THE SIGNIFICANCE OF AIR EMBOLISM DURING CARDIOPULMONARY BYPASS

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THE harmful effects of coronary air embolism, causing coronary artery occlusion with resulting myocardial ischemia, cardiac arrest, or ventricular fibrillation, are well known.[5] During cardiopulmonary bypass, however, air emboli are thought to be better tolerated because constant coronary perfusion from the pump oxygenator propels air through the coronary vessels. Concern has arisen, however, as to whether small, undetected amounts of air might be responsible for unexplained myocardial injury following cardiopulmonary bypass. Recently, Goldfarb and Bahnson[6] found that amounts of air as small as 0.05 ml. in the left coronary artery could cause definite myocardial injury. Such an injury might either cause a low cardiac output for several hours following bypass or even result in permanent impairment of myocardial function from multiple focal areas of myocardial infarction. These possibilities were extensively investigated in the 45 experiments described in this report.

METHODS

Preliminary observations were made in six experiments with perfusion of an isolated beating heart. In these studies the heart was removed from a donor dog and aortic perfusion was quickly established with a circuit that included a pump and a small disc oxygenator. In such a preparation, myocardial contractions continued with vigor for 1 to 2 hours. In six experiments the acute effects of coronary air emboli on coronary vascular resistance and oxygen consumption were studied. With each study, injected air quickly passed through the coronary circulation, causing no permanent change in coronary vascular resistance or myocardial oxygen consumption. Subsequent studies were then performed in intact animals while supported with cardiopulmonary bypass.

Thirty-nine mongrel dogs (weighing 12 to 30 kilograms) were anesthetized with pentobarbital or ether and mechanically ventilated with a respirator. Before operation was begun, a blood volume determination and an electrocardio-

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gram were obtained. Donor blood used to prime the oxygenator was examined for microfilaria. With a left anterolateral thoracotomy, the heart was exposed and the right atrial appendage was cannulated for venous return to a disc pump oxygenator; oxygenated blood was returned through a femoral artery.

Once cardiopulmonary bypass had been instituted, with a flow rate of 70 to 100 ml. per kilogram per minute, the apex of the left ventricle was exposed. A foamy mixture of air and blood (Group I—20 dogs), carbon dioxide and blood (Group II—13 dogs), or saline solution (Group III—6 dogs) was then injected into the left ventricle, the amount varying from 0.5 to 1.0 ml. per kilogram. (The air volume was measured before mixing with blood to produce foam.) Immediately prior to the left ventricular injection, the ascending aorta was cross-clamped in order to force the injected material into the coronary arteries. The clamp was left in place for only 1 to 2 minutes. Ten minutes after the first injection, another similar injection was made; 20 minutes later bypass was stopped, if effective cardiac contractions had returned.

If air was still visible in the coronary vessels 20 minutes after injection, several methods to displace it were evaluated. These included elevation of the blood pressure with injections of epinephrine, manual massage of the heart, epicardial incisions over the vessels occluded by air, and decompression of the left ventricle through a catheter previously inserted through the left atrium. Experiments were terminated if repeated use of these methods could not restore effective cardiac action.

After cardiopulmonary bypass was stopped and the heparin had been neutralized with protamine (heparin 3 mg./Kg., protamine 4 to 4.5 mg./Kg.), small polyvinyl catheters were inserted into the left atrium and pulmonary artery before the thoracic incision was closed. Intracardiac pressures and oxygen saturations were subsequently measured through these catheters for 3 to 4 hours after operation. Seven days after operation, surviving animals were sacrificed for histologic examination of the myocardium. An electrocardiogram was obtained after operation, the following day, and prior to sacrifice of the animal.

With most operations, blood volume, plasma hemoglobin, and serum electrolyte (sodium, potassium, calcium), lactate, and pyruvate concentrations were measured before and after bypass. No significant variations were found in these data in the three groups of experiments performed.

In a few experiments the effect of myocardial contraction on air emboli was evaluated by inducing fibrillation before the gas was injected. After injection into the ventricle, manual cardiac massage was briefly used to force the air into the coronary vessels before the occluding aortic clamp was removed. As the results were similar to those in which air was injected into the beating heart, a procedure which itself often resulted in ventricular fibrillation, the majority of experiments were later performed by direct injection without prior induction of ventricular fibrillation.

RESULTS

A. *Cardiac Function Immediately Following Injection of Emboli.*—*Group I experiments:* Immediately following injection of air into the left

ventricle, many gaseous emboli were visible throughout the coronary vessels. These rapidly progressed to the smaller tributaries, where they remained for variable lengths of time. Soon thereafter bubbles appeared in the small coronary veins from which they collected into larger venous tributaries and disappeared. Great variation was seen among different animals; in some, all visible bubbles were gone within 5 minutes after injection, whereas in a few animals some bubbles could never be removed. All variations between these two extremes were seen. Usually the bubbles lingered longest in the distal branches of the left anterior descending coronary artery. This may have been a manifestation of the effect of buoyancy on air bubbles, for, in the left anterolateral position used in these studies, this part of the heart was uppermost.

As soon as the air bubbles lodged in the coronary tributaries, the adjacent myocardium became cyanotic; feeble, ineffective cardiac contractions quickly ensued and were often followed by ventricular fibrillation. Signs of severe ischemia appeared in the electrocardiogram, with a wide QRS complex, depressed or elevated S-T segments, and inverted T waves. As the air bubbles disappeared, the patchy areas of cyanotic myocardium developed a bright pink color, apparently from reactive hyperemia, as blood flow was restored. With the disappearance of the areas of cyanosis, effective cardiac contractions gradually resumed.

It was repeatedly noted, however, that disappearance of visible air did not always indicate restoration of normal myocardial capillary blood flow. The areas of cyanosis remained much longer than did the visible air bubbles. This was probably due to occlusion of capillaries by air emboli too small to be seen by the naked eye. In some experiments with repeated air emboli, areas of cyanosis persisted and were associated with progressive cardiac failure.

Rarely, visible air emboli remained or reappeared despite a variety of efforts to remove them (Nos. 1, 2, 3, Table II). In such experiments the heart gradually failed and developed a deep cyanotic color as effective contractions disappeared. In 7 of the 20 experiments in which air was injected, effective cardiac action was never restored (Tables I and II).

