Brit. Heart J., 1967, **29**, 883.

Hæmodynamic Studies in Shock Associated with Infection*

HENRY S. LOEB, ANTONIO CRUZ, CHENG YEE TENG, JEB BOSWELL, RAYMOND J. PIETRAS, JOHN R. TOBIN, JR., AND ROLF M. GUNNAR

From the Department of Adult Cardiology and the Hektoen Institute for Medical Research of Cook County Hospital; and from the Departments of Medicine of the University of Illinois College of Medicine and the Stritch School of Medicine of Loyola University, Chicago, Illinois, U.S.A.

The circulatory responses of experimental animals to bacterial products vary among species, and data from such experiments are not necessarily translatable to man (Gilbert, 1960). The hæmodynamic alterations occurring in man when infection is associated with shock were investigated originally by Gilbert *et al.* (1955). Similar investigations conducted by Udhoji *et al.* (1963), Udhoji and Weil (1965), Cohn and Luria (1964), and Wilson, Jablonski, and Thal (1964) have contributed to our knowledge of the basic mechanisms producing shock, but further evaluations of the efficacy of therapeutic measures used to combat shock associated with sepsis are necessary.

Since few patients are available for such investigations, the studies in this paper were devised so that each patient served as his own control. Short-acting therapeutic agents were usually evaluated before long-acting agents, which might result in a new steady state. These studies demonstrate that vasopressors commonly fail to increase blood flow significantly without prior expansion of the plasma volume and that maintenance of an adequate central aortic pressure may be essential for preservation of coronary flow and cardiac function.

Subjects and Methods

Shock was defined as (1) a decrease in the arterial pressure to below 80 mm. Hg systolic (or below 90 mm. Hg in known hypertensive patients) accompanied by (2) certain clinical manifestations, such as a pulse of low volume and a dulled sensorium. The presence of infection was established by the recovery of a micro-organism from the blood, by the presence of infection at necropsy, or by unequivocal clinical evidence of infection such as cellulitis and pneumonia. There was no evidence of myocardial infarction or pulmonary embolism in any of these patients.

Twenty-one patients (Table I) fulfilled the criteria for infection associated with shock. The age of the patients varied from 42 to 88 years with an average age of 62. There were 5 patients with pyelonephritis, 1 patient with cholangitis, 4 patients with lobar pneumonia, and 2 patients with bronchopneumonia; 1 patient had an extensive empyema of the chest; 1 had portal cirrhosis and a blood culture positive for *Staphylococcus albus*; 1 with acute pancreatitis had a non-hæmolytic streptococcus cultured from the blood; 3 had bacteræmia as manifested by blood culture, but the site of the infection remained undetermined; 1 had *Staphylococcus aureus* endocarditis, and there were 2 patients with cellulitis.

Studies were conducted at the bedside. Central venous pressure was measured with a water manometer through a PE-160 catheter threaded into the superior vena cava or right atrium. Central aortic pressure was measured with a Statham P 23 Db transducer through a PE-160 catheter threaded from the brachial artery into the central aorta. Cardiac output was measured by the indicator-dilution method using indocyanine green. Blood was drawn through a Gilford 103 (IR) densitometer using a Harvard pump. Recordings were made with a Sanborn 564-100A photographic recorder. A Sanborn Model 130 Cardiac Output Computer was used to assess the progress of the patient. All measurements of cardiac output for data analysis were obtained using the standard Stewart-Hamilton method (Kinsman, Moore, and Hamilton, 1929), and represent an average of two to five determinations made in rapid succession. Systemic vascular resistance (SVR) was calculated as follows.

$$SVR = \frac{\text{Mean aortic pressure (mm. Hg)} - \text{central venous pressure (mm. Hg)}}{\text{Cardiac output (l./minute)}}.$$

Received January 13, 1967.

* Supported in part by a grant from the National Institutes of Health, Bethesda, Maryland, U.S.A.

