CARDIOPULMONARY BYPASS, MYOCARDIAL MANAGEMENT, AND SUPPORT TECHNIQUES

RETROGRADE CARDIOPLEGIA PRESERVES MYOCARDIAL FUNCTION AFTER INDUCED CORONARY AIR EMBOLISM

Aqeel A. Sandhu, MD[a]
Henry M. Spotnitz, MD[a]
Marc L. Dickstein, MD[b]
Eric A. Rose, MD[a]
Robert E. Michler, MD[a]

Coronary air embolism is a potential complication of cardiopulmonary bypass. We compared left ventricular function before and after the administration of antegrade or retrograde cardioplegic solution in a porcine model of coronary air embolism. Nineteen pigs were placed on cardiopulmonary bypass support and cooled to 32° C. The heart was initially arrested with antegrade cold blood cardioplegic solution. The aortic crossclamp was released at 30 minutes and 0.02 cc/kg body weight of air was injected into the left anterior descending artery distal to the first diagonal branch. After 5 minutes the aorta was reclamped and the animals treated with 15 ml/kg body weight of 1:4 blood cardioplegic solution delivered by the antegrade ($n = 6$) or retrograde ($n = 7$) method. Control animals ($n = 6$) were not treated. Changes in regional preload recruitable stroke work were used to assess left ventricular performance before and after cardiopulmonary bypass. Two control animals could not be weaned from cardiopulmonary bypass. Left ventricular function was best preserved after treatment of induced coronary air embolism with retrograde cardioplegia (90% of baseline). Coronary air embolism treatment with antegrade cardioplegia resulted in diminished left ventricular performance (68% of baseline). In control animals left ventricular contractility was significantly impaired (39% of baseline). We conclude that administration of retrograde cardioplegic solution may be an effective method of treating coronary air embolism. The favorable outcome seen with cardioplegia may be in part because of its ability to protect the ischemic myocardium while the solution mechanically dislodges air from the vascular bed. (J Thorac Cardiovasc Surg 1997;113:917-22)

It is recognized that arterial air embolism is hazardous and may result in permanent organ injury.[1-9] Coronary air embolism (CAE), a potential complication of cardiopulmonary bypass (CPB), may cause cardiac arrhythmia, myocardial infarc-

tion, low cardiac output syndrome, intractable ventricular fibrillation, and death.[6, 8-10] Present therapeutic options for acquired CAE in the operating room focus on its prevention by mechanical deairing of the heart and great vessels before release of the aortic crossclamp. In one study Spiess and associates[9] demonstrated that pretreatment with the perfluorocarbon emulsion FC-43 may protect the myocardium from the sequelae of CAE in a spontaneously perfusing dog model. Although the idea is tempting, pretreatment of all patients undergoing cardiac operations with perfluorocarbon emulsion FC-43 is impractical. Others have advocated the use of pharmacologic agents, mechanical systole, and extracorporeal circulation to raise mean arterial pressure in an effort to dislodge air from the coronary vasculature.[6-8] Interpre-
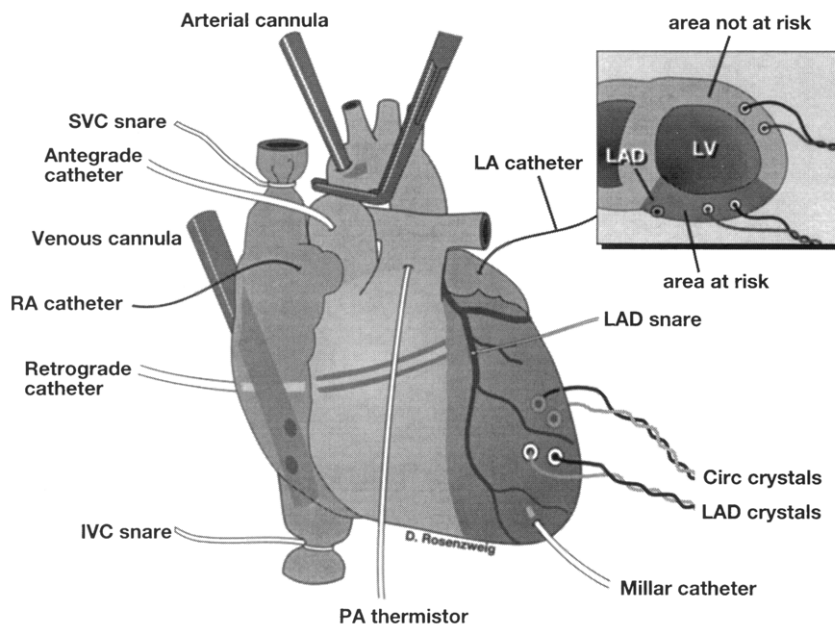
Fig. 1. Diagram illustrating the instrumentation of hearts in experimental animals. *SVC,* Superior vena cava; *RA,* right atrium; *IVC,* inferior vena cava; *PA,* pulmonary artery; *LAD,* left anterior descending; *circ,* circumflex; *LA,* left atrium.

