Respiratory Fluctuations in Right and Left Ventricular Outflows in Conscious Dogs* (33315)

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(Introduced by E. J. Van Liere)

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With two pumps, such as the right and left ventricles, whose outflows are arranged in series to supply their respective vascular beds equal flows must be maintained over a relatively short period of time to preserve a physiological partition of blood volume. That the consequence of an imbalance in their flows would result in excessive fluid accumulation and be detrimental to normal function is generally recognized (1,2). In the normal subject the principle of restoration of a balance between the right and left ventricular outflows during breathing has been formulated and assigned to the Starling autoregulation mechanism, whereby stroke output of each ventricle is regulated by its end-diastolic volume (1–3). However, this principle of restoration presupposes a temporal imbalance between the two ventricular outflows with respiration, i.e., with the cyclical changes of breathing, fluctuations in the magnitudes of the right and left ventricular stroke outputs would be out of phase. In order to determine the importance of this concept it is necessary to examine the phase relationship between the outflows of the two pumps in the conscious subject during normal spontaneous breathing.

The present investigation was undertaken to quantitate the fluctuations in right and left ventricular outflows and their phase relationship associated with breathing in unanesthetized dogs. Aortic and pulmonary artery flows were measured simultaneously with the respiratory changes of intrathoracic pressure. Respiratory fluctuations in right and left ventricular peak outflows and stroke volumes were analyzed by repetitively plotting the beat by beat values over a series of respiratory cycles. Summation of the beat by beat differences in stroke volumes plotted in this manner was used to estimate the cyclic changes in thoracic blood volume with breathing.

Methods. Animal surgery. Ten male dogs ranging from 11.0 to 22.5 kg in weight, were anesthetized with 25–30 mg/kg of sodium pentobarbital. The animal was fixed in the right lateral position and the chest was entered on the left side between the third and fourth rib during artificial respiration. The heart was exposed and the ascending aorta and main pulmonary artery were carefully separated from the surrounding tissues. Flowprobes were then installed around each blood vessel (Fig. 1). The ground electrodes were sutured to the pericardium. A small capsule was positioned in the thorax at the fifth intercostal space for the measurement of intrapleural pressure. The chest was then tightly closed. Insulated lead wires from the flowprobes and vinyl tubing connection from the intrathoracic capsule were pulled through a dorsal thoracic skin incision. These surgical operations were carried out under aseptic conditions, and the animals were carefully tended throughout the chronic experiments. Antibiotics were given intramuscularly for about 1 week after surgery.

Measurement of blood flow. Two gated, sine wave, electromagnetic flowmeters, (Microflow, Type K-2000, Medicon), slightly modified, were used to measure the blood flow through the pulmonary artery and ascending aorta simultaneously. Each flowmeter was connected to a flowprobe equipped with a

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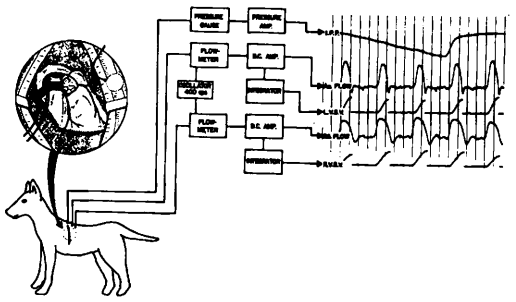

FIG. 1. Diagram illustrating an unanesthetized instrumented dog (17.0 kg) and the measurements obtained: top to bottom, intrapleural pressure, aortic flow, left ventricular stroke volume, pulmonary artery flow, and right ventricular stroke volume.