TABLE I

CLINICAL DATA OF PATIENTS WITH SHOCK ASSOCIATED WITH INFECTION

Patient, age, race, and sex				Diagnosis	Bacteriological study	Clinical observations	Outcome
M.K.	50	W	M	*Aerobacter aerogenes* septicæmia of undetermined origin	*A. aerogenes* cultured from blood	Melæna and hæmatemesis; given transfusions, bleeding stopped, developed temp. 41°C. next day and went into shock; Levine tube failed to reveal evidence of active bleeding	Recovered from shock, but died 36 h. later from massive gastro-intest. bleeding; necropsy revealed fatty cirrhosis
L.S.	80	W	F	Chronic urinary tract infection; arteriosclerotic heart disease	*A. aerogenes* cultured from urine	Treated for chronic urinary tract infection as out-patient; admitted in shock with pyuria and azotæmia	Died 4 hours after onset of study; no necropsy
J.L.	56	W	M	Pancreatitis, alcoholism, septicæmia	Non-hæmolytic streptococcus cultured from blood	Admitted with abdominal pain, vomiting and tachycardia; developed temp. 40°C. and developed shock	Recovered from shock and became afebrile; laparoscopy 5 wk. later showed old pancreatitis and peritonitis with adhesions
C.M.	66	W	M	Bronchopneumonia	Coagulase-negative staphylococcus cultured from blood	Admitted in respiratory distress with temp. 41°C.; tracheotomy; went into shock	Died 2 dy. after study; necropsy revealed bilateral bronchopneumonia
J.A.R.	69	W	F	Bacterial endocarditis	*Staph. aureus* cultured from blood	Cachectic and debilitated with decubitæ; became febrile and went into shock	Recovered from shock, but died 12 dy. later of infection and debility; necropsy revealed bacterial endocarditis of the aortic valve and a myocardial abscess
A.R.	53	W	M	Pneumonia	None reported	Debilitated alcoholic with pneumonia; WBC—10,200 with left shift; admitted in shock	Died 5 hr. after study; necropsy revealed lobar pneumonia with abscess formation
D.S.	55	W	M	Staphylococcal bacteræmia; source undetermined	*Staph. albus* cultured from blood	Debilitated alcoholic with multiple petechiæ and anæmia; WBC—22,000 with left shift; admitted in shock	Died 9 hr. after study; no necropsy
J.D.R.	57	W	M	Cirrhosis, alcoholism, septicæmia	*Staph. albus* cultured from blood	Chronic alcoholic with cirrhosis developed shock; WBC —22,000 with left shift; no evidence of gastro-intest. bleeding	Recovered from shock, died 4 dy. later in hepatic coma; necropsy revealed advanced cirrhosis, gastritis and chronic pancreatitis
R.C.H.	53	N	M	Chronic pyelonephritis	Pseudomonas cultured from blood; enterococcus from urine	Alcoholic in shock, comatose, œdematous, and hypothermic with a BUN of 138 and creatinine of 9·5	Expired 12 hr. after onset of study; no necropsy
W.J.	55	N	M	Pneumonia, alcoholism, bronchogenic carcinoma	*Diplococcus pneumoniæ* cultured from blood	Cachexia and dehydration; admitted in shock with lobar consolidation	Died 3 hr. after onset of study; no necropsy
C.D.C.	67	W	M	Parkinson's disease, decubitus ulcer	Blood and urine cultures—no growth (taken after antibiotics were started)	Awaiting nursing-home placement; developed decubitus —2 dy. later found in shock, comatose, and temp. 39°C.	Died 9 hr. after onset of study; no necropsy
W.M.	70	W	M	Pyelonephritis	*Strep. fæcalis*	Admitted in shock with temp. 41°C.; studied 24 hr. after onset of shock	Remained toxic; died 6 dy. after study; no necropsy
C.B.	45	W	M	Left upper lobe pneumonia	*Diplococcus pneumoniæ* on sputum smear	Chronic alcoholic admitted 3 dy. before study for pneumonia and delirium tremens, developed shock 12 hr. before study	Died 24 hr. after study; no necropsy
S.M.	74	W	M	*Esch. coli* bacteræmia of undetermined origin; arteriosclerotic heart disease	Hæmolytic *Esch. coli* cultured from blood	Chronic congestive heart failure, admitted with marked respiratory distress and in shock	Died 18 hr. after study; necropsy revealed arteriosclerotic heart disease, confluent bronchopneumonia, and dilated common bile-duct

Table continued on next page.

TABLE I—*contd.*

Patient, age, race, and sex	Diagnosis	Bacteriological study	Clinical observations	Outcome
P.B. 58 W F	Acute cholangitis; Laennec's cirrhosis	Paracolon species cultured from blood	Chronic alcoholic admitted in shock and studied 24 hr. later after onset of shock	Improved; died 6 dy. after study from cardiac failure; no necropsy
G.L. 71 W M	Empyema right chest; chronic obstructive pulmonary emphysema	*Diplococcus pneumoniæ* in postmortem smear of empyema	Chronic obstructive pulmonary emphysema; increasing dyspnœa and cough with purulent sputum for several wk.; chest pains 1 day before admission; admitted in shock and studied immediately	Died 8 hr. after study; necropsy revealed extensive empyema
W.B. 71 N M	Pyelonephritis	*P. mirabilis* cultured from blood	Chronic alcoholic with cirrhosis of liver; developed chills, fever, dysuria, frequency, and nocturia 3 dy. before admission; admitted in shock and studied immediately	Recovered
R.U.H. 63 W F	Pneumonia right lung; arteriosclerotic heart disease	*Diplococcus pneumoniæ* in sputum	Old hemiplegia, chronic congestive failure; chills and collapse night before admission; admitted in shock	Died 16 hr. after admission; no necropsy
J.S.R. 42 N M	Pneumonia right lung; pulmonary sarcoidosis with cor pulmonale	*Diplococcus pneumoniæ* in sputum	Diffuse pulmonary sarcoidosis, chronic cough, chest pains, fever, and chills 2 wk. before admission; abdominal pain, vomiting, and diarrhœa day before admission; admitted in shock, temp. 39°C., studied immediately	Recovered
W.H. 88 W M	Pyelonephritis	*Esch. coli* cultured from blood	Developed chills, fever, and diarrhœa day before admission; admitted comatose, in shock, with temp. 40°C.; studied immediately	Died 9 hr. after study; no necropsy
W.P. 57 W M	Cellulitis and gangrene left foot; diabetes mellitus; severe peripheral vascular disease	No organism isolated	Frostbite 7 wk. before admission followed by gangrene of left foot; admitted wk. before study; developed shock 1 dy. before study	Died 5 hr. after study; no necropsy

If, when first seen, the patient was receiving a pressor agent, the infusion was continued until the catheters could be introduced and pressure pulses and indicator-dilution curves recorded. The pressor agent was then discontinued, and control records were obtained after arterial pressure stabilized at the shock level. Following control studies a series of drugs was given, and subsequent to each drug indicator-dilution curves and pressure pulses were recorded.

1. Methoxamine (0·5 mg./ml.) was given intravenously to 6 patients until the arterial systolic pressure exceeded 100 mm. Hg or until a maximum of 80 mg. had been given.

2. Norepinephrine (16 μg./ml.) was infused in 16 patients at a rate sufficient to raise the arterial systolic pressure to 100 mm. Hg.

3. Isoprenaline (2 μg./ml.) was infused in 8 patients at rates of 2 to 5 ml. per minute.

4. The plasma volume of 15 patients was expanded by rapid infusion of a 10 per cent solution of low molecular weight dextran (40,000 molecular weight—rheomacrodex) in a volume of 500 to 1000 ml. Infusion was discontinued before 1000 ml. had been given if the central venous pressure had reached 10 mm. Hg. After completion of the dextran infusion, indicator-dilution curves and pressure pulses were recorded, and these measurements served as the control values in evaluating further therapy.

5. Nine patients were digitalized with lanatoside C (1·2 mg.) and two with strophanthin (0·5 mg.). Twenty minutes were permitted to elapse before measurements were repeated. Nine patients had either been digitalized previously or their level of digitalization was impossible to determine and therefore were not included in this portion of the study.

6. Seven patients whose central venous pressures were high or normal after plasma volume expansion were given chlorpromazine intravenously in an initial amount of 10 mg. followed in some by 5 to 10 mg. 30 minutes later.

