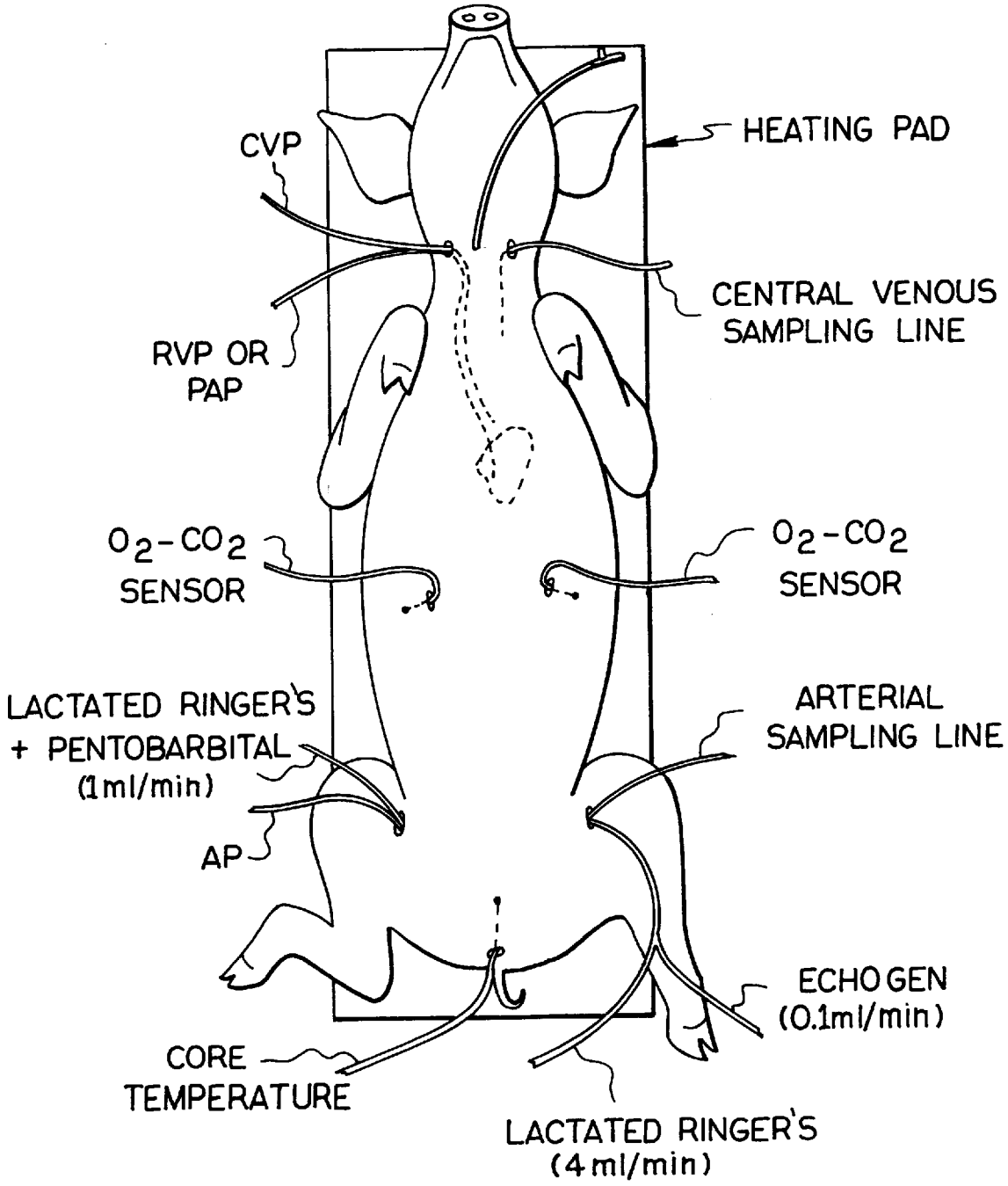
CVP
HEATING PAD
CENTRAL VENOUS SAMPLING LINE
RVP OR PAP
O_2-CO_2 SENSOR
O_2-CO_2 SENSOR
LACTATED RINGER'S + PENTOBARBITAL (1ml/min)
ARTERIAL SAMPLING LINE
AP
ECHOGEN (0.1ml/min)
CORE TEMPERATURE
LACTATED RINGER'S (4ml/min)

FIG. 18

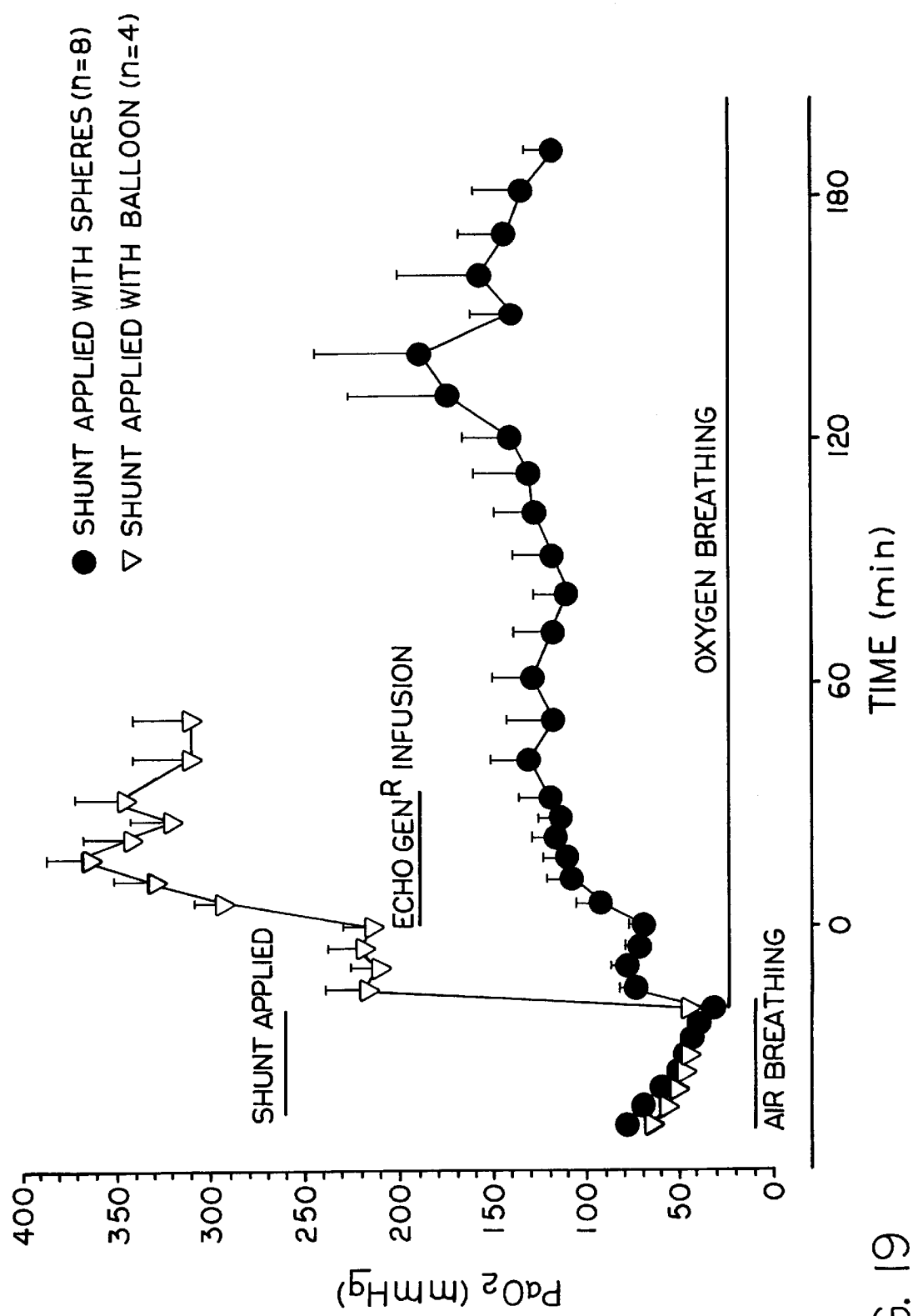
● SHUNT APPLIED WITH SPHERES (n=8)
▽ SHUNT APPLIED WITH BALLOON (n=4)
SHUNT APPLIED
ECHO GEN^R INFUSION
OXYGEN BREATHING
AIR BREATHING
Pa_{O_2} (mmHg)
400
350
300
250
200
150
100
50
0
0
60
120
180
TIME (min)