coreless electromagnet and pickup electrodes. The magnet was energized by a 400 cps sine wave current. Since the two probes were located adjacently in the chest of the animal, the magnitude of flow and the nonflow base line were altered by mutual interference if the two flowmeters were independently operated at the same time. In order to avoid these interference effects, the modifications suggested by Elliot *et al.* (4) were used. This modification eliminates the beat frequency interaction, by driving both probes by a single oscillator (Fig. 1). Another source of potential mutual interference is related to the relative position change between the two adjacent probes in the chest of the animal. Fortunately, these geometrical relationships between the probes were fixed firmly in a few days after operation by the fibrous tissue growth around the probes and vessels. The nonflow base line setting of each meter was determined by the pulsatile method (Medicon's Operation Manual for Microflo K-2000) when the magnetic field of the other probe was turned off. This method was checked in the living animals under resting conditions where zero flow presumedly occurs for a finite time during each cardiac cycle. The magnitude of the output from the flowmeters at a given input flow differed very slightly in the two cases of independent and simultaneous operation of the flowmeters. Flow rate calibrations were done by using excised blood vessels with saline perfusion and checked again *in situ* after sacrifice of the animal. Calibration curves were linear for flow rates ranging from zero to 200 ml/sec. The use of saline instead of whole blood for these calibrations will lead to an overestimation in absolute flow of approximately 5% (5). The outputs of the flowmeters during the forward flow phase were integrated electronically, reset after each cardiac cycle and the resulting stroke volumes were recorded. The flow measurements were not corrected for coronary flow and backflow. Coronary flow is considered to constitute about 4–5% of cardiac output (6) and mean backflows calculated from the flow curves were 3.3% and 5.4% of left and right stroke volume, respectively. Since aortic backflow probably contributes to coronary flow these errors tend to cancel.

Measurement of intrapleural pressure. A thin tambour-shaped intrapleural capsule made of solid plastic rim and silastic membranes (Dow Corning), was positioned in the intrapleural cavity of the animal and connected to a differential pressure transducer (Statham model PM-6) with vinyl tubing. Two ml of air added to the capsule provided a linear relationship between pressure and deflection of the recorder. Intrapleural pressure was recorded simultaneously with aortic and pulmonary arterial blood flows and corresponding stroke volumes by optical recording (Electronics for Medicine, model DR 8).

Results. Table I summarizes the data of the numerical analysis of the ventricular outflow pulses. It should be noted that the right ventricular outflow pulses began earlier and lasted longer, resulting in a mean total ejection phase 1.4 times that of the left ventricle. Also the mean acceleration ejection duration (7) of the right ventricle was prolonged 1.42 times over that of the left. Nevertheless, the respective stroke volumes were essentially equal because of the greater rate of flow out of the left ventricle. The minute output calculated from these data was 89 ml/min/kg. The flow waveforms were further characterized by a shape constant Ks (8), given by the equation, $Ks = \Delta V\ (\dot{V}p \times Te)$, where ΔV = stroke volume, $\dot{V}p$ = peakflow, and Tw = ejection duration. Aortic Ks was 0.63, which is very close to that of a

TABLE I. Pattern Analysis of Aortic and Pulmonary Arterial Blood Flow in the Unanesthetized Dogs.[a]

No. of dogs		10
Av body wt. (kg)		16.2
No. of expts.		17
Total no. of strokes analyzed		585
Pulse interval (sec)		0.437 ± 0.094
Total ejection phase (Te) (sec)[b]	Ao	0.130 ± 0.015
	PA	0.182 ± 0.028
Acceleration ejection duration (sec)[c]	Ao	0.057 ± 0.009
	PA	0.081 ± 0.020
Onset time lead ($\dot{V}_{PA}$—$\dot{V}_{Ao}$) (sec)[d]		0.016 ± 0.009
Peakflow ($\dot{V}p$) (ml/sec)	Ao	142.2 ±24.9
	PA	87.6 ±14.8
Stroke volume (ΔV) (ml)	Ao	11.7 ± 2.3
	PA	11.6 ± 2.2
Shape constant $[Ks=\Delta V/(Te\times\dot{V}p)]$	Ao	0.63 ± 0.07
	PA	0.73 ± 0.10

[a] Each number represents the mean value and its standard deviation.

[b] Onset of ventricular outflow to end of forward flow.

[c] Onset of ventricular outflow to time of peakflow.

[d] Onset of right ventricular outflow to onset left ventricular outflow.

half sine curve (0.636). Pulmonary artery Ks was 0.73, and this is close to that of a half circle or half ellipse (0.785).