Histologic examination of the myocardium in 5 of the 7 animals showed areas of focal interstitial hemorrhage (Fig. 1) and occasional myocardial necrosis.

Group II experiments: Injection of carbon dioxide into the left ventricle produced immediate emboli of gas throughout the coronary vessels, but, in all 13 experiments, visible emboli disappeared within 2 to 3 minutes after caus-

TABLE I. MORTALITY FOLLOWING CORONARY EMBOLIZATION FROM INJECTION OF EMBOLI INTO LEFT VENTRICLE IN 39 EXPERIMENTS

MATERIAL INJECTED	NO. OF EXPERIMENTS	ACUTE DEATH (NO.)	DEATH WITHIN 24 HOURS (NO.)	SURVIVAL (7 DAYS) (NO.)
Air	20	7	7	6
Carbon dioxide	13	0	5	8
Saline	6	0	0	6

TABLE II. ACUTE DEATH FOLLOWING LEFT VENTRICULAR

EXP. NO. WEIGHT (KG.)	AMOUNT OF AIR INJECTED (ML./KG.)	PERFUSION RATE (ML./MIN.); DURATION (MIN.)	SYSTOLIC BLOOD PRESSURES (MM. Hg)				BLOOD O_2 SATURATION (PER CENT)	
			ARTERIAL	VENOUS	LEFT ATRIAL	PULM. ARTERIAL	PULM. ARTERY	LEFT ATRIUM
1; 17 Kg.	0.5 ml.(×5)	1,100; 65 min.	Died after bypass				52	–
2; 16 Kg.	0.66 ml.	13-1,800; 68 min.	Died after bypass				–	–
3; 17 Kg.	0.5 ml. (×3)	1,600; 34 min.	Died after bypass				–	–
4; 17 Kg.	1 ml. (×2)	—; 45 min.	150	14	12-16	20-28	32	93
5; 12 Kg.	1 ml.	1,200; 30 min.	100	12	25	40	35	78
6; 12 Kg.	1 ml.	800-1,000; 50 min.	120	15	–	–	48	82
7; 14.5 Kg.	0.5 ml.	10-1,600; 116 min. (90 + 26)	45	8	6	35	42	88

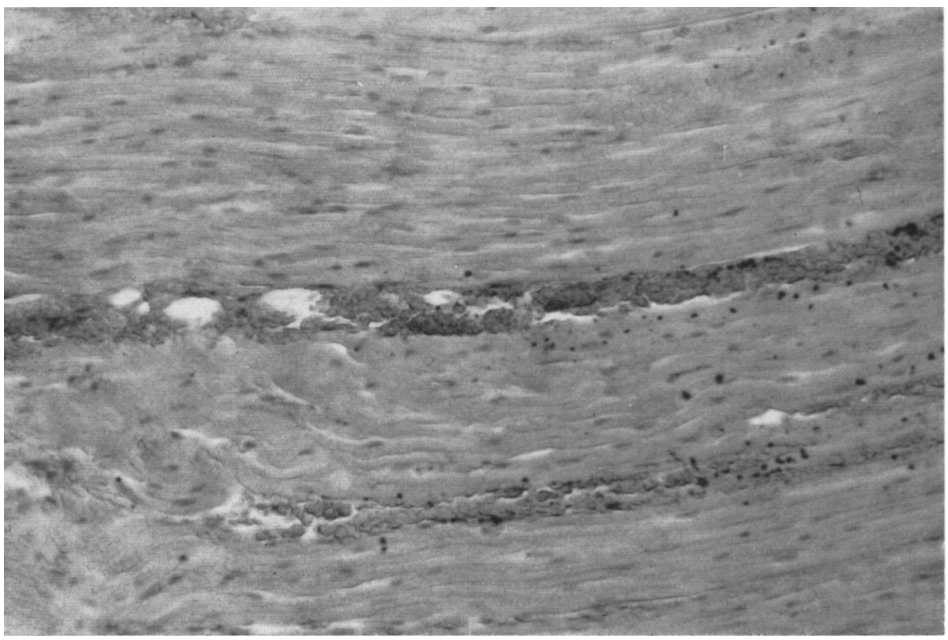

Fig. 1.—Histologic section of myocardium from dog that died shortly after air embolism. Interstitial hemorrhage between the myocardial bundles is the only abnormality visible. (Hematoxylin & eosin, ×125; reduced ¼.)

INJECTION OF AIR (DATA SOON AFTER BYPASS)

BLOOD pH		MYOCARDIAL HISTOLOGIC FINDINGS (0-4+)			
ARTERIAL	VENOUS	HEMORRHAGE	MUSCLE NECROSIS	TISSUE REPAIR	REMARKS
7.34	7.28				Died after bypass; persistent cyanosis after 5th injection
–	–				Coronary bubbles could not be removed despite use of adrenaline, massage, and prolonged bypass; died immediately after bypass
–	–	2+	2+	0	Coronary bubbles could not be removed
7.50	7.45	2+	0	0	Persistent cyanosis of ventricle
7.36	7.24	1+	1+	0	Repeated ventricular fibrillation after bypass
7.31	7.28	3+	3+	0	Death 7 min. after bypass
7.31	7.03	0	0	0	Acute cardiac failure 1 hr. post-perfusion

ing transient myocardial cyanosis. Increased myocardial irritability was the only sign of impairment of cardiac function for, despite frequent extrasystoles, the myocardial contractions remained vigorous and forceful. Changes in the electrocardiogram were similarly transient, no abnormalities being visible within a short time after injury. All animals recovered after perfusion was stopped.

Group III experiments: In the 6 control experiments, injection of saline into the left ventricle produced no changes in cardiac function. All animals recovered and were sacrificed 7 days later (Table I).

B. *Cardiac Function Following Bypass* (2-24 Hours).—

Group I experiments: Seven of the 13 dogs surviving the immediate effects of air emboli died within 2 to 24 hours. In Tables III and IV these 7 are compared with the 6 which recovered. Three differences, all of them slight, can be seen between the two groups. The dogs which died had slightly larger amounts of air injected, greater elevation of left atrial pressure following perfusion (12 to 20 mm. Hg in 5 experiments), and more depression of cardiac output (pulmonary artery oxygen saturation 35 to 46 per cent in 5 experiments). Arterial pressure, venous pressure, and arterial blood oxygen saturation and pH were normal in both groups; also no significant differences were found in the electrocardiograms. At autopsy, examination of the heart revealed scattered areas of epicardial and subendocardial hemorrhage; a finding often seen with a recent myocardial infarction (Fig. 2). In addition, focal areas of myocardial necrosis were present in some sections (Table III).