FIG. 19

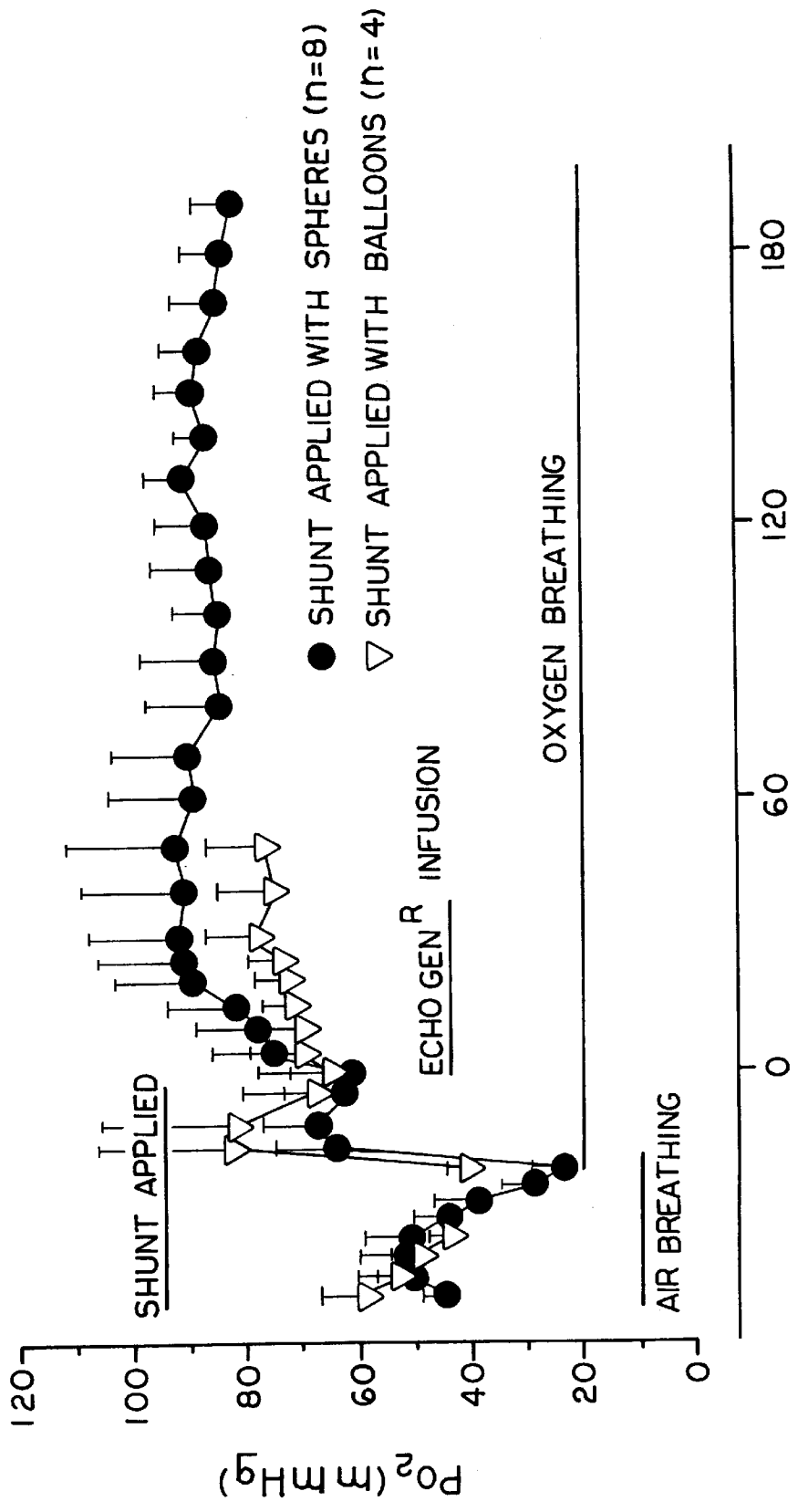
SHUNT APPLIED WITH SPHERES (n=8)
SHUNT APPLIED WITH BALLOONS (n=4)
SHUNT APPLIED
ECHO GEN R INFUSION
OXYGEN BREATHING
AIR BREATHING
P_{O_2} (mmHg)
120
100
80
60
40
20
0
0
60
120
180
TIME (min)

FIG. 20

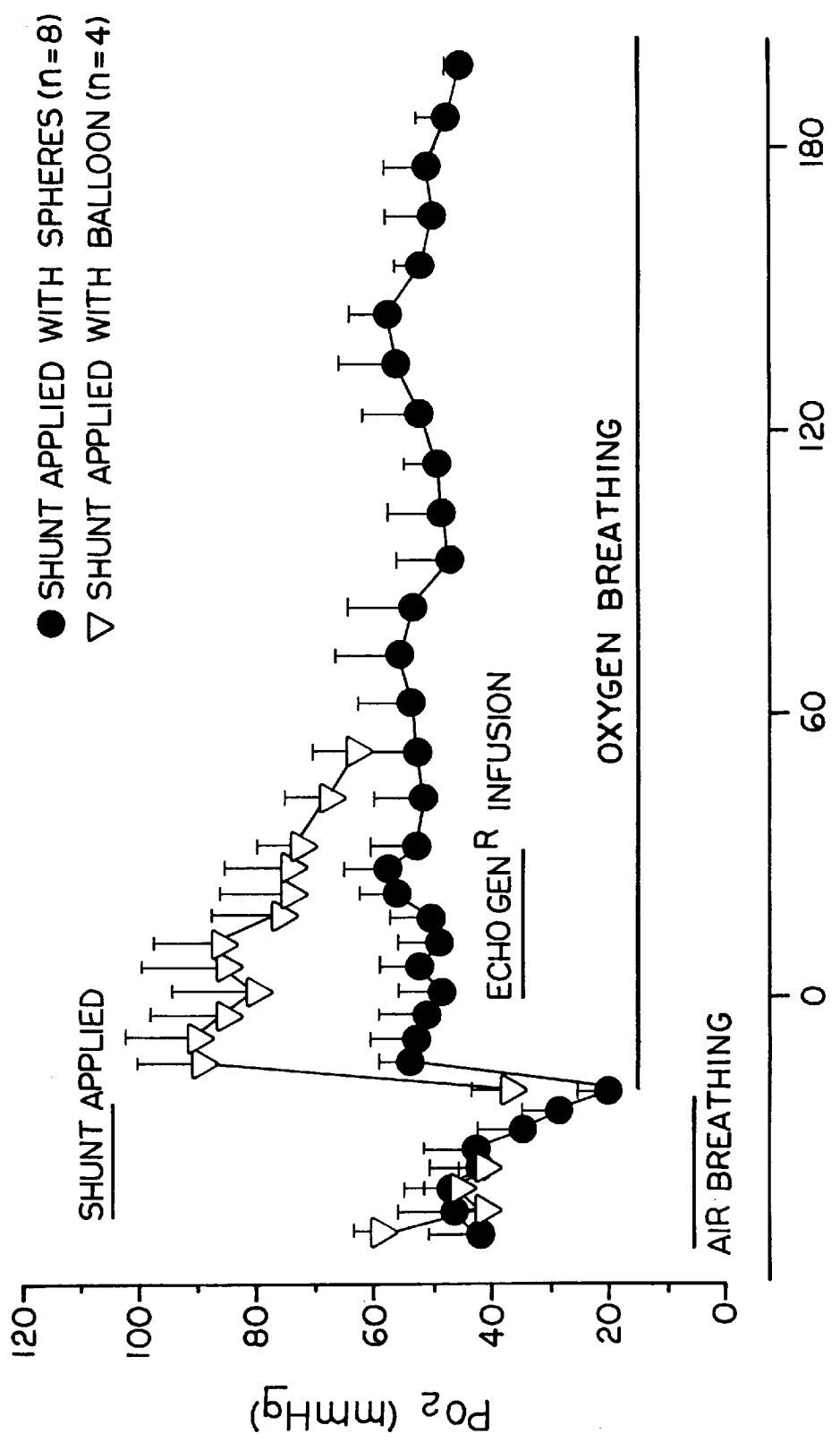
● SHUNT APPLIED WITH SPHERES (n=8)
▽ SHUNT APPLIED WITH BALLOON (n=4)
SHUNT APPLIED
ECHO GEN R INFUSION
OXYGEN BREATHING
AIR BREATHING
P_{O_2} (mmHg)
120
100
80
60
40
20
0
0
60
120
180
TIME (min)