7. Nine patients received 2·0 g. of hydrocortisone intravenously before digitalization. The hæmodynamic measurements were repeated 30 to 60 minutes after giving the hydrocortisone.

All patients received appropriate antibiotic therapy.

Results

Control Data. Mean cardiac output was 6·1 ± 2·7 l./min. (Table II). Stroke volume was

TABLE II

SHOCK ASSOCIATED WITH INFECTION: CONTROL MEASUREMENTS IN 21 PATIENTS

Patient	Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
M.K.	6·5	62	53	9·0	6·8
L.S.	1·4	10	59	0·5	4·2
J.L.	6·7	47	65	1·0	9·6
C.M.	9·9	97	60	3·0	5·8
J.A.R.	8·0	92	60	3·0	6·9
A.R.	7·3	70	39	3·0	4·9
D.S.	4·7	51	73	2·0	15·1
J.D.R.	9·8	100	57	5·0	5·3
R.C.H.	7·4	94	67	0·5	9·1
W.J.	8·8	70	31	0·5	3·5
C.D.C.	9·7	94	54	1·0	5·5
W.M.	4·7	39	64	2·0	13·2
C.B.	9·5	56	42	11·0	3·2
S.M.	5·6	56	42	2·0	7·1
P.B.	2·2	22	48	4·0	19·9
G.L.	3·5	23	58	8·0	14·2
W.B.	5·0	63	70	9·6	12·0
R.U.H.	1·4	14	44	3·1	29·2
J.S.R.	7·3	53	56	1·5	7·4
W.H.	4·3	48	53	1·0	12·0
W.P.	4·5	43	42	6·6	7·8
Mean	6·1	57	54	3·6	11·5
S.D. ±	2·7	27·4	11	3·3	9·3

57 ± 27·4 ml., mean arterial pressure 54 ± 11 mm. Hg., systemic vascular resistance 11·5 ± 9·3 mm. Hg/l./min., and central venous pressure 3·6 ± 3·3 mm. Hg.

Results of Therapy. Methoxamine (Table III) was given to 6 patients and was, in each instance, the initial drug given after the control period. Cardiac output decreased in 3 patients and was unchanged in one. Two patients showed a small but significant increase in cardiac output. One was 88 years old and the other, though only 57, had diabetes mellitus and severe peripheral vascular disease. Both these patients probably had significant coronary artery disease.

Mean aortic pressure rose above control values 18 to 71 per cent in all 6 patients but exceeded 70 mm. Hg in only 2 patients. Central venous pressure increased significantly (1 mm. Hg or greater) or did not change in the patients whose cardiac output decreased and was unaltered in the 2 patients in whom cardiac output increased signifi-

TABLE III

HÆMODYNAMIC EFFECTS OF METHOXAMINE IN SHOCK ASSOCIATED WITH INFECTION

Patient		Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure* (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
S.M.	Control	5·3	56	42	0	7·9
	Methoxamine	4·3	49	58	4·0	12·5
	% Change	−19	−12	+38	+4	+58
G.L.	Control	3·5	23	58	8·0	14·2
	Methoxamine	2·6	17	68	11·9	21·5
	% Change	−26	−26	+17	+3·9	+51
W.B.	Control	5·0	63	70	9·6	12·0
	Methoxamine	4·6	62	108	10·0	21·3
	% Change	−8	−1	+54	+0·4	+77
J.S.R.	Control	7·3	53	56	1·5	7·4
	Methoxamine	6·9	55	70	3·6	9·6
	% Change	−5	+4	+25	+2·1	+30
W.H.	Control	4·3	48	53	1·0	12·0
	Methoxamine	5·0	52	91	1·0	18·0
	% Change	+16	+8	+71	0	+50
W.P.	Control	4·5	43	42	6·6	7·8
	Methoxamine	5·3	53	70	6·2	12·0
	% Change	+18	+23	+67	−0·4	+54

* Change expressed as absolute change in mm. Hg.

TABLE IV

HÆMODYNAMIC EFFECTS OF NOREPINEPHRINE IN SHOCK ASSOCIATED WITH INFECTION

Patient		Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure* (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
L.S.	Control	1·4	10	59	0	42·0
	Norepinephrine	1·5	14	111	0	74·0
	% Change	+7	+40	+88	0	+76
C.M.	Control	8·8	80	56	10·0	5·8
	Norepinephrine	8·4	79	88	10·0	9·3
	% Change	−5	−1	+57	0	+60
A.R.	Control	6·7	71	37	10·0	4·0
	Norepinephrine	8·8	85	71	9·0	7·0
	% Change	+31	+20	+90	−1	+75
D.S.	Control	5·4	63	70	4·0	12·2
	Norepinephrine	5·7	66	94	4·0	15·8
	% Change	+6	+5	+34	0	+30
R.C.H.	Control	7·4	95	67	0	9·1
	Norepinephrine	10·1	120	84	0	8·3
	% Change	+37	+26	+25	0	−9
W.J.	Control	8·8	70	31	0	3·5
	Norepinephrine	7·1	49	44	0	6·3
	% Change	−19	−30	+42	0	+80
C.D.C.	Control	8·8	85	58	1·0	6·5
	Norepinephrine	9·1	86	77	2·0	8·3
	% Change	+3	+1	+33	+1	+28
W.M.	Control	4·7	39	64	2·0	13·2
	Norepinephrine	4·4	36	57	2·0	12·5
	% Change	−6	−8	−11	0	−5
S.M.	Control	5·6	56	42	2·0	7·1
	Norepinephrine	5·3	88	80	7·0	13·7
	% Change	−5	+57	+90	+5	+94
P.B.	Control	2·2	22	48	4·1	19·9
	Norepinephrine	2·2	20	94	4·1	40·9
	% Change	0	−9	+96	0	+105
G.L.	Control	3·5	23	58	8·0	14·3
	Norepinephrine	4·2	27	106	9·1	23·1
	% Change	+20	+17	+83	+1·1	+61
W.B.	Control	5·0	63	70	9·6	12·1
	Norepinephrine	5·2	70	108	9·6	18·9
	% Change	+4	+11	+54	0	+56
R.U.H.	Control	1·4	14	44	3·1	29·2
	Norepinephrine	2·0	18	64	4·5	29·7
	% Change	+42	+28	+45	+1·4	+2
J.S.R.	Control	7·3	52	56	1·5	7·5
	Norepinephrine	7·7	59	80	3·6	9·9
	% Change	+5	+11	+43	+2·1	+32
W.H.	Control	4·3	48	53	1·0	12·1
	Norepinephrine	11·0	104	105	1·0	9·4
	% Change	+156	+117	+98	0	−22
W.P.	Control	4·5	43	42	6·6	7·9
	Norepinephrine	5·3	55	64	6·0	10·9
	% Change	+18	+28	+52	−0·6	+38