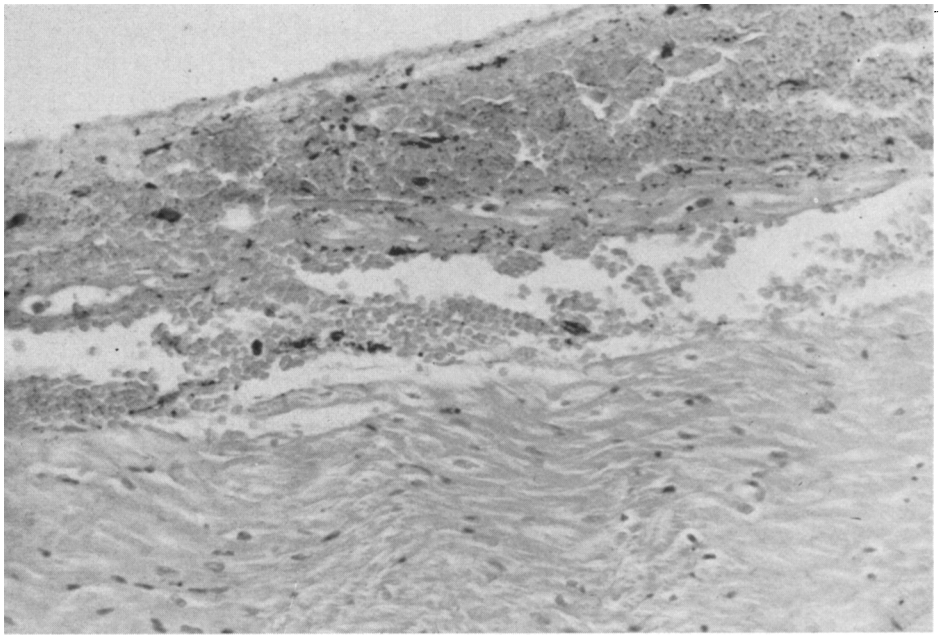

Fig. 2.—Histologic section of myocardium from dog that died several hours after air embolism. Extensive subendocardial hemorrhage is present. This is commonly seen in acute myocardial infarction. (hematoxylin & eosin, ×125; reduced ¼.)

TABLE III. DEATH WITHIN 24 HOURS AFTER LEFT VENTRICULAR

EXP. NO. WEIGHT (KG.)	AMOUNT OF AIR INJECTED (ML./KG.)	PERFUSION RATE (ML./MIN.); DURATION (MIN.)	SYSTOLIC BLOOD PRESSURES (MM. Hg)				BLOOD O_2 SATURATION (PER CENT)	
			ARTERIAL	VENOUS	LEFT ATRIAL	PULM. ARTERIAL	PULM. ARTERY	LEFT ATRIUM
8; 17 Kg.	1 ml. (×4)	1,200-1,400; 56 min.	115	0	17	25	62	90
9; 18 Kg.	1 ml. (×2) 3.5 ml. 2 ml.	1,200-1,800; 75 min.	125	6	12	25	38	92
10; 13 Kg.	1 ml. (×3)	1,200-1,400; 44 min.	175	10	15	35	35	93
11; 17 Kg.	0.5 ml. (×3) 1 ml.	1,200-1,800; 52 min.	100	12	5	15	39	89
12; 16 Kg.	0.5 ml. (×2)	1,300-1,400; 41 min.	150	–	8	20	46	92
13; 14 Kg.	0.5 ml.	1,000-2,000; 52 min.	90	7	20	35	–	98
14; 14 Kg.	0.5 ml.	1,500; 37 min.	35-50	–	18	27	45	95

Group II and III experiments: All animals survived perfusion following injection of carbon dioxide in 13 experiments, but 5 died within 24 hours. Significant data on these 5 are listed in Table V, while that on the survivors are shown in Table VI. Measurement of cardiac function included arterial, venous, pulmonary arterial, and left atrial blood pressures, oxygen saturation of blood in the pulmonary artery and left atrium, and pH of arterial and venous blood. None of the data indicated the cause of death, for the majority were within normal limits. Death may have resulted from an arrhythmia in some dogs, for signs of myocardial irritability were frequently seen. The onset of ventricular fibrillation was observed in 1 dog struggling while awakening from anesthesia. Histologic examination of the myocardium in the fatal experiments (Table V) disclosed areas of focal interstitial hemorrhage and myocardial necrosis in 2 of 5 animals examined.

In the control experiments (Group III) with injection of saline, an uneventful recovery followed perfusion.

C. *Late Cardiac Function After Emboli (2-7 Days).*—

In all experiments (Groups I, II, III), animals that were alive 24 hours after perfusion survived until sacrificed 6 days later. No differences among the 3 groups were found; all had normal electrocardiograms. Seven days after perfusion, the electrocardiograms were similarly normal with a single exception of one carbon dioxide experiment in which widening of the QRS complex was present.

Despite the normal electrocardiogram, histologic examination of the myocardium showed multiple areas of focal necrosis and repair in *all* six of the air

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INJECTION OF AIR (DATA 1-2 HOURS AFTER OPERATION)

BLOOD pH		MYOCARDIAL HISTOLOGIC FINDINGS (0-4+)			
ARTERIAL	VENOUS	HEMORRHAGE	MUSCLE NECROSIS	TISSUE REPAIR	REMARKS
7.32	7.21	–	–	–	Died 3 hr. post.op. in heart failure; bubbles seen in coronary veins
7.46	7.39	–	–	–	Died during night; air in coronary vessels at autopsy
7.42	7.34	–	–	–	Died 6 hr. after operation; residual coronary air found
7.32	7.25	1+	0	0	Died during night
7.40	7.33	2+	2+	0	Died 8 hr. postop.
7.38	7.30	0	1+	0	Died suddenly 3 hr. postop. in ventricular fibrillation
7.34	7.28	2+	1+	0	Died in 2 hr.; sudden cardiac arrest