FIG. 21

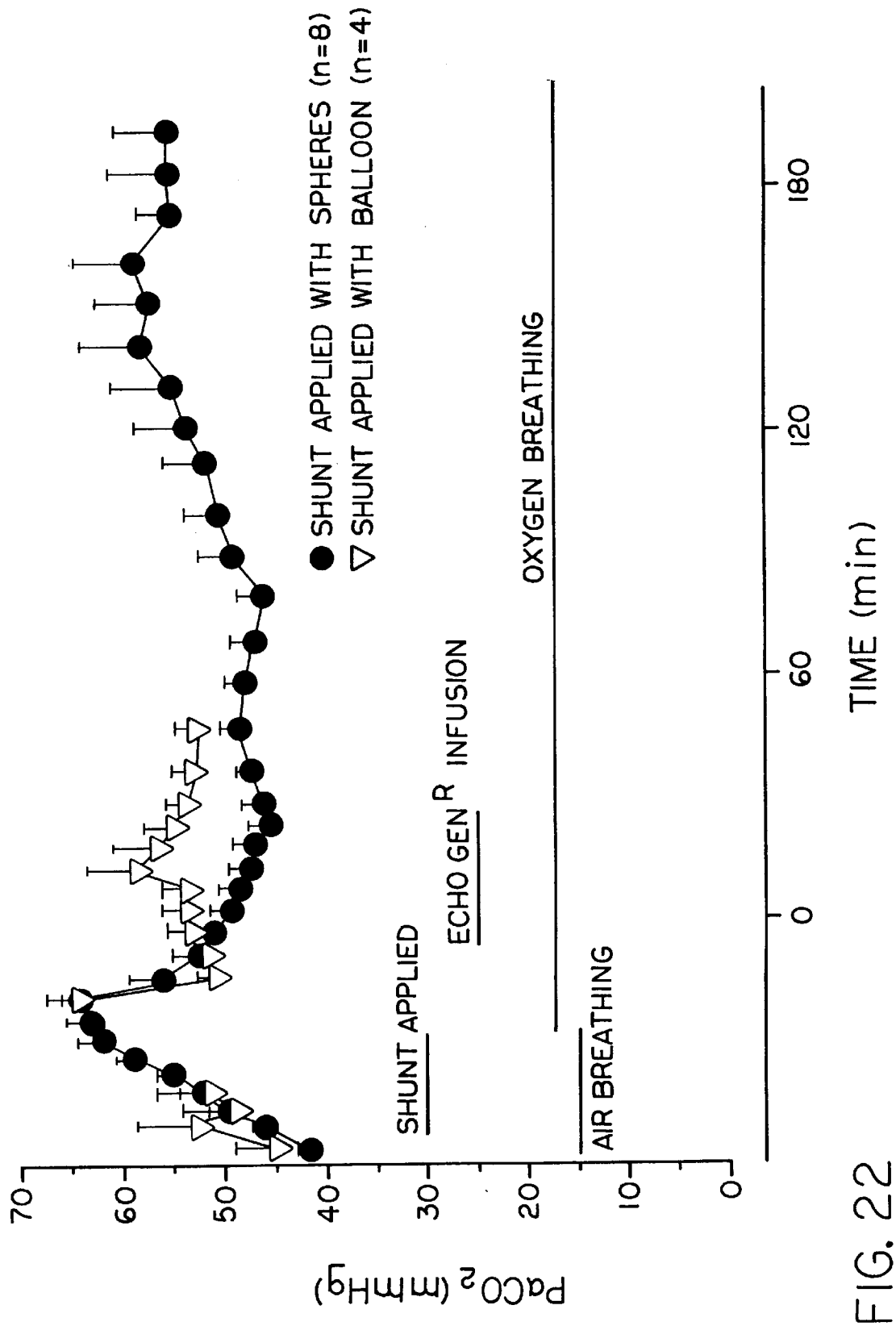
● SHUNT APPLIED WITH SPHERES (n=8)
▽ SHUNT APPLIED WITH BALLOON (n=4)
SHUNT APPLIED
ECHO GEN R INFUSION
OXYGEN BREATHING
AIR BREATHING
PaCO2 (mmHg)
70
60
50
40
30
20
10
0
0
60
120
180
TIME (min)

FIG. 22

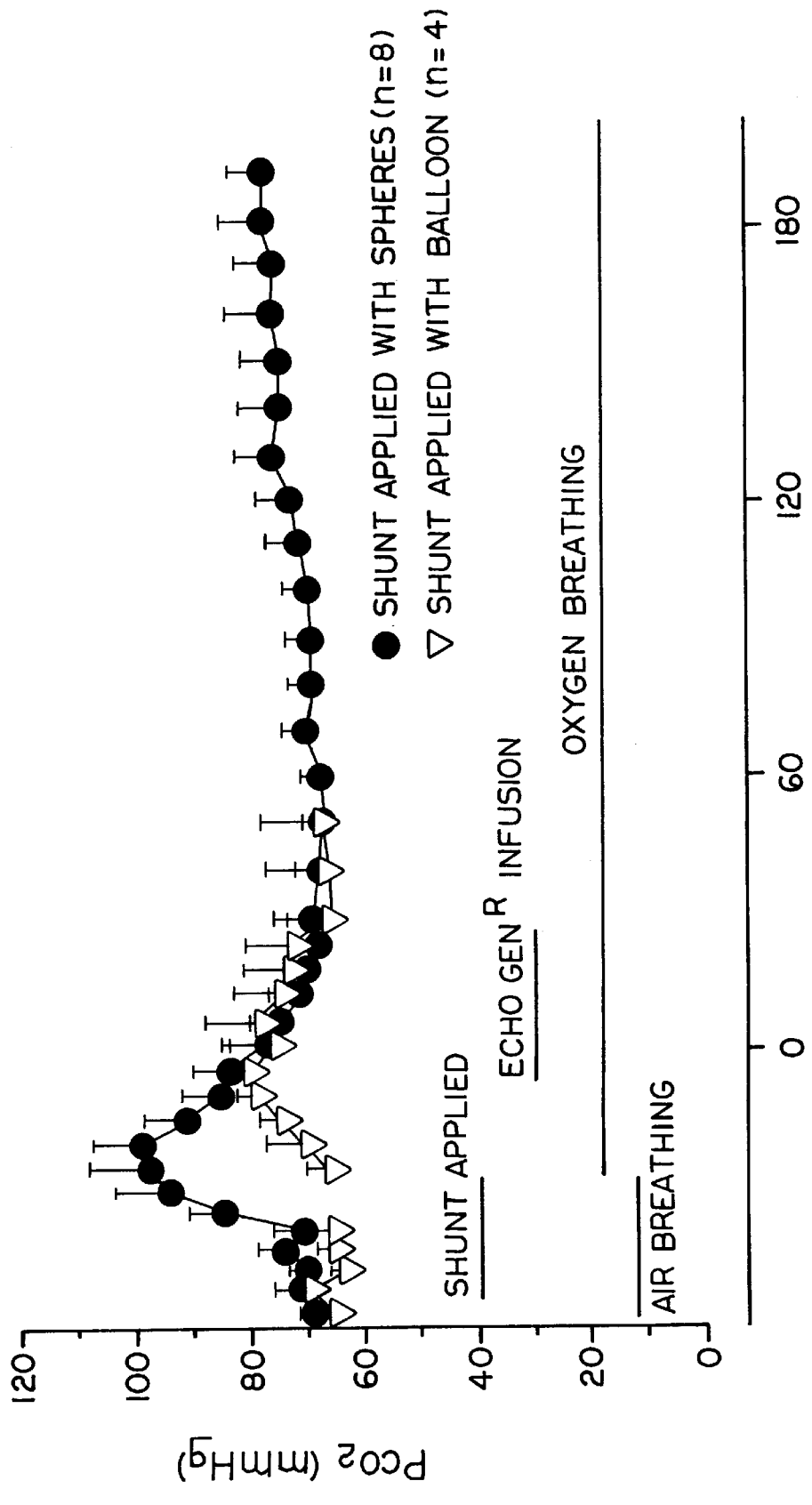
● SHUNT APPLIED WITH SPHERES (n=8)
▽ SHUNT APPLIED WITH BALLOON (n=4)
SHUNT APPLIED
ECHO GEN R INFUSION
OXYGEN BREATHING
AIR BREATHING
PCO2 (mmHg)
120
100
80
60
40
20
0
0
60
120
180
TIME (min)