* Change expressed as absolute change in mm. Hg.

cantly. Systemic vascular resistance increased between 30 and 77 per cent over control values in all patients.

Norepinephrine (Table IV) was given to 16 patients; 6 had previously received methoxamine. Compared to control values, cardiac output decreased 6 and 19 per cent in 2 patients, remained unchanged in 6, and increased 6 to 156 per cent in 8. Patients showing the greatest increase in cardiac output with norepinephrine had significant increases in mean aortic pressure and no significant changes in central venous pressure, indicating an improvement in cardiac function. The greatest increase in cardiac output (156%) occurred in patient W. H., who had a 98 per cent increase in mean arterial pressure and a 22 per cent decrease in sys-

TABLE V

HÆMODYNAMIC EFFECTS OF ISOPRENALINE IN SHOCK ASSOCIATED WITH INFECTION

Patient		Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure* (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
M.K.	Control	6·5	62	53	9	6·8
	Isoprenaline	11·7	98	92	7	7·3
	% Change	+80	+58	+74	−2	+7
C.M.	Control	8·8	88	56	10	5·8
	Isoprenaline	10·6	105	62	9	5·0
	% Change	+20	+19	+11	−1	−14
J.A.R.	Control	6·1	68	70	11	9·7
	Isoprenaline	7·0	70	61	13	6·8
	% Change	+15	+3	−13	+2	−30
A.R.	Control	6·7	71	37	10	4·0
	Isoprenaline	8·2	68	32	6	3·2
	% Change	+22	−4	−14	−4	−20
W.J.	Control	8·8	70	31	0	3·5
	Isoprenaline	9·7	72	29	0	3·0
	% Change	+10	+3	−6	0	−14
C.D.C.	Control	8·8	85	58	1	6·5
	Isoprenaline	10·0	83	49	1	4·8
	% Change	+14	−2	−15	0	−26
S.M.	Control	5·3	53	54	2	10·0
	Isoprenaline	5·4	61	50	4	9·0
	% Change	+2	+15	−7	+2	−10
P.B.	Control	5·4	60	64	7	10·6
	Isoprenaline	7·9	65	58	7	6·4
	% Change	+46	+8	−9	0	−39

* Change expressed as absolute change in mm. Hg.

temic vascular resistance, with no change in central venous pressure.

Norepinephrine caused a greater increase in cardiac output than methoxamine in the 6 patients to whom both drugs were given, but in only 2 of these patients did norepinephrine produce a greater increase in systemic vascular resistance.

Three patients were again given norepinephrine infusions after their central venous pressures had increased in response to low molecular weight dextran infusion. These patients had increases in cardiac output (19%, 319%, and 330%) when compared to the measurement made just after giving low molecular weight dextran.

Isoprenaline (Table V) was given to 8 patients; 6 had previously received norepinephrine. Cardiac output increased in all except one patient. Mean arterial pressures increased in 2 and decreased in 4 patients. Systemic vascular resistance values decreased in 7 and increased in 1 patient.

The mean increase in cardiac output was not significantly greater than with norepinephrine, and more important, mean aortic pressure was maintained at adequate levels (above 70 mm. Hg) by isoprenaline in only 1 patient, and he had the greatest increase in cardiac output.

Low molecular weight dextran (Table VI) was given to 15 patients; 9 had received norepinephrine and had stabilized their blood pressures above shock levels. In comparison with new control values obtained during the "steady state" existing before dextran infusion, cardiac output decreased in 3, was unchanged in 1, and increased in 11 patients. Mean arterial pressures declined in 6 patients, remained unchanged in 2 and increased in 7. Central venous pressures increased in all patients, and systemic vascular resistance values decreased in 13.

Digitalis (Table VII) preparations were given to 11 patients, lanatoside C to 9, and strophanthin to 2. Of these 11 patients, 6 had received low molecular weight dextran and had had significant increases in central venous pressures and cardiac outputs before digitalization. Cardiac outputs were increased in 8 patients and remained unchanged in 2. A fall in cardiac output occurred in 1 patient with a low central venous pressure, and this may reflect inadequate prior volume expansion. Aortic mean pressures increased in 7 patients. Central venous pressure declined in 5 patients and did not change appreciably in 5. The systemic vascular resistance values increased in 4 and decreased in 5 patients.