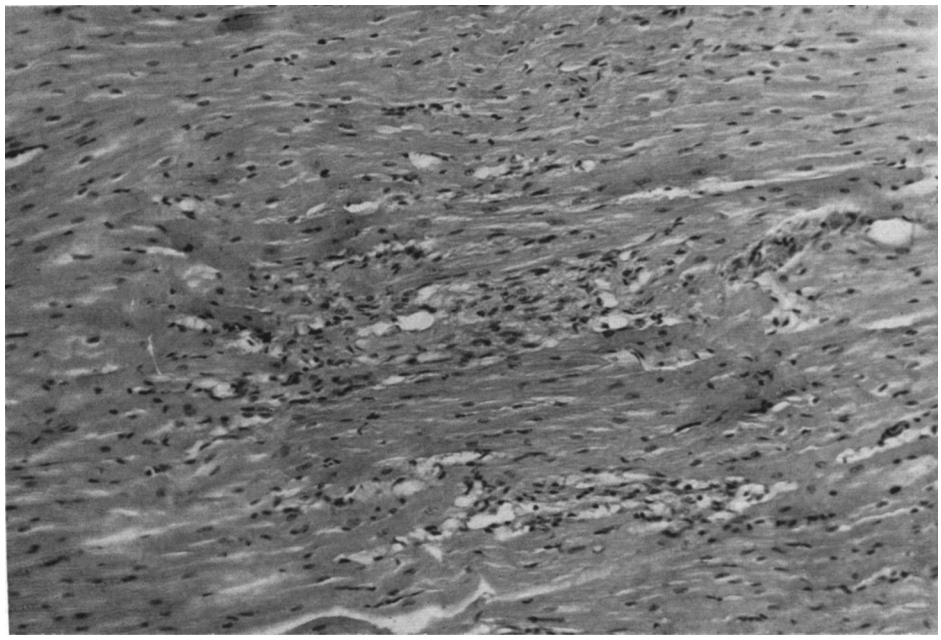

Fig. 3.—Histologic section of myocardium of dog who had received two injections of 0.5 ml./Kg. of air 7 days earlier. There are focal areas of replacement of myocardium with fibroblasts, presumably a result of earlier necrosis. (Hematoxylin & eosin, ×125; reduced ¼.)

TABLE IV. SURVIVAL FOLLOWING LEFT VENTRICULAR

EXP. NO.; WEIGHT (KG.)	AMOUNT OF AIR INJECTED (ML./KG.)	PERFUSION RATE (ML./MIN.); DURATION (MIN.)	SYSTOLIC BLOOD PRESSURES (MM. Hg)				BLOOD O_2 SATURATION (PER CENT)	
			ARTERIAL	VENOUS	LEFT ATRIAL	PULM. ARTERIAL	PULM. ARTERY	LEFT ATRIUM
15; 30 Kg.	0.5 ml. (×2)	2,200; 52 min.	130	0	13	19	48	92
16; 30 Kg.	0.5 ml. (×2)	– 55 min.	150	14	2	15	38	86
17; 12 Kg.	0.5 ml.	1,200-1,900; 40 min.	100	-1	15	20	32	94
18; 12.4 Kg.	0.5 ml. (×2)	1,200; 30 min.	80	-3	-3	18	53	97
19; 13.5 Kg.	0.5 ml.	1,200-1,400; 26 min.	100	10	9	15	65	98
20; 15 Kg.	0.5 ml. (×2)	1,200; 26 min.	85	11	11	21	53	94

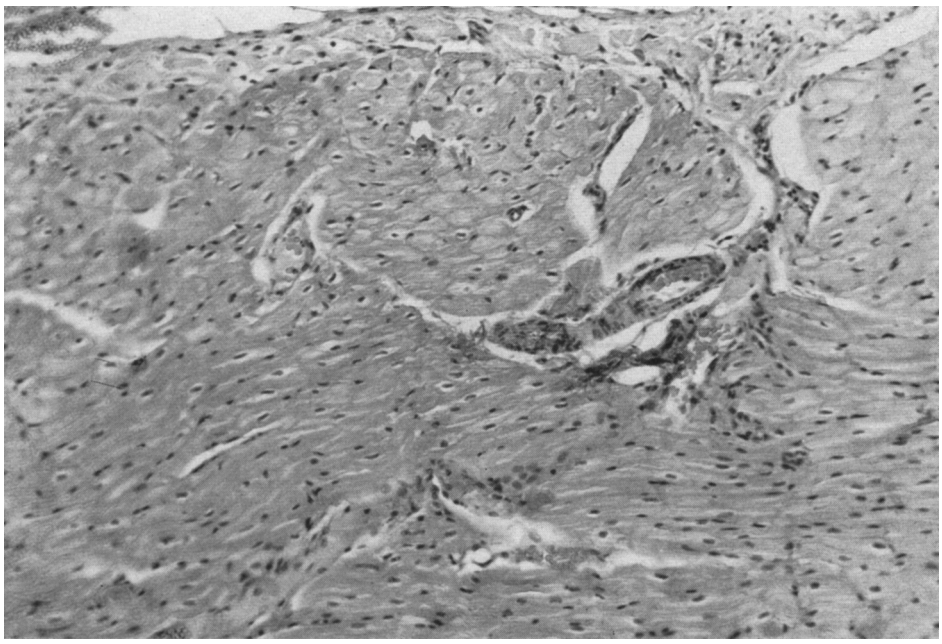

Fig. 4.—Histologic section of myocardium, from same experiment as Fig. 3, shows focal congestion of capillaries and perivascular edema following myocardial injury. (Hematoxylin & eosin, ×125; reduced ¼.)