FIG. 23

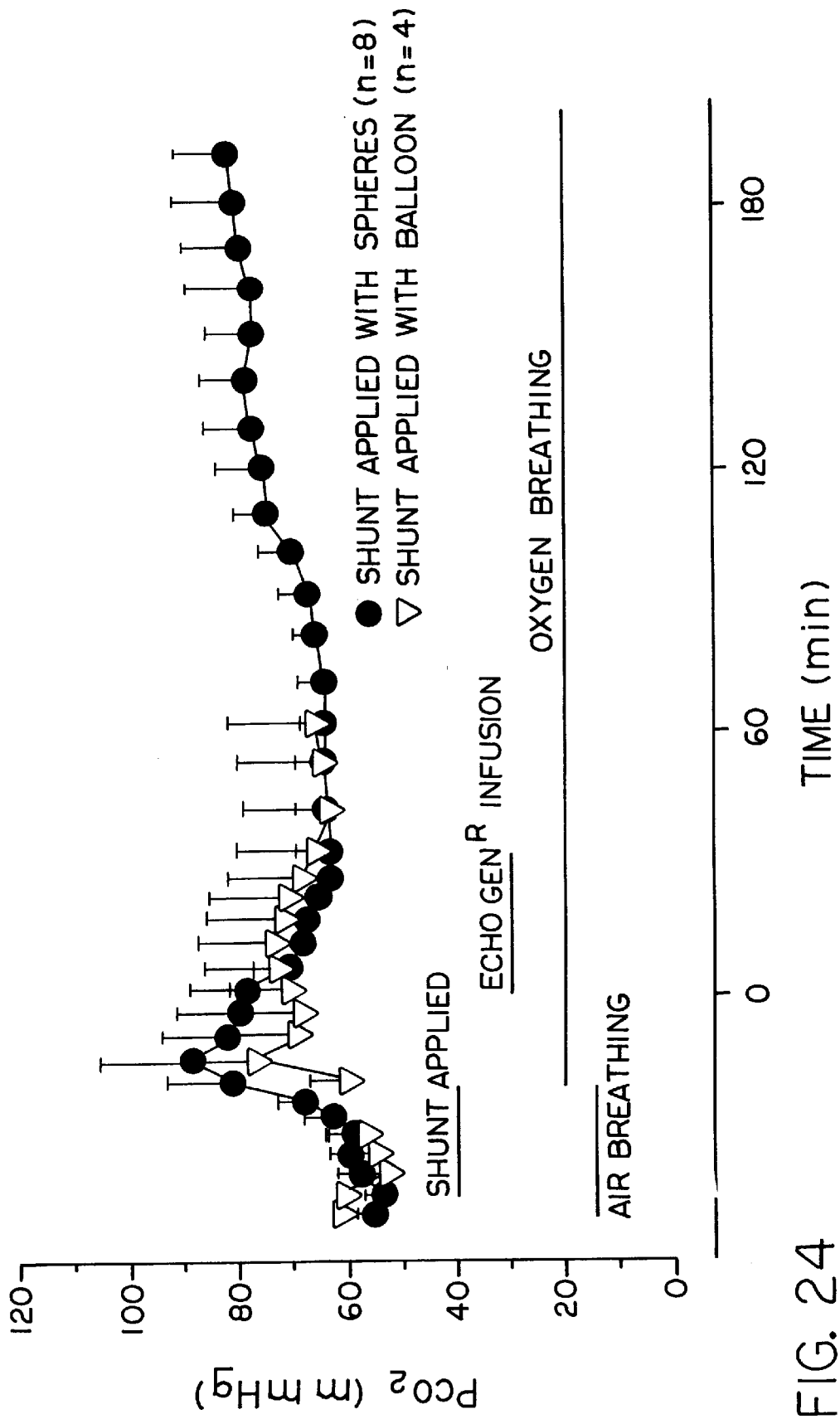
SHUNT APPLIED WITH SPHERES (n=8)
SHUNT APPLIED WITH BALLOON (n=4)
SHUNT APPLIED
ECHO GEN R INFUSION
OXYGEN BREATHING
AIR BREATHING
PCO2 (m mHg)
TIME (min)
120
100
80
60
40
20
0
0
60
120
180

FIG. 24

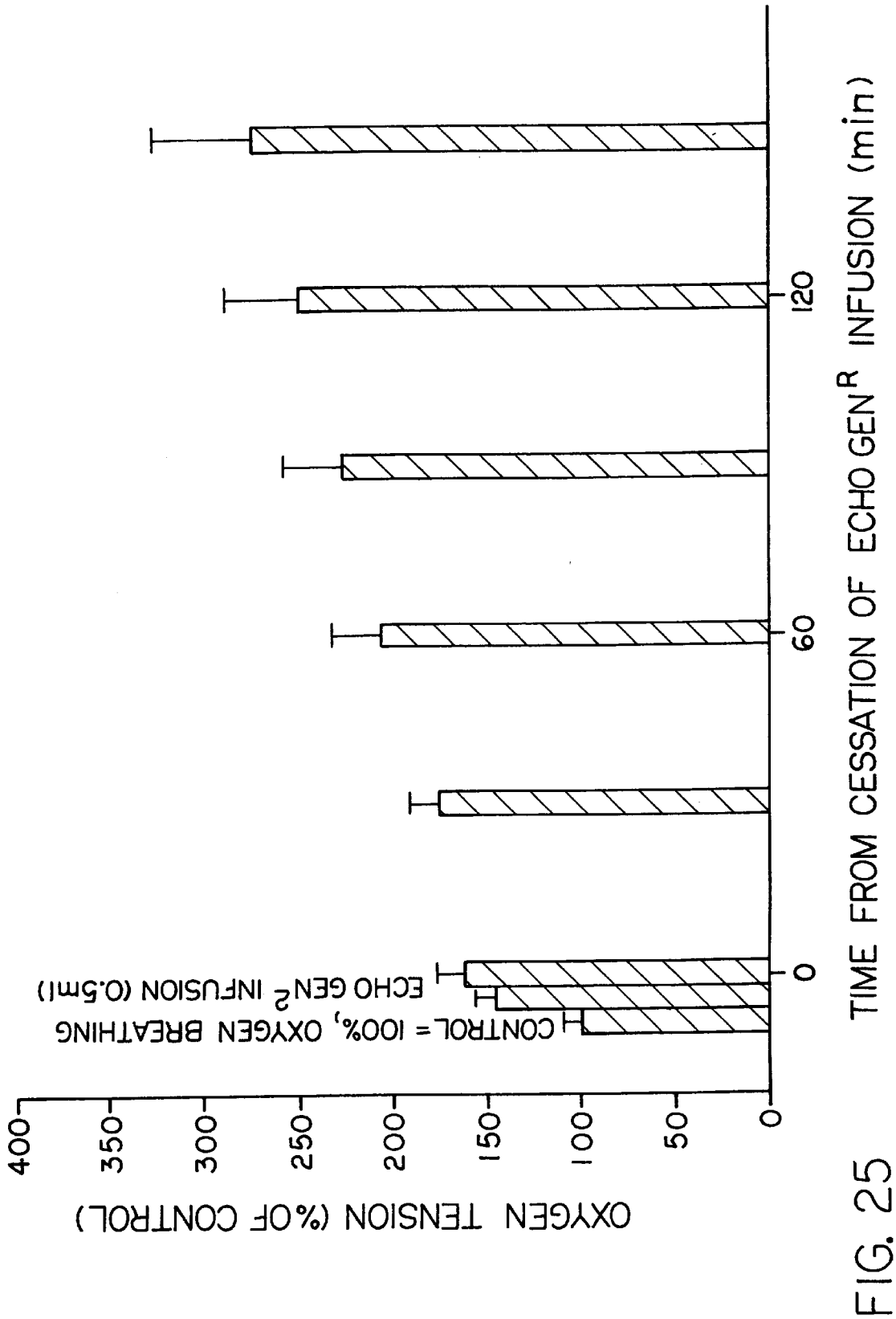
OXYGEN TENSION (%OF CONTROL)
400
350
300
250
200
150
100
50
0
CONTROL = 100% OXYGEN BREATHING
ECHO GEN² INFUSION (0.5ml)
0
60
120
TIME FROM CESSATION OF ECHO GEN® INFUSION (min)

