Diaphragmatic Fatigue and its Recovery are Influenced by Cardiac Output

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The effects of cardiac output (Qt) on diaphragmatic blood flow (Qdi) and diaphragmatic fatigue and its recovery were studied in dogs. Qdi was estimated by measurement of the left inferior phrenic arterial blood flow (QdiL). There was a significant positive correlation between % Qt and % QdiL. Transdiaphragmatic pressure (Pdi) was significantly smaller in the lowered Qt group than the control at the end of fatigue, and the speed of recovery from the fatigue was also significantly slower in the lowered Qt group. It is concluded that Qt was considered to play an important role in the pathogenesis of diaphragmatic fatigue and its recovery in the mechanically ventilated dogs. (Key words: cardiac output, diaphragmatic blood flow, transdiaphragmatic pressure, diaphragmatic fatigue)

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Fatigue may occur when the energy demands of the muscle exceed the ability of energy supply[1]. One of the factors determining energy available to the respiratory muscle is the respiratory muscle blood flow particularly diaphragmatic blood flow (Qdi)[2], and cardiac output (Qt) has been reported as one of the major factors to control Qdi[3–5]. Although previous data indicate that lowered Qt may induce respiratory failure in spontaneous breathing dogs, there has no distinct data on the effect of lowered Qt on diaphragmatic fatigue and its recovery. In addition, the studies of relationship between Qt and Qdi has been controversial. Therefore, the present study was performed in an attempt to clarify the relationship between Qt and Qdi and also to determine the effects of Qt on diaphragmatic fatigue and its recovery.

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Materials & Methods

Experiment 1

Ten healthy mongrel dogs whose weights ranged from 10 to 15 kg were anesthetized with a dose of 20 $mg \cdot kg^{-1}$ of ketamine intramuscularly and placed in a supine position. Anesthesia was maintained with 4 $mg \cdot kg^{-1} \cdot hr^{-1}$ of secobarbital intravenously. They were intubated with a cuffed endotracheal tube and mechanically ventilated with an O_2 and air gas mixture to maintain about 100 torr of Pa_{O_2}, 35 to 40 torr of Pa_{CO_2}, and 7.35 to 7.45 of pH. The right femoral artery was cannulated to monitor arterial pressure and to obtain blood samples for blood gas analysis. The right femoral vein was cannulated to allow fluid and drugs administration. Rectal temperature was monitored and maintained at 37 ± 1°C.

A right thoracotomy was performed at the 4th or 5th intercostal space and a probe (MFV-1100, Nihon Koden) was placed on the ascending aorta for measuring Qt. An abdominal incision below the left costal arch was performed and an another probe was placed on the left inferior phrenic artery for measuring its blood flow (QdiL). A

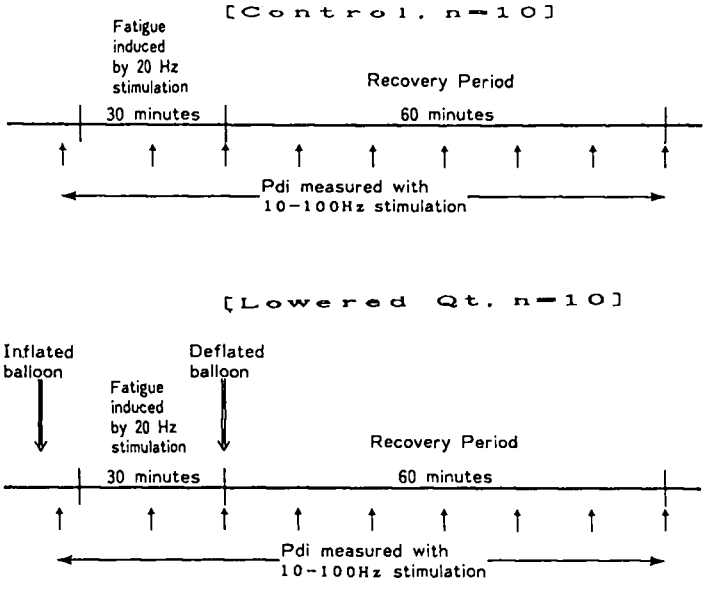

Fig. 1. Schematic diagram of the experimental protocol.

catheter with balloon was inserted through left femoral vein and the balloon was placed in the inferior vena cava. The decrease in Qt was induced by inflating the balloon, and both Qt and QdiL were measured simultaneously.

Arterial blood gases were measured every 30 min. Sodium bicarbonate was administered for correcting metabolic acidosis as needed. After inserting a catheter, 5000 units of heparin were administered intravenously to prevent blood coagulation.