tation of results with these modalities is difficult, although all claim variable success, increasing myocardial oxygen demand in an already ischemic myocardium may exacerbate injury. We hypothesized that administration of retrograde cardioplegic solution, via the coronary sinus, might effectively eliminate air embolism from the coronary circulation and preserve myocardial function.

Methods

Surgical preparation. Nineteen domestic pigs of either sex (45 to 60 kg) were anesthetized with an intramuscular injection of ketamine (20 mg/kg), glycopyrrolate (0.01 mg/kg), and acepromazine (0.5 mg/kg). The animals were intubated and the lungs mechanically ventilated with a volume-cycled ventilator. Anesthesia was maintained with inhalation of isoflurane (1.5% to 2.5%) and oxygen. The electrocardiogram, heart rate, and mean arterial blood pressure were continuously monitored throughout the experiment. After median sternotomy and pericardiotomy the heart and great vessels were exposed. The superior and inferior venae cavae were isolated and ensnared. The heart was instrumented as follows (Fig. 1). A 5F micromanometer-tipped catheter (MPC 500-5F, Millar Instruments, Inc., Houston, Tex.) was introduced into the left ventricle (LV) via the apex to measure LV pressure. An injection catheter was placed in the right atrium through the right atrial appendage and a thermodilution catheter was inserted into the main pulmonary artery for cardiac output determinations. Another catheter was inserted into the left atrium through the left atrial appendage for

methylene blue stain injection. Two pairs of piezoelectric sonomicrometry crystals (Triton Technology Inc., San Diego, Calif.), spaced approximately 1 cm apart, were imbedded into the midmyocardium in the regions supplied by the left anterior descending artery (LAD) (area at risk) and left circumflex artery (area not at risk). Determination of the area at risk was accomplished by rapidly injecting dilute methylene blue stain (100 mg in 20 ml 0.9% saline solution) into the left atrium while temporarily (<30 seconds) occluding the LAD.[11] Baseline hemodynamic and LV function data were collected during steady-state conditions before CPB. Caval snares were used to vary preload during LV function data collection.[12]

After systemic heparinization (300 IU/kg) the animals were cannulated for CPB (Fig. 1). The ascending aorta was cannulated with an angled arterial cannula (Sarns, Ann Arbor, Mich.) and the right atrium was cannulated with a single dual-stage venous cannula (Biomedicus, Minneapolis, Minn.). The extracorporeal circuit consisting of a roller pump, membrane oxygenator (Medtronic-Minimax, Minneapolis, Minn.), and water bath heat exchanger (Sarns TCM) was primed with 1 L each of Plasma-Lyte solution and 6% hetastarch (Hespan). CPB was instituted and the animals cooled to 32° C. Mechanical ventilation was discontinued and anesthesia was maintained with isoflurane and oxygen via the oxygenator.