FIG. 25

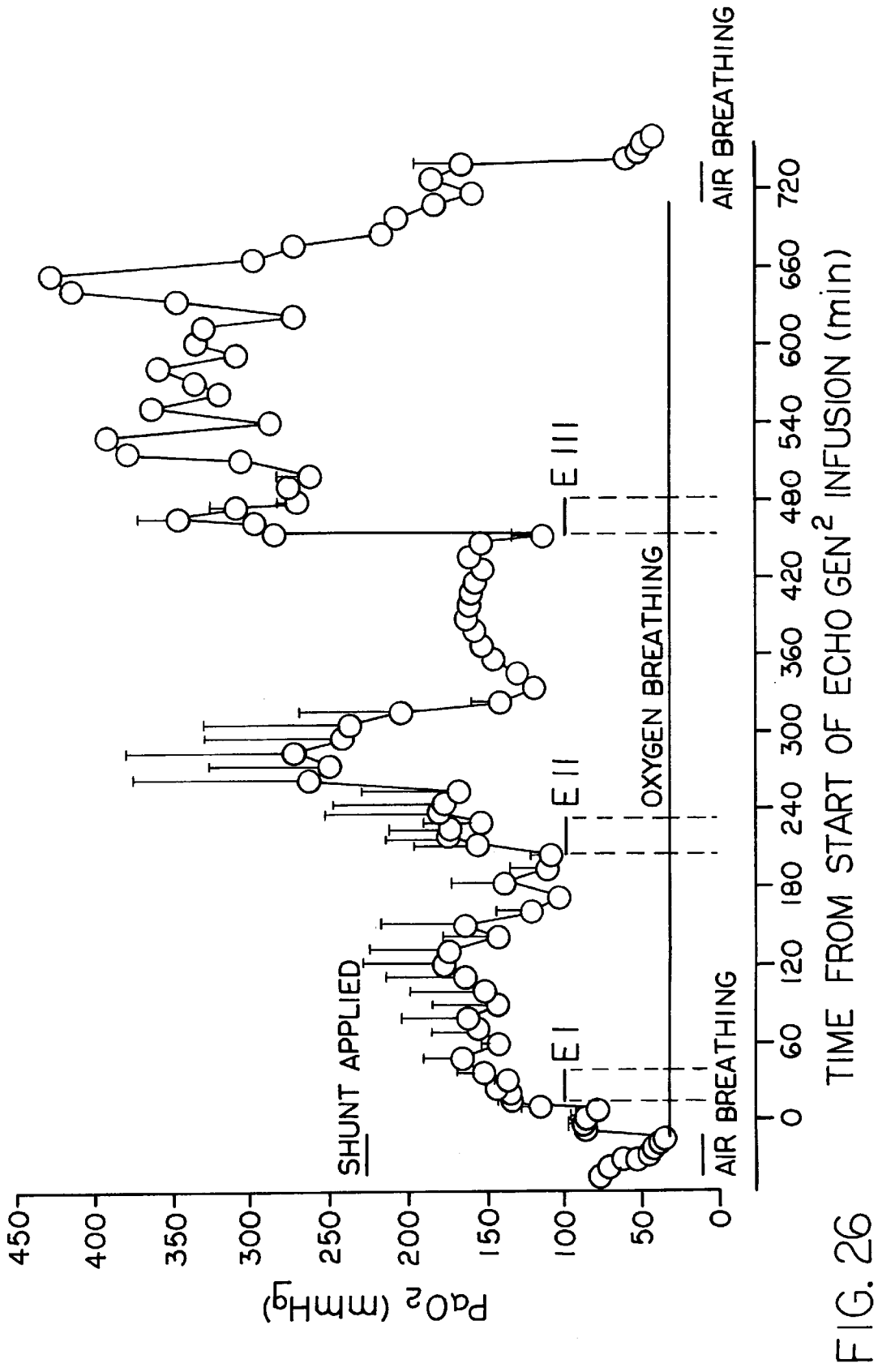
Pa_{O_2} (mmHg)
450
400
350
300
250
200
150
100
50
0
SHUNT APPLIED
AIR BREATHING
E I
E II
OXYGEN BREATHING
E III
AIR BREATHING
0
60
120
180
240
300
360
420
480
540
600
660
720
TIME FROM START OF ECHO GEN^2 INFUSION (min)

FIG. 26

FIG. **11** is a graphic representation showing dependence of microbubble O_2 content (solid) and radius (dotted) on P_{O2} in the surrounding environment for differing amounts of gas X in the microbubble.

FIG. **12** is a graphic representation illustrating the curves for O_2 content of blood alone, microbubbles alone, and a combination of blood and microbubbles (the microbubble concentration is 4.7×10^8/ml).

FIG. **13** is a graphic representation illustrating the curves for O_2 content of blood alone, microbubbles alone, and a combination of blood and microbubbles (the microbubble concentration is 1.8×10^9/ml).

FIG. **14** is a graphic representation showing CO_2 content of a single, gas-stabilized microbubble as a function the P_{O2} in the surrounding blood and tissue locations.

FIG. **15** is a graphic representation showing preparation of aan animal for monitoring physiologic values during microbubble treatment.

FIG. **16** is a graph showing variations of muscle PO_2 after infusion of stabilized microbubbles.

FIG. **17** is a graphic representation showing variations of gas volumes in a microbubble in a person who breathes 100% O_2, but has N_2 in the tissues.

FIG. **18** is a schematic representation of an instrumented pig.

FIG. **19** is a graph showing the time course of arterial oxygen tension (PaO_2) during application of right to left circulatory shunt in the lungs, inhalation of oxygen and microbubbles infusion.

FIG. **20** is a graph showing the time course of oxygen tension in abdominal muscle (PO_2) measured with Kontron transcutaneous PO_2_PCO_2 sensor during the application of right to left shunt, inhalation of oxygen and microbubbles infusion.

FIG. **21** is a graph showing the time course of oxygen tension in abdominal muscle (PO_2) measured with Radiometer transcutaneous PO_2_PCO_2 sensor during the application of right to left shunt, inhalation of oxygen and microbubbles infusion.

FIG. **22** is a graph showing the time course of carbon dioxide tension in arterial blood ($PaCO_2$) during the application of right to left shunt, inhalation of oxygen and stabilized microbubbles infusion.

FIG. **23** is a graph showing the time course of carbon dioxide tension in abdominal muscle (PCO_2) measured with Kontron transcutaneous PO_2_PCO_2 sensor during the application of right to left shunt, inhalation of oxygen and stabilized microbubbles infusion.

FIG. **24** is a graph showing the time course of carbon dioxide tension in abdominal muscle (PCO_2) measured with Radiometer transcutaneous PO_2-PCO_2 sensor during the application of right to left shunt, inhalation of oxygen and stabilized microbubbles infusion.

FIG. **25** is a representation of the effects of stabilized microbubbles infusion on oxygen tension in arterial blood during right to left circulatory shunt in the lungs of Group 2 animals.

FIG. **26** is a representation of oxygen tension in arterial blood during right to left circulatory shunt in the lung treated with stabilized microbubbles and oxygen breathing in seven animals.

DETAILED DESCRIPTION OF THE INVENTION

By the term "right to left circulatory shunt" for the purposes of specification and claims is meant a condition wherein deoxygenated venous blood for whatever reason is not subject to reoxygenation in the lungs before making its way to the left heart and the systemic circulation.

In a preferred embodiment of the methods of the present invention, a specific type of gas carrier is utilized for optimal transport of gases to or from tissue. Particularly, the gas carrier comprises microbubbles formed by suspending, in a liquid, a quantity of gas, preferably gaseous PFC. Thus, microbubbles are formed which contain a foreign gas that, when introduced into the bloodstream, permeates through the microbubble/blood interface very slowly. The slowly permeating gas serves as a stabilizer of the microbubble structure. It will be appreciated by those skilled in the art that the size of the microbubbles formed can be controlled by the manufacturing process to be sufficiently small so as not to obstruct the systemic or pulmonary capillaries. Particularly useful in producing such microbubbles are compounds comprising gases and PFCs which are a liquid at temperatures of manufacturing the compound, but become a vaporized gas at body temperature thereby forming microbubbles (such compounds are available from SONUS Pharmaceuticals). The gases and PFCs useful in the production of such microbubbles are disclosed in, for example, U.S. Pat. Nos. 5,393,524, and 5,409,688 (also in U.S. Ser. Nos. 08/380,085, 08/008,172, 08/148,284, and 08/182,024) all of which are incorporated herein by reference. Thus, while other such compounds are useful for methods according to the present invention, for purposes of illustration, but not limitation, microbubbles used in the examples comprise perfluoropentane, and more particularly contain the PFC dodecafluoropentane (DDFP). The microbubbles are prepared by a phase-shift technology (See, for example, U.S. Pat. No. 5,393,524), whereby an emulsion of liquid DDFP droplets is prepared in a cool environment, and then when infused or injected into the body of an individual, the droplets become gas microbubbles. Depending on the particular compound, the microbubbles are stabilized to laste in the bloodstream for a time ranging from a few minutes to several hours. The following examples illustrate novel properties of these microbubbles and other stabilized microbubbles, and parameters to consider relating to their use for the methods of the present invention.

EXAMPLE 1

Oxygen Transport By Stabilized Microbubbles

The mechanisms involved in O_2 transport by stabilized gas microbubbles can be illustrated using equations based on physical principles. Equation 1 is based on the equality of hydrostatic pressures on a microbubble (lefthand side of the equation) with the sum of partial pressures of the gases inside (righthand side of the equation) where: X represents the gas that permeates slowly from the microbubble; P_B is barometric pressure; γ is surface tension; R is microbubble radius; Pb1 is blood pressure; and Pbub is the partial pressure of the respective gas inside the microbubble.