Experiment 2

Experiments were performed on 20 mongrel dogs weighing 10 to 15 kg. No muscle relaxants were used. A Swan-Ganz catheter was advanced via right external jugular vein into the pulmonary artery for measuring Qt by using a continuous cardiac output measuring-instrument (CCOM, Terumo, Japan).

Transdiaphragmatic pressure (Pdi) was measured by means of two thin-walled latex balloons positioned in the stomach and in the middle third of the esophagus with a differential pressure transducer (PRESSURE HEAD, Tokyo Keiki) and an amplifier (ATTENUATOR TYPE 1212, Nihondenki San-ei) during phrenic nerve stimulation described below. Transpulmonary pressure (Ptp), the difference between airway and esophageal pressures, was kept constant for maintaining the same lung volume throughout the experiment.

Bilateral phrenic nerves were exposed at the neck and the stimulating electrodes were attached to them. For the measurement of Pdi, the nerves were stimulated with supramaximal voltage (10–15 voltages) by an electrical stimulator (ELECTRONIC STIMULATOR 3F37, Nihondenki San-ei). Supramaximal stimulation of 0.1 msec duration and 2 sec stimulation were applied at frequencies of 10, 20, 30, 50 and 100 Hz. The isometric contraction of diaphragm was evaluated by measuring maximal Pdi at FRC level while the airway occluded, so that the diaphragmatic initial length and geometry before stimulation were maintained on the same level throughout the experiment.

The electrical activity of diaphragm (EMGdi) was measured using needle electrodes inserted percutaneously from the upper abdominal area, and was rectified and integrated with a leaky integrator (TYPE 1310, Nihondenki San-ei) with a time constant of 0.1 msec. This was regarded as the integrated diaphragmatic electric activity (Edi). The method for decreasing Qt was the same as experiment 1. Rectal temperature

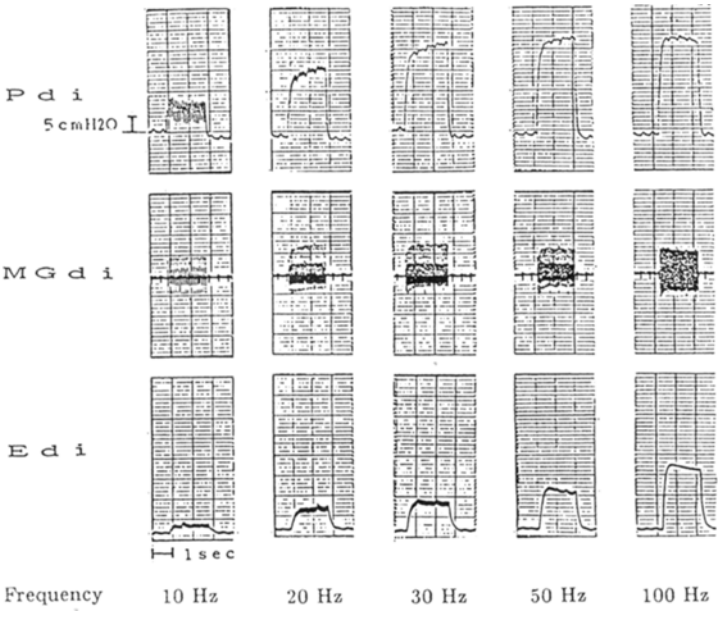

Fig. 2. Typical record of Pdi (upper trace), EMGdi (middle trace) and Edi (lower trace) during stimulation at various frequencies.
• Abbreviations: Pdi = transdiaphragmatic pressure, EMGdi = electrical activity of the diaphragm, Edi = electrical integrated activity of the diaphragm.

