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The Comparison of Myocardial Dysfunction in Three Forms of Experimental Septic Shock

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ABSTRACT. A rabbit model of septic shock was used to determine if 1) myocardial dysfunction is a common component of shock due to diverse neonatal pathogens, and 2) prostaglandins modulate septic myocardial dysfunction. The infusion of heat-killed *Escherichia coli* (group I), *Haemophilus influenzae* (group II), or *Staphylococcus epidermidis* (group III) produced significant decreases in the first derivative of left ventricular pressure with respect to time ($p < 0.05$). Each organism also produced significant changes in mean arterial pressure, cardiac output, and heart rate, while pulmonary artery pressure was altered in groups I and III. Saline-infused control animals (group IV) exhibited no significant changes in any hemodynamic variable. Blood gas variables were not significantly changed in any group. These cardiovascular changes appeared dependent on arachidonic acid metabolism since indomethacin pretreatment prevented the cardiovascular changes induced by bacterial infusion. These results suggest that septic myocardial dysfunction is a common component of gram-negative and gram-positive septic shock, and that myocardial dysfunction is modulated by prostaglandin products. (*Pediatr Res* 20: 1240–1242, 1986)

Abbreviations

GBS, group B streptococcus
PAP, pulmonary artery pressure
LVdP/dt, the first derivative of left ventricular pressure with respect to time
MAP, mean arterial pressure
HR, heart rate
CO, cardiac output
EC, *Escherichia coli*
HI, *Haemophilus influenzae*
SE, *Staphylococcus epidermidis*
IND, indomethacin
LVEDP, left ventricular end diastolic pressure
PG, prostaglandin

The pathogenesis of septic shock is poorly understood. Although hypotension, hypoxia, acidosis, and pulmonary hypertension appear to be common pathophysiologic events in septic shock, the mechanisms through which bacterial products act to precipitate these untoward events remain unclear. Clinical studies of septic adult and pediatric patients have suggested primary myocardial dysfunction as a contributor to the evolution of shock (1, 2). In addition, depressed myocardial function has been demonstrated in a number of *in vivo* and *in vitro* studies using gram-negative organisms or endotoxin (3–5). Endogenous agents, primarily arachidonic acid metabolites, have been implicated as modulators of endotoxin-induced myocardial depression (1, 6).

In a previous study, we demonstrated myocardial dysfunction in response to experimental gram-positive septic shock (7). In our study, the infusion of GBS, caused a rapid decline in left ventricular dP/dt that was independent of decreases in preload, increases in afterload, or changes in HR. The fall in left ventricular dP/dt was prevented by prior administration of IND, suggesting a role for prostanoids in the modulation of GBS-induced myocardial dysfunction.

It appears likely that septic myocardial dysfunction is not unique to a particular organism, but is a common pathophysiologic response to many infectious agents. The purposes of this study were 1) to determine if acute myocardial dysfunction is produced by neonatal pathogens other than GBS and if so 2) is the myocardial dysfunction induced by these pathogens inhibited by the prior administration of IND.

MATERIALS AND METHODS

Animal preparation. Adult New Zealand White rabbits received pentobarbital anesthesia (30 mg/kg intravenous) and were placed on a small animal ventilator after tracheostomy. A midline sternotomy was performed, and catheters were inserted into the main pulmonary artery and left ventricle for measurement of PAP, the LVdP/dt, and LVEDP. Femoral arterial and venous catheters were placed for measurement of MAP, HR, arterial blood gases, and administration of bacteria. A 5.0 mm Statham flow probe attached to a Zepada flow meter was placed on the ascending aorta for measurement of CO. All hemodynamic variables were recorded on a model R411 Beckman chart recorder. After surgery, animals were stabilized for 30 min. Arterial blood gases were measured every 15 min and ventilation adjusted to maintain an alkalotic, hyperventilated state (pH $\geq$ 7.5) so that anticipated bacterial induced decreases in pH would not cause severe acidosis and affect MAP, CO, and LVdP/dt.

Bacterial preparation. Clinical isolates of EC, HI (nontypable), or SE were used in all experiments. Bacteria were grown overnight on blood agar, suspended in sterile, nonpyrogenic saline to a quantified density of 10^{11} colony-forming units per milliliter, and then killed by heating to 100° C for 15 min.

Experimental sequence. Part I. Four experimental groups were used. Animals receiving bacterial suspensions were given heat killed EC (group I), HI (group II), or SE (group III) by constant infusion (0.3 to 0.5 ml/kg/min of 10^{11} organisms/ml) to a total dose of 10^{12} organisms per kg. Values for hemodynamic variables and arterial blood gases were obtained immediately before (base-

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line) and 30 min after the beginning of the infusion. Control animals (group IV) received a volume of sterile saline equal to the volume of heat-killed organisms used in the other three groups and had each variable assessed at before and 30 min after the saline infusion.

Part II. Four animals randomly selected to receive either EC, HI, or SE were pretreated with IND (4 mg/kg), and then infused with the bacterial suspension as described in part I. Two of the four animals received SE, one received EC and one received HI. Values for hemodynamic variables and blood gases were obtained immediately before IND, 15min after the IND bolus, and 30 min from the beginning of the bacterial infusion.