Respiratory fluctuations in aortic and pulmonary arterial flow and stroke volume. Each of the variables (IPP, $\dot{V}p$Ao, ΔV_L, $\dot{V}p$PA, and ΔV_R) was plotted in time corresponding to the onset of the respective left and right ventricular outflow in repetitive fashion for several breathing cycles of similar durations and amplitudes (Fig. 2). In the early postoperative period (approx 4 days) peakflow and stroke volume from the left heart decreased with a decrease in intrapleural pressure during inspiration, and returned to the initial level with increase in intrapleural pressure during expiration and the respiratory pause. These parameters from the right heart increased with a decrease in intrapleural pressure during inspiration and returned with expiration. Thus, the relationship between the variation of intrapleural pressure and left

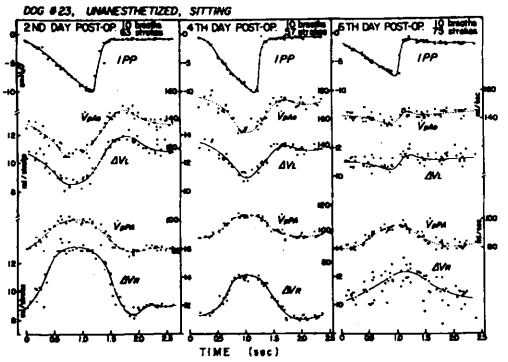

FIG. 2. Variation of intrapleural pressure (IPP), aortic peakflow ($\dot{V}p$Ao), left ventricular stroke volume (ΔV_L), pulmonary arterial peakflow ($\dot{V}p$PA), and right ventricular stroke volume (ΔV_R). Each of the variables is plotted in time corresponding to the onset of ventricular outflow in repetitive fashion for 10 breathing cycles of similar durations and amplitudes.

ventricular outflow was almost in phase. Contrarily, right ventricular outflow was about 180 degrees out of phase with the left ventricular outflow and intrapleural pressure. These respiratory fluctuations in both left and right ventricular outflows diminished in amplitude as the postoperative days increased. The left and right ventricle had a negative phase relationship with respect to beat by beat stroke volume before the fourth postoperative day (Fig. 3). However, after the fifth postoperative day this relationship usually shifted and became positive. Variation in left and right ventricular output remained but no longer displayed a prepondenrant respiratory influence. This is observed in Fig. 2 on the sixth postoperative day.

Beat by beat changes in pulmonary vascular blood volumes have been estimated from the difference between right and left ventricular stroke volumes. The imbalance between right and left ventricular stroke volumes plotted in repetitive fashion during several respiratory cycles is shown in Fig. 4. In the early postoperative period, as intrapleural pressure decreased and then increased, the estimated pulmonary vascular blood volume increased and then decreased in reciprocal fashion. This calculated volume change also diminished with an increase in postoperative

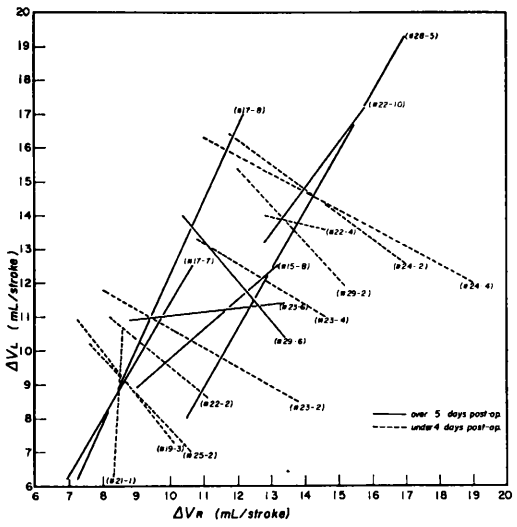

FIG. 3. Correlation lines between the corresponding left and right ventricular stroke volumes (ΔV_L and ΔV_R) from 17 experiments in 9 dogs at different postoperative times. The numbers indicated by each line represent the dog number and postoperative day.

time. The change in duration of pulmonary arterial ejection paralleled the changes in difference between stroke volume of the right and left ventricles. There was no significant variation in aortic ejection time (Fig. 4). Variation of the pulse interval accompanying the change in intrapleural pressure was slight.