Equation 1: $P_B+2\gamma/R+Pb1=Pbub_{N2}+Pbub_{O2}+Pbub_{CO2}+Pbub_{H2O}+Pbub_X$

Equation 2 shows that when gas X does not permeate the microbubble/blood interface, the partial pressure of gas X will increase or decrease when parameters (righthand side of the equation) change, and shows that pressure due to surface tension is inversely proportional to microbubble radius. Blood pressure and partial pressures, in blood, of O_2 and CO_2 ($Pb1_{O2}$ and $Pb1_{CO2}$) differ in parts of the circulatory

EXAMPLE 6

Method of Using Stabilized Microbubbles as a Carrier of Anesthetic Gas

Stabilized microbubbles, such as those formulated from slowly permeating gas, may be used to carry anesthetic gases to and from tissues, with the intent of delivering such gases in a rapid and controlled manner, in a method of anesthetizing an individual rapidly and in reversing the anesthetized state rapidly. Generally, anesthetic gases are more soluble in blood than N_2. According to this method of the present invention, a therapeutically-effective amount of microbubbles is introduced into the blood circulation of an individual, wherein the microbubbles function to carry anesthetic gas(es) from the lungs in adequate amounts and at adequate pressures to allow exchange with tissues to anesthetize the treated individual. One skilled in the art would appreciate that the amount of microbubbles to be introduced (number of microbubbles/ml) depends on a number of factors including the particular stabilizing mechanism used for microbubble preparation, the size (radius) range of the microbubbles in the preparation, the volume of blood in the individual to be treated, and the efficacy of the anesthetic gas carried by the microbubbles. For example, if a microbubble carries 60% N_2O, and if N_2O solubility is 0.45 ml N_2O ml blood/atm and blood PN_{20} is 0.8 atm, then the microbubble would carry approximately 1.5 times more N_2O than an equal volume of blood. The maximal enhancement of solubility for N_2O would be 1/0.45=2.2. Potentially such solubility enhancement will be magnified by differences in diffusional transport from blood to tissues mediated by the presence of microbubbles. The therapeutically effective amount of microbubbles, containing one or more anesthetic gases, can be administered into the blood circulation of the individual to be treated by methods known in the art, including intravenous administration.

EXAMPLE 7

Method of Using Stabilized Microbubbles to Remove Inert Gas From Tissues

Stabilized microbubbles, such as those formulated from slowly permeating gas, may be used to carry nitrogen or other inert gas in a breathing mixture out of tissue, in a method of preventing or absorbing dangerous bubbles which contain inert gas. Such bubbles are encountered in gaseous emboli, and are the initial cause of decompression sickness in underwater divers, aviators in unpressurized aircraft, and astronauts engaged in extravehicular activities. Carriage of inert gas, such as N_2, from tissue to the lung by microbubbles in the blood is a logical corollary of the idea that microbubbles can carry oxygen. References that demonstrate the usefulness of liquid PFC emulsions in denitrogenating tissue are Cassuto et al., 1974, *Aerospace Med* 45:12–14; Novotny et al., 1993, *J Appl Physiol* 74:1356–1360; and Speiss et al., 1988, *Undersea Biomed Res* 15:31–37. Microbubbles can be expected to be more efficacious and more practical than perfluorocarbons.

FIG. **17** illustrates that when N_2 is present in tissue of a person who breathes pure O_2, the microbubble will accumulate large amounts of N_2 as it passes through the tissue and will unload N_2 in the lungs. The amount of N_2 carried is about two-thirds of the amount of O_2 carried. The microbubbles can carry much more N_2 than blood. If N_2 comprises 60% of a microbubble in venous blood of a person breathing pure O_2, as in FIG. **17**, the microbubble will carry 0.6 ml N_2/ml gas/atm. Contrasted with blood solubility of N_2 of 0.015 ml N_2/ml blood/atm and assuming that P_{N2} of blood is 0.8 atm, it is seen that the microbubble can carry 50 times more N_2 than the same volume of blood.

EXAMPLE 8

Use of Stabilized Microbubbles in Right-to-Left Shunts

This embodiment illustrates the use of the microbubbles of the present invention in alleviating the effects of a right-to-left circulatory shunt (RLS). To illustrate this embodiment, RLS was created in pigs, which is an accepted animal model for such studies because their lungs lack interlobular vascular connections. Pigs weighing between 32–160 pounds were anesthetized by standard procedures. The trachea was exposed, opened and a cuffed tracheal tube was introduced. The right femoral artery and vein were cannulated and arterial pressure (AP) and heart rate (HR) were measured continuously using a COBE disposable pressure transducer (COBE, Lakewood, Colo.). A constant, continuous intravenous infusion of 1 ml/min of lactated Ringer's solution and sustaining doses of sodium pentobarbital were given. Samples were obtained from the left femoral artery for arterial blood gas measurements. Blood gases were measured at 5–15 min intervals using standard measuring equipment (Ciba-Corning Blood Gas System, model 278). Stabilized bubbles in lactated Ringer's solution was infused via the left femoral vein. The right external jugular vein was exposed and cannulated with a Swan-Ganz catheter (size 5 F). The catheter was introduced into the right cardiac ventricle, the balloon partly inflated and floated in the blood stream until positioned in the pulmonary artery. The pulmonary arterial pressure (PAP) was measured using a COBE disposable pressure transducer. In some cases the Swan-Ganz catheter tip was placed in the right ventricle to measure the right ventricular pressure (RVP). A catheter was placed in the right external jugular vein alongside the Swan-Ganz catheter with the tip in the right atrium to measure the central venous pressure (CVP) and the respiratory frequency (RF). The left external jugular vein was cannulated and the catheter introduced into the superior vena cava. Blood samples were obtained for determination of venous blood gases. Two transcutaneous O2-CO2 combisensors (Kontrol, Zurich, Switzerland, and Radiometer, Copenhagen, Denmark) were placed in small pouches over abdominal muscle tissue for continuous measurements of tissue O2 and CO2.

Following surgery, the pigs were allowed to stabilize for a period of 30 min while breathing air. Measurements of AP, PAP, CVP, RF, and HR were recorded over the next 15 min. At least two sets of control blood samples were collected for arterial and venous blood gas analysis. The blood was sampled with airtight glass syringes and analyzed within 20 seconds. The circulatory RLS was established as follows.

In Group I, a Swan-Ganz catheter was introduced into one main bronchus, and the cuff inflated in order to close off that part of the lung. This reduced the arterial O_2 tension (PaO2) somewhat, but inhalation of a high concentration of oxygen increased the PaO2 regularly to above 250 mmHg.

In Group II, in 8 pigs, steel or glass beads of about 1 mm diameter were injected into the bronchial tree, creating atelectasis by multiple endo bronchial obstructions (Eyal et al., 1996), until the arterial PaO2 had fallen to approximately to 30 mm Hg. This procedure caused a more pronounced RLS since inhalation of pure O2 could only partly compen-

sate for the applied shunt, limiting the rise in the PaO2 to less than 70 mm Hg.

While the pigs breathed air, after the shunt was established, arterial and central venous blood samples were taken, analyzed and shunt fraction calculated according to standard methods (Levitzky 1991). At the end of the air breathing period, the animals were given pure oxygen to breathe. During the first 20–30 min of O_2 breathing, new baseline values were established and then the I.V. infusion of stabilized microbubbles was started at a rate of 0.1–0.2 ml/min in 4 ml/min lactated Ringer's solution. A total of 2–6 ml of microbubbles was given during the next 30 min. Arterial blood samples were taken and analyzed for blood gases every 5 min during the infusion period and every 10 min for the rest of the experimental period. The criterion for terminating the stabilized microbubbles infusion was a substantial increase in arterial PaO_2 and tissue PO_2 tension. Regularly, the maximal effect was seen 50–80 min after the infusion of DDFP emulsion was terminated and started to wear off 150–300 min later. The blood gases gradually returned to the baseline value. In seven pigs, a second and third dose of 2–5 ml were infused in an identical manner as described above until a rise in PaO_2 was established. Blood samples were analyzed for the next 5–12 three hours.

The spontaneously breathing pigs were administered 100% O_2 before, during, and after stabilized microbubbles infusion. A schematic overview of the experiments is indicated by the time lines in the figures and tables.

At the end of the experiments, the pigs were sacrificed with a lethal I.V. dose of pentobarbital sodium (100 mg/kg). No adverse effects of stabilized microbubbles infusion were found on HR, RF, and blood pressure during any of the experiments (maximal duration 16 h in seven pigs). The body temperature was kept within 1° C. of the core temperature observed at the start of each specific experiment.

During air breathing control periods, all blood pressures, HR, and RF were similar and within normal ranges (Tables 7 and 8) in the two types of shunts. Though the PaO_2 was somewhat different in the two groups, i.e. 66.2±3.7 (mean+ SE) mm Hg in Group 1 and 80.3±3.0 mm Hg in group 2, the O_2 saturation was similar and normal, at 93.8+0.3 and 95.3+0.5%, respectively (Tables 9 and 10, FIG. **19**). At the same time, $PaCO_2$ was 45.1±4.0 and 41.8±1.3 mm Hg in the two groups (Tables 10 and 11, FIG. **22**. The muscle PO_2 was 58±8 (Kontron electrode) and 59±3 mm Hg (Radiometer electrode) in Group 1 and 44±5 and 41±8 mm Hg in Group 2 (Tables 9 and 10, FIGS. **20**, and **21**), and the tissue PCO_2 was 66±3 and 62±2, and 69±2 and 55±3 mm Hg, respectively (Tables 9 and 10, FIGS. **23** and **24**).

