly increased. Mean net-changes of pulmonary vascular resistance and pulmonary arterial pressure were 2.22 ± 0.72 mm. of mercury/liter/minute ($P < 0.01$) and 2.4 ± 0.6 cm. of water ($P < 0.01$), respectively. During deep anesthesia, both left and right ventricular end-diastolic pressures were significantly altered. The net-changes in left ventricular and right ventricular end-diastolic pressure were on the average 4.5 ± 0.7 cm. of water ($P < 0.01$) and 2.7 ± 0.4 cm. of water ($P < 0.01$), respectively. Changes in other hemodynamic parameters during deep anesthesia were not significant (table 3).

Discussion

The findings of this study reveal that deep diethyl ether anesthesia causes a differential

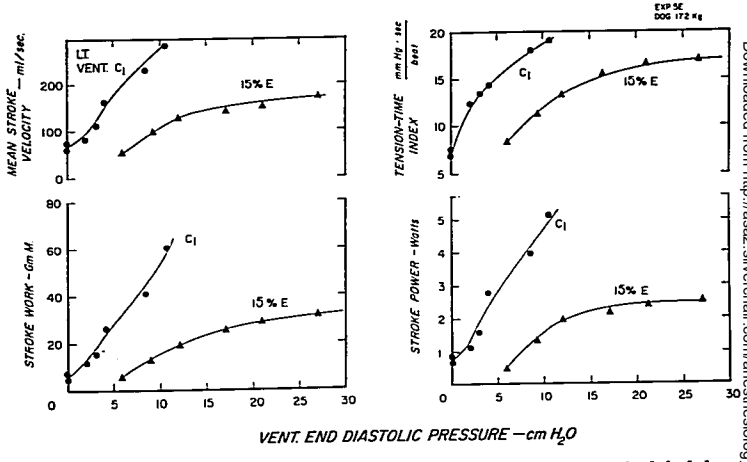

FIG. 4. Left ventricular performance before and during deep ether anesthesia. Blood diethyl ether concentration: 150 mg./100 ml.

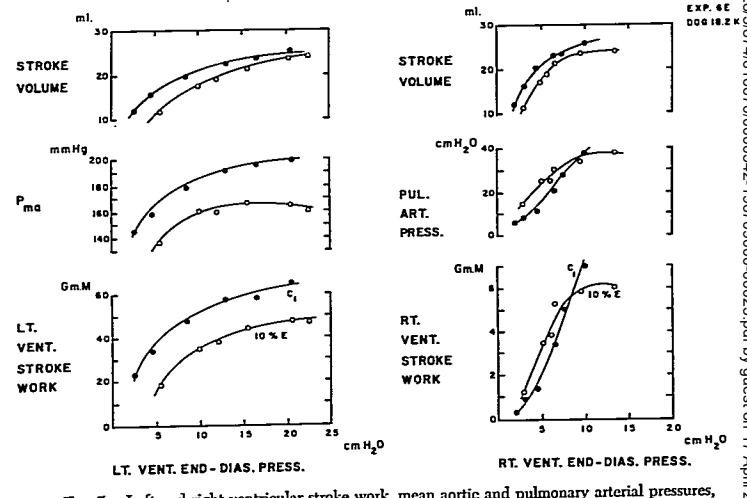

FIG. 5. Left and right ventricular stroke work, mean aortic and pulmonary arterial pressures, and stroke volume plotted against respective ventricular end-diastolic pressure before and during deep ether anesthesia. Blood diethyl ether concentration: 105 mg./100 ml.