INJECTION OF AIR (DATA 1-2 HOURS AFTER OPERATION)

BLOOD pH		MYOCARDIAL HISTOLOGIC FINDINGS (0-4+)			
ARTERIAL	VENOUS	HEMORRHAGE	MUSCLE NECROSIS	TISSUE REPAIR	REMARKS
7.36	7.36	0	0	1+	Sacrificed 7th day
7.48	7.35	2+	3+	2+	Sacrificed 7th day
7.48	7.25	0	0	2+	Sacrificed 10th day
7.55	7.38	0	0	2+	Sacrificed 7th day
7.52	7.40	0	1+	2+	Sacrificed 7th day
7.55	7.40	0	0	2+	Sacrificed 7th day

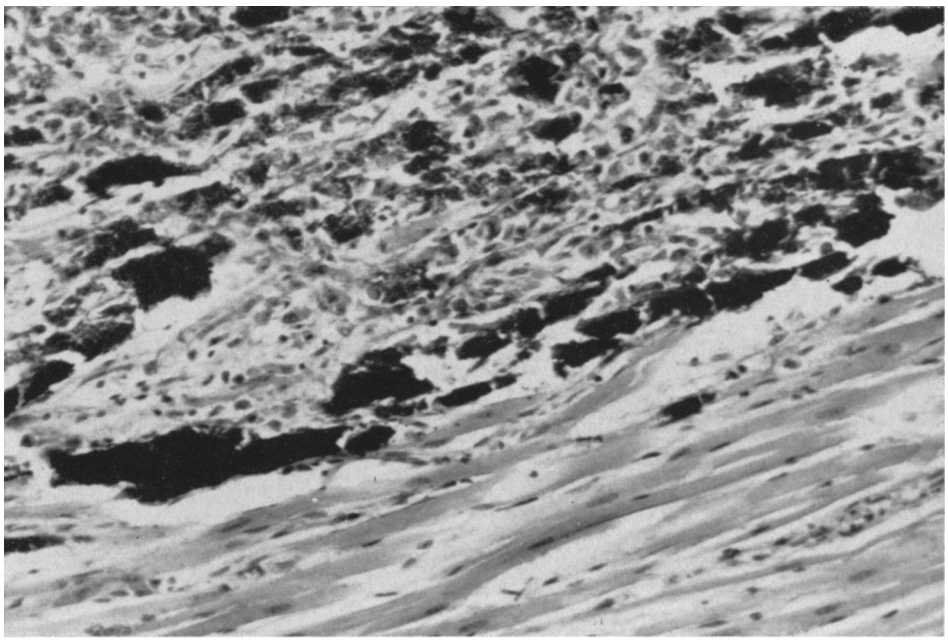

Fig. 5.—Histologic section of myocardium shows extensive injury from air embolism 7 days before. Extensive areas of necrosis and granular calcification of degenerated myocardium are present. Myocytes resulting from the myocardial injury and proliferating fibroblasts are also visible. (Hematoxylin & eosin, ×125; reduced ¼.)

TABLE V. DEATH WITHIN 24 HOURS AFTER LEFT VENTRICULAR

EXP. NO. WEIGHT (KG.)	AMOUNT OF CO_2 INJECTED (ML./KG.)	PERFUSION RATE (ML./MIN.); DURATION (MIN.)	SYSTOLIC BLOOD PRESSURES (MM. Hg)				BLOOD O_2 SATURATION (PER CENT)	
			ARTERIAL	VENOUS	LEFT ATRIAL	PULM. ARTERIAL	PULM. ARTERY	LEFT ATRIUM
21; 19 Kg.	0.5 ml. (×6)	1,600; 60 min.	80	14	10	25	30	–
22; 21 Kg.	0.5 ml. (×2) 1.5 ml.	1,200-2,400; 59 min.	80-110	9	3	17	52	93
23; 25 Kg.	0.4 ml. (×4)	2,000; 75 min.	120	12	10	20	50	85
24; 10 Kg.	1 ml.	900-1,000; 30 min.	135	10	5	25	56	93
25; 13.5 Kg.	0.5 ml. (×2)	1,400; 30 min.	125	3	1	12	47	91

Fig. 6.—Histologic section of myocardium, from an area of focal necrosis following embolization, shows a large collection of myocytes as well as capillary congestion.[8] (Hematoxylin & eosin, ×600; reduced ¼.)

INJECTION OF CARBON DIOXIDE (DATA 1-2 HOURS AFTER OPERATION)

BLOOD pH		MYOCARDIAL HISTOLOGIC FINDINGS (0-4+)			
ARTERIAL	VENOUS	HEMORRHAGE	MUSCLE NECROSIS	TISSUE REPAIR	REMARKS
7.40	7.28	0	0	0	Hypotension; died during night
7.44	7.35	0	0	0	Died next day; cause of death unclear
7.4	7.4	0	0	0	Died next day; gastric dilatation
7.46	7.36	2+	2+	0	Ventricular fibrillation in early postop. period while struggling
7.24	7.35	0	1+	0	

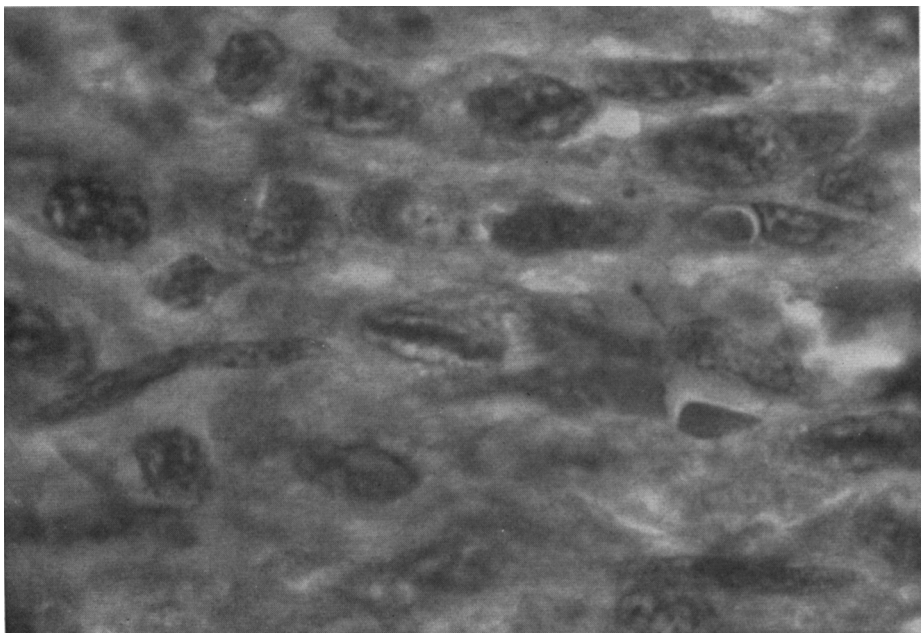

Fig. 7.—A high-power view of the same field shown in Fig. 6 shows nuclear detail of a myocyte. These cells are morphologically identical with Anitschkow myocytes, which develop following sublethal injuries to myocardial cells.[8] (Hematoxylin & eosin, ×1,500; reduced ¼.)