Protocol. Animals were divided into three groups: antegrade (*n* = 6), retrograde (*n* = 7), and control (*n* = 6). Two animals were excluded from the study because of pneumonia discovered after median sternotomy. Experiments were randomized. Induced CAE was treated with cardioplegic solution delivered via the aortic root in the antegrade group and via the coronary sinus in the retro-
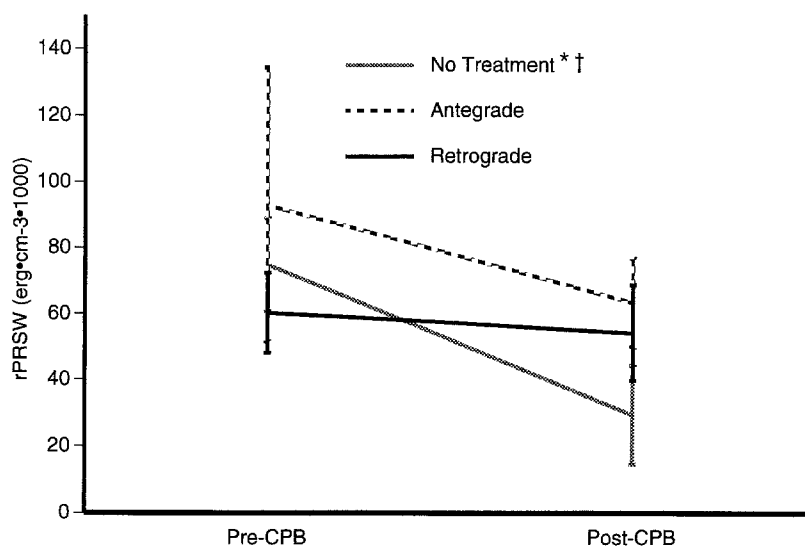
Fig. 2. Data demonstrate statistically significant decrease in rPRSW after induced CAE in control animals, but not in treated animals. Additionally, postembolism rPRSW values were significantly lower in control animals compared with those in animals in the retrograde group. Data shown as means plus or minus the standard deviation. $*p = 0.0017$ compared with baseline values; $\dagger p = 0.0159$ compared with retrograde group.

grade group. The aortic root was not vented during retrograde administration of cardioplegic solution. Control animals were not treated. Mean arterial perfusion pressures during CPB before and after CAE were maintained higher than 60 mm Hg in all experiments. Fifteen minutes after CPB was begun, and during steady-state conditions, all hearts were initially arrested for 30 minutes with antegrade cardioplegic solution (15 ml/kg body weight) of 1 part blood to 4 parts crystalloid solution delivered at 4° C. This was done largely to mimic the clinical scenario; however, it also facilitated further instrumentation of the heart. With the heart arrested a 24-gauge catheter was inserted into the LAD just distal to its first diagonal branch. Additionally, the coronary sinus was cannulated after ligation of the azygos vein in the retrograde group. The azygos vein was ligated to ensure that delivered retrograde cardioplegic solution was distributed to the heart, because in pigs this vein drains into the coronary sinus. Ligation of the azygos vein was thought not to have any significant physiologic effects and therefore was only done for retrograde-group animals.

After 30 minutes the aortic crossclamp was removed and 0.02 cc/kg body weight of air was simultaneously injected into the LAD. Immediate blanching of the LAD and its branches after air injection confirmed successful CAE. Experimental studies have established 0.02 cc/kg of air in the coronary arteries as an appropriate dose to cause significant myocardial injury with acceptable mortality rates.[8, 9, 13, 14] Bretylium (5 mg/kg) was administered prophylactically to each animal before crossclamp release.[15] The heart was allowed to reperfuse for 5 minutes before any therapeutic intervention was attempted. Animals in the antegrade and retrograde groups underwent

Table I. *LV function data before and after induced CAE in area at risk*

	Pre-CPB	Post-CPB
rPRSW (erg · cm^{-3} · 10^{-3})		
No treatment ($n = 4$)	73 ± 18	$29.45 \pm 14.86*\dagger$
Antegrade ($n = 6$)	108 ± 39	63 ± 37
Retrograde ($n = 7$)	62 ± 30	51 ± 38
SF (%)		
No treatment ($n = 4$)	15.25 ± 4.57	5 ± 5.83
Antegrade ($n = 6$)	16.71 ± 9.12	13 ± 13.46
Retrograde ($n = 7$)	17.28 ± 9.69	3.86 ± 16.83

Values given as mean plus or minus the standard deviation; $n = 19$. *SF,* Segment shortening.

$*p = 0.0017$ compared with baseline values.

$\dagger p = 0.0159$ compared with retrograde group.

reclamping and were treated with hypothermic (4° C) 1:4 blood/crystalloid cardioplegic solution (15 ml/kg) via the aortic root (at 150 mm Hg) and coronary sinus (50 mm Hg), respectively. The mean cardioplegic solution administration time was 4.29 ± 1.38 minutes for antegrade and 4.86 ± 1.07 minutes for retrograde delivery. The aortic crossclamp was removed immediately after the treatment dose of cardioplegic solution was completely infused. Control animals did not undergo reclamping. All animals were rewarmed and weaned from CPB with use of a single vasopressor agent (norepinephrine 0.05 to 0.15 μg/kg per minute). The pressor requirements and support intervals during rewarming varied in all groups. Animals in the retrograde and antegrade groups were easily weaned from

