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Myocardial Depression During *Diplococcus pneumoniae* Infection in Monkeys[1] (37759)

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Decreased cardiac output was found to be one of the cardiovascular disturbances in some patients with acute pneumococcal pneumonia (1, 2). The primary mechanism for the low cardiac output was thought to be due to a depression of myocardial activity. A search of the literature dealing with the relationship between *Diplococcus pneumoniae* infection and cardiac contractility in animal models revealed that no work has been done.

In this study, we applied muscle mechanics principles (3–5) to evaluate one of the determinants of cardiac output, myocardial contractility, in a conscious monkey model experimentally infected with *D. pneumoniae* organisms. Within 16 hr postinfection, cardiac contractility decreased significantly but gradually returned to normal or slightly above normal levels throughout the experimental period. Tachycardia and a febrile response were demonstrated coincident with myocardial depression.

Method. Six healthy, mature rhesus monkeys (*Macaca mulatta*) weighing 4–5 kg, were used. A high-fidelity micromanometer (Model P-15, Konigsberg Instruments, Inc., Pasadena, CA) was surgically implanted into the left ventricle of each monkey, as described elsewhere (6). Monkeys were allowed to convalesce for 2 weeks after surgery and become adapted to metabolic chair restraint and laboratory environment before initiating the study. All monkeys were housed in a room separate from the recording systems and investigators to minimize emotional disturbances during data-recording periods. Implanted micromanometers were connected to recording equipment by wire circuitry. In addition to the left ventricular pressure (LVP), a corresponding first derivative (dP/dt) was obtained by passing the pressure signal through an active, noninverting differentiator (Model 620 analog computer, Biotronex Laboratory, Inc., Silver Spring, MD). The midpoint during diastole, on the LVP recording, was selected as the estimated zero pressure reference because the sealed manometer could no longer be referenced to atmosphere after implantation into the left ventricle. Recorder paper speed was 200 mm per sec.

Two indices of cardiac contractility that reflect changes in myocardial inotropism were determined by the developed pressure method (3). These included estimation of the maximum velocity of contractile element shortening (V_{max}) (7) and the velocity of contractile element shortening (V_{ce}) at the peak rate of pressure rise (peak dP/dt) in the left ventricle (8). V_{ce} was calculated at 5-msec intervals during the isovolumic contraction period as:

$$V_{ce} = \frac{dp/dt}{32 \cdot DIP}$$

where DIP = developed isovolumic LVP, according to the method of Mason (3). A pressure-velocity curve relating V_{ce} to the corresponding DIP was constructed to deter-

[1] In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences–National Research Council. The facilities are fully accredited by the American Association of Accreditation of Laboratory Animal Care.

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mine V_{max}. By least-squares linear regression, the descending portion of the pressure-velocity curve was extrapolated to zero pressure to obtain V_{max} in muscle lengths (ML) per sec.

All monkeys were given 1–4 $\times$ 10^8 virulent, Type I, *D. pneumoniae* microorganisms suspended in 1 ml of sterile saline diluent, administered intravenously (iv) as a single injection. Bacteremia was verified from daily blood cultures. A thermistor probe implanted deeply into the *longissimus dorsi* muscle permitted continuous recording of body temperature. Since each monkey served as its own control, control data were collected at 2- to 6-hr intervals for 1–5 days prior to infection. After inoculation of pneumococcal organisms, data were obtained at 2-hr intervals up to postinoculation Day 5 and four times daily through postinoculation Day 8. The contractility values for each time period was the mean of five consecutively analyzed waveforms.

For statistical analyses, temperature, heart rate, V_{max}, and V_{ce} at peak dP/dt were graphed for each monkey and partitioned into two 12-hr segments. Each segment was denoted as day and night (0800–2000 hr and 2000-0800 hr, respectively) and the area under the curve was calculated. The area under the curve for each 12-hr interval after infection was subtracted from each monkey's own control period values for comparison. A Student's t test statistic and the 95% confidence level were employed for significance.

Results. The responses of one monkey during acute pneumococcal infection are shown in Fig. 1. Beginning about 6 hr after infection, both V_{max} and V_{ce} at peak dP/dt were significantly lower ($P < 0.05$) than control values for a duration of 14–16 hr and then intermittently through Day 7 postinfection. Detectable bacteremia persisted for 6 days, which is longer than usual for this model. Hyperthermia and tachycardia occurred during the acute phase of *D. pneumoniae* infection. Similar responses occurred in four other monkeys. However, the sixth monkey in our study failed to have an altered contractility response in spite of a 3-day bacteremia; therefore, data from this unresponsive monkey were excluded from the combined analyses.

When the data of the five responsive monkeys were pooled (Fig. 2), the findings indicated that myocardial contractility was significantly reduced from control values ($P <$ 0.05) between 12 and 36 hr postinfection.