TABLE VI. SURVIVAL FOLLOWING LEFT VENTRICULAR

EXP. NO.; WEIGHT (KG.)	AMOUNT OF CO_2 INJECTED (ML./KG.)	PERFUSION RATE (ML./MIN.); DURATION (MIN.)	SYSTOLIC BLOOD PRESSURES (MM. Hg)				BLOOD O_2 SATURATION (PER CENT)	
			ARTERIAL	VENOUS	LEFT ATRIAL	PULM. ARTERIAL	PULM. ARTERY	LEFT ATRIUM
26; 19.4 Kg.	0.5 ml. (×2)	1,500; 64 min.	150	2	12-15	25-30	49	96
27; 19 Kg.	0.5 ml. (×2)	1,800; 33 min.	170	-1	15	30	48	97
28; 13 Kg.	1.5 ml.	—	100	4	5	30	48	92
29; 14 Kg.	0.5 ml.	1,200; 33 min.	150	4	5	18-20	46	93
30; 8.3 Kg.	0.5 ml.	800; 23 min.	95	2	7	30	34	96
31; 14 Kg.	0.5 ml.	1,200; 28 min.	110	3	2	16	58	95
32; 14 Kg.	0.5 ml.	1,200; 24 min.	110	2	3	18	72	94
33;	1.5 ml.	1,100; 34 min.	125	2	14	25	43	93

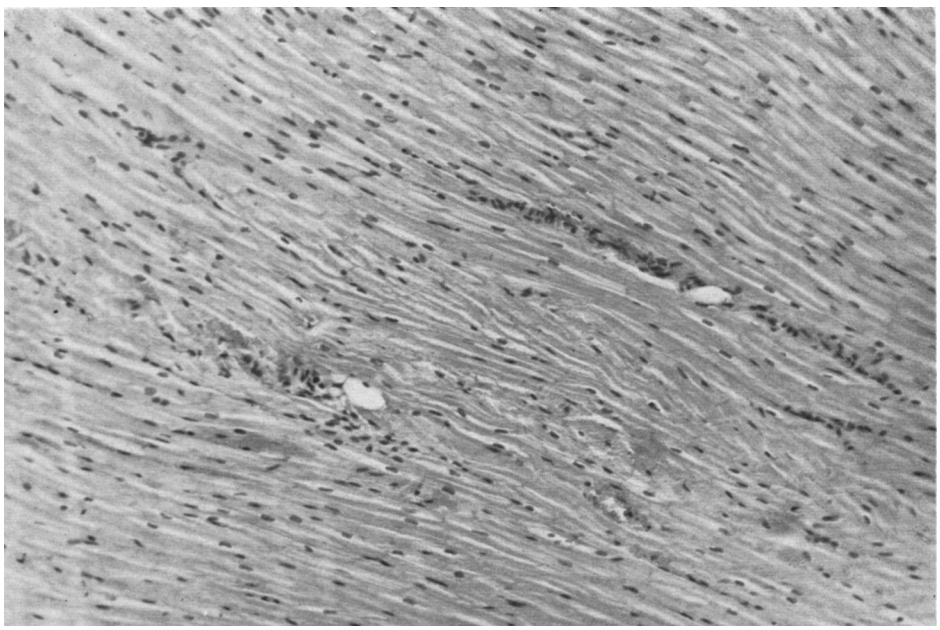

Fig. 8.—Histologic section of myocardium following injection of 0.5 ml./Kg. of carbon dioxide 7 days before. Only minimal evidence of injury is present and consists of a light infiltrate of inflammatory cells (see Fig. 10). (Hematoxylin & eosin, ×125; reduced ¼.)

INJECTION OF CARBON DIOXIDE (DATA 1-2 HOURS AFTER OPERATION)

BLOOD pH		MYOCARDIAL HISTOLOGIC FINDINGS (0-4+)			
ARTERIAL	VENOUS	HEMORRHAGE	MUSCLE NECROSIS	TISSUE REPAIR	REMARKS
7.58	7.47	0	0	2+	Autopsied 7 days
7.57	7.45	0	2+	2+	Autopsied 9 days
7.56	7.48	2+	0	0	Autopsied 21 days
7.46	7.38	0	0	0	Autopsied 7 days
7.45	7.38	0	2+	2+	Autopsied 7 days
7.48	7.40	0	0	0	Autopsied 7 days
7.38	7.29	0	1+	0	Autopsied 7 days
7.41	7.52	3+	0	0	Died 6th day; empyema

Fig. 9.—Histologic section of myocardium shows more extensive injury from injection of 0.5 ml./Kg. of carbon dioxide 7 days before. Extensive focal areas of necrosis are present in which proliferating fibroblasts and myocytes are easily seen. (Hematoxylin & eosin, ×125; reduced ¼.)

TABLE VII. SURVIVAL FOLLOWING LEFT VENTRICULAR

EXP. NO.; WEIGHT (KG.)	AMOUNT OF SALINE INJECTED (ML./KG.)	PERFUSION RATE (ML./MIN.); DURATION (MIN.)	SYSTOLIC BLOOD PRESSURES (MM. Hg)				BLOOD O_2 SATURATION (PER CENT)	
			ARTERIAL	VENOUS	LEFT ATRIAL	PULM. ARTERIAL	PULM. ARTERY	LEFT ATRIUM
34; 21 Kg.	0.5 ml. (×2)	1,100; 40 min.	120	5	3	30	50	91
35; 18 Kg.	0.5 ml. (×2)	1,100; 49 min.	110	8	5	20	52	94
36; 19 Kg.	0.5 ml. (×2)	2,000; 33 min.	130	3-7	−1	20	40	95
37; 22 Kg.	0.5 ml. (×2)	12-1,600; 30 min.	120	0	3	25	43	93
38; 12 Kg.	1 ml. (×2)	11-1,500; 29 min.	150	4	15	40	34	89
39; 12 Kg.	1 ml. (×2)	1,100; 30 min.	135	4	9	20	62	92