Table II. *LV function data before and after induced CAE in area not at risk*

	Pre-CPB	Post-CPB
rPRSW (erg · cm^{-3} · 10^{-3})		
No treatment (n = 3)	86 ± 47	95 ± 101
Antegrade (n = 6)	93 ± 39	81 ± 38
Retrograde (n = 7)	73 ± 26	57 ± 47
SF (%)		
No treatment (n = 4)	11.75 ± 4.92	5 ± 3.16
Antegrade (n = 6)	17 ± 3.55	10.43 ± 8.85
Retrograde (n = 7)	10.28 ± 7.43	12 ± 8.14

Values given as mean plus or minus the standard deviation; n = 19. *SF*, segment shortening.

Table III. *Hemodynamic data before and after induced CAE*

	Pre-CPB	Post-CPB
HR (beats/min)		
No treatment	100 ± 5.47	132 ± 32.86
Antegrade	93 ± 16.35	132 ± 24.42
Retrograde	100.87 ± 19.5	129.37 ± 32.96
MAP (mm Hg)		
No treatment	55.5 ± 6.15	42.25 ± 8.30
Antegrade	53.17 ± 11.82	40.39 ± 14.29
Retrograde	58 ± 10.35	59.17 ± 31.07
CO (L/min)		
No treatment	4.59 ± 0.90	2.30 ± 0.67*†
Antegrade	5.19 ± 1.14	4.03 ± 0.77
Retrograde	5.03 ± 1.76	4.62 ± 0.93
SW (mm Hg · ml)		
No treatment	2611.19 ± 1025.92	731.62 ± 262.9‡
Antegrade	3130.95 ± 755.9	1223.67 ± 286.14§
Retrograde	3085.26 ± 1331.62	2221.47 ± 962.2

Values given as mean plus or minus the standard deviation; n = 19. *HR*, Heart rate; *MAP*, mean atrial blood pressure; *CO*, cardiac output; *SW*, stroke work.

*p = 0.0002 compared with baseline values.

†p = 0.0016 compared with retrograde group.

‡p = 0.0223 compared with baseline values.

§p = 0.0007 compared with baseline values.

CPB with minimal support in 14 ± 6.68 and 21 ± 7.53 minutes, respectively. In contrast, the mean support interval for control animals was 37 ± 14.24 minutes. Data were collected again during steady-state conditions after discontinuation of CPB.

Data analysis. Data were digitized in real time at 200 Hz on a multichannel analog-digital converter (MacLab/8, ADInstruments, Pty., Ltd.) after being filtered by a 50 Hz low-pass analog filter and recorded on a personal computer (Macintosh IIsi, Apple Computer, Inc., Cupertino, Calif.). Data were analyzed with use of a specific macro written for commercial software (Igor, Wavemetrics, Lake Oswego, Ore.).

Regional myocardial function was quantified, before and after CPB, by determining the regional stroke work–dimension relationship or regional preload recruitable stroke work (rPRSW).[12, 16] Preload was varied by caval occlusion and data from 10 beats before onset of caval occlusion to steady-state maximal caval occlusion were used to evaluate regional stroke work over a range of end-diastolic lengths. For each individual cycle, regional stroke work was defined as the area under the LV pressure-segment length loop during systole. The start of systole (end diastole) was identified as the point just preceding the upstroke of the LV pressure wave. The end of systole (end systole) was defined with use of the first time derivative of the LV pressure wave as previously described.[12, 16] rPRSW was then calculated as the slope of the regression line that best defined the relation between regional stroke work and end-diastolic segment length. Regression lines with a correlation coefficient less than 0.8 were excluded from analysis.

The percent fiber shortening (FS) was also determined and calculated as follows:

$$\%\Delta FS = EDL - ESL/EDL \cdot 100$$

where EDL is end-diastolic segment length and ESL is end-systolic segment length.[14, 16]

Heart rate and mean arterial pressure were continuously recorded throughout the experiment. Cardiac output was measured by thermodilution before and after CPB. Only data with less than a 10% change were considered.

LV function data and hemodynamic data were compared in each animal before and after CPB with each other and with data in control animals by analysis of variance. A value of $p < 0.05$ was considered statistically significant. Data are presented as the mean plus or minus the standard deviation.