Chlorpromazine (Table VIII) was given to 7

TABLE VI

HÆMODYNAMIC EFFECTS OF LOW MOLECULAR WEIGHT DEXTRAN (LMWD) IN SHOCK ASSOCIATED WITH INFECTION

Patient		Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure* (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
L.S.	Control	1·3	11	59	0	45·0
	LMWD	2·6	18	81	9	28·0
	% Change	+100	+64	+37	+9	−38
J.L.	Control	7·7	96	74	5	8·7
	LMWD	9·5	99	83	8	7·6
	% Change	+22	+3	+12	+3	−13
C.M.	Control	9·9	97	60	3	5·8
	LMWD	8·2	82	60	9	6·2
	% Change	−17	−15	0	+6	+7
J.A.R.	Control	5·0	62	70	5	13·0
	LMWD	6·1	68	70	11	9·7
	% Change	+22	+10	0	+6	−25
A.R.	Control	7·3	70	39	3	4·9
	LMWD	6·7	71	37	10	4·0
	% Change	−8	+1	−5	+7	−18
D.S.	Control	5·4	63	70	4	12·2
	LMWD	4·7	57	84	17	14·2
	% Change	−13	−10	+20	+13	+16
J.D.R.	Control	12·7	130	67	6	4·7
	LMWD	16·8	172	83	9	4·4
	% Change	+32	+32	+24	+3	−6
R.C.H.	Control	8·7	109	75	0	8·6
	LMWD	10·5	125	77	10	6·4
	% Change	+21	+15	+3	+10	−26
C.D.C.	Control	10·2	96	76	3	7·2
	LMWD	10·4	100	73	8	6·3
	% Change	+2	+4	−4	+5	−12
W.M.	Control	4·7	39	64	2·0	13·2
	LMWD	8·0	63	70	9·4	7·5
	% Change	+70	+61	+9	+7·4	−43
C.B.	Control	6·6	50	98	6·0	13·9
	LMWD	7·8	60	80	12·5	8·6
	% Change	+18	+20	−18	+6·5	−38
P.B.	Control	2·2	20	94	4·1	40·8
	LMWD	4·4	49	86	6·0	18·2
	% Change	+100	+145	−8	+1·9	−55
W.B.	Control	6·2	89	66	5·2	9·8
	LMWD	7·3	101	72	15·0	7·8
	% Change	+18	+13	+9	+9·8	−20
R.U.H.	Control	2·0	18	60	3·5	28·2
	LMWD	6·7	56	58	6·2	7·7
	% Change	+235	+211	−3	+2·7	−73
J.S.R.	Control	7·3	53	56	1·5	7·4
	LMWD	8·6	72	50	10·3	4·6
	% Change	+18	+36	−11	+8·8	−38

* Change expressed as absolute change in mm. Hg.

patients; all had received low molecular weight dextran. The mean arterial pressures decreased, and systemic vascular resistance values decreased in all except one. One patient had a significant increase in central venous pressure without increase in cardiac output, suggesting poor cardiac function. This patient, after further volume expansion with low molecular weight dextran, showed an excellent response in cardiac output (+70%) and drop in central venous pressure when strophanthin was given.

Hydrocortisone (Table IX) was given to 9 patients. Systemic resistance increased in 5, decreased in 3, and did not change in 1. Mean aortic pressure was increased in 3 patients, decreased in 4, and was unchanged in 2. All the changes noted were of small magnitude.

Responses of Survivors Compared with Those Who Died. In order to determine factors that may be involved in survival of patients in shock associated

TABLE VII

HÆMODYNAMIC EFFECTS OF LANATOSIDE C IN SHOCK ASSOCIATED WITH INFECTION

Patient		Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure* (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
M.K.	Control	6·8	65	49	9·0	5·9
	Lanatoside C	9·4	90	76	7·0	7·3
	% Change	+38	+38	+55	−2	+24
L.S.	Control	2·6	18	81	9·0	28·0
	Lanatoside C	3·9	38	103	8·5	25·0
	% Change	+50	+110	+27	−0·5	−11
C.M.	Control	8·4	79	88	10·0	9·3
	Lanatoside C	9·2	90	93	9·0	9·1
	% Change	+10	+14	+6	−1	−2
J.A.R.	Control	6·1	68	70	11·0	9·7
	Lanatoside C	9·1	91	77	8·5	7·5
	% Change	+49	+34	+10	−2·5	−23
D.S.	Control	5·0	63	75	12·0	12·6
	Lanatoside C	5·1	71	85	12·0	14·3
	% Change	+2	+13	+13	0	+13
R.C.H.	Control	10·1	120	84	0	8·3
	Lanatoside C	8·7	109	75	0	8·6
	% Change	−14	−9	−11	0	+4
W.M.†	Control	6·9	56	70	11·0	8·5
	Strophanthin	8·0	63	70	9·4	7·6
	% Change	+16	+12	0	−1·6	−10
C.B.†	Control	9·2	71	62	11·0	5·5
	Strophanthin	9·5	73	78	12·5	6·9
	% Change	+3	+3	+26	+1·5	+25
W.B.	Control	5·0	63	70	9·6	12·1
	Lanatoside C	6·3	90	100	6·0	14·9
	% Change	+26	+43	+43	−3·6	+23
R.U.H.	Control	5·0	50	100	7·9	18·4
	Lanatoside C	5·5	50	100	7·9	16·7
	% Change	+10	0	0	0	−9
J.S.R.	Control	8·0	64	64	6·7	7·2
	Lanatoside C	9·1	70	60	6·6	5·9
	% Change	+14	+9	−6	−0·1	−18

* Change expressed as absolute change in mm. Hg.
† Patients given strophanthin.

with infection, the patients were divided into two groups: Group 1, "survivors", 8 patients who recovered from shock, could be maintained without vasopressors and lived more than 24 hours; and Group 2, "non-survivors", 13 patients who died without recovering from shock, or died within the first 24 hours after onset of the studies. The mean ages of the two groups did not differ significantly, being 59 years for the survivors, and 64 years for the non-survivors. However, there was only 1 patient over 70 years in the former group, while 4 patients over 70 were in the latter group.

Gram-negative bacteria were recovered from the blood in 3 of the survivors and 4 of the non-survivors. The mean temperature in the surviving group was 102·2°C., with none under 97°C. Among the non-survivors, the mean temperature was 100°C., and 3 patients had temperatures under 97°C. The difference in mean temperature between the two groups, however, was not significant.

There were no significant differences between the means of the cardiac outputs, arterial mean pressures, central venous pressures, or systemic vascular resistances in these two groups during the initial control period. The response of the cardiac output to low molecular weight dextran in these two groups is not significantly different ($p > 0{\cdot}10$ and $< 0{\cdot}20$), though a difference may become apparent in a larger group. The survivors had a mean increase in cardiac output of 2·1 l./min., and each of the seven increased his cardiac output with this form of plasma volume expansion. The cardiac output of non-survivors had a mean increase of 0·8 l./min., and 3 of the 8 given low molecular weight dextran responded with a decrease in cardiac output.