TABLE 2. Hemodynamic Data Before and During Ether Anesthesia

Dog	Insp. Conc. (vol. %)	C.O. (liter)/(min.)	S.V. (ml.)/(beat)	H.R. (beats)/(min.)	P_{aa} (mm. Hg)	TPR (dynes./sec)/cm.^{5}	P.V.R. (mm./Hg)/(liter)	P_{PA} (cm. H_2O)	LVEPP (cm. H_2O)	RVEDP (cm. H_2O)	LVSW (GM)	RVSW (GM)
1	0	1.51	11.6	130	155	8.23	10.28	25.0	5.0	4.0	23.5	2.6
	5	1.69	9.9	170	160	7.56	11.83	30.8	6.8	3.8	20.6	2.7
2	0	1.61	10.2	156	134	6.66	5.29	12.0	0	0.5	18.5	1.2
	4	1.69	11.3	150	130	6.14	5.26	13.5	1.5	1.5	19.6	1.4
	20	1.43	11.9	120	125	7.00	6.44	15.5	7.0	3.0	19.2	1.5
3	0	2.14	10.8	198	142	5.31	6.22	18.0	1.0	0	20.6	1.9
	4	1.74	8.4	207	155	7.14	8.13	19.0	1.0	0	17.5	1.6
	8	2.23	14.3	156	120	4.30	6.64	23.0	3.0	3.0	22.7	2.9
	15	1.98	13.7	144	113	4.56	7.49	23.0	3.5	3.0	20.5	2.8
4	0	1.06	6.3	168	125	9.41	9.77	14.0	2.0	0	10.6	0.9
	4	0.82	4.7	174	107	10.40	12.62	14.0	3.0	0	6.7	0.7
	4	1.06	6.4	165	100	7.53	10.84	16.0	4.0	0.5	8.4	1.0
5	0	1.01	4.6	222	105	8.28	10.55	15.0	0	0.5	6.5	0.7
	4	0.89	4.5	198	90	8.05	12.91	17.5	3.0	2.0	5.4	0.7
	15	0.86	5.5	156	75	6.94	17.19	23.0	6.0	3.0	5.2	1.1
6	0	1.50	10.2	147	160	8.56	7.69	17.0	1.0	1.5	21.9	1.6
	10	1.52	11.0	138	135	7.11	5.86	15.0	5.5	3.0	19.4	1.3
7	0	2.60	20.1	129	155	4.77	3.43	12.0	4.0	0	40.7	2.4
	4	1.61	11.9	135	180	8.91	6.20	13.9	3.9	0.4	28.6	1.6
	4	1.78	10.2	174	175	7.88	6.69	14.8	3.3	0	23.8	1.6
8	0	1.13	5.0	228	140	9.87	12.46	19.6	1.1	0.6	9.4	1.0
	15	1.73	10.5	165	76	3.52	13.01	34.6	6.1	4.2	10.2	3.2
9	0	1.11	6.6	168	120	8.69	9.77	14.0	2.5	0	10.5	1.0
	8	0.81	4.4	186	120	11.84	18.25	18.5	0	0	7.1	0.9
10	0	1.43	7.0	204	130	7.52	5.23	10.6	0.6	0.6	12.7	0.7
	6	1.47	7.2	204	120	6.52	5.03	10.4	0	0.4	11.7	0.7

effect upon the left and right "work-performance" in the intact dog. These findings are in accordance with the concept that simultaneous, separate determinations of the left and right VFCs are important for determining "myocardial contractility."[11-13] This is substantiated by the fact that left and right ventricular function curves change independently during ether anesthesia. It should be pointed out that the difference in work-performance between the left and right ventricles is not related to the difference in the inotropic state of the two ventricles, but related to the fact that each ventricle was stressed differentially during deep ether anesthesia. This concept is based upon the findings that the decreased slopes of the left ventricular function curves as compared with the relatively unaltered slopes of the right ventricular function curves were associated with a decreased mean aortic pressure and an unchanged pulmonary arterial pressure (fig. 5). At any given end-diastolic pressure, the mean aortic pressure was reduced concomitantly with the reduction of the calculated left ventricular stroke work. Therefore, the apparent lowering of the left ventricular function curve is a direct consequence of the decrease of the mean aortic pressure.

Sonnenblick,[14,15] Abbott and Mommaerts[16] have shown that one of the most important parameters in characterizing the basic con-

TABLE 3. Changes in Hemodynamic Parameters During Diethyl Ether Anesthesia
Mean Difference From the Control Values

Insp. Conc. (vol. %)	No. of Exp.	Cardiac Output (liter/min.)	Stroke Volume (ml./beat)	Heart Rate (beats/min.)	P aortic (mm. Hg)	TTI (dyne sec)/cm.²	PVR (mm. Hg/liter)	P_{PA} (cm. H_2O)	LVEDP (cm. H_2O)	RVEDP (cm. H_2O)	LVSW (G.M.)	RVSW (G.M.)
4–8	11	−0.23±0.12 ($P>0.05$)	−1.9±1.2 ($P>0.1$)	4.5±7.5 ($P>0.5$)	−2.8±5.1 ($P>0.5$)	0.72±0.61 ($P>0.2$)	2.23±0.72 ($P<0.01$)	2.4±0.6 ($P<0.01$)	0.7±0.5 ($P>0.1$)	0.5±0.3 ($P>0.1$)	−4.0±1.7 ($P<0.05$)	−0.1±0.2 ($P>0.5$)
10–15	4	0.08±0.18 ($P>0.5$)	2.5±1.1 ($P>0.1$)	−48±13.3 ($P<0.05$)	−37±9.1 ($P<0.05$)	−2.47±1.30 ($P>0.1$)	1.60±1.70 ($P>0.4$)	6.5±3.5 ($P>0.4$)	4.5±0.7 ($P<0.01$)	2.7±0.4 ($P<0.01$)	−0.8±0.7 ($P>0.3$)	0.8±0.5 ($P>0.2$)