Experiments were performed under the regulations of the Institutional Animal Care and Use Committee of Columbia University. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

Results

All treated animals were successfully weaned from CPB. Two untreated pigs could not be weaned from CPB because of intractable ventricular fibrillation in one and low cardiac output syndrome in the other. Hearts treated with retrograde cardioplegia spontaneously returned to sinus rhythm without defibrillation. The mean dilutional hematocrit during CPB was 22.38% ± 4.59%. In an effort to minimize myocardial edema the hematocrit during CPB was maintained higher than 20% by fluid restriction.

Changes in rPRSW were used to assess regional LV performance before and after induced CAE. Myocardial function was best preserved in animals treated with retrograde cardioplegic solution (90%

of baseline). Animals treated with antegrade cardioplegic solution demonstrated diminished LV performance (68% of baseline) and untreated animals showed significantly impaired LV contractility (39% of baseline).

Mean rPRSW values before the onset of CPB were similar in all groups: 74.83 ± 14.21, 92.94 ± 41.21, and 60.22 ± 12.16 erg $\cdot$ cm^{-3} $\cdot$ 10^{-3} in the area at risk and 110 ± 41.31, 63.42 ± 43.15, and 53.15 ± 19.29 erg $\cdot$ cm^{-3} $\cdot$ 10^{-3} in the area not at risk in animals in the untreated, antegrade, and retrograde groups, respectively. After induced CAE (after CPB), rPRSW was significantly reduced in the area at risk in the untreated group (29.45 ± 14.86 erg $\cdot$ cm^{-3} $\cdot$ 10^{-3}, $p = 0.0017$ compared with values before CPB). Additionally, when rPRSW values for the areas at risk after CPB were compared among groups, animals not treated had significantly lower values ($p = 0.0159$) than animals treated with retrograde cardioplegic solution (Fig. 2). In the areas not at risk, rPRSW did not significantly change from baseline values after induced CAE in any group (Tables I and II). Percent fiber shortening did not decrease significantly after induced CAE in any experimental group (Tables I and II).

Hemodynamic data before and after CPB are shown in Table III. Values for heart rate and mean arterial blood pressure did not vary significantly among experimental groups; however, values of cardiac output fell significantly in untreated animals ($p = 0.0002$). Additionally, values for stroke work were significantly reduced in animals in both the control ($p = 0.0223$) and antegrade ($p = 0.0007$) groups.

Discussion

Air embolism to the coronary vasculature is a potential life-threatening complication of any procedure requiring CPB. Unfortunately, CAE is often undetected and diagnosed by exclusion. Myocardial injury from CAE results from ischemia caused by trapped air that blocks coronary blood flow and from possible endothelial damage by intrinsic reactions that occur at the blood/air interface.[10, 17] Current surgical practices to prevent CAE are documented[1-6, 9, 10]; however, no study to date has demonstrated an effective, reproducible, and safe method of treating CAE once it has occurred. In the present study we have demonstrated, with indices of regional myocardial function, that administration of retrograde cardioplegic solution after CAE may preserve heart function.

The effects of air embolism have been long stud-

ied. In 1929, Van Allen, Hrdina, and Clark[18] demonstrated that large amounts of air were required to cause death in dogs when injected into the venous circulation. In contrast, injection of small amounts of air into the circulation of the left side of the heart was noted to be lethal. Geoghegan and Lam[1] found 1.5 cc/kg of air in the LV to be 100% fatal in dogs. Reduction of LV air correspondingly reduced mortality: 0.75 cc/kg and 0.5 cc/kg of air resulted in 83% and 33% mortality rates, respectively. Later, others showed that even minute amounts of air, as little as 0.01 to 0.02 cc/kg, in the coronary arteries produced significant myocardial injury.[3, 8, 13]

Several experimental studies have documented variable success in the treatment of established CAE by augmenting coronary perfusion pressure to supernormal levels in an effort to push the air embolism across the capillary bed to the venous circulation.[1, 3, 4, 6, 7] Such methods have included mechanical systole, partial occlusion of the ascending aorta, increasing the pump flow rate, and administration of vasopressors and inotropic agents. Such techniques are potentially dangerous. The high perfusion pressures required to rid the coronary arteries of air may damage endothelium, cause interstitial hemorrhage, and exacerbate myocardial ischemia. During study of the effects of small air bubbles produced by laser angioplasty in coronary arteries of pigs, Van Blankenstein and associates[14] estimated that blood pressures as high as 200 mm Hg were required to drive air emboli through capillary vessels of 6 μm in diameter. Additionally, Tuman and coworkers[10] found that maintaining normal coronary perfusion after CAE in pigs did not significantly alter myocardial ischemia.