Of the 8 patients given isoprenaline, 3 survived and showed a mean increase in arterial mean pressure of 17 per cent over the control level and a mean increase in cardiac output of 2·9 l./min. with no change in central venous pressure. Of the patients given isoprenaline, 5 did not survive and had a mean increase in arterial mean pressure of

TABLE VIII

HÆMODYNAMIC EFFECTS OF CHLORPROMAZINE IN SHOCK ASSOCIATED WITH INFECTION

Patient		Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure* (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
J.L.	Control	8·7	95	83	5·0	8·7
	Chlorpromazine	7·7	96	74	5·0	8·7
	% Change	−11	+1	−11	0	0
A.R.	Control	9·0	75	70	10·0	6·7
	Chlorpromazine	11·8	91	49	6·0	3·6
	% Change	+31	+21	−30	−4	−46
D.S.	Control	4·7	57	84	17·0	14·2
	Chlorpromazine	6·2	76	77	12·0	10·5
	% Change	+32	+35	−8	−5	−26
J.D.R.	Control	16·8	172	83	9·0	4·4
	Chlorpromazine	16·4	164	45	9·0	2·2
	% Change	−2	−5	−46	0	−50
W.M.	Control	6·4	51	62	5·5	8·8
	Chlorpromazine	6·2	52	54	8·0	7·4
	% Change	−3	+2	−13	+2·5	−16
C.B.	Control	7·8	60	80	12·5	8·6
	Chlorpromazine	8·6	65	64	11·0	6·1
	% Change	+10	+8	−20	−1·5	−29
W.B.	Control	7·3	101	72	15·0	7·8
	Chlorpromazine	11·3	120	62	9·0	4·7
	% Change	+55	+19	−14	−6	−40

* Change expressed as absolute change in mm. Hg.

TABLE IX

HÆMODYNAMIC EFFECTS OF HYDROCORTISONE IN SHOCK ASSOCIATED WITH INFECTION

Patient		Cardiac output (l./min.)	Stroke volume (ml.)	Mean aortic pressure (mm. Hg)	Central venous pressure* (mm. Hg)	Systemic vascular resistance (mm. Hg/l./min.)
L.S.	Control	1·4	10	59	0	42·0
	Hydrocortisone	1·3	11	59	0	45·0
	% Change	−7	+10	0	0	+7
J.A.R.	Control	8·3	92	60	3	6·9
	Hydrocortisone	6·9	69	60	3	8·0
	% Change	−17	+25	0	0	+16
J.D.R.	Control	9·8	100	57	5	5·3
	Hydrocortisone	12·7	130	67	6	4·7
	% Change	+30	+30	+17	+1	−11
R.C.H.	Control	11·7	122	94	9	7·3
	Hydrocortisone	3·9	98	62	10	13·3
	% Change	−67	−20	−34	+1	+82
C.B.	Control	9·5	75	64	11·5	5·5
	Hydrocortisone	10·4	84	74	11·3	6·0
	% Change	+9	+12	+16	−0·2	+9
P.B.	Control	5·3	59	60	7·3	9·9
	Hydrocortisone	5·4	60	64	7·0	10·5
	% Change	+2	+2	+7	−0·3	+6
W.B.	Control	6·1	82	82	5·2	12·5
	Hydrocortisone	6·2	89	66	5·2	9·8
	% Change	+2	+8	−19	0	−21
R.U.H.	Control	5·0	50	100	7·9	18·4
	Hydrocortisone	5·2	46	96	4·0	17·7
	% Change	+4	−8	−4	−3·9	−4
W.H.	Control	11·3	98	105	8·5	8·5
	Hydrocortisone	12·2	80	98	8·5	7·3
	% Change	+8	−18	−7	0	−14

* Change expressed as absolute change in mm. Hg.

6 per cent over control levels with a mean increase in cardiac output of 1·1 l./min. and 1 mm. Hg drop in central venous pressure. The difference in the means of the cardiac outputs was not statistically significant ($p > 0·10$ and $< 0·20$), but the small size of the groups makes demonstration of a difference difficult.

When given a digitalis preparation, the 5 patients who survived had a mean increase in cardiac output of 1·8 l./min., a mean increase of 20 per cent in the arterial mean pressure, and a mean decrease in the central venous pressure of 2 mm. Hg. In contrast, when given digitalis preparations, the non-survivors showed a mean increase in cardiac output of only 0·3 l./min., which is significantly lower than that of the survivors ($p < 0·02$), a mean increase in mean arterial pressure of 10 per cent, and no change in the central venous pressure.

The non-survivors, therefore, responded to volume loading with low molecular weight dextran by raising central venous pressure and little increase in cardiac output. This would be similar to the patients described by Brown and associates thought to be in cardiac failure after hæmorrhage, trauma, or sepsis and shock (Brown *et al.*, 1966), but unlike their patients, the patients in our series also responded poorly to isoprenaline. The patients who survived appeared to be the ones with the greatest response to volume loading, isoprenaline, and digitalis.

Hæmodynamic Derangement—Gram-negative vs. Gram-positive Infection. If we divide our patients into the 7 with Gram-negative infections and the 11 with infections due to Gram-positive organisms, there are significantly lower cardiac outputs and higher systemic vascular resistances in the group of patients with Gram-negative infections ($p < 0·10$). This may be due to the fact that Gram-negative bacterial endotoxin has some direct effect on the arterioles or potentiates the effect of norepinephrine on the arterioles (Gilbert, 1960). However, the patients with Gram-negative infections were significantly older than the patients with Gram-positive infections.

Effect of Cirrhosis on Control State. The mean of cardiac outputs of the patients with cirrhosis was not significantly higher than the rest of the group. However, the 3 patients who had control cardiac outputs above 9 l./min. had hepatic cirrhosis. Since patients with cirrhosis have increased basal cardiac outputs (Murray, Dawson, and Sherlock, 1958), it is probable that this difference will become recognizable in a larger series of patients and should be taken into account in evaluating other causes for differences in basal cardiac outputs (Udhoji and Weil, 1965).