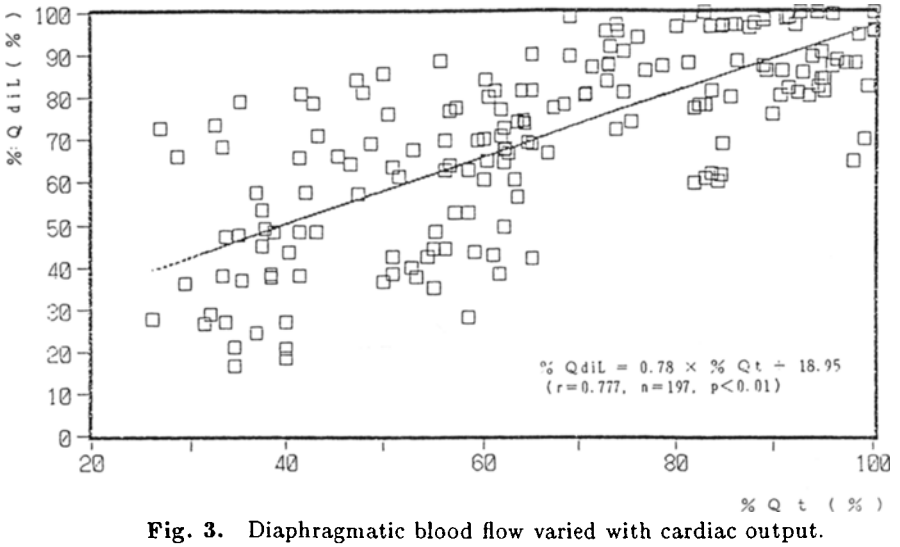

Fig. 3. Diaphragmatic blood flow varied with cardiac output.
There was a significant correlation between % Qt and % QdiL. %Qt = changes in cardiac output, %QdiL = changes in blood flow in the left inferior phrenic artery.

was monitored continuously and maintained at 37 ± 1°C.

The studies were performed as shown in figure 1. The dogs were divided into two groups at random; the control group (n = 10) and the other with decreased Qt to 60% of control value (lowered Qt group, n = 10). Diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz, an entire cycle of 4 sec, and a duty cycle of 0.5 for 30 min (low frequency fatigue)[6]. After 30 min of fatigue producing period, the lowered Qt was returned to control levels by deflating the balloon in the IVC. Then the observations were made for 60 min after deflating the balloon. Both Pdi and Edi were measured during fatigue and recovery peri-

Table 1. Hemodynamic data and changes between the control and lowered Qt groups

	Control group	Lowered Qt group (balloon inflated)	(balloon deflated)
n	10	10	
Qt ($l \cdot min^{-1}$)	1.63 ± 0.36	0.98 ± 0.16*	1.62 ± 0.35
MAP (mmHg)	103 ± 20	62 ± 21*	101 ± 22

All values are expressed as mean ± SD. Qt=cardiac output, MAP=mean arterial pressure.

*: $P < 0.001$ (lowered Qt vs control group).

Table 2. Pdi/Pdi100 during pre-fatigue and fatigue period between the control and lowered Qt groups

Period	Group	Frequency of stimulation 10 Hz	20 Hz	30 Hz	50 Hz	100 Hz
Pre-fatigue period	Control	35.9 ± 7.0	74.1 ± 8.6	89.7 ± 4.7	98.4 ± 2.6	100.0 ± 0.0
	Lowered Qt	36.4 ± 6.6	74.1 ± 8.4	89.1 ± 5.4	98.3 ± 3.4	99.6 ± 1.5
Fatigue period 10 min	Control	30.7 ± 5.9	67.2 ± 8.9	84.8 ± 6.3	97.2 ± 3.2	99.2 ± 1.1
	Lowered Qt	28.1 ± 5.7**	61.5 ± 9.1**	83.7 ± 5.5*	94.8 ± 4.2	98.1 ± 2.6
20 min	Control	28.0 ± 5.2*	62.4 ± 8.6**	81.1 ± 6.0**	96.0 ± 3.0	97.9 ± 2.4
	Lowered Qt	23.4 ± 4.2$^{**}_{+}$	53.5 ± 8.6**	78.5 ± 4.8**	92.4 ± 5.1	97.0 ± 2.9
30 min	Control	26.4 ± 5.6**	59.8 ± 8.8**	78.6 ± 5.4**	94.9 ± 3.3	97.0 ± 2.9
	Lowered Qt	21.6 ± 5.2$^{**}_{+}$	47.7 ± 8.1$^{**}_{++}$	74.3 ± 6.7**	91.3 ± 6.3	96.3 ± 4.1

All values are expressed as mean ± SD.

*: $P < 0.05$, **: $P < 0.01$ (vs pre-fatigue period).

+: $P < 0.05$, ++: $P < 0.01$, +++: $P < 0.001$ (lowered Qt vs control group).

ods at the intervals of 10 min throughout the experiment. During the fatigue period, Pdi and Edi were measured at frequencies of 10, 20, 30, 50, 100 Hz (fig. 2). During the recovery period, Pdi and Edi measured with two frequencies of 20 and 100 Hz to avoid unexpected fatigue by repeated measurements.

All values were expressed as mean ± standard deviation (SD). Statistical analysis was performed by Student's t test for Qt and MAP for the two groups, and using ANOVA and multiple comparison (Dancan) for Pdi and Edi values before and during fatigue period and recovery process. The values of Pdi between the two groups were examined by Student's t test. A probability value of less than 0.05 was regarded as statistically significant.