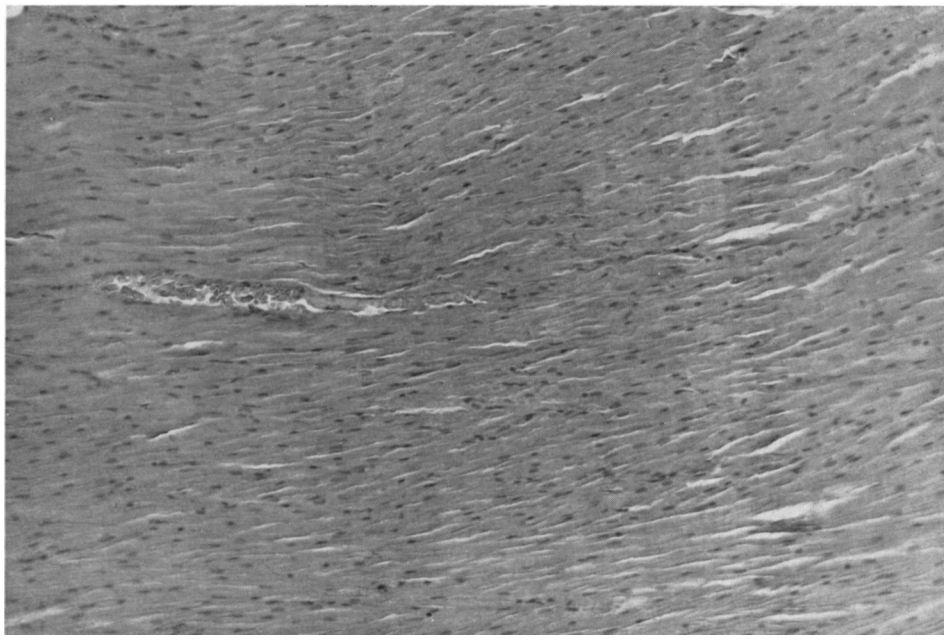

Fig. 10.—Histologic section of myocardium of dog that had injection of saline 7 days previously. In contrast to the histologic sections from animals receiving carbon dioxide or air, this section shows a striking absence of any necrosis focal hemorrhage, or infiltration with inflammatory cells or repair. (Hematoxylin & eosin, ×125; reduced ¼.)

INJECTION OF SALINE (DATA 1-2 HOURS AFTER OPERATION)

BLOOD pH		MYOCARDIAL HISTOLOGIC FINDINGS (0-4+)			
ARTERIAL	VENOUS	HEMORRHAGE	MUSCLE NECROSIS	TISSUE REPAIR	REMARKS
7.58	7.5	0	0	0	All sacrificed in 7 days
7.59	7.48	1+	0	0	
7.50	7.32	0	0	0	
7.60	7.50	0	0	0	
7.58	7.43	0	0	0	
7.44	7.31	0	0	0	

emboli experiments (Table IV; Figs. 3, 4, and 5). The histologic abnormalities consisted of necrosis and the presence of fibroblasts and myocytes (Figs. 6, 7). Myocytes originate from myocardial muscle cells which have been subjected to a sublethal injury.[7]

Of particular interest was the finding of similar areas of myocardial injury in dogs previously injected with carbon dioxide (Table VI). Through less frequent and less extensive, these changes were identical to those following air embolism (Figs. 8, 9).

No myocardial abnormalites were found in the control dogs which had been injected with saline (Table VII), indicating that the areas of myocardial injury found after injection of carbon dioxide resulted from the injected gas and not from some other unknown factor associated with perfusion (Fig. 10).

DISCUSSION

Injury From Air Emboli.—In the absence of cardiopulmonary bypass, the lethal effects of air embolism in the pulmonary veins or left heart have long been clearly defined by several investigators. In 1929, Van Allen and Hrdina's[14] demonstration of lethal coronary air emboli helped clarify the mode of fatal collapse occurring with thoracentesis or surgical incision of the lungs; previously such episodes were vaguely diagnosed as "pleural shocks." Their studies emphasized the role of buoyancy in determining the behavior of air emboli. Eleven years later, Moore and Braselton[11] reported that air injections of 0.5 ml. per pound were fatal to cats, but carbon dioxide was tolerated up to 3 ml. per pound. This was one of the first reports comparing the results of injections of air and carbon dioxide. A year later Kent and Blades[8] reported similar findings in dogs.

Changes in the electrocardiogram with air emboli were studied by Durant[2] in 1959, who found the alterations identical to those of myocardial ischemia from other causes. In surviving animals the electrocardiographic abnormalities quickly disappeared. A comparison of air and carbon dioxide emboli was made by Kunkler and King[9] in 1959, who found the latter was tolerated five times as well. Large bubbles of carbon dioxide were not totally innocuous, however, perhaps because of equilibration with other gases dissolved in tissue fluids. The mode of obstruction from gas emboli was demonstrated by Eiseman[4] to be a surface tension phenomenon. Moving bubbles did not impede flow, but static bubbles caused obstruction because of surface tension developing at the interface between the bubble and the vessel wall. Chemical agents which decreased surface tension similarly decreased the mortality from air emboli.

With cardiopulmonary bypass, the hazards of air emboli are much less obvious.[1] Visible air bubbles are usually quickly pushed through the coronary vessels without obvious harm except from transient myocardial ischemia. One of the first demonstrations of the harmful effects of coronary air emboli, even though visible bubbles had disappeared, was made by Eguchi and Bosher in 1962.[3] In acute experiments, ventricular function was seriously impaired both 10 and 30 minutes following air embolization. Subsequently Goldfarb and Bahnson[6] emphasized that minute amounts of air, even as small as 0.05 ml.,

directly injected into a coronary artery could not only transiently impair ventricular function but, also, could cause focal myocardial infarction.

The results obtained in our experiments amply confirm the potentially lethal hazard of air emboli. This lethal potentiality has been difficult to recognize because of two characteristics of air embolism: (1) the wide variation in tolerance among different animals; and (2) the subtle mode of development of the resulting myocardial injury.

The great variation in tolerance to air is emphasized in the data shown in Tables I-IV. In 7 of 20 experiments, cardiac injury was so profound that immediate death occurred when cardiopulmonary bypass was stopped, whereas in 6 similar experiments uneventful recovery ensued. The remaining 7 of the 20 died within 24 hours after operation with signs of impaired cardiac function. This variation in tolerance was readily shown by the speed with which air bubbles moved through the coronary vessels and disappeared; in some experiments all visible air was gone within 3 to 4 minutes. In others the bubbles formed a permanent focal vascular obstruction, and, at times, resisted all efforts to remove them. The basis for the variation in tolerance is not known. It could result from variation in size or location of myocardial arteriovenous shunts which would aid the removal of air from the capillary bed.