Statistical analyses were performed on each variable between groups (unpaired data) using one-way analysis of variance then Duncan's new multiple range test and within groups (paired data) using the paired *t* test, or randomized block design analysis of variance then Duncan's new multiple range test. A p value of < 0.05 was considered significant for all comparisons.

RESULTS

Part I. Table 1 shows the values for LVdP/dt, MAP, PAP, % change in CO and HR before and 30 minutes after beginning the bacterial infusion in the four groups. Animals in groups I (EC), II (HI), and III (SE) had significant falls in LVdP/dt and MAP ($p < 0.05$), while the control group did not elicit a significant change in either variable (group IV). Animals in groups I (EC) and III (SE) showed significant rises in PAP ($p < 0.05$), while group II (HI) and group IV (control) did not. Infusion with EC, HI, and SE bacterial suspensions caused a significant fall in both CO and HR. In contrast, the control animals did not have significantly altered CO or HR compared to baseline presaline infusion values. In no group was LVEDP or systemic vascular resistance significantly altered (data not shown).

Table 2 lists values for pH and pO_2 before (baseline) and at 30 min following the beginning of infusion with either the bacterial suspensions (groups I–III) or saline (group IV). Each group had a baseline pH of 7.5 or greater and no group had a statistically significant fall in pH, although group III (SE) had a mean decline of 0.11 pH units (7.52 to 7.41). Mean values for pO_2 30 min after beginning the infusion in the four groups were not significantly lower than the baseline preinfusion values in any group.

Part II. Table 3 shows the effects of bacterial suspensions infusion on MAP, LVdP/dt PAP, CO, and HR in animals pretreated with IND. IND pretreatment abolished the expected fall in CO, MAP, and LVdP/dt and rise in PAP associated with the bacterial infusion. HR and LVEDP were not significantly altered in animals in part II. Thus, IND protected against the bacterial induced alterations in the cardiovascular hemodynamic parameters.

DISCUSSION

Our study demonstrates myocardial dysfunction in response to three diverse bacterial pathogens. These results are similar to those previously obtained in the same model using heat-killed GBS (7), and suggests that myocardial dysfunction is a common component of septic shock induced by various types of bacteria. Defining the mechanism for a single pathophysiological alteration is difficult in *in vivo* studies. In our model LVdP/dt could have been altered by changes in preload (LVEDP), HR, afterload, and the intrinsic contractile state of the heart (8, 9). In the present study only HR was significantly decreased in any group, and by a maximum of only 16% (group I). Thus, it would appear that the decrease in LVdP/dt primarily reflects alterations in the contractile state of the myocardium.

In part II of this study, pretreatment with IND prevented the myocardial dysfunction observed in part I. These results are similar to those seen in our previous study of GBS-induced myocardial dysfunction and add further evidence that septic myocardial dysfunction is modulated through prostanoid production (7). Prostanoid alteration of myocardial function could

Table 2. *Baseline and postinfusion arterial blood gas values (mean ± SE)*

Group*	pH	pO_2	pCO_2
I ($n = 4$)			
Baseline	7.60 ± 0.01	76 ± 9	16 ± 1
EC	7.56 ± 0.03	59 ± 12	15 ± 3
II ($n = 4$)			
Baseline	7.54 ± 0.04	54 ± 2	17 ± 2
HI	7.51 ± 0.05	53 ± 9	12 ± 6
III ($n = 6$)			
Baseline	7.52 ± 0.02	63 ± 7	18 ± 2
SE	7.41 ± 0.05	48 ± 10	22 ± 4
IV			
Baseline	7.62 ± 0.04	77 ± 11	23 ± 6
Saline	7.59 ± 0.03	76 ± 12	24 ± 6

* No significant differences were noted.

Table 1. *Baseline and postinfusion values for selected hemodynamic variables (mean ± SE)*

Group	MAP (mm Hg)	LVdP/dt (mm Hg/s)	PAP (mm Hg)	CO (% of change from baseline)	LVEDP	HR (beats/min)
I ($n = 4$)						
Baseline	90 ± 6	7373 ± 1700	18.3 ± 1.3		1.5 ± 0.6	304 ± 11
EC	52 ± 5*	2439 ± 932*	26 ± 0.6*	52 ± 12*	1.3 ± 0.5	253 ± 12*
II ($n = 4$)						
Baseline	91 ± 10	5506 ± 1082	15.3 ± 4		2.5 ± 1.7	280 ± 9
HI	57 ± 11*	2931 ± 946*	17.8 ± 4.6	36 ± 8*	1.0 ± 0.7	265 ± 11*
III ($n = 6$)						
Baseline	83 ± 4	5539 ± 334	14.3 ± 2.4		5.1 ± 1.7	314 ± 9
SE	45 ± 4*	2234 ± 429*	22.8 ± 2.6*	60 ± 12*	2.8 ± 0.9	270 ± 20*
IV ($n = 4$)						
Baseline	90 ± 5	5862 ± 605	17.3 ± 0.6		1.5 ± 0.5	242 ± 10
Saline	90 ± 4	5952 ± 428*	18.5 ± 1.3	5 ± 3	3.0 ± 1.2	263 ± 5

* Significant difference from base ($p < 0.05$).