tractile state of the heart muscle is the force-velocity relationship: the inverse relationship between the force generated and the velocity of shortening during myocardial contraction. Recently, Fry *et al.*,[17] Levine and Britman,[18] Covell *et al.*[19] have demonstrated that the inverse relationship between force and velocity also applies to the intact canine left ventricle. In the intact heart during ventricular contraction, the pressures in the arch of aorta or main pulmonary artery are encountered only with the onset of myocardial contraction when the aortic or pulmonic valve is opened, and therefore, the mean arterial pressure or mean pulmonary arterial pressure may be considered analogous to an afterload in the isolated muscle preparation. Ross *et al.*[20] recently demonstrated in the intact, canine, left ventricle that stepwise increases in the mean aortic pressure (afterload) result in progressive decrements in the velocity of ejection. It has been also emphasized that left ventricular stroke work is not only a function of end-diastolic pressure (preload), but also a function of resistance to ejection or mean aortic pressure (afterload).[21] Therefore, it is reasonable to state that the unilateral depression of the left ventricular function curve with an unchanged right ventricular function curve was related to a) the reduction of the mean aortic pressure or afterload level for the left ventricle and b) an unaltered afterload level for the right ventricle, and that both ventricles are at the same inotropic state during deep ether anesthesia.

The increases in stroke work and power in some experiments during light diethyl ether anesthesia were similar to those produced by electrical stimulation of the left stellate ganglion[22] and by the intravenous infusion of catecholamines.[11] Recent studies have revealed that norepinephrine concentration is increased in the myocardial and cardiovascular tissue in dogs during ether anesthesia.[7] Thus, positive inotropism of the myocardium and the increase in the pulmonary arterial pressure which occurred during light anesthesia may be correlated with the increased rate of catecholamine liberation.

Another significant finding is that the changes in the tension-time index (TTI)

per beat paralleled the left ventricular stroke work and power at any given end-diastolic ventricular pressure during ether anesthesia (figs. 3 and 4). It has been reported that the tension-time index is the principal hemodynamic determinant of myocardial oxygen consumption at any given functional state of the heart.[12] The parallel reduction of the TTI per beat, the mean aortic pressure and left ventricular stroke work during deep ether anesthesia, suggest that the mechanical efficiency of the heart is probably maintained during ether anesthesia. The changes in the hemodynamic parameters, however, such as cardiac output and stroke volume during ether anesthesia do not indicate the work-and-power-performance of the heart. For example, the cardiac output increased, decreased or remained unchanged and was not accompanied by the same directional changes in the ventricular function curves (tables 2 and 3).

Summary

Results of this study show that the left and right ventricles may perform work and exert power at different functional levels according to their respective levels of afterload (mean aortic or pulmonary arterial pressure), at any given end-diastolic volume or pressure (preload). The "work-and power-performances" of the right ventricle were unchanged at any given end-diastolic ventricular pressure and those of the left ventricle were depressed during deep ether anesthesia. These changes were not related to differences in inotropic state of the two ventricles. The differential effects of diethyl ether anesthesia upon the two afterloads, causing a decrease in mean aortic pressure with an unchanged mean pulmonary arterial pressure, were responsible for the apparent depression of the left ventricular function curve. The reduction of the work-performance of the left ventricle was related to the parallel reduction of the tension-time index, indicating that the mechanical efficiency of the left ventricle was not altered.

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Drugs

MEMBRANES Biological membranes appear to be thin structures 50 to 100 Angstroms thick composed of a double layer of lipid covered by adherent layers of protein or polysaccharide, or both. The polar head groups are oriented toward the aqueous phases. The hydrocarbon region is likely to be more or less liquid. Electron micrographs seem to indicate that the membranes are continuous lamellar structures. Ion permeation is likely to occur either through a site-free interior or by means of a mobile associated mechanism utilizing lipid-soluble polar molecules as the mobile carriers. It has been postulated that ion permeation utilizes one or more of the following mechanisms: pores lined by fixed charges, lipid-soluble carrier molecules, diffusion in a homogenous dialectic medium having rate limiting "gating mechanisms" at its surface and translocation of vesicles. Variables considered are the presence or absence of ion exchange sites, their fixation or freedom of motion, their degree of dissociation, and the extent to which their chemical properties depend on external forces. A membrane can be categorized according to whether it contains sites for ion exchange or is site-free, and if it is an ion exchanger, according to whether its sites are fixed or mobile and whether the sites of their counter-ions are associated or dissociated. (*Eisenman, G., Sandblom, J. P., and Walker, J. L., Jr.: Membrane Structure and Ion Permeation, Science 155: 965 (Feb.) 1967.*)