Discussion

The cardiac output in patients with shock associated with infection may be normal (Gilbert *et al.*, 1955), low (Udhoji *et al.*, 1963), or high (Udhoji and Weil, 1965). This disturbing discrepancy has been explained by two mechanisms. (1) Gilbert *et al.* postulated that because febrile states are usually associated with increased cardiac outputs, one must consider patients who have normal recorded cardiac outputs while in shock associated with infection to have, in fact, inadequate cardiac outputs (Gilbert *et al.*, 1955). These workers attributed the inadequate circulatory response to a decrease in the right atrial pressure, secondary to a decreased venous tone, since blood volumes in these patients were within normal limits. (2) Udhoji and Weil first proposed that decreased cardiac outputs in patients with shock associated with infection were related to the ætiological agents (Udhoji *et al.*, 1963). However, in 1965 Udhoji and Weil suggested that patients with normal and high cardiac outputs had a high incidence of hepatic cirrhosis which is known to be associated with a high basal cardiac output (Udhoji and Weil, 1965; Murray *et al.*, 1958). They therefore concluded that all patients had a reduction in cardiac output with the onset of shock, and in most, this was associated with a low central venous pressure.

In evaluating the hæmodynamic response of adults to infection, a third factor must be considered. Underlying cardiovascular disease may exist and not have been evident before the imposed stress. The coronary blood flow has been shown to be fairly steady over a wide range of aortic pressures in experimental animals (Mosher *et al.*, 1964) and adjusts to the needs of the myocardium by an autoregulatory mechanism sensitive to anoxia or the products of anoxia (Berne, 1963). However, in patients with arteriosclerotic heart disease, coronary arteries behind areas of partial obstruction may be maximally dilated at normal aortic pressure (Gorlin *et al.*, 1959), making the blood flow to these areas pressure-dependent. Should this be the case in a patient in shock, the heart may be unable to respond to volume loading of the right atrium with an increase in cardiac output until adequate coronary blood flow is established by an increase of aortic pressure.

It cannot, therefore, be assumed that drug therapy designed to correct any one parameter of cardiovascular function will be adequate for the therapy of shock associated with infection. Drugs

that primarily increase blood pressure by increasing systemic vascular resistance may reflexly decrease flow, and drugs that increase cardiac output may be ineffective until central aortic pressure has been increased sufficiently to ensure adequate coronary perfusion pressure. In most instances, both increased pressure and increased flow cannot be accomplished until the intravascular volume has been increased sufficiently to increase right ventricular filling pressure (central venous pressure) to normal or slightly above normal levels.

Plasma volume expansion can be accomplished with either stored plasma or low molecular weight dextran. Low molecular weight dextran has a slight advantage in de-aggregation of erythrocyte aggregates, but with the return of renal function the drug is excreted rapidly (Metcalf, 1962). Both agents increase the blood volume because of their osmolar effect and the mobilization of erythrocytes which, by aggregation, have been removed from the effective circulating blood volume (Suzuki *et al.*, 1965). The decline in peripheral resistance noted with low molecular weight dextran is due not only to the effect of the drug on viscosity, but also to the reopening of vascular beds by removal of erythrocyte aggregates (Gelin, 1962).

Methoxamine, which has its primary action in increasing systemic vascular resistance (Goldberg *et al.*, 1953), is not indicated in the therapy of shock associated with infection, since it has no direct effect on the heart and usually reflexly reduces cardiac output. Any observed increase in cardiac output must be explained either by improved venous return or increased coronary filling. Because the two patients in this series who had an increase in cardiac output following methoxamine had increased central aortic pressure but not central venous pressure, it is assumed that cardiac function improved (Guyton, 1963) and that the improvement was due to better coronary blood flow.

Isoprenaline can be a very effective agent for increasing blood flow after plasma volume expansion has increased the central venous pressure. It has the disadvantage of causing vasodilatation and may decrease the central aortic pressure to dangerously low levels—levels inconsistent with adequate coronary perfusion. This disadvantage may become particularly evident in the patient with coronary artery disease.

Norepinephrine, when given in small amounts, is a very effective drug in increasing cardiac output after adequate volume expansion. It has fallen into disrepute partly because it has been used in too large amounts, before volume replacement, and for too long a time. It has been shown to be effective in the treatment of hæmorrhagic shock after retransfusion (Lansing and Stevenson, 1958) and more effective than isoprenaline in the treatment of shock due to myocardial infarction (Gunnar *et al.*, 1967). Norepinephrine has the advantage of raising aortic pressure, and if given in small amounts, this increase will be accompanied by little or no increase in systemic vascular resistance.

Digitalis is more difficult to evaluate because of the delay in the onset of the action of this drug. As a therapeutic agent in shock associated with infection, it appears to be of little value unless the central venous pressure has been increased by prior volume expansion. It may be of great value in patients with high central venous pressure and inadequate cardiac output. Variation in its effect on the peripheral vascular resistance can be accounted for by a balance between the direct effect of the drug on the arterioles causing vasoconstriction and the vasodilatation due to the decreasing sympathetic tone accompanying improvement of the patient (Braunwald, Mason, and Ross, 1965).

Hydrocortisone had no measurable hæmodynamic effect on our patients and appears to be a poor vasodilator, even in pharmacological doses.

Chlorpromazine used in small amounts intravenously is an effective vasodilator (*Lancet*, 1955) and is used most effectively when volume expansion causes a precipitous rise in venous pressure. It can also be used in patients remaining vasoconstricted after volume expansion and return of the blood pressure to adequate levels. The latter group of patients will need further volume expansion as they are vasodilated.

The rational therapy for a patient in shock associated with infection is, therefore, dependent on knowledge of the central venous pressure (Johnson, 1964) and some estimate of peripheral perfusion. Initially, therapy should include volume expansion until the filling pressure of the heart has been increased to normal levels. During the period of volume expansion, the mean arterial pressure should be maintained near 70 mm. Hg, with the use of norepinephrine. With restoration of normal central venous pressure, norepinephrine infusion should be slowed as volume expansion is continued. An estimate of cardiac output from urine flow, pulse volume, and warmth of the extremities, along with central venous and arterial pressure, determine further therapy. If the cardiac output is low despite adequate arterial and high venous pressures, isoprenaline and digitalis with further volume expansion are indicated. If arterial pressure falls, small amounts of norepinephrine should be substituted for isoprenaline. Chlorpromazine should be used in patients whose blood pressure has returned to normal and who appear vasoconstricted (small pulse,

cold cyanotic extremities, poor urine flow), realizing that the intravascular space thus created must be filled in simultaneously with a plasma volume expander. Chlorpromazine should be used immediately in patients who have a precipitous rise in central venous pressure during plasma volume expansion.