The shunt fractions were calculated to be 0.27 in one representative animal in Group 1 and 0.20±0.02 (SE) in Group 2.

Establishment of Pulmonary Shunt

When one lung or parts of one lung was closed off from the ventilation by an inflated balloon in Group 1 pigs, PaO_2 fell to 45.7±1.5 mm Hg reducing the O_2 saturation to 80.8±3.4%, and local muscle PO_2 to 40±2 and 37±5 mm Hg. The $PaCO_2$ increased to 51.1±5.4 mm Hg, and tissue PCO_2 was raised to 66±4 and 61 ±5 mm Hg. The shunt fraction increased to 0.43. When beads were used to block ventilation (Group 2 pigs), PaO_2 fell to 32.2 ±2.2 mm Hg and arterial O_2 saturation to 61.2±5.9%. The muscular PO_2 fell to 23±5 and 20±5 mm Hg. The $PaCO_2$ increased to 63.1±2.5 mm Hg and muscular PCO_2 to 98±9 and 81±10 mm Hg. The shunt fraction increased to 0.57±0.06 (SE).

When O_2 breathing was established, the PaO_2 increased in both groups of animals, but to different levels. The PaO_2 in Group 1 animals increased to 216.6±15.2 mm Hg (FIG. **19**) and an oxygen saturation of 99.5±0.1% was obtained, whereas in Group 2 animals PaO_2 was also increased, but did not reach the control level in air (68.6±9.1 mm Hg) (FIG. **19**) giving a saturation of 89.5±5.3%.

During the initial phase of O_2 breathing, the respiration ceased in the 3 animals which had the most marked increases in $PaCO_2$ and artificial ventilation had to be administered for the next 5–15 min.

Infusion Id Microbubbles Aqenerating DDFP Emulsion

During infusion of DDFP emulsion, the PaO_2 started to increase within 1 min of infusion or 0.1 ml, and continued to rise during the infusion in both animal groups (FIG. **19**). The 3 animals with high $PaCO_2$ and respiratory arrest, started to breathe spontaneously again after 5 min of infusion of DDFP. In all animals in Group 2, $PaCO_2$ and tissue PCO_2 fell during the infusion (FIG. **22**).

After infusion of DDFP emulsion less than 1 ml (10 min of infusion), the PaO_2 was significantly increased wether the initial PaO_2 was hyperoxic (>150 mm Hg of O_2) or hypoxic (<80 mm Hg of O_2) . At the same time the muscle PCO_2 fell on the two monitoring devices (FIGS. **21–24**).

The PaO_2 increased steadily over the next 20 min in both groups whereupon it remained at between 130 and 350% of the initial value for the remaining infusion period and for the next 2 h (FIG. **19**). After a period of 2–3 h, the PaO_2 and muscle $P0_2$ (FIGS. **20**,21) began to decline and $PaCO_2$ (FIG. **22**) and muscle PCO_2 (FIGS. **23**,24) increased. Depending on the amount of infused DDFP emulsion, the control levels of O_2 and CO_2 were approached after approximately 3 h.

The systolic AP, mean AP and diastolic AP remained stable and within 10 mm Hg of the control values during the experiments (Tables 7,8). The HR remained constant throughout the experiments. The changes provoked by inducing the RLS, were all corrected during the infusion of DDFP emulsion so that RVP, CVP, and PAP remained mainly unaltered throughout the experimental period (Tables 7,8).

FIG. **25** shows the general effect of an EchoGen® infusion on PaO_2 when all infusions in Group 2 pigs were summarized, whether they were the first, 2nd, or 3rd. This graph indicates an effective O_2 carrying capacity of the DDFP micro-bubbles exceeding 4 h.

When repeated doses of microbubbles were given in seven of Group 2 animals as shown in FIG. **26**, the PaO_2 followed the same pattern as during and after the first infusion, though higher levels were obtained with a lower dose of infused DDFP emulsion. Furthermore, the high PaO_2 tended to be sustained longer after the 2nd and 3rd infusion than after the first infusion.

These results demonstrate that stabilized microbubbles in combination with oxygen breathing, is capable of effectively counteracting the adverse effects of severe right-to-left circulatory shunt on gas exchange. With the doses used, animals that before treatment were severely hypoxic, hypercapnic, and hypertensive, became hyperoxic, nearly normocapnic and their circulatory parameters normalized to control levels. Already one minute after instituting the therapy, the PaO_2 began to increase and after 10 min it had reached 155% (106.5±15.1 mm Hg, $p<0.01$) of the control level (68.2±9.1 mm Hg) and within 150 min it had reached approximately 200%.(134.9±9.1 mm Hg, $p<0.01$).

Those skilled in the art will recognize that a considerably lower rate of infusion can be used while still attaining adequate O_2 and CO_2 exchange. It should be noted that even with the intense treatment used in this study, no adverse effects of microbubbles infusion were observed although they were repeated up to 3 times and the animals were monitored up to 12 hours.

The absence of side effects in this large animal model and the long duration (4h) of the treatment effect indicates that this application of stabilized microbubbles can be used in the treatment of right to left shunt as described herein.

TABLE 7

Blood pressures, heart rate and respiratory frequency in animals treated with EchoGen ® for right-to left circulatory shunts in the lungs induced by partial airway blockage with an airfilled balloon. The shunt fraction increased from 0.27 to 0.43 after the balloon was inflated (measured in one representative animal).

	SAP mm Hg	DAP mm Hg	MAP mm Hg	HR beats/ min	RF breaths/ min	PAP sys mm Hg	PAP dia mm Hg	PAP mean mm Hg	RVP max mm Hg	RVP ed mm Hg	dCVP mm Hg	CVP mean mm Hg
Control	135 ± 5	88 ± 6	104 ± 6	148 ± 14	24 ± 2	28 ± 2	21 ± 2	22 ± 2	25	0	5 ± 1	4 ± 2
Shunt Induced												
air breathing	162 ± 91	10 ± 11	127 ± 8	178 ± 9	26 ± 3	28 ± 1	22 ± 1	24 ± 1	40	1	5 ± 1	4 ± 1
oxygen breathing	135 ± 6	90 ± 4	105 ± 4	156 ± 8	26 ± 3	27 ± 1	22 ± 1	24 ± 1	26	−2	4 ± 0	3 ± 1
EchoGen ® Infusion												
10 min	125 ± 5	75 ± 4*	92 ± 4	163 ± 11	24 ± 3	28 ± 2	22 ± 1	24 ± 1	22	3	3 ± 0	6 ± 3
at end of infusion	137 ± 3	87 ± 5	103 ± 4	183 ± 4	26 ± 4	26 ± 1	18 ± 1	20 ± 1	26	2	2 ± 0	4 ± 2
After Infusion 30 min	140 ± 4	90 ± 5	107 ± 5	178 ± 10	24 ± 4	27 ± 1	18 ± 1	21 ± 1	25	2	3 ± 0	5 ± 2

All values are means ± SE, n = 4, *p < 0.05, baseline values during oxygen breathing versus values during and after EchoGen ® infusion. SAP — systolic arterial pressure; DAP — diastolic arterial pressure; MAP — mean arterial pressure; HR — heart rate; RF — respiratory frequency; PAPsys — systolic pulmonary arterial pressure; PAPdia — diastolic pulmonary arterial pressure; PAPmean — mean pulmonary arterial pressure; RVPmax — maximal right ventricular pressure; RVPed — end diastolic right ventricular pressure; dCVP — central venous pulse pressure; CVPmean — mean central venous pressure.

TABLE 8

Blood pressures, heart rate and respiratory frequency in animals treated with EchoGen ® for severe right-to left circulatory shunts in the lungs induced by intratrachael injections of steel beads. The shunt fraction increased from 0.20 ± to 0.02 in control to 0.57 ± 0.06 after beads were given.