Results

Experiment 1

All the values of Qt and Qdi were expressed as a percent of the control value before inflating the balloon. There was a significant positive correlation between percent change in Qt and QdiL (fig. 3) and the regression equation was; % QdiL (%) = 0.78 × % Qt (%) + 18.95 (r = 0.777, n = 197, $P < 0.01$)

Experiment 2

The changes in Qt and MAP in the control and lowered Qt group are shown in table 1.

All Pdi values shown in table 2 and 3 were the percentage of Pdi at 100 Hz stimulation during pre-fatigue period in the control group (Pdi/Pdi100). During the fatigue period, Pdi/Pdi100 decreased more signifi-

Table 3. Pdi/Pdi100 during pre-fatigue and recovery period between the control and lowered Qt groups

Period	Group	Frequency of stimulation 10 Hz	20 Hz	30 Hz	50 Hz	100 Hz
Pre-fatigue period	Control	35.9 ± 7.0	74.1 ± 8.6	89.7 ± 4.7	38.4 ± 2.6	100.0 ± 0.0
	Lowered Qt	36.4 ± 6.6	74.1 ± 8.4	89.1 ± 5.4	98.3 ± 3.4	99.6 ± 1.5
Recovery period 10 min	Control		60.2 ± 9.0**			97.0 ± 2.9
	Lowered Qt		47.7 ± 8.1$^{**}_{++}$			96.3 ± 4.1
20 min	Control		61.3 ± 8.4**			98.5 ± 2.4
	Lowered Qt		48.5 ± 9.1$^{**}_{++}$			96.3 ± 4.1
30 min	Control		62.9 ± 7.5**			100.0 ± 1.5
	Lowered Qt		48.5 ± 9.1$^{**}_{++}$			96.3 ± 4.1$_{+}$
40 min	Control		64.8 ± 8.4*			100.0 ± 1.4
	Lowered Qt		48.5 ± 9.1$^{**}_{+++}$			96.7 ± 4.3$_{+}$
50 min	Control		66.7 ± 8.2			100.0 ± 1.6
	Lowered Qt		48.5 ± 9.1$^{**}_{+++}$			97.6 ± 3.2$_{+}$
60 min	Control	31.5 ± 7.3	67.2 ± 8.0	84.7 ± 4.8	98.4 ± 2.6	100.0 ± 1.5
	Lowered Qt	22.1 ± 5.5$^{**}_{++}$	48.5 ± 9.1$^{**}_{+++}$	76.3 ± 7.1$^{**}_{++}$	92.7 ± 6.0$_{+}$	97.6 ± 3.2$_{+}$

All values are expressed as mean ± SD.
*: $P < 0.05$, **: $P < 0.01$ (vs pre-fatigue period).
+: $P < 0.05$, ++: $P < 0.01$, +++: $P < 0.001$ (lowered Qt vs control group).

cantly with low frequency (10–30 Hz) stimulation than with high frequency (50–100 Hz) stimulation ($P < 0.05$) in both the control and lowered Qt group. However, with high frequency stimulation, there was no significant difference between the two groups. At 20 and 30 min of fatigue producing period, with low frequency stimulation, Pdi/Pdi100 of the lowered Qt group showed significantly lower values compared to the control group ($P < 0.05$).

In the recovery period, the difference in the values of Pdi/Pdi100 in the two groups was more remarkable with low frequency stimulation than with high frequency stimulation. With 100 Hz stimulation, Pdi/Pdi100 in the two groups showed a slight tendency to recover. With low stimulation of 20 Hz, Pdi/Pdi100 in the lowered Qt group did not show any tendency to recover.

Figure 4 illustrated changes of Pdi/Pdi100 with high (100 Hz) and low (20 Hz) stimulation between the two groups throughout the experiment. With 20 Hz stimulation, the extent of fatigue in the lowered Qt was larger than in the control group. The speed of recovery with low frequency stimulation was much slower in the lowered Qt group.

No significant difference in Edi was observed between the two groups throughout the experiment.

Discussion

The arterial blood supply to diaphragm in dogs is mainly derived from the inferior phrenic arteries originated from the abdominal aorta or the celiac artery[7]. The inferior phrenic arteries have left and right branches and they supply blood flow to left and right semisphere of diaphragm respectively.

The diaphragmatic blood flow (Qdi) was measured by several different methods. In the present study, Qdi was estimated by measuring the left inferior phrenic arterial blood flow with an electromagnetic flowmeter. Although the total blood flow to diaphragm cannot be measured, this method has the advantage of allowing continuous direct measurement of Qdi. The relationship between Qdi and Qt in the present study was in good accordance with a series of studies by Rochester using the inert gas[3–5].