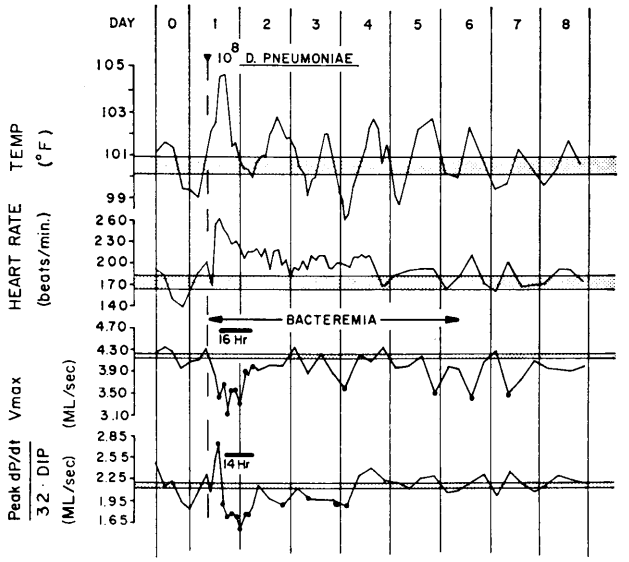

FIG. 1. Graphed data of one monkey's response before and after *D. pneumoniae* infection. The stippled horizontal bar through each variable is the standard error of the mean. The solid circles on each of the contractility indices (V_{max} and V_{ce} at peak dP/dt) response line represent a significant change from control values ($P < .05$). ML = muscle lengths.

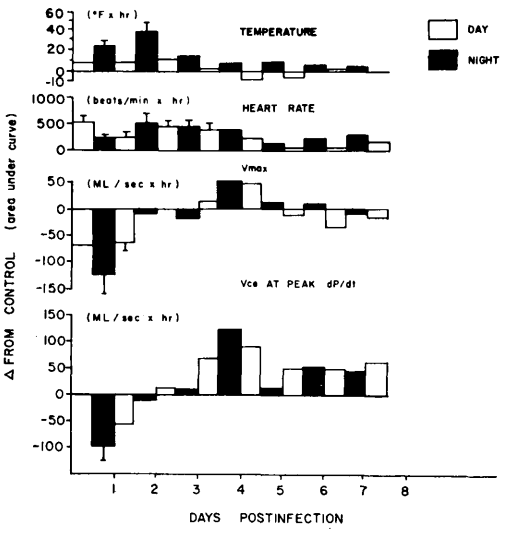

FIG. 2. Effects of *D. pneumoniae* infection on body temperature, heart rate, and myocardial contractility indices (V_{max} and V_{ce} at peak dP/dt) of five monkeys. The difference between the control and infected areas under the curve of the plotted graph was calculated for each variable at 12-hr intervals. SE bars represent those time periods which were significantly different from control values ($P < .05$). ML = muscle lengths.

Although myocardial depression occurred early during the acute phase of the infection, reduction of cardiac contractility was greatest during the second 12-hr time interval. During the 4th and 5th days postinfection, a trend toward augmented cardiac contractility was found. Statistically, it was not significant. Body temperature was elevated during the period of myocardial depression (Fig. 2). Peak fever occurred at varying times, reaching 105°F in some individual monkeys, but greater than 103.5°F in all cases. Heart rate was generally increased throughout the experimental period. There was no correlation between heart rate and cardiac contractility (Fig. 2). Estimated left ventricular end-diastolic pressure (LVEDP) was less than 8 mmHg throughout the study in all monkeys.

Discussion. This is the first report known to us whereby the muscle mechanics principle was applied to study cardiac function in a conscious, infected primate. The conscious monkey, conditioned to chair restraint, affords the advantages of a subhuman primate model with cardiovascular responses more analogous to man than the classic anesthetized dog or monkey models (9). When physiological monitoring devices are implanted for chronic studies, this model eliminates undesirable variables due to the effects of anesthesia and the stress of surgically induced trauma.

The measurement of myocardial contractility, defined as an altered response in myocardial function independent of changes in myocardial fiber length, was based upon the muscle mechanics principle relating left intraventricular pressure to the velocity of contractile element shortening. Two different techniques, namely, the contractile force principle (10) and V_{max} extrapolated from pressure–velocity relations (7), are commonly utilized for the assessment of ventricular function in animal models. We selected the latter method because it is a more appropriate measure of myocardial contractility; contractile force is dependent upon initial myocardial fiber length (11), whereas V_{max} is not (7). V_{ce} at peak dP/dt is also fiber-length dependent (7), but was incorporated into this study as a comparison to V_{max} since it could be computed easily from the V_{max} pressure–velocity relationship. An additional advantage to the pressure–velocity technique is the relative ease by which it can be quantitated from a single systolic event (6).

LVEDP, which was estimated because the sealed manometer could not be referenced to atmosphere after implantation, was consistent and within normal limits (12) for all monkeys for the duration of the study. The inability to determine absolute LVEDP does not affect the accuracy of V_{max} or V_{ce} at peak dP/dt since, by the developed pressure method, LVEDP is considered zero pressure.

The pneumococcus organism was selected for several reasons: (i) It is not known to produce toxins; therefore, any changes in myocardial contractility would be expected to be influenced by the organism *per se*, the infectious processes, or both. (ii) A decreased cardiac output associated with pneumococcal pneumonia has been reported in man (1, 2). (iii) The clinical response of the rhesus monkey to 10^8 *D. pneumoniae* organisms,

given iv, has been reported earlier from this laboratory (13).