Summary

Twenty-one patients in shock associated with infection were studied at the bedside. Cardiac output, central venous pressure, and central aortic pressure were measured. Systemic vascular resistance was calculated. Measurements were made before and after infusions of methoxamine, norepinephrine, isoprenaline, low molecular weight dextran, chlorpromazine, digitalis, and hydrocortisone.

The importance of maintaining adequate central aortic pressure is emphasized and is illustrated by an improvement in cardiac function in two patients with coronary artery disease when methoxamine was used to increase central aortic pressure.

Norepinephrine, when used in small amounts after plasma volume expansion, is an effective drug for improving cardiac output.

Isoprenaline may increase cardiac output and blood pressure but frequently will not increase central aortic pressure above shock levels. In the elderly patient these low pressures are associated with clinical deterioration.

Low molecular weight dextran is an effective plasma volume expander and lowers systemic vascular resistance.

Digitalis is often effective in increasing cardiac output in patients who have high central venous pressures after plasma volume expansion.

Chlorpromazine is an active vasodilator and is useful when there is a precipitous rise in central venous pressure with plasma volume expansion. It is useful also in the patient who remains vasoconstricted after return of central venous and arterial pressures to normal levels.

Hydrocortisone is ineffective as a vasodilator in pharmacological doses.

The authors wish to express their appreciation to Dr. Harold M. Schoolman and Mr. Jack Becktel of the Veterans Administration Biostatistical Research Support Center, Hines, Illinois, for their help in the experimental design and statistical analysis.

We wish also to acknowledge the invaluable technical assistance of Mrs. Nancy Slodki, without whose help the studies at the bedside could not have been accomplished.

References

Berne, R. M. (1963). Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow. *Amer. J. Physiol.*, **204**, 317.

Braunwald, E., Mason, D. T., and Ross, J., Jr. (1965). Studies on the cardiocirculatory actions of digitalis. *Medicine (Baltimore)*, **44**, 233.

Brown, R. S., Carey, J. S., Mohr, P. A., Monson, D. S., and Shoemaker, W. C. (1966). Comparative evaluation of sympathomimetic amines in clinical shock. *Circulation*, **34**, 260.

Cohn, J. N., and Luria, M. H. (1964). Studies in clinical shock and hypotension: the value of bedside hemodynamic observations. *J. Amer. med. Ass.*, **190**, 891.

Gelin, L. E. (1962). Hemato-rheological properties of low molecular weight dextran and other dextrans. In *Conference on Evaluation of Low Molecular Weight Dextran in Shock*, p. 6. National Academy of Sciences, Washington, D.C.

Gilbert, R. P. (1960). Mechanisms of the hemodynamic effects of endotoxin. *Physiol. Rev.*, **40**, 245.

——, Honig, K. P., Griffin, J. A., Becker, R. J., and Adelson, B. H. (1955). Hemodynamics of shock due to infection. *Stanf. med. Bull.*, **13**, 239.

Goldberg, L. I., Cotten, M.deV., Darby, T. D., and Howell, E. V. (1953). Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines. *J. Pharmacol. exp. Ther.*, **108**, 177.

Gorlin, R., Brachfeld, N., MacLeod, C., and Bopp, P. (1959). Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. *Circulation*, **19**, 705.

Gunnar, R. M., Pietras, R. J., Stavrakos, C., Loeb, H. S., and Tobin, J. R., Jr. (1967). The physiologic basis for treatment of shock associated with myocardial infarction. *Med. Clin. N. Amer.*, **51**, 69.

Guyton, A. C. (1963). *Circulatory Physiology: Cardiac Output and its Regulation.* Saunders, Philadelphia.

Johnson, H. D. (1964). Venous pressure, its physiology and pathology in hæmorrhage, shock, and transfusion. *Brit. J. Surg.*, **51**, 276.

Kinsman, J. M., Moore, J. W., and Hamilton, W. F. (1929). Studies on the circulation. I. Injection method: Physical and mathematical considerations. II. Cardiac output determination; comparison of the injection method with the direct Fick procedure. *Amer. J. Physiol.*, **89**, 322.

Lancet (1955). Editorial. Pharmacology of chlorpromazine. **1**, 337.

Lansing, A. M., and Stevenson, J. A. F. (1958). Mechanism of action of norepinephrine in hemorrhagic shock. *Amer. J. Physiol.*, **193**, 289.

Metcalf, W. (1962). Physiological characterization and clinical evaluation of the new dextran. In *Conference on Artificial Colloidal Agents, September* 1962, p. 105. National Academy of Sciences, Washington, D.C.

Mosher, P., Ross, J., Jr., McFate, P. A., and Shaw, R. F. (1964). Control of coronary blood flow by an autoregulatory mechanism. *Circulat. Res.*, **14**, 250.

Murray, J. F., Dawson, A. M., and Sherlock, S. (1958). Circulatory changes in chronic liver disease. *Amer. J. Med.*, **24**, 358.

Suzuki, F., Shoemaker, W. C., Baker, R. J., and Carey, J. S. (1965). Use of labeled red cells and low viscosity dextran in the study of trapped blood. *Surg. Gynec. Obstet.*, **121**, 51.

Udhoji, V. N., and Weil, M. H. (1965). Hemodynamic and metabolic studies on shock associated with bacteremia. Observations on 16 patients. *Ann. intern. Med.*, **62**, 966.

——, ——, Sambhi, M. P., and Rosoff, L. (1963). Hemodynamic studies on clinical shock associated with infection. *Amer. J. Med.*, **4**, 461.

Wilson, R. F., Jablonski, D. V., and Thal, A. P. (1964). The usage of dibenzyline in clinical shock. *Surgery*, **56**, 172.