Discussion. The mechanisms which might produce a temporal imbalance between the two ventricular outflows must involve multiple factors. Transient changes in venous flow into the right heart accompanying the change in intrapleural, or more precisely transdiaphragmatic, pressure gradient may cause respiratory fluctuations in the outflow from the right ventricle (9–12). Changes in resistance and capacity characteristics of the pulmonary vascular bed accompanying inflation and deflation of the lung should also influence the right and left ventricular outflow and their reciprocal phase relationship. A current view is that extrapulmonary and large intrapulmonary vessels become longer and wider during inspiration, and shorter and narrower during expiration. The small intrapulmonary vessels, however, tend to become flattened as the alveoli are inflated during inspiration (13–16). Consequently, the pulmonary blood may be stored in the large vessels during inspiration, and propelled toward the left heart during expiration.

These explanations seem to support the experimental data observed in the early postoperative period, at which time there was a reciprocal phase relationship between right and left ventricular outflows. However, they do not fully explain the later postoperative period, when there was negligible imbalance between the resepctive ventricular outflows (Fig. 4). In fact, the in phase relationship between the two ventricular pumps, which were consistently recorded after the fifth postoperative day, confirms previous direct evidence (17) that the right and left ventricular outflow phase relationship is balanced during normal spontaneous breathing. The previous nonquantitative study showed that an out of phase imbalance could be produced by pneumothorax or atelectasis, factors which probably cause an increase in pulmonary vascular resistance.

Additional understanding of the dynamic relationship between the respiratory changes in intrathoracic pressure and the balance between right and left ventricular outflows could be obtained by adding elastic opposition to breathing or by adding airflow resistance during one or both phases of the respiratory cycle. Such studies could contribute to

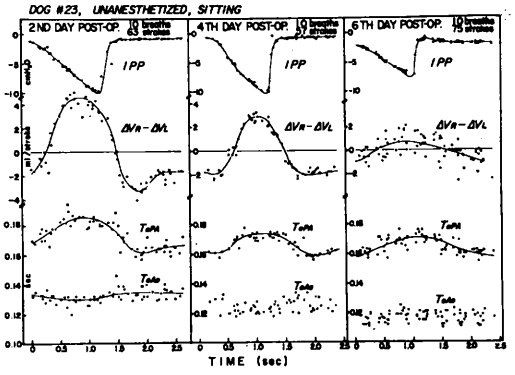

FIG. 4. Variation of IPP, difference between right and left ventricular stroke volume ($\Delta V_R - \Delta V_L$) pulmonary arterial and aortic ejection durations (TePA and TeAo) are plotted in repetitive fashion as in Fig. 2.

our understanding of the cardiovascular implications of changes in pulmonary mechanics with chronic lung disease.

Summary. Respiratory fluctuations in ventricular outflows were measured in unanesthetized dogs by simultaneously recording aortic and pulmonary artery flows and intrathoracic pressure. The respective stroke volumes were computed and the beat by beat values were plotted over a series of respiratory cycles. The data showed that in the early postoperative period there was an imbalance between the ventricular outflows during normal breathing. This imbalance was characterized by an increase in right ventricular stroke output and a decrease in left ventricular stroke output during inspiration with a reversal during expiration, that is, they were out of phase. However, this temporal imbalance diminished with recovery from the surgical procedure, so that by the fifth postoperative day the right and left ventricular stroke outputs were essentially in phase. Therefore, our data indicate that the principle of restoration to correct a temporal imbalance between the two ventricular outflows with normal spontaneous breathing is of minor importance.

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Daily Rhythm in Plasma Tyrosine and Phenylalanine (33316)

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A daily rhythm in plasma tyrosine concentration in humans was reported recently by Wurtman *et al.* (1), who pointed out several factors that could contribute to the rhythm. The work described in this paper represents an attempt to clarify the possible role of three factors, (1) metabolism by transamination, (2) dietary intake of protein, and (3) formation of tyrosine from phenylalanine, in the daily rhythm of tyrosine and to see if similar rhythmic variations occur in phenylalanine levels. The first two factors were studied in rats by altering the daily pattern of food intake, which in turn alters the daily rhythm that occurs in liver tyrosine transaminase (2–7). The third factor was studied in human phenylketonuric subjects lacking the enzyme phenylalanine hydroxylase.

Methods. Male Sprague-Dawley rats weighing about 150 g were maintained for two weeks individually in cages and were fed Purina Lab Chow. One group of rats had