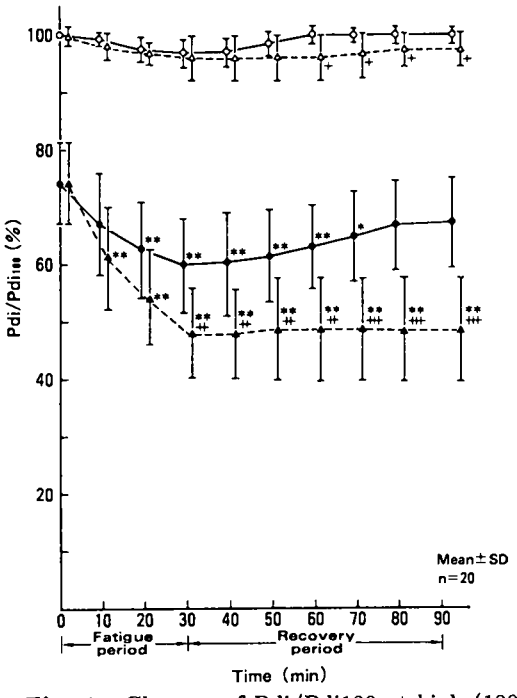

Fig. 4. Changes of Pdi/Pdi100 at high (100 Hz) and low (20 Hz) frequency stimulation between the two groups during fatigue and recovery period.

All values are expressed as mean ± SD. Pdi/Pdi100 = percentages of Pdi at 100 Hz stimulation during pre-fatigue period in the control group.

○—○ : Pdi/Pdi100 at 100 Hz stimulation in the control group

●—● : Pdi/Pdi100 at 20 Hz stimulation in the control group

△···△ : Pdi/Pdi100 at 100 Hz stimulation in the lowered Qt group

▲···▲ : Pdi/Pdi100 at 20 Hz stimulation in the lowered Qt group

*: $P < 0.05$, **: $P < 0.01$ (vs pre-fatigue period).

+: $P < 0.05$, ++: $P < 0.01$, +++: $P < 0.001$ (lowered Qt vs control group).

It has been reported that the blood flow to diaphragm is maintained relatively constant within a certain limit of perfusion pressure[8] and is autoregulated when systemic blood pressure rises above 70 torr[9]. On the other hand, there is also a report that an autoregulation of Qdi is not present[5]. The existence in autoregulation of Qdi has not been confirmed, but the result of the present study is negative to its existence.

The present study revealed that there was a significant positive correlation between Qt and Qdi, and Qdi decreased proportionally in accord with the decrease in Qt. Therefore, it can be assumed that Qt is one of the important factors to regulate Qdi. However, this direct proportion between Qt and Qdi seems to be appropriate only when the dogs are mechanically ventilated, and may not be applied to spontaneous breathing dogs. Viires et al reported that blood flow to the respiratory muscle increased significantly during the lowered Qt in the spontaneous breathing group, while it decreased in mechanically ventilated group[10]. The exact mechanism for this is unknown, but during spontaneous breathing there must be some mechanisms for regulating Qdi other than Qt.

The present study showed that diaphragmatic fatigue was developed much faster and earlier with low frequency stimulation than with high frequency stimulation in the both the control and lowered Qt groups. The result may be a proof to suggest that diaphragm muscle fatigue is mainly concerned with a low frequency fatigue and has almost nothing to do with high frequency fatigue.

It has been known that energy supplies to diaphragm are critically dependent on blood flow. In the present study, Pdi/Pdi100 in the lowered Qt group decreased more significantly than that of control group during 30 min of fatigue period. After 60 min of recovery period, Pdi/Pdi100 of the control group returned to the almost pre-fatigue value. But the lowered Qt group showed no tendency to recover and remained at the decreased level even after 60 min of recovery period. These results clearly show that a decreased Qt is one of the critical factors affecting on development and recovery of diaphragm muscle fatigue.

After releasing the balloon in the recovery period, there was no difference in Qt between the control and lowered Qt groups, so that the blood supplies to the two groups were probably the same. The difference of the recovery process in the two groups, therefore, may attribute to the disturbance in avail-

ability of energy supplied in the lowered Qt group.

In conclusion, the present study demonstrated that in the mechanically ventilated dogs; (a) Qdi decreased in accordance with the decrease in Qt, (b) diaphragmatic fatigue in the lowered Qt group was developed earlier and faster than that in the control group, and (c) the speed of recovery from the fatigue was much slower in the lowered Qt group.

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