In our study, although animals treated with antegrade cardioplegic solution after CAE demonstrated improved cardiac function compared with results in untreated animals, there was significant evidence of residual myocardial injury. One explanation for this might be that the perfusion pressure of the delivered cardioplegic solution (150 mm Hg) might have been insufficient to adequately remove the CAE. In contrast, animals treated with retrograde cardioplegic solution after CAE showed dramatic recovery of myocardial function (90% of baseline). This is perhaps because retrograde cardioplegia more effectively protects the heart while the solution mechanically dislodges air emboli and restores blood flow. We know from prior work that breaking the air lock restores forward flow of blood.[17] In other words it is not necessary to com-

pletely remove all the air from the vessels to reestablish perfusion. Tracking the path of the dislodged air was beyond the scope of this study; however, this should be investigated with contrast echocardiography or microspheres.

In summary, we found that CAE caused significant impairment in regional function. Administration of retrograde cardioplegic solution was found to be an effective treatment for air embolism, as evidenced by preservation of regional function. These data represent the first evidence that administration of cold blood retrograde cardioplegic solution might offer an effective treatment for established CAE and restore cardiac function to near baseline levels.

REFERENCES
1. Geoghegan T, Lam CR. The mechanism of death from intracardiac air and its reversibility. Ann Surg 1955;138: 351-9.
2. Kunkler A, King H. Comparison of air and carbon dioxide embolization. Ann Surg 1959;149:95-9.
3. Goldfarb D, Bahnson HT. Early and late effects on the heart of small amounts of air in the coronary circulation. J Thorac Cardiovasc Surg 1963;46:368-78.
4. Spencer FC, Rossi NP, Yu SC, Koepke A. The significance of air embolism during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1965;49:615-34.
5. Gomes OM, Pereira SN, Castagna RC, Bittencourt D, Amaral RVG, Zerbini EJ. The importance of the different sites of air injection in the tolerance of arterial air embolism. J Thorac Cardiovasc Surg 1973;65:563-8.
6. Justice C, Leach J, Edwards WS. The harmful effects and treatment of coronary air embolism during open-heart surgery. Ann Thorac Surg 1972;14:47-53.
7. Rhoades GR, McIntosh CL. An experimental evaluation of coronary air embolism. Surg Forum 1976;27:275-8.
8. Stegmann T, Bellmann DL, Trenkler G, Oelert H, Borst G. Experimental coronary air embolism: assessment of time course of myocardial ischemia and the protective effect of cardiopulmonary bypass. Thorac Cardiovasc Surg 1980;28:141-9.
9. Spiess BD, McCarthy RJ, Tuman KJ, Ivankovich AD. Protection from coronary air embolism by a perfluorocarbon emulsion (FC-43). J Cardiothorac Anesth 1987;1: 210-5.
10. Tuman KJ, McCarthy RJ, Spiess BD, Overfield DM, Ivankovich AD. Effects of nitrous oxide on coronary air embolism. Anesthesiology 1987;67:952-9.
11. Yano OJ, Bielefeld MR, Jeevanandam V, et al. Prevention of acute regional ischemia with endocardial laser channels. Ann Thorac Surg 1993;56:46-53.
12. Glower DD, Spratt JA, Snow ND, et al. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. Circulation 1985;71:994-1009.
13. Fornaro M, Hess O, Benoist F, Turina M. Myocardial damage in coronary air embolism. Thoraschirurgie 1978;26: 190-3.
14. Van Blankenstein JH, Slager JC, Schuurbiers JCH, Strikwerda S, Verdouw PD. Heart function after injection of small air bubbles in coronary artery of pigs. J Appl Physiol 1993; 75:1201-7.
15. Schumann RE, Harold ME, Gillette PC, Swindle MM, Gaymes CH. Prophylactic treatment of swine with bretylium for experimental cardiac catheterization. Lab Anim Sci 1993; 43:244-6.
16. Glower DD, Spratt JA, Kabas JS, Davis JW, Rankin JS. Quantification of regional myocardial dysfunction after acute ischemic injury. Am J Physiol 1988;255:H85-93.
17. Eiseman B, Baxter BJ, Prachuabmoh K. Surface tension reducing substances in the management of coronary air embolism. Ann Surg 1959;149:374-80.
18. Van Allen CM, Hrdina LS, Clark J. Air embolism from the pulmonary vein. Ann Surg 1929;19:567-8.