Table 3. *Hemodynamic values assessed at baseline and 30 min after infusion of bacteria in rabbits pretreated with IND (mean ± SE)*

Group	MAP (mm Hg)	PAP (mm Hg)	LVdP/dt	CO (% of change from baseline)	LVEDP	HR (beats/min)
Baseline	91 ± 9	18.5 ± 1.0	6494 ± 1333		3.0 ± 0.9	299 ± 10
IND	86 ± 6	18.3 ± 1.4	5360 ± 812	2 ± 5	3.8 ± 0.5	303 ± 9
Bacteria	75 ± 4*	20.0 ± 0.9	5511 ± 894	−4 ± 12	1.5 ± 1.5	303 ± 17

* Denotes significant difference between baseline and bacteria. No statistically significant differences were found between baseline and IND or between IND and bacteria.

be produced through changes in coronary perfusion (10, 11), by production of right ventricular afterload and secondary left ventricular dysfunction (12), via a direct effect of prostanoids on myocardial contractile function (13, 14), or secondary to increased free radical production via oxygen radical production during the reduction of PGG_2 to PGH_2 (15–17).

In summary, we have shown that myocardial dysfunction occurs in a rabbit model of septic shock caused by EC, HI, and SE, and can be prevented by the PG synthetase inhibitor, IND. These data support the concept that septic myocardial dysfunction is a common component of both gram-negative and gram-positive septic shock and that myocardial dysfunction is modulated by PG products. Further work is needed to elucidate the mechanism(s) for septic myocardial dysfunction.

REFERENCES

1. Parrillo J 1985 Cardiovascular dysfunction in septic shock: new insights into a deadly disease. Int J Cardiol 7:314–321
2. Hess M, Hastillo A, Greenfield L 1981 Spectrum of cardiovascular function during gram-negative sepsis. Prog Cardiovasc Dis 23:279–298
3. Archer L, Benjamin B, Beller-Todd B, Brackett D, Wilson M, Hinshaw L 1982 Does LD_{100} *E. coli* shock cause myocardial failure? Circ Shock 9:7–16
4. Parker J, Adams H 1979 Myocardial effects of endotoxin shock: characterization of an isolated heart muscle model. Adv Shock Res 2:163–175
5. Parker J 1983 Contractile function of heart muscle isolated from endotoxin-shocked guinea pigs and rats. Adv Shock Res 9:133–145
6. Carli A, Auclair M, Vernivumen C 1983 Indomethacin suppresses early cardiodepressant factor released by endotoxin in the rat: possible involvement of a prostacyclin related material. Adv Shock Res 10:161–171
7. Peevy K, Chartrand S, Wiseman H, Boerth R, Olson R 1985 Myocardial dysfunction in group B streptococcal shock. Pediatr Res 19:511–513
8. Neill W 1976 Regulation of cardiac output. In: Levin HJ (ed) Pediatric Clinical Cardiovascular Physiology. Grune and Stratton New York, pp 121–142
9. Skelton C, Sonnenblick E 1976 Physiology of cardiac muscle. In: Levin HJ (ed) Clinical Cardiovascular Physiology. Grune and Stratton, New York, pp 57–120
10. Gerritsen M, Cheli C 1983 Arachidonic acid and prostaglandin endoperoxide metabolism in isolated rabbit and coronary microvessels and isolated and cultivated coronary microvessel endothelial cells. J Clin Invest 72:1658–1671
11. Posner P, Lambert C 1982 Study of prostaglandin E_1 and F_2a on isolated mammalian cardiac tissue. Pharmacology 25:26–3212
12. Ghignone M, Girling L, Prewitt R 1984 Effect of increased pulmonary vascular resistance on right ventricular systolic performance in dogs. Am J Physiol 246:H339–H343
13. Fozzard H 1977 Heart: excitation-contraction coupling. Ann Rev Physiol 39:201–220
14. Kecskemeti V, Keleman K, Knoll J 1976 Dose-dependent effect of prostaglandins on cardiac transmembrane potential. Acta Biol Med Germ 35:1173–1174
15. Kuehl FA, Ham EA, Egan RN, Dougherty HW, Bonney RJ, Humes JL 1982 Studies on a destructive oxidant released in the enzymatic reduction of prostaglandin G_2 and other hydroporoxy acids. In: Autor A (ed) Pathology of Oxygen. Academic Press, New York, pp 175–188
16. Egan RN, Paxton J, Kuehl FA 1976 Mechanisms for irreversible self-deactivation of prostaglandin synthetase. J Biol Chem 251:7329–7335
17. Egan RN, Gale PH, Kaehl FA 1979 Reduction of hydroperoxide in the prostaglandin biosynthetic pathway by a microsomal peroxidase. J Biol Chem 254:3295–3302