	SAP mm Hg	DAP mm Hg	MAP mm Hg	HR beats/ min	RF breaths/ min	PAP sys mm Hg	PAP dia mm Hg	PAP mean mm Hg	RVP max mm Hg	RVP ed mm Hg	dCVP mm Hg	CVP mean mm Hg
Control	137 ± 8	93 ± 5	108 ± 6	165 ± 10	40 ± 5	17 ± 2	9 ± 4	12 ± 3	32 ± 4	4 ± 1	4 ± 1	4 ± 1
Shunt Induced												
air breathing	163 ± 8	103 ± 8	123 ± 7	179 ± 9	28 ± 4	19 ± 3	8 ± 2	11 ± 2	43 ± 5	8 ± 2	6 ± 1	5 ± 1
O_2 breathing	147 ± 7	98 ± 5	114 ± 5	176 ± 7	34 ± 6	15 ± 3	7 ± 2	10 ± 3	33 ± 3	6 ± 1	6 ± 1	3 ± 1
EchoGen ® Infusion												
10 min	141 ± 6	96 ± 4	111 ± 4	181 ± 9	36 ± 3	18 ± 3	8 ± 2	11 ± 2	32 ± 3	4 ± 1	5 ± 1	3 ± 0
at end of infusion	145 ± 5	99 ± 4	115 ± 4	185 ± 10	39 ± 4	19 ± 2	9 ± 2	12 ± 2	33 ± 3	4 ± 1	5 ± 1	2 ± 0
After Infusion												
30 min	149 ± 6	100 ± 5	116 ± 5	186 ± 10	38 ± 4	18 ± 3	9 ± 2	12 ± 2	33 ± 3	3 ± 0*	7 ± 2	3 ± 1
60 min	155 ± 6	107 ± 4	123 ± 4	182 ± 12	39 ± 4				35 ± 3	4 ± 1	7 ± 1	2 ± 1
90 min	153 ± 7	111 ± 6	125 ± 8	186 ± 10	34 ± 5				35 ± 2	4 ± 1	6 ± 1	2 ± 1*
120 min	±9	108 ± 6	121 ± 7	178 ± 8	34 ± 6				35 ± 4	4 ± 1	7 ± 1	2 ± 1*
150 min	151 ± 11	106 ± 7	121 ± 8	175 ± 11	28 ± 7				34 ± 3	4 ± 1	6 ± 1	2 ± 1*

All values are means ± SE, n = 4, *p < 0.05, baseline values during oxygen breathing versus values during and after EchoGen ® infusion. SAP — systolic arterial pressure; DAP — diastolic arterial pressure; MAP — mean arterial pressure; HR — heart rate; RF — respiratory frequency; PAPsys — systolic pulmonary arterial pressure; PAPdia — diastolic pulmonary arterial pressure; PAPmean — mean pulmonary arterial pressure; RVPmax — maximal right ventricular pressure; RVPed — end diastolic right ventricular pressure; dCVP — central venous pulse pressure; CVPmean — mean central venous pressure.

TABLE 9

Arterial blood gases, acid base chemistry and tissue O_2 and CO_2 tensions in animals treated with EchoGen ® for severe right-to-left circulatory shunts in the lungs induced by partial airway blockage with an airfilled balloon. The shunt fraction increased from 0.27 in control to 0.43 after balloon was inflated (measured in one representative animal).

	PaO_2 mm Hg	$PaCO_2$ mmHG	pH	HCO_3 mm/l	O_2 sat %	PO_2K mm Hg	PO_2R mm Hg	PCO_2K mm Hg	PCO_2R mm Hg
Control	62.2 ± 7	45.1 ± 4.0	7.45 ± 0.06	27.5 ± 2.5	93.8 ± 0.3	58 ± 8	59 ± 3	66 ± 3	62 ± 2
Shunt Induced									
air breathing	45.7 ± 1.5	51.1 ± 5.4	7.41 ± 0.07	28.4 ± 2.0	80.3 ± 3.4	40 ± 2	37 ± 5	66 ± 4	61 ± 5
O_2 breathing	216.6 ± 15.2	53.2 ± 2.1	7.37 ± 0.09	31.7 ± 1.3	99.5 ± 0.1	64 ± 8	80 ± 12	80 ± 5	71 ± 8
EchoGen ® Infusion									
10 min	332.5 ± 23.8**	53.5 ± 2.4	7.44 ± 0.06	32.3 ± 1.3	99.7 ± 0.1	70 ± 6	86 ± 10	77 ± 9	74 ± 9
at end of infusion	344.2 ± 29.5**	53.7 ± 1.9	7.45 ± 0.04	31.9 ± 1.4	99.8 ± 0.1	77 ± 7	80 ± 7	66 ± 8	66 ± 9
After Infusion 30 min	309.6 ± 32.5**	53.0 ± 2.0	7.42 ± 0.04	32.1 ± 1.4	99.7 ± 0.1	76 ± 8	63 ± 6	68 ± 9	65 ± 9

All values are means ± SE, n = 4, *p < 0.05, baseline values during oxygen breathing versus values during and after EchoGen ® infusion. PaO_2 — oxygen tension in arterial blood; $PaCO_2$ — carbon dioxide tension in arterial blood, pH and [HCO_3] measured in arterial blood; O_2 sat — oxygen saturation in arterial blood; PO_2K and PO_2R — oxygen tension in abdominalmuscle measured with Kontron's and Radiometer's transcutaneous combisensors, respectively; PCO_2K and PCO_2R — carbon dioxide tension in abdominal muscle measured with Kontron's and Radiometer's transcutaneous combisensors, respectively.

TABLE 10

Arterial blood gases, acid base chemistry and tissue O_2 and CO_2 tensions in animals treated with EchoGen ® for severe right-to-left circulatory shunts in the lungs induced by intra tracheal injections of steel beads. The shunt fraction increased from 0.27 in control to 0.43 after balloon was inflated (measured in one representative animal).

	PaO_2 mm Hg	$PaCO_2$ mmHG	pH	HCO_3 mm/l	O_2 sat %	PO_2K mm Hg	PO_2R mm Hg	PCO_2K mm Hg	PCO_2R mm Hg
Control	80.3 ± 3.0	41.8 ± 1.3	7.44 ± 0.01	28.3 ± 0.9	95.3 ± 0.5	44 ± 5	41 ± 8	69 ± 2	55 ± 3
Shunt Induced									
air breathing	32.2 ± 2.2	63.1 ± 2.5	7.29 ± 0.02	30.4 ± 1.2	61.2 ± 5.9	23 ± 5	20 ± 5	98 ± 9	81 ± 10
O_2 breathing	58.6 ± 9.1	50.8 ± 2.6	7.34 ± 0.04	27.9 ± 1.4	89.5 ± 5.3	60 ± 10	49 ± 6	83 ± 5	78 ± 8
EchoGen ® Infusion									
10 min	106.5 ± 15.1**	48.1 ± 2.2	7.37 ± 0.02	28.4 ± 1.7	94.1 ± 3.6*	77 ± 10*	50 ± 6	75 ± 4	69 ± 6
at end of infusion	120.3 ± 19**	46.3 ± 2.2	7.40 ± 0.02	29.1 ± 1.9	95.0 ± 3.2	91 ± 13*	54 ± 6	69 ± 4	64 ± 4
After Infusion									
30 min	126.1 ± 25.0**	47.3 ± 1.8	7.43 ± 0.01	30.9 ± 1.3	93.0 ± 4.7	88 ± 13*	55 ± 8	68 ± 3	63 ± 4
60 min	116.0 ± 22.2*	48.1 ± 3.4	7.43 ± 0.02	31.2 ± 2.1	92.6 ± 2.9	85 ± 11*	48 ± 7	69 ± 4	66 ± 5
90 min	137.6 ± 26.8**	52.6 ± 5.0	7.41 ± 0.02	32.1 ± 1.8	98.0 ± 0.5**	85 ± 7*	53 ± 8	71 ± 5	74 ± 8
120 min	138.8 ± 25.0**	56.2 ± 5.4	7.39 ± 0.02	32.8 ± 1.6	97.8 ± 0.6**	86 ± 6*	53 ± 4	74 ± 5	76 ± 7
150 min	134.9 ± 26.6**	54.7 ± 5.4	30.8 ± 1.5	30.8 ± 1.5	98.2 ± 0.4**	81 ± 6*	49 ± 5	77 ± 6	79 ± 9

All values are means ± SE, n = 8, *p < 0.05 and **p < 0.01, baseline values during oxygen breathing versus values during and after EchoGen ® infusion. PaO_2 — oxygen tension in arterial blood; $PaCO_2$ — carbon dioxide tension in arterial blood, pH and [HCO_3] measured in arterial blood; O_2 sat — oxygen saturation in arterial blood; PO_2K andPO_2R — oxygen tension in abdominal muscle measured with Kontron's and Radiometer's transcutaneous combisensors, respectively; PCO_2K and PCO_2R — carbon dioxide tension in abdominal muscle measured with Kontron's and Radiometer's transcutaneous combisensors, respectively.

It should be understood that the embodiments and the examples of the present invention, as described herein, are for purposes of illustration only, and not limitation, and any changes or modifications as will become apparent to one of ordinary skill in the art from the foregoing description and accompanying figures are intended to be included within the scope of the appended claims and the equivalents thereof.

What is claimed is:

1. A method for reducing the effects of right to left circulatory shunt comprising the steps of introducing into a blood vessel of an individual in need of treatment a therapeutically-effective amount of stabilized microbubbles.

2. The method according to claim **1**, further comprising administering oxygen during treatment with the stabilized microbubbles.

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