The other characteristic of air embolization—the frequent subtle development of the myocardial injury—was also impressive. With visible air bubbles in a failing heart, the injury was obvious. By contrast, though, was the occasional persistence of a feebly contracting cyanotic heart after all visible air had disappeared. This was probably due to widespread capillary occlusion from microscopic emboli. It was clear, though, that if the earlier air emboli had not been seen, the origin of the cardiac injury would have been obscure and could have been erroneously attributed to a number of causes—metabolic acidosis, rate of perfusion, gas or silicone emboli from the pump oxygenator, et cetera.

The obscure development of myocardial injury was also shown by the occurrence of death between 2 and 24 hours in about one third of the animals (Table III). Certainly postoperative deaths following perfusions in dogs can result from many causes, only one of which is air embolism, but similar events did not occur in control experiments. Of greater significance, though, is the uniform finding of multiple focal areas of myocardial infarction in all surviving animals when autopsied 7 days following air embolization. This myocardial injury could not be detected by several measurements of cardiac function, including an electrocardiogram obtained just before the animals were sacrificed. The inability to detect the myocardial injury without histologic examination is a reflection of the large myocardial reserve in a normal heart. The same event is seen clinically in patients who fully recover from a proved myocardial infarction.

Carbon Dioxide Emboli.—Carbon dioxide emboli are obviously much better tolerated than air emboli, for they quickly disappear from the coronary vessels, causing little or no change in cardiac function. The difference of carbon dioxide from air is due to the fact that it is more than thirty times as soluble as air in body fluids. Carbon dioxide was not totally innocuous, however, for arrhythmias

occurred in some experiments; 5 of 13 animals died within 24 months after perfusion, and focal myocardial injury was found on histologic examination in 2 of the 5 survivors. Similar results were found by Kunkler and King, who estimated that carbon dioxide was tolerated five times better than air. Larger injections, 3 to 4.75 ml. per kilogram, frequently caused ventricular fibrillation.

Prevention and Treatment of Air Embolization.—

A. *Prevention:* As air emboli originating in a pump oxygenator system results from obvious mechanical defects in design or maintenance, the method of prevention is usually obvious. With a properly functioning pump oxygenator, the usual source of air emboli during a bypass operation is embolization from the left ventricle. This occurs if air is present in the left atrium or ventricle when cardiac contractions are forceful enough to open the aortic valve, which is normally held closed by the perfusion pressure generated by the pump oxygenator. As virtually all intracardiac operations are associated with an opening into the left heart, air embolization is a constant hazard, except possibly in operations for pulmonary valvular stenosis. The risk is lessened by the fact that the contracting left ventricle cannot open the aortic valve unless the left ventricular cavity is "closed." Hence, air embolization cannot occur as long as the mitral valve is kept "incompetent," or a septal defect is present. This principle is the basis for the effectiveness of a left ventricular vent, first suggested by Miller and Gibbon,[10] which will keep the left ventricle "decompressed" until air has been expelled.

Flooding the operative field with carbon dioxide while the left heart is open is another frequently used technique.[12] The theoretical advantages of carbon dioxide over air are unquestionable, but attaining a high concentration of carbon dioxide in the operative field requires a flow rate of several liters per minute. Objective data proving its clinical effectiveness are difficult to assess.

Induction of ventricular fibrillation, first suggested by Senning,[13] is a highly effective technique, now being employed with increasing frequency. No physiological injury from fibrillation up to 2 hours in duration has occurred as long as ventricular distention is avoided. It can be induced before the heart is opened and continued until all cardiotomies are closed and air is removed from the heart. One electrical shock (120 volts, 0.1 second) will usually change the fibrillation to a sinus rhythm. We now routinely employ induced fibrillation for many procedures, including closure of an atrial septal defect, "open" mitral commissurotomy, or operations for mitral insufficiency.

B. *Treatment of air embolism:* In the experimental studies, several techniques for removal of coronary air emboli were evaluated. The simplest and most effective of these was prompt elevation of the perfusion pressure by the injection of epinephrine. The value of this transitory increase in perfusion pressure in displacing air emboli was repeatedly demonstrated. Of equal importance was immediate decompression of the left ventricle; the decompression seemingly aided mechanical displacement of emboli, as well as preventing further ventricular injury from overdistention.

If ventricular fibrillation was present, forceful cardiac massage was helpful in displacing emboli, after which electrical defibrillation could be attempted.

When all other methods were ineffective, small incisions made in the epicardium near the emboli were useful; often foam would be expelled as quickly as the incisions were made.

Finally, prolonged support of the injured left ventricle with continued extracorporeal circulation while the left ventricle is decompressed was of value, if serious injury had occurred. With prolonged support, recovery from a serious degree of anoxic injury was possible.

SUMMARY

1. In 39 experiments in dogs with extracorporeal circulation, the effects of coronary embolization with air (20 experiments), carbon dioxide (13 experiments), and saline (6 experiments) were studied. One or two injections of 0.5 to 1.0 ml. per kilogram were employed in each experiment.

2. A wide variation in tolerance to air emboli was found; air passed rapidly through the coronary capillaries in some while forming a permanent obstruction in others. In 7 of 20 experiments, air promptly caused lethal myocardial injury; 7 other dogs died within 24 hours. Six recovered uneventfully, but histologic examination of the myocardium 7 days after operation showed multiple areas of focal infarction in each animal.

3. Difficulties in the recognition of air emboli as a cause of myocardial injury were apparent, for myocardial function was impaired long after visible emboli had disappeared. It was repeatedly noted that serious myocardial injury from air emboli could be easily overlooked.

4. Carbon dioxide emboli, though causing much less injury than air, were not completely innocuous. Five of 13 animals died within 24 hours after operation, and signs of focal myocardial injury were found in surviving animals autopsied 7 days after operation.

5. The most effective method for prevention of air emboli is the use of induced ventricular fibrillation in combination with decompression of the left ventricle. If emboli have occurred, increasing the perfusion pressure and manually massaging the heart are usually effective. Prolonged pump support, while decompressing the injured left ventricle, may be needed.

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