Emotional depression and anorexia have been reported to occur within 12 hr and persist for 1–3 days after experimental *D. pneumoniae* infection of monkeys (13). Peak febrile response usually occurs within 24 hr, with body temperature remaining elevated for 2—5 days. Although no deaths occurred in this study, an occasional death may result from this infection. The clinical course of pneumococcal infection in all six monkeys was in general agreement with the findings reported by Kastello *et al.* (13). *D. pneumoniae* bacteremia persists generally for no longer than 3 days when the organisms are given iv. The prolonged bacteremia in one responsive monkey (Fig. 1) may account for the intermittent myocardial depression occurring on Days 2–7 postinfection.

Although changes in V_{max} and V_{ce} at peak dP/dt vary in degree and duration in individual monkeys, they are sufficiently consistent in five of the six monkeys studied to show significant cardiac depression (Fig. 2). It is evident that either V_{max} or V_{ce} at peak dP/dt can be used for measuring myocardial contractility changes during pneumococcus infection. Since an increment in myocardial temperature is known to augment intrinsic myocardial functions (14–17), and tachycardia indicates increased sympathetic activity, one would expect contractility to parallel changes in body temperature and heart rate. It is unclear why myocardial contractility decreased during peak fever and tachycardia after pneumococcal infection; however, we feel that this paradox indicates an alteration in the energetics of myocardial contraction. Our observation of myocardial depression in subhuman primates also suggest that this may be one mechanism for decreased cardiac output associated with pneumococcal pneumonia reported in man (1, 2). During Days 4 and 5 postinfection, a trend toward increased cardiac contractility occurred. It is possible that this trend resulted in part from tachycardia, despite no significant correlation in our study.

Summary. This report describes the extent to which 10^8 *D. pneumoniae* organisms, administered iv, caused changes in heart rate, body temperature, and myocardial contractility in five of six conscious, chair-restrained mature rhesus monkeys. Within 16 hr after pneumococcal infection, hyperthermia, tachycardia, and decreased cardiac contractility were observed. All parameters returned to relatively normal levels 4 days postinfection. It is unknown why myocardial depression occurred coincident with febrile response and tachycardia.

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1. Benson, H., Akbarian, M., Adler, L. N., and Abelmann, W. H., J. Clin. Invest. **49**, 791 (1970).

2. Kumar, R., Wallace, W. A., Ramirez, A., Benson, H., and Abelmann, W. H., J. Clin. Invest. 49, 799 (1970).

3. Mason, D. T., Zelis, R., Amsterdam, E. A., and Massumi, R. A., *in* "Progress in Cardiology" (P. N. Yu and J. F. Goodwin, eds.), Vol. 1, p. 121. Lea & Febiger, Philadelphia (1972).

4. Braunwald, E., Ross, J., Gault, J. H., Mason, D. T., Mills, C., Gabe, I. T., and Epstein, S. E., Ann. Intern. Med. **70**, 369 (1969).

5. Brutsaert, D. L., and Sonnenblick, E. H., Progr. Cardiovasc. Dis., **16**, 337 (1973).

6. Zech, W. H., Boucher, J. H., Hilmas, D. E., and Spertzel, R. O., Amer. J. Vet. Res., **35**, 83 (1974).

7. Mason, D. T., Spann, J. F., and Zelis, R., Amer. J. Cardiol. **26**, 248 (1970).

8. Finkelstein, L. J., Keefe, J. F., Wolk, M. J., Bing, O. H. L., and Levine, H. J., Circulation **40** (Suppl. 3), 80 (1969).

9. Wyler, F., Forsyth, R. P., Nies, A. S., Neutze, J. M., and Melmon, K. L., Circ. Res. **24**, 777 (1969).

10. Walton, R. P., and Hauck, A. L. (eds.), "Direct Recording of Heart Force by the Strain Gage Principle — An Annotated List of References," 618 ref. Department of Pharmacology, Medical College of South Carolina, Charleston (1967).

11. Aygen, M. M., and Braunwald, E., Circulation **26**, 516 (1962).

12. Hoffbrand, B. I., and Forsyth, R. P., Surg. Gynecol. Obstet. **132**, 61 (1971).

13. Kastello, M. D., and Spertzel, R. O., Amer. J. Phys. Anthropol. **38**, 501 (1973).

14. Walton, R. P., Goldberg, L. I., Glazes, P. C.,

Leary, J. S., Ezell, H. K., Hanna, C. B., and Prystowsky, R. P., Amer. J. Physiol. **169**, 78 (1952).

15. Goldberg, L. I., Ezell, H. K., and Walton, R. P., Amer. Heart J. **44**, 754 (1952).

16. Templeton, G. H., Reardon, W. C., and Wildenthal, K., Clin. Res. **20**, 31, abstr. (1972).

17. Yeatman, L. A., Parmley, W. W., and Sonnenblick, E. H., Amer. J. Physiol. **217**, 1